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Armin de Meijere, François Diederich

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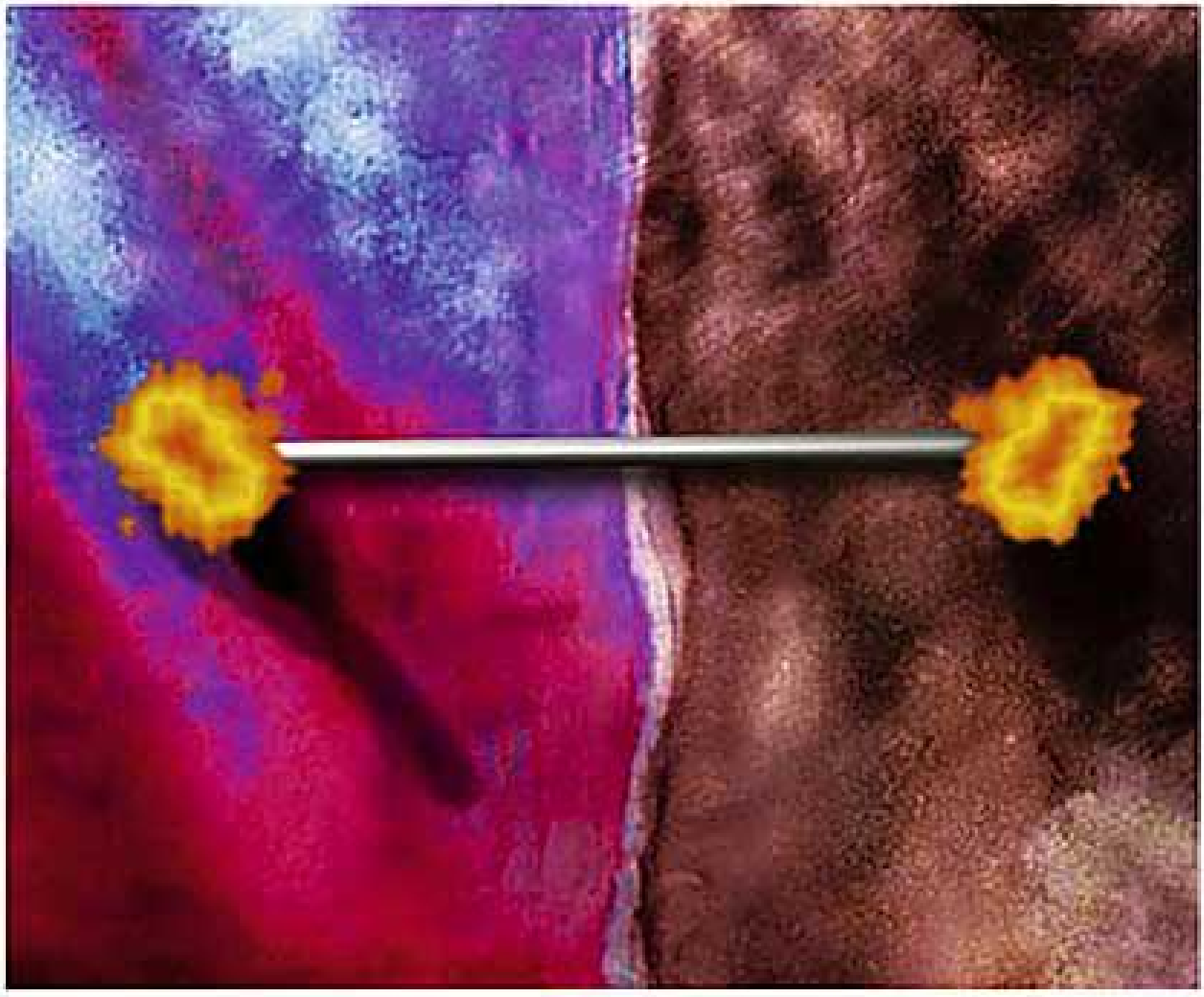
Metal-Catalyzed Cross-Coupling Reactions

Second, Completely Revised and Enlarged Edition

Volume 1



Metal-Catalyzed
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Volume 1

Edited by
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Editors:

Prof. Dr. Armin de Meijere
Institut für Organische und
Biomolekulare Chemie der
Georg-August-Universität
Tammannstrasse 2
D-37077 Göttingen
Germany

Prof. Dr. François Diederich
Swiss Federal Institute of Technology Zürich
Department of Chemistry
and Applied Biosciences
ETH Hönggerberg/HCI G 313
CH-8093 Zürich
Switzerland

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Preface

The development of metal-catalyzed cross-coupling reactions over the past 30 years has revolutionized the way, carbon-carbon bonds between sp and sp^2 C-atoms are formed. These methods have profoundly changed the protocols for the construction of natural products, building blocks for supramolecular chemistry and self-assembly, organic materials and polymers, and lead compounds in medicinal chemistry from simpler entities. Therefore, in the mid 90s, a documentation and critical analysis of the development and uses of metal-catalyzed cross-coupling reactions was mandated which led in 1998 to the publication of a first multi-authored monograph on the subject, to which a dozen experts and leaders in the field contributed. This earlier monograph has received wide attention and acclaim from scientists in both academia and industry. Since its appearance, the development of efficient new carbon-carbon bond forming reactions by metal-catalyzed cross-coupling has continued to progress dramatically. Thus, the number of publications concerning the various types of such reactions has significantly increased in the last 6 years (a quick search for the keyword "cross-coupling" revealed more than 6500 papers in the period 1998–2003. and still keeps growing (e. g. from 762 in 1998 to 1351 in 2003). In addition, sp^3 C-atoms can now increasingly participate in the transformations and some of the reactions are finding industrial application on the multiple-ton scale. Furthermore, mechanistically related new protocols for C–N couplings have been introduced that find particular use in the synthesis of biologically active compounds for pharmaceutical and agrochemical applications.

All of these vigorous developments mandate today the launch of a sequel to the first successful monograph. However, the present volume is not simply an update, but rather represents another unique treatise. Fifteen experts and leaders in the field have contributed (i) to report on the important progress made in the transformations described in the first volume, (ii) to describe extremely important transformations that were not previously included, and (iii) to present novel developments that are profoundly changing the art of organic synthesis. Thus, the monograph starts with a Chapter on the mechanistic aspects of metal-catalyzed C–C and C–X bond forming reactions, summarizing the enhanced insights into the "oxidative addition-transmetallation-reductive elimination cycle", gathered by the combined effort of many research groups over the past years. Several subsequent Chapters describe the use of the key organometallic reagents (organo-boron, -tin, silicon-,

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-magnesium, -zinc, -zirconium, etc.) as nucleophiles in the transmetallation step. Carbometallations, couplings via π-allylmetal intermediates, 1,4-additions to conjugated dienes, and cross-couplings with acetylenes and propargylic compounds are related transformations that are treated in separate Chapters. Finally, directed *ortho*-metallations for the formation of aryl-aryl and aryl-heteroaryl bonds and palladium-catalyzed aromatic C–N bond forming reactions are important developments that were not included in the first monograph.

The aim of the various Chapters is not to cover a direction comprehensively and in full detail; emphasis rather is placed upon key developments and important advances that are illustrated with attractive and useful examples. Carefully selected references provide ready access to the extensive literature in the field. As in the first volume, key synthetic protocols in experimental format, chosen for broad utility and application, are included at the ends of most Chapters. We are confident to present a monograph that will be of great practical value to both industrial and academic researchers and will increasingly also find its way into advanced teaching, since metal-catalyzed cross-coupling reactions are today an important topic in upper-level organometallic and organic synthesis courses.

Finally, we would like to warmly thank all the authors that have contributed with their excellent Chapters to the realization of this monograph. We greatly acknowledge the assistance of co-workers from both the groups in Göttingen and in Zürich in the editorial process, in particular ensuring the accuracy of all the references. Finally, we thank the team at Wiley-VCH, in particular Dr. Elke Maase and Dr. Peter Gölitz for their diligence and their guidance during the entire project.

Göttingen and Zürich
February 2004

Armin de Meijere
François Diederich

Contents

Metal-Catalyzed Cross-Coupling Reactions, 2nd Edition. Edited by Armin de Meijere, François Diederich

ISBN 3-527-30518-1

List of Contributors

Dr. Eric J.-G. Anctil
Queen's University
Department of Chemistry
Frost Wing, Room F513
Kingston, Ontario, K7L 3N6
Canada

Dr. David J. Babinski
Department of Chemistry
Purdue University
West Lafayette
Indiana 47907-1393
USA

Prof. Dr. Jan-E. Bäckvall
Department of Organic Chemistry
Arrhenius Laboratory
Stockholm University
S-10691 Stockholm
Sweden

Dr. Daniella Banon-Tenne
Department of Chemistry and Institute
of Catalysis Science and Technology
Technion – Israel Institute
of Technology
Technion City
3200 Haifa
Israel

Prof. Dr. Stefan Bräse
Institut für Organische Chemie
Universität Karlsruhe (TH)
Fritz-Haber-Weg 6
Geb. 30.42
D-76131 Karlsruhe
Germany

Prof. Dr. Stephen L. Buchwald
Department of Chemistry
Massachusetts Institute of Technology
Room 18-488
Cambridge, MA 02139
USA

Dr. M. Isabel Calaza
Ludwig-Maximilians-Universität
München
Department of Chemistry
Butenandtstrasse 5–13, Haus F
D-81377 München
Germany

Dr. Diego J. Cárdenas
Departamento de Química Orgánica
Universidad Autónoma de Madrid
Cantoblanco
E-28049 Madrid
Spain

Metal-Catalyzed Cross-Coupling Reactions, 2nd Edition. Edited by Armin de Meijere, François Diederich

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Dr. Nicka Chinkov
Department of Chemistry and Institute of Catalysis Science and Technology
Technion – Israel Institute of Technology
Technion City
3200 Haifa
Israel

Professor Scott E. Denmark
Department of Chemistry
University of Illinois
600 South Mathews Avenue
Urbana, IL 61801
USA

Prof. Dr. Antonio M. Echavarren
Depto. de Química Orgánica
Universidad Autónoma de Madrid
Cantoblanco
E-28049 Madrid
Spain

Dipl. Chem. Nina Gommermann
Ludwig-Maximilians-Universität München
Department of Chemistry
Butenandtstrasse 5–13, Haus F
D-81377 München
Germany

Prof. Dr. Michael M. Haley
Department of Chemistry
University of Oregon
1253 Franklin Road
Eugene, OR 97403-1253
USA

Dr. Qian Hu
Department of Chemistry
Purdue University
West Lafayette
Indiana 47907-1393
USA

Dr. Zhihong Huang
Department of Chemistry
Purdue University
West Lafayette
Indiana 47907-1393
USA

Dr. Eike Hupe
Ludwig-Maximilians-Universität München
Department of Chemistry
Butenandtstrasse 5–13, Haus F
D-81377 München
Germany

Dr. Lei Jiang
Department of Chemistry
Massachusetts Institute of Technology
Room 18-488
Cambridge, MA 02139
USA

Prof. Dr. Uli Kazmaier
FB 11, Organische Chemie
Universität des Saarlandes
Im Stadtwald
Gebäude 23.2
D-66123 Saarbrücken
Germany

Prof. Dr. Paul Knochel
Ludwig-Maximilians-Universität München
Department of Chemistry
Butenandtstrasse 5–13, Haus F
D-81377 München
Germany

Dr. Tadakatsu Mandai
Tsu 602-128
Kamakura
Kanagawa 248-0032
Japan

Prof. Dr. Ilan Marek
Department of Chemistry and
Institute of Catalysis Science
and Technology
Technion – Israel Institute
of Technology
Technion City
3200 Haifa
Israel

Dr. Jeremiah A. Marsden
Department of Chemistry
University of Oregon
1253 Franklin Road
Eugene, OR 97403-1253
USA

Prof. Dr. Armin de Meijere
Institut für Organische und
Biomolekulare Chemie der
Georg-August-Universität Göttingen
Tammannstrasse 2
D-37077 Göttingen
Germany

Prof. Dr. Terence N. Mitchell
Universität Dortmund
Fachbereich Chemie
Otto-Hahn-Strasse 6
D-44221 Dortmund
Germany

Prof. Dr. Norio Miyaura
Division of Molecular Chemistry
Graduate School of Engineering
Hokkaido University
Sapporo 060-8628
Japan

Prof. Dr. Ei-ichi Negishi
Department of Chemistry
Purdue University
West Lafayette
Indiana 47907-1393
USA

Dr. Matthias Pohlman
FB 11, Organische Chemie
Universität des Saarlandes
Im Stadtwald, Gebäude 23.2
D-66123 Saarbrücken
Germany

Dr. Mingxing Qian
Department of Chemistry
Purdue University
West Lafayette
Indiana 47907-1393
USA

Dipl. Chem. Ioannis Sapountzis
Ludwig-Maximilians-Universität
München
Department of Chemistry
Butenandtstrasse 5–13, Haus F
D-81377 München
Germany

Dr. Ramzi F. Sweis
Department of Chemistry
University of Illinois
600 South Mathews Avenue
Urbana, IL 61801
USA

Prof. Dr. Victor Snieckus
Queen's University
Department of Chemistry
Frost Wing, Room F513
Kingston, Ontario, K7L 3N6
Canada

Prof. Dr. Jiro Tsuji
Tsu 602-128
Kamakura
Kanagawa 248-0032
Japan

Dr. Ze Tan
Department of Chemistry
Purdue University
West Lafayette
Indiana 47907-1393
USA

Dr. Xingzhong Zeng
Department of Chemistry
Purdue University
West Lafayette
Indiana 47907-1393
USA

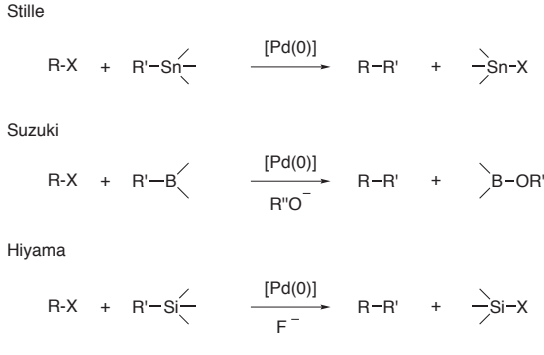
1
Mechanistic Aspects of Metal-Catalyzed C,C- and C,X-Bond-Forming Reactions

Antonio M. Echavarren and Diego J. Cárdenas

1.1
Mechanisms of Cross-Coupling Reactions

Cross-coupling reactions, such as the Stille reaction of organostannanes [1–3] and the Suzuki (or Suzuki-Miyaura) cross-coupling of organoboron compounds [4] have settled amongst the more general and selective palladium-catalyzed cross-coupling reactions [5] (Scheme 1-1). These reactions are closely related to other cross-couplings based on transmetallations of a variety of hard or soft organometallic nucleophiles [6] such as the Hiyama [7, 8], Sonogashira [9], Kumada (or Kumada-Corriu), and other related couplings [10–12].

Coupling reactions are somewhat related to the Heck alkenylation of organic electrophiles [13, 14], which is often referred to in the literature as a coupling process. However, although the first steps in both processes are identical, in the Heck reaction there is no transmetallation step. In the alkenylation reaction, the C-C bond is formed by an insertion process, which is followed by a β-hydride elimination to form the substituted alkene product. Cross-coupling (transmetallation-based) processes are a family of closely related catalytic processes that share most mechanistic aspects, although some differences exist on the activation of the organometallic nucleophile. So far, most of the detailed mechanistic studies have cen-



Scheme 1-1 Representative palladium-catalyzed cross-coupling reactions.

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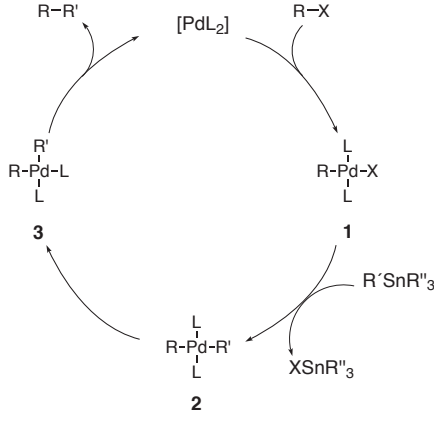
tered on the coupling of organostannanes with organic electrophiles catalyzed by palladium (Stille reaction) [1, 2, 15]. However, the conclusions that arise from studies conducted on this reaction probably pertain to other cross-couplings. Although nickel, copper – and occasionally also platinum – have also been used as catalysts for cross-coupling processes, the vast majority of mechanistic studies concern palladium chemistry.

The mechanisms of palladium-catalyzed formations of C-X (X = N, O, S) from organic electrophiles bonds are roughly related to cross-coupling processes. However, recent mechanistic investigations point to differences with regards to some of the details in the catalytic cycle.

1.1.1 The Earlier Mechanistic Proposal: The Stille Reaction

The extensive synthetic and mechanistic studies carried out by Stille since 1978 [1, 2, 15, 16] have allowed this reaction to be established as a mature synthetic method for organic synthesis [17]. The original mechanistic proposal for the Stille reaction, summarized in the influential review of 1986 [1] is shown in Scheme 1-2. In the generalized mechanism, a $[PdL_2]$ (L = PPh_3) complex was assumed to be the active catalytic species, which reacts with the organic electrophile R-X to form complex **1**. Complex **1** was the only observable species in the catalytic cycle, even in the presence of excess organostannane, which demonstrated that the slow step is the transmetallation reaction with the organostannane. This transmetallation was believed to lead to the formation of complex **2.** A *trans*-to-*cis* isomerization to give **3** was then required for the reductive elimination to yield the organic product R-R′.

This mechanistic interpretation of the Stille reaction has been the base for the formulation of the mechanisms of other cross-coupling reactions. Model studies carried out by Stang on the coupling of alkynes with vinyl triflates with $[Pt(PPh_3)_4]$ were in overall agreement with that proposal [18], although involvement of cationic complexes in the transmetallation step was strongly suggested by this



Scheme 1-2 The original proposal for the mechanism of the Stille reaction.

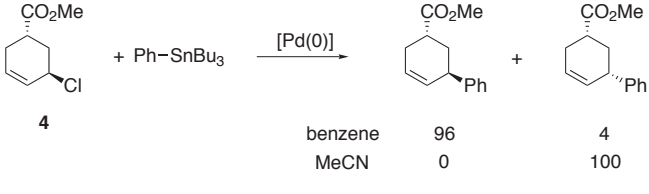
work. Farina [19] and Brown [20] also found that the intermediates formed upon oxidative addition of organic triflates to Pd(0) are cationic complexes such as $[PdR^1(S)L_2]^+$ and $[PdR^1L_3]^+$.

Although these studies shed some light on the transmetallation step, this transformation has remained somewhat mechanistically obscure. Thus, for example, either inversion [21] or retention [22] of the configuration of alkyl stannanes has been found. In addition, theoretical studies and experimental results were in contradiction with several aspects of the mechanistic model of Scheme 1-2. In effect, intermediates of the type *trans*-$[PdR^1R^2L_2]$ (**2**) might be expected to be quite long-lived, as *trans*-to-*cis* isomerizations in this type of complexes are not facile processes [23–25]. However, complexes **2** have never been detected under catalytic conditions [26].

1.1.2 The Oxidative Addition

The oxidative addition of organic electrophiles (halides, sulfonates, and related activated compounds) to Pd(0) is the first step in cross-coupling and Heck reactions. Many studies have been conducted on the mechanisms of the oxidative addition reactions of aryl and alkenyl halides and triflates ($C(sp^2)$-X electrophiles) [27], the most common organic electrophiles in the cross-coupling reactions.

The oxidative addition of $C(sp^3)$-X electrophiles to Pd(0) complexes PdL_4 (L = phosphine) takes place usually by associative bimolecular process (S_N2 reaction) [27]. The anion then adds to the metal to give the product. However, the reaction of allylic electrophiles is more complex, since, in addition, S_N2' substitutions are conceivable pathways. The coupling of *trans* allylic chloride **4** with $PhSnBu_3$ proceeds with overall retention of configuration when the reaction was performed in benzene with a Pd(0) complex made in situ from $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and maleic anhydride, while clean inversion was observed in polar, coordinating solvents [28] (Scheme 1-3). The observed stereochemistry is a consequence of the oxidative addition step. This reaction proceeds with complete or predominant retention in noncoordinating solvents as benzene, CH_2Cl_2, tetrahydrofuran (THF), or acetone [28, 29], which is in agreement with theoretical studies on the oxidative addition of Pd(0) to CH_3X [30]. On the other hand, in coordinating solvents such as MeCN or dimethylsulfoxide (DMSO), complete or near-complete inversion was observed [28]. *Syn*-oxidative addition has also been observed on related substrates [31]. However, with $[Pd(PPh_3)_4]$, the usual inversion of configuration in the oxidative addition was observed [28, 32].



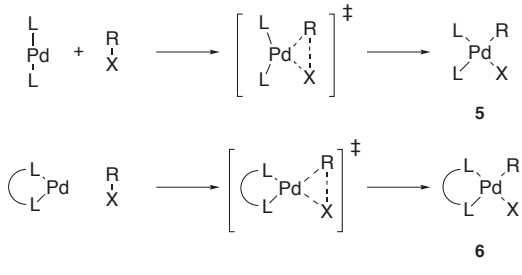
Scheme 1-3 Retention or inversion in the oxidative addition as a function of solvent polarity.

An earlier study on the mechanism of the oxidative addition of aryl iodides to [PdL_2] was consistent with an aromatic nucleophilic substitution [33]. Accordingly, electron-withdrawing substituents on aryl electrophiles led to rate acceleration [34, 35]. In general, increasing the bite angle of bidentate ligands leads to a decrease in the rate of the oxidative addition [35, 36]. However, the opposite effect has also been observed [37], although in this case ligands of very different basicity were considered [38].

1.1.2.1 *Cis*-Complexes in the Oxidative Addition

The observed intermediates after the oxidative addition are *trans*-[$PdRXL_2$] complexes (**2**, Scheme 1-2), which had led to the general proposal that these complexes are the primary products of the reaction. However, the oxidative addition (at least for the most common C(sp^2)-X electrophiles) proceeds by a concerted interaction of a reactive [PdL_2] or [Pd(L-L)] (L-L = diphosphine) species with R-X via a three-center transition state that should necessarily lead to *cis*-[$PdRXL_2$] complexes (Scheme 1-4). In the *cis* isomers a destabilizing interaction exists between mutually *trans* phosphorus donor and aryl ligands, which has been termed "transphobia" [39]. Therefore, in the case of complexes with monodentate phosphines, the initially formed *cis*-[$PdRXL_2$] (**5**) complexes undergo isomerization to form the more stable *trans*-[$PdRXL_2$] complexes [40]. Such isomerization is not possible for complexes **6** with *cis*-coordinating bidentate phosphines.

The isomerization process has been analyzed in detail by Casado and Espinet in the case of complex **7**, formed by the oxidative addition of $C_6Cl_2F_3I$ to [$Pd(PPh_3)_4$] [41] (Scheme 1-5). The isomerization of *cis*-**7** to *trans*-**8** is a rather complex process that takes place by four major parallel pathways. Two of these pathways involve associative replacements of PPh_3 by an iodide ligand of a second palladium com-



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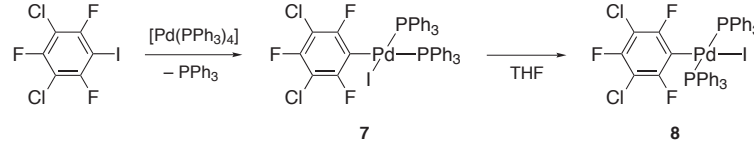
Scheme 1-4 Oxidative additions of C(sp^2)-X electrophiles to Pd(0).



7 **8**

Scheme 1-5 *Cis*-to-*trans* isomerization of primary oxidative addition product.

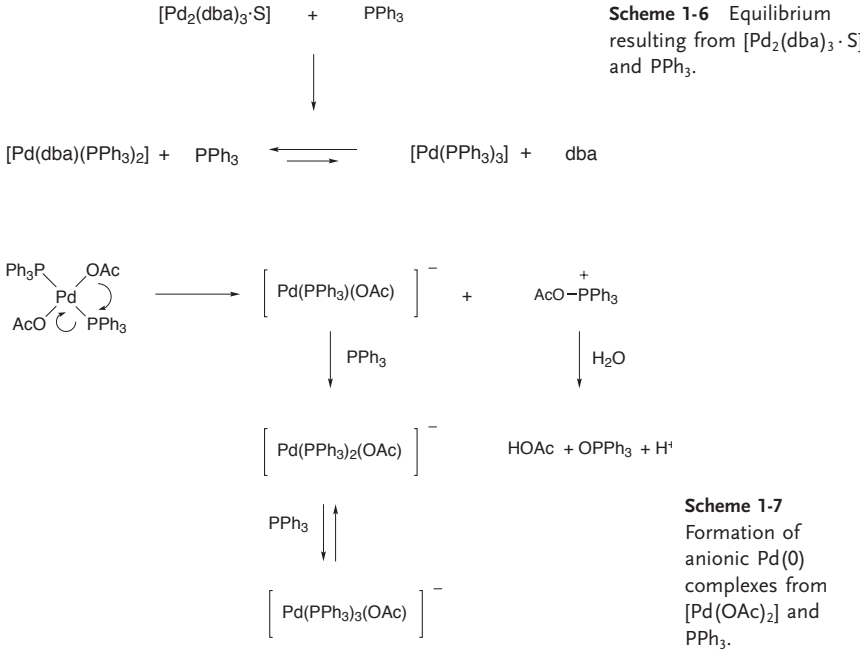
plex. Two additional routes involve two consecutive Berry pseudorotations on pentacoordinated species formed by coordination of the solvent (THF) [41].

1.1.2.2 The Role of Alkene and Anionic Ligands

Complex $[Pd_2(dba)_3 \cdot S]$ (dba = dibenzylideneacetone, S = dba or solvent molecule) [42, 43] has been used as a source of Pd(0) in many palladium-catalyzed reactions [5]. Early work by Roundhill [44], and subsequent detailed studies by Amatore and Jutand [37, 45–47], established that the dba ligands are not completely substituted in the reactions of $[Pd_2(dba)_3 \cdot S]$ with phosphines under mild conditions. With PPh_3, mixtures of $[Pd(PPh_3)_3]$ in equilibrium with $[Pd(dba)(PPh_3)_2]$ are formed (Scheme 1-6) [44, 48]. As a result, starting from $[Pd_2(dba)_3]$ and 2 equiv. of PPh_3, the oxidative addition of PhI proceeds at an overall rate that is *ca.* 10 times less than that starting from $[Pd(PPh_3)_4]$. Similar equilibria were found for L = tri-(2-furyl)phosphine (TFP) [49] and L = $AsPh_3$ [50].

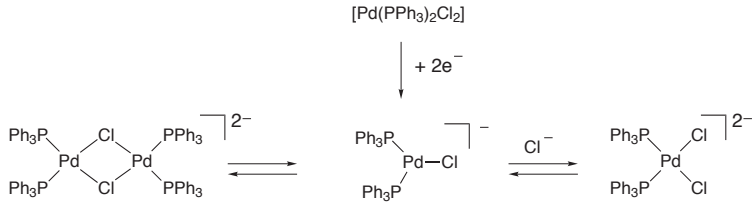
Anionic ligands play an important role in oxidative addition reactions [51, 52]. Amatore and Jutand concluded that, in the presence of acetate, tricoordinated anionic species $[PdL_2(OAc)]^-$ [53, 54] (Scheme 1-7) are the effective complexes in oxidative addition [55], instead of the usually postulated neutral $[PdL_2]$ complex.

In the presence of chloride, anionic complexes are also formed [56–59] (Scheme 1-8. In general, the following order of stabilization of the anionic Pd(0) species is observed: $I^- > Br^- > Cl^-$ [59].



Scheme 1-6 Equilibrium resulting from $[Pd_2(dba)_3 \cdot S]$ and PPh_3.

Scheme 1-7 Formation of anionic Pd(0) complexes from $[Pd(OAc)_2]$ and PPh_3.



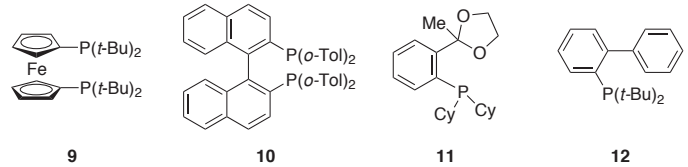
Scheme 1-8 Formation of anionic Pd(0) complexes from $[Pd(PPh_3)_2Cl_2]$.

1.1.2.3 Cross-Couplings in the Presence of Bulky Phosphines

It may be risky to raise mechanistic conclusions on qualitative observations regarding rate accelerations upon changes on any reaction variable in complex catalytic processes such as cross-coupling reactions. Nevertheless, some interesting hints can be obtained from recent work aimed at developing new conditions for the coupling of the less reactive organic substrates such as aryl chlorides [60, 61] and alkyl electrophiles [62].

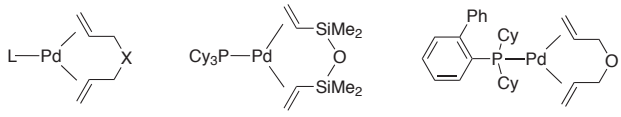
Aryl chlorides react more sluggishly in cross-coupling reactions than bromides, iodides, and triflates due to their reluctance to oxidatively add to Pd(0) [63]. Initially, the focus was on the development of sterically hindered, chelating ligands to activate these substrates. Thus, Milstein reported that $[Pd(dippp)_2]$ (dippp = 1,3-bis(diisopropylphosphino)propane) was an efficient catalyst for the carbonylation, formylation, and Heck reactions of aryl chlorides [35, 64]. The groups of Hartwig and Buchwald also demonstrated the importance of a variety of sterically hindered, chelating phosphines such as **9** and **10** in palladium-catalyzed transformations (Scheme 1-9). In particular, the amination and etherification of aryl electrophiles [65], as well as the ketone and malonate arylation processes [66–68], benefit greatly from the use of this type of ligands. Another complex with a bulky chelating ligand (**11**) was developed by Guram as an efficient catalyst for general Suzuki reactions of a wide variety of arylboronic acids and aryl chlorides, bromides, and iodides [69].

Of note was the finding that relatively simple, monodentate phosphines also promote the coupling of the less reactive substrates under relatively mild conditions. This accelerating effect on the oxidative addition had been demonstrated in the context of the formation of (η^3-allyl)palladium complexes [70]. Particularly useful for the activation of aryl chlorides are palladium complexes of the bulky phosphine $P(t\text{Bu})_3$ [71–74]. Bulkier phosphines such as (1-Ad)$P(t\text{Bu})_2$ (Ad = adamantyl) have been used in the palladium-catalyzed arylation of malonates and cyanoesters [75]. The related bulky phosphine $P(t\text{Bu})_2$-(*o*-biphenyl) (**12**) has been developed by Buch-



9 **10** **11** **12**

Scheme 1-9 Representative bulky ligands for the activation of the less reactive organic electrophiles.



13: X = O, NH **14** **15**

Scheme 1-10 Coordinatively unsaturated palladium complexes with bulky phosphines.

wald as a ligand for the palladium-catalyzed reaction of amines with aryl bromides, chlorides, and triflates [69a, 76–78] and in Suzuki coupling reactions [76a, 79].

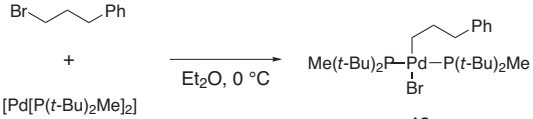
Beller has shown that a series of coordinatively unsaturated [(1,6-diene)PdL] (L = phosphine) complexes **13**–**15** (Scheme 1-10) catalyzes efficiently the Suzuki coupling of aryl chlorides with phenylboronic acid [80, 81]. Particularly effective as a catalyst was the complex bearing the phosphine ligand (*o*-biphenyl)PCy_2 (**15**) [80]. In all cases, the [(1,6-diene)PdL] complexes were more effective as catalysts than mixtures of $[Pd(OAc)_2]$ or $[Pd_2(dba)_3]$ and the phosphines.

Fu reported that complex $[Pd(PCy_3)_2]$ (**16**), formed in situ from $[Pd(OAc)_2]$ and PCy_3, catalyzes the room-temperature coupling of primary alkyl bromides that posses β-hydrogens with alkyl-BBN (BBN = 9-borabicyclo[3.3.1]nonane) [82]. A similar complex, formed from $[Pd_2(dba)_3]$ and PCy_3 (1:2 ratio of Pd to phosphine), allowed coupling of primary alkyl chlorides that posses β-hydrogens with alkylboranes [83]. Complex **16**, and related complexes with other monodentate bulky phosphines, catalyzed the Kumada coupling of alkyl chlorides [84].

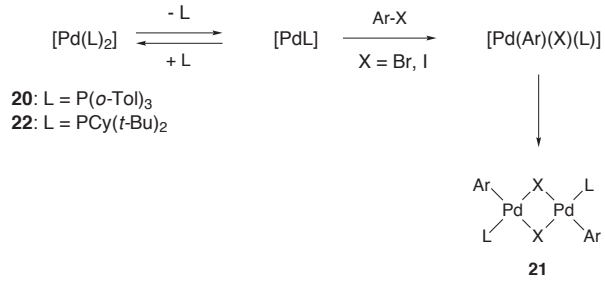
For the coupling of primary alkyl tosylates, the bulkier phosphine $P(t\text{Bu})_2\text{Me}$ gave the best results [85]. The reactive complex is probably $[Pd(P(t\text{Bu})_2\text{Me})_2]$ (**17**). As expected, the oxidative addition of the alkyl tosylate to Pd(0) results in predominant inversion of configuration, while the transmetallation occurs with retention [85]. Complex $[Pd(P(t\text{Bu})_2\text{Me})_2]$ also catalyzes the room-temperature coupling of primary alkyl bromides that possess β-hydrogens with boronic acids [86]. Complex **18**, the oxidative addition product of an alkyl bromide to **17**, has been isolated and structurally characterized [86] (Scheme 1-11).

Menzel and Fu also found that the Stille coupling of alkenyl stannanes with alkyl bromides that possess β-hydrogens is also possible at room temperature with $[Pd(P(t\text{Bu})_2\text{Me})_2]$ as the catalyst [87]. In this case, the addition of fluoride was required to enhance the reactivity of the stannane.

Interestingly, while with isolated $[Pd(P(t\text{Bu})_3)_2]$ (**19**) high temperatures are required for the activation of aryl halides in the Suzuki coupling [88], as well the amination [72d] and Heck reaction [71a, 89], the complex that results from the reaction of $[Pd_2(dba)_3 \cdot dba]$ and one equivalent of $P(t\text{Bu})_3$ allows these reactions



Scheme 1-11 Oxidative addition of a primary alkyl bromide to palladium complex **17**.



Scheme 1-12 Oxidative addition from $[PdL_2]$ complexes with very bulky monodentate phosphines.

to be performed at room temperature [66d, 89, 90–92]. Remarkably, under these conditions, aryl chlorides coupled in preference to aryl triflates [90]. Less bulky PCy_3 could be used for the Suzuki reaction of aryl triflates. Related bulky phosphines also allow to carry out Suzuki couplings under relatively mild conditions [77].

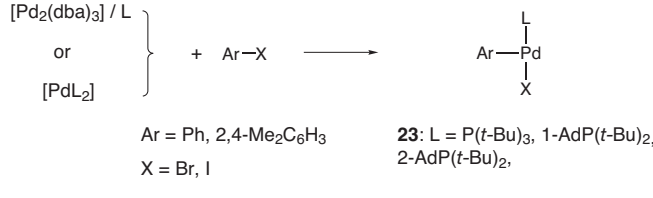
The $Pd/P(tBu)_3$ system was also applied by Fu for the Stille reaction with aryl electrophiles [93]. As an activator for the stannane, CsF was used. Mechanistic studies suggested that a palladium monophosphine complex [PdL] is the active catalyst in the cross-coupling of aryl halides [89].

In accord with the mechanistic observations made by Fu on the $Pd/P(tBu)_3$-catalyzed couplings [89, 90], Hartwig proposed that the oxidative addition of aryl bromide to complex $[Pd(P(o\text{-}Tol)_3)_2]$ (**20**) involved prior dissociation of a phosphine ligand giving a 12e-complex $[Pd(P(o\text{-}Tol)_3)]$ [94–96] (Scheme 1-12). The addition of a second equivalent of ligand to the dimeric complexes of type **21** promotes the reductive elimination with formation of ArX. This process involves the dissociative ligand substitution and cleavage to the monomers, prior to the reductive elimination [97].

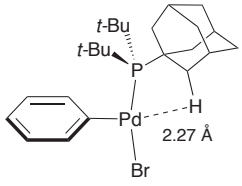
Brown, Jutand, and co-workers reported that $[Pd(PCy_3)_2]$ (**16**) reacts with PhOTf by an associative mechanism [98]. Reaction of PhI with **16** or $[Pd(PCy_2(tBu))_2]$ also proceeded associatively. In contrast, complexes $[Pd(P(tBu)_3)_2]$ (**19**) or $[Pd(PCy(tBu)_2)_2]$ (**22**) (Scheme 1-12), with bulkier phosphines, behaved like $[Pd(P(o\text{-}Tol_3))_2]$ (**20**).

Hartwig also reported the isolation of formally tricoordinated, T-shaped, Pd(II) complexes **23** in the oxidative addition of Ar-X to $[PdL_2]$ or [Pd(dba)L] bearing very bulky phosphines (Scheme 1-13) [99].

Two of these complexes, **23a-b**, were structurally characterized (Scheme 1-14). In both cases, agostic interactions with C-H bonds of the phosphine were suggested

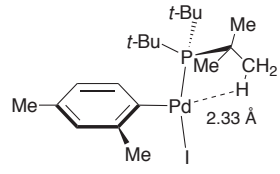


Scheme 1-13 Formation of tricoordinated Pd(II) complexes from $[PdL_2]$ with very bulky monodentate phosphines.



P-Pd-Br angle = 162.6°

23a



P-Pd-I angle = 164.6°

23b

Scheme 1-14 Simplified models for the solid-state structures of complexes **23a** and **23b**.

[99], which resemble distorted square-planar Pd(II) complexes. A related platinum complex shows a seemingly three-coordinate Pt(II) core [100], although the metal is actually stabilized by an agostic interaction with one of the methyl groups of the phosphine ligand.

In support of the involvement of [$Pd(PR_3)$] in the oxidative addition, Pd(I) dimers **24** and **25** have been found to catalyze the room-temperature amination and Suzuki couplings of aryl chlorides and bromides [101] (Scheme 1-15). These palladium dimers decompose to form the palladium dibromide [$Pd(PR_3)Br_2$] and a highly reactive Pd(0) complex [$Pd(PR_3)$].

In the quest for coordinatively unsaturated palladium catalysts, the more radical approach uses "ligandless conditions" [102, 103] following work pioneered by Beletskaya [14b, 104]. However, the mechanism of cross-coupling reactions under these conditions is not known [105]. In this context, it is worth mentioning that ferrocenylmethylphosphine-containing polymer and [$Pd(OAc)_2$], which allow the formation of local, highly reactive [PdL] active sites, catalyze the coupling of aryl chlorides with arylboronic acids at room temperature [106].

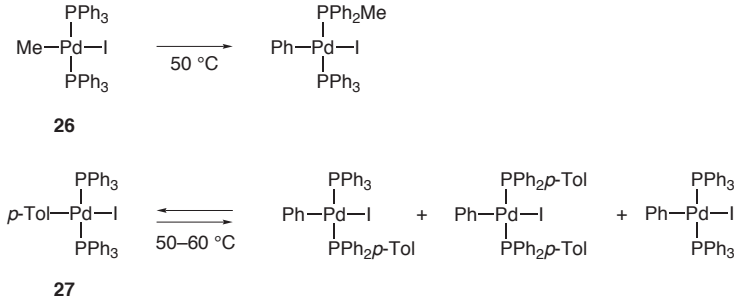
24: PR_3 = P(1-Ad)(*t*-Bu)$_2$
25: PR_3 = P(*t*-Bu)$_3$

Scheme 1-15 Formation of highly reactive [PdL] complexes from Pd(I) dimers.

Scrambling with the phosphine

Exchange between R residues on palladium and the phosphine ligand can take place under very mild conditions (Scheme 1-16), which may lead to homocoupling [107–109]. Contradictory mechanistic results emerged from the study of the methyl/phenyl and the aryl/phenyl exchange. In the first study with complexes such as **26** [107], the rate was not affected by added PPh_3. However, in the second example, the rearrangement of aryl palladium(II) complexes **27** was almost completely inhibited by PPh_3 [108].

The contradiction has been addressed by Novak [110], who demonstrated that the aryl-aryl interchange reaction of [$PdArL_2X$] proceeds first through a reductive elim-

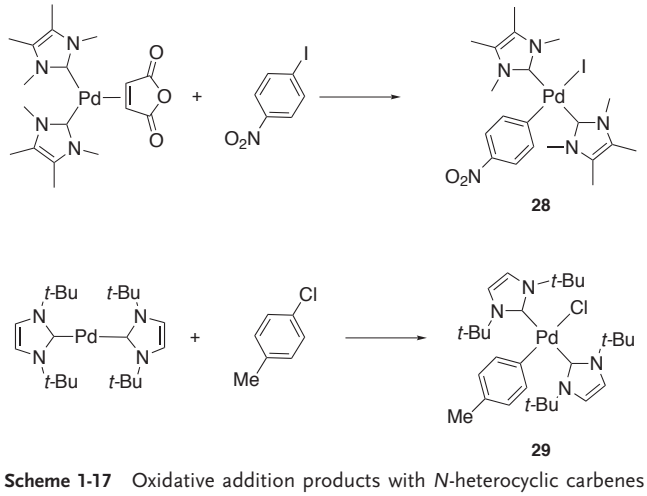


Scheme 1-16 Scrambling of R with the phosphine ligands.

ination to form a phosphonium salt, followed by an oxidative addition of a different phosphorus-carbon bond. The interchange and phosphonium salt formation reactions alike are facilitated by predissociation of either phosphine or iodide.

1.1.2.4 *N*-Heterocyclic Carbenes as Ligands

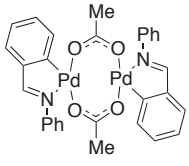
Although *N*-heterocyclic carbenes have demonstrated their utility as ligands in a variety of cross-coupling reactions [111], very few mechanistic investigations have been carried out thus far on the reactions with complexes bearing this type of ligand. Nevertheless, the oxidative addition of $[PdL_2]$ (L = heterocyclic carbene) to aryl halides has been shown to furnish the expected *trans*-square planar complexes such as **28** and **29** [112, 113] (Scheme 1-17).



Scheme 1-17 Oxidative addition products with *N*-heterocyclic carbenes as ligands.

1.1.2.5 **Palladacycles as Catalysts**

Many palladacycles have also been described as useful catalysts of cross-coupling and related reactions [114–122]. However, strong evidence has been accumulated that indicates that the palladacycles merely act as a reservoir of Pd(II), that requires reduction to Pd(0) to enter into the catalytic cycle [119, 120, 123]. Thus, in a detailed study of the Heck reaction catalyzed by palladacycles **30** and **31** (Scheme 1-18), Pfaltz and Blackmond concluded that the resting state of the catalyst within the catalytic cycle was a Pd(II) intermediate derived from oxidative addition, while the majority of Pd remained outside the catalytic cycle as a dimer in equilibrium with the oxidative addition species [123].



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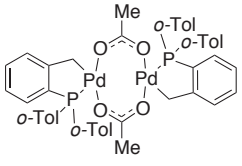


31

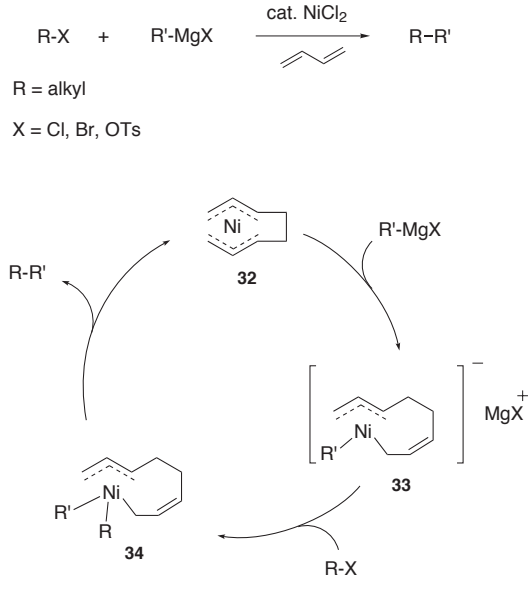
Scheme 1-18 Representative Pd(II)-palladacycles used as precatalysts in cross-coupling and Heck reactions.

On the involvement of Pd(IV) in catalytic cycles

There is strong evidence for the formation of Pd(IV) intermediates by oxidative addition of alkyl halides to Pd(II) complexes [124, 125]. However, $C(sp^2)$-X electrophiles, such as aryl halides, are much less reactive in the oxidative addition to Pd(II) complexes and, therefore, the formation of Pd(IV) species from these electrophiles is less likely. Indeed, there is no experimental evidence for such a process in the organometallic chemistry of Pd(II) complexes [126, 127].

A genuine coupling based on a group 10 M(II)/M(IV) catalysis is probably involved in the nickel-catalyzed coupling of alkyl halides and tosylates with Grignard reagents discovered by Kambe [128] (Scheme 1-19). A similar system has been developed for the catalytic C-C bond-forming reaction using nonactivated alkyl fluorides by coupling of alkyl Grignard reagents with $CuCl_2$ or $NiCl_2$ as the catalysts [128b].

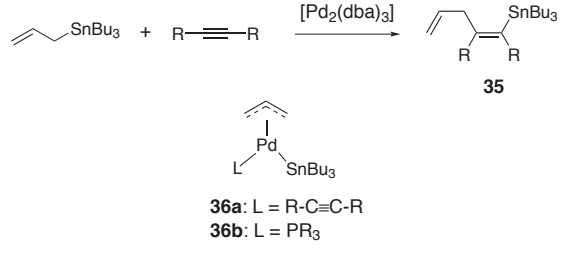
In this system, a bis(η^3-allyl)nickel(II) complex such as **32** formed by an oxidative dimerization of butadiene is probably involved in the catalytic cycle (Scheme 1-19). The oxidative addition of the alkyl halide or tosylate to the electron-rich intermediate **33** may form Ni(IV) complex **34.** A reductive elimination of **34** would then form the C-C bond and the active Ni(II) complex.



Scheme 1-19 Ni-catalyzed coupling of alkyl halides and tosylates with Grignard reagents.

1.1.2.6 **Oxidative Addition of Stannanes to Pd(0)**

Oxidative addition of certain stannanes to Pd(0) complexes also appears to be a possible pathway. Thus, alkynyl stannanes have been shown to react with Pd(0) complexes [129, 130]. Additionally, the Pd(0)-catalyzed reaction of allyl stannanes with alkynes has been found to afford allylstannylation products **35** (Scheme 1-20) [131]. A likely mechanism involves an oxidative addition of the allyl stannanes to Pd(0) to give (η^3-allyl)palladium complexes **36a** (Scheme 1-20). In this transformation, the usually nucleophilic allyl stannanes behave as electrophiles. Complexes of type **36b** are probably formed by transmetallation of (η^3-allyl)palladium complexes with hexamethylditin [132]. An oxidative addition to form complexes **36b** has been proposed in the Pd(0)-catalyzed carboxylation of allyl stannanes with CO_2 [133]. Although complexes of type **36** have never been isolated as stable species, studies on the intramolecular reaction of allyl stannanes with alkynes and theoretical calculations provide support to the formation of these complexes by the oxidative addition of allyl stannanes to Pd(0) [134].



Scheme 1-20 Allyl-stannylation of alkynes by oxidative addition of allyl stannanes to Pd(0).

1.1.3 Transmetallation in the Stille Reaction

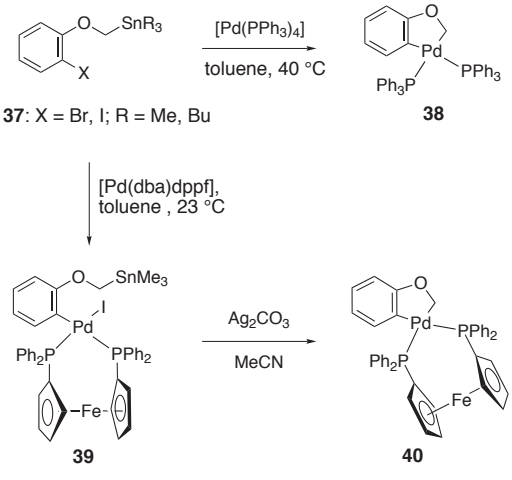
1.1.3.1 Isolation of the Transmetallation Step

The transmetallation step has been studied intramolecularly with systems **37** (X = Br, I), which undergo oxidative addition to $[Pd(PPh_3)_4]$ to give intermediate complexes that suffered transmetallation to form palladacycles **38** [135] (Scheme 1-21). The isolated palladacycles **38** are stable species that do not reductively eliminate due to the high ring strain of the expected four-membered ring heterocycles.

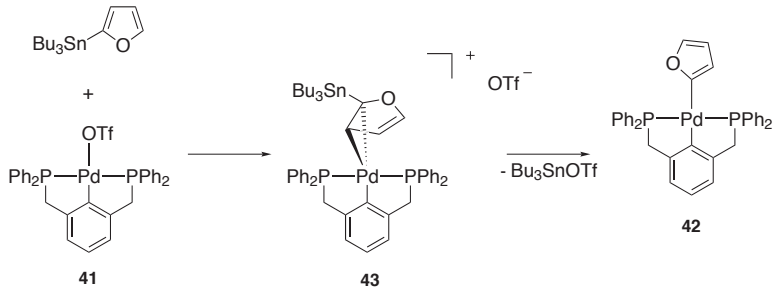
Intermediate **39** was isolated from the oxidative addition of **37** (X = I, R = Me) to the Pd(0) complex [Pd(dba)(dppf)]. Presumably, the steric bulk of the dppf ligand does not favor the necessary alignment of the Pd-I and C-Sn bonds in the transition state of the transmetallation (cyclic transmetallation; see Section 1.1.3.3). However, smooth transmetallation was observed in the presence of Ag_2CO_3 to form palladacycle **40** [135b]. Under these conditions, replacement of the iodo by a carbonato ligand might facilitate transmetallation through an open transition state. Analogous models have been applied for the study of the transmetallation of silanes [136] as well as the related transmetallation of stannanes with Pt(II) [137].

The reaction between pincer triflato complex **41** and 2-(tributylstannyl)furan led to transmetallation derivative **42** as a stable compound (Scheme 1-22) [138]. When the reaction was performed at low temperature, an intermediate cationic complex **43** was observed with the furan η^2-coordinated to the palladium center.

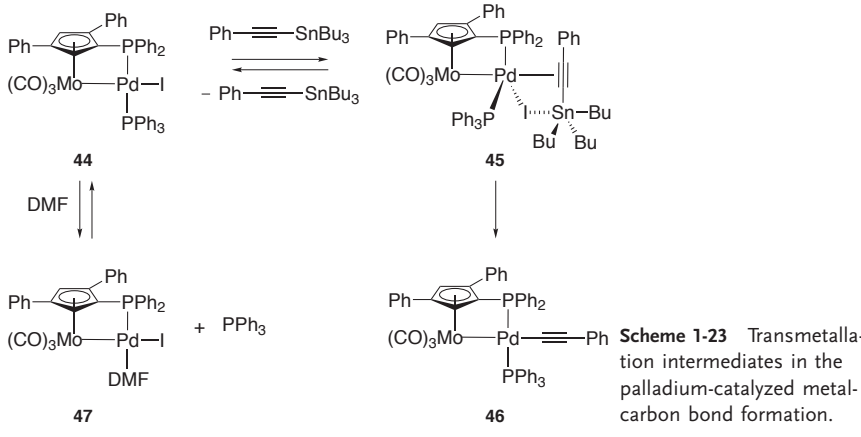
Lo Sterzo has observed a different precoordination complex in the transmetallation of bimetallic complex **44** with alkynyl stannanes (Scheme 1-23) [139], one of the key steps of the palladium-catalyzed metal-carbon bond formation [139, 140]. Pentacoordinated palladium complex **45** was detected spectroscopically and shown to evolve to **46** by first eliminating PPh_3.



Scheme 1-21 Isolation of transmetallation intermediates in the Stille reaction.



Scheme 1-22 Isolation of a η^2-furyl palladium(II) complex in a transmetallation reaction.



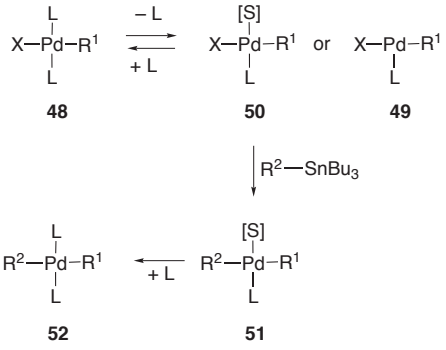
Scheme 1-23 Transmetallation intermediates in the palladium-catalyzed metal-carbon bond formation.

Complex **44** exchanged PPh_3 in DMF to form complex **47** and the corresponding iodo-bridged palladium dimer [139]. The involvement of this complex in a parallel transmetallation with the organostannane was proposed to support the dissociative mechanism for the transmetallation reaction [139].

1.1.3.2 **Dissociative Mechanistic Proposals**

It has been shown that the addition of neutral ligand L retards the coupling [141, 142]. In addition, ligands such as trifurylphosphine [143, 144] and triphenylarsine [19, 142, 145], which are of lower donicity that PPh_3, have a beneficial effect in the Stille reaction. These results have been taken as an indication that ligand dissociation is a key step in the transmetallation.

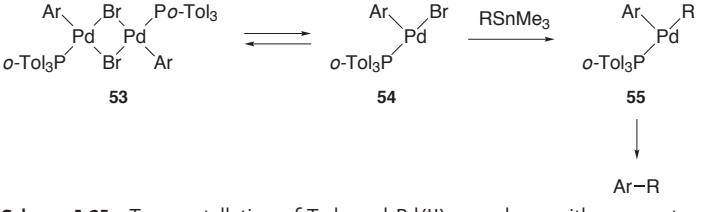
Thus, the simplified mechanism in Scheme 1-24, involving a dissociative X-for-R^2 substitution (X = I, Br) with preservation of the configuration at Pd, was proposed for vinyl and aryl stannanes. It was assumed that **48** cannot undergo transmetallation, probably because it is too electron-rich, and ligand dissociation occurs previous to the transmetallation to form coordinatively unsaturated **49** or, more likely, **50**, with a coordinated solvent molecule, S. More electrophilic complex **50**



Scheme 1-24 Mechanistic scheme for the dissociative transmetallation in the Stille reaction.

would then be involved in the transmetallation with the stannane to give **51**, which could then afford *trans* complex **52**.

Although the above interpretation has been disputed (see Sections 1.1.3.3 and 1.1.3.4), a dissociative transmetallation probably takes place with complexes bearing very bulky ligands. Thus, Hartwig found that for the transmetallation of dimers $[PdArBr\{P(o\text{-}Tol)_3\}]_2$ (**53**) [96] the rate depended on the square root of the concentration of dimer (Scheme 1-25). This is consistent with a dissociative mechanism, in which T-shaped monomers **54** [141] react with the organostannane, presumably through **55**, to give the coupled product Ar-R.

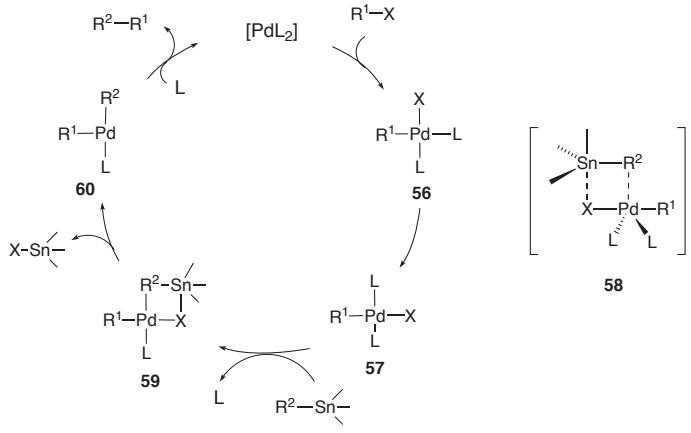


Scheme 1-25 Transmetallation of T-shaped Pd(II) complexes with organostannanes.

1.1.3.3 **Cyclic Associative Transmetallation**

The dissociative proposals for the transmetallation assume that the *trans* configuration of complex **48** to give a *trans*-$[PdR^1R^2L_2]$ complex (**52**) is preserved (Scheme 1-24). Since the reductive elimination of R^1-R^2 is well established to occur on *cis* derivatives, a rapid isomerization of *trans*- to *cis*-$[PdR^1R^2L_2]$ needs to be postulated (Scheme 1-2). An important additional problem with mechanisms based on ligand dissociation is that this type of substitution is rare for Pd(II) [146].

The observed dependence on the ligand concentration has recently been explained by Espinet within the framework of an associative mechanism (Scheme 1-26) [147, 148]. These studies were based on kinetic measurements of the palla-



Scheme 1-26 Mechanism of the Stille reaction based on a cyclic associative transmetallation.

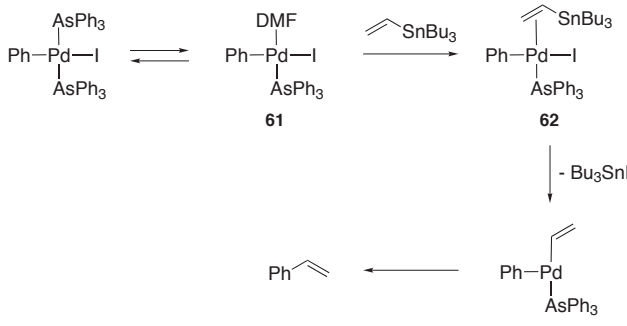
dium-catalyzed coupling with substrates such as 1,3-dichloro-2,4,6-trifluoro-5-iodobenzene ($C_6Cl_2F_3I$) and vinyl- or (4-methoxyphenyl)tributyltin. The proposed mechanism also takes into account the known formation of *cis*-complexes **56** in the oxidative addition, which subsequently isomerize to *trans*-**57**.

Importantly, the transmetallation involves an associative L-for-R^2 substitution, through transition state **58**, to give bridged intermediate **59** (S_E2 reaction). This intermediate evolves to give directly a *cis*-R^1/R^2 (**60**) rather than a *trans*-R^1/R^2 arrangement in the resulting complex, from which the coupled product will immediately eliminate the organic product R^1-R^2.

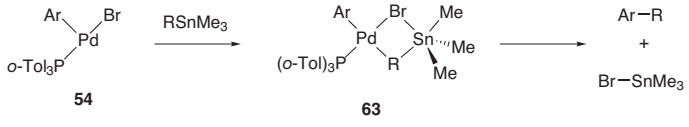
The proposal of Scheme 1-26 explains the observed dependence on L, and produces immediately the *cis*-arrangement needed for rapid R^1-R^2 coupling. The known inverse relationship between ligand donor ability and transmetallation rate [2, 17, 141, 142] supports the dissociative model because ligands of modest donicity (such as $AsPh_3$) would be more easily displaced in an associative substitution process.

The coupling of PhI and vinyl tributyl stannane with $[Pd(dba)(AsPh_3)_2]$ in dimethylformamide (DMF) has been recently examined by Amatore and Jutand [50, 149]. This study revealed that, under those conditions, the species preceding the transmetallation steps is complex **61**, bearing a DMF as a ligand (Scheme 1-27). In this case, the relatively weak ligand $AsPh_3$ is displaced by the coordinating solvent DMF. The alkenyl stannane then substitutes the DMF ligand to form complex **62**, which undergoes transmetallation (associative cyclic mechanism) as shown in Scheme 1-26. A similar process might be operating in the system studied by Lo Sterzo (see Scheme 1-23) [139].

Although, as stated above (Section 1.1.3.2), when very bulky ligands are used, a dissociative mechanism probably operates through T-shaped intermediates such as **54** [96, 141] (Scheme 1-28), these intermediates may then evolve by a S_E2 (cyclic) transmetallation with the organostannane via **63**.



Scheme 1-27 Mechanism of the Stille reaction from [Pd(dba)$(AsPh_3)_2$] in DMF.



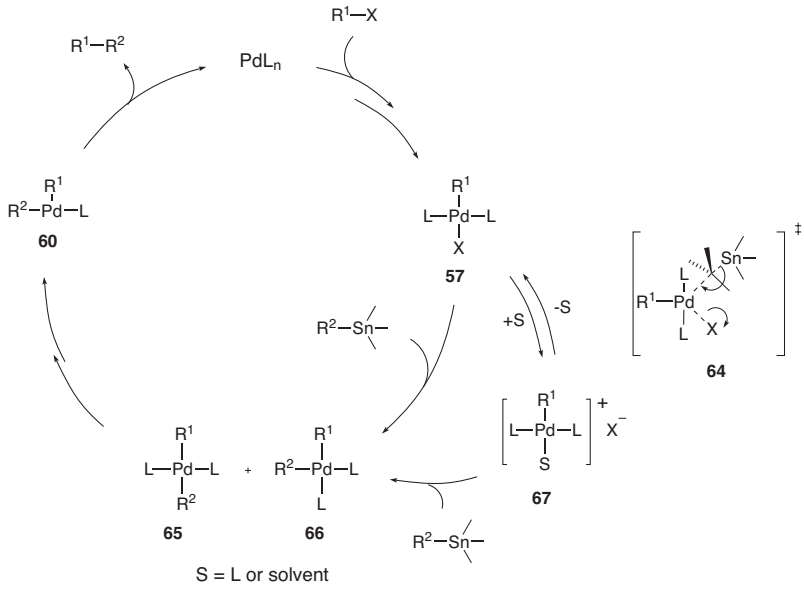
Scheme 1-28 Transmetallation from T-shaped Pd(II) complex **54**.

1.1.3.4 **Open Associative Transmetallation**

Scheme 1-26 pertains to the coupling of aryl or vinyl halides under the experimental conditions most commonly applied for the Stille reaction, involving the use of moderately coordinating solvents, palladium complexes with monodentate ligands of normal steric bulk, and ratios L:Pd > 2:1. This mechanism predicts retention of configuration at the carbon of the group transferred from the nucleophilic stannane.

A study of the coupling of aryl triflates with organostannanes by Espinet led to the conclusion that an open transition state operates in cases where no bridging groups are available on the coordination sphere of Pd(II) to produce a cyclic intermediate [150, 151]. The S_E2(open) transmetallation mechanism, proceeding through transition state **64**, is summarized in Scheme 1-29. This is the only possible path in the absence of bridging ligands, but can also operate in their presence. It implies X-for-R^2 or L-for-R^2 replacement at the Pd center, leading competitively to *cis* and *trans* arrangements to give **65** and **66**, and produces inversion of configuration at the α-carbon transferred from the stannane. This mechanism should be favored by the use of polar, coordinating solvents, lacking bridging ability. It might also operate in the presence of an excess of L and with easily leaving anionic ligands lacking bridging ability, in which case transmetallation proceeds from cationic complexes **67**. This mechanism is also followed in the coupling aryl triflates with vinyl tributyl stannane in the presence of dppe as the ligand [151].

The fact that the transmetallation step in the Stille reaction can follow two different paths – S_E2(cyclic) and S_E2(open) – has important stereochemical consequences, as this transformation determines the stereochemical outcome of the overall coupling reaction for C(sp^2)-X electrophiles. Therefore, retention of configuration would be expected for a S_E2(cyclic) pathway, while a S_E2(open) mechanism

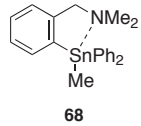


Scheme 1-29 Mechanism of the Stille reaction based on an open associative transmetallation.

would result in overall inversion of configuration. This clarifies the contradictory stereochemical results reported in the literature. Thus, Falck reported 98 % retention of configuration in the coupling of chiral α-alkoxystannanes with acyl chlorides in toluene [22], which would proceed by a cyclic pathway. On the other hand, Labadie and Stille found inversion (≥ 65 %) in the coupling of a chiral benzylic stannane to an acyl chloride in HMPA [21]. In this last example, the use of highly polar and coordinating solvent favors the open pathway, even in the presence of potentially bridging chloride ligand.

The open-associative mechanism probably operates in the Stille reaction carried out in the presence of additives such as fluorides [93] and hydroxide anion [152]. Similarly, coordination of tin to the nitrogen of benzyl amines (**68**) [153] and stannatrane derivatives (**69**) [154, 155] (Scheme 1-30) presumably led to transmetallation by an S_E2(open) mechanism.

A different type of coordination is involved in a system developed by Yoshida for the selective transfer of the Me_3SiCH_2- group from **70** [156] (Scheme 1-31). In this case, coordination of the pyridine nitrogen to Pd(II) as shown in **71** favors the intramolecular transmetallation through a S_E2(cyclic) intermediate. However, a *trans* to *cis* isomerization is now required for the reductive elimination of complex **72**.



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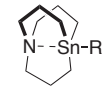

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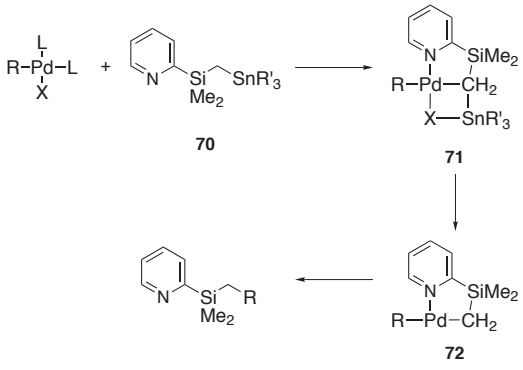
Scheme 1-30 Internal coordination to tin favors transmetallation to Pd(II).



Scheme 1-31 Coordination to Pd(II) for the selective alkyl transmetallation.

1.1.3.5 **The "Copper Effect" and Copper-Catalyzed Couplings**

A remarkable phenomenon in Stille couplings is the effect of the addition of CuI or other Cu(I) salts, which is known to accelerate some couplings catalyzed by [PdL_4] [17, 19, 22, 157–159].

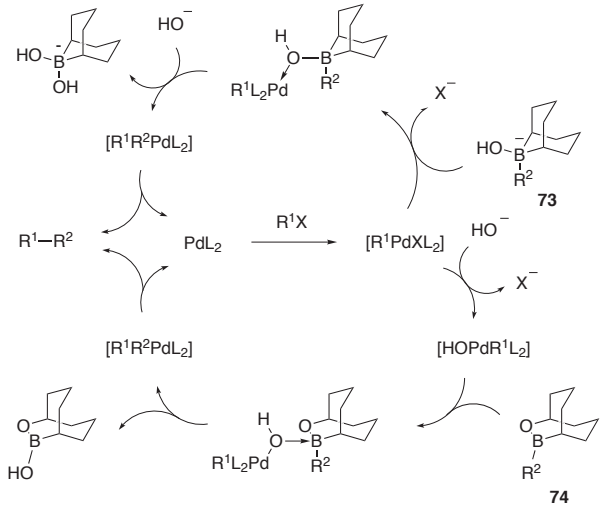
The "copper effect" has been rationalized by Espinet within the framework provided by the associative mechanism. Accordingly, CuI does not promote the dissociation of L from *trans*-[PdR^1IL_2] [159], but it captures part of the free neutral ligand L released during the oxidation of [PdL_4] that yields the species actually undergoing transmetallation, *trans*-[PdR^1IL_2], plus 2 L. Therefore, the effect of CuI is to mitigate the "auto-retardation" produced by the presence of free L on the rate determining associative transmetallation [160].

Farina and Liebeskind [159] already proposed that in very polar solvents, a Sn/Cu transmetallation could take place, leading to the in situ formation of organocopper species – a proposal that later developed into effective coupling systems. Thus, Piers demonstrated that the intramolecular coupling of alkenyl iodides with alkenyl stannanes can be carried out by using CuCl under stoichiometric conditions [161, 162]. Better results were later obtained by using other Cu(I) salts, which allow the reaction to proceed under catalytic conditions [163–169].

1.1.3.6 **Transmetallation in the Suzuki Reaction**

Due to the low nucleophilicity of the borane reagents (compared with organostannanes, for example), the Suzuki reaction requires the use of base in order to take place. Stronger bases such as NaOH, TlOH, and NaOMe perform well in THF/H_2O solvent systems, whereas weaker bases such as K_2CO_3 and K_3PO_4 are usually more successful in DMF. The base is involved in several steps of the catalytic cycle, most notably in the transmetallation process.

Soderquist has performed detailed mechanistic studies on the coupling of trialkyl boranes and alkoxy(dialkyl) boranes with aryl and alkenyl electrophiles (Scheme 1-32) [170]. This study allowed the determination of the stereochemistry of the transmetallation step [170, 171] and the role of the base in the catalytic cycle.



Scheme 1-32 Catalytic cycles for the coupling of trialkylboranes (upper cycle) and alkoxo derivatives (lower).

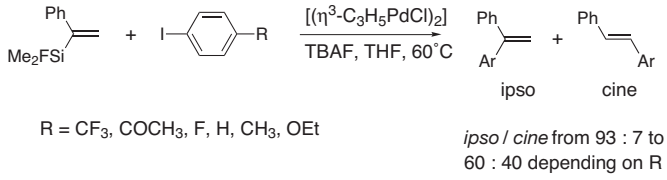
The main role of base is to generate a more reactive borate **73** by coordination of hydroxide to boron, which will react with the intermediate R-Pd(II)-X complex. On the other hand, in the case of the alkoxoboranes **74**, the base also reacts with the intermediate R-Pd(II)-X derivatives to form the more reactive R-Pd(II)-OH species (Scheme 1-32). Several intermediates in the Suzuki coupling of bromopyridines with arylboronic acid have been identified by using in situ analysis of the reaction by electrospray mass spectrometry [172].

Complexes of other metals have been recently described which catalyze other Suzuki-type reactions. Thus, platinum complexes catalyze the coupling between arylboronic acids and aryl halides [137], and $[Ni(PCy_3)_2Cl_2]$ is effective in the cross-coupling of arylboronic acids and aryl tosylates [173]. In this case, the usual mechanism involving oxidative addition of the aryl tosylate to $[Ni(PCy_3)_2]$, followed by transmetallation and reductive elimination has been proposed. The study of the effects of the substituents on the electrophile and the boronic acid indicate that transmetallation is the rate-determining step. The mechanism of the Pd-catalyzed homo-coupling of arylboronic acids has also been studied [174].

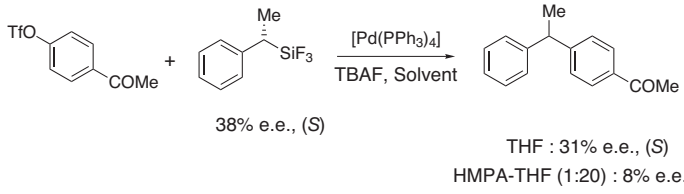
1.1.3.7 **Transmetallation in the Hiyama Reaction**

The lower reactivity of the Si-C bond requires the use of activating reagents to enhance the reactivity of silanes and to promote the Si-Pd transmetallations. Fluoride is the common additive, although other nucleophiles such as hydroxide, metal oxides and alkoxides are also effective [175]. Fluoride converts the starting silanes into pentacoordinate fluorosilicates, which are the actual transmetallation reagents.

Transmetallation of alkenyl silanes takes place with retention of the double bond configuration, as in other cross-coupling reactions [176]. Due to the lower transmetallation rate, competing 1,2-insertion of the alkene in the intermediate organopal-



Scheme 1-33 Hiyama reaction involving alkene insertion (Heck-type) prior to transmetallation.



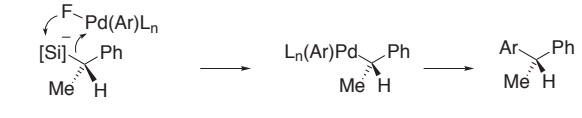
Scheme 1-34 Solvent effect on the stereoselectivity of Si-Pd alkyl transmetallation.

ladium complex (Heck-type) may take place, which affects the regioselectivity of the Hiyama reaction in some cases [177] (Scheme 1-33). This results in *cine*-substitution – a process that has also been observed in Stille coupling reactions of some hindered alkenyl stannanes [178].

Hiyama studied the stereoselectivity of alkyl transmetallation in the $[Pd(PPh_3)_4]$-catalyzed reaction of aryl triflates with enantiomerically enriched (*S*)-1-phenylethyltrifluorosilane in the presence of TBAF [179]. At 50 °C, retention of the configuration resulted, but at higher temperatures, a linear decrease of the degree of retention takes place and finally, inversion is observed above 75 °C. A significant solvent effect was also observed. Thus, the reaction in THF resulted in retention. On the other hand, inversion was found in HMPA-THF (1:20) (Scheme 1-34).

The retention of configuration at low temperatures in THF can be explained assuming a fluorine-bridged S_E2(cyclic) transition state (**75**), analogous to that proposed for the Stille reaction (see Scheme 1-26) formed from a pentacoordinate silicate (Scheme 1-20).

In polar solvents or at higher temperatures, the fluorine-silicon bridge would be cleaved to switch the transition-state model to the S_E2(open) (**76**), thus resulting in inversion. On the other hand, open and cyclic S_E2' mechanisms have been pro-



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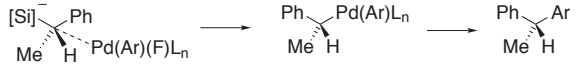

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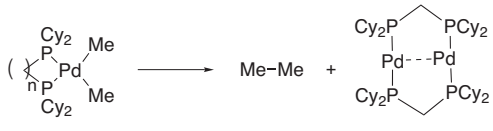
Scheme 1-35 Possible mechanisms for alkyl Si-Pd transmetallation reactions.

posed to justify the observed stereochemistry in the γ-selective cross-coupling of allyl silanes [180].

1.1.4 Reductive Elimination

1.1.4.1 The Effect of Bidentate Ligands

Formation of T-shaped intermediates from square-planar complexes greatly accelerates the reductive elimination of $[Pd(L)_2RR']$ complexes [26]. The same is true for complexes bearing bidentate diphosphanes [23, 24, 26]. The reductive elimination of a series of $[Pd(L\text{-}L)Me_2]$ complexes revealed that only complex **77a** with $Cy_2PCH_2PCy_2$, with the smallest bite-angle, leads to a smooth elimination of ethane (Scheme 1-36). The reductive elimination from these complexes is most probably preceded by dissociation of one of the diphosphine arms to form a T-shaped intermediate [181]. The resulting Pd(0) complex [Pd(L-L)] undergoes dimerization to form complex **78**. Complexes **77b-d**, with more stable chelates, do not eliminate ethane under mild conditions.



77a-d: n = 1–4 **78**

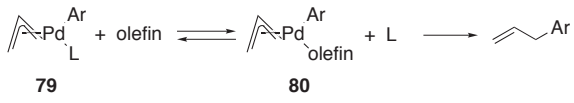
Scheme 1-36 Reductive elimination of ethane from $[Pd(L\text{-}L)Me_2]$.

On the other hand, for a series of $[Pd(L\text{-}L)Me_2]$ with L-L = dppp, dppf, and 1,1′-bis(diphenylphosphino)ruthenocene (dppr), the fastest elimination was observed with the ligand with the largest bite angle [182, 183]. This effect on the reductive elimination was also found by Hayashi [184] and van Leeuwen [185] in the palladium-catalyzed cross-coupling reaction of Grignard reagents with aryl halides.

1.1.4.2 Coupling with Allylic Electrophiles: The Slow Reductive Elimination

The rate-determining step in the coupling of aryl halides or triflates with aryl- or alkenyl stannanes can be either the transmetallation or the oxidative addition, depending on the exact circumstances of the reaction [147, 150]. On the other hand, in the coupling of allylic electrophiles, the reductive elimination step might become rate-determining. Schwartz has shown that the coupling of allylic halides and allylic organometallics does not proceed unless electron-withdrawing olefins such as maleic anhydride are used [186, 187]. Kurosawa also noted the promoting effect of electron-withdrawing olefins on the reductive elimination [188].

Transmetallation of (η^3-allyl)palladium complexes with aryl stannanes gives aryl allyl palladium complexes **79** (Scheme 1-37) [189]. The reductive elimination from these complexes is slow, and controls the reaction outcome. In order to produce

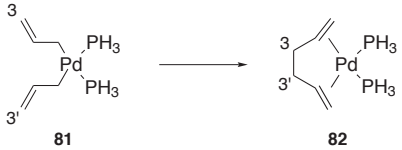


79 80

Scheme 1-37 Reductive elimination aryl allyl palladium complexes promoted by π-acceptor alkenes.

an efficient coupling, coordination of a promoter of reductive elimination such as *p*-benzoquinone or other electron-withdrawing olefin to form **80**, is very effective. Under catalytic conditions, the allyl electrophile acts as the electron-withdrawing olefin itself [189].

Bis(η^3-allyl)palladium complexes are not productive intermediates in the coupling of allyl stannanes with allyl carboxylates or halides [190], as these complexes do not show any tendency to undergo reductive elimination [191, 192]. In the presence of phosphine ligands, (η^1-allyl)(η^3-allyl)palladium complexes are formed [193–195]. On the other hand, addition of diphosphines gives bis(η^1-allyl)palladium diphosphine complexes [196], which undergo smooth reductive elimination at low temperatures [197]. Calculations also support the idea that the most favorable pathway for the reductive elimination involves bis(η^1-allyl)palladium complexes bearing two phosphine ligands (Scheme 1-38) [198]. Interestingly, the formation of a bond between C3 and C3′ of the allyls in **81** is significantly preferred to form **82** (Scheme **1-**38), regardless of the *syn* or *anti* arrangement of both allyl moieties, compared with the formation of C1-C1′ or C1-C3′ bonds.



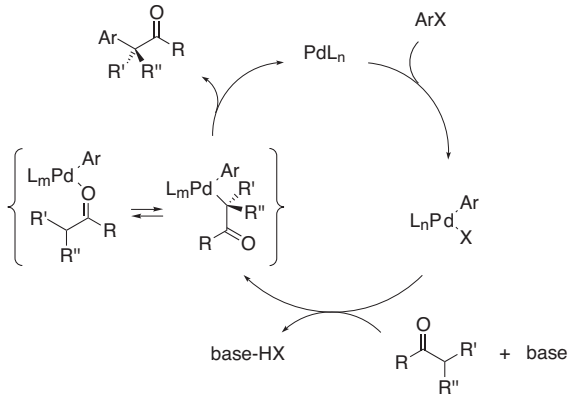
81 82

Scheme 1-38 Most favored reductive elimination of bis(η^1-allyl)palladium complexes.

1.2 Formation of C,C-Bonds in the Palladium-Catalyzed α-Arylation of Carbonyl Compounds and Nitriles

The palladium-catalyzed α-arylation of ketones has become a useful and general synthetic method [67]. Initial studies required preformed zinc [199] or tin enolates [200]. By contrast, Ni-mediated [201] or -catalyzed couplings were also identified. A major development of the reaction has occurred since 1997 based on the use of new catalysts with electron-rich alkyl phosphines and *N*-heterocyclic carbenes as ligands [111, 202]. The reactions resemble cross-coupling processes in which the enolates behave as the nucleophilic organometallic reagents (Scheme 1-39).

The reductive elimination step has been studied on isolated Pd complexes containing both an aryl group and an enolate as ligands. A suitable choice of phosphine is necessary to afford complexes sufficiently stable to be isolated and suffi-



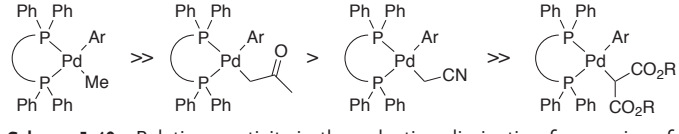
Scheme 1-39 General catalytic cycle for the α-arylation of carbonyl compounds.

ciently reactive to undergo reductive elimination. In the case of ketone enolate complexes, both C- and O-bound species are formed, depending on the type of ketone and the phosphine ligand. Reductive elimination rates of complexes for a series of 1,2-bis(diphenylphosphino)benzene (dppBz) aryl palladium complexes with different C-enolate ligands groups parallel the nucleophilicity of the R group (Scheme 1-40).

As far as the influence of the phosphine ligand in the catalyzed reactions is concerned, P(*t*Bu)$_3$ is effective in most cases. The rates of the reductive elimination of enolate complexes containing this and other bulky phosphines are higher, and the scope of many couplings catalyzed by complexes of these ligands is broader. Recently, it has been shown that a catalytic quantity of phenol causes a remarkable increase in the efficiency of ketone enolate arylation [203].

The formation of a (PCy$_3$)-Pd-L (L = *N*-heterocyclic carbene) has been proposed as the catalytically active species in the aryl amination and α-arylation of ketones by Nolan in a system starting from a palladacycle containing a *N*-heterocyclic carbene [204].

Copper-catalyzed arylation of malonates [205] and other activated methylene compounds (malononitrile, ethyl cyanoacetate) [206] has been also reported. It is likely that the catalytically active species is a Cu(I) enolate.



Scheme 1-40 Relative reactivity in the reductive elimination for a series of dppBz-aryl palladium complexes.

1.3
Key Intermediates in the Formation of C-X (X = N, O, S) bonds in Metal-Catalyzed Reactions

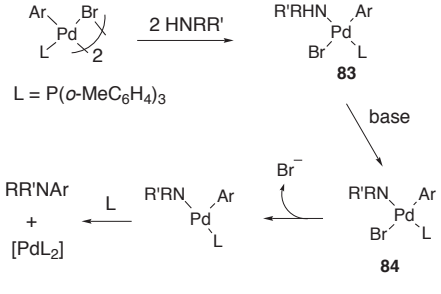
Pd(II) complexes formed by oxidative addition of organic electrophiles to Pd(0) may react with amines, alcohols or thiols in the presence of base to give the key amido, alkoxide, or sulfide complexes. These complexes will, in turn, afford the C-X (X = O, N, S) containing organic products by reductive elimination [65, 207, 208]. The palladium-catalyzed cyanation of aryl halides [209] is most likely related mechanistically to these reactions.

The mechanism of the formation of the C-Pd-X complexes depends on the type of nucleophile. For the palladium-catalyzed reactions involving tin amides or tin thiolates, monophosphine-palladium complexes are involved as intermediates [141]. Bidentate phosphines are not effective in the amination of electrophiles involving tin amides [210].

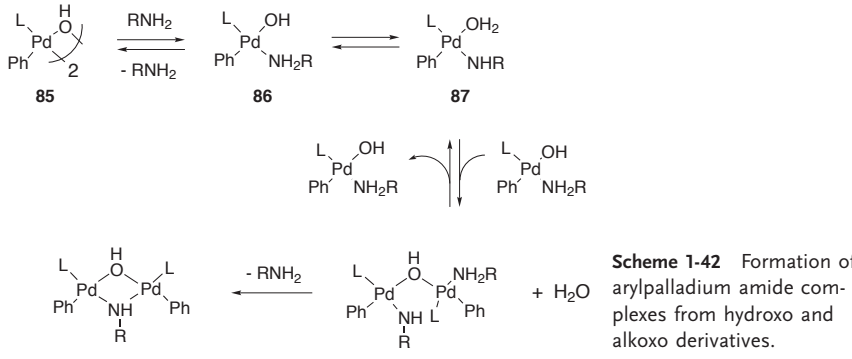
The amination reactions involving amines as the nucleophiles in the presence of base are mechanistically different. Stoichiometric reactions of different arylpalladium complexes suggest that two different mechanisms may be involved in the formation of the amido species from the oxidative addition complexes. Thus, amine-containing arylpalladium complexes **83** formed by ligand substitution or by cleavage of dimeric species react with base to give organopalladium-amido derivatives **84**, which then suffer reductive elimination to give the aryl amines (Scheme 1-41) [94, 211].

Alternatively, alkoxides or silylamides may first coordinate the palladium precursor to form an intermediate that might react with the amine to form the required amido-aryl intermediate. Extensive kinetic studies on stoichiometric reaction models support the mechanism in Scheme 1-42, in which the amine cleaves the dimeric hydroxo complex **85** to give an amine intermediate **86** which would suffer intramolecular proton transfer to give **87** [212]. A similar process is proposed for a dppf derivative [213].

Detailed kinetic studies have been carried out by Blackmond and Buchwald under synthetically relevant conditions to study the mechanism of the amination of bromobenzene with primary and secondary amines using $[Pd_2(dba)_3]$/binap mixtures as well as preformed [Pd(binap)(dba)], [Pd(binap)(*p*-Tol)(Br)], and $[Pd(binap)_2]$ complexes [214]. The presence of a significant induction period in the reaction was



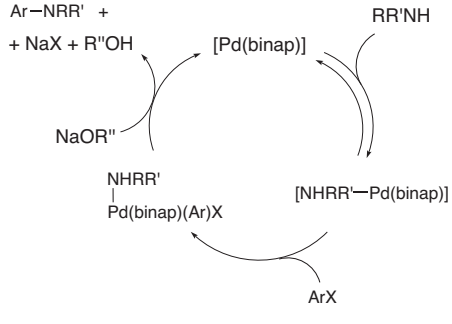
Scheme 1-41 Formation of arylpalladium amide complexes from amine precursors and subsequent reductive elimination.



Scheme 1-42 Formation of arylpalladium amide complexes from hydroxo and alkoxo derivatives.

attributed to the slow activation of the catalytic precursor, resulting in an increase in the concentration of active species within the catalytic cycle. It was also confirmed that the bis-ligand complex [Pd(binap)$_2$] does not play a role directly on the catalytic cycle [37, 90]. In addition to a pathway involving oxidative addition of the aryl halide to [Pd(binap)] as the first step, a pathway initiated by addition of the amine to Pd(0) was also proposed (Scheme 1-43). These results are consistent with deprotonation of the amine by base occurring only after both amine binding and oxidative addition have taken place. They also exclude the intermediacy of Pd-alkoxo complexes.

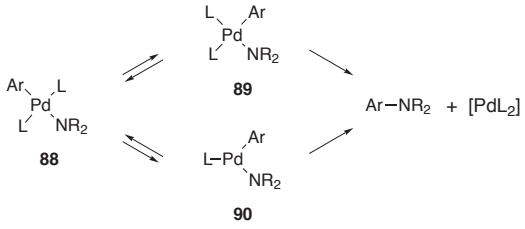
Thus, Pd(0) complexes of type [(RR′NH)Pd(binap)] are proposed to be the actual species which oxidatively add bromobenzene, as this process proceeds more rapidly than the direct oxidative addition on the Pd(0) complex with no coordinated amine [214].



Scheme 1-43 Alternative catalytic cycle for the Pd-binap-mediated amination of bromobenzene. Amine coordination takes place before oxidative addition.

1.3.1
Reductive Elimination of C-N, C-O, and C-S Bonds From Organopalladium(II) Complexes

Reductive elimination of amine and ethers is the key bond-forming step in the catalytic amination and etheration reactions. Kinetic studies on stoichiometric reactions from isolated amido and alkoxo organopalladium complexes have shed



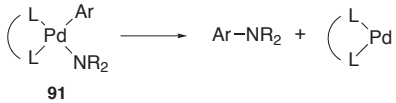
Scheme 1-44 Possible competing pathways for the C-N reductive elimination from monodentate phosphine complexes.

light into the mechanism by identifying the actual species involved and the factors controlling this process. The most extensively studied of these reactions is the reductive elimination of C-N bonds from amido arylpalladium complexes [215, 216]. Both monomeric and dimeric species have been studied. In the case of monomeric complexes, some differences occur depending on the nature (mono- or bidentate) of the coordinating phosphines.

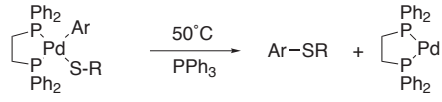
Thus, the reductive eliminations from *trans*-bis(triphenylphosphine) amido aryl complexes **88** showed first-order kinetics demonstrating that the reductive elimination takes place from monomeric species (Scheme 1-44). The dependence of the reaction rate on the concentration of added PPh_3 is compatible with two competing mechanisms, one involving C-N bond formation to a *cis* 16-electron species **89** formed by isomerization of the *trans* derivative. The other mechanism involves initial reversible phosphine dissociation to give a 14-electron, three-coordinate intermediate **90** that would undergo C-N bond formation (Scheme 1-44). Dimeric monophosphine complexes follow a dissociative pathway to give three-coordinate amido monomers, which suffer reductive elimination. The formation of the 14-electron intermediates can be reversible or irreversible depending on the type of amine.

Amido organopalladium complexes containing bidentate phosphines have the *cis* configuration necessary to provide the reductive elimination. The zero-order dependence on the concentration of the added ligand is consistent with a direct concerted formation of the amine from the square planar complexes **91** (Scheme 1-45).

The influence on the reductive elimination of the substituents on both the amido and the R ligand has been studied on dppf model derivatives, as it appears to be a one-step process. The relative rates for elimination from different amido groups is alkylamido > arylamido > diarylamido. This trend implies that the more nucleophilic is the amido ligand, the more rapid the reductive elimination occurs. On the other hand, the presence of substituents on the aryl group also affects the reductive elimination rate, with electron-withdrawing groups accelerating the process. A similar behavior is observed for the reductive elimination of C-S bonds from aryl sulfide palladium complexes **92** (Scheme 1-46) [184a].



Scheme 1-45 C-N reductive elimination from dppf complexes.



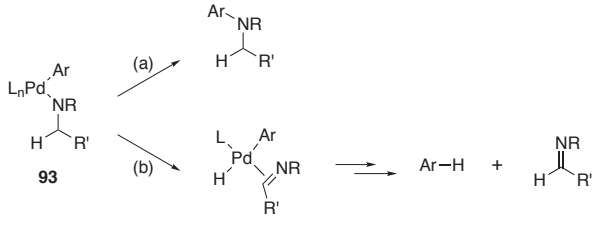
92

Scheme 1-46 Reductive elimination of C-S bonds.

The formation of ethers by reductive elimination from alkoxo organopalladium complexes faces some difficulties due to the lower nucleophilicity of the alkoxides compared with metal amides. The choice of suitable phosphine ligands is crucial for this type of reaction. Bulky aryldialkylphosphines allow the reaction of aryl chlorides, bromides, and triflates with a variety of isolated alkoxides [217] or, more interestingly, phenols and base [218] regardless of the substitution of the aryl groups. Intermediate alkoxo organopalladium complexes have been proposed to form by transmetallation from alkali metal alkoxides to organopalladium derivatives. The rate of the reductive elimination from these intermediates is significantly slower than the corresponding rate to form C-N bonds. Two possible mechanisms exist for the intimate mechanism of the elimination. The first is the occurrence of a three-center transition state or an initial attack of the alkoxide on the aryl ipso carbon followed by elimination of the metal complex. The second mechanism would be more probable in the case of aryl electrophiles containing electron-withdrawing groups. It has been proposed that the bulkier ligands are necessary to destabilize the ground state of the intermediate [$L_nPd(OR)Ar$] complex, forcing the palladium bound aryl and alkoxide groups together. In this way, the complex is distorted toward the three-center transition state geometry [218a]. Stoichiometric reductive elimination reactions of C-N and C-O bonds from Ni complexes have also been described [219].

As it happens in the case of C-C cross-coupling reactions, β-hydrogen elimination is a competitive pathway in the palladium-catalyzed amination and etheration reactions. The conversion of the organic electrophiles to amines or ethers depends on the reductive elimination being faster than β-hydrogen elimination from amido or alkoxo intermediates. The extension of the undesired β-hydrogen elimination in C-N couplings has been studied on stoichiometric elimination reactions from amido arylpalladium complexes **93** (Scheme 1-47). The C-N β-hydrogen elimination has been proposed to take place also from amido complexes in some cases [220].

The final amount of β-hydrogen elimination products (arenes) depends on several factors [208a]. Thus, electron-withdrawing groups on the aryl ring increase the rate of the reductive elimination and minimize the formation of the arene.



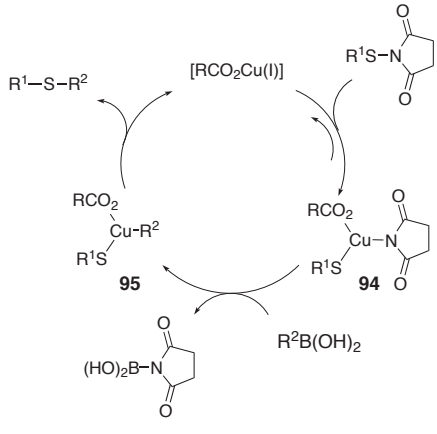
Scheme 1-47 Competitive pathways in the evolution of amido organopalladium complexes: (a) reductive elimination; (b) β-hydrogen elimination.

As it has been observed for etheration reactions, bulkier monophosphines enhance the rate of the C-N reductive elimination. In the case of bidentate phosphines, the results are more difficult to rationalize. Thus, electron-poor derivatives of dppf produce more arene than dppf itself, albeit a more deficient metal center is thought to suffer an easier reductive elimination. Ligands with smaller bite angles yield less β-hydrogen elimination products, in contrast with the observed dependence for C-C reductive eliminations. Detailed studies have been performed on amido [221] and alkoxo [222] Ir(I) square-planar complexes, which indicate that reversible phosphine dissociation takes place prior to the β-hydrogen elimination for both amide and alkoxo complexes.

1.3.2
Copper-Catalyzed Formation of C-X Bonds

Other metal salts and complexes also catalyze the formation of C-N, C-O, and C-S bonds from organic electrophiles. Thus, a mixture of $[Ni(COD)_2]$ and a bidentate phosphine catalyzes the formation of aryl ethers from aryl halides and alkoxides [223]. In some cases, the reactions occur under milder conditions and with higher yields than when catalyzed by Pd complexes.

By contrast, Cu(I) complexes have been reported to catalyze the formation of C-C, C-N, C-O [224], and C-S [225] bonds. Cu(II) also catalyzes the reaction of boronic acids with phenols and amines under oxidative conditions to form Ar-O and Ar-N bonds [226]. Copper also catalyzes the halogen exchange [227] and the cyanation [228] of aryl halides. Interestingly, important differences exists between the Pd- and Cu-catalyzed amination [229]. Thus, whereas palladium catalysts favor amination, copper complexes promote the reactions with carboxamides. In addition, anilines are better nucleophiles than alkylamines in the Pd-catalyzed amination, while the opposite occurs with Cu(I) as the catalyst [229]. Similar systems catalyze the coupling of secondary phosphines and phosphites with aryl and vinyl halides [230].



Scheme 1-48 Proposed mechanism for the Cu(I)-catalyzed synthesis of thioethers from *N*-thioimides and boronic acids.

Alkyl aryl sulfides might also be formed by the reaction of arylboronic acids and alkyl thiols in the presence of Cu(II) [230]. However, Liebeskind demonstrated that in this case the actual catalyst is Cu(I), which led to the development of an efficient method for the synthesis of thioethers by using *N*-thioimides [231]. For this transformation, the mechanism outlined in Scheme 1-48 has been proposed. Accordingly, an oxidative addition of the *N*-thioimide to Cu(I) would form Cu(III) intermediate **94**, which could transmetallate with the boronic acid to form **95**. The reductive elimination from **95** then gives the thioether.

1.4 Summary and Outlook

A unified view emerges for the mechanism of cross-coupling reactions. The formation of C-X bonds with palladium catalysts loosely follows the same catalytic pathways of cross-coupling transformations. However, significant differences exist for both types of processes with regard to the rate-determining step(s) that depend on the nature of the electrophile, nucleophile, and the ligands on palladium.

The original proposal for cross-coupling reactions has evolved considerably. First, the oxidative addition of $C(sp^2)$-X electrophiles has been shown to give first *cis*-palladium(II) complexes, which subsequently isomerize to more stable *trans* complexes. Of greater significance is a clarification of the mechanism of the reaction between soft nucleophilic organometallic reagents and Pd(II). Based on studies on the Stille and Hiyama couplings, transmetallations to palladium appear to follow two major mechanisms. In poorly coordinating solvents and in the presence of bridging ligands, the associative S_E2(cyclic) mechanism operates, whereas the S_E2(open) mechanism proceeds when highly coordinating solvents are used. These two mechanisms pertain to conditions usually followed with palladium complexes coordinated to typical phosphine or arsine ligands. A third type of mechanism, which proceeds through T-shaped intermediates, most likely takes place when the starting Pd(0) catalyst bears two very bulky phosphine ligands such as $P(o\text{-Tol})_3$ or $P(t\text{Bu})_3$.

When monodentate phosphine or arsine ligands are used, the transmetallation reaction leads directly to T-shaped intermediates bearing two mutually *cis* R ligands (Schemes 1-26 and 1-29). Therefore, in general, there is no need for the *trans*- to *cis*-isomerization originally proposed for the Stille reaction (see Scheme 1-2) and later assumed for other transmetallation-based catalytic processes.

Many of the sound mechanistic investigations described have been conducted on palladium-catalyzed processes. Although recently developed reactions catalyzed by Ni(0), Pt(0), or Cu(I) may follow similar schemes, additional mechanistic studies are needed to develop more efficient reactions. In this regard, it is also important to stress that, although studies conducted on isolated complexes are of major value in understanding these processes, more general mechanistic conclusions on these and related rather complex schemes will emerge from studies performed under realistic catalytic conditions.

Abbreviations

Ad	adamantyl
BBN	9-borabicyclo[3.3.1]nonane
binap	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
Cy	cyclohexyl
dba	dibenzylideneacetone
dippp	1,3-bis(diisopropylphosphino)propane
dppBz	1,2-bis(diphenylphosphino)benzene
dppe	bis(1,2-diphenylphosphino)ethane
dppf	bis(1,1′-diphenylphosphino)ferrocene
dppp	bis(1,3-diphenylphosphino)propane
dppr	bis(1,1′-diphenylphosphino)ruthenocene
HMPA	hexamethylphosphoric triamide
TBAF	tetrabutylammonium fluoride
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
TFP	tri-(2-furyl)phosphine

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2
Metal-Catalyzed Cross-Coupling Reactions of Organoboron Compounds with Organic Halides

Norio Miyaura

2.1
Introduction

In 1979, cross-coupling reactions of organoboron compounds, which involve transmetallation to palladium(II) halides as a key step, were found to proceed smoothly in the presence of an aqueous base. The protocol has been proved to be a general reaction for a wide range of selective carbon-carbon bond formations, in addition to related coupling reactions of organomagnesiums, -zincs, -silicones, and -stannanes [1]. Many organometallic reagents are now used for analogous cross-coupling reactions, but much attention has recently been focused on the use of organoboron compounds within laboratory and industrial environments as they are convenient reagents, are generally thermally stable, and are inert to water and oxygen, thus allowing handling without special precautions. A review of metal-catalyzed cross-coupling reactions of these compounds is presented here, with particular emphasis on the reaction conditions, including catalysts, bases, and side-reactions for achieving selective coupling, along with a survey of the representative C-C bond-forming reactions. As previous reviews have included studies carried out to the end of 1999 [2, 3], new developments during the period from 2000 to the end of 2002 are mainly discussed herein, and this will, in part, overlap previously published, related articles [4–8].

2.2
Advances in the Synthesis of Organoboron Compounds

2.2.1
Hydroboration

Hydroboration of alkenes and alkynes is one of the most extensively studied reactions in the synthesis of organoboron compounds and their applications to organic synthesis. Catalyzed hydroboration is a complementary strategy to achieve the dif-

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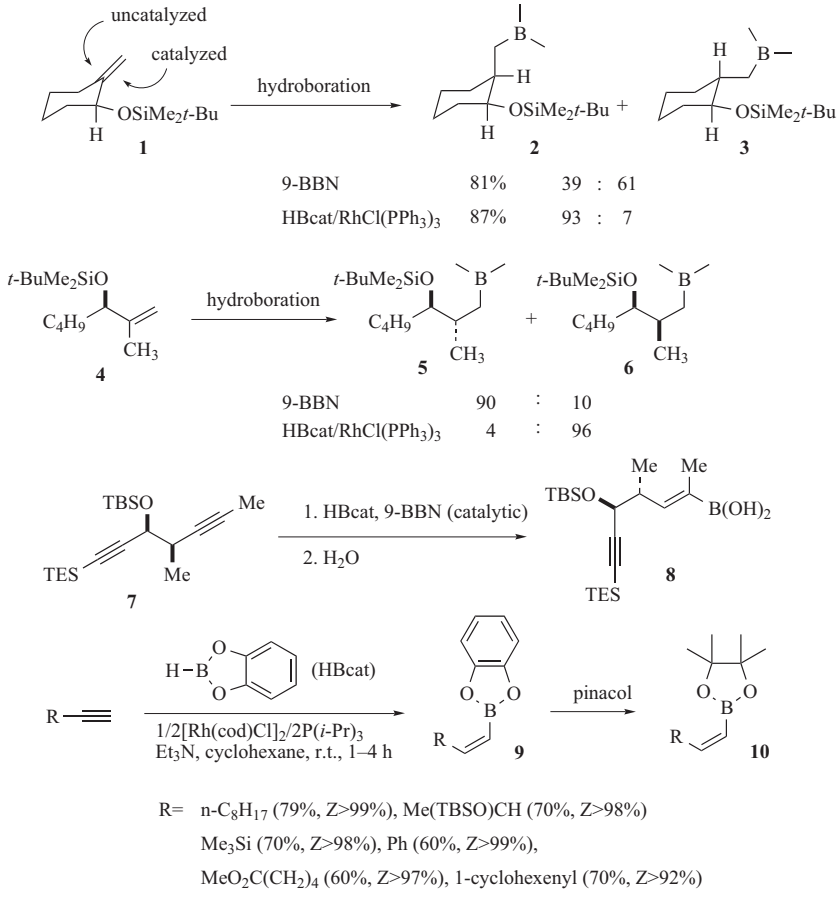


Scheme 2-1 Organoboron compounds via hydroboration.

ferent chemo-, regio-, diastereo-, and enantioselectivities, relative to the uncatalyzed reaction [8b, 9] (Scheme 2-1).

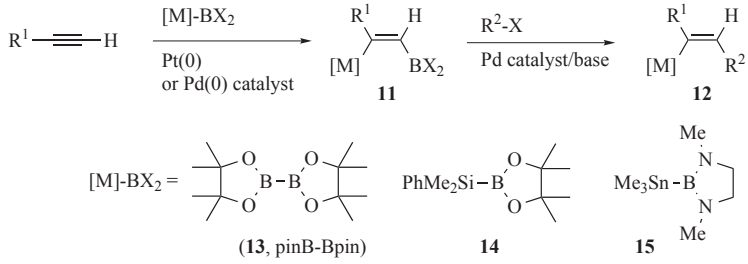
The hydroboration of *exo*-cyclic alkenes affords stereochemically complementary products between the catalyzed and uncatalyzed reactions. The hydroboration of **1** with 9-BBN yields two isomers, with the *trans*-product **3** predominating in a ratio of 39:61 [10]. The reaction contrasts strongly with the catalyzed hydroboration, which yields the *cis*-product **2** with 93 % selectivity by addition to the *R*-face of the alkene. Thus, the catalyzed reaction is more sensitive to steric effects than to electronic effects, whereas 9-BBN prefers to attack from the more electron-rich face of the double bond (stereoelectronic effect) [11]. Diastereoselective hydroboration of acyclic alkenes is one of the most successful results achieved by catalyzed hydroboration [10, 12]. Rhodium-catalyzed hydroboration of allylic alcohol **4** yields a *syn*-adduct **6**, whereas the uncatalyzed reaction of 9-BBN preferentially produces an *anti*-adduct **5** [12]. The origin of diastereofacial selectivity arises from differences

between the mechanisms of π-complexation of transition metals and main metals, together with the steric effect of the substituents [12]. The stereoselection of catalyzed hydroboration is optimal if the OH-protecting group is a good σ-acceptor and is sufficiently large (e. g., $SiMe_2tBu$) relative to the other substituents on the asymmetric center. The hydroboration of alkynes is especially valuable in the synthesis of stereodefined 1-alkenylboron compounds [13]. Disiamylborane ($HB(Sia)_2$), dicyclohexylborane, and 9-BBN are very mild and selective hydroboration reagents by which to obtain 1-alkenylboranes, which can be directly used for subsequent cross-coupling reactions. The addition of catecholborane (HBcat) or dihaloborane ($HBCl_2 \cdot SMe_2$, $HBBr_2 \cdot SMe_2$) to alkynes, followed by hydrolysis with water, is a common method for the synthesis of air-stable 1-alkenylborinic acids **8** [14]. Hydroboration of alkynes with catecholborane is slow in tetrahydrofuran (THF), with the reaction occurring at room temperature in the presence of a catalytic amount of 9-BBN or dicyclohexylborane (*ca*. 10 mol %) [15].

Both uncatalyzed and catalyzed hydroborations yield (*E*)-adducts through the *anti*-Markovnikov and *syn*-addition of HBcat to terminal alkynes. Thus, (*Z*)-1-alkenylboronates have been synthesized by a two-step method based on intramolecular S_N2-type substitution of 1-halo-1-alkenylboronates with metal hydrides [16] or *cis*-hydrogenation of 1-alkynylboronates [17]. Rhodium(I)/$P(i\text{Pr})_3$-catalyzed hydroboration is a new variant for the one-step synthesis of *cis*-1-alkenylboron compounds (**9**) from terminal alkynes [18]. The dominant factors reversing the conventional *E*-selective hydroboration to *Z*-selective reaction are the use of alkyne in excess of catecholborane, the use of more than 1 equivalent of Et_3N, and bulky, electron-donating $P(i\text{Pr})_3$ or Cy_3P for a rhodium(I) precursor. The conversion into air- and water-stable pinacol esters **10** allows isolation by distillation or chromatography on silica gel.

2.2.2
Diboration, Silylboration, and Stannylboration

Various B-B, B-Si and B-Sn compounds are available for metal-catalyzed borylation of alkenes and alkynes (Scheme 2-2). The addition of bis(pinacolato)diboron **13** to alkynes is catalyzed by a platinum(0) complex such as $[Pt(PPh_3)_4]$, $[Pt(C_2H_4)(PPh_3)_2]$, and $[Pt(CO)_2(PPh_3)_2]$ at 80 °C, giving *cis*-1,2-diborylalkenes **11** in high yields [19, 20]. A highly unsaturated platinum(0) complex prepared from $Pt(nbe)_2$ and $P(2\text{-}MeC_6H_4)Ph_2$ or PCy_3 catalyzes the reaction at room temperature [20a]. Stannylboration with **15** [21] takes place at room temperature, whereas silylboration with **14** [22] only proceeds at a temperature above 100 °C due to the slow oxidative addition of a B-Si bond to a Pd(0) or Pt(0) catalyst. Both reactions selectively provide *cis*-products **11** *via* addition of silicon or tin to the internal carbon, and boron to the terminal carbon. The reactions are compatible with various functional groups for both terminal and internal alkynes. Cross-coupling reaction of **11** with organic halides or rhodium-catalyzed conjugate addition of **11** to enones occurs selectively at the terminal C-B bond to provide regio- and stereodefined alkenylboron, -silicon, and tin compounds **12** [22–24]. Analogous catalyzed addi-



[M]-BX_2	catalyst	Ref.
pinB-Bpin (**13**)	$[Pt(PPh_3)_4]$/DMF/80 °C	[19, 20b,c]
pinB-Bpin (**13**)	$[Pt(nbe)_3]$/P(*o*-MeC_6H_4)Ph_2 or PCy_3/r.t.	[20a]
$PhMe_2SiBpin$ (**14**)	$Pd(OAc)_2$/15*t*-$BuCH_2CMe_2NC$/110 °C	[22]
$Me_3SnB(NR_2)_2$ (**15**)	$[Pd(PPh_3)_4]$/r.t.	[21]

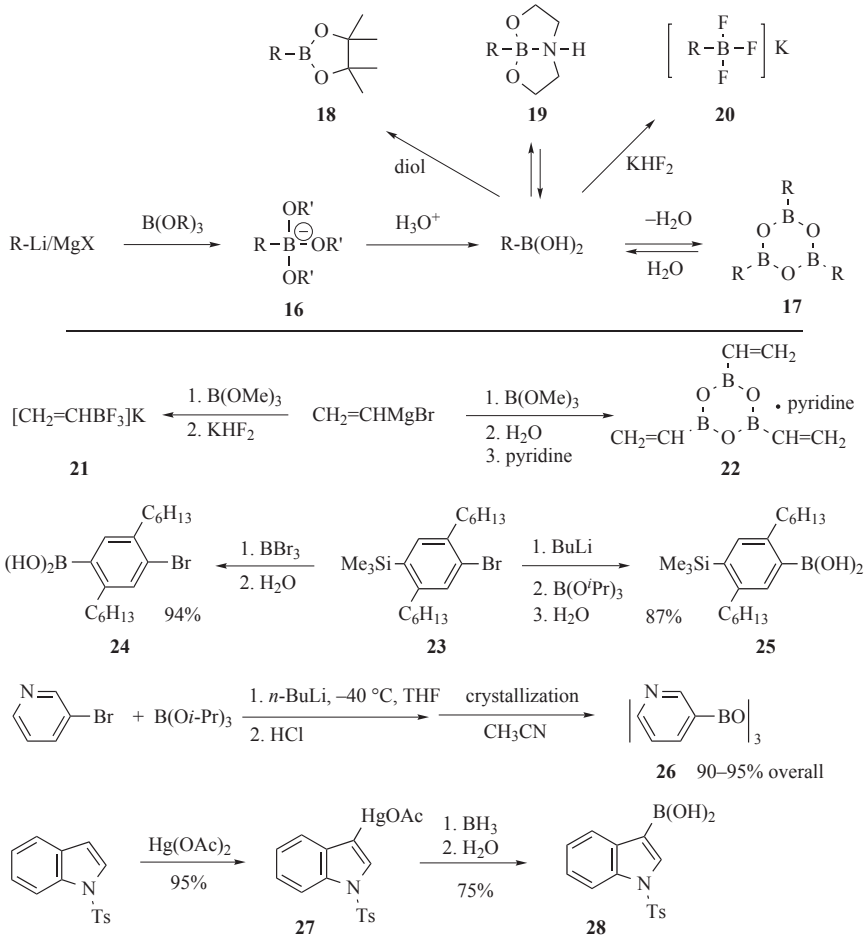
Scheme 2-2 Addition of B-M (M = B, Si, Sn) compounds to alkynes.

tion reactions of diboron provide 1,2-bisborylalkanes from 1-alkenes [25], *cis*-1,4-bisboryl-2-alkenes from 1,3-dienes [26] and 2,3-bisboryl-1-propene from allene [27]. The metal-catalyzed reactions of diboron [8, 28], silylboron [28, 29], and stannylboron [28, 30] compounds have recently been reviewed.

2.2.3 Transmetallation

Transmetallation is perhaps the most straightforward method for preparing organoboron compounds if the requisite organometallic reagent is easily available. For laboratory-scale synthesis, organomagnesium or -lithium reagents are most widely used because of their availability and ease of preparation. Other organometallic derivatives of Al, Zn, Si, Sn, and Hg also undergo transmetallation to alkoxyboranes or haloboranes. (Scheme 2-3). The transmetallation between $(R'O)_3B$ and R-M (M = Li, MgX) at low temperature (typically at –78 °C) proceeds by the initial formation of a relatively unstable $[RB(OR')_3]M$ (**16**), which is in equilibrium with $RB(OR')_2$ and R′OM. If $[RB(OR')_3]M$ can be cleanly formed and if the equilibrium favors this complex, then $RB(OH)_2$ will be obtained selectively upon treatment with an aqueous acid [31]. Otherwise, successive steps will give rise to di-, tri-, or tetraorganoborates. Such multiple alkylation can be serious when relatively small organolithium or -magnesium reagents are used. Triisopropoxyborane has been shown to be the best available trialkyl borate to prevent such disproportionation. A number of alkyl-, aryl-, and 1-alkenylboronic acids or esters [31], and 1-alkynylboronic esters [32] have been synthesized from organolithiums and $B(OiPr)_3$ in high yields, often over 90 %.

A common method for the isolation of organoboronic acids is crystallization of the crude product from hot water, or from an aqueous organic solvent. Organo-



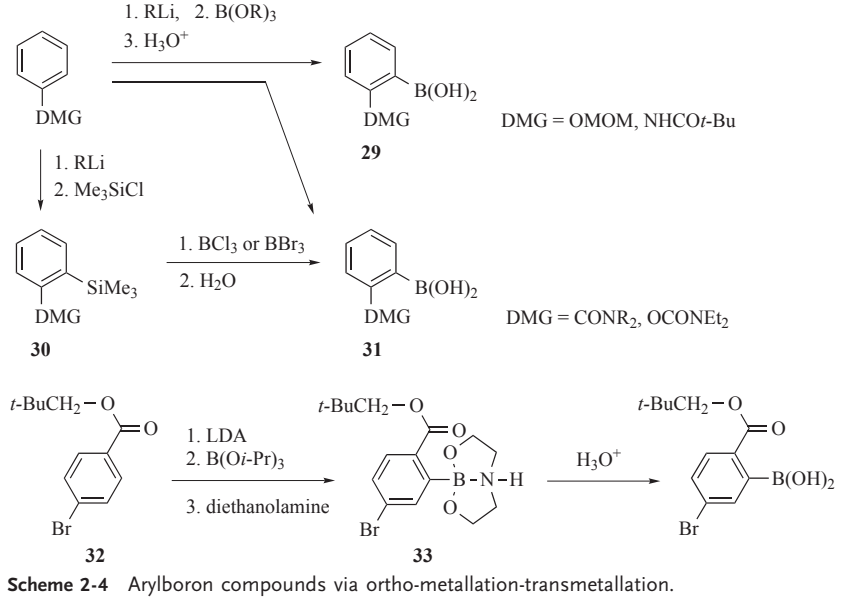
Scheme 2-3 Organoboron compounds via transmetallation.

boronic acids generally present a host of difficulties with regard to their analysis due to their spontaneous condensation to various degrees to boroxines **(17)** [33]. Thus, NMR spectroscopy in $CDCl_3$ shows two pairs of signals corresponding to a boronic acid and a boroxine. A convenient analytical method is dissolution of the dry sample in $NaOD/D_2O$ to give a single signal of $[RB(OD)_3]Na$. An alternative isolation method is their conversion into the corresponding diethanolamine complex **19**, which is easily crystallized from an organic solvent and restored back to free boronic acid by treatment with an aqueous acid [34]. Chromatographic separation of the corresponding boroxine **17** is also convenient for isolating arylboronic acids [35]. The reaction of organoboronic acids with 1,2- or 1,3-alkanediols yields stable cyclic esters. Some bulky diol esters such as pinacol **18** may have sufficient stability for chromatographic separation and gas chromatography (GC) analysis.

Treatment of boronic acids with KHF_2 results in the spontaneous precipitation of stable and highly insoluble $[RBF_3]K$ (**20**) [36]. All of these derivatives have been successfully used for various cross-coupling reactions, as discussed in later sections.

Some recent examples are shown in the syntheses of **21** to **28** (Scheme 2-3). Since small organoboronic acids such as an ethenyl derivative are highly susceptible to oxidation or polymerization, trifluoroborate **21** [37] and boroxine-pyridine adducts **22** [38] are alternatively recommended as bench-stable reagents for the cross-coupling. Many aryl- and 1-alkenylboronic acids have been synthesized from organolithiums generated in situ by halogen-metal exchange **25** [35]. Although the method often suffers from incompatibility of functional groups sensitive to lithium reagents, or instability of aromatic heterocyclic lithium reagents, in situ quenching of the lithium intermediates *via* the addition of BuLi to a mixture of ArBr and $B(O^iPr)_3$ allows the syntheses of pyridine- (**26**), quinoline-, 2-chlorophenyl-, and 4-cyanophenylboronic acid in high yields [39]. On the other hand, transmetallation between BX_3 (X = Cl, Br) and arylsilanes **23** [35] or 1-alkenylsilanes [40] is compatible with various functional groups. Mercuration of arenes **27** followed by transmetallation with BH_3 or BCl_3 is advantageous over the lithiation route in the synthesis of indole-3-boronic acid **28** [41].

The *ortho* lithiation of arenes directed by $CONR_2$ [42], $OCONR_2$ [43], OMe [44], OMOM [45], SO_2NEt_2 [46], and NHCOR [47] provides aryllithiums regioselectively. In situ treatment of lithium intermediates with $B(OR)_3$ (**29**, **31**) or a sequential Li-Si-B transmetallation (**30** to **31**) gives various *ortho*-functionalized arylboronic acids (Scheme 2-4). The protocol has been extensively applied to the synthesis of polycyclic hetereoarenes *via* cross-coupling, with simultaneous condensation between two *ortho* functionalities [48, 49]. Recently, LDA has come to be recognized

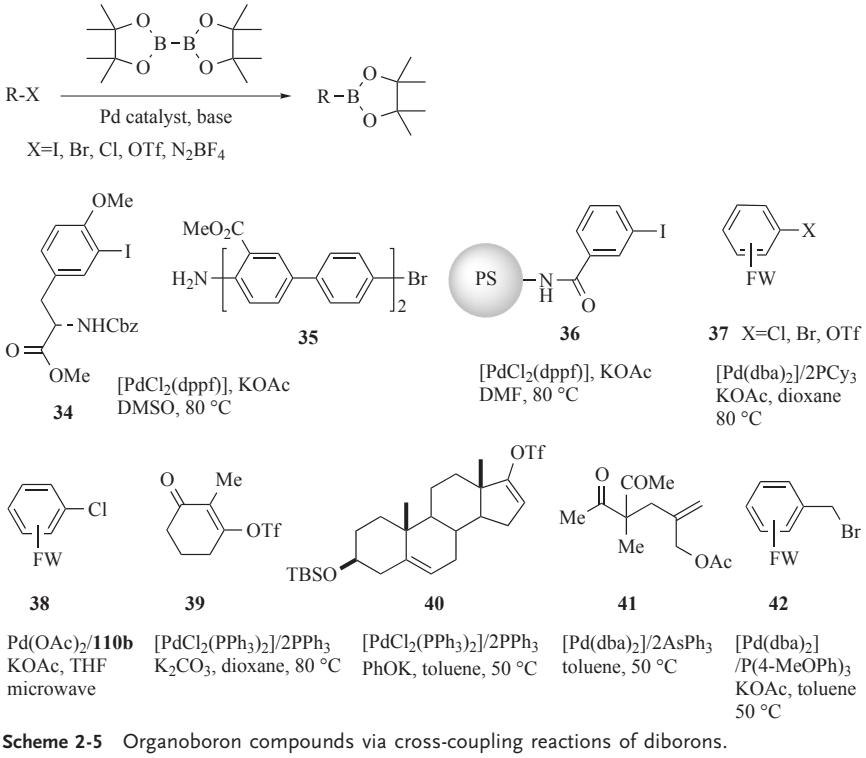


Scheme 2-4 Arylboron compounds via ortho-metallation-transmetallation.

as the better reagent for selective *ortho*-metallation of **32**, which has an aromatic C-Br bond that is susceptible to BuLi [34]. Lithium 2,2,6,6-tetramethylpiperidide (LTMP) is a milder reagent that allows the preparation of *ortho*-substituted arylboronic acids from ethyl benzoate, benzonitrile, chlorobenzene, and fluorobenzene [50].

2.2.4 Cross-Coupling Reactions

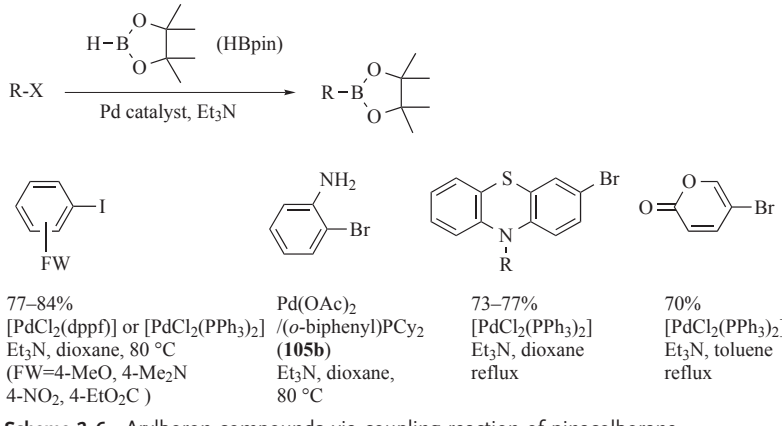
The cross-coupling reaction of diborons with organic halides [51, 52] and triflates [53] directly yields organoboronic esters [8b,c] (Scheme 2-5). Since strong bases, such as K_3PO_4 and K_2CO_3, promote further coupling that results in the competitive formation of homocoupling products (36–60 % yields), KOAc is recognized to be a more suitable base for borylation of aryl iodides **34** [54] and **36**, bromides **35** [55], chlorides **37** [52] and **38** [56], and triflates [53, 57] except for ArN_2BF_4, which is borylated without the aid of base [58]. $PdCl_2(dppf)$ is better than $Pd(PPh_3)_4$ because palladium-triphenylphosphine complexes often yield byproducts derived from coupling of the diboron with a phenyl group on triphenylphosphine in the reaction of electron-rich aryl halides [51]. Electron-donating PCy_3 [52] and N-heterocyclic car-



Scheme 2-5 Organoboron compounds via cross-coupling reactions of diborons.

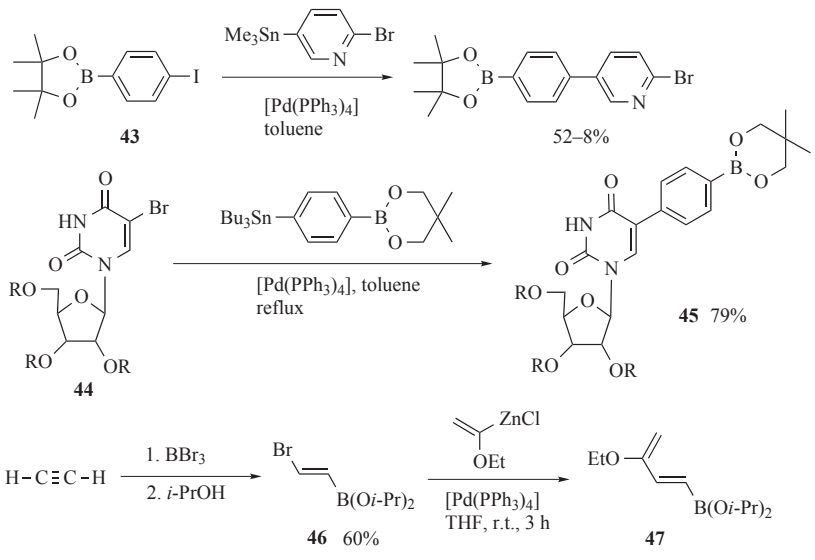
bene [56] complexes afford better results than arylphosphine for aryl chlorides and electron-rich aryl bromides or triflates (**37**, **38**) due to the rate-determining role of oxidative addition and prevention of the participation of phosphine-bound aryls. These reactions can be further accelerated in ionic liquids [59], or by irradiation with microwaves [56]. On the other hand, the borylation of 1-alkenyl halides or triflates requires a stronger base than that used for aryl halides. Fine K_2CO_3 suspended in dioxane is recommended for triflates conjugated to a carbonyl group (**39**) [60], while KOPh suspended in toluene gives the best results for unconjugated bromides or triflates (**40**) [61]. The cross-coupling reaction of diboron with allyl acetates (**41**) is better than the transmetallation method for the synthesis of functionalized allylboronic esters, as the reaction occurring under neutral conditions tolerates various functional groups [62]. Coupling at the less-hindered terminal carbon and formation of (*E*)-allylboronates are commonly observed in various allyl acetates. The reaction is also efficient for the synthesis of benzylboronic esters (**42**) [63]. The protocol has been applied extensively to parallel and combinatorial syntheses on a polymer surface (**36**) [24, 64].

Pinacolborane (HBpin) is an unique and economical boron nucleophile for the borylation of aryl and 1-alkenyl halides or triflates [65] (Scheme 2-6). It is interesting that various reducible functional groups remain intact during the reaction at 80 °C, whereas the reaction is generally accompanied by the formation of some undesirable dehalogenation products (ArH, 10 ~ 20 %). Borylation of 2-bromoaniline [66] or bromophenothiazine [67] is directly followed by cross-coupling with haloarenes in high yields. The ester group remains intact at 120 °C in the synthesis of 2-pyrone-5-boronate [68]. The presence of Et_3N plays a key role in not only preventing the production of ArH but also facilitating the B-C bond formation. The mechanism has not yet been established, but the displacement of Pd-X with a weakly nucleophilic boryl anion ($Et_3NH^+Bpin^-$) or σ-bond metathesis between H-Pd-Bpin and ArX have been proposed for the process, leading to the formation of an Ar-Pd-Bpin intermediate [65].



77–84%	$Pd(OAc)_2$	73–77%	70%
$[PdCl_2(dppf)]$ or $[PdCl_2(PPh_3)_2]$	/(*o*-biphenyl)PCy_2	$[PdCl_2(PPh_3)_2]$	$[PdCl_2(PPh_3)_2]$
Et_3N, dioxane, 80 °C	(**105b**)	Et_3N, dioxane	Et_3N, toluene
(FW=4-MeO, 4-Me_2N	Et_3N, dioxane,	reflux	reflux
4-NO_2, 4-EtO_2C)	80 °C		

Scheme 2-6 Arylboron compounds via coupling reaction of pinacolborane.

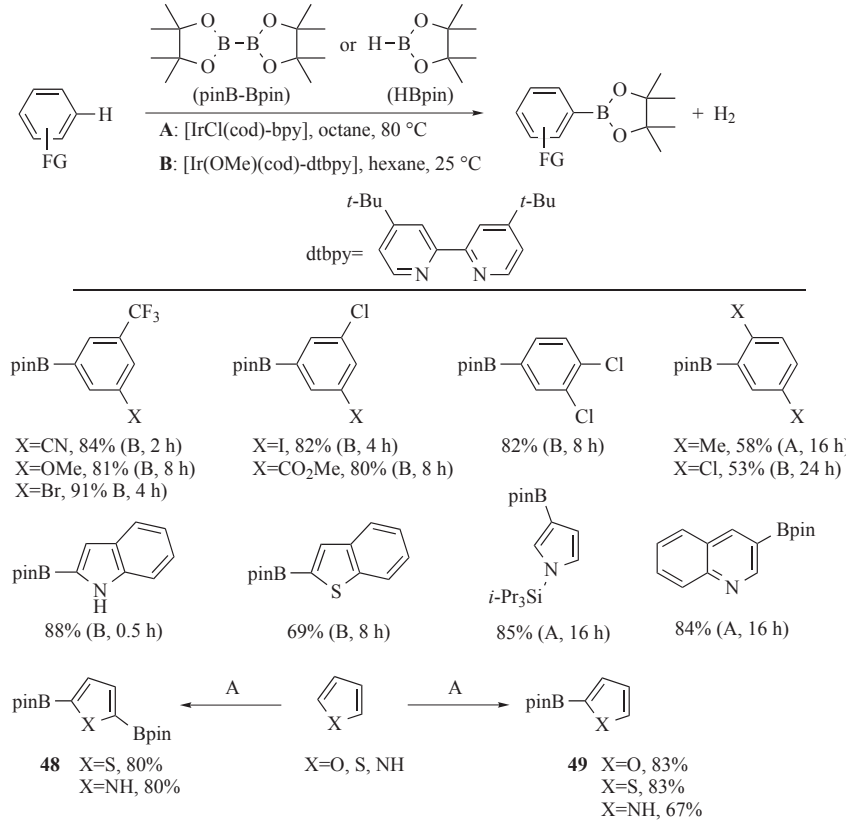


Scheme 2-7 Homologation of organoboron compounds via cross-coupling reactions.

The cross-coupling protocol provides a simple method for homologation of aryl- and 1-alkenylboronic esters (Scheme 2-7). Since the C-B bond is inert to transmetallation in the absence of a base, and oxidative addition of the C-I bond is faster than that of the C-Br bond, arylation of **43** with arylstannanes selectively occurs at the C-I bond, without affecting the C-B and C-Br bonds [69]. A drug substance for neutron capture therapy (**45**) is synthesized by analogous Stille coupling of **44** [70]. Tribromoborane is added to terminal alkynes in a *cis anti*-Markovnikov manner to yield *cis*-2-bromo-1-alkenylboranes [71]. In contrast, addition of BBr_3 to acetylene yields *trans*-2-bromoethenylboronate (**46**) *via* secondary isomerization of the *cis*-adduct [72]. Palladium-catalyzed alkylation of the C-Br bond with organozinc halides affords stereodefined 1-alkenylboronates (**47**) [73]. The two-step procedure is synthetically equivalent to carboboration of acetylene with a variety of organic groups.

2.2.5
Aromatic C-H Borylation

Direct borylation of hydrocarbons would provide an efficient and convenient access to organoboron compounds because of the wide availability and low cost of hydrocarbons. C-H borylation of alkanes and arenes with bis(pinacolato)diboron (pin_2B_2) or pinacolborane (HBpin) was first achieved by using Cp*Rh(III) or Cp*Ir(III) catalysts [74, 75]. Although various catalysts are now available, a combination of air-stable $[Ir(X)(COD)]_2$ (X = Cl, OMe) and a small and strongly electron-donating 2,2′-bipyridine (bpy) or 4,4′-di-(*t*-butyl)-2,2′-bipyridine (dtbpy) is probably the most practical catalyst for aromatic C-H borylation [76–79] (Scheme 2-8).



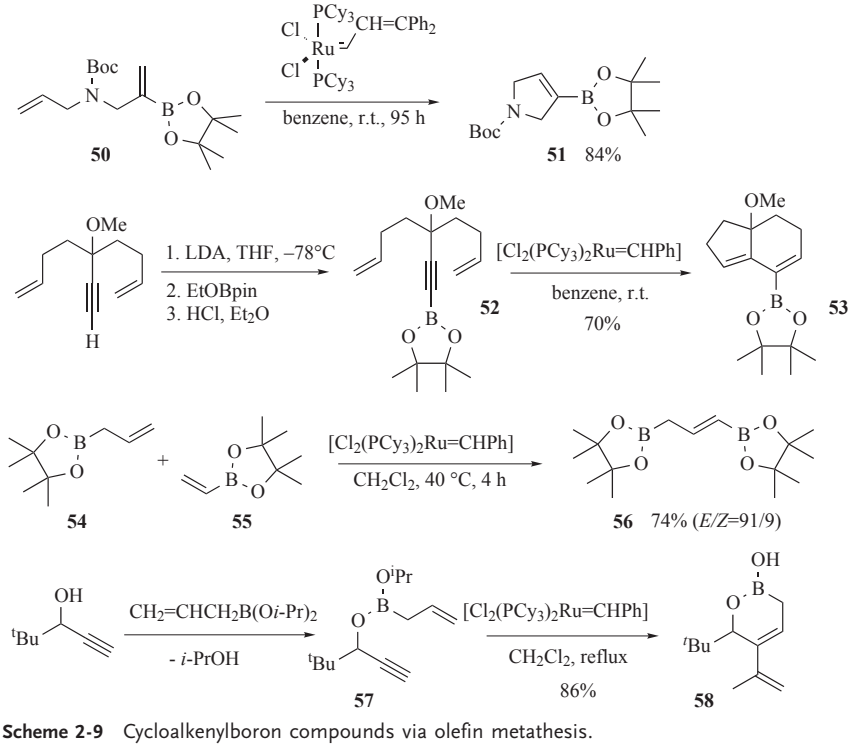
Scheme 2-8 Arylboron compounds via aromatic C-H borylation.

The reaction was first carried out by using a $[IrCl(cod)]_2$/bpy or dtbpy catalyst at 80 °C (method A) [76, 77], but a combination of $[Ir(OMe)]_2$ and dtbpy was later recognized to be the best complex catalyzing the reaction at room temperature (method B) [78]. The reaction provides 2 equiv. of borylarenes from 1 equiv. of pin_2B_2 because pinBH generated at the first coupling also participates in the catalytic cycle. The reaction results in a mixture of *meta* and *para* coupling products in statistical ratios (*ca.* 2:1) for monosubstituted arenes, but 1,2- and 1,4-disubstituted arenes bearing identical substituents yield borylarenes as a single isomer. The reaction of 1,3-disubstituted arenes occurs at the common *meta* position; therefore, isomerically pure products are obtained even for two distinct substituents. Heteroarenes such as pyrrole, furan, thiophene, and benzo-fused derivatives are selectively borylated at the *α*-carbon, though *N*-triisopropylsilylated pyrrole or quinoline yield a *β*-borylated product, and pyridine results in a mixture of *β*- and *γ*-borylation [77]. 2,5-Bis(boryl)pyrrole, -furan, and -thiophene are useful intermediates for the synthesis of poly(heteroarylene)s. These reagents (**48**) are selectively obtained when an equimolar amount of heteroaromatic substrate and

pin_2B_2 are used, whereas mono-borylation (**49**) predominates in the presence of an excess of substrate. It was shown recently that these coupling reactions of pin_2B_2 can be replaced by analogous reactions of pinBH under the conditions of method B [79]. The reaction is more economical for large-scale preparation and suitable for arenes possessing CN, I, Br, Cl, CO_2Me, and CF_3 groups or benzylic C-H bonds. The reactions and the catalytic cycles were recently reviewed elsewhere [75].

2.2.6
Olefin Metathesis

Ring-closing metathesis is advantageous compared to the transmetallation method for the synthesis of cyclic alkenylboronic esters due to its compatibility for a wide range of functional groups (Scheme 2-9). Grubbs' alkylidene-ruthenium complexes catalyze five- or six-membered ring-closing metathesis to yield cyclic 1-alkenylboronic esters at room temperature (**51**, **53**, *via* **50**, **52**) [80, 81]. The cross-coupling reaction of **53** with 3-bromobenzonitrile in the presence of CsF and $PdCl_2$(dppf) in refluxing DME furnishes the coupling product in 88 % yield. Metathesis between pinacol allyl- (**54**) and ethenylboronate (**55**) provides a novel *γ*-borylallylboron compound (**56**), which undergoes a double allylboration of aldehydes yield-

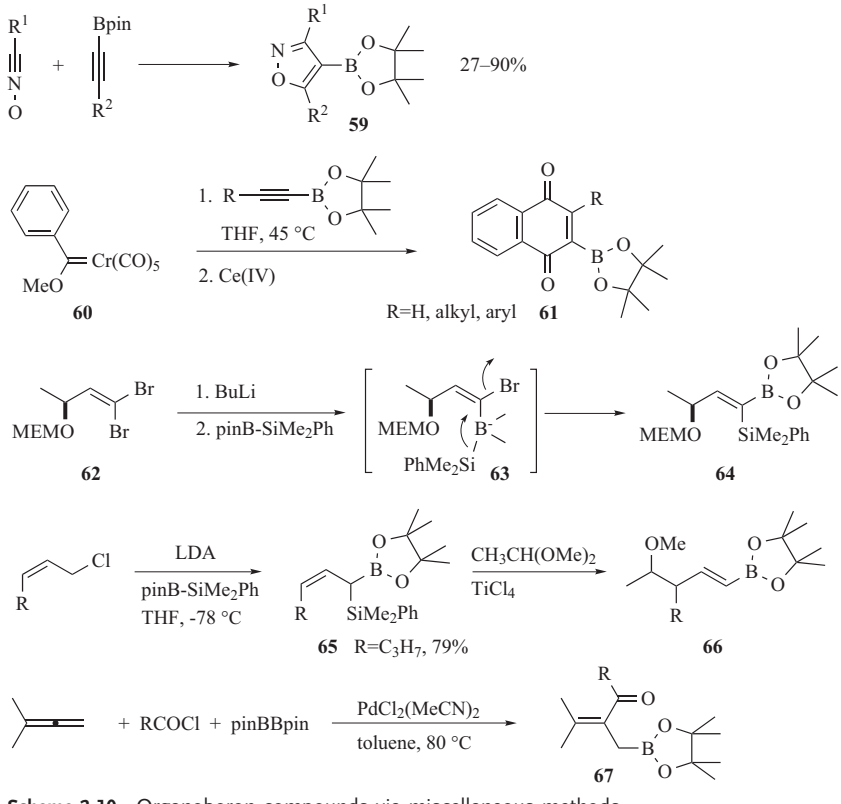


Scheme 2-9 Cycloalkenylboron compounds via olefin metathesis.

ing 2-penten-1,5-diol derivatives [82, 83]. Transesterification of allylboronic esters with allylic or propargylic alcohols (**57**) followed by metathesis yields cyclic allylboronates (**58**) [84].

2.2.7 Miscellaneous Methods

1-Alkynylboronates participate in 1,3-dipolar cycloaddition reactions with nitrile oxides to provide isoxazoleboronic esters (**59**) with excellent levels of regiocontrol [85]. The reaction can be applied to phenyl and alkyl (R^1)-substituted 1,3-dipolar substrates (Scheme 2-10). A novel class of quinoneboronic esters (**61**) are synthesized by utilizing a highly regioselective benzannulation of Fischer carbene complexes (**60**) with 1-alkynylboronates [86]. The utility of the benzannulation-cross-coupling sequence has been demonstrated in the synthesis of a dimeric carbazole, bis-*N*-dimethylbismurrayaquinone A. The reaction between lithium carbenoids and diboron (**13**) or silylboron (**14**) [87] is particularly attractive for preparing a new class of boron compounds such as 1,1-bisborylalkenes and 1-silyl-1-borylalkenes (**64**) [87–89]. The addition of **14** to a solution of alkenylidene carbenoid at



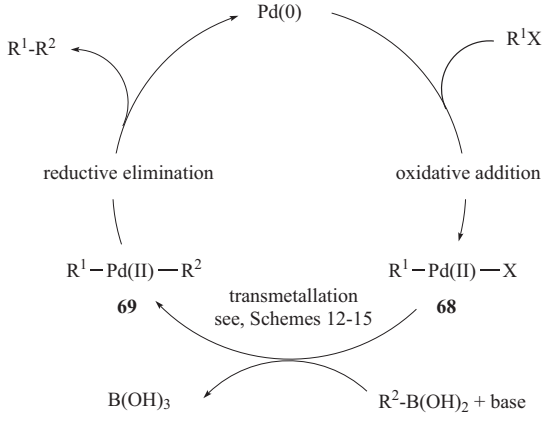
Scheme 2-10 Organoboron compounds via miscellaneous methods.

–110 °C forms an ate-complex (**63**), which is then followed by intramolecular S_N2 substitution with complete inversion of the configuration at the α-carbon. Analogous insertion of the B-Si bond into allylic carbenoid affords **65**, which can be selectively transformed into (*E*)-1-alkenylboronates (**66**) by allylsilylation of dimethyl acetals [90]. A three-component coupling reaction of acyl chlorides, allene, and diboron has been reported for a regio- and stereoselective acylboration of allenes (**67**) [91].

2.3 Reaction Mechanism

2.3.1 Catalytic Cycle

The cross-coupling reaction of organoboron compounds follows a similar catalytic cycle to that of other main metal reagents, involving: (a) oxidative addition of organic halides or other electrophiles to a palladium(0) complex yielding R^1-Pd-X (**68**); (b) transmetallation between R^1-Pd-X and R^2-B with the aid of bases; and (c) reductive elimination of R^1-R^2 to regenerate the palladium(0) complex [1–3] (Scheme 2-11). Among these processes, oxidative addition of chloroarenes has been studied extensively from the viewpoints of cost and availability [6]. Palladium catalysts based on bulky, electron-donating alkylphosphines are recognized to be excellent catalysts for carrying out cross-coupling reactions of chloroarenes. Another topic is oxidative addition of haloalkanes possessing β-hydrogens because the reaction allows C-C bond formation between two sp^3 carbons. Electron-rich and coordinatively unsaturated palladium catalysts such as $Pd(OAc)_2/2PCy_3$ have been found to be very efficient for cross-coupling between 9-primary alkyl-9-BBN and primary-alkyl bromides or chlorides with no significant β-hydride elimination [92, 93].

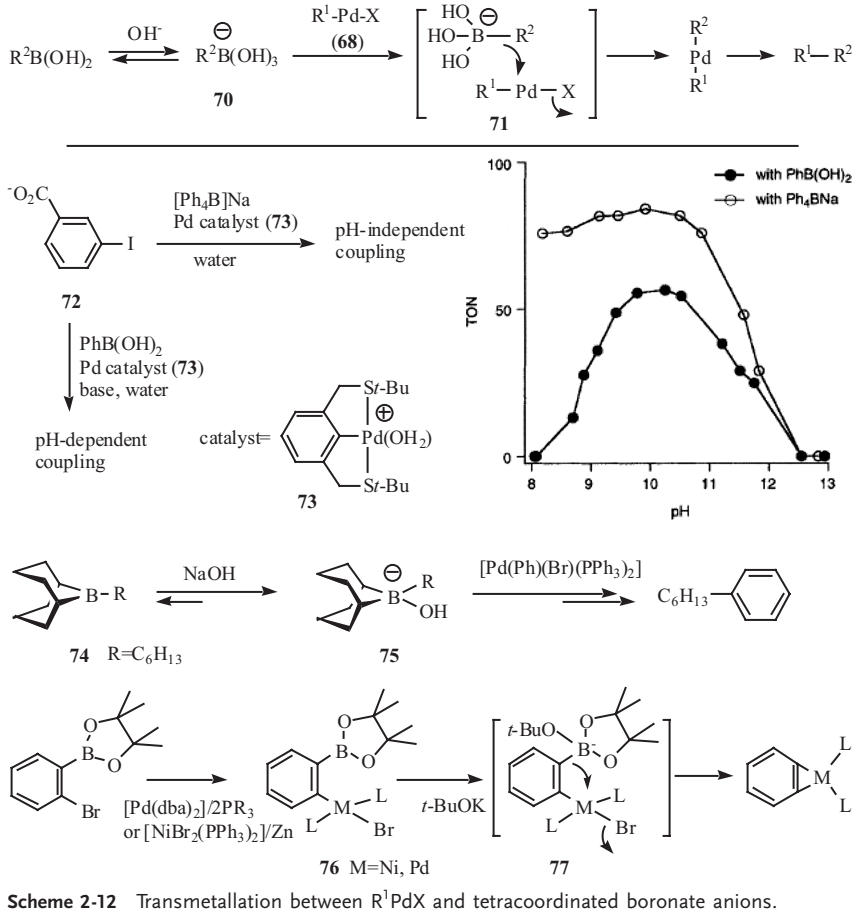


Scheme 2-11 Catalytic cycle.

2.3.2
Transmetallation Processes

Although the two steps of oxidative addition and reductive elimination are reasonably well understood, less is known about the transmetallation process. Available information indicates that there are several processes for transferring the organic group onto R^1-Pd-X (**68**).

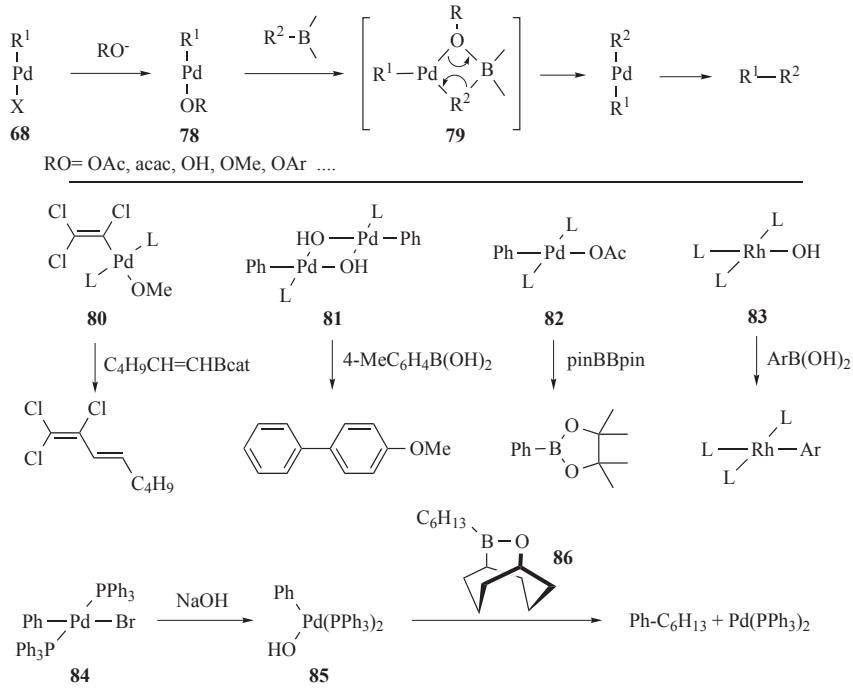
The addition of sodium hydroxide or other bases exerts a remarkable accelerating effect on transmetallation between R^1-Pd-X and trialkylboranes or organoboronic acids that is quite different from the effect on related reactions of other organometallics [2–8] (Scheme 2-12). Organoboron compounds do not react with R^1-Pd-X (X = halogen, OTf), but ate-complexes such as $[RBBu_3]Li$ (R = alkyl, aryl, 1-alkenyl, 1-alkynyl) [2], Ph_4BNa [94], $[R_3BOMe]Na$ [95], and $[ArB(R)(OR)_2]Li$ [96, 97] directly undergo a palladium- or nickel-catalyzed coupling reaction. Thus, quarternization



Scheme 2-12 Transmetallation between R^1PdX and tetracoordinated boronate anions. TON = turnover number. (Figure reproduced by permission of the American Chemical Society.)

of the boron atom with a negatively charged base enhances the nucleophilicity of the organic group on the boron atom for alkylation of R^1-Pd-X (**68**). A hydroxyboronate anion [$R^2B(OH)_3^-$] (**70**), which exists in equilibrium with a free organoboronic acid, could similarly alkylate **68**. Since the pKa of $PhB(OH)_2$ is 8.8, the concentration of [$R^2B(OH)_3$]$^-$ (**70**) will increase at pH over 9. Indeed, the coupling reaction between phenylboronic acid and 3-iodobenzoic acid (**72**) in $NaHCO_3$/NaOH buffers significantly increases in rate upon increasing the pH from 8 to 10; this is in striking contrast to the pH-independent reaction of Ph_4BNa [98]. It should also be noted that both reactions are strongly retarded at pH over 11, though the reason for this is not well understood. Another support for this process is obtained from the cross-coupling reaction of 9-hexyl-9-BBN (**74**) with bromobenzene [99]. Kinetic studies using NMR have shown exclusive formation of analogous hydroxyborate complexes (**75**) and its contribution to the transmetallation process. The catalytic reaction of bromobenzene is zero-order in **74**, suggesting that there is no rate-determining role of transmetallation among the three processes involved in the catalytic cycle. Arylnickel(II) or -palladium(II) complexes *ortho*-substituted with a (pinacolato)boryl group (**76**) react with KO*t*Bu to form the corresponding benzyne complexes at room temperature [100]. The reaction can be regarded as an intramolecular version of transition metal-boron transmetallation assisted by a base, as indicated by **77**. Although little information is available on the nucleophilicity of such hydroxyborate complexes, it was found recently that arylboronic acids substitute for 4-bromoacetophenone at 150 °C in the presence of Bu_4NBr and K_2CO_3 without any assistance of metal catalysts [101]. Although the mechanism is not known, the results may suggest a high nucleophilicity of [$ArB(OH)_3$]NBu_4 that can substitute the aromatic C-Br bond.

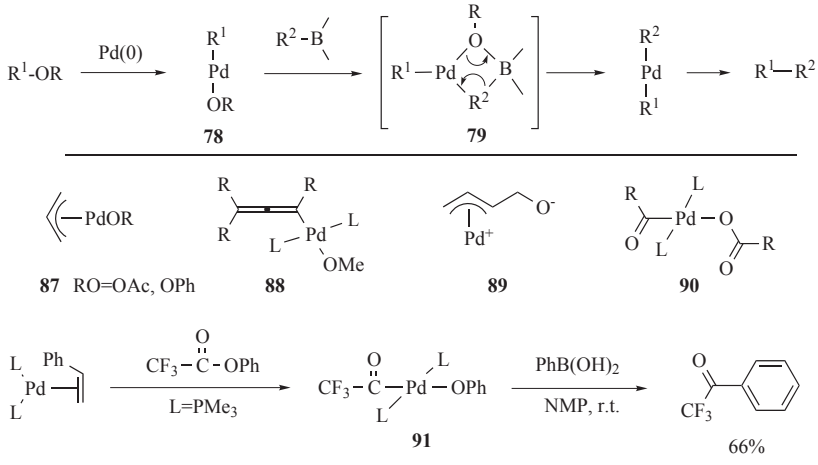
An alternative process is transmetallation to an alkoxo-, hydroxo-, acetoxo-, or (acetylacetoxo)palladium(II) complex (**78**) formed in situ by ligand exchange between R^1-Pd-X (**68**) and a base (RO^-). Such RO-Pd(II) complexes undergo transmetallation of organoboronic acids without the aid of a base (Scheme 2-13). Methoxo- (**80**) [102], hydroxo- (**81**) [103], and (acetoxo)palladium(II) (**82**) [51] complexes, synthesized by ligand exchange between R^1-Pd-X and a base, react with 1-alkenyl- and arylboronic acids or bis(pinacolato)diboron to give the corresponding coupling products. It has also been reported that analogous transmetallation to a (hydroxo)-rhodium complex (**83**) occurs under neutral conditions [104] as the key step in rhodium-catalyzed 1,4-addition of organoboronic acids to enones [105] or Grignard-type addition to aldehydes [106]. The reaction may involve a rate-determining coordination of the RO^- ligand to the boron atom *via* a transition state depicted by **79**. As a result of complex formation, the transfer of an activated organic group from boron to palladium then takes place. The strong reactivity of RO-Pd complexes is attributed to both the high basicity of Pd-O species and the high oxophilicity of the boron center. The basicity of R^1-Pd-OH is not known, but related platinum complexes, such as PtH(OH)[P(*i*Pr)$_3$]$_2$ and *trans*-Pt(OH)(Ph)(PPh_3)$_2$, have been reported to be more basic than NaOH [107]. Thus, available information indicates that there are two transmetallation processes depending on the reaction conditions and including reactants for cross-coupling reactions in an alkaline solution, as shown



Scheme 2-13 Transmetallation to Pd-OR complexes in situ generated from Pd-X and base.

in Schemes 2-12 and 2-13. The coupling reaction of 9-alkyl-9-BBN (**74**) with bromobenzene proceeds *via* alkylation of **84** with hydroxyborate anion (**75**) [99], as shown in Scheme 2-12. In contrast, less-acidic **86** is not changed by the addition of NaOH, indicating that there is no significant formation of a hydroxyborate complex. By adding two equivalents of aqueous NaOH in refluxing THF, **84** is converted into a (hydroxo)palladium(II) complex (**85**, 90 % after 2 h), which yields a coupling product upon treatment with **86** (Scheme 2-13). The catalytic reaction is first-order in $[OH]^-$, thus suggesting a rate-determining role of Pd(II)X-hydrolysis (**84** to **85**) [99].

Coupling reactions proceed without any assistance of bases for organic electrophiles, directly yielding RO-Pd complexes (**78**) *via* oxidative addition (Scheme 14). The reactions of allyl acetate or phenoxide [108], propargyl carbonates [109], 1,3-butadiene monoxide [110], phenyl trifluoroacetate [111], and carboxylic acid anhydrides [112] proceed in the absence of bases, because oxidative addition yields RO-Pd species (**87**–**91**) which can transmetallate with organoboron compounds. Among these intermediates, the reaction of phenylboronic acid with **91** has been shown to occur at room temperature under neutral conditions [111]. PMe_3 is not suitable for the catalytic process, but it is an excellent ligand to prepare phosphine-bound model intermediates due to its high basicity and small steric hindrance toward oxidative addition. The reaction between phenyl trifluoroacetate

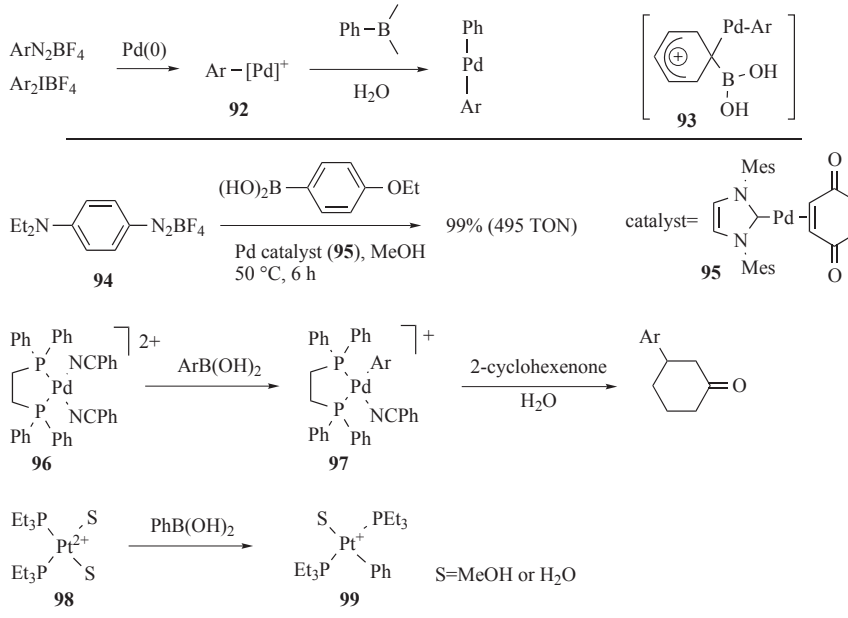


Scheme 2-14 Transmetallation to Pd-OR complexes in situ generated by oxidative addition.

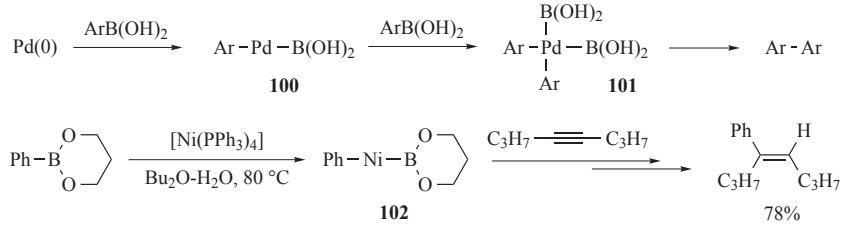
and a coordinatively unsaturated palladium-styrene complex takes place at room temperature to yield **91** [113]. No information is available on the transmetallation process; however, the reaction may lead to *cis*-Pd(Ph)(CF_3CO)(PMe_3)$_2$, which can directly undergo reductive elimination. Indeed, a reaction of arylboronic acids with phenyl perfluoroalkanecarboxylates catalyzed by Pd(OAc)$_2$/3PBu_3 at 80 °C in NMP does not require the presence of any base to prepare aryl perfluoroalkyl ketones in high yields.

Cross-coupling reactions of Ph_2IBF_4 [114] and ArN_2BF_4 [115–117] in an aqueous solvent or MeOH have been carried out in the absence of bases (Scheme 2-15). As such electrophiles, giving cationic palladium intermediates (**92**), are very liable to phosphonium salt formation between a phosphine ligand and an electrophile, free-phosphine catalysts such as Pd(OAc)$_2$ and Na_2PdCl_4 [115] or a combination of Pd(OAc)$_2$ and N-cyclic carbenes (**95**) [116, 117] are generally recommended. Transmetallation occurring through a Wheland intermediate **93** is a probable candidate for such smooth conversion under neutral conditions; however, its contribution may not be significant because ArN_2BF_4 analogously reacts with 1-alkenyl- and alkylboronic acids without any added base [116]. Another example reported in this category is the transmetallation of arylboronic acids with $[Pd(PhCN)_2(dppe)]^{2+}$ (**96**) to **97**, in which 1,4-addition of arylboronic acids to enones is carried out under neutral conditions [118]. $[Ph_4B]Na$, Ph_3B, and $PhB(OH)_2$ transfer a phenyl group to $[Pt(S)_2(PEt_3)_2][CF_3SO_3]_2$ (**98**, S = MeOH or H_2O) [119]. The finding that the reaction of $[B(Me)Ph_3]Na$ with **98** yields both methyl and phenyl complexes in ratio of about 1:1 also suggests that **93** does not contribute to the transmetallation process.

A catalytic process involving the oxidative addition of $ArB(OH)_2$ to a palladium(0) complex (**100**) has been reported as the mechanism of homocoupling of arylboronic acids [120] and Heck-type arylation of styrene [121] (Scheme 2-16). Analogously,



Scheme 2-15 Transmetallation to cationic palladium(II) or platinum(II) complexes.



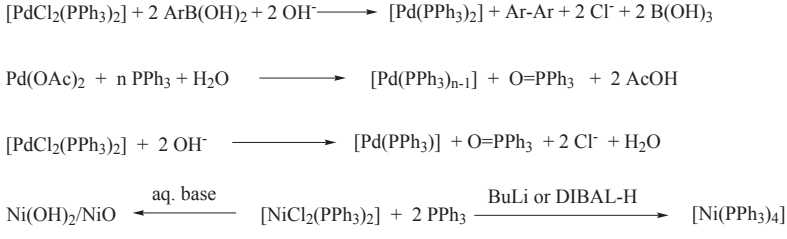
Scheme 2-16 Oxidative addition of C-B bond to Pd(0) or Ni(0) complex.

the oxidative addition of $ArB(OH)_2$ to nickel(0) catalysts under formation of **102** has been proposed as the mechanism by which arylboronic acids or esters are added to alkynes [122] or 1,3-dienes [123]. Although this process is very popular in addition and coupling reactions of organomercury [124] and -tin compounds [125], no related relevant information has yet been reported for organoboron compounds.

2.4
Reaction Conditions

2.4.1
Catalysts

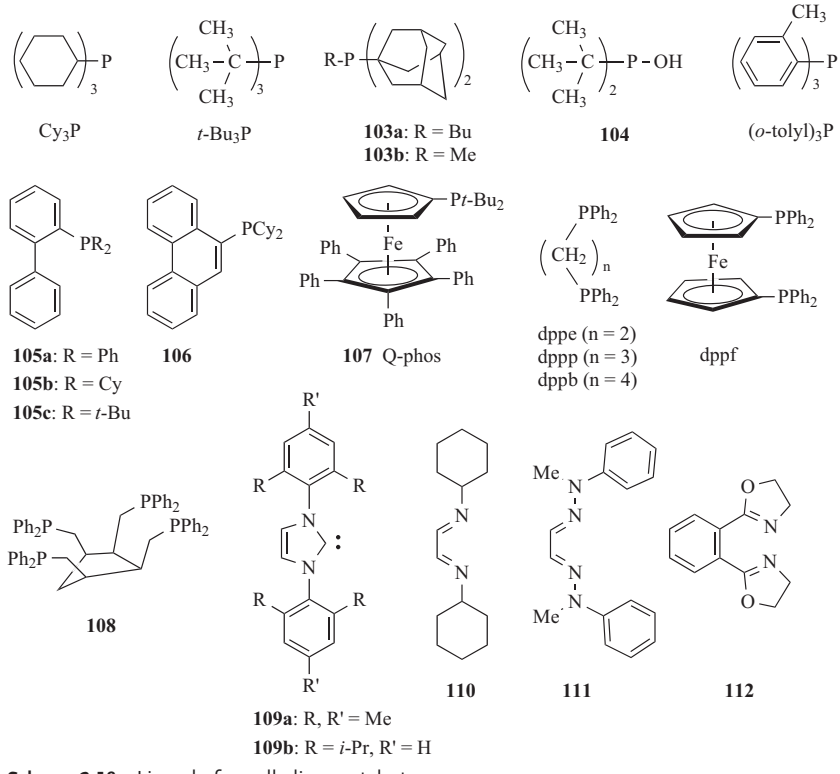
The reaction can be carried out using various catalysts, bases, and solvents, and their combinations significantly affect the yields and selectivity of products. $[Pd(PPh_3)_4]$ is the most common catalyst, and the addition of a phosphine ligand to $[Pd_2(dba)_3]$ or $[Pd(dba)_2]$ is an alternative method for preparing analogous palladium(0)/phosphine complexes while adjusting the Pd/P ratio. $Pd(OAc)_2$ and $PdCl_2$/phosphines are also good precursors because they are reduced in situ to the corresponding palladium(0) complexes [126] (Scheme 2-17). The reduction of $Pd(OAc)_2$ with phosphine is instantaneous [127], and $PdCl_2$/phosphines can be aided by the presence of a base [128, 129]. On the other hand, the reduction of nickel(II) complexes is slow, and results in the formation of catalytically inactive nickel(II) hydroxide or oxide in the presence of an aqueous base. Thus, treatment with BuLi or DIBAL-H is recommended for the in-situ reduction of $NiCl_2$/phosphine complexes [130, 131]. Reduced palladium complexes are commonly abbreviated as $Pd(0)L_n$, but the reduction leads to the formation of anionic palladium(0) species such as $Pd(0)L_2Cl^-$ and $Pd(0)L_2(OAc)^-$. Thus, the rate of oxidative addition or other efficiencies of catalysts can be affected by the anionic ligand involved in catalyst precursors [126].



Scheme 2-17 In-situ reduction of palladium(II) and nickel(II) complexes.

2.4.1.1 **Palladium catalysts**

A number of new ligands have been designed and synthesized to attain high catalyst efficiency or selectivity in order expand the scope of the reactions [6] (Scheme 2-18). Various phosphine ligands are effective in stabilizing the palladium(0) species, but the stoichiometry of phosphine to palladium and the bulkiness or donating ability of phosphine ligands change the reactivity of catalysts toward oxidative addition, transmetallation, and reductive elimination. $[Pd(PPh_3)_4]$ and other Pd(0)/phosphine complexes are in equilibrium with coordinatively unsaturated species depending upon the bulkiness of the ligands (cone angle) [132] (Scheme 2-19). Among them, either a bisphosphine $Pd(0)L_2$ or monophosphine Pd(0)L complex



Scheme 2-18 Ligands for palladium catalysts.

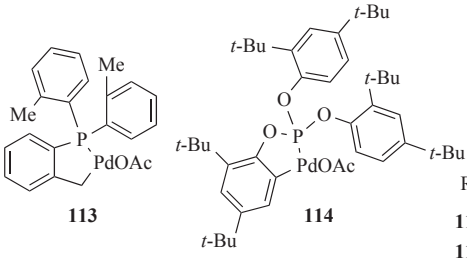
	PEt_3	PPh_3	$P(i\text{-}Pr)_3$	$P(c\text{-}C_6H_{11})_3$	$P(Ph)(t\text{-}Bu)_2$	$P(t\text{-}Bu)_3$
cone angle (°)	132	145	160	170	170	182
coordination number (n)	3, 4	3, 4	2, 3	2	2	2

Scheme 2-19 Cone angles and coordination numbers $M(PR_3)_n$ (M = Pd, Pt).

is responsible for the oxidative addition of organic halides [133, 134]. Thus, palladium complexes that have fewer than four phosphine ligands, or a weakly coordinating ligand such as $AsPh_3$, or a bulky phosphine serve as highly reactive catalysts because of the easy formation of coordinatively unsaturated species. Another role of the ligand is electron donation to the palladium(0) metal center, which has been extensively demonstrated in cross-coupling reactions of chloroarenes [6, 135]. Air-stable triarylphosphines are effective ligands for coupling reactions of organic iodides, bromides, triflates, and activated chlorides, including 2-chloropyridine derivatives [136], but they do not catalyze reactions of electron-rich chlorides [137]. This limitation can be overcome by the use of bulky and

highly donating ligands; for example, P(*t*Bu)$_3$ [134], di(adamanthyl)phosphine (**103**) [138] and 2-(di-*t*-butylphosphino)biphenyl (**105c**) [135] and Qphos (**107**) [139] provide highly active catalysts for chloroarenes, even at room temperature. The large accelerating effect of these ligands is attributed to their ability to donate electrons to the metal center and the easy dissociation to generate coordinatively unsaturated species. However, less bulky phosphines are generally recommended for slow reactions of functionalized substrates since they yield stable complexes at high temperature. PCy$_3$ [134, 140], (*o*-biphenyl)PCy$_2$ (**105b**) [135, 141], (*t*Bu)$_2$POH (**104**) [142] and N-heterocyclic carbene (**109**) [56, 116, 117, 143] have been successfully used for such purposes. On the other hand, bisphosphines having a large P-M-P angle, such as dppp, dppb, and dppf, have been designed to accelerate the reductive elimination in the coupling reaction of alkylmetals (sp^3-coupling) [144]. Among these ligands, dppf is recognized as an excellent ligand for various coupling reactions of alkylboron compounds with suppression of β-hydride elimination [95]. The ligand also works well for coupling reactions of 1-alkenyl- and arylboronic acids. Tedicyp (**108**) is an unique ligand, and for the respective catalyst, an exceptionally high turnover number (TON) of up to 100 000 000 has been achieved for the biaryl coupling reaction of iodo- or bromoarenes, due to the strong ability of the ligand to prevent the precipitation of palladium black [145]. Diimine **110** [146], bis(hydrazone) **111** [147], and dioxazolidine **112** [148] are air-stable N-ligands that are effective for iodo- and bromoarenes. P-N ligands consisting of Ph$_2$P and a pyridine or iminophosphines have also been reported [149].

Palladacycles derived from tris(*o*-tolyl)phosphine (**113**) [150], triarylphosphite (**114**) [151], benzoxime (**115**) [152], and bis(phosphinite) (**116**) [153] are air-stable catalysts exhibiting exceptionally high catalyst efficiency in coupling reactions of arylboronic acids with bromoarenes or activated chloroarenes (**113**, **114**, and **115** are shown as monomeric forms in Scheme 2-20). The TON of catalyst achieved



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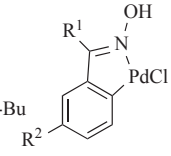
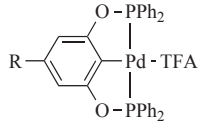
114



115a: R^1= 4-ClC$_6$H$_4$, R^2= Cl
115b: R^1= CH$_3$, R^2= OH



116

catalyst	conditions	yield(%)[a]	TON[a]
113	K_2CO_3/xylene/130 °C	74	74 000
114	K_2CO_3/toluene/110 °C	100	1 000 000
115a	K_2CO_3/toluene/110 °C	99	198 000
116	K_2CO_3/toluene/130 °C	92	92 000

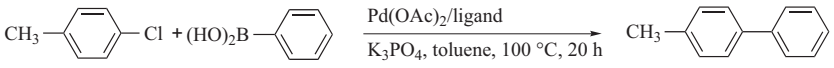
[a]A biaryl coupling between phenylboronic acid and 4-bromoacetophenone

Scheme 2-20 Palladacycles.

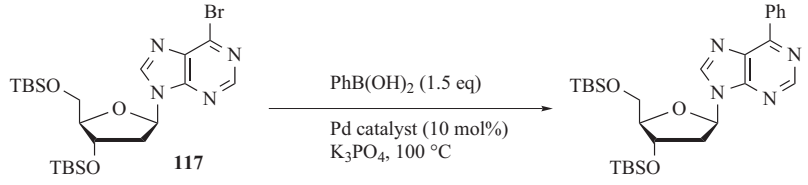
for phenylboronic acid coupling with 4-bromoacetophenone are in the range of 74000 ~ 1000000. These catalysts are also efficient for electron-rich 4-bromoanisole (975–7600 TON) and activated chloroarenes such as 4-chloroacetophenone. A phenol derivative of benzoxime complex **115b** catalyzes the reaction of 4-chloroacetophenone in pure water as solvent in the presence of Bu_4NBr (0.5 equiv.) (69–77 %; 6000–7000 TON) [152b]. Glyoxal bis(methylphenylhydrazone) **111** yields a strongly reactive palladacycle that completes the reaction of electron-rich boromoarenes within a few hours at room temperature [147]. Although what determines their activities has not yet been identified, nor whether the reaction proceeds through a Pd(0)-Pd(II) cycle or a Pd(II)-Pd(IV) cycle, the metallation may contribute to stabilizing the resting state of the palladium species in order to prevent the precipitation of palladium-black.

The effects of representative ligands in the coupling reactions of arylboronic acids with haloarenes are shown in Scheme 2-21. Since the best catalyst is strongly dependent upon the reaction conditions, including reactants and solvents, the screening of representative ligands is a common method of selecting an appropriate catalyst. Despite their sensitivity to air-oxidation, bulky and strongly electron-donating alkylphosphines such as tBu$_3$P, P(Bu)(Ad)$_2$ (**103a**), or [Pd(Me)(Ad)$_2$] are very effective for chloroarenes, and presumably also for slow reactions of electron-rich boromoarenes [138]. Since tBu$_3$P is highly sensitive to air, tBu$_3$P · HOTf is recommended as a suitable replacement [154]. The effects of ligands for more functionalized substrates have been demonstrated in the arylation of C(6)-iodo- [155], C(6)-bromo- (**117**) [156], C(6)-chloro- [156], or C(6)-arylsufonyloxy [157] nucleoside derivatives. Although the reaction is relatively slow, [Pd(PPh$_3$)$_4$] is a good catalyst for C(6)-iodo and C(6)-bromo (**117**) derivatives, the yields being 79 % and 87 % respectively. Dppf and (*o*-biphenyl)PCy$_2$ (**105b**) complexes complete the reaction within 1–2 h, but the effects of (*o*-biphenyl)PtBu$_2$ (**105c**) and tBu$_3$P are not significant for such electron-deficient bromoarene since the oxidative addition is not rate-determining. Among the catalysts screened, the (*o*-biphenyl)PCy$_2$ complex is recognized as being the best catalyst for C(6)-bromo (**117**, 91 %), C(6)-chloro (93 %), and C(6)-arylsufonyloxy derivatives (76 %) [156, 157], due to its high reactivity towards oxidative addition and stability at high temperature. A general method for biaryl coupling has been limitedly used for tri-*ortho*-substituted biaryls. A phenanthrene ligand (**106**) -based catalyst exceptionally allows the synthesis of sterically hindered biaryls, where each reactant possesses two *ortho*-substituents [158]. The phenanthrene ring is critical as the corresponding biphenyl- and naphthyl-based ligands result in significantly low yields and low conversions. Crystallographic analysis of a **106**/[Pd(dba)$_2$] complex shows the formation of a highly stabilized monophosphine-palladium(0) species by an unusual π-coordination of the phenanthrene moiety to a palladium metal center along with σ-coordination of a dicyclohexylphosphino group.

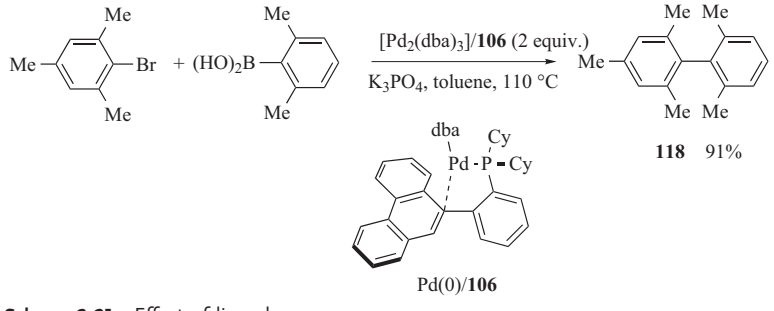
Free-phosphine palladium nanoparticles generated in situ from Pd(OAc)$_2$ serve as an excellent catalyst for biaryl coupling in water or in aqueous organic solvents (Scheme 2-22). The advantage of such a ligandless catalyst is that it eliminates



ligand (equiv.)	mol (%)	yield (%)	TON
PPh_3 (2)	0.1	5	50
(*o*-biphenyl)PCy_2 (**105b**, 2)	0.05	93	1860
PCy_3 (2)	0.1	23	230
P(*t*-Bu)$_3$ (2)	0.01	92	9 200
$BuPAd_2$ (**103a**, 2)	0.005	87	17 400

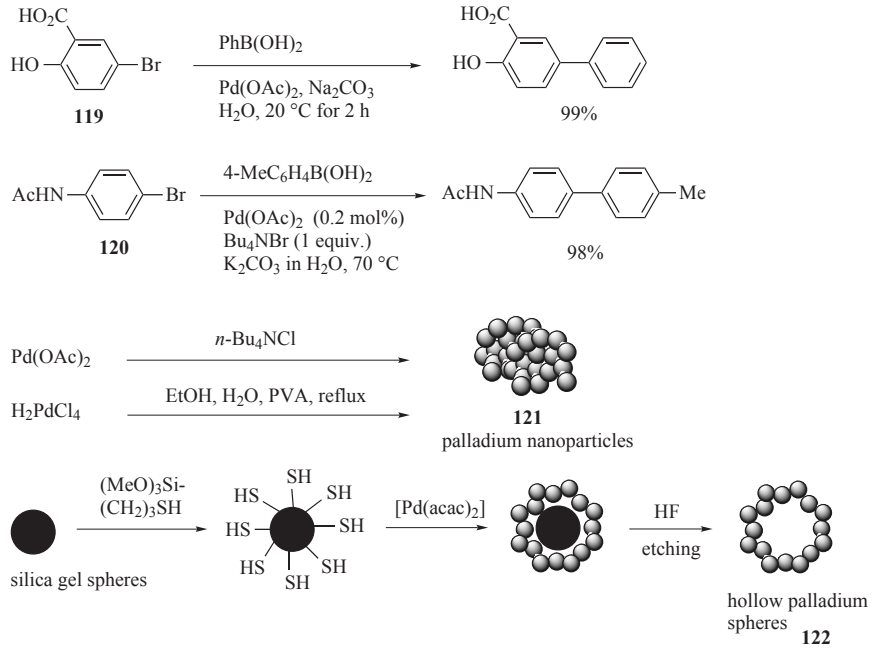


catalyst (equiv.)	solvent	time (h)	yield (%)
$[Pd(PPh_3)_4]$	toluene	8	87
$Pd(OAc)_2$/dppf (1.5)	dioxane	1.75	73
$Pd(OAc)_2$/(*o*-biphenyl)PCy_2 (**105b**, 1.5)	dioxane	1	91
$Pd(OAc)_2$/(*o*-biphenyl)P*t*-Bu_2 (**105c**, 1.5)	dioxane	48	50
$Pd(OAc)_2$/P(*t*-Bu)$_3$ (1.5)	dioxane	48	50



Scheme 2-21 Effect of ligands.

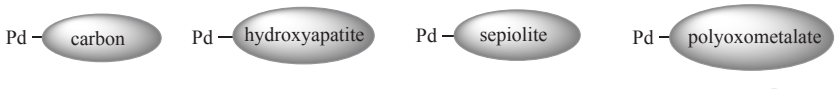
phosphine-related side reactions such as participation of phosphine-bound aryls and phosphonium salt formation (see Section 2.5.1), and it has high catalytic efficiency resulting in shorter reaction times [159]. For example, $Pd(OAc)_2$ completes the reaction of water-soluble bromoarenes such as **119** within 2 h at room temperature [160]. The addition of 1 equiv. Bu_4NBr results in quantitative conversion of both water-soluble and -insoluble bromoarenes (e. g., **120**) in a single water phase with 0.2 mol % of catalyst loading [161]. The role of Bu_4NCl is attributable to the formation of palladium nanoparticles (**121**) stabilized by the ammonium salt that are highly reactive towards the oxidative addition of iodo- and bromoarenes [162]. Reduction of H_2PdCl_4 in PVA/EtOH is an alternative method for the preparation of such stabilized nanoparticles (2–8 nm) [163]. Hollow palladium



Scheme 2-22 Ligandless palladium nanoparticles.

spheres (**122**) are unique catalysts composed of an empty core with a uniform nanoparticles shell of 15 nm [164]. For the preparation of such a catalyst, $[Pd(acac)_2]$ is adsorbed onto uniform silica gel spheres functionalized by mercaptopropyltrimethoxysilane. Thermolysis at 250 °C yields palladium metal-coated spheres, which are then treated with aqueous HF to remove the silica gel template. The catalyst size can be easily controlled by the size of the silica gel sphere, while maintaining the high reactivity of the nanoparticles. The catalyst maintains high activity to attain 95–98 % yields, even after seven recyclings in the reaction of 2-iodothiophene and phenylboronic acid. It has been reported recently that copper and copper-based nanocolloids can catalyze the biaryl coupling. A copper nanocluster gave a 62 % yield, but a mixed nanocluster of copper and palladium (1.6–2.1 nm) exhibited high activity to attain 100 % conversion for iodoarenes and 62–100 % conversion for bromoarenes with a 2 mol % catalyst loading at 110 °C [165].

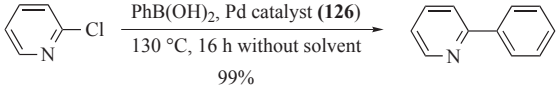
The basic problems of homogeneous catalysts, namely separation and recycling of the catalyst, can be solved by using a supported palladium catalyst, particularly adapted for industrial applications (Scheme 2-23). Palladium or nickel metal supported on charcoal, Pd/C [166, 167], Ni/C [168], and palladium supported on hydroxyapatite (**123**) [169], sepiolite (**124**) [170], polyoxometalate (**125**, **126**) [171] or other clays [172], have been successfully used for the coupling reactions of arylboronic acids. It is notable that the reaction occurs smoothly in a multi-phase system consisting of a solid catalyst, organic solvent, and basic aqueous phase, or even in a



Pd/C $[Ca_9(HPO_4)(PO_4)_5(OH)]$ **123** $[Mg_8Si_{12}O_{30}(OH)_4]$ **124**

125: $[(PW_{11}O_{39})^{7-}]$
126: $[PW_{11}O_{39})^{7-}$-KF-Al_2O_3

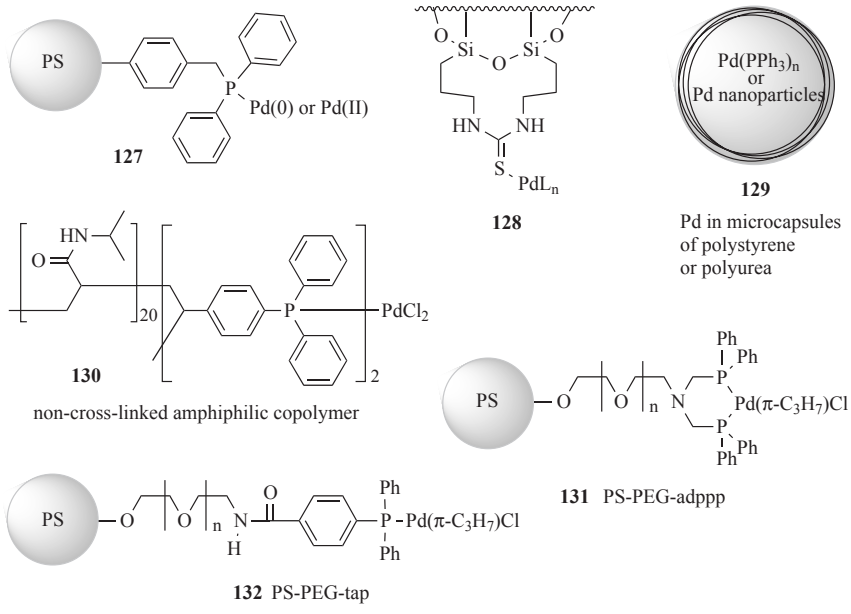
catalyst	base/solvent	yield (%)	TON
$Pd(OAc)_2$	K_2CO_3, DMF, 100°C	44	2 200
Pd/C	K_2CO_3, DMF, 100 °C	40	2 000
123	K_2CO_3, *o*-xylene, 130 °C	91	45 500
124	K_2CO_3, DMF, 100 °C	85	4 250



Scheme 2-23 Palladium catalysts supported on inorganic solids.

solvent-less solid-phase system. Such palladium particles stabilized by the clay or other supports give better results than do unsupported particles, especially for slow reactions of electron-rich haloarenes. For example, $Pd(OAc)_2$ exhibits a high initial rate, but supported catalysts such as **123** and **124** finally give better yields (85–91 %; 4000–45000 TON) than does $Pd(OAc)_2$ (44 %; 2200 TON) in the reaction of 4-bromoanisole with phenylboronic acid. The reaction can take place on the surface, without the palladium leaching into the filtrate, thus allowing recycling of the catalysts without loss of their activity. Palladium-polyoxymetalate-KF impregnated on alumina (**126**) undergoes unique solvent-free solid-phase reactions of arylboronic acids [171, 173]. The biaryls obtained from chloroarenes, including 2- and 3-chloropyridines, are easily recovered by extraction with CH_2Cl_2 and the catalyst can be re-used with essentially no loss of activity. The catalyst can be used to a limited extent for liquid haloarenes as solid substrates such as poly(4-bromostyrene) are unreactive under analogous conditions.

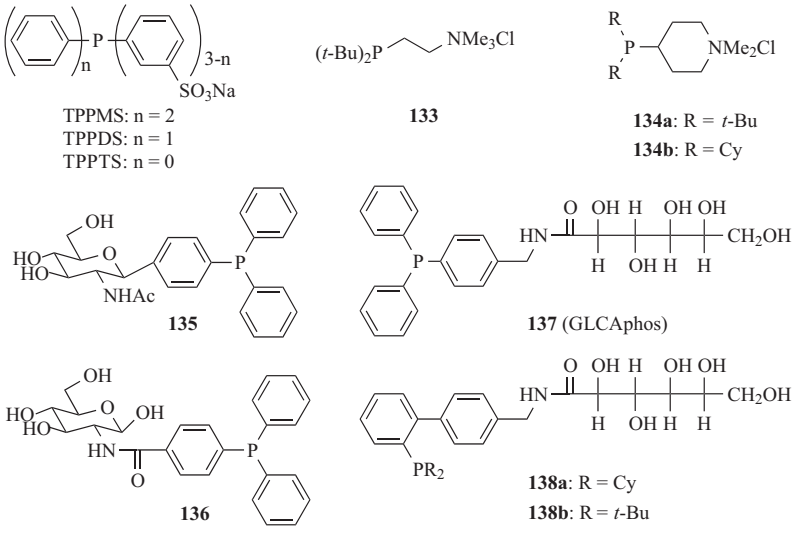
A number of supported palladium complexes, particularly palladium-phosphine complexes, have been designed to combine the advantages of both homogeneous and heterogeneous catalysts [174]. A palladium-phosphine complex anchored on polystyrene resin (**127**) is a traditional polymer catalyst that has been used for the reactions of 1-alkenyl- and arylboronic acids with organic halides or triflates [167, 175] (Scheme 2-24). Deloxane consists of a cross-linked macroporous polysiloxane backbone (**128**) and the commercially available, suitably functionalized resin supports palladium to catalyze biaryl couplings in refluxing aqueous isopropanol [176]. A palladium-triphenylphosphine catalyst encapsulated in polystyrene matrixes [177] and palladium nanoparticles (average diameter 5 nm) in polyurea microcapsules [178] are recyclable catalysts that are effective for bromoarenes (**129**). The reaction of $[(NH_4)_2PdCl_4]$ with an amphiphilic copolymer made from 4-diphe-



Scheme 2-24 Palladium catalysts supported on polymers.

nylphosphinostyrene and *N*-isopropylacrylamide (12 equiv.) yields an insoluble palladium catalyst self-assembled by a Pd-P bonding network (**130**) [179]. The complex catalyzes the biaryl coupling reaction of aryl iodides, bromides, and triflates at 100 °C in a pure water medium with a 50 ppm catalyst loading for the iodides and a 500 ppm loading for the bromides and triflates. Palladium catalysts anchored on a polystyrene-poly(ethylene glycol) graft resin (**131**, **132**) are also designed for palladium-catalyzed reactions in water [180, 181]. Since a palladium/phosphine complex and most organic substrates are insoluble in water, the inclusion of both a catalyst moiety and reactants in an amphiphilic polymer cavity is critical to achieve high catalyst efficiency in a pure aqueous medium. The accelerating effect of amphiphilic complexes (**130–132**) is indeed greater than that of a lipophilic **127** or hydrophilic TPPTS complex for water-insoluble substrates. Unlike normal palladium(0)-phosphine catalysts, these supported catalysts are relatively air-stable, easily separated from the reaction mixture, and are able to be reused with no significant decrease in activity.

Reactions in aqueous media have advantages for large-scale industrial processes because of the simplicity of catalyst-product separation, economy, and safety in using water as the solvent [182]. Although ligandless catalysts such as $Pd(OAc)_2$ often achieve rapid coupling in aqueous media, complete conversion is not always possible, particularly for the slow reactions of electron-rich and sterically hindered substrates. For such substrates, catalysts derived from water-soluble phosphines have been successfully used in a pure aqueous environment (Scheme 2-25). Sulfo-

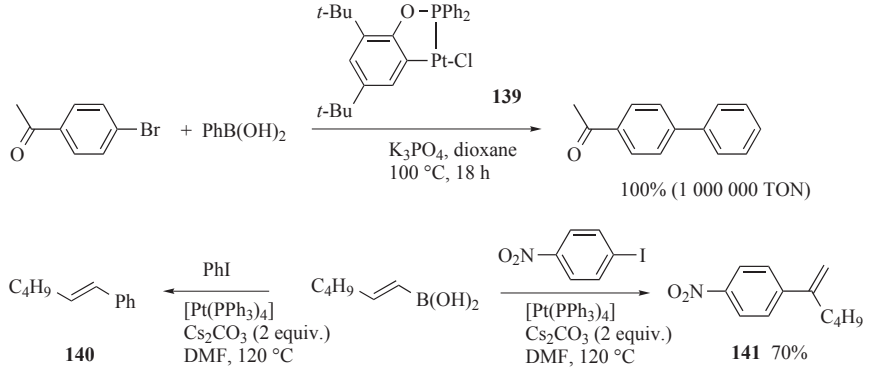


Scheme 2-25 Water-soluble ligands for palladium catalysts.

nated phosphines such as TPPMS and TPPTS are traditional ligands for homogeneous catalysts in aqueous media, and are now utilized in several industrial processes. A Pd/TPPTS complex has been used for the cross-coupling reactions of aryl- or 1-alkenylboronic acids with haloarenes in mixed solvents consisting of water and DMSO or alcohol [183]. Quaternary ammonium salt derivatives of di-*t*-butylphosphines such as **133** and **134** are designed for reactions of chloroarenes in aqueous acetonitrile [184]. The glycosides of arylphosphines **135** [185], **136** [186], **137** [187], and **138** [188] are a new class of ligands used for two-phase or single-water-phase catalysis. Their relative efficiency for oxidative addition is in the order of the electron-donating ability of phosphine ligands to the palladium metal center (**138** > **135** ~ **137** > TPPMS > TPPTS). Another role of the glycoside moiety consists of its providing solubility both in water and organic phases, which is critical for reactions of water-insoluble substrates. Indeed, a palladium-**135** complex achieves a higher TON than that of TPPTS for water-insoluble 4-chlorobromobenzene and 4-bromoacetophenone [185]. A palladium-**138a** complex, which exhibits a TON of 96000 for 4-bromoacetophenone with a 0.001 mol % loading, has proven to be very effective for a wide range of substrates, including solid and liquid haloarenes as well as water-soluble haloarenes, in a single water phase [188]. It is particularly interesting that the catalyst is highly efficient for water-soluble substrates. The complex catalyzes the reaction of 4-bromobenzoic acid, with the conversion being complete within 30 min at 80 °C and within 16 h at room temperature, with a 0.1 mol % loading.

2.4.1.2 **Platinum catalysts**

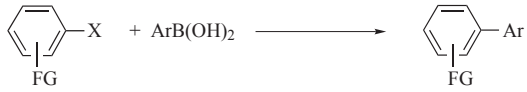
Platinum catalysts have been used to a limited degree for cross-coupling reactions of organoboronic acids as both oxidative addition and reductive elimination are slower than those of palladium complexes (Scheme 2-26). However, platinum(II) complexes of a π-acidic, *ortho*-metallated triarylphosphite (**139**) have been reported to catalyze the reaction of bromoarenes with a low catalyst loading [189]; this is in contrast to $[Pt(PPh_3)_4]$, which is used to a limited degree for iodoarenes at 120 °C [190]. Although there is no great difference between the selectivities of palladium- and platinum-catalyzed reactions, 4-nitroiodobenzene exceptionally yields an *ipso*-coupling product (**141**) in the coupling reaction with 1-alkenylboronic acids [190].



Scheme 2-26 Platinum-catalyzed cross-coupling reactions.

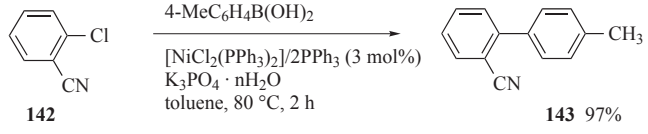
2.4.1.3 **Nickel catalysts**

Nickel(0) catalysts have an advantage over palladium complexes because of their high level of activity toward aryl chlorides and mesylates [130, 131, 191, 192] and economy as recycling of the catalyst is not required (Scheme 2-27). Since the direct use of nickel(II) complexes results in the formation of catalytically inactive nickel hydroxide/oxides in the presence of an aqueous base [131], the reduction of nickel(II) complexes with zinc powder, BuLi, or DIBAL is generally recommended for the in-situ preparation of air-sensitive nickel(0) species. Thus, preliminary studies on coupling reactions of chloroarenes or aryl mesylates were carried out by using an Ni(0)/dppf complex in situ generated from $[NiCl_2(dppf)]$ and BuLi or zinc powder [130, 192]. However, nickel(II) complexes can be reduced in situ when dry arylboronic acid and $K_3PO_4 \cdot nH_2O$ are used in toluene, as has been demonstrated in the synthesis of 2-tolylbenzonitrile (**143**) [131]. It should also be noted that a triphenylphosphine complex works better than a dppf complex when the reaction is carried out in toluene. A reduced nickel catalyst supported on charcoal [168] has also been studied as a catalyst for analogous biaryl coupling. On the other hand, ate-complexes of aryl- or 1-alkenylboronates such as **144** smoothly undergo cross-coupling in the absence of a base or reducing reagent. Reactions with iodo- or bromoalkenes [193, 194], allyl acetates [195, 196], and aryl mesylates [96]

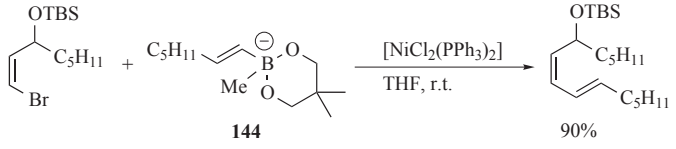


X=OSO_2CH_3 : $[NiCl_2(dppf)]$/Zn, K_3PO_4, dioxane, 80 °C

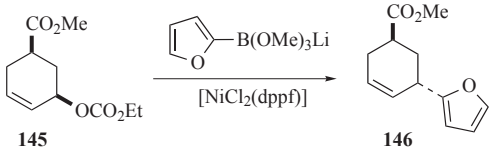
X=Cl : $[NiCl_2(dppf)]$/BuLi, $K_3PO_4 \cdot nH_2O$, dioxane, 80 °C



142 **143** 97%

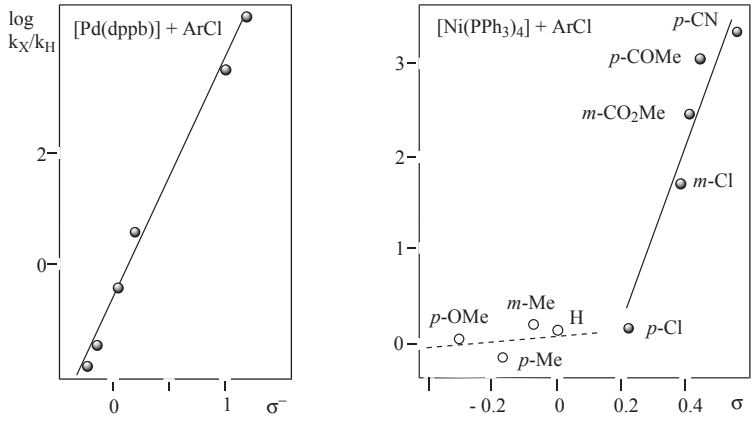


144 90%



145 **146**

Scheme 2-27 Nickel–catalyzed cross-coupling reactions.



147 **148**

Scheme 2-28 Oxidative addition of chloroarenes to Pd(0) and Ni(0) complexes. (Figures reproduced by permission of The Royal Society of Chemistry and the American Chemical Society.)

proceed smoothly at room temperature. The reaction of cyclic allyl carbonate (**145**) occurs with inversion of the stereochemistry *via* oxidative addition (with inversion) and arylation (from the same face of the nickel) [195].

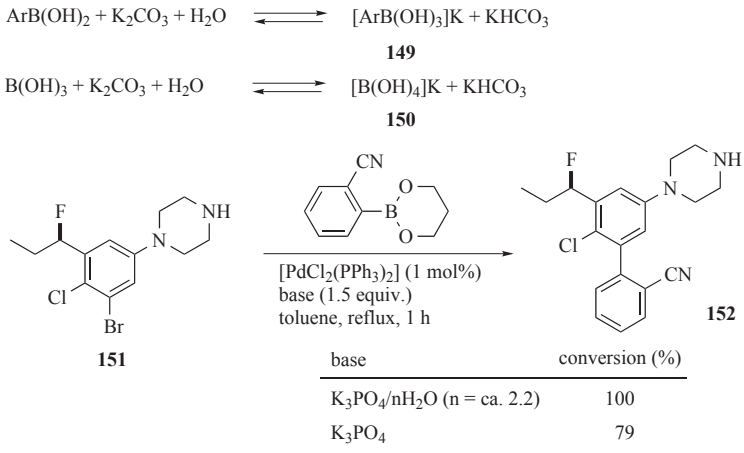
The oxidative addition of chloroarenes to nickel(0) complexes shows a Hammett correlation that is quite different from that of palladium(0) complexes (Scheme 2-28). Oxidative addition is often the rate-determining step in a catalytic cycle, especially for bromo- and chloroarenes. The relative reactivity generally decreases in the order of I > Br > OTf >> Cl for aryl electrophiles, but the order can be reversed depending on phosphine ligands. For example, the coupling reaction of 4-chlorophenyl triflate occurs at the C-Cl bond with a Pd(0)/P(*t*Bu)$_3$ catalyst and at the C-OTf bond with a Pd(0)/PCy$_3$ catalyst [134]. Palladium-catalyzed reactions have been used to a limited degree for chloroarenes possessing a substituent with $\sigma > 0.45$, and have recently been expanded to more electron-rich chloroarenes by using bulky and electron-donating alkylphosphine ligands, as shown in Scheme 2-18. In contrast, all substituents in a range of −0.83 to 0.66 accommodate nickel-catalyzed reactions [130, 131]. [Ni(PPh$_3$)$_4$] exhibits a unique Hammett correlation where reactivity increases linearly by electron-withdrawing groups with $\sigma > 0.23$, and it is insensitive to donating substituents with $\sigma < 0.23$ [197], which is in sharp contrast to that of a palladium(0) complex showing a linear correlation for both donating and withdrawing groups [137]. Oxidative additions to both Pd(0) and Ni(0) can be rationalized by the aromatic nucleophilic substitution mechanism (**147** → **148**) reported by Milstein [137].

2.4.2 Bases, Water, and Solvents

2.4.2.1 Effect of water

Cross-coupling reactions of organoboronic acids with organic halides or triflates require the presence of a negatively charged base, such as an aqueous solution of sodium or potassium carbonate, phosphate, or hydroxide. Since the reactions are generally carried out in a two-phase system consisting of organic and basic aqueous solutions, phase-transfer catalysts have also been used. The difficulties encountered during the reaction in basic solutions are saponification of esters, racemization of optically active compounds, or Aldol condensations of carbonyl compounds. These difficulties associated with bases can be overcome by the use of bases in heterogeneous phase systems. Esters can remain intact in a two-phase system using aqueous K_2CO_3 and toluene, or by using a solid $K_3PO_4 \cdot nH_2O$ or K_2CO_3 suspended in DMF, dioxane, or toluene. For example, the synthesis of arylalanines suffered from base-induced racemization, but optically pure compounds are finally obtained when anhydrous K_2CO_3 is suspended in toluene [198].

Although anhydrous inorganic bases mediate the reactions as suspensions in organic solvents, the presence of water or the use of hydrated inorganic bases is preferable because the presence of water greatly accelerates the reaction (Scheme 2-29). The results of a kinetic study on the cross-coupling reaction of arylboronic



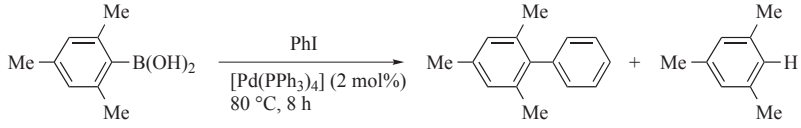
base	conversion (%)
K_3PO_4/nH_2O (n = ca. 2.2)	100
K_3PO_4	79

Scheme 2-29 Stoichiometry of water and bases.

acid with a bromoarene for the synthesis of the drug losartan showed that the overall stoichiometry required 2 equiv. water and 2 equiv. K_2CO_3 [199]. The reaction requires 1 equiv. water and 1 equiv. K_2CO_3 for the formation of $[ArB(OH)_3]K$. As the coupling reaction produces $B(OH)_3$, another equivalent each of water and K_2CO_3 is used to neutralize the boric acid. Thus, the reaction rate is unchanged when anhydrous K_2CO_3 is substituted for $K_2CO_3 \cdot 1.5H_2O$. Since organoboronic acid is easily dehydrated to boroxine with the elimination of 1 equiv. water, such water can also be supplied from arylboronic acids [33]. The cross-coupling reaction of **151** with 2-cyanophenylboronic acid in aqueous media suffered from incomplete conversion due to very rapid hydrolytic B-C bond cleavage [200]. On the other hand, the reaction was also not completed under strictly anhydrous conditions using boronic ester and anhydrous K_3PO_4. It finally furnished the drug **152** within 1 h when the water content was optimized by using a boronic ester and hydrated $K_3PO_4 \cdot nH_2O$ ($n = 2 \sim 3$). Since the system is heterogeneous, a finely powdered $K_3PO_4 \cdot nH_2O$ with a particle size of about 240 μm is much more effective than that with a size of 410 μm. Such an accelerating effect of water is commonly observed in most coupling reactions of organoboron compounds.

2.4.2.2 **Effect of bases**

Although Na_2CO_3 is a mild base that is effective for a wide range of coupling reactions of arylboronic acids, it is not suitable for reactants that are sterically hindered by several *ortho*-substituents. The reaction of mesitylboronic acid with iodobenzene shows the following order of reactivity: TlOH > $Ba(OH)_2$, Tl_2CO_3 > NaOH > Cs_2CO_3, K_3PO_4 > Na_2CO_3 > $NaHCO_3$ [201] (Scheme 2-30). Since thallium bases are poisonous and not effective for other arylboronic acids or haloarenes, $Ba(OH)_2$ has been used for the synthesis of sterically hindered tri-*ortho*-substituted biaryls [202]. Cesium bases such as Cs_2CO_3 and CsOH exhibit a greater accelerat-



base	DME/H_2O[a]	benzene/H_2O[a]
Na_2CO_3	50 (1)	25 (6)
Cs_2CO_3	93 (0)	-
K_3PO_4	70 (0)	-
NaOH	95 (2)	82 (18)
$Ba(OH)_2$	99 (2)[b]	92 (13)
TlOH	74 (20)	91 (20)

[a]Yields of mesitylene are in parentheses.
[b]After 4 h.

stability constants for X^- (log K at 25 °C)

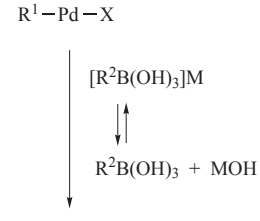
	K^+	Cs^+	Ba^{2+}	Bu_4N^+	Tl^+	Cu^+	Ag^+
Cl^-	(-0.7)	(-0.39)	(-0.13)	(0.40)	0.49	2.7	3.3
Br^-	-	(0.03)	-	(0.49)[a]	0.91	5.9	4.7
I^-	(-0.19)	(-0.03)	-	(0.78)	-	8.9	6.6

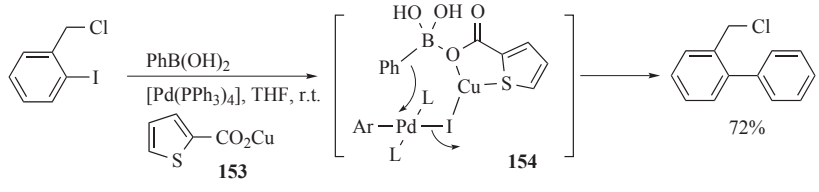
[a]for $(C_3H_7)_4N^+$

stability constants for OH^- (log K at 25 °C)

Li^+	Na^+	K^+	Cs^+
0.36	-0.2	-0.5	-

Displacement of Pd-X (Scheme 2-12)

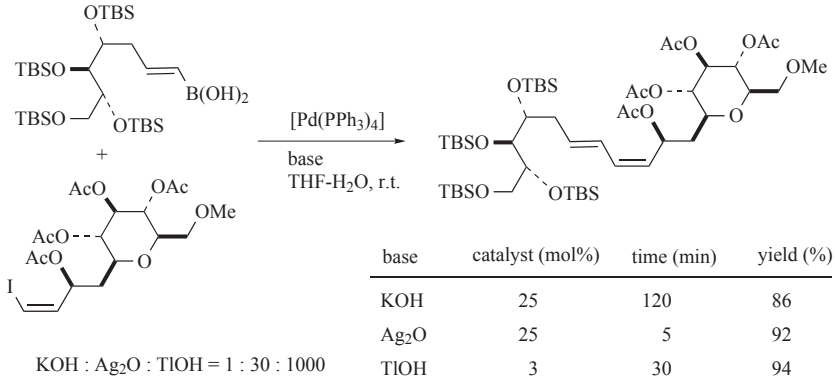




Scheme 2-30 Effect of bases for aryl-aryl coupling.

ing effect than sodium or potassium salts. The advantage of a combination of silver(I) salt and an inorganic base has been repeatedly reported in recent publications [73, 203].

Such effect of bases can be roughly estimated by the basic strength and affinity of counter cations for halide ions (stability constant) [204]. The transmetallation involves nucleophilic displacement of R^1-Pd-X with $[R^2B(OH)_3]M$, yielding R^1-Pd-R^2, $B(OH)_3$, and MX for the mechanism shown in Scheme 2-12, and the mechanism in Scheme 2-13 proceeds *via* displacement of R^1-Pd-X with MOH. Thus, the reaction can be fast for counter cations (M^+) that have a high stability constant for halide ions ($Ag^+ > Tl^+ >> Ba^{2+} > Cs^+ > K^+$). The concentration of hydroxyborate anion $[R^2B(OH)_3]M$, which exists in an alkaline solution in equilibrium with a free



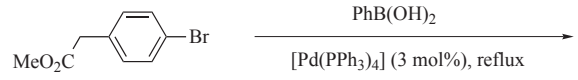
base	catalyst (mol%)	time (min)	yield (%)
KOH	25	120	86
Ag_2O	25	5	92
TlOH	3	30	94

KOH : Ag_2O : TlOH = 1 : 30 : 1000

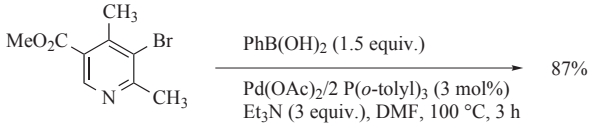
Scheme 2-31 Effects of bases for alkenyl-alkenyl coupling in the synthesis of palytoxine.

organoboronic acid, increases by increasing the basic strength ($OH^- > MPO_4^- > MCO_3^- > HCO_3^-$). The stability constant of Cs^+ for OH^- is not known, but it becomes smaller as we move down the periodic table ($Cs^+ < K^+ < Na^+ < Li^+$). Thus, it is reasonable to assume that cesium bases yield a higher concentration of $[R^2B(OH)_3]Cs$ than do the corresponding smaller alkali metals. The counter cation may also affect the solubility of $[R^2B(OH)_3]M$ in organic solvents. For example, $[ArBF_3]NBu_4$, which is soluble in a wide range of polar and nonpolar organic solvents, completes the coupling reaction within a shorter reaction time than does highly insoluble $[ArBF_3]K$ [36]. Copper 2-thiophenecarboxylate (**153**) is a unique base that mediates the cross-coupling reactions of organic iodides [205] and sulfides [206, 207] at room temperature under almost-neutral conditions. A six-membered transition state consisting of three reactants (**154**) has been proposed in the mechanism of transmetallation. The formation of Ar-Pd-O_2CR by displacement of R^1-Pd-X with RCO_2Cu is an alternative process discussed in Scheme 2-13. In both mechanisms, the driving force can be rationalized by a strong affinity of Cu^+ for I^-, and presumably also for RS^-.

Cross-coupling reactions of 1-alkenylboronic acids with 1-halo-1-alkenes require a stronger base than those of arylboronic acids, with the order of efficiency being $K_2CO_3 < K_3PO_4 < KOH < Ag_2O < TlOH$ [208] (Scheme 2-31). Among these bases, aqueous TlOH exhibits an exceptionally strong accelerating effect, completing the reaction within 1 h at room temperature. The high stability constant of the highly insoluble metal halides formed by the thallium cation enables smooth transmetallation at room temperature. These significantly mild conditions, when modified by Kishi and coworkers, were very successful for the synthesis of palytoxine, which has a molecular weight of 6754 Da in its protected form [209]. The applicability for the synthesis of such a large molecule and the significantly mild conditions achieving 70 % yield within 1 h at room temperature have had a great impact not only on the cross-coupling chemistry of organoboron compounds but also on the related chemistry of other organometallic reagents.



fluoride (equiv.)	solvent	time (h)	yield (%)
Bu_4NF (2)	MeOH/DME (1/2)	8	80
CsF (2)	MeOH/DME (1/2)	8	95
CsF (2)	DME	2	100
KF (2)	MeOH/DME (1/2)	8	91
KF (2)	PhMe/H_2O (1/1)	6	98

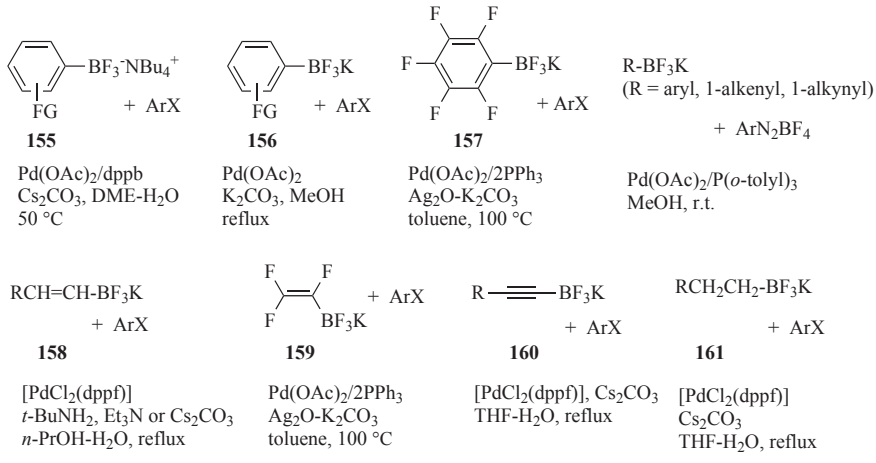


Scheme 2-32 Fluoro and amine bases for base-susceptible reactants.

Fluoride salts such as CsF, Bu_4NF, or Bu_4NHF_2 (2–3 equiv.) are very mild for reactants sensitive to bases [210] (Scheme 2-32). Although the reaction is slow for sterically crowded halides or boronic acids, a wide range of functional groups can be tolerated. The use of a combination of arylboronic esters and fluoride salts under strictly anhydrous conditions is advantageous for boronic acids that are sensitive to hydrolytic B-C bond cleavage [211]. Triethylamine and other amines are less efficient than inorganic bases, but they function well in DMF at 100 °C or in refluxing EtOH for relatively electron-deficient aryl halides [212, 213].

2.4.3 Coupling Reactions of $[RBF_3]K$

Coupling reactions of organotrifluoroborates $[RBF_3]K$ have been extensively studied because of the simplicity of the preparation of pure and stable crystalline material compared to the preparation of the corresponding boronic acids (Scheme 2-33). Representative boron reagents, including aryl- (**155** [36], **156** [214], **157** [215]), 1-alkenyl- (**158** [37, 216], **159** [215]), 1-alkynyl (**160** [217]), and alkylboron derivatives (**161** [218]), have been easily synthesized and successfully used for cross-coupling reactions with organic halides in the presence of bases. On the other hand, the reaction of ArN_2BF_4 exceptionally proceeds under neutral conditions [115b,d], as shown in Scheme 2-15. $[RBF_3]K$ obtained by treatment of boronic acids with KHF_2 [36]. K^+ salts are generally insoluble in common organic solvents and require polar solvents such as MeCN and H_2O at high temperatures. Bu_4N^+ salts (**155**), which are soluble in a wide range of polar and nonpolar organic solvents, are prepared by sequential treatment of organoboronic acids with HF and Bu_4NOH [36]. Although both salts undergo various cross-coupling reactions, Bu_4N^+ salts often afford yields that are 25–50 % greater than the corresponding K^+ salts due to their higher solubility in organic solvents, and presumably also due to the higher

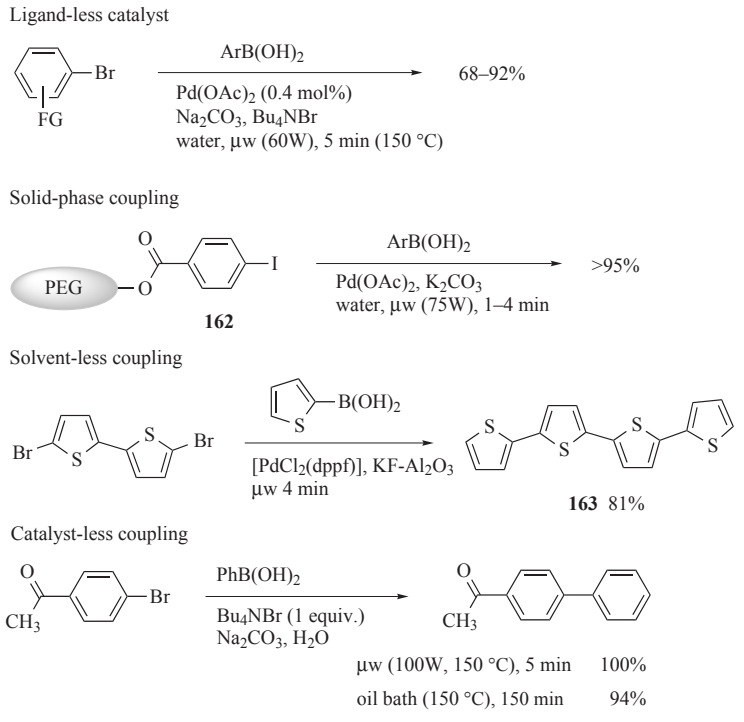


Scheme 2-33 Cross-coupling reactions of organotrifluoroborates.

stability constant of Bu_4N^+ for halide anions. Alternatively, the catalytic use of Bu_4NI (*ca.* 10 %) in the presence of the K^+ salts may give comparable results to those obtained using pure Bu_4N^+ salts. $[RBF_3]K$ is a boron species that has been speculated to participate in the transmetallation step of a fluoride base-assisted cross-coupling reaction [210]; however, it induces no reaction in the absence of both water and a base, analogously to related reactions of organoboronic acids or esters. Thus, $[RBF_2(OH)]^-$ or $[RBF(OH)]^{2-}$ generated by hydrolysis of trifluoroborate salts in (basic) aqueous solution have been proposed as boron species that participate in the transmetallation [36].

2.4.4
Microwave-Assisted Reactions

The effect of microwave irradiation has not yet been fully elucidated; however, it is significant that many metal-catalyzed reactions are completed within a few minutes. Since polar solvents efficiently absorb microwaves, reactions have been carried out in water, ethylene glycol, or DMF (Scheme 2-34). The use of microwaves was first reported in 1996 both for homogeneous [219] and solid-phase coupling reactions of arylboronic acids [220]. Microwave irradiation significantly increases the efficiency of ligandless palladium acetate. The reactions with aryl iodides, bromides, and activated chlorides in water in a sealed ampoule are completed within 5 min with a 0.4 mol % catalyst loading [221]. Microwave irradiation is also efficient for solid-phase coupling reactions, which have been used extensively in combinatorial syntheses for the discovery of new drugs. The thermal reaction of **162** at 70 °C suffers from competitive saponification of the ester group due to slow reaction on the resin surface, but this side reaction is suppressed by shorting the reaction time to 4 min under microwave conditions [222]. A solid-phase system consist-

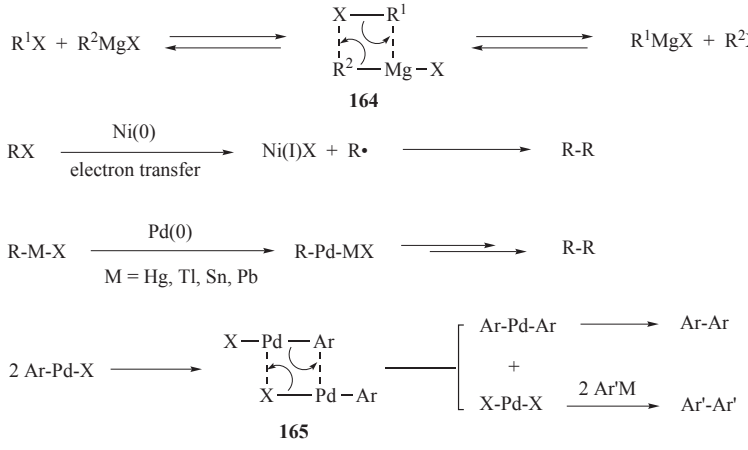


Scheme 2-34 Microwave-assisted cross-coupling.

ing of 40 % KF-γ-alumina and a palladium catalyst allows the coupling reaction of aryl- or 1-alkenylboronic acids at 100 °C without the use of any solvents [173]. Microwave irradiation is very efficient for such a highly heterogeneous system. The protocol furnishes oligothiophenes such as **163** within 4 min at 80 °C [223]. It is significant that microwave irradiation has recently enabled arylation of bromoarenes in the absence of any metal catalyst [101]. Arylboronic acids directly arylate bromoarenes possessing an electron-withdrawing or -donating group in the presence of Bu_4NBr (1 equiv.) and Na_2CO_3 in water. Although conventional heating at 150 °C is limitedly effective for activated bromides, microwave irradiation enables reactions of both activated and deactivated bromoarenes to be completed within 5 min.

2.5 Side Reactions

Representative side reactions giving undesirable homocoupling products are summarized in Scheme 2-35. Cross-coupling reactions of organomagnesium and zinc reagents have suffered from homocoupling resulting from metal-halogen exchange

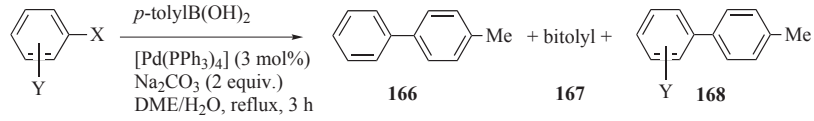


Scheme 2-35 Homocoupling in Pd- and Ni-catalyzed reactions.

reaction, presumably *via* **164**. Homocoupling of electrophiles has been reported in the oxidative addition to nickel(0) complexes *via* an electron transfer mechanism [224]. The oxidative addition of metal-carbon bonds to low-valent transition metals is another route leading to the formation of organometallic dimers [225]. The metathesis of R-M-X to R_2M and MX_2 (M = Ni, Pd) *via* **165** yields both dimers of electrophiles and organometallics when the transmetallation step is relatively slow due to the low nucleophilicity of organometallic reagents [226]. Although there are several probable processes leading to the formation of homocoupling products, these reactions do not disturb the coupling reactions of organoboronic acids with palladium or nickel catalysts.

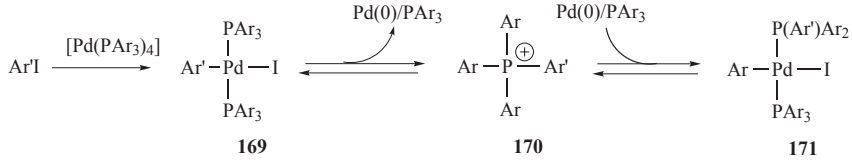
2.5.1
Participation of Phosphine-Bound Aryls

Triarylphosphines are excellent ligands for stabilizing the palladium species; however, there is an undesirable side reaction of aryl-aryl interchange between palladium- and phosphine-bound aryls, leading to the coupling product of phosphine-bound aryls [227]. A phenyl-coupling product (**166**) derived from triphenylphosphine is an important side-product with electron-rich haloarenes, whilst it is obtained in very small amounts with electron-deficient haloarenes [228] (Scheme 2-36). On the other hand, the presence of an *ortho*-substituent has an effect on the haloarene to reduce the yield of such a byproduct. It is also interesting to note that bromoarenes always afford a better selectivity than the corresponding iodides, though iodoarenes have been widely used due to their high reactivity to a palladium(0) complexes. Thus, phosphine-bound aryls can participate in the cross-coupling reaction of electron-rich haloarenes having no steric hindrance of an *ortho* substituent.



ArX	Hammett σ	distribution of biaryls (%)		
		166	**167**	**168**
p-$MeCOC_6H_4Br$	+ 0.847	< 1	1	98
m-$MeOC_6H_4Br$	+ 0.115	4	1	95
p-MeC_6H_4I	- 0.170	29	0	71
p-$MeOC_6H_4I$	- 0.268	49	3	48
p-$MeOC_6H_4Br$	- 0.268	33	1	66
o-$MeOC_6H_4Br$		0	2	98

Scheme 2-36 Participation of phosphine-bound aryls (**166**).

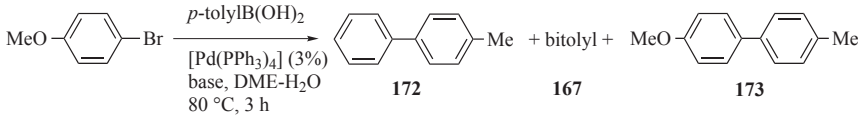


Ar	Ar'	interchange (%) (**171**)
4-$MeOC_6H_4$	C_6H_5	28
C_6H_5	4-$MeOC_6H_4$	99
C_6H_5	2-$MeOC_6H_4$	11
C_6H_5	4-MeC_6H_4	64
C_6H_5	2-MeC_6H_4	0
C_6H_5	4-$CF_3C_6H_4$	0
4-$CF_3C_6H_4$	C_6H_5	trace

statistical mixture

Scheme 2-37 Aryl-aryl interchange (**169** to **171**) at 50 °C for 1 h.

Aryl-aryl interchange is highly sensitive to electronic and steric effects of the phosphine ligand and the haloarenes [229–231] (Scheme 2-37). An electron-donating group in either phosphine or haloarenes increases the aryl-aryl interchange, whereas both electron-withdrawing groups and steric hindrance of an *ortho*-substituent, reversely, slow down the equilibration. Since the interchange of **169** to **171** proceeds through phosphonium salt formation (**170**) [232, 233], it is retarded by steric hindrance and is accelerated by electron-rich aryls stabilizing **170**. The results indicate the superiority of sterically bulky and low-donating phosphines as ligands of a palladium catalyst, but donating phosphines having large steric hindrance are generally recommended because of rapid oxidative addition of organic halides to coordinatively unsaturated and electron-rich palladium(0) com-



172 **167** **173**

base (equiv.)	conversion (%)	distribution (%)		
		172	**167**	**173**
Na_2CO_3 (2)	100	33	1	66
K_3PO_4 (2)	88	4	2	94
NaOH (3)	82	1	7	92

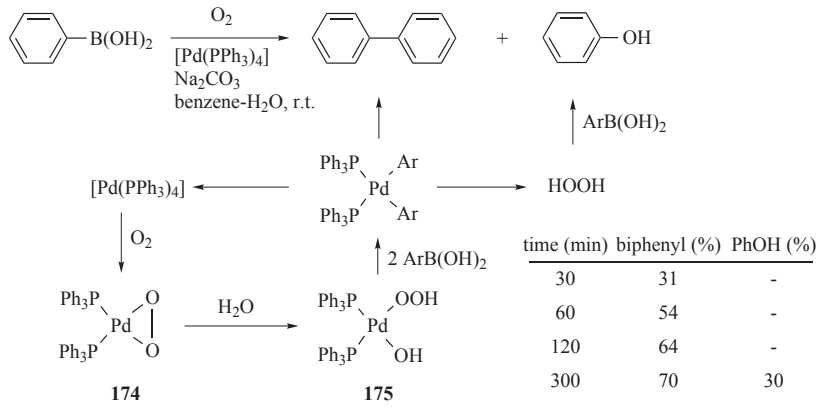
Scheme 2-38 Effect of bases on selectivity.

plexes. P(*o*-tolyl)$_3$, P(*t*Bu)$_3$, (dialkylphosphino)arenes (**105**), N-cyclic carbene (**109**), and N-ligands (**110–112**) have been successfully used to eliminate the participation of phosphine-bound aryls. The dppf complexes are better catalysts than the complexes of triphenylphosphine. The advantages of ligandless $Pd(OAc)_2$ are discussed in Scheme 2-22.

Aryl exchange occurs before transmetallation; thus, slow transmetallation due to steric and electronic reasons results in an increase in the participation of phosphine-bound aryls. The transmetallation is slowed down in electron-rich haloarenes, but strong bases will sufficiently accelerate transmetallation relative to aryl-aryl interchange. The phenyl coupling product **172** significantly decreases indeed in the order of basic strength: $Na_2CO_3 > K_3PO_4 >$ NaOH [228] (Scheme 2-38). Since the rate of transmetallation to R^1-Pd-X (**68**) is in the order of X = Cl > Br > I [234], the choice of haloarene also serves to minimize such a side-reaction.

2.5.2
Oxygen-Induced Homocoupling

The reactions shown in Scheme 2-35 may provide very small amounts of homocoupling products of arylboronic acids. However, a large degree of homocoupling has been often reported. In the experimental operation, careful consideration must be given to oxygen (Scheme 2-39). When the reaction mixture is exposed to air, arylboronic acids readily yield homocoupling products [228]. The reaction is slow under neutral conditions, but is very rapid in the presence of an aqueous base. It is also probable that such dimerization takes place during the work-up operation in air when there is unreacted arylboronic acid. Since the interaction between a palladium(0) complex and dioxygen yields a peroxopalladium(II) complex (**174**), which is susceptible to hydrolysis by water, a catalytic cycle involving transmetallation of two arylboronic acids with **175** is reasonable to presume [235]. Hydrogen peroxide thus generated oxidizes some of the arylboronic acids to phenols. The oxygen-induced dimerization of arylboronic acids is also discussed in Section 2.11.



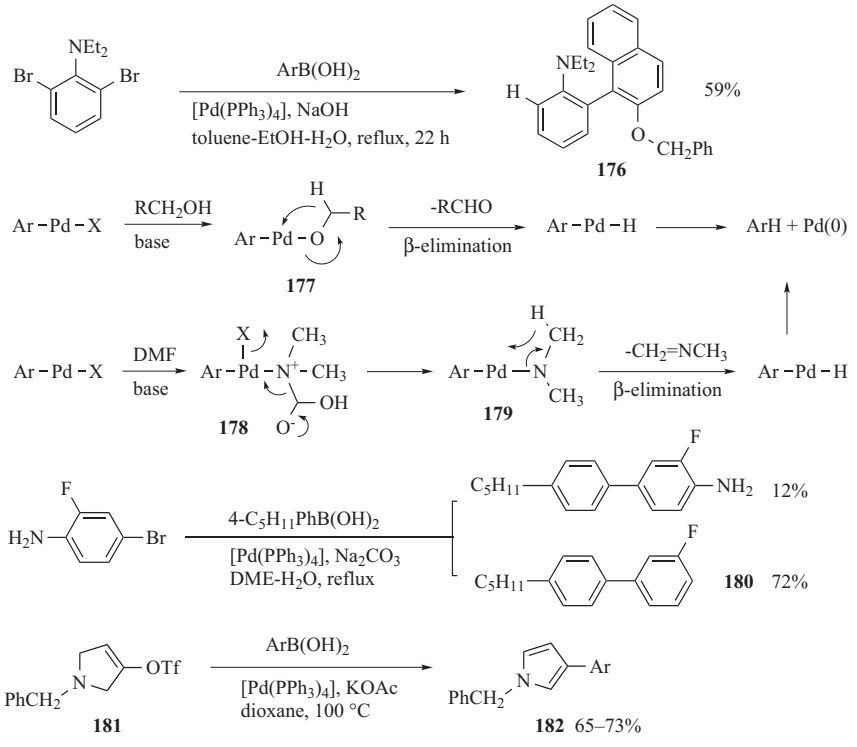
Scheme 2-39 Homocoupling of arylboronic acids induced by oxygen.

2.5.3
Dehalogenation, Deamination, and Dehydrogenation

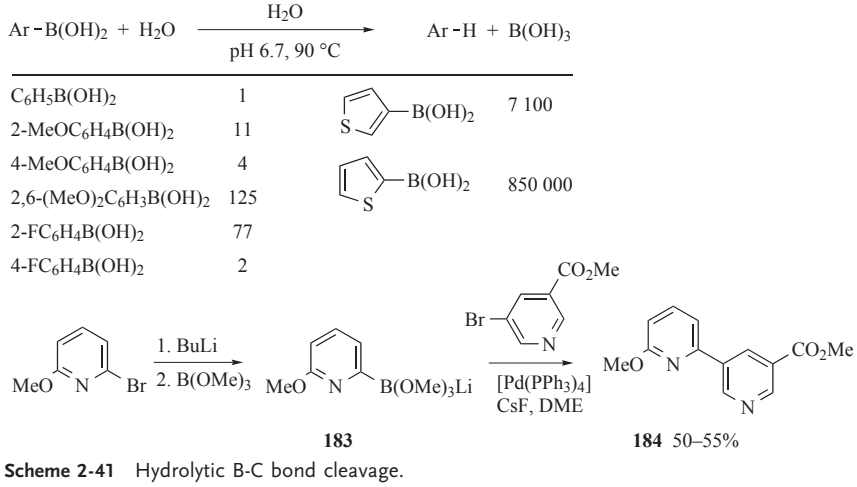
Cross-coupling reactions often result in dehalogenation of organic halides (RX to RH, **176**) [236], particularly when alcohols are used as the solvents (Scheme 2-40). In most cases, the hydride is derived from *β*-hydride elimination of Ar-Pd-OCH_2R (**177**), yielding Ar-Pd-H and RCHO [102, 237]. Such a side reaction has also been reported in the reactions of arylboronic esters, as hydrolysis yields alcohols as hydride donors, except the tertiary-alcohol esters such as pinacol [200a]. DMF is also assigned the role of hydride donor in the presence of a base (**178**, **179**), and dehalogenation is completely eliminated by replacing DMF with DMA [238]. The coupling reaction of 4-bromoaniline unexpectedly resulted in deamination ($ArNH_2$ to ArH) for an unknown reason [239]. The deamination predominates significantly when an *ortho*-fluoroaniline derivative is used as the electrophile (**180**). Since various transition metals catalyze the aromatization of cyclic alkenes and dienes, the reaction of 2,5-dihydropyrole triflate (**181**) with arylboronic acids directly affords pyrrole derivatives (**182**) *via* in-situ dehydrogenation [240].

2.5.4
Hydrolytic B-C Bond Cleavage (Protiodeboronation)

Even if there is no major steric hindrance, the reaction under aqueous conditions gives undesirable results due to competitive hydrolytic B-C bond cleavage. Such cleavage is accelerated by *ortho*-substituents, and significantly accelerated by adjacent heteroatoms in the boronic acid derivative [241, 242] (Scheme 2-41). There may be no difficulty in using 2-thiopheneboronic acid itself, but hydrolytic B-C bond cleavage is a serious side-reaction for more electron-deficient derivatives such as 3-formyl-2-thiopheneboronic acid [243] and bis(thiophene)boronic acids [244]. Weak bases such as aqueous $KHCO_3$ suppress the B-C bond cleavage [244]; however, anhydrous conditions, using a boronic ester and an anhydrous



Scheme 2-40 Dehalogenation, deamination, and dehydrogenation.

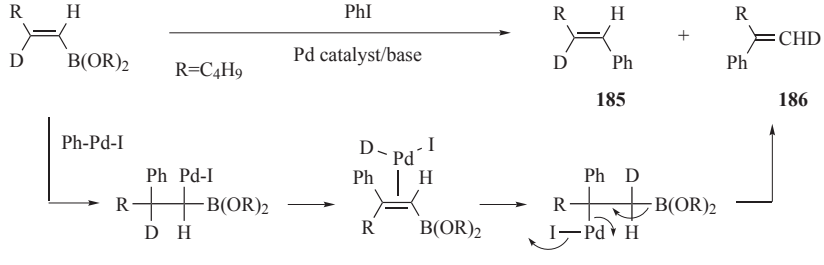


Scheme 2-41 Hydrolytic B-C bond cleavage.

base, are desirable for such reactants. A 1,3-bis(thiophene)boronic ester of 1,3-propanediol has been reported to be sufficiently stable in the presence of CsF in refluxing THF for carrying out biaryl-coupling without significant B-C bond cleavage (see Scheme 2-56) [211]. 2-Pyridylboronic acid does not give coupling products because of its very rapid protodeboronation. Thus, the in-situ preparation of an ate-complex (**183**) is directly followed by cross-coupling for the preparation of bipyridine derivatives (**184**) [245]; however, Negishi coupling of 2-pyridinylzinc reagents [246] or Stille coupling [247] of tin reagents are convenient alternatives for such reactions.

2.5.5
Heck-Type Coupling of B-Alkenyl Compounds (*ipso*-Coupling)

The reaction between 1-alkenylboronic acids and esters yields *ipso*-coupling products (**186**) when a ligandless palladium catalyst and a weak base such as triethylamine are used, whereas they are negligible with a combination of palladium-phosphine catalysts and strong bases [248] (Scheme 2-42). The formation of an *ipso*-coupling product is best understood by the mechanism of the Heck reaction for alkenyl compounds, which has been commonly observed for weakly nucleophilic compounds, such as 1-alkenylmercurials [249], -silanes [250], and -tin [251] compounds. A deuterium labeling study suggests an addition-elimination mechanism where a *β*-hydrogen transfers to the terminal carbon [248]. A highly selective *ipso*-coupling has also been reported in the platinum(0)-catalyzed reaction of 4-nitroiodobenzene with 1-hexenylboronic acid [190].



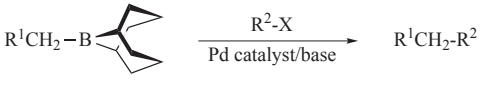
catalyst	base	solvent	time (h)	yield (%)	**185**/**186**
$[Pd(PPh_3)_4]$	NaOH	benzene	2	99	(100/0)
$Pd(OAc)_2$	NaOH	DMF	6	86	(56/44)
$Pd(OAc)_2$	Et_3N	DMF	20	94	(4/96)

Scheme 2-42 Heck-type coupling (*ipso*-coupling).

2.6
Reactions of B-Alkyl Compounds

Trialkylboranes, including 9-alkyl-9-BBN and alkyl(disiamyl)borane, readily undergo cross-coupling with 1-alkenyl or aryl halides or triflates [95] (Scheme 2-43). The reaction is limitedly used for primary alkylboranes; thus, hydroboration of terminal alkenes with 9-BBN or $HB(Sia)_2$ is the most convenient method to furnish the desired boron reagents. The trialkylboranes thus obtained are highly sensitive to air, but they can be used directly for the subsequent coupling reaction without isolation. The coupling reaction of organic iodides proceeds at room temperature in the presence of $[PdCl_2(dppf)]$ [95] or $[PdCl_2(dppf)]/2Ph_3As$ [260]. Since the presence of water greatly accelerates the reaction, the use of aqueous bases or hydrated inorganic bases such as $K_3PO_4 \cdot nH_2O$ is generally recommended [260]. On the other hand, solid sodium methoxide added to 9-alkyl-9-BBN dissolves in THF by forming the corresponding ate-complex, which enables coupling to occur under nonaqueous conditions at room temperature [95]. Treatment of 9-methoxy-9-BBN with primary-alkyllithiums is an alternative for in-situ preparation of analogous boron ate-complexes [252]. The presence of KBr (1 equiv.) is often critical to prevent decomposition of the catalyst for reactions of aryl and 1-alkenyl triflates [253]. Although the reactivity of trialkylboranes such as 9-alkyl-9-BBN is significantly higher than that of air-stable alkylboronic acids, it has been shown recently that they can be used for analogous cross-coupling reactions, as discussed in a later section. The cross-coupling reactions of B-alkyl compounds have been recently reviewed [7].

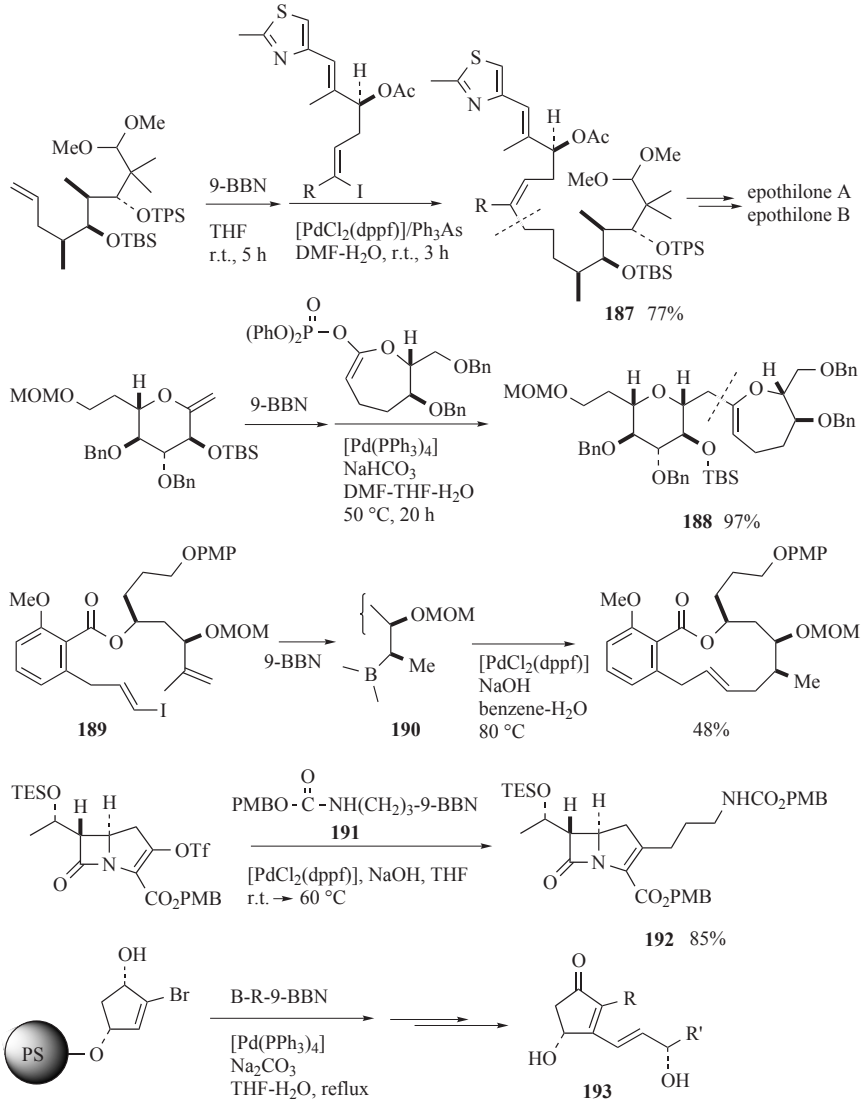
The connection of two fragments *via* the hydroboration-cross-coupling sequence has found a wide range of applications in the synthesis of natural products and



R^2-X	catalyst	base/solvent	temp (°C)	Ref.
alkenyl, aryl I, Br	$[PdCl_2(dppf)]$	$K_3PO_4 \cdot nH_2O$/DMF	r.t.→50	[95, 252–255]
alkenyl, aryl I, Br	$[PdCl_2(dppf)]$	NaOH/THF-H_2O	r.t.-reflux	[95, 256, 257]
alkenyl, aryl I, Br	$[PdCl_2(dppf)]$	NaOMe/THF	r.t.-reflux	[95, 258, 259]
alkenyl, aryl I	$[PdCl_2(dppf)]/AsPh_3$	Cs_2CO_3/DMF-H_2O	r.t.	[260–262]
aryl Br	$[Pd(PPh_3)_4]$	NaOH/toluene-H_2O	80	[263]
aryl Cl	$Pd(OAc)_2$/**109b**	KOMe/THF	reflux	[264]
aryl OTf	$[PdCl_2(dppf)]$	NaOMe/KBr/THF	reflux	[253, 265]
alkenyl I	$[PdCl_2(dppf)]/AsPh_3$	TlOEt/THF-H_2O	r.t.	[266]
alkenyl OTf	$[PdCl_2(dppf)]/AsPh_3$	Cs_2CO_3/KBr/DMF-H_2O	r.t.	[267]
alkenyl $OP(O)(OPh)_2$	$[Pd(PPh_3)_4]$	$NaHCO_3$/DMF-H_2O	50	[268]
alkyl Br	$Pd(OAc)_2/PCy_3$	K_3PO_4/THF	r.t.	[92]
alkyl Cl	$[Pd_2(dba)_3]/PCy_3$	CsOH/dioxane	90	[93]

Scheme 2-43 Conditions for alkyl-alkenyl, alkyl-aryl, and alkyl-alkyl coupling.

functional molecules [7] (Scheme 2-44). The bacterial metabolites epothilone A and B are powerful cytotoxic agents that function through stabilization of cellular microtubules. Hydroboration of the terminal alkene is directly followed by cross-coupling with iodoalkene to furnish the desired *cis*-alkene (**187**) [261, 269]. A general method for the convergent assembly of polyethers (e. g., **188**) based on the hydroboration-cross-coupling protocol has been developed. Triflates have been used for six-membered ketene acetals [267], but phosphates have been found to be better substrates for seven-, eight-, and nine-sized ketene acetals be-

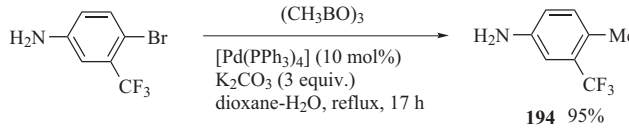


Scheme 2-44 Cross-coupling reactions of B-alkyl-9-BBN derivatives.

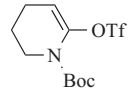
cause of their stability in alkaline solution [268, 270]. This strategy provides a highly convergent route for the synthesis of naturally occurring polycyclic ethers, including ciguatoxin [271]. Although the hydroboration of such polyfunctionalized alkenes is slow, and often requires a large excess of 9-BBN (3–5 equiv.), the remaining borane does not disturb the subsequent coupling reaction. The intramolecular version allows macrocyclization of (*E*)- or (*Z*)-iodoalkenes [266, 272]. Hydroboration of **189** with 9-BBN (5 equiv.) follows the Houk model for stereospecific synthesis of **190**, as shown in Scheme 2-1. The macrocyclization is carried out under high-dilution conditions by adding the borane solution *via* a syringe pump to a mixture of a palladium catalyst and NaOH in benzene-H_2O at 80 °C [272a]. The advantage of intramolecular B-alkyl coupling over the complementary ring-closing metathesis reaction is the higher degree of control of olefin geometry among the resulting macrocyclic adducts. Clinically useful 2-alkylcarbapenems (**192**) are synthesized *via* coupling reaction of the appropriate alkenyl triflate [273]. Protection of the amino group with a *t*-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), or *p*-methoxybenzyloxycarbonyl group (**191**) allows smooth hydroboration of allylic amines with 9-BBN and subsequent cross-coupling with organic halides for the synthesis of amine derivatives [254, 256, 274]. The B-alkyl coupling reaction proceeds readily on the polymer surface, as has been demonstrated in the preparation of members of several structurally distinct prostaglandin (PG) classes (**193**) [275].

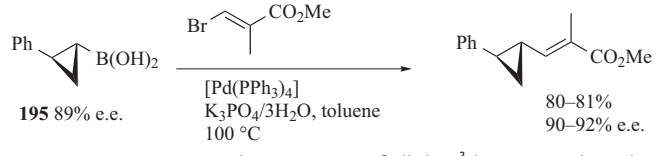
A hydroboration-cross-coupling strategy has been extensively studied in the synthesis of biologically active compounds, including: a novel class of glycomimetic compounds, aza-C-disaccharides [276]; sphingofungin F (which acts as a serinepalmitoyl transferase inhibitor) [262]; aloperine, a member of a rare family of C_{15} *Lupine* alkaloids [277]; 5-alkylresorcinols with DNA-cleaving properties [258]; a fungal metabolite, caloporoside [265]; (+)-aspicilin [278], an inhibitor of VCAN-1; (+)-halichlorine [279], a cytotoxic polyketide marine natural product, callystatin A [280]; a macrolide antibiotic, 5,6-dihydrocineromycin B [281]; natural and unnatural pinnanic acids which mediate anti-inflammatory properties [282]; a chemically and metabolically stable prostaglandin analogue, carbacyclin [283]; and enantiomerically pure *α*-amino acids [254, 256, 274, 284, 285].

The coupling reaction of alkylboronic acids and esters is slower than that of trialkylboranes, but it has recently been found that they also participate in the catalytic cycle of palladium-catalyzed cross-coupling (Scheme 2-45). Methylboroxine $(MeBO)_3$ or methylboronic acid alkylates bromoarenes with a common palladium/triphenylphosphine catalyst [286]. On the other hand, the coupling reactions of alkylboronic acids possessing *β*-hydrogen are achieved by the use of a dppf ligand for iodides, bromides, and triflates [203b, 218, 287, 288], Q-phos (**107**) for bromides, triflates, and chlorides [139], and N-cyclic carbene (**109b**) for arene diazonium salts [117]. Analogous reactions of alkyltrifluoroborates $[RBF_3]K$ are shown in Scheme 2-33. These reactions may be of limited use for primary alkylboronic acids; however, cyclopropylboronic acids such as **195** exceptionally alkylate various electrophiles, including aryl and 1-alkenyl halides or triflates [290] and acyl chlorides [291], without loss of stereochemistry of the cyclopropane ring.



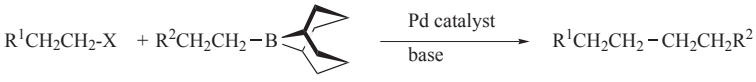
RCH=CHX or ArX $\xrightarrow[\text{catalyst, base}]{RCH_2CH_2B(OH)_2}$ RCH=CHCH$_2$CH$_2$R or ArCH$_2$CH$_2$R

$RCH_2CH_2B(OH)_2$	ArX	conditions	yield (%)	Ref.
$PhCH_2CH_2B(OH)_2$	4-ClC_6H_4OTf	[$PdCl_2$(dppf)], K_2CO_3, THF-H_2O, reflux	94	[218, 287]
n-$C_4H_9B(OH)_2$	ICH=CHR	[$PdCl_2$(dppf)], Ag_2O-K_2CO_3, THF, 80°C	90	[203b]
n-$C_4H_9B(OH)_2$	3-$MeOC_6H_4Cl$	[$Pd(dba)_2$]-**107**, K_3PO_4, toluene, 100 °C	94	[139]
$Br(CH_2)_4Bcat$	4-$MeC_6H_4N_2BF_4$	$Pd(OAc)_2$-**109b**, THF, r.t.	80	[116]
n-$C_4H_9B(OH)_2$		[$PdCl_2$(dppf)], K_2CO_3-Ag_2O, toluene, 80 °C	88	[288]

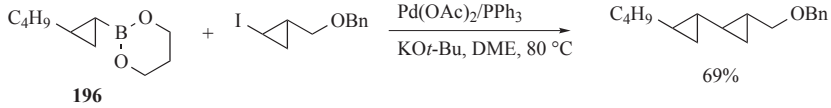


Scheme 2-45 Cross-coupling reactions of alkyl(sp^3)boronic acids and esters.

The sp^3-sp^3 C-C bond formation between alkyl derivatives has been much less successful among the possible combinations of different-type nucleophiles and electrophiles (Scheme 2-46). Difficulties arise from the oxidative addition of haloalkanes (RCH_2CH_2X) to a palladium(0) complex with accompanying formation of $RCH{=}CH_2$ and RCH_2CH_3, and from the susceptibility of alkylpalladium(II) intermediates to *β*-hydride elimination [292]. In spite of these difficulties, sp^3-sp^3 C-C bond formation occurs smoothly between primary alkyl halides and primary alkylboron compounds, where each reactant possesses *β*-hydrogen [92, 93, 292]. Since reductive elimination from a dialkylpalladium(II) complex occurs from an unsaturated three-coordinate species generated by dissociation of a phosphine ligand [293], monodentate phosphine complexes are more desirable than those of bidentate ligands. A complex prepared from $Pd(OAc)_2$ or [$Pd_2(dba)_3$] and PCy_3 (2 equiv.) has been found to be highly efficient for primary alkyl bromides, and even for chlorides. The reaction of 9-alkyl-9-BBN with bromoalkanes proceeds easily at room temperature [92], and chloroalkanes [93] react at 90 °C without significant *β*-hydride elimination. Since the conditions are compatible with a variety of functional groups – including potential ligands such as nitriles and amines – the protocol provides a very practical method for direct alkyl-alkyl coupling that has been long-awaited by synthetic organic chemists. Secondary alkyl-alkyl cross-coupling is used to a limited degree for cyclopropylboronic acids or esters (**196**) in the synthesis of symmetrical or unsymmetrical contiguous cyclopropanes [294]. A relatively strong base such as *t*BuOK shows a large accelerating effect.



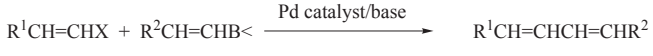
$R^1CH_2CH_2$-X	$R^2CH_2CH_2$	conditions	Ref.
Me-I	$MeO_2C(CH_2)_{10}$	$[Pd(PPh_3)_4]$, $K_3PO_4 \cdot nH_2O$, dioxane, 60 °C	[292]
n-C_6H_{13}-I	$MeO_2C(CH_2)_{10}$	$[Pd(PPh_3)_4]$, $K_3PO_4 \cdot nH_2O$, dioxane, 60 °C	[292]
n-$C_{12}H_{25}$-Br	*n*-C_8H_{17}	$Pd(OAc)_2/2PCy_3$, $K_3PO_4 \cdot nH_2O$, THF, r.t.	[92]
n-$C_{12}H_{25}$-Cl	*n*-C_8H_{17}	$[Pd_2(dba)_3]/2PCy_3$, $CsOH \cdot H_2O$, dioxane, 90 °C	[93]



Scheme 2-46 Alkyl-alkyl (sp^3-sp^3) coupling possessing β-hydrogen.

2.7
Reactions of B-Alkenyl Compounds

Cross-coupling reactions of 1-alkenylboron compounds with 1-alkenyl halides require a relatively strong base in the presence of a palladium/phosphine catalyst (Scheme 2-47). The relative rate depends upon the basicity and affinity of the counter cations for halide anions (TlOH > NaOH > K_3PO_4 > Na_2CO_3 > NaOAc) [102, 208]. Aqueous KOH has been used for 1-alkenylboronic acids or esters in refluxing THF-H_2O, DME-H_2O, or benzene-H_2O and aqueous LiOH for disiamylborane derivatives. In spite of its toxicity, TlOH is an excellent base that enables completion



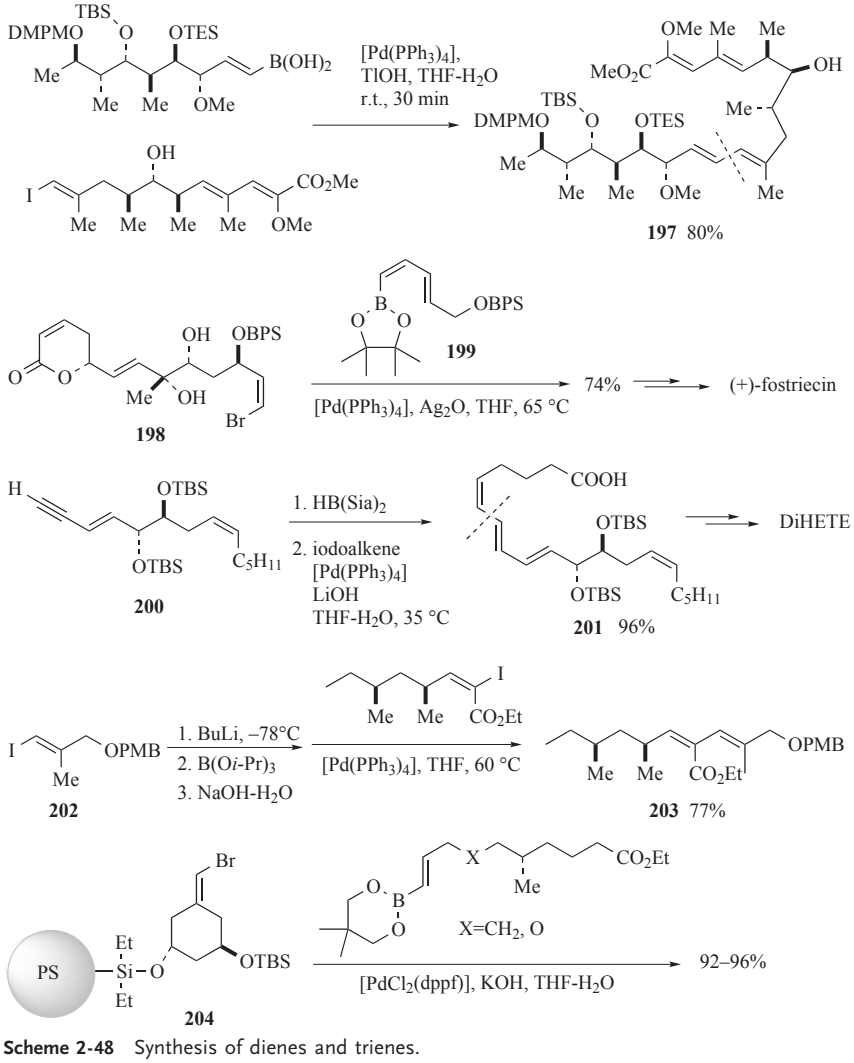
X	B<	catalyst	base/solvent	temp (°C)	ref.
Br	$B(OH)_2$	$[Pd(PPh_3)_4]$	NaOEt, benzene-EtOH	reflux	[102, 295]
I	$B(Sia)_2$	$[Pd(PPh_3)_4]$	LiOH, THF-H_2O	reflux	[296, 297]
I, Br	$B(OR)_2$	$[Pd(PPh_3)_4]$	NaOH, THF or DME-H_2O	reflux	[298–300]
I	$B(OH)_2$	$[Pd(PPh_3)_4]$	TlOH, THF-H_2O	r.t.	[209, 301, 302]
I	$B(OH)_2$	$[Pd(PPh_3)_4]$	TlOEt, THF-H_2O	r.t.	[303], 304]
I, Br	$B(OR)_2$	$[Pd(PPh_3)_4]$	NaOH, benzene-H_2O	70	[102, 305]
OTf	$B(OR)_2$	$[Pd(PPh_3)_4]$	$K_3PO_4 \cdot nH_2O$, dioxane	80	[253]
OTf	$B(OR)_2$	$[PdCl_2(PPh_3)_2]$	Na_2CO_3, THF-H_2O	40	[306]
OTf	$B(OH)_2$	$[PdCl_2(dppf)]$	KF, THF-H_2O	60	[307]

Sia = $CHMeCHMe_2$; $(OR)_2$ = dilo esters of boronic acids

Scheme 2-47 Conditions for alkenyl-alkenyl (sp^2-sp^2) coupling.

of the alkenyl-alkenyl coupling within a few hours at room temperature [208, 301, 302]. Since an aqueous solution of TlOH produces a brown-black precipitate even under careful storage conditions, the addition of TlOEt to aqueous THF was recently recommended as a suitable replacement for air-sensitive TlOH [303]. The reactions of $[RCH{=}CHBF_3]K$ are shown in Scheme 2-33.

Alkenyl-alkenyl cross-coupling affords stereodefined dienes, trienes, and further conjugated polyenes (Scheme 2-48). Hydroboration of terminal alkynes with catecholborane followed by hydrolysis provides various 1-alkenylboronic acids. The boronic acids thus obtained couple with iodoalkenes at room temperature when a thallium base is used in the presence of $[Pd(PPh_3)_4]$. The protocol has been suc-



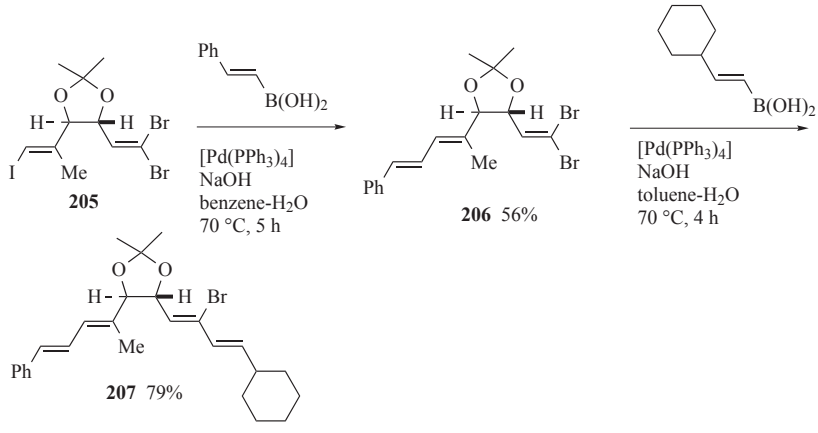
Scheme 2-48 Synthesis of dienes and trienes.

cessfully used for a number of syntheses of natural products, including (–)-bafilomycin A (**197**) [308, 309]. The (*Z,Z,E*)-triene structure in (+)-fostriecin [310] is synthesized by the cross-coupling reaction of (*Z,E*)-alkadienylboronic ester **199**, which is obtained *via* rhodium-catalyzed *Z*-selective hydroboration of terminal alkynes [18]. Disiamylborane is a chemo- and regioselective hydroboration reagent that strongly directs the addition of boron at the terminal carbon for conjugate enynes. Hydroboration of **200** with $HB(Sia)_2$ is directly followed by cross-coupling for the synthesis of DiHETE via **201** [297]. Aqueous LiOH is recognized as being the best base for achieving high yields for disiamylborane derivatives. Transmetallation between alkenyllithium compounds and trialkyl borates is a general method for obtaining 1-alkenylboron compounds that are not available by hydroboration. One-pot, sequential reactions of **202** involving lithium/halogen exchange, boron/lithium exchange and cross-coupling provide the desired diene (**203**) as a single stereoisomer [311]. Synthesis on a solid support has recently played an important role in parallel synthesis and combinatorial chemistry, particularly in the field of drug discovery. Alkenyl-alkenyl coupling for the synthesis of vitamin D_3 derivatives proceeds on a resin surface (**204**) in high yields under typical conditions for alkenyl-alkenyl coupling [312].

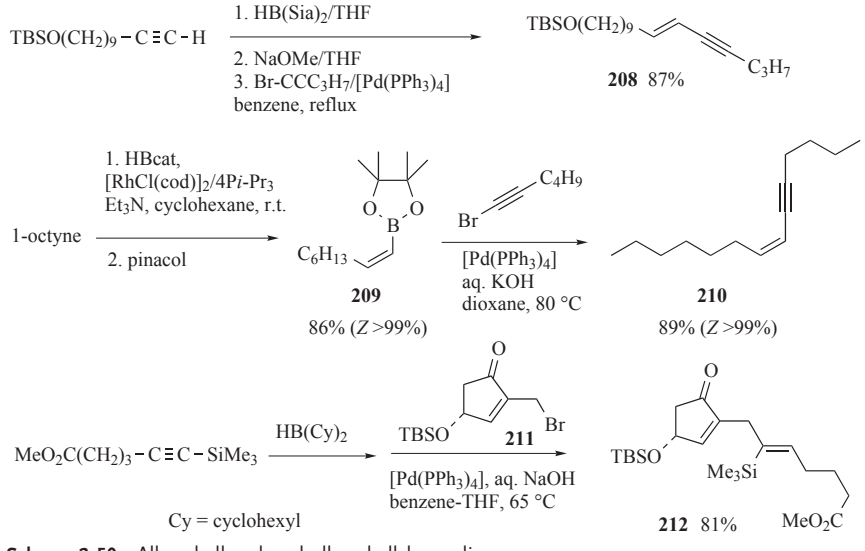
Since a variety of 1-alkenylboron compounds, including (*E*)- and (*Z*)-isomers, are now available, the alkenyl-alkenyl coupling reaction has been used for the synthesis of various biologically active natural products, including: a macrolide antibiotic, rutamycin B [313]; (5*Z*,8*Z*,10*E*,12*R*,14*Z*)-12-hydroxy-5,8,10,14-icosatetraenoic acid [(12R)-HETE] [314], an antiproliferative agent; (+)-curacin A [298], an aglycone of chlorothricin; (–)-chlorothricolide [315], a member of a small family of C_{15} lupinine alkaloids; (+)-aloperine [316], restrictinols that exhibit antifungal activity [317]; marine alkaloids, (–)-lepadins A, B, and C [318]; a highly unsaturated 20-membered macrocyclic system having four carbohydrate units, apoptolidin [14]; and cytotoxic substances FR 182877 and clinic acid [319]. The synthesis of polyene natural products *via* metal-catalyzed protocol has recently been reviewed [320].

Iodo- and bromoalkenes or arenes are well differentiated by palladium/phosphine catalysts, thus allowing a stepwise double-coupling of two different alkenylboronic acids for **205** [305] (Scheme 2-49). Since the oxidative addition is highly susceptible to the steric hindrance of the β-substituent *cis* to the carbon-halogen bond, the monocoupling of the 1,1-dibromoalkene moiety (**206**) selectively occurs at the less-hindered *trans*-C-Br bond [295, 302, 321]. This strategy is used for the sterodirected synthesis of polyunsaturated butenolides such as peridinin [305]. Analogous stepwise double-coupling of two different organoboronic acids has been reported for (*E*)-CHI=CHCl [322], (*E*)-CHCl=CHCl, and $Me_3SiCH{=}CHCH{=}CHI$ [40].

Due to the difficulty in purifying a stereoisomeric mixture, the stereoselective method is critical for the synthesis of natural products that involve enyne or diene structures. Alkenyl-alkynyl coupling reactions provides a method for synthesizing such enynes or dienes (Scheme 2-50). The reaction between (*E*)-1-alkenylborane and 1-bromo-1-alkyne stereoselectively provides (*E*)-enyne (**208**), which is then converted into (*E,Z*)-hexadeca-10,12-dienal, a sex pheromone of the melon worm [323]. On the other hand, (*Z*)-enyne (**210**) is obtained from the correspond-



Scheme 2-49 Sequential double coupling.



Scheme 2-50 Alkenyl-alkynyl and alkenyl-allyl coupling.

ing coupling reaction of the (*Z*)-1-alkenylboron compounds (**209**) [324]. The synthesis of PGE_1 derivatives (**212**) is achieved by alkenyl-allyl cross-coupling [325]. Since a 4-silyloxy group is susceptible to base-induced elimination and an ester group to saponification, the reaction is carried out in a two-phase system, in which the organic and basic aqueous phases are separated. The total syntheses of monocillin I and radicicol involve an analogous hydroboration-cross-coupling sequence [326].

2.8
Reactions of B-Aryl Compounds

The mixed Ullman reaction in which two haloarenes couple in the presence of copper powder is still commonplace in industrial processes, but the catalyzed cross-coupling reactions of organometallic reagents appear to be productive and provide reliable results in the synthesis of unsymmetric biaryls [5]. Various combinations of catalysts, bases, and solvents allow biaryl coupling of arylboronic acids with aryl halides or triflates if there are no side-reactions such as hydrolytic B-C bond cleavage or participation of phosphine-bound aryls (Scheme 2-51). The representative reaction conditions are summarized in the scheme, and the effects of catalysts and bases are discussed in Sections 2.4.1 and 2.4.2.

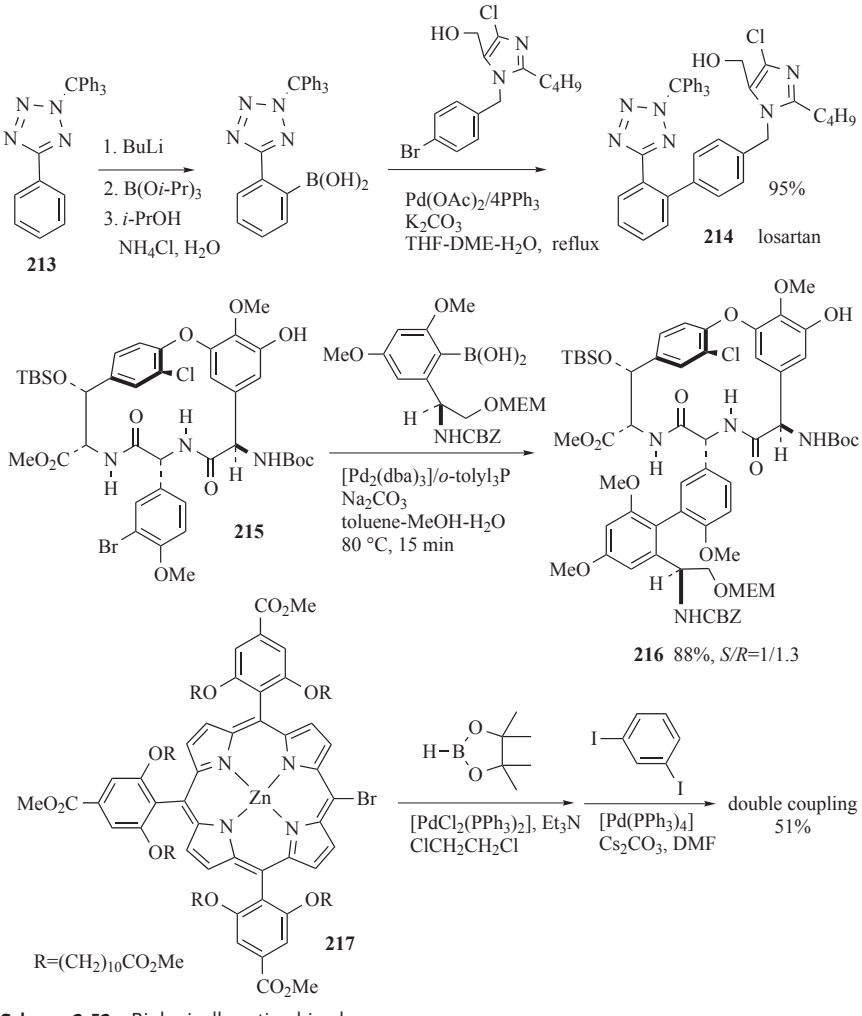
$$Ar^1X + Ar^2B(OR)_2 \xrightarrow{\text{Pd catalyst, base}} Ar^1\text{–}Ar^2$$

X=	catalyst	base/solvent	temp (°C)	Ref.
I, Br	$[Pd(PPh_3)_4]$	$NaHCO_3$ or Na_2CO_3, DME-H_2O	reflux	[327–329]
I, Br, OTf	$[Pd(PPh_3)_4]$	$K_3PO_4 \cdot nH_2O$, dioxane or DMF	80	[50, 253, 330]
I, Br	$[Pd(PPh_3)_4]$	CsF, DME	reflux	[210, 331]
I, Br	$[Pd(PPh_3)_4]$	Na_2CO_3, MeOH-H_2O	reflux	[332, 333]
I, Br, OTf	$[Pd(PPh_3)_4]$	Na_2CO_3 or K_3PO_4, toluene-H_2O	80–100	[334–336]
I, Br, OTf	$[Pd(PPh_3)_4]$	$Ba(OH)_2$, DME-H_2O	reflux	[201b, 202]
I	$[Pd(PPh_3)_4]$	2-thienylCO_2Cu, THF	r.t.	[205]
Br	$Pd(OAc)_2$	K_2CO_3, Bu_4NBr-H_2O	70	[161, 162]
I	$Pd(OAc)_2$	K_2CO_3 or Cs_2CO_3, acetone-H_2O	reflux	[159]
Br	Pd/C	K_2CO_3, EtOH-H_2O	r.t.	[166, 167]
Br, Cl	$[Pd_2(dba)_3]$/*t*-Bu_3P	Cs_2CO_3, dioxane	r.t.	[134]
Br, Cl	$[Pd_2(dba)_3]$/**105b**	K_3PO_4, toluene	80–100	[135]
Br, Cl	$[Pd_2(dba)_3]$/**109a**	Cs_2CO_3, dioxane	80	[143]
Br, Cl	$[Pd(dba)_2]$/**107**	KF, dioxane	100	[139]
Br, Cl	$PdCl_2$/**104**	K_2CO_3, THF-H_2O	reflux	[142]
Cl, OSO_2Ar	$[NiCl_2(dppf)]$	$K_3PO_4 \cdot nH_2O$, dioxane	80	[130, 192]
Cl	$[NiCl_2(PPh_3)_2]$	$K_3PO_4 \cdot nH_2O$, toluene	80	[131]
N_2BF_4	$Pd(OAc)_2$	MeOH-H_2O	reflux	[115–117]

Scheme 2-51 Conditions for aryl-aryl coupling.

2.8.1
Unsymmetric Biaryls

The first synthesis of unsymmetric biaryls *via* a cross-coupling reaction of arylboronic acids was reported in 1981 [337]. Following this discovery, numerous syntheses of natural and unnatural biaryls have been explored [5] (Scheme 2-52). Starting with **213**, the *ortho*-metallation-cross-coupling sequence provides a one-pot, two-



Scheme 2-52 Biologically active biaryls.

step procedure for the synthesis of the angiotensin II receptor antagonist losartan **214**, which plays a critical role in the regulation of blood pressure [338]. A highly efficient, convergent approach overcomes many of the drawbacks associated with previously reported syntheses, thus providing a method for large-scale industrial preparations (Merck, *ca.* 1000 kg per year). The biaryl coupling of arylboronic acid furnished the AB biaryl ring system of the vancomycin aglycone with a mixture of two atropisomers (**216**, $S/R = 1/1.3$), which is then thermally equilibrated to the natural isomer [339]. A palladium/triphenylphosphine or dppf complex is unsuccessful, but the preparation of a highly unsaturated palladium catalyst from $Pd_2(dba)_3$ and P(*o*-tolyl)$_3$ completes such a sterically crowded combination within

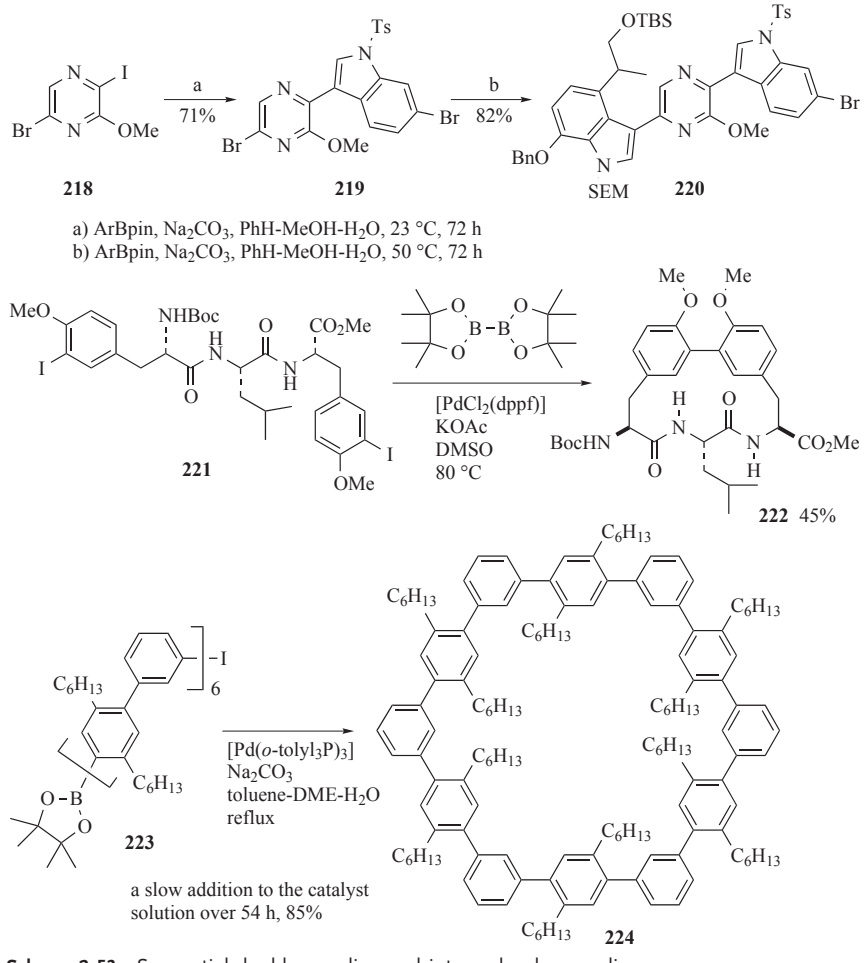
15 min at 80 °C. Bisporphyrin-based synthetic receptors, having large contact surface areas that bind to DNA intercalators as guests with unprecedented affinity in water, are synthesized by a sequential double cross-coupling reaction. The borylation of bromoporphyrin (**217**) with pinacolborane is followed by cross-coupling with 1,3-diiodobenzene to give a bisporphyrin receptor that has a molecular weight of 4198 Da [340].

Biaryls are useful in designing functional molecules and materials. The semi rigid structure which is caused by restricted rotation allows the rational design of various molecular recognition compounds, including drugs. Coupling reactions of arylboronic acids have provided porphyrin derivatives [340–342], molecular-scale motors that rotate by chemical power or light [334, 343], photoswitchable electron transfer aromatic compounds for the design of molecular photonic devices [344], single-layer 2,5-diarylsilole electroluminescent devices [345], chiral sensory materials based on 1,1′-binaphthyl oligomers [346], stable thioaminyl radicals [347], dendrimers [348], polycyclic aromatic materials [349], and a promising lead for synthesis of a reversible proteasome inhibitor TMC-95A [54]. The mild reaction conditions, broad tolerance for functional groups, and high reaction conversions on a polymer surface are suitable for creating combinatorial libraries of various pharmaceutically or materially interesting lead structures [244, 350].

Stepwise double-coupling of two different arylboronic acids with a dihaloarene affords a one-pot, two-step method for synthesizing unsymmetrical teraryls, quateraryls, and other higher-order polyaryls (Scheme 2-53) [351]. The first total synthesis of dragmacidin D (**220**) involves a sequential double-coupling of two different pinacol 3-indoleboronic esters (ArBpin) [351a]. The coupling positions are well differentiated between C-I and C-Br bonds in the pyrazine ring (**218**) when the reaction is carried out at room temperature. The second coupling also needs precise temperature control to keep the C-Br bond in the indole ring intact. A new intramolecular reaction for the synthesis of cyclic biaryls or polyaryls has recently been developed. Ring closure *via* an intramolecular coupling has been applied to the synthesis of biaryl-bridged macrocycles [352]. The desired **222** is obtained in 45 % yield when diiodide (**221**) in DMSO (0.02 *M*) is treated with bis(pinacolato) diboron (**13**) under standard conditions as required for the borylation of haloarenes. Difficulties arising from competition between monoborylation and bisborylation, and between intramolecular and intermolecular reactions, can be overcome by using high-dilution of the ω-haloarylboron compound. The high-dilution method in which (ω-iododododecaphenyl)borate (**223**) is added to the catalyst solution by using a syringe pump furnishes macrocyclic oligophenylene (**224**) in 85 % yield [353].

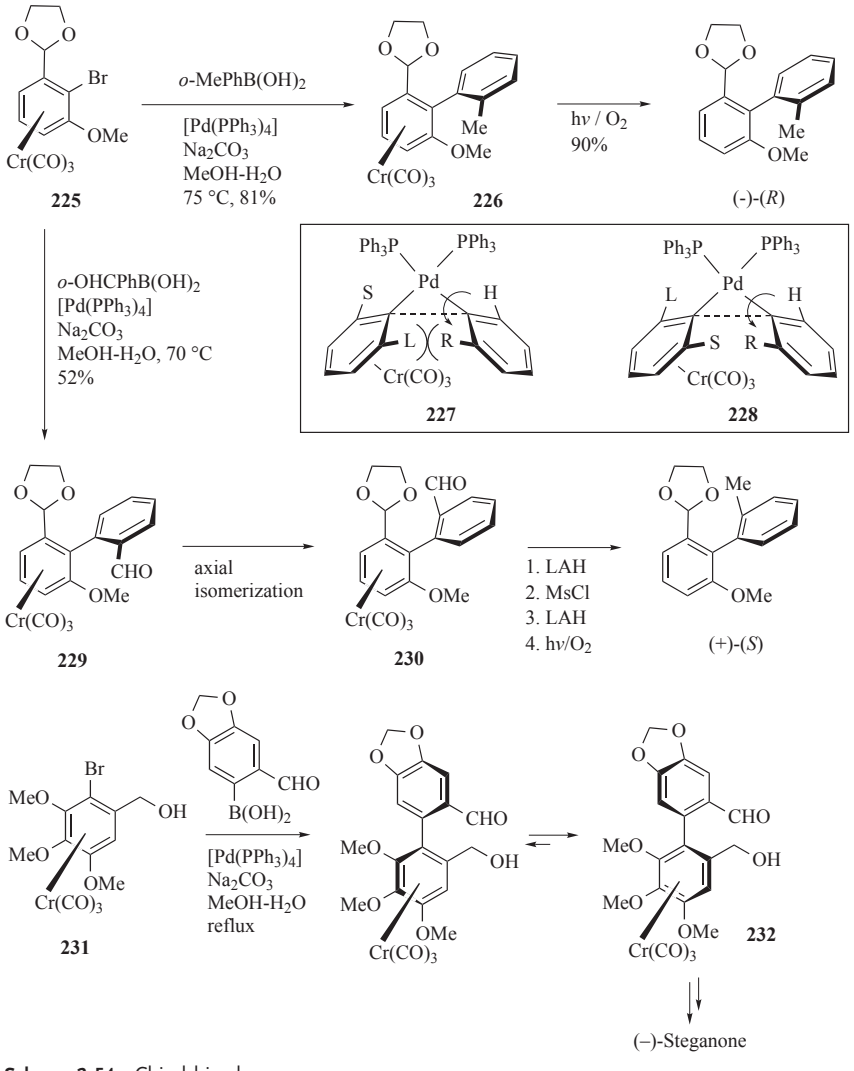
2.8.2 Chiral Biaryls

Biaryls with axial chirality are of potential importance not only as chiral ligands for asymmetric reactions but also as intermediates in the synthesis of biologically active natural compounds. An arene-$Cr(CO)_3$ complex (**225**) exists in two enantio-



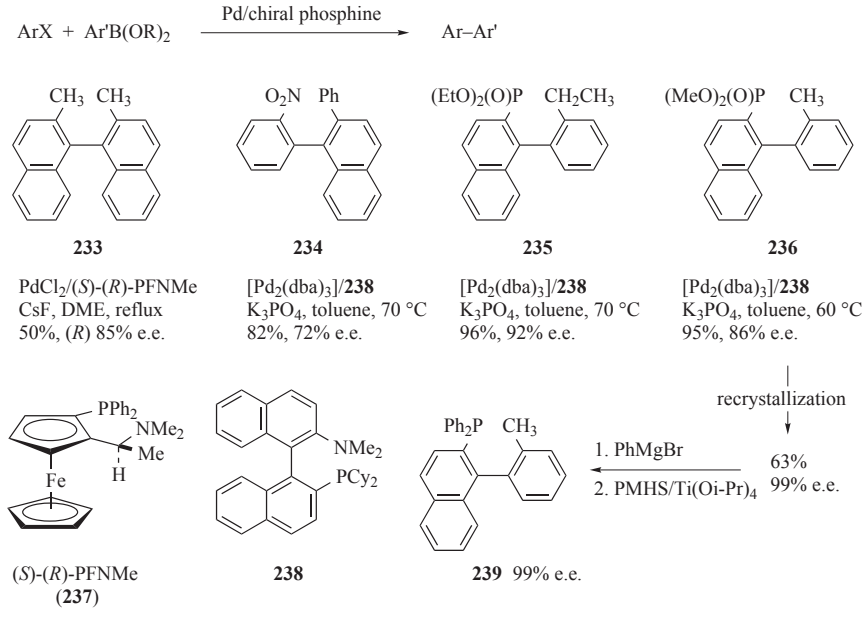
Scheme 2-53 Sequential double coupling and intramolecular coupling.

meric forms based on planar chirality. The cross-coupling reaction of **225** provides both optically pure atropisomers, starting from a single chromium complex [333] (Scheme 2-54). The reaction with *o*-tolylboronic acid diastereoselectively produces a kinetically controlled product (**226**) in which the 2-methyl group is in *syn*-orientation to the $Cr(CO)_3$ fragment. The selective formation of **226** proceeds through transition state **228**, where the R substituent rotates toward the $Cr(CO)_3$ moiety, preventing a large nonbonding interaction between R and PPh_3 during the C-C bond formation. On the other hand, a less-hindered 2-formylphenyl group allows axial isomerization of a (*R,R*)-chromium complex (**229**) to a thermodynamically more-stable (*R,S*)-isomer (**230**). The utility of the latter selective transformation has been demonstrated in the synthesis of (–)-steganone (**232**) [332].



Scheme 2-54 Chiral biaryls.

Asymmetric cross-coupling reactions using a chiral catalyst are straightforward for the synthesis of axially chiral biaryls (Scheme 2-55). The first attempt resulted in 85 % *e.e.* with $PdCl_2$/(*S*)-(*R*)-PFNMe (**237**) in the reaction of 1-iodo-2-methylnaphthalene with 2-methyl-1-naphthaleneboronic ester (**233**) [354]. Since at least three *ortho* substituents are needed to obtain configurationally stable biaryls, the catalyst must allow such a sterically hindered combination at a temperature that does not induce racemization of the product. A monocoordination of chiral bulky, electron-rich monophosphine (**238**) based on a binaphthyl backbone to a

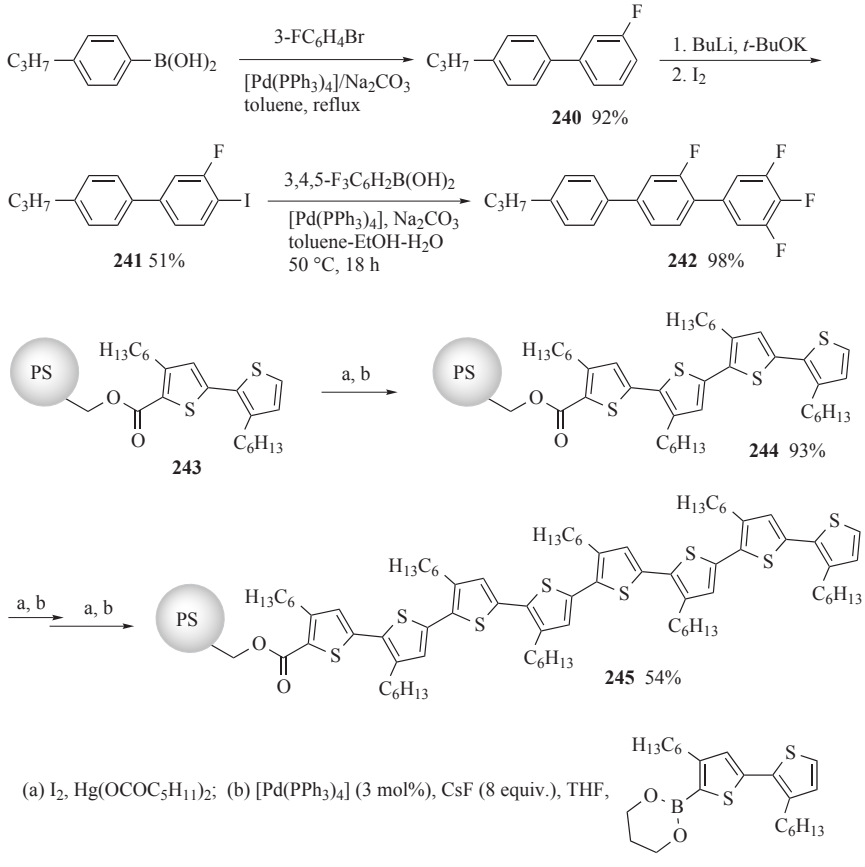


Scheme 2-55 Asymmetric biaryl-coupling.

palladium-dba complex meets this requirement rather than dicoordination of chiral bisphosphines such as BINAP. A variety of axially chiral biaryls (**234**–**236**) have been synthesized in high yields, and with *e.e.* values up to 92 % [355]. The reaction realizes the best results for 1-bromonaphthalenes possessing a $(RO)_2P(O)$-group at the 2-position. The utility of the protocol has been demonstrated in the synthesis of a chiral phosphine ligand (**239**). One recrystalization of **236** to enrich the enantiopurity to 99 % *e.e.* is followed by phenylation and reduction to yield **239** with 99 % *e.e.*.

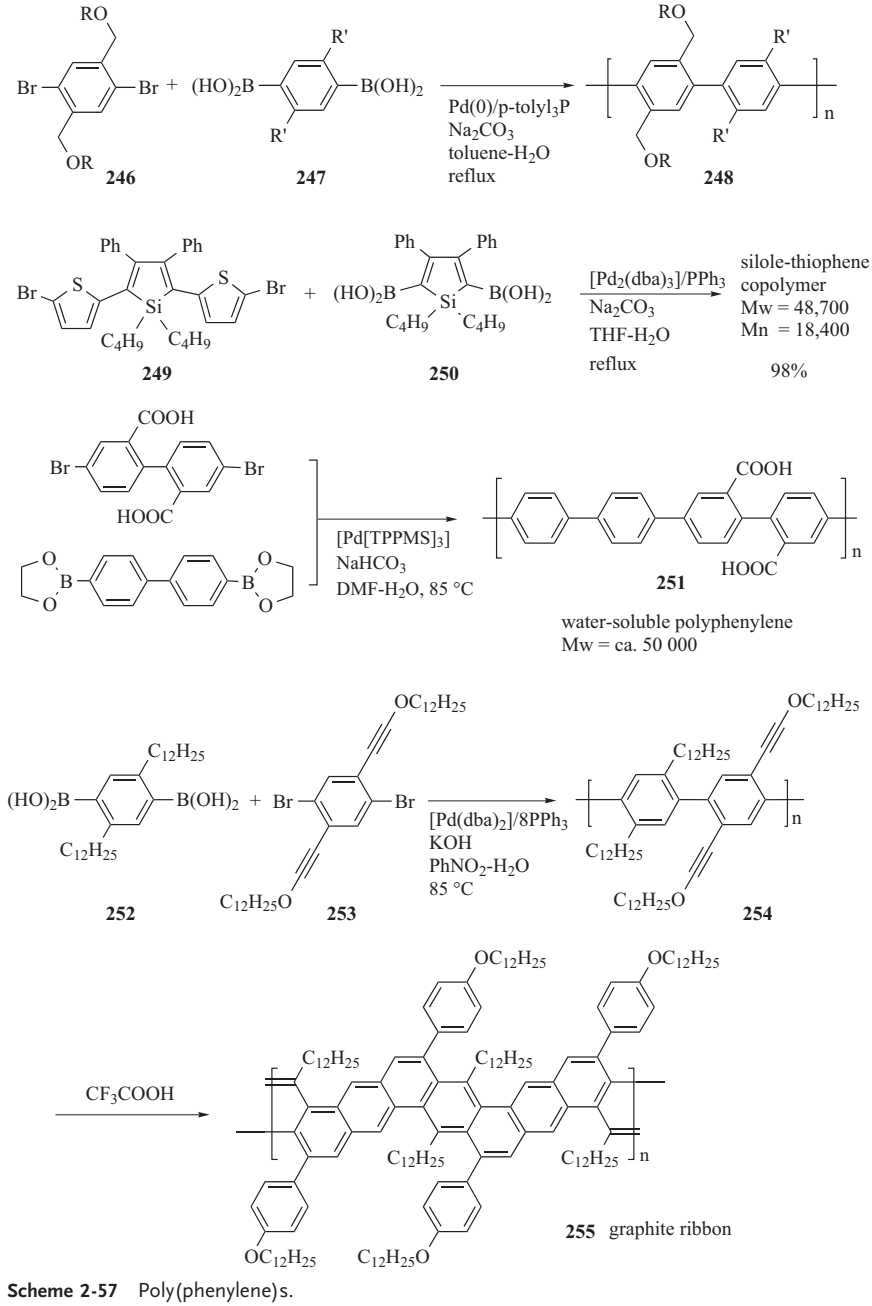
2.8.3
Biaryls for Functional Materials

The log, lath-like molecular structure of most liquid crystalline compounds makes the cross-coupling protocol very important in syntheses [356] (Scheme 2-56). The method simplifies the production of liquid crystal materials of complex substitution patterns by stepwise extension of aryl units [357]. For example, a sequence of *ortho*-metallation and iodination (**240** to **241**) and subsequent cross-coupling with arylboronic acid provides materials for displays with low driving voltages (**242**) [358]. Liquid crystals based on biaryl cores are produced using a cross-coupling protocol (Merck in Germany, *ca.* 3 tons per year) [359]. There is a considerable interest in the development of conjugate oligomers and polymers for application to electronic devices, including all-organic, field-effect transistors and light-



Scheme 2-56 Electronic and photonic materials.

emitting devices [360]. Among them, thiophene- and fluorene-based materials have attracted particular interest. Isomerically pure head-to-tail-coupled oligo(thiophene)s are obtained by a solid-phase reaction in which a sequence of iodination, and coupling of two thiophene units is repeated [211, 244]. The protocol provides a simple method for preparation of tetramer (**244**, 93 %), octamer (**245**, 54 %), and dodecamer (15 %) with high isomeric purities, though the corresponding solution-phase reaction suffers from isolation of a pure compound from a mixture of several oligo(thiophene)s [211]. Since bis(thiophene)boronic acid is susceptible to hydrolytic deboronation, the reaction is carried out under strictly anhydrous conditions using a boronic ester and CsF. The synthesis of a series of oligofluorenes has been accomplished by analogous cross-coupling reactions of arylboronic acids. The preparation of various fluorenyl bromides and boronic esters, that each have one to eight fluorene units is followed by the parallel cross-coupling of different units [361].



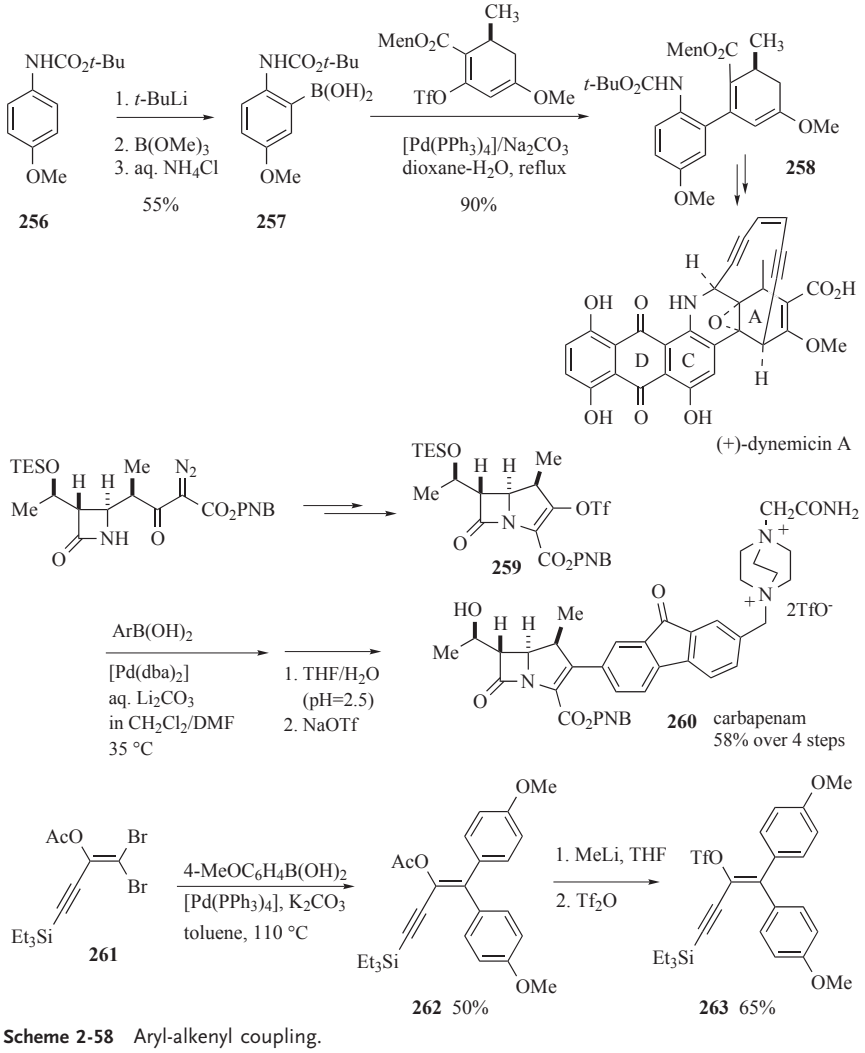
Scheme 2-57 Poly(phenylene)s.

The synthesis of poly(*p*-phenylene) *via* the homocoupling of *p*-bromophenylboronic acids was first demonstrated by Wenger, Feast, and coworkers [362]. After this discovery, various new poly(*p*-phenylene)s have been designed and synthesized on the basis of cross-coupling of arylboronic acids. The synthesis of poly(phenylene)s based on arylboronic acids has recently been reviewed [363] (Scheme 2-57). The reaction between dihaloarenes and arene diboronic acids or esters yields high molecular-weight polymers having regular repeated structures (**248**) [364]. Long alkyl side-chains ($R' = C_6$-C_{12}) serve to maintain the solubility so that the polymerization proceeds smoothly in organic solvents and the polymer backbone is modified with the desired functional groups (RO). The synthesis of silole-thiophene copolymers (EL device) has been hampered by the limited availability of suitable boron precursors. Silole-2,5-diboronic acid (**250**) can now be obtained using a one-pot procedure starting from the intramolecular reductive cyclization of bis(alkynyl)silane [365]. A water-soluble complex prepared from $PdCl_2$ and TPPMS catalyzes the polymerization in aqueous media to provide a rigid-chain polyelectrolyte (**251**) which is soluble in aqueous Na_2CO_3 [366]. The synthesis of poly(*p*-phenylene)s has been studied extensively for their possible electronic and photonic applications, but they have a 23° twist between the consecutive aryl units due to *ortho* hydrogen interactions. The polymerization is followed by cyclization to give planar polyaromatic materials which keep the aryl units planar while maximizing the extended π-conjugation through the poly(*p*-phenylene) backbone, for example, in the graphite-like ribbon **255** [367].

The protocol is a versatile tool for synthesizing a wide range of functional materials such as rigid and sterically regular chiral polymers possessing BINOL [368] and BINAP [368g] units in the main chain, ionophoric poly(phenylene-dithiophene)s having a calixarene-based ion receptor that displays exceptional selectivity for Na^+ ions [369], poly(*p*-phenylene)s substituted with oligo(oxymethylene) [370], crown ether [371] or dendrimer side chains [372], anisotropic adsorbates based on nanometer-sized and tripod-shaped oligophenylenes [348], poly(phenylene ethenylene)s containing 2,3-dialkoxybenzene and iptycene units [373], and poly(arylene)s having azobenzene units [374], fluorene units [375], thiophene units [376], or pyridine units [377] in the main chain.

2.8.4
Arylation of Miscellaneous Substrates

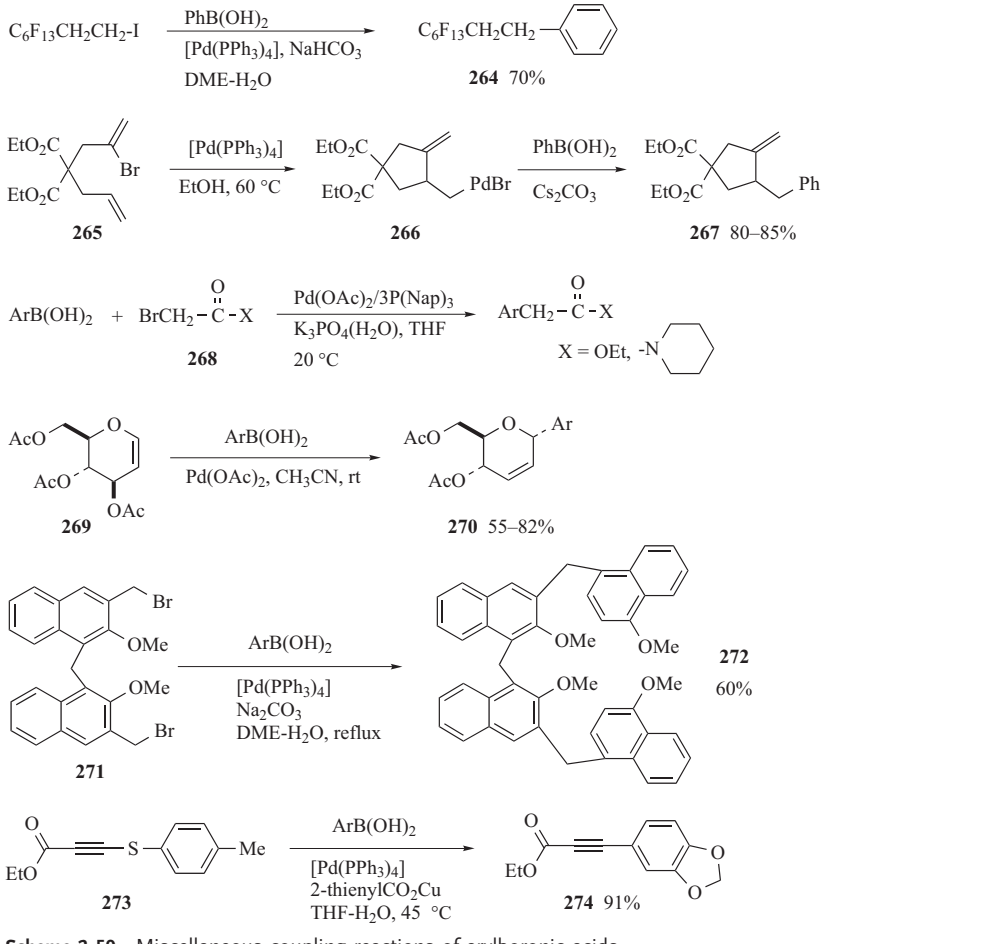
Arylation of 1-alkenyl halides and triflate occurs under conditions similar to those used for aryl-aryl coupling (Scheme 2-58). The ready availability of *ortho*-functionalized arylboronic acids by a metallation-boronation sequence provides a synthetic link to the cross-coupling protocol. Various polycyclic heteroaromatics have been synthesized when the preparation of arylboronic acids having an *ortho*-CON*i*Pr_2, -OCONEt_2, -NH*t*Boc (**257**), or -CHO is followed by cross-coupling and cyclization between two *ortho*-functionalities [5, 48]. For example, the strategy *via* **258** provides a short-step synthesis of the ABC ring system of (+)-dynemicin A [47a]. The introduction of aryl moieties at the 2- position of carbapenam (**259**) was first demon-



Scheme 2-58 Aryl-alkenyl coupling.

strated by the Stille coupling of arylstannanes. The procedure is being reinvestigated using arylboronic acids to prevent contamination by toxic tin compounds in an industrial process [378]. Although the reaction suffered from low yields due to the thermal instability of the carbapenam triflate, ligand-less $Pd(dba)_2$ has finally been recognized as an excellent catalyst for carrying out the reaction at a low temperature (**260**). Arylation of 1,1-dibromoalkene (**261**) affords **262** in yields of 50–85 %, which is then converted into the corresponding triflate (**263**) [379]. Both vinyl acetate and triethylsilyl moieties tolerate the reaction conditions, as long as the reaction is kept strictly anhydrous.

Among the representative organoboronic acids, arylboronic acids are exceptionally reactive reagents that allow a wide range of cross-coupling reactions for representative organic electrophiles (Scheme 2-59). Very few reports exist on the arylation of alkyl halides possessing β-hydrogen, but there should be no difficulty if oxidative addition proceeds smoothly for haloalkanes, as shown in Scheme 2-46. For example, a common palladium-phosphine complex has been used to carry out the reaction between *primary* alkyl iodides and arylboronic acids affording alkylarene **264** [380]. Cascade cycloalkylation of 2-bromo-1,6-dienes (**265**) also involves the coupling reaction with sp^3 carbon that is produced by the intramolecular insertion of a terminal double bond (**266**) [381]. The reaction to yield **267** is accompanied by the formation of direct coupling products without cyclization and alkene products *via* β-hydride elimination from **266**. Thus, the reaction results in high yields when

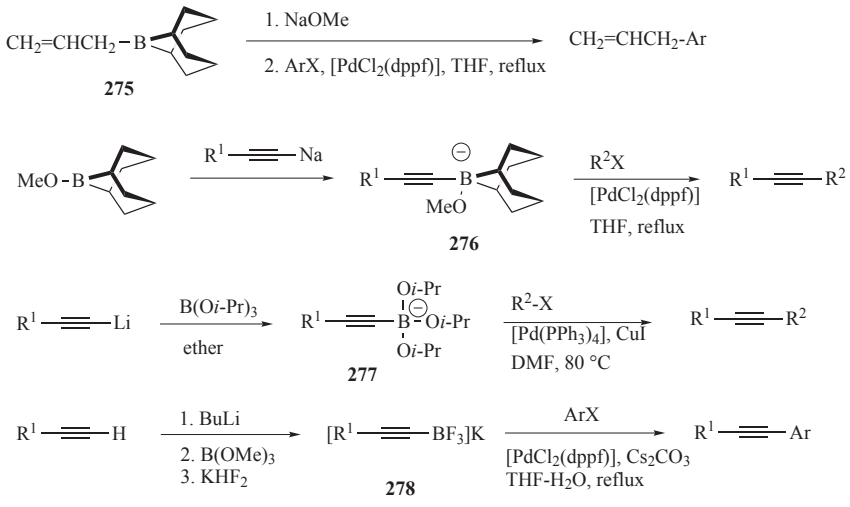


Scheme 2-59 Miscellaneous coupling reactions of arylboronic acids.

the relative rates of insertion and transmetallation are optimized by choosing appropriate bases, solvents, and reagent concentrations. Arylation of α-bromoacetates or amides (**268**) [382–384] is particularly interesting. Since oxidative addition of α-halocarbonyl compounds yields C-bound ketone which can easily rearrange to the O-bound enolate, they have been used as reoxidizing reagents of palladium(0) species for the dimerization of arylboronic acids [384]. In the presence of $Pd(OAc)_2$/tri(naphthyl)phosphine ($P(Nap)_3$), K_3PO_4, and a small amount of water, the cross-coupling reaction proceeds selectively at room temperature for both arylboronic acids and pinacol esters [382]. Palladium(II) acetate catalyzes the regio- and stereoselective arylation of glycals (**269**) at room temperature [385]. The observed selectivities suggest an addition-elimination mechanism involving the formation of Ar-Pd-OAc *via* transmetallation between $Pd(OAc)_2$ and $ArB(OH)_2$, *syn*-addition to the glycal double bond and finally *anti*-elimination of $Pd(OAc)_2$. This is in sharp contrast to the nickel-catalyzed arylation of cyclic allyl carbonates (**145**), which gives analogous inversion products *via* an oxidative addition-transmetallation process [195]. The aryl-benzyl coupling reaction provides a simple method for the synthesis of open-chained mixed calix[4]arene analogs (**272**) [386]. The palladium-catalyzed C-S bond cleavage of 1-alkynylsulfides (**273**) links to the cross-coupling reaction of arylboronic acids [207b]. Copper 2-thiophenecarboxylate mediates the reaction under neutral conditions.

2.9 Reactions of B-Allyl and B-Alkynyl Compounds

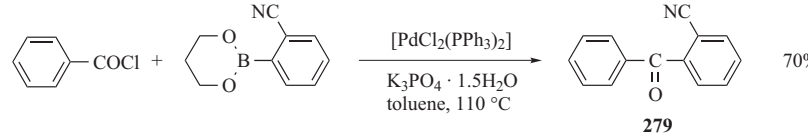
Less is known about the reactions of allylboron compounds; however, allylation will occur smoothly in the presence of a base and palladium catalyst (Scheme 2-60). The reaction of tri(crotyl)borane with iodobenzene in THF in the presence of aqueous NaOH and $[Pd(PPh_3)_4]$ produces a mixture of 3-phenyl-1-butene (74 %) and 1-phenyl-2-butene (13 %) [228]. An analogous reaction of an ate-complex between B-allyl-9-BBN (**275**) and NaOMe affords allylarenes in high yields within 0.5–1 h [259]. Although allylboron compounds are smoothly added to carbonyl compounds, the coupling reaction is considerably faster than allylboration of aromatic ketones, though aldehydes are not tolerated. Alkynyl(methoxy)borates (**276**) prepared in situ from an alkynyllithium or sodium and 9-methoxy-9-BBN couple with 1-alkenyl and aryl halides [387]. Alternatively, the addition of sodium acetylide NaC≡CH to $(MeO)_3B$ (1.5 equiv.) give a borate complex that reacts with haloarenes in good yields in the presence of $[PdCl_2(dppf)]$ [387a]. The addition of triisopropylborate to lithium acetylide yields an air-stable and isolatable ate-complex (**277**) that couples with aryl and alkenyl halides [388]. Air- and moisture-stable alkynyltrifluoroborates (**278**) are probably the most convenient reagents that allow handling in air and coupling reactions to be conducted in basic aqueous media [217].

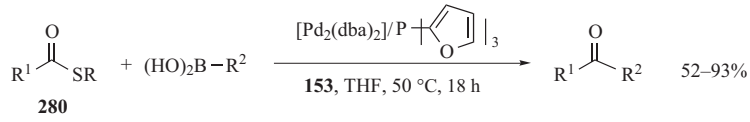


Scheme 2-60 Cross-coupling reactions of allyl and 1-alkynylboron compounds.

2.10
Reactions Giving Ketones

Cross-coupling reactions of acyl chlorides, thiol esters, or carboxylic anhydrides produce ketones (Scheme 2-61). The reaction of acid chlorides in aqueous bases suffers from competitive hydrolysis [389], but such decomposition can be minimized when arylboronic esters and $K_3PO_4 \cdot nH_2O$ (n = 1.5, 1.5 equiv.) are used in toluene at 110 °C, so that aromatic or aliphatic acyl chlorides provide aromatic ketones (e. g., **279**) in yields of 68–95 % [390]. Although anhydrous bases are desirable for such substrates, the reaction requires the presence of water for the transmetallation process. The cross-coupling reaction of thiol esters (**280**) with organoboronic acids gives ketones under strictly nonbasic reaction conditions when aqueous copper(I) thiophene-2-carboxylate (**153**) is used as the base [206]. Aromatic and aliphatic *S*-alkyl and *S*-aryl thiol esters couple with a variety of aryl- and 1-alkenylboronic acids at room temperature (52–93 % yields). The complexation of a soft sulfur atom to a copper(I) ion has been proposed as the driving force of both oxidative addition and transmetallation because **280** does not undergo oxidative addition to a palladium(0) complex in the absence of copper ion. An analogous coupling reaction proceeds for $RC(=O)SCH_2CH_2CH_2CH_2Br$ in the presence of a palladium catalyst (**113**, $Pd(OAc)_2$/o-tolyl$_3$P), K_2CO_3, and NaI in DMA at 90 °C [391]. Palladium-catalyzed reaction of phenyl trifluoroacetate [111] or carboxylic anhydrides (**281**) [112] affords the corresponding ketones. Since the oxidative addition yields a phenoxo- (**91**) or (acetoxo)palladium(II) intermediate (**90**) (as discussed in Scheme 2-14), the reaction occurs in the absence of a base. Carbonylative cross-coupling is an attractive approach for the large-scale preparation of unsymmetrical ketones, particularly in industrial situations. The protocol allows various

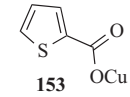


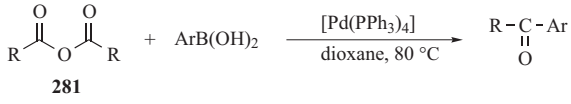


R^1= Ph, 4-NO_2Ph, 4-HOPh, 2-pyrazyl, $C_{11}H_{23}$, $ClCH_2$, $AcOCH_2$, CF_3

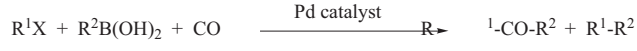
R^2= aryl, 1-alkenyl

R= C_2H_5, phenyl, *p*-tolyl, CH_2CONMe_2





Carbonylative cross-coupling



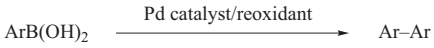
R^1X	R^2B	catalyst	CO (atm)	base/solvent/temp	Ref.
alkyl-I	9-alkyl-9-BBN	$[Pd(PPh_3)_4]$/hν	1	K_3PO_4/benzene/r.t.	[392]
alkenyl-I	9-alkyl-9-BBN	$[Pd(PPh_3)_4]$	3	K_3PO_4/dioxane	[393]
Ar-I	$ArB(OH)_2$	$[PdCl_2(PPh_3)_2]$	1	K_2CO_3/anisole/80 °C	[394, 395]
2-Br-pyridine	$PhB(OH)_2$	$[PdCl_2(PPh_3)_2]$	5	K_2CO_3/THF/120 °C	[396]
ArN_2BF_4	$ArB(OH)_2$	$Pd(OAc)_2$/**109b**	1	dioxane/100 °C	[397]

Scheme 2-61 Synthesis of ketones.

combinations of halides and organoboron compounds possessing alkyl, 1-alkenyl, or aryl groups in either of coupling partners [392–397]. Iodoarenes and iodoalkenes are cleanly carbonylated under low pressure carbon monoxide; however, iodoarenes possessing an electron-withdrawing group and bromoarenes are more prone to yield direct coupling products without carbonyl insertion [395]. For such substrates, the relative reaction rates of migratory CO insertion into a C-Pd bond and transmetallation of organoboronic acids to Pd-X must be optimized by choosing an appropriate base, solvent and CO pressure [395, 396].

2.11
Dimerization of Arylboronic Acids

The oxidative homo-coupling of arylboronic acids provides a method for synthesizing symmetrical biaryls (Scheme 2-62). However, the reaction has not been extensively studied because the dimerization of aryl halides, rather than using arylmetal



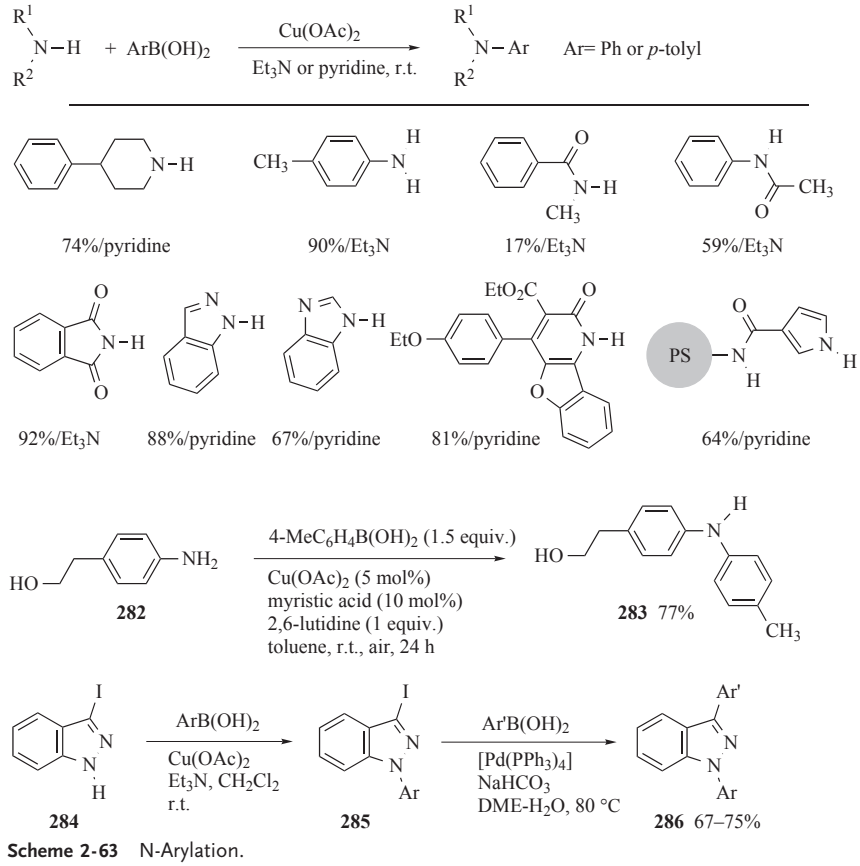
catalyst	reoxidant	base/solvent/temp	Ref.
$[PdCl_2(dppb)]$	$PhCHBrCHBrCO_2Et$	K_2CO_3/THF-H_2O, 70 °C	[399]
$PdCl_2$/BINAP	$Ph(Br)CHCO_2Me$	KF/dioxane-H_2O/100 °C	[384]
$PdCl_2$	4-$MeC_6H_4SO_2Cl$	Na_2CO_3/MeOH-H_2O/r.t.	[400]
$Pd(OAc)_2$	O_2	Na_2CO_3/EtOH-H_2O/r.t.	[401b]
$Pd(OAc)_2$	O_2	NaOAc-R_4NX/H_2O/r.t.	[401a]
$Pd(OAc)_2$/dppp	O_2	DMSO/80 °C	[402]

Scheme 2-62 Dimerization.

reagents, is a straightforward route to synthesize symmetrical biaryls. Since the reaction involves stepwise, double transmetallation to PdX_2 followed by reductive elimination of biaryl to generate a palladium(0) species, a suitable oxidant that selectively oxidizes palladium(0) complexes in the presence of arylboronic acids is critical for recycling the palladium catalyst. Typically, $Cu(OAc)_2$ [398], $PhCH(Br)CH(Br)CO_2Et$ [399], $PhCH(Br)CO_2Me$ [384], 4-$MeC_6H_4SO_2Cl$ [400], and O_2 [401, 402] have been used for this purpose. Molecular oxygen employed for the Wacker process is the cleanest oxidant, but the reaction suffers from the formation of phenols *via* oxidation of arylboronic acids because the catalytic cycle yields hydrogen peroxide (as shown in Scheme 2-39). Recently, it has been found that the occurrence of such a side-reaction can be prevented when boronic esters are used in DMSO [402].

2.12
N-, O-, and S-Arylation

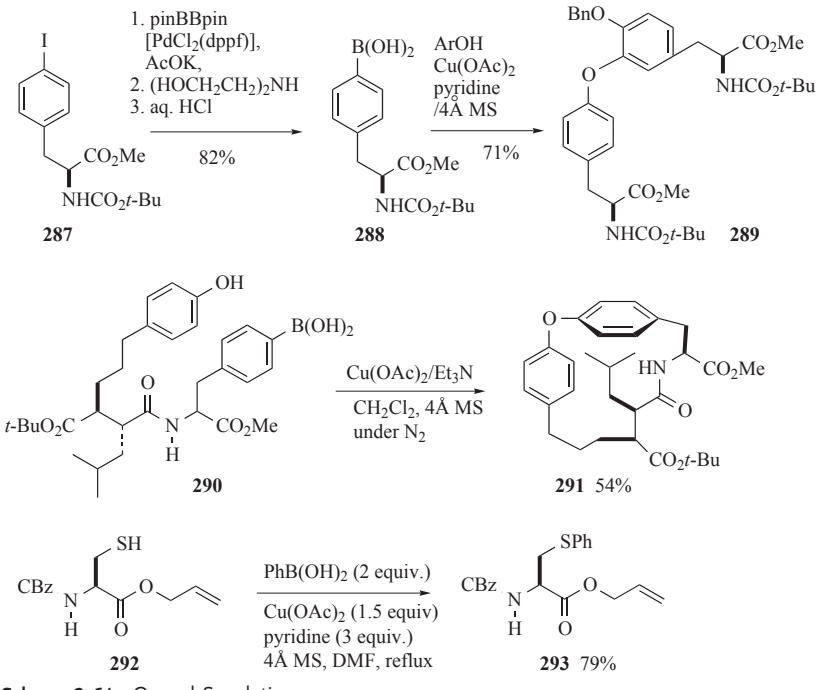
Copper-promoted C-N bond cross-coupling reactions of NH-containing substrates with arylboronic acids proceed at room temperature in the presence of $Cu(OAc)_2$ and an amine base [403–412] (Scheme 2-63). The mild reaction conditions and simple operation in the air are very convenient for the preparation of N-aryl compounds in the pharmaceutical and material sciences. The representative procedure involves the addition of 2 equiv. arylboronic acid and 2–5 equiv. Et_3N or pyridine to 1 equiv. NH substrate, followed by $Cu(OAc)_2$ (1.5 equiv.) and 4 Å molecular sieves in CH_2Cl_2 or 1,4-dioxane. Since the reaction is significantly accelerated in the presence of oxygen, the mixture is stirred while being exposed to air at room temperature for 1–2 days, with protection from any atmospheric moisture. The addition of NH_3 in MeOH is often used to free up the products from copper salts. The mechanism involves first, the formation of $[Cu(II)(OAc)(NR_2)]$, transmetallation of arylboronic acid to give $[Cu(II)(Ar)(NR_2)]$, air oxidation or disproportionation of the Cu(II) species to $[Cu(III)(Ar)(NR_2)]$, and finally reductive elimination to yield $ArNR_2$ and Cu(I) species [408, 409]. Thus, the reaction can be rendered catalytic



Scheme 2-63 N-Arylation.

when a suitable oxidant of Cu(I) species is used. An air oxidation can be used for N-arylation of imidazoles with $[[Cu(OH) \cdot TMEDA]_2Cl_2]$ [408]. Pyridine *N*-oxide or TEMPO is effective for N-arylation of amines, NH-heterocycles, and phenols with a catalytic $Cu(OAc)_2$ [412]. A catalytic system consisting of $Cu(OAc)_2$ (5–10 mol %), 2,6-lutidine(1 equiv.), and myristic acid (10–20 mol %) in air has a wide scope for aromatic and aliphatic amines [410]. The procedure accomplishes N-selective arylation of **282** to give **283** in 77 % yield. Two coupling reactions at N-H and C-I bonds of 3-iodoindazole (**284**) are perfectly controlled by the catalysts [411]. The C-I bond remains unchanged during N-arylation of **284** with $Cu(OAc)_2$, thus allowing second arylation of **285** with a palladium catalyst. 1,3-Diarylindazoles (**286**) are also available when the coupling reaction at the C-I bond is followed by N-arylation.

Under conditions similar to those used for N-arylation, arylboronic acids undergo O-arylation of phenols [413–415] and *N*-hydroxyphthalimide [416] (Scheme 2-64). The utility of this methodology has been demonstrated in the short-step synthesis of (*S*,*S*)-isodityrosine (**289**) from two natural amino acids [413]. The intramo-



Scheme 2-64 O- and S-arylation.

lecular copper-mediated O-arylation furnishes macrocyclic inhibitors of collagenase 1 and gelatinase A and B (e. g., **291**) [415]. The mild conditions using a weak base at room temperature allow the synthesis of such base-sensitive amino acids without racemization. In contrast, the reaction of alkylthiols at a temperature lower than 70 °C is very slow. This is presumably due to the reaction having to be conducted under an inert gas atmosphere in order to prevent air-oxidation of free thiols to dithianes. S-Arylation of L-cysteine (**292**) has been carried out in refluxing DMF [417].

Abbreviations

acac	acetylacetone
ArBpin	pinacol arylboronate
BBN	9-borabicyclo[3.3.1]nonane
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
bpy	2,2′-bipyridine
cod	cyclooctadiene
Cp*	pentamethylcyclopentadienyl
Cy	cyclohexyl

dba	dibenzylideneacetone
DMSO	dimethylsulfoxide
dppe	bis(diphenylphosphinyl)ethane
dppf	1,1′-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphinyl)propane
dppb	1,4-bis(diphenylphosphinyl)butane
dtbpy	4,4′-di(*t*-butyl)-2,2′-bipyridine
EtOBpin	pinacol ethoxyboronate
GLCAphos	D-gluconic acid (diphenylphosphanyl)benzylamide
HBcat	catecholborane
HBpin	pinacolborane
$HB(Sia)_2$	disiamylborane
LDA	lithium diisopropylamide
LHA	lithium aluminum hydride
LTMP	lithium-2,2,6,6-tetramethylpiperidide
MOM	methoxymethyl
MSCl	mesylchloride
Nap	naphthyl
nbe	norbornene
OTf	triflate
PEG	poly(ethylene glycol)
PFNMe	(5)-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethyl dimethylamine
PG	prostaglandin
pinBH	pinacolborane
pin_2B_2	bis(pinacolato)diboron
PMB	*p*-methoxybenzyl
PS	polystyrene bead
PS-PEG-tap	polystyrene-poly(ethylene glycol) resin-supported triarylphosphine
PS-PEG-adppp	polystyrene-poly(ethylene glycol) resin-supported 2-aza-1,3 bis((diphenylphosphino)propane)
PVA	poly(vinyl alcohol)
Q-phosph	di-*tert*-butylphosphinopentaphenylferrocene
r. t.	room temperature
TBS	*tert*-butyldimethylsilyl
Tedicyp	*cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane
TEMPO	2,2,6,6-tetramethyl-l-piperidinyloxy
TES	triethylsilyl
TPPTS	trisodium salt of triphenylphosphane trisulfonate
TPPMS	sodium salt of triphenylphosphane monosulfonate

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3
Organotin Reagents in Cross-Coupling Reactions

Terence N. Mitchell

3.1
Introduction

Although cross-coupling reactions involving organotin derivatives are today linked indivisibly with the name of the late J. K. Stille, it is known that he was not in fact the true "inventor" of this type of chemistry. Many reviews on what is now known either as "Stille coupling" or "Stille cross-coupling" have been written, and in the first edition of this book the present author attempted to provide a critical survey of the investigations carried out in this area between 1991 and mid-1996.

Now, at the end of the year 2003, it is clear that "Stille chemistry" has really come of age. The number of references which came to light when the period 1997–2002 was searched was around 700, whilst in the first edition only 220 references were cited for a comparable period of time.

Thus, the earlier approach of dividing up the material according to the type of residue transferred from tin to carbon (alkenyl, aryl, alkyl, etc.) no longer seems appropriate.

Instead, the chapter will be divided according to a number of subject areas. First and foremost will be provided information on new catalyst systems which have served to increase the applicability of this chemistry. Second, some examples of recent uses of Stille chemistry in natural product synthesis will be given; this area is increasing explosively in importance. Applications in organic chemistry will then be presented, followed by selected examples dealing with the synthesis of polymeric and inorganic target molecules.

Initially, however, we will mention recent reviews which can be used to complement the presentation in this chapter. Farina et al. have performed invaluable work in reviewing the Stille reaction, and the article (with 865 references!) published in 1997 in the series *Organic Reactions* [1] was republished in 1998 in book form [2]. The intramolecular variant of the reaction is of great importance, particularly for the preparation of macrocycles, and has been reviewed recently by Duncton and Pattenden [3].

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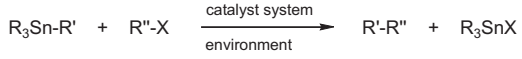
3.2 Mechanism and Methodology

To some readers, this may be the most important section of the chapter, as it deals with advances in various areas. The Stille reaction can be formulated as follows:



Scheme 3-0

where R′-R″ is the target molecule, and R_3SnX the unwanted byproduct. Because of the toxicity of organotin compounds, the ideal reaction system would be one in which the product can be obtained free from organotin residues.

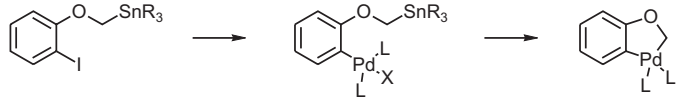
The term "environment" is used in a broad sense. Normally it can be replaced by the word "solvent", but as we shall see it now encompasses more. The term "catalyst system" comprises the catalyst precursor and any additives used (such as phosphines or copper salts). The range of functionalities which are available as R′ and R″ is very broad, but in some cases (e. g., bulky organotins, aryl halides) there have been – or still are – problems to overcome.

All of these aspects will be considered below, but first we will discuss recent work concerned with the mechanism of the reaction.

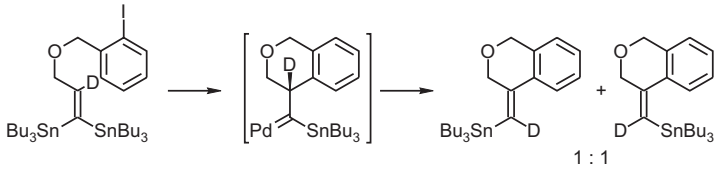
3.2.1 Mechanism

It is generally agreed that the first step in the catalytic cycle is oxidative addition of R″-X to the active catalyst (which is a palladium(0) species PdL_n) to give $R'PdXL_n$, followed by transmetallation to give $R'PdR''L_n$ and finally reductive elimination to give R′-R″. The number of ligands, n, is generally accepted to be 2, except in certain special cases. The first and third steps appear to be normally slower than the transmetallation step, which is thus the least understood.

The product of oxidative addition of R″-X to the palladium(0) species is thus a square planar complex, and by reacting 2-iodo- or 2-bromophenyloxymethyl-stannanes with a Pd(0) complex with a bidentate diphosphine, Echavarren and co-workers were able to isolate such a complex, the arylpalladium(II) intermediate of oxidative addition [4]. If $Pd(PPh_3)_4$ was used, reductive elimination of the tin halide to give the corresponding oxapalladacycle was observed; in the same way, the corresponding derivative of 2-iodoaniline gave an azapalladacycle.



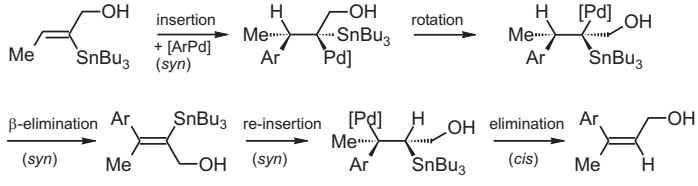
Scheme 3-1 Conditions: $Pd(PPh_3)_4$, toluene, 45 °C. X = Br, I: R = Me, Bu. L_2 can also be dppe, dppf [4].



Scheme 3-2 Conditions: $Pd(OAc)_2$ (10 mol %), $(oTol)_3P$, Et_3N (3 % v/v), MeCN, 80 °C [6].

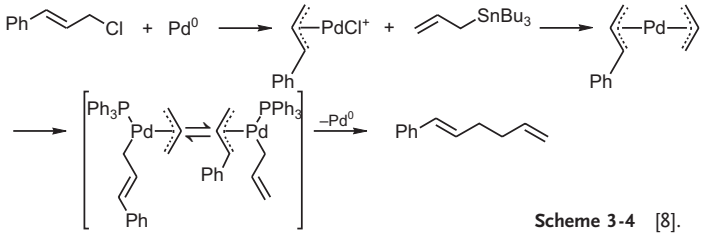
A complication sometimes observed is the formation of products arising from a *cine*-substitution rather than the desired *ipso*-substitution; thus Quayle et al. showed [5] that an attempted intramolecular Stille coupling of a bis-stannylethene proceeded by 6-*exo*-cyclization to give a *cine* product rather than by 7-*endo*-cyclization to give the expected *ipso* product (Scheme 3-2). These authors carried out deuterium labeling studies, the results of which indicated that the Pd-carbene mechanism, as proposed by Busacca [6], appeared probable.

Flohr [7] carried out studies designed to find a system suitable for Stille coupling between hindered vinyltins and aryl iodides or triflates: he found that under certain conditions the iodides gave *ipso* products while the triflates under somewhat different conditions afforded *cine* substitution (Scheme 3-3).



Scheme 3-3 Conditions: *ipso* from *p*-IC_6H_4OMe, Pd_2dba_3, $AsPh_3$, CuI, NMP, room temperature; *cine* from *p*-$TfOC_6H_4OMe$, Pd_2dba_3, $AsPh_3$, CuI, NMP, 45 °C [7]

Coupling reactions between allyltins and allyl chlorides are assumed to proceed via bis(π-allyl)palladium intermediates; Yamamoto [8] has recently shown that in the presence of aldehydes or imines it is possible to control the chemoselectivity of the reaction so that either the allylic halide or the aldehyde/imine is allylated by the organotin. The key element is triphenylphosphine, which is suggested (Scheme 3-4) to form a trigonal palladium complex with an η^3- and an η^1-allyl



Scheme 3-4 [8].

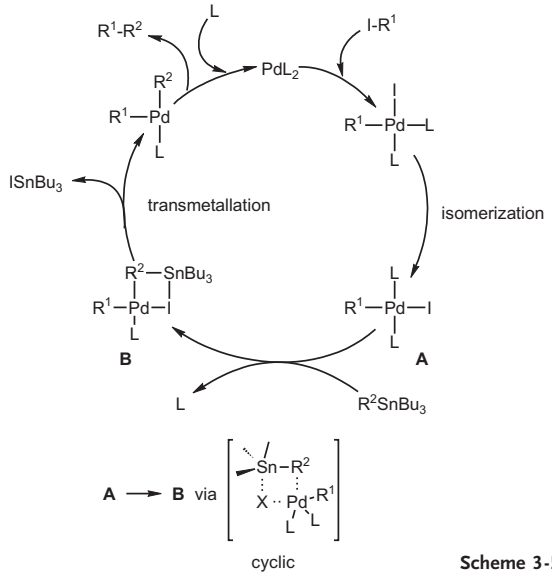
ligand as well as a phosphine; the two allyl ligands take part in an equilibrium involving a change in their hapticity.

In a similar area, Tsutsumi et al. [9] had previously looked at cross-coupling between propargyl electrophiles and organotins which led to both alkynes and allenes; these authors invoked the intermediacy of η^3-propargylpalladium species as well as the η^1-propargyl or η^1-allenyl intermediates which they had previously proposed.

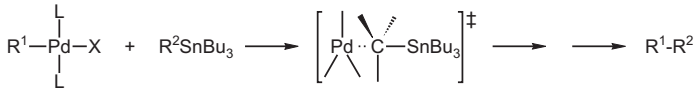
Espinet and co-workers have published several mechanistic papers on the Stille reaction. They determined [10] that the addition of a molecule RI to a palladium(0) species PdL_2 gives *cis*-L_2PdRI, but that rapid isomerization to give the palladium(II) species *trans*-L_2PdRI then occurs. Kinetic investigations [11] involving 3,5-dichlorotrifluorophenyltin iodide as RI and vinyl- or *p*-methoxyphenyltributyltin (Bu_3SnR') were then carried out with *trans*-$L_2PdRI(AsPh_3)_2$ as the catalyst.

These authors suggest that this complex reacts with Bu_3SnR' *via* an S_E2(cyclic) mechanism with displacement of $AsPh_3$ to give a cyclic intermediate as shown below (Scheme 3-5). A further intermediate is invoked prior to elimination of Bu_3SnI to give a trigonal palladium species which undergoes reductive elimination of the coupling product and concomitant readdition of the arsine ligand.

A third paper [12] deals with catalysis of the reaction between vinyltributyltin and pentahalophenyl triflate by compounds PdL_4 with L = PPh_3 or $AsPh_3$. The often-used additive LiCl accelerates the reaction when $AsPh_3$ is used because it increases the here rate-determining oxidative addition of the aryl triflate, but slows it when the ligand is PPh_3. Here, it is suggested that the transmetallation is rate-determining, its rate depending on the ligand X in *trans*-L_2PdRX and being slowest for X = Cl, the predominant species in a complex equilibrium when LiCl is present. The



Scheme 3-5 [10, 11].



Scheme 3-6 [12].

S_E2(cyclic) mechanism is invoked for X = Cl, but for X = OTf or L an alternative S_E2(open) mechanism is proposed (Scheme 3-6).

The use of the chelating diphosphine dppe rather than PdL_4 has allowed the observation and characterization of the main intermediates, which are [PdAr($CH{=}CH_2$)dppe] and [Pd(dppe)(η^2-$CH_2{=}CHAr$) [13].

Coordination-driven transmetallation has been observed by Itami et al. [14], who studied the reaction between 2-$PyMe_2SiCH_2SnBu_3$ (Py = pyridine) and aryl iodide with $PdCl_2(MeCN)_2/PPh_3$ via an S_E2 cyclic or open pathway. The rate of transfer of $PhMe_2SiCH_2$ is very much slower, comparable with that of a butyl group. The coordination between nitrogen and palladium was demonstrated in the isolable system 2-$PyMe_2SiCH_2PdCl(PPh_3)$ by X-ray structure analysis.

3.2.2 Methodology

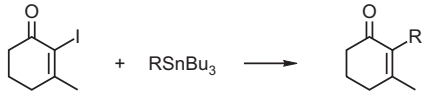
Traditionally, organic synthesis has involved reactions carried out in organic solvents. While this is true of the Stille reaction as originally designed, advances include the use of aqueous media, ionic liquids, fluorous biphasic systems, supercritical carbon dioxide, and of solid supports. New catalysts and ligands are also being introduced, although the "traditional favorite", $Pd(PPh_3)_4$, is still very commonly used. The use of various additives has been recommended for some time, but new ones are being discovered. We shall attempt to survey such advances in methodology in a systematic manner.

3.2.2.1 Reaction Medium

Genet and Savignac [15] have reviewed palladium-catalyzed cross-coupling reactions carried out in aqueous media; in the context of Stille reactions we should mention that the initial work was carried out as long ago as 1995 [16, 17].

Supercritical carbon dioxide has been used for reactions between aryl iodides and vinyltins [18], the best ligand tested being tris[3,5-bis(trifluoromethyl)phenyl]phosphine, which gave conversions up to 99%. In later work [19], $Pd(OCOCF_3)_2$ and $Pd(F_6\text{-acac})_2$ were found to be suitable when used in combination with various phosphines. Reactions between aryl bromides and aryl or 2-furyltributyltin can be carried out with the "traditional" catalyst $PdCl_2(PPh_3)_2$ as well as more expensive perfluoro-tagged catalysts; yields are generally very good, the fluoro-tagged complexes generally giving slightly higher yields [20].

A recent paper [21] has introduced the use of the room-temperature ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate (BMIM BF_4); recycling of the sol-



Scheme 3-7 R = aryl, vinyl; yields 72–92 %. Conditions: $PdCl_2(PhCN)_2$, $AsPh_3$, CuI, BMIM BF_4, 80 °C [21].

vent and catalyst system has been shown to give little loss of activity, even after five cycles (Scheme 3-7).

The use of microwave irradiation has been known for some time [22], and was later applied [23] to reactions involving "fluorous" organotins such as $(C_6F_{13}CH_2CH_2)_3SnAr$. Reaction times are reduced from about 1 day to 90–120 s, and $PdCl_2(PPh_3)_2$ is a suitable catalyst. The same methodology can be applied to compounds containing the $C_{10}F_{21}$ tag, which gives poor results under conventional conditions [24].

3.2.2.2 New Ligands, Catalysts, and Additives

Schneider and Bannwarth [25] have prepared three new perfluoroalkyl-tagged catalysts which can be used in fluorous biphasic systems; these can be recycled up to six times, without significant reduction in yield.

Several years ago, Mathey, Regitz and colleagues [26] reported on the use of Pd complexes of a ten-membered tetraphosphane, which they suggested to be more cost-effective than the Pd/trifurylphosphane catalyst. Albisson et al. [27] carried out orthopalladation of the inexpensive, commercially available tris(2,4-di-*tert*-butylphenyl)phosphite; the product, a dimeric complex, was very effective in biaryl coupling reactions with turnover numbers of up to 830 000. In related work, Alonso et al. [28] prepared oxime palladacycles which are not air- or moisture-sensitive and are easily prepared from cheap starting materials and found them to be very efficient catalysts for various carbon-carbon coupling reactions including Stille biaryl synthesis.

Majoral et al. [29] used third-generation metalladendrimers with 24 terminal Pd-diphosphine complexes in various coupling reactions; these catalysts could easily be recycled without loss of activity. Herrmann et al. [30] prepared a series of mixed palladium(II) complexes bearing N-heterocyclic carbenes and trialkyl- or triarylphosphines, and showed them to be active in various cross-coupling reactions. Grasa and Nolan [31] used a $Pd(OAc)_2$-imidazolium chloride system to catalyze coupling reactions of organotins and aryl halides; tetrabutylammonium fluoride is used as an additive, which is suggested to have two functions. First, it deprotonates the imidazolium ring to give a carbene which coordinates to palladium; and second, it forms hypervalent tin species and is beneficial in product work-up. Tin byproducts are removed by water extraction.

Fu et al. [32] recommend the commercially available catalyst $Pd[P(t\mathrm{Bu})_3]_2$ as an unusually reactive catalyst for reactions involving aryl bromides and chlorides. Thus, the relatively unreactive tetrabutyltin can be coupled with aryl chlorides, highly hindered biaryls can be synthesized, and aryl bromides undergo coupling at room temperature.

Several years ago, Roth et al. [33] described the use of an apparently heterogeneous catalyst system: Pd/C (0.5 %)/CuI(10 %)/$AsPh_3$(10 %); this system was suited for use in a number of different couplings and has recently [34] been applied to the reaction between 4-iodoacetophenone and 2-(tributylstannyl)thiophene.

A few examples of organotin cross-coupling reactions in which metals other than palladium are involved have been reported. Kang et al. [35] have carried out a variety of Stille couplings involving various organic groups using either 10 % CuI or 10 % $MnBr_2$ together with 1 equivalent of NaCl in NMP. In earlier reports [36–38], stoichiometric amounts (or an excess) of copper compounds were required; Falck et al. [39] used CuI without the addition of NaCl.

Shin and Ogasawara [40] have reported a coupling between vinyltributyltin and an α-iodoenone in which $ZnCl_2$ is required as an additive to the catalyst $PdCl_2(PPh_3)_2$. Corey and co-workers [41] have made considerable progress in couplings of 1-substituted vinylstannanes, where yields are negligible or low and much *cine*-substitution is observed, by adding CuCl and LiCl to $Pd(PPh_3)_4$. In DMSO or NMP, yields of 90 % or better of the required *ipso* product are obtained. Similar chemistry was reported by Sugiyami et al. [42], but their conditions were less attractive (40 % $Pd(PPh_3)_4$, 5 equiv. CuCl and 6 equiv. LiCl).

Amine addition is known to be effective in some cases: thus, Barros et al. [43] recommend diethylamine as it improves yields (e. g., in reactions between α-iodoenones and allyltriphenyltin) and can be used as a substitute for CuI. The use of Hünig's base DIPEA is becoming common, and will be referred to later.

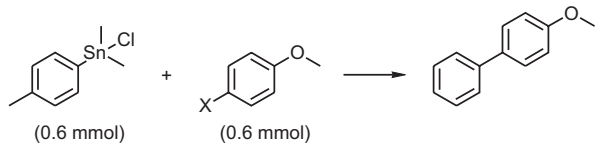
Netherton and Fu [44] recommend the conversion of air-sensitive triphenylphosphines to their phosphonium salts (e. g., using HBF_4); the phosphine is liberated in situ by a Brønsted base under the reaction conditions.

Liebeskind and co-workers [45] introduced $Ph_2PO_2NBu_4$ as a so-called "tin scavenger"; it has since been employed by other groups [46, 47] for intramolecular vinyl/vinyl coupling in natural product synthesis (see below).

3.2.2.3 New Organic and Organotin Coupling Partners

The beauty of the Stille reaction is that it is so flexible, so that new coupling partners may be hard to find. The use of phenyliodonium dipoles has been discussed by two groups, in one case for coupling with aryltrimethyltins [48] and in the second for reactions with alkynyltins [49]. Reactions involving heterobenzylic sulfonium salts have been reported [50]; here a highly complex system was used, namely (Pd_2dba_3/$(PhO)_3P$/CuI/$Ph_2PO_2NMe_3Bn$ in NMP).

Fouquet and Rodriguez [51, 52] have reported the in-situ preparation and activation of monoorganotins as suitable reagents for coupling with alkenyl and aryl triflates. The reactions require the use of a fluoride source, and the addition of tetrabutylammonium fluoride to various organotins apparently generates what have been referred to as "hypervalent" organotin species. Fugami et al. [53] carried out biaryl syntheses using $ArSnBu_2Cl$ as the aryl donor (Scheme 3-8); this is significant because triorganotin halides do not undergo coupling under conventional conditions.



Scheme 3-8 Conditions: 0.8 mol % Pd_2dba_3, 4 PPh_3, dioxane, reflux, 24 h. X = I, TBAF (2 equiv.). Yield 72 % [53].

The same authors also used various tetraorganotins and were able, for example, to transfer a butyl group from the relatively unreactive tetrabutyltin. In related work, Garcia Martinez et al. [54] have extended this methodology to other coupling partners. In either case, the separation of the product from the unwanted organotin species is stated to become relatively simple.

3.2.2.4 Stille Reactions with Polymer-Supported Substrates and Reagents

Franzen [55] has reviewed advances in the Suzuki, Heck and Stille reactions in solid-state organic synthesis.

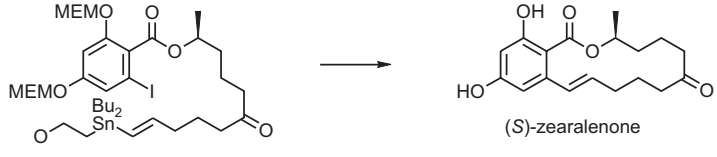
There are basically two ways of adapting the Stille reaction to solid-state conditions – that is, either the organotin moiety or the organic residue can be attached to a solid support.

Neumann and Pereyre carried out much pioneering work on the attachment of organotin substrates to polymer matrices, but this approach has not been greatly used in Stille couplings. Nicolaou et al. [56] reported a very elegant intramolecular reaction of a polystyrene-supported vinyltin species bearing a terminal vinyl iodide moiety to give a 1,3-diene (Scheme 3-9); this reaction formed part of a synthesis of the natural product (*S*)-zearalenone.

Brody and Finn [57] used a polystyrene-bound aryltin in a biaryl synthesis which was catalyzed by a new palladacycle complex.

During the course of the synthesis of estradiol derivatives, Lee and Hanson [58] attached the precursors, which contained a vinyltin moiety, to Wang and other polystyrene resins and carried out couplings with various aryl halides.

The alternative approach, in which the organic residue is attached to the polymer matrix, has become that of choice. Early work in this direction was done by Tempest and Armstrong [59], who reacted tributyltin derivatives of squaric acid with aryl halide moieties bound to a Wang resin; product yields after work-up were around 95 %. Wang resin and polyethylene glycol 5000 monomethyl ether resin



Scheme 3-9 Conditions: a) $Pd(PPh_3)_4$ (0.1 equiv.) toluene, 100 °C, 48 h, 54 %; b) 5 % HCl/THF (1:2), 23 °C, 80 °C, 5 days [56].

were used by Blaskovich and Kahn [60] to support vinyl bromide moieties incorporating amino acids or peptides, which underwent coupling with vinyltins to form 1,3-dienes; they noted that alternative approaches based on Suzuki or Wittig-Horner-Wadsworth-Emmons protocols were unsuccessful.

Malenfant and Frechet [61] have reported the first solid-phase synthesis of oligothiophenes on a chloromethylated macroporous resin. Couplings of aromatic iodides linked to a polystyrene resin [62] and of Merrifield resin-linked halobenzoates involving various organotin substrates [63] have been reported. Hermkens and Van Tilborg [64] studied reactions of a Rink amide-bound 4-chloropyrimidine moiety with various organotins; the conditions used were however forcing in the extreme (10 equiv. organotin/$PdCl_2(PPh_3)_2$/PPh_3/CuI/LiCl (4.5 equiv.)/DIPEA (2.5 equiv.)/DMF/125 °C).

Three-component coupling reactions on a Rink amide resin using both strategies have been described [65]: either the aryl bromide or the organotin functionality was immobilized on the resin and then allowed to react with either an aryltin or an aryl bromide in the presence of carbon monoxide to give diaryl ketones.

The polymer support does not necessarily have to be insoluble in the reaction medium. Thus, Sieber et al. [66] used poly(ethyleneglycol) as a soluble polymer matrix: an iodobenzoate moiety linked to the support was allowed to react with tributylphenyltin to determine optimum conditions ($PdCl_2(PPh_3)_2$ (10 %)/LiCl (10 equiv.)/DMF/80 °C). Precipitation into ether allows the removal of side products, excess reagents and organotin byproducts, leaving the polymer which is recovered in 99 % yield. Similar work has been carried out in an aqueous medium [67].

Coupling on a polymeric support can of course readily be applied to library building *via* combinatorial techniques. Several groups have reported work of this type: thus, Havranek and Dvorak [68] have carried out repeated coupling of 3-substituted 3-(tributylstannyl)allyl alcohols with substrates linked to a Tenta Gel S OH resin to obtain a 21 × 21 library of skipped dienes and a 21 × 21 × 21 library of skipped trienes.

In a completely different approach to reactions on a solid support, Villemin and Caillot [69] ground the catalyst, $Pd(OAc)_2$, with KF on alumina and used the support thus formed to carry out coupling in the absence of solvent using microwave heating; these included reactions involving aryl iodides and either tetramethyltin or tributylvinyltin; the organotin byproduct remained on the support.

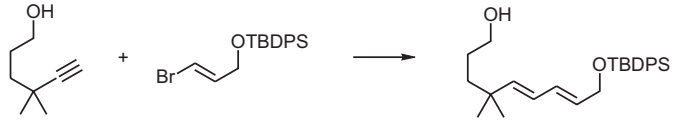
3.2.2.5 Other Advances in Methodology

Solution-phase combinatorial synthesis

Boger et al. [70] constructed mixtures containing 64980 iminodiacetic acid diamides; functionalized diamide precursors were dimerized by means of reactions with bis(tributylstannyl)acetylene using $Pd(PPh_3)_4$ as the catalyst and BHT as an additive to give product libraries suitable for probing protein-protein interactions.

Reactions catalytic in tin

Maleczka et al. have published several papers in this area. They first [71] developed a one-pot hydrostannylation/Stille coupling protocol for reactions between 1-alkynes and bromostyrene to give 1,3-dienes. A combination of Bu_3SnCl (catalytic amount), PMHS and aqueous sodium carbonate (to convert the chloride to TBTO which reacts with PHMS to give Bu_3SnH in situ) in combination with Pd_2dba_3 and trifurylphosphine leads to diene formation. Use of Me_3SnCl instead of the tributyltin chloride [72] improves yields drastically (to up to 90%). Further improvement is obtained in the third protocol reported [73], which was used to prepare (*E*)-alkenes and dienes in shorter reaction times: sodium carbonate is replaced by aqueous KF and catalytic tetrabutylammonium fluoride, which are suggested to render both PMHS and the intermediate trimethylstannylalkene "hypercoordinate" (Scheme 3-10).



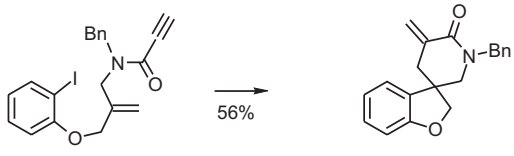
Scheme 3-10 Conditions: 6 mol% Me_3SnCl, aq. KF, cat. TBAF, PMHS, $PdCl_2(PPh_3)_2$ (1 mol%), Pd_2dba_3 (1 mol%), tris(2-furyl)phosphine (4 mol%), ether, 37 °C, 11 h. Yield 72% [73].

Microwave heating has also been used by this group to accelerate one-pot hydrostannylation/Stille coupling reactions [74], which are carried out in a sealed tube.

Cascade processes

Grigg et al. have continued to develop cascade reactions involving palladium-catalyzed hydrostannylation-cyclization-anion capture processes. Thus [75], starting from *O*- and *N*-*a*,*ω*-enyne derivatives of 2-iodoaryl ethers and 2-iodoarylamides and Bu_3SnH, the hydrostannylation (at 25 °C) was followed (at 100–110 °C) by 5-*exo*-*trig* cyclization and finally an intramolecular sp^3-sp^2 Stille coupling to give a wide range of bicyclic spiro- and bridged-ring heterocycles (Scheme 3-11).

Use of a "zipper molecule" with aryl iodide and double bond functionalities [76] results in an increase in molecular complexity, the overall sequence resulting in the formation of five bonds, five stereocenters, two rings, and a tetrasubstituted carbon center.



Scheme 3-11 Conditions: a) Bu_3SnH, $Pd(OAc)_2$, Ph_3P, toluene, 0 °C, 5 min; b) Warm to room temperature; c) 100 °C, 16 h; d) aq. KF [75].

In a further development [77], the "zipper molecule" with an aryl iodide functionality was bound to a Wang resin; Suzuki chemistry was also used, and three small libraries each of 16 compounds were prepared.

Synthesis of ^{11}C-labeled molecules

The use of ^{11}C-labeled methyl iodide in Stille coupling reactions has become a useful, rapid method for preparing substances which can be used for medical applications in positron emission tomography (PET). Thus, Bjorkman et al. [78] have prepared a prostaglandin $F_{2\alpha}$ analog in a synthesis time of 30 min from the end of radionuclide preparation. The same team [79] synthesized labeled tolylisocarbacyclins according to two different protocols; these were used as precursors for PET tracers destined for studies in a living human brain. Tarkiainen et al. [80] labeled a selective ligand for the serotonin transporter; again total synthesis time, including HPLC purification, was 30 min.

3.3 Natural Product Synthesis

Stille reactions are finding increasing use in natural product synthesis, using both intermolecular and the more attractive intramolecular reaction modes. The individual coupling which is made the most use of is that between vinyltins and vinyl halides to form 1,3-dienes.

We shall first discuss intramolecular couplings and then intermolecular processes, which we shall classify according to the coupling partners involved.

3.3.1 Intramolecular Couplings

The intramolecular coupling between a vinyltin moiety and a vinyl iodide moiety has to be called a "success story" in Stille coupling chemistry. It has been applied recently to ring sizes with between 10 and 24 atoms, with reported yields lying between 30 and 92 %. The protocols tend to be similar, and normally involve the use of Pd_2dba_3 in a dipolar aprotic solvent such as DMF or NMP. In the majority of cases, triphenylarsine is used as a co-ligand. DIPEA is often used as an additive.

Pattenden and colleagues have been particularly active in this area. The 19-membered thiazole-based bis-lactone core of pateamine [81] was first synthesized, and later [82] a total synthesis of (–)-pateamine was reported; here, side-chain construction involved an intermolecular vinyltin/vinyl iodide coupling. There followed a further total synthesis, that of the 23-membered 14,15-anhydropristinamycin IIB, a member of the virginiamycin family [83]. Ring closure to give the 16-membered macrolide rhizoxin D [84] used a similar protocol. Finally, we mention the total synthesis of the 20-membered presumed amphidinolide A and its diastereomer in 21 steps [85]; again, inter- and intramolecular Stille couplings were used. Ring closure involved two C_{10}-subunits, one bearing two terminal vinyltin moi-

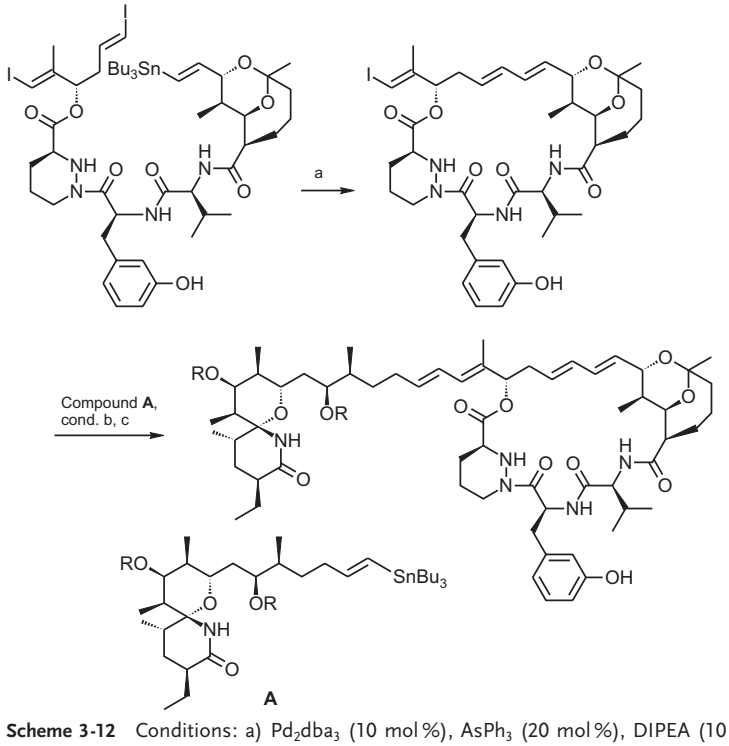
eties, the other a vinylic iodide and an allylic acetate terminus. The vinyl-vinyl coupling was first carried out using the by now standard protocol, and was followed by what is probably the first example of an intramolecular vinyl-alkyl coupling, which required lithium chloride as an additive.

Smith has carried out the first total synthesis of (–)-macrolactin A [86], an effective anti-HIV-1 agent in vitro which contains a 24-membered macrolide ring, and the related (+)-macrolactin E and (–)-macrolactinic acid [46, 86]; intramolecular Stille reactions were also used for constructing diene units prior to cyclization.

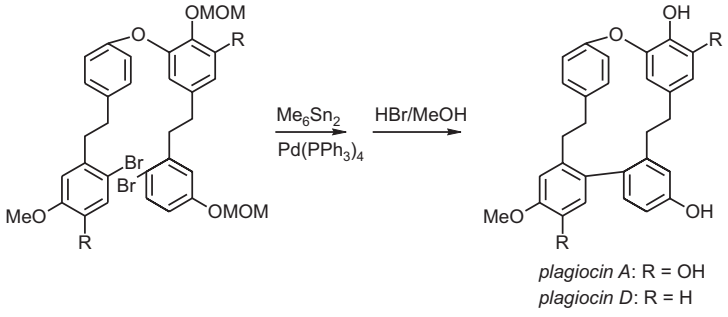
Hodgson et al. [87] synthesized a 10-membered dienone ring in 96 % yield by an intramolecular vinyl-vinyl coupling, one of the double bonds forming the diene unit being exocyclic.

Nicolaou et al. [88] used an inventive strategy (Scheme 3-12) involving a building block with two terminal vinylic iodide moieties, which differ in reactivity, as part of a total synthesis of sanglifehrin.

Thomas et al. [89] prepared two 17-membered macrocyclic tetraenes which are possible precursors to the natural product lankacidin C; in this case, a trisubstituted vinyl iodide was involved and the amount of Pd_2dba_3 required was relatively high (30 mol %).



Scheme 3-12 Conditions: a) Pd_2dba_3 (10 mol %), $AsPh_3$ (20 mol %), DIPEA (10 equiv.), DMF, 25 °C, 72 h, yield 40 %; b) Pd_2dba_3 (10 mol %), $AsPh_3$ (80 mol %), DIPEA (10 equiv.), DMF, 35 °C, 10 h; c) TBAF (4 equiv.), THF, 25 °C, yield 40 % over two steps [88].



Scheme 3-13 [91].

Toshima et al. [90] reported a highly stereoselective total synthesis of the macrolide antibiotic concanamycin F; again, intermolecular and intramolecular vinyl-vinyl couplings were used. While LiCl was used as an additive in the former, it was replaced by DIPEA in the latter.

In a recent publication [47], Toshima et al. reported the use of $PdCl_2(MeCN)_2$ in an intramolecular vinyl-vinyl coupling to provide a 20-membered ring precursor to the macrolide antibiotic apoptolidin; LiCl and $Ph_2PO_2NBu_4$ were used as additives.

Finally, mention must be made of a strategy [91] for an intramolecular aryl-aryl coupling leading to plagiochin A and D: the precursors for both macrocyclic bis(bibenzyls) bear terminal bromoarene moieties, which can undergo reaction with hexamethylditin and $Pd(PPh_3)_4$. This reaction leads to intermediates in which one of the Br atoms has been replaced by an $SnMe_3$ moiety, and further heating gives the coupling product (Scheme 3-13). This procedure can be carried out either stepwise or in one step; yields in all cases are however only moderate (17–44 %).

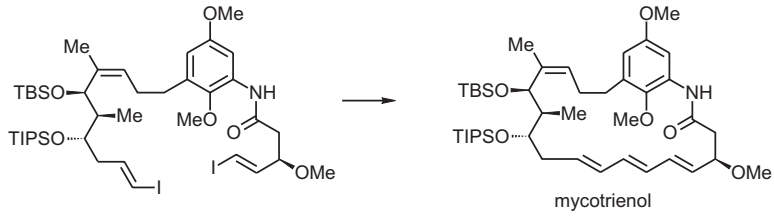
3.3.2 Intermolecular Couplings

3.3.2.1 Vinyl-Vinyl Couplings

There are many reports on intermolecular couplings between vinyltins and vinyl iodides in the recent literature; some of these use the same type of protocol as that discussed above for the intramolecular variant, but several other catalysts have been used successfully, for example $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $PdCl_2(MeCN)_2$, $PdCl_2$(dppf), and $PdCl_2(PhCN)_2$. The list of additives which have been used is correspondingly long.

Nonconventional approaches have been used: thus, Panek and Masse [92] used the reaction between *E*-bis(tributylstannyl)ethene and a macrocycle precursor bearing terminal vinyl iodide moieties in a one-pot coupling-macrocyclization (Scheme 3-14).

A stepwise use of the same organotin in a synthetic approach to taxol was reported by Delaloge et al. [93]; the coupling partner in the second step was a spirocyclic vinyl triflate.



Scheme 3-14 Conditions: a) (*E*)-$Bu_3SnCH{=}CHSnBu_3$, $PdCl_2(MeCN)_2$, DMF, THF; b) CAN, THF/H_2O; c) aq. HF/MeCN (54 % over three steps) [92].

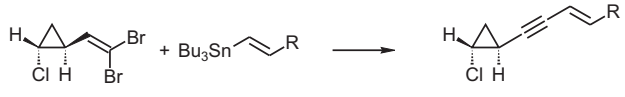
Macrocyclization via dimerization which involves a double cross-coupling is also a highly unusual process: Paterson and Man [94] reported a copper(I) thiophene-2-carboxylate-mediated reaction (in other words, not strictly a Stille coupling) to give a 16-membered macrodiolide. The protocol used was devised by Allred and Liebeskind [95]; although it was mentioned in the First Edition of this book, no other authors appear to have made use of it to date.

A vinyl-vinyl coupling has been made use of in an elegant manner to form an enyne. In studies on the *trans*-chlorocyclopropyldienyne side chain of callipeltoside A, Olivo et al. [96] reacted a dibromovinylcyclopropane derivative with the required vinyltin; the coupling was immediately followed by dehydrobromination (Scheme 3-15); Trost et al. [97] later used this method in a total synthesis of callipeltoside A.

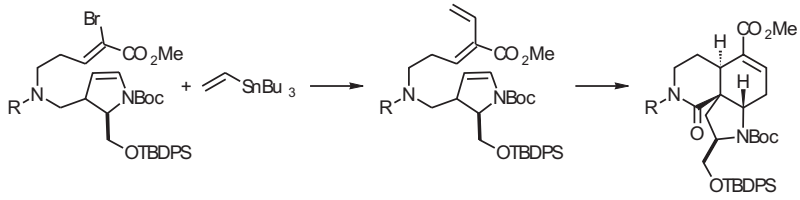
The more conventional vinyl-vinyl coupling methodology has been used in a total synthesis of stipiamide [98], for the completion of the side chain in a total synthesis of (–)-pateamine A [99], and in attaching the tetraenyl moiety (from the tin component) in syntheses of retinoic acid and some ring-modified analogs thereof [100].

A catalyst system first used by Negishi et al. [101] a quarter of a century ago ($PdCl_2(PPh_3)_2$/Dibal-H) was employed [102] in the completion of the lower side chain in (+)-manumycin A. A total synthesis of the manzamine alkaloid ircinal A was reported [103] in which the vinyl-vinyl coupling was followed by a spontaneous intramolecular Diels-Alder reaction (Scheme 3-16).

Meyers et al. [104] used a vinyl-vinyl coupling, which proceeded in 100 % yield, in a synthesis designed to afford the 24-membered macrocycle viridenomycin; the final ring closure was, unfortunately, not successful. Hanessian and co-workers [105] reported a total synthesis of the 16-ring macrolide bafilomycin A1. In a total synthesis of (+)-crocacin C, Dias and de Oliveira [106] constructed an (*E,E*)-dienamide moiety via a vinyl-vinyl coupling, and Feutrill et al. incorporated such a coupling in the first asymmetric synthesis of crocacin D [107].



Scheme 3-15 R = CH_2OH (65 %), $CH{=}CHCH_2OH$ (95 %), $CH{=}CHCO_2Et$ (80 %). Conditions: Pd_2dba_3, $(4\text{-}MeOC_6H_4)_3P$, DIPEA, DMF, 80 °C [96].



Scheme 3-16 Intermediate not isolated. Conditions: $Pd(PPh_3)_4$, toluene, Δ Yield 68 % [103].

A key step in the formal total synthesis of the marine metabolite (+)-calyculin A reported by Barrett and co-workers [108] involves the construction of the cyanotetraene unit via a dienyl iodide/dienyltin coupling, the latter being itself derived from bis-(tributylstannyl)ethene. Final assembly of the 25-carbon chain (containing 12 stereocenters) of bafilomycin V1 by Marshall and Adams [109] involved an acetylene-derived vinyltin and a vinyl iodide of similar complexity.

Paquette et al. [110] reported a highly convergent three-component, 64-step total synthesis of the potent immunosuppressive agent (–)-sanglifehrin A, with the penultimate step involving a vinyl-vinyl coupling.

Sinz and Rychnovsky [111] carried out a total synthesis of the 36-membered macrolide dermostatin A, which contains an acid- and light-sensitive polyene sequence; this was constructed from a vinyl iodide and a stannyl tetraenol which was used in excess (4:1). A (2*E*, 4*Z*, 6*E*)-conjugated triene system was obtained in 95 % yield with 90 % geometrical purity as part of a total synthesis of two so-called AK-toxins [112].

In an interesting synthesis of *β*-carotin and the closely-related (*3R*,*3′R*)-zeaxanthin, three building blocks (C_{14}, C_{12}, C_{14}) were linked together by means of a Stille reaction in which the C_{12} unit was an *α*,*ω*-bis(tributylstannyl)pentaene [113].

Similar Stille-coupling-based strategies for the construction of himbacine analogs have been reported by Van Cauwenberge et al. [114] and Wong et al. [115].

Finally, in this section a report which shows just how effective a Stille coupling can be under ideal conditions: during the course of a synthesis of analogs of 9-*cis*-retinoic acid, Otero et al. [116] carried out a vinyl-vinyl coupling which proceeded in yields between 75 and 95 %, with reaction times of 5 min at room temperature being achieved.

3.3.2.2 Other Couplings Involving Vinyltins

Brückner et al. [117] used a coupling between vinyltins and butenolide triflates in the synthesis of analogs of the antibiotics lissenolide and tetrenolin. Smith and co-workers [118] used a coupling between a vinyltin and an oxazole triflate as a key step in the 27-step total synthesis of the antiproliferative agent (–)-phorboxazole A. Buynak et al. [119] used a number of coupling strategies involving vinyl and organotins bearing other functionalities (aryl, 2-pyridyl, vinyl) as well as hexamethylditin in the synthesis of 7-[(*E*)-alkylidene]cephalosporins, which are potential enzyme inhibitors.

Kanekiyo et al. [120] used couplings between vinyl or alkynyltins and organyliodides in the total syntheses of three β-carboline alkaloids, while Feutrill et al. [121] made use of couplings between either a vinyltin and an aryl bromide or an allyltin and an aryl triflate in the synthesis of 12-membered unsaturated benzolactones present in the so-called salicylhalamides, which are highly cytotoxic marine metabolites.

During the course of the synthesis of an analog of the antibiotic medermycin, Brimble and Brenstrum [122] converted an aryl bromide functionality to an aryl methyl ketone moiety by coupling the former with α-ethoxyvinyltributyltin and then carrying out an acid hydrolysis. Shipe and Sorensen [123] used a coupling reaction between a vinyltin and an allylic acetate as a key step in a convergent synthesis of the tricyclic carbon framework of the guanacastepene family of natural products.

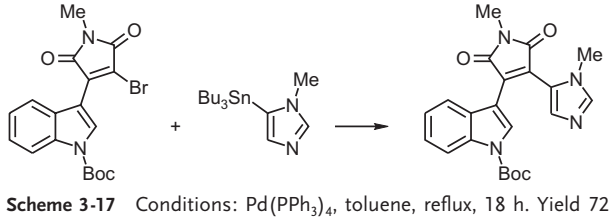
A report of an unusual double coupling between a hexacyclic species bearing two aryl iodide moieties and a highly sterically congested vinyltin was published by Overman and co-workers [124]; this formed part of the total synthesis of the polypyrrolidinoindoline alkaloids quadrigemine C and psycholeine.

3.3.2.3 Couplings of Heterocyclic Organotins

Richecour and Sweeney [125, 126] used a coupling between a stannylfuranone and a vinyl iodide in a highly enantioselective total synthesis of the 2(5*H*)-furanone, hamabiwalactone B. Nicolaou and co-workers [127, 128] reported the first total synthesis of epothilone E and analogs with modified side chains; the latter (thiazol-4-yl, 2-furyl, 2-thienyl, 3-pyridyl, Ph) were derived from the organotin species involved in the couplings.

A stannylpyridine was made use of in the key step of the synthesis of the nonopiate alkaloid (±)-epibatidine [129]. Steglich and co-workers [130] prepared the marine alkaloid didemnimide C by a coupling (Scheme 3-17) between a stannylimidazole and a maleimide.

Pattenden et al. [131] carried out a total synthesis of a bis-deoxylophototoxin (the probable biological precursor of the neurotoxin lophotoxin) which proceeded via a coupling between a highly functionalized vinyl iodide and a trisubstituted stannylfuran.



Scheme 3-17 Conditions: $Pd(PPh_3)_4$, toluene, reflux, 18 h. Yield 72 % [130].

3.3.2.4 Other Intermolecular Couplings

A reaction between an allyltin and an allyl halide was used in the total synthesis of (±)-A80915G, a member of the napyradiomycin family of antibiotics [132]. The key step in the total synthesis reported by Bringmann and Günther [133, 134] of dioncophylline B, a naphthylisoquinoline alkaloid, was a biaryl coupling.

Alkynyltins served as coupling partners in the total synthesis of (+)- and (–)-furocaulerpin [135] and (–)-ichthyothereol [136].

Two unusual stannyl coupling partners also deserve mention: in the total synthesis of the marine natural product eleutherobin reported by Danishefsky and coworkers [137], a nortriterpenoid tricycle (containing a vinyl triflate functionality) was coupled with a trimethylstannylmethyl derivative of arabinose. The key step in the synthesis of a carbapenem active against methicillin-resistant *Staphylococcus aureus* was the cross-coupling of an enol triflate and an amino-substituted sp^3 carbon center bound to a stannatrane moiety [138].

3.4 Organic Synthesis

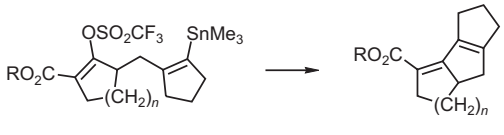
The distinction between organic synthesis and natural product synthesis is to some extent artificial, but an attempt has been made to include molecules in this section which are of synthetic interest, without being natural products or analogs thereof.

The coupling reactions discussed will be classified as in the previous section; this may well be useful from a retrosynthetic as well as a systematic point of view. Publications involving the use of various types of organotin will however be mentioned only once.

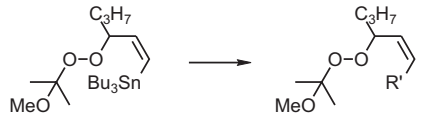
3.4.1 Vinyl-Vinyl Couplings

Few intramolecular reactions of this type have been reported, but Piers et al. [139] have shown that it is possible to use Stille coupling to form five-membered rings which link a bicyclic system, and in doing so convert it to a tricyclic system (Scheme 3-18).

Marsault and Deslongchamps [140] have employed vinyl-vinyl coupling in the formation of macrocycles as well as of tricyclic systems in high yields and of high purity. The aim of this work was to increase the efficiency of the transannular Diels-Alder reaction to form tri- and tetracycles; another type of combination of a Stille and a Diels-Alder reaction has been reported by Skoda-Földes et al. [141], who coupled steroidal iodoalkenyl substrates with vinyltributyltin in the presence of



Scheme 3-18 $n = 1$, R = Me: 80 %; $n = 2$, R = Et: 99 %; $n = 3$, R = Me: 74 %. Conditions: $Pd(PPh_3)_4$, CuI, THF or NMP [139].



Scheme 3-19 X = Cl, Br; R′ = PhCO (69 %), (*E*)-PhCH=CHCH$_2$ (55 %). Conditions: Pd_2dba_3 (5 mol %), (2-furyl)$_3$P (10 mol %) [142].

dienophiles. The products were novel pentacyclic steroids, which in some cases were formed in high yields and with high stereoselectivity.

The high tolerance of Stille couplings to the presence of reactive functional groups is illustrated by work published by Dussault and Eary (Scheme 3-19) [142], who coupled vinyltins bearing a peroxide functionality with vinyl as well as allyl, acyl, and alkynyl halides.

Shen and Wang [143] have carried out reactions between 1,1-dibromo-1-alkenes and vinyl, furyl, or aryltins. The nature of the product depends on the reaction conditions: (*Z*)-bromoalkenes are generally formed when the reaction is run in toluene or dioxane with tris(2-furyl)phosphine as the ligand, and these can be converted in a one-pot procedure to trisubstituted alkenes. However, under appropriate conditions (DMF, tris(4-methoxyphenyl)phosphine as ligand) internal alkynes can be prepared in high yields under very mild reaction conditions.

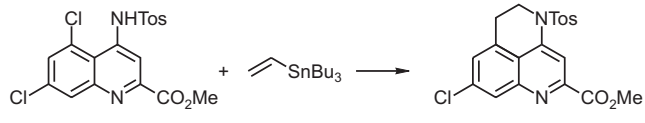
3′-Spirosultone nucleosides can be prepared [144] by means of couplings involving vinyl-, allyl-, and aryltins.

3.4.2
Other Couplings Involving Vinyltins

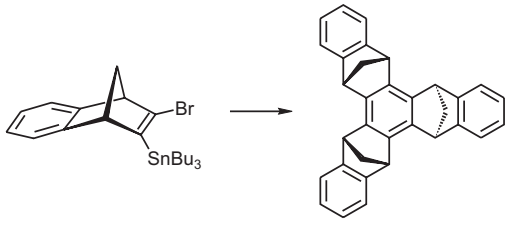
A sequential reaction leading directly from an azabicyclic to a diazatricyclic system has been reported by Hume and Nagata (Scheme 3-20) [145].

Paley et al. [146] have achieved the preparation of a series of enantiomerically pure 1- and 2-sulfinyldienes starting from vinyltins and halovinyl sulfoxides. Reactions involving vinyl, 2-furyl, and 1-methyl-3-indolyltins were used for the functionalization of *β*-lactam rings [147]. Stereoselective construction of conjugated trienoic acids via two successive Stille couplings was reported by Thibonnet et al. [148].

Li et al. [149] have prepared ribonucleotide reductase inhibitors by couplings of vinyltributyltin with substituted 2-chloropyridines or the corresponding triflates. Quayle et al. [150] have carried out sequential couplings starting from 1,1-bis(tributylstannyl)-1-alkenes to afford (*E*)-vinylstannanes and thence defined trisubstituted alkenes. However, in certain cases involving bulky electrophiles butyl migration is observed.



Scheme 3-20 Conditions: Pd(PPh$_3$)$_4$, NMP, 100 °C. Yield 63 % [145].



Scheme 3-21 $Pd(OAc)_2$ (7 mol %), PPh_3 (14 mol %), toluene, 110 °C, 24 h. Yield 58 % [157].

Dykstra and Dinnino [151] have prepared alkenyl- and alkynyl-functionalized carbapenems starting from the corresponding organotins. Littke and Fu [152] reported a general method for the Stille cross-coupling of aryl chlorides; vinyl, phenyl, and butyl groups were transferred from tin, the catalyst system used being Pd_2dba_3/tBu$_3$P/CsF.

Sato and Narita [153] synthesized acetyl- and propionylpyrazines by couplings between bromopyrazines and tributyl(1-ethoxyalkenyl)tins and subsequent hydrolysis; CuI was used as an additive. Xu et al. [154] carried out syntheses of non-nucleoside reverse transcriptase inhibitors both in solution and on a Wang resin support using couplings between vinyltins and aryl iodides or aryltins and vinyl iodides.

Couplings involving stannylenamines [155] and stannylenamides [156] have also been reported recently.

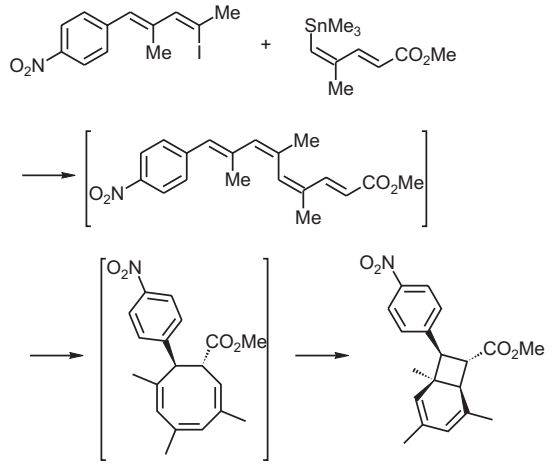
Finally, some less conventional approaches to the use of vinyltins: Paulon et al. [157] have carried out Pd-catalyzed trimerization reactions of oligocyclic alkenes "under Stille or Grigg reaction conditions". Interestingly, the direct reaction between molecules containing the 1,2-dibromoalkene moiety and hexabutylditin gives only the *anti*-cyclotrimer, while trimerization of the corresponding preformed 1-bromo-2-trialkylstannylalkene gives a mixture of *syn* and *anti* isomers (Scheme 3-21).

Beaudry and Trauner [158] report a cascade Stille coupling/electrocyclization between a dienylstannane and a dienyl iodide as part of an approach to the immunosuppressants SNF3345 C and SNF4435 D (Scheme 3-22).

The reactions between acyl chlorides and an *O*-stannyl ester-functionalized vinyltin [159] also involve a subsequent cyclization to give α-pyran-2-ones in good yields (Scheme 3-23).

3.4.3
Couplings of Aryltins

The use of fluorous tin reagents is still not common, but one example of the transfer of the phenyl group from tris[(perfluorohexyl)ethyl]phenyltin in a biaryl coupling has been reported [160]. Aryl transfer has also been used in the synthesis of 5,8-disubstituted α-tetralones [16], of bis-C-glycosylated diphenylmethanes [162], of C-glycosylated biphenyls [163], and of 8-substituted tetracycline derivatives [164] (here alkynyl transfer was also reported).



Scheme 3-22 Conditions: $PdCl_2(MeCN)_2$, DMF, room temperature, 40 % [158].

Scheme 3-23 Conditions: $Pd(PPh_3)_4$ (5 mol %), dioxane, 50 °C, 6 h. 15 Examples, yields 43–85 % [159].

Reactions between sterically congested arylstannanes and 2-bromonaphthoquinones were reported by Echavarren et al. [165], while Albrecht and Williams [166] synthesized the biaryl moiety of the TMC-95 natural products by Stille coupling and Gundersen et al. [167] prepared a series of 6-arylpurines and studied their antibacterial activity.

Okujima et al. [168] prepared 6-tributylstannylazulene (the first organotin azulene) from 6-bromoazulene and hexabutylditin; coupling with aryl and azulenyl halides was successful. Scott and Soderberg [169] used a Stille coupling between aryltributyltins and iodocyclohexenones in a novel synthesis of carbazolones.

3.4.4
Couplings of Heterocyclic Organotins

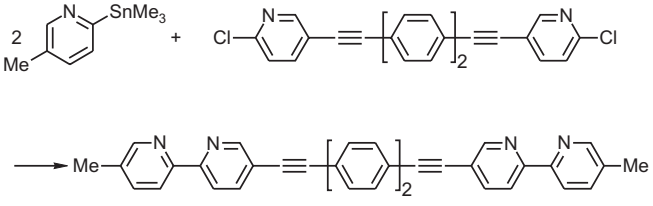
Carbonylative coupling between a protected 1-stannylglucal derivative and 5-bromo-7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives was reported by Jeanneret et al. [170]; vinyl and 2-furyl groups could also be transferred from tin to this bicyclic system. Kelly et al. [171] synthesized quater- and quinquepyridyls by Stille coupling. 2-Trimethylstannylpyrroles underwent coupling with bromobenzene and 1,4-dibromobenzene, as shown by Dijkstra et al. [172].

Fan and Haseltine [173] prepared novel 1,3,5-tripyridylbenzenes using a threefold Stille coupling involving stannylpyridines. The latter were employed by Romero-Salguero and Lehn [174] in reactions leading to ditopic bidentate ligands, and thence to linear tetradentate ligands with four pyridine and two pyridazine

rings. Lam et al. [175] used pyridyltins in the synthesis of phenol-bridged dinucleating phenanthroline-pyridine ligands. Jones and Glass [176] used reactions of 2-pyridyltins in the construction of bis-tridentate metal ligands containing pyridine and pyrimidine rings. Michl and co-workers [177] synthesized 5-brominated and 5,5′-dibrominated 2,2′-bipyridines and 2,2′-bipyrimidines, which can be used in the preparation of metal-complexing molecular rods, via couplings of stannylpyridines.

Mabon et al. [178] carried out coupling reactions between 3,4-bis(tributylstannyl)-2(5*H*)-furanone and various organoiodides, the 4-stannyl group being selectively replaced. Clapham and Sutherland [179] coupled 4-stannyloxazoles with various electrophiles, while Alvarez et al. [180] synthesized 5-arylpyrrolo[1,2-c]pyrimidin-1(2*H*)-ones by replacing a trimethylstannyl moiety by aryl residues.

Baxter [181] has reported the preparation of conjugatively bridged bis- and tris-5-(2,2′-bipyridines) of nanoscopic dimensions (length up to 350 nm) via Stille coupling reactions involving 2-trimethylstannylpyridines and bis (tributylstannyl)-ethyne (Scheme 3-24).



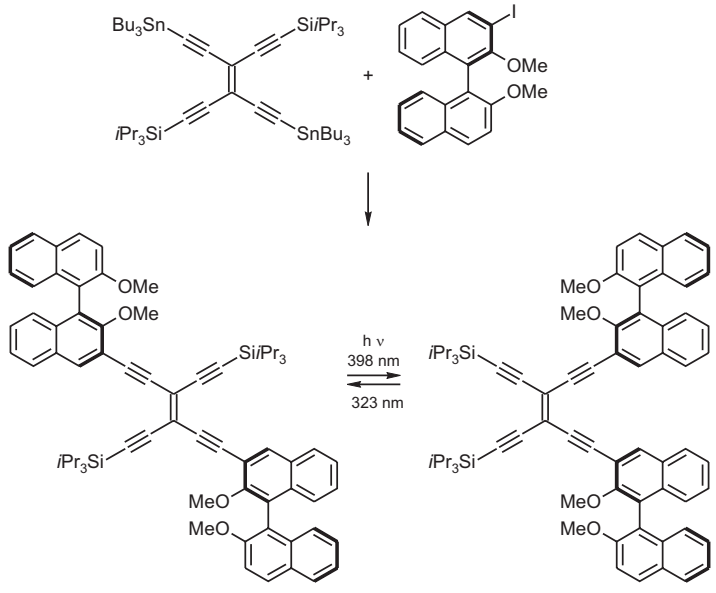
Scheme 3-24 Conditions: $Pd(PPh_3)_4$, DMF, 150 °C, 48 h [181].

3.4.5
Couplings of Alkynyltins

Godt [182] coupled arylbutadiynylstannanes with substituted aryl iodides. Saalfrank et al. [183] allowed stannylalkynes or bis(trimethylstannyl)alkyne to react with bromoallenes to afford conjugated alkynylallenes or diastereomeric ynediallenes.

Diederich et al. [184] synthesized a novel fully reversible, light-driven molecular switch by a cross-coupling between a stannylated tetraethynylethene and a 3-iodo-1,1′-binaphthyl derivative (Scheme 3-25).

Palmer et al. [185] prepared a stable dehydro[14]annulene by a reaction of a 1-silyl-2-stannylethyne and a bromoarene moiety. Lukevics and co-workers [186] synthesized unsymmetric diynes by reacting alkynylstannanes with terminal bromoalkynes.



Scheme 3-25 Conditions: Pd_2dba_3, $(2\text{-furyl})_3P$, CuI, THF, reflux, 30 min [184].

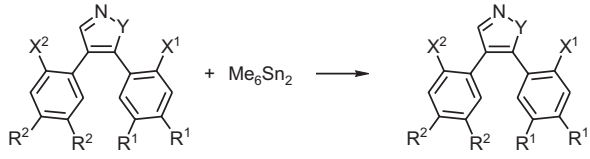
3.4.6
Couplings of Miscellaneous Organotins

Bach and Krüger [187] have used Stille couplings in the preparation of 2,3-di- and 2,3,5-trisubstituted furans: regioselective replacement of the bromine in 2-position of the 2,3-dibromofuran moiety by an allyl group was observed, followed by replacement of the remaining bromine in the 3-position by a methyl group originating from the relatively unreactive tetramethyltin.

Reactions between allenylstannanes and β-iodovinylic acids lead selectively to α-pyrones [188].

Bach and Heuser [189] have prepared 2′-substituted 4-bromo-2,4′-bithiazoles by regioselective cross-coupling involving transfer of a series of groups, mainly alkyl, from tin to the thiazole moiety.

Olivera et al. have carried out intramolecular couplings involving the use of hexamethylditin; in one case [190] 4,5-bis(2-halopyrimidines) and the ditin underwent a cascade stannylation-biaryl coupling, while in the other [191] phenanthro[9,10-d]pyrazoles and phenanthro[9,10d]isoxazoles were prepared using a similar methodology (Scheme 3-26). In both cases, the reactions were carried out in heavy-wall sealed pressure tubes to avoid dehalogenation.



Scheme 3-26 Conditions: $PdCl_2(PPh_3)_2$ (5 mol%), dioxane, 140 °C, sealed tube [191].

3.5 Polymer Chemistry

A very considerable body of work on polymeric (and oligomeric) materials has been published in the past few years, but a closer look reveals that the majority of it deals with systems based on the thiophene nucleus, either alone or in combination with other repeating units. Pyrrole and furan moieties have also been used in polymer formation. A further group of papers deals with polyphenylenevinylene and related systems.

3.5.1 Materials Based Solely on Thiophene (or Selenophene) Units

Regioregular head-to-tail polythiophenes can be prepared by Stille reactions of thiophenes bearing bromine and trimethylstannyl substituents in positions 2 and 5; this approach was used by McCullough et al. [192] and Goto and colleagues [193]. Functionalization of the thiophene moiety in position 3 leads to variations in the properties of the polymer obtained: thus, the latter authors used oxazolin-2-yl residues separated from the thiophene ring by an ethyl or a *p*-phenylene spacer. Stepwise synthesis involving a second monomer with silyl and stannyl substituents in positions 2 and 5 introduces end groups and makes possible the formation of defined oligomers [194].

Iraqi and Barker [195] have prepared thiophene polymers bearing 3-hexyl substituents, while Moreau and co-workers [196] used 3-octyl substituents to prepare poly(4-octylbithiophene) starting from the corresponding tributylstannyl-substituted monomer. Ewbank et al. prepared amine-functionalized polythiophenes (in a CuO-co-catalyzed coupling) [197, 198].

Solid-phase synthesis of thiophene oligomers on a (polystyrene/divinylbenzene) Merrifield resin has been described by Malenfant et al. [199]. The same group [200] used Stille reactions of 4-octyl-2-trimethylstannylthiophene and 5-trimethylstannyl-2,2′-bithiophene to construct a series of asymmetric oligothiophenes to serve as model compounds for solid-phase synthesis.

An organometallic functionalization has been reported by Higgins et al. [201], who carried out Stille couplings between 1,1′-bis(tributylstannyl)ferrocene and 5-iodooligothiophenes to give 1,1′-bis(5-oligothienyl)ferrocenes which were then polymerized.

A different approach to oligothiophenes was reported by Van Keuren et al. [202], who coupled 2,5-bis(trimethylstannyl)thiophene (and other stannylthiophenes)

with 5,7-dibromo-2,3-didecylthieno[3,4]bipyrazine under controlled conditions. Hicks and Nodwell [203] prepared a series of oligothiophenes with 2-mesitylthio substituents by coupling 2-stannylthiophenes with 2-bromo-5-mesitylthio-thiophenes. 3,4-Ethylenedioxy-substituted thiophene rings were also used.

Ng et al. [204] prepared a homologous series of regioregular oligo(3-alkyl)thiophenes via an alternating sequence of bromination and Stille cross-coupling. The tin building block involved was a bithiophene with terminal tributylstannyl and trimethylsilyl groups.

Malenfant et al. [205] synthesized a conducting polythiophene with aliphatic ether dendritic solubilizers: 2,5-bis(trimethylstannyl)thiophene was coupled with second- and third-generation dendrimer-oligothiophene dibromide hybrid macromonomers.

Post-functionalization of polythiophenes is another interesting approach: thus, Li et al. [206] brominated poly(3-hexylthiophene) and used the resulting polymer for cross-coupling with tributyltin compounds containing aryl, thiophene, furyl, vinyl, or alkynyl groups; a similar procedure was used later by Holdcroft et al. [207].

Conducting polymers containing tungsten-capped calixarenes were reported by Vigalok and Swager [208], the organotin species involved in the preparation of the monomers being 2-tributylstannyl-3,4-ethylenedioxythiophene. Xia et al. [209] have prepared dendritic thiophene derivatives using Kumada, Stille and Suzuki coupling methods.

Selenophenes do not appear to have been the subject of much interest, though the first examples of oligoselenophenes were first reported several years ago by Nakanishi et al. [210].

3.5.2
Materials Based on Thiophene in Combination with Other Repeating Units

Hucke and Cava [211] synthesized a series of mixed thiophene/furan oligomers consisting of up to 11 rings starting from 2-trialkylstannylfuran and -thiophene. Mello et al. [212] reported the formation of Langmuir and Langmuir-Blodgett films from a semi-amphiphilic *N*-hexylpyrrole-thiophene AB copolymer; the starting materials were 1,5-dibromothiophene and 1,5-bis(trimethylstannyl)-*N*-hexylpyrrole. Langmuir films were also prepared by Dhanabalan et al. [213] from polymers of the type $(ABAC)_n$ and $(ABAA)_n$; the unit ABA was formed from N-dodecyl-2,5-bis(trimethylstannylthienyl)pyrrole, the second unit being 2,5-thienylene, *p*-phenylene or dioctyloxy-*p*-phenylene.

Van Mullekom et al. [214] prepared three series of alternating donor-acceptor-substituted co-oligomers using 2-trimethylstannylthiophene and *N*-*t*Boc-2-trimethylstannylpyrrole as electron-rich starting materials, and bromosubstituted quinoxaline or 2,1,3-benzothiadiazole as the electron-poor component. Nurulla et al. [215] co-polymerized 2,5-bis(trimethylstannyl)thiophene or 5,5′-bis(trimethylstannyl)-2,2′-bithiophene with 2-decyl-4,7-dibromobenzimidazole or *N*-methyl-2-decyl-4,7-dibromobenzimidazole and [216] prepared copolymers of thiophene and various 2-alkyl-4,7-dibromobenzimidazoles.

Trouillet et al. [217] were able to obtain soluble copolymers starting from a bis-stannyl-substituted 3-octylthiophene tetramer and 5,5′-dibromo-2,2′-bipyridine, either alone or (perhaps more interestingly) as its Ru(II) complex ($Ru(bipy)_3^{2+}$).

Aromatic building blocks have also been used: thus, Saadeh et al. [218] prepared poly(2,5-pentylphenylene-*co*-furan) and poly(2,5-pentylphenylene-*co*-thiophene) starting from 2,5-tributylstannylfuran and -thiophene. Devasagayaraj and Tour [219] prepared a donor/acceptor/passivator polymer with sequential electron-rich *N*,*N*′-dimethyl-3,4-diaminothiophene, electron-deficient 3,4-dinitrothiophene and passivating phenylene repeat units. Bras et al. [220] synthesized conjugated gels based on thiophene units derived from thiophene and oligothiophene units bearing chloro and tributylstannyl moieties on the one hand and 1,3,5-tribromobenzene on the other.

Poly(*p*-phenylene-*co*-2,5-thiophenylene) polymers were prepared by Song and Shim [221] and Forster et al. [222]. Saadeh et al. [223] extended the methodology by using more complex *p*-dibromoaromatics and two bromoaromatic moieties linked by a spacer. Vigalok et al. [224] reported the formation of conducting polymers of tungsten (VI)-oxo calixarenes substituted by bithiophene groups; the Stille chemistry involved was the reaction of 2-tributylstannylbithiophene with bromoarene functionalities of the tungsten calixarene complex.

Reactions carried out by Loewe and McCullough [225] between (*E*)-bis(tributylstannyl)ethene and 2,5-dibromo-3-dodecylthiophene led to a polymer which was at least 90 % regioregular.

It is also possible to incorporate silole units into the copolymer chain, as was shown by Lee et al. [226] who reacted 2,5-dibromosilole with 2-stannylethylenedioxythiophene derivatives.

3.5.3
Materials Based on Pyrrole and Furan

Groenendaal et al. [227] have prepared a series of donor-oligopyrrole-acceptor molecules by an initial reaction between *p*-nitrobromobenzene and *N*-*t*Boc-2-trimethylstannylpyrrole followed by bromination with NBS and a further cross-coupling with *p*-trimethylstannylanisole; oligomers with up to four pyrrole units were isolated. Dhanabalan et al. [228] synthesized an alternating copolymer with *N*-dodecylpyrrole and 2,1,3-benzothiadiazole units starting from the distannylpyrrole; this work was later extended [229] to include incorporation of *p*-phenylene units.

3.5.4
Polyphenylenevinylene and Related Materials

The basic chemistry involved here is the reaction between (*E*)-bis(tributylstannyl)-ethene and a substituted 1,4-dibromobenzene moiety, the nature of which determines the polymer properties. Examples have been provided by Chiavarone et al.

[230], who incorporated a 2,5-O$(CH_2)_{12}$O bridge, and by Naso et al., who used various substituents [231] as well as starting from 2,3,5,6-tetrafluoro-1,4-diiodobenzene [232]. A pyridopyrazine substituent was introduced by Jonforsen et al. [233], while the same group synthesized poly(quinoxaline vinylene)s and poly(pyridopyrazine vinylene)s [234].

3.5.5
Other Materials

Bromine-containing polyether dendrimers were functionalized by Groenendaal and Frechet [235] using coupling reactions of 2-trimethylstannylthiophene and 2-trimethylstannylpyridine. 4-Tributylstannyl-2,6-oligopyridines and 4-bromo-2,6-ologopyridines can undergo cross-coupling to yield branched oligopyridines with 8 to 14 pyridine units, as shown by Pabst and Sauer [236].

Stille coupling of dihaloarenes and a bis(tributylstannyl)aromatic species has been used by Bouachrine et al. [237] to prepare conjugated polymers functionalized by chelating subunits such as a dibenzo-18-crown-6 ether or 2,2′-bipyridyl. Morin et al. [238] have synthesized poly(*N*-alkyl-2,7-carbazoles).

3.6
Inorganic Synthesis

Many chemists regard organotin compounds themselves as being inorganic, but this section will almost without exception not involve their synthesis. It seems only logical to organize this section, as above, in terms of the organotin substrate involved.

3.6.1
Couplings of Vinyltins

The synthesis of heterobimetallic sesquifulvalene and hydrosesquifulvalene manganese(I) chromium(0) complexes was reported by Tamm et al. [239]; it involved the reaction between cycloheptatrienyltrimethyltin and (iodocyclopentadienyl)tricarbonylmanganese with subsequent chromium functionalization. Elaboration of (fluoroaryl)tricarbonylchromium complexes by reaction with vinyltributyltin was described by Wilhelm and Widdowson [240].

Coupling reactions of 1,1-bis-stannyl-1-alkenes carried out by Quayle et al. have already been referred to in the "organic" section [150]. Closely related chemistry has been reported by Kang et al. [241], who successfully coupled (*Z*)-1,2-bis(trimethylstannyl)alkenes with hypervalent iodonium salts using 5 % $PdCl_2$ as catalyst at room temperature in DMF. When a 1:1 ratio was used, the tin in the 1-position was replaced selectively, while the use of two equivalents of the iodonium salts afforded trisubstituted alkenes. Carbonylative couplings were also possible, and the palladium could be replaced by 5 % CuBr.

David-Quillot et al. [242] prepared (*E*)-aryl- or heteroarylvinylgermanes starting from (*E*)-1-tributylstannyl-2-trialkyl (or triphenyl)germylethenes and organohalogens, while Hoshi et al. [243] replaced the stannyl moiety in (*E*)-1-(tributylstannyl)-1-(trimethylstannyl)-1-alkenes by a phenyl group; though this alkene can be considered as clearly sterically congested, the product yield (using conditions earlier described by Corey et al. [244]) was 93 %.

3.6.2
Couplings of Aryltins

The aryltins discussed in this section are all derivatives of ferrocene, which have been the object of much study by Ma et al. These authors have carried out reactions of tributylstannylferrocene with bromopyridines [245], bromothiophenes [246], and other haloheterocycles [247] as well as of a diaminomethyl-substituted stannylferrocene [248]. Similar reactions of bis(tributylstannyl)ferrocene with heterocyclic bromides have also been reported [249–251]. Bis(trimethylstannyl)ferrocene has been allowed to undergo coupling with enantiopure 2,2′-diiodo-1,1′-binaphthyl [252]. The yield, however, was poor and the enantiomeric excess zero; the main product (46 %, 0 % *e.e.*) was that of methyl transfer to the binaphthyl moiety.

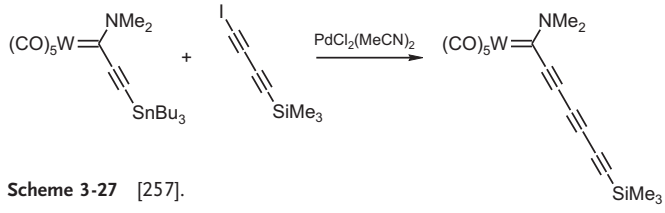
3.6.3
Couplings of Heterocyclic Organotins

Pabst et al. [253] used a coupling of the type heteroaryltin/heteroaryl bromide to prepare a dimeric tris(2,2′-bipyridine)Ru(II) complex. Constable et al. [254] reported couplings between uncomplexed 6-stannyl-2,2′-bipyridine with tetrakis(4-bromophenyl)methane and of a 6(4-stannylphenyl)-2,2′-bipyridine with 1,3,5-trichlorotriazine; these were carried out with the goal of preparing metallodendrimers containing ruthenium.

Rose-Münch and colleagues [255] reacted the tricarbonylchromium complex of chlorobenzene with a 2-tributylstannylthiophene to form an intermediate used for the synthesis of organochromium/organoiron dipoles. The same group [256] coupled the same type of organotin with (η^5-(1-chloro)(4-methoxy)cyclohexadienyl)-tricarbonyl manganese, the product subsequently undergoing aromatization to give the cationic arene complex.

3.6.4
Couplings of Alkynyltins

Hartbaum and Fischer synthesized complexes of tungsten and molybdenum by reacting a complex containing an ethynyltin moiety with an iododialkynylsilane [257] (Scheme 3-27) and with complexes of the type $HalML_n$ with M = Fe, Ru, Mn, Re [258].

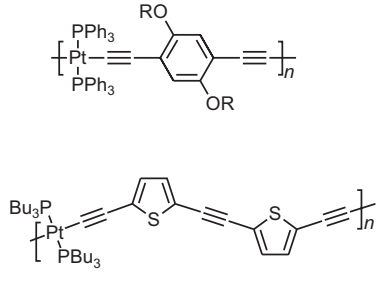


Scheme 3-27 [257].

In an extension of work referred to above, Rousset et al. [259] prepared (*E*)-5-(tributylstannylmethylidene)-5*H*-furan-2-ones from tributylstannylethyne and *O*-tributylstannyl 3-iodopropenoate derivatives.

LoSterzo et al. have published several papers in this area, and LoSterzo has given a personal account of much of his research [260]. Thus, this group used the Stille coupling to label steroids with the ethynylcyclopentadienyltricarbonylmanganese moiety (via steroidal triflates) [261]. Coupling of diiodobenzene or -thiophene with tributylstannylethyne yields bis(stannylethynyl) derivatives, which can be allowed to react further in a one-pot procedure with either aromatic diiodides or iron or platinum iodides to form acetylenic and metallaacetylenic polymers in high yields (degree of polymerization, DP, 3–9) [262]. The same methodology ("extended one pot") used a series of coupling reactions, starting from 2,5-diiodothiophene and tributylethynyltin, to form palladium-ethynylthiophene oligomers [263].

In a further modification [264], platinum-connected 1,4-diethynylbenzene derivatives (Scheme 3-28), and analogous rigid-rod compounds with other aromatic or thiophene moieties incorporated, were prepared.



Scheme 3-28 [264].

3.7 Conclusions

In spite of their known toxicity, organotin compounds are still invaluable in cross-coupling reactions because of the large variety of residues on tin that can be transferred. The main advantage of organotins over derivatives of other elements is the ease of their preparation and their stability once prepared.

The advances in methodology described above will certainly contribute to the development of Stille-type chemistry, and in the years ahead we can expect a further rapid expansion in its use.

3.8 Experimental Procedures

3.8.1 Spirocycle A (Scheme 3-11) [75]

A mixture of palladium acetate (11 mg, 0.05 mmol), triphenylphosphine (26 mg, 0.1 mmol) and the alkyne (0.5 mmol) in toluene (5 mL) was stirred at 0 °C under nitrogen whilst tributyltin hydride (160 mg, 0.5 mmol, 0.148 mL) was added dropwise over 5 min. The reaction mixture was then allowed to warm to room temperature over 1 h before being heated at 100 °C for 16 h. After cooling to room temperature, a saturated aqueous solution of potassium fluoride (5 mL) was added and the mixture stirred for 1 h, filtered, the organic phase dried (Na_2SO_4), filtered and the filtrate evaporated. The residue was purified by column chromatography (SiO_2) eluting with mixtures of ether:petroleum ether. The spirocyclic product was obtained in 67 % yield as colorless needles from petroleum ether/ether, m. p. 85–86 °C.

3.8.2 *tert*-Butyl 3-[1-Methyl-4-(3-methyl-3*H*-imidazol-4-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl]indole-1-carboxylate (Scheme 3-17) [130]

A solution of 5-tributylstannyl-1-methyl-1*H*-imidazole (3.0 g, 8 mmol), the bromo-(indolyl)maleimide (1.65 g, 4 mmol), and tetrakis(triphenylphosphine)palladium(0) (96 mg, 0.08 mmol) in toluene (100 mL) was heated at 110 °C for 20 h. After evaporation of the solvent, the product was purified by repeated flash chromatography on silica gel ($CHCl_3/CH_3OH$ = 10:1 and EtOAc/PE = 7:1). The product was a dark orange solid (1.19 g, 72 %), m. p. 82–84 °C.

3.8.3
4,4′-Bis[5-ethynyl(5′-methyl-2,2′-bipyridyl)]1,1′-biphenyl (Scheme 3-24) [181]

2-Trimethylstannyl-5-methylpyridine (80 mg, 1.88×10^{-4} mol), the bridged bis-(2-chloropyridine) (270 mg, 1.05×10^{-3} mmol), and $Pd(PPh_3)_4$ (23 mg, 1.99×10^{-5} mmol) in 8 mL of DMF were heated at 150 °C for 48 h. Upon cooling to ambient temperature, a solid formed which was isolated by filtration under vacuum, washed with DMF, and twice recrystallized from 4-mL portions of boiling DMF to yield 40 mg (40 %) of the product (m. p. > 320 °C) after drying under vacuum as a khaki-yellow powder.

3.8.4
Pentacarbonyl[1-dimethylamino-7-trimethylsilyl-2,4,6-heptatriynylidene]tungsten (Scheme 3-27) [258]

A solution of 1-dimethylamino-3-(tributylstannyl)propynylidenepentacarbonyltungsten (3.47 g, 5.00 mmol), $IC{\equiv}C{-}C{\equiv}CSiMe_3$ (1.24 g, 5.00 mmol), and $[Cl_2Pd(MeCN)_2]$ (130 mg, 0.50 mmol) in 20 mL toluene was stirred at room temperature for 10 h. The solvent was removed in vacuo. The remaining dark brown residue was dissolved in 60 mL THF and filtered with 150 mL THF:CH_2Cl_2 (1:1) through a 10-cm layer of silica. The solvent of the filtrate was removed in vacuo, the residue dissolved in 40 mL pentane, and chromatographed at −40 °C on silica. With pentane:CH_2Cl_2 (9:2) a red-orange band was eluted. Removal of the solvent in vacuo afforded 130 mg (5 %) of the product as a red powder.

Abbreviations

dba	dibenzylideneacetone
Dibal-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine (Hünig's base)
DMF	*N,N*-dimethylformamide
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1′-bis(diphenylphosphino)ferrocene
MEM	methoxymethyl
NBS	*N*-bromosuccinimide
PMHS	poly(methylhydrosiloxane) $(MeHSiO)_n$
TBAF	tetrabutylammonium fluoride
TBDPS	*t*-butyldiphenylsilyl
*t*Boc	*t*-butoxycarbonyl
TBTO	tetrabutyltin oxide

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4
Organosilicon Compounds in Cross-Coupling Reactions

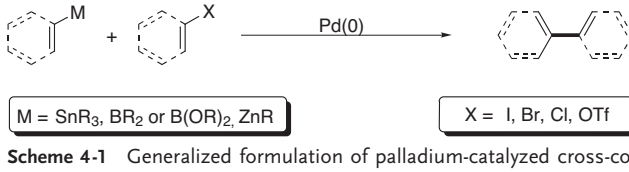
Scott E. Denmark and Ramzi F. Sweis

4.1
Introduction

4.1.1
Background of Silicon-Based Cross-Coupling Reactions

Silicon, an element widely used in many facets of organic chemistry [1], was not effectively employed in cross-coupling reactions until sixteen years after the first reported transition metal-catalyzed coupling reactions by Corriu, Kumada, and Tamao [2]. Most early developments in this field were achieved through the use of organoboron (1979) [3], organozinc (1977) [4], and organotin (1977) [5] coupling partners (Scheme 4-1).

Environmentally benign and of low molecular weight, silicon possesses many properties that make it an ideal donor of organic groups in a cross-coupling reaction. However, despite its location in Group 14 of the Periodic Table, along with tin of similar electronegativity (1.9 to 1.96 for tin) [6], tetracoordinate organosilanes are not capable of transferring one of the attached organic groups to palladium, as is possible with tetracoordinate organostannanes [7]. To overcome this limitation, several research groups have provided the framework upon which modern organosilicon-cross-coupling is based, namely, the use substituted organosilicon compounds that are capable of expanding their valency [8]. Through the addition of an appropriate silicophilic nucleophile, an in-situ-generated pentacoordinate silane can effectively transfer an unsaturated organic group (Scheme 4-2). This



Scheme 4-1 Generalized formulation of palladium-catalyzed cross-coupling reactions.

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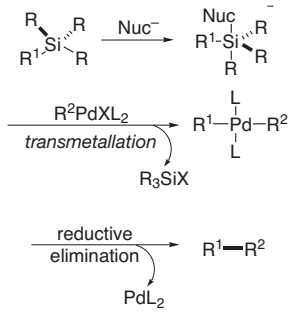


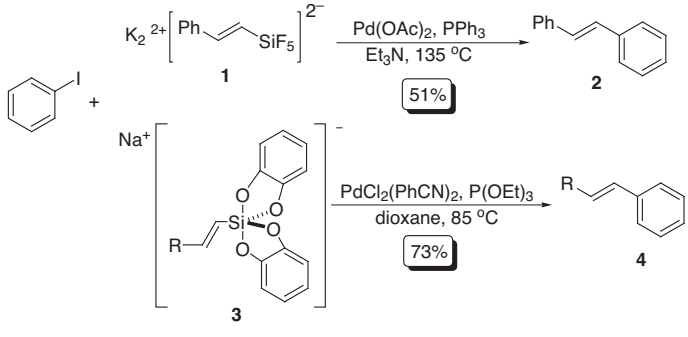
Scheme 4-2 Mechanistic pathway of palladium-catalyzed cross-coupling.

feature allowed for the rapid development of silicon-cross-coupling methods which continues today.

The current advanced state of organosilicon coupling has now become a practical, viable, and – in some cases – superior, cross-coupling method compared to the more commonly employed organoboron and -tin couplings. The early developments and exemplification of organosilicon-cross-coupling were thoroughly reviewed by Hiyama in the first edition of this book [9]. This review will present a brief account of the early discoveries and advances, as well as a thorough overview of the recent progress in this field. The relevant literature published during the first half of 2003 will be covered.

4.1.2 Discovery and Early Development Work

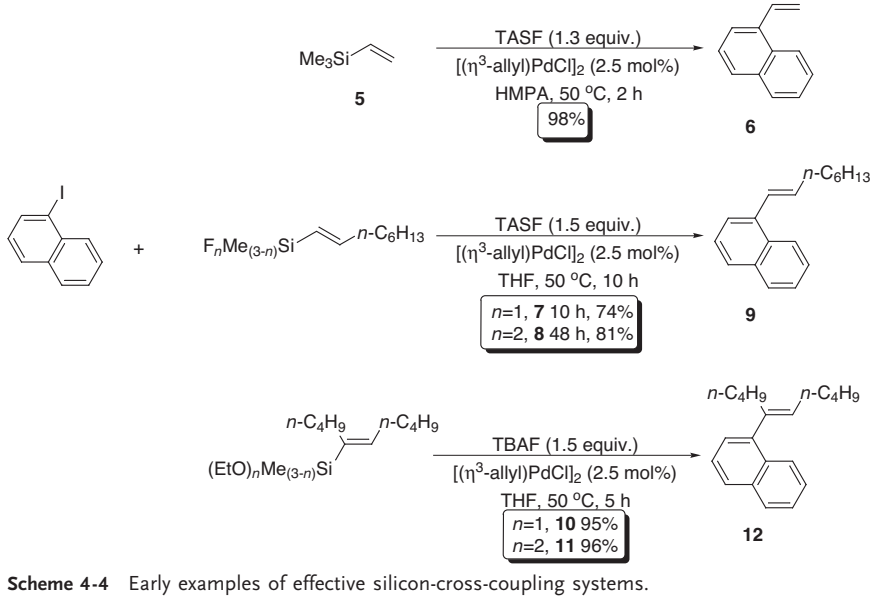
One of the earliest reports of silicon cross-coupling by Kumada and Tamao involved the use of the dipotassium salt of pentafluorostyrylsilicate **1** (Scheme 4-3) [10]. Despite the harsh conditions employed, this reaction provided the first indication that higher valent silanes could become viable donors in palladium-catalyzed cross-coupling reactions. This concept was further reinforced in a finding by Hosomi et al. that a pentacoordinate silane, sodium alkenylbis(catecholato)silicate **3**, could



Scheme 4-3 Use of pentacoordinate silanes in cross-coupling reactions.

effectively undergo coupling with several aryl iodides, albeit at elevated temperatures (Scheme 4-3) [11].

The use of penta- and hexacoordinated silanes illustrated what was required to polarize the carbon-silicon bond sufficiently for successful cross-coupling. Yet the technology at this stage was very limited in substrate scope and reaction efficiency. Beginning in 1988, several reports by Hiyama and Hatanaka demonstrated that such limitations could be overcome through the use of an additive to generate the requisite pentacoordinate siliconate moieties in situ (Scheme 4-4) [12]. By employing stable and easily synthesized tetracoordinate silanes, the substrate scope could be significantly expanded. Nucleophilic fluoride sources were found to be the additive of choice due to the high enthalpy (159 kcal mol^{-1}) of a Si-F bond [13]. Yet this was not sufficient in all cases. Whereas vinyltrimethylsilane readily coupled in the presence of a fluoride source [tris(dimethylamino)sulfonium difluorotrimethylsilicate or TASF], other alkenyltrimethylsilanes such as (1-octenyl) trimethylsilane did not [14]. It was reasoned that this failure was due to the reduced polarity of the carbon-silicon bond because of the additional substitution on the alkene. The problem was overcome through the use of the corresponding fluorosilanes **7** and **8**, which possessed more polarized carbon-silicon bonds (Scheme 4-4). This finding clearly demonstrated that the addition of a nucleophilic fluoride source was not sufficient to promote all organosilane cross-coupling, but that polarized silane precursors such as fluorosilanes would have to be employed. Tamao and coworkers demonstrated that alkoxysilanes **10** and **11** (Scheme 4-3) exhibited similar reactivity to Hiyama's fluorosilanes with tetra-*n*-butylammonium fluoride (TBAF) as the promoter [15].



Scheme 4-4 Early examples of effective silicon-cross-coupling systems.

Numerous reports highlighting several permutations of the fluorosilane cross-coupling with aryl, alkenyl, and even alkyl halides were published in the following years after these initial developments [16]. As shown in Chart 4-1, this body of work encompassed a wide range of fluorosilane precursors, electrophiles, and even documented multicomponent permutations. This provided a glimpse into the prodigious potential of organosilicon cross-coupling, and therefore suggested that its continued refinement could match the efficiency, selectivity, and versatility of the more actively studied Suzuki-Miyaura coupling of organoboron compounds and the Stille-Migita-Kosugi coupling of organotin compounds.

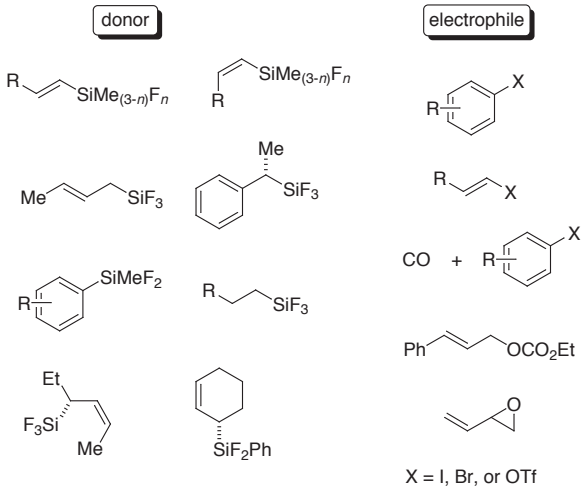


Chart 4-1 Permutations of organofluorosilane cross-coupling reactions.

4.2 Modern Organosilicon-Cross-Coupling

As a result of intensive investigation into many permutations of transition metal-catalyzed cross-coupling and its growing popularity in organic synthesis, the impetus behind modern research in this area has shifted from the exploratory phase of 10–20 years ago to that of an optimization phase. The existence of the organotin, -boron, -zinc, -copper, and -silicon cross-coupling methods provides the synthetic chemist with many options from which to consider a cross-coupling reaction. The question of which process constituted the superior method did not have a clear and distinct answer. The characteristics of a truly superior cross-coupling system can be summarized as the following:

1. Diverse and readily accessible methods to install the coupling substrate functionality from commercially available starting materials.
2. Easily activated, high-yielding coupling under mild conditions.

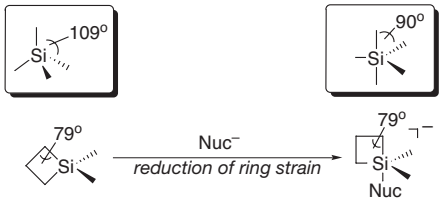
3. Minimal byproduct generation, preferably by employing low molecular-weight donors.
4. Excellent functional group compatibility.
5. General stability of the cross-coupling substrates.
6. Low toxicity of precursors, substrates, and generated byproducts.

These constraints posed many difficult challenges to those developing silicon-based cross-coupling because the standard by which any advancement would be judged was the Stille and Suzuki coupling methods that, to date, were the most commonly employed. Despite the fact that these venerable methods embody several of the characteristics of an ideal cross-coupling, there was still room for improvement, and silicon-based cross-coupling methods have recently been engineered to address these shortcomings [17].

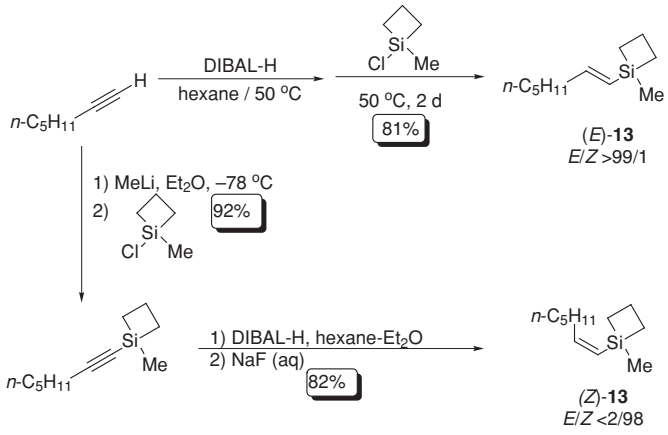
4.2.1 Organosiletanes

In view of the accepted dogma that the generation of a pentacoordinated siliconate is a prerequisite to successful cross-coupling, a more reactive organosilicon cross-coupling system was developed by employing siletanes (silacyclobutanes) as the nucleophilic coupling partner. The use of siletanes is based on previous work on the aldol addition reaction that manifested the enhanced Lewis acidity of siletanes compared to simple trialkylsilanes [18]. This property – known as "strain release Lewis acidity" – has its origins in the difference in coordination geometry between four-coordinate (tetrahedral) and five-coordinate (trigonal bipyramidal) silicon species (Scheme 4-5). Thus, the angle strain in a four-coordinate siletane (79° versus 109°) is significantly relieved upon binding a fifth ligand to produce a trigonal bipyramidal species (79° versus 90°) in which the siletane bridges an apical and an equatorial position [19]. Thus, the propensity of the siletane toward activation as the siliconate complex is enhanced and hence the ate complex is activated to transfer a group in the key transmetallation.

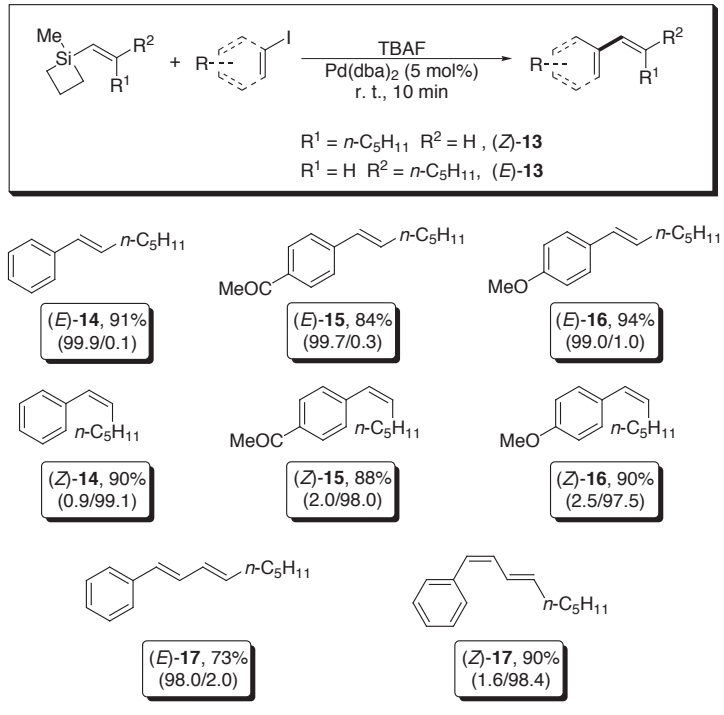
Silacyclobutanes (*E*)-**13** and (*Z*)-**13** are readily synthesized in geometrically homogeneous form in one or two steps from commercially available precursors (Scheme 4-6). In addition, they are easy to handle as they are air-stable and can be purified by simple distillation. These substrates undergo cross-coupling reactions with aryl halides when promoted by an activator in the presence of a palladium catalyst (Scheme 4-7) [20]. The use of TBAF as the nucleophilic activator



Scheme 4-5 The concept of "strain release Lewis acidity."



Scheme 4-6 Synthesis of (*E*)- and (*Z*)-heptenylsiletanes.

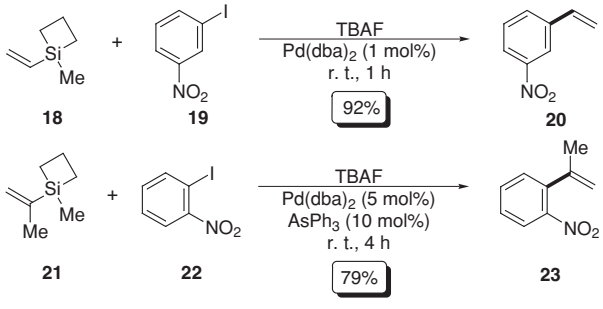


Scheme 4-7 Coupling of (*E*)- and (*Z*)-heptenylsiletanes to aryl and alkenyl iodides.

is most effective, whereas other fluoride activators (TASF, tetra-*n*-butylammonium triphenyldifluorosilicate – TBAT, and KF) are incapable of promoting the reaction. A survey of catalysts reveals the "ligandless" palladium(0) source, $Pd(dba)_2$ or $Pd_2(dba)_3$, to be superior to other palladium sources. The reactions are remarkable for the extremely mild conditions employed (*ca.* 10 min at ambient temperature) to

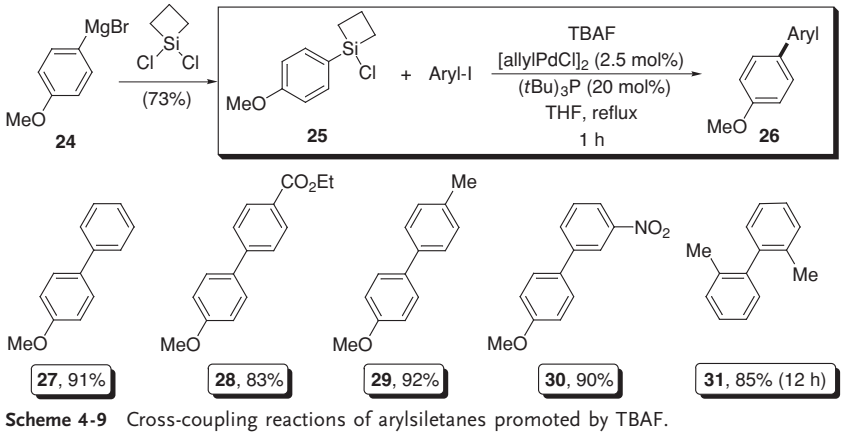
cross-couple with a variety of alkenyl and aryl iodides. This high reactivity is not affected by the electronic environment at the aryl iodides. In addition, the high stereoselectivity with respect to the olefin configuration in the coupling is notable (greater than 98 % in most cases). Even in coupling to alkenyl iodides, the olefin configuration of both coupling partners is highly conserved.

The scope of transferable groups can be extended to simple vinyl and propenyl moieties (Scheme 4-8) [21]. In certain cases wherein the reaction times are longer, the use of triphenylarsine is added to prevent precipitation of the catalyst when turnover is slow. The generality of the electrophilic substrate is found to reflect that of the alkenylations in Scheme 4-7.



Scheme 4-8 Cross-coupling reactions of vinyl and propenyl siletanes.

The synthesis of unsymmetrical biaryls remains an active area of organic synthesis [22]. Accordingly, mild biaryl coupling was also investigated by use of the siletane moiety (Scheme 4-9) [23]. However, heteroatom substitution on the silicon atom of the siletane is necessary to enhance the polarity and thus reactivity of the sp^2 carbon-silicon bond. The starting siletanes are easily synthesized from aryl Grignard reagents and 1,1-dichlorosiletane. Unlike the coupling reactions with alkenyl siletanes, the biaryl couplings are slow at room temperature, and therefore, the reactions are run in THF under reflux. Addition of tri-*t*-butylphos-



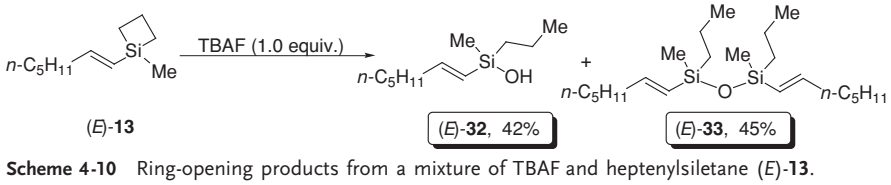
Scheme 4-9 Cross-coupling reactions of arylsiletanes promoted by TBAF.

phine is necessary to suppress competing homocoupling of the aryl iodide. Most of the biaryl coupling reactions are complete within 1 h, independent of the electronic nature of the iodides. Steric factors reduce the rate of coupling, but even 2,2′-dimethylbiphenyl (**31**) is readily prepared by this method.

The unique characteristics of each siletane coupling system (aryl, vinyl, alkenyl) required optimization of catalyst, ligand, temperature, and solvent. A mild and highly efficient siletane cross-coupling method that is compatible with a variety of substrates with varying electronic and steric demands was achieved for all systems investigated. The ease of siletane incorporation, stability, and high coupling reactivity was, when initially disclosed, a significant advance in the field of silicon cross-coupling chemistry.

4.2.2 Organosilanols

In the course of studying the organosiletane cross-coupling reactions, it was noted that a significant amount of heat is generated when combining the siletane with the TBAF solution. Isolation of the products of this mixture revealed that two compounds are generated: the silanol (*E*)-**32** and disiloxane (*E*)-**33** (Scheme 4-10) [24]. These products are clearly derived from ring opening of (*E*)-**13** by the combined action of TBAF and water (from the crystal hydrates in commercial TBAF · $3H_2O$). These products were subsequently evaluated as cross-coupling substrates with successful results. This finding contradicted the hypothesized source of siletane coupling efficiency, namely, strain-release Lewis acidity. Ironically, although the initial hypothesis was shown to be false, the recognition that silanols and disiloxanes could react with equal efficiency allowed for an expanded set of substrates to be examined for new silicon cross-coupling methods.



Scheme 4-10 Ring-opening products from a mixture of TBAF and heptenylsiletane (*E*)-**13**.

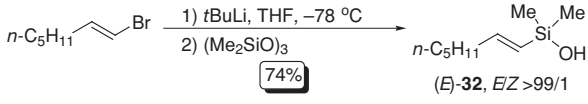
4.2.2.1 Tetrabutylammonium Fluoride (TBAF)-Promoted Coupling

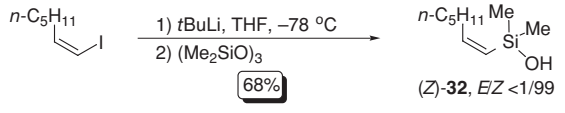
An organosilanol cross-coupling system, developed by Denmark et al., was devised and developed on the basis of insights obtained in organosiletane coupling. In this system, alkenyldimethylsilanols (*E*)-**32** and (*Z*)-**32**, along with two analogs, diisopropylsilanols (*E*)-**34** and (*Z*)-**34** were employed.

The heptenylsilanols (*E*)-**32** and (*Z*)-**32** are synthesized from established procedures as outlined in Scheme 4-11 [25]. In both cases, reaction of the appropriate alkenyllithium agent with hexamethylcyclotrisiloxane (D3) produces the desired

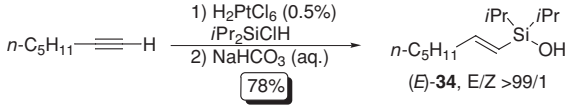
dimethylsilanol in good yield and high geometrical purity to a variety of aryl and alkenyl iodides (Scheme 4-11).

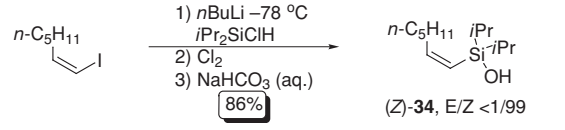
The preparation of 1-heptenyldiisopropylsilanols (*E*)-**34** and (*Z*)-**34** illustrates two other methods for the synthesis of silanols, both of which employ chlorodiisopropylsilane (Scheme 4-12). In the former case, the silicon group is installed by platinum-catalyzed hydrosilylation of 1-heptyne, followed by alkaline hydrolysis. In the latter case, chlorodiisopropylsilane serves as an electrophile in a reaction with the lithioalkene to afford the intermediate (1-heptenyl)diisopropylsilane in 95 % yield. This, in turn, is converted to the (*Z*)-**34** by chlorination and mild hydrolysis.





Scheme 4-11 Synthesis of (*E*)- and (*Z*)- heptenyldimethylsilanols.

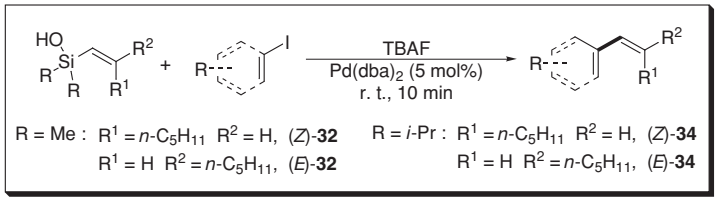


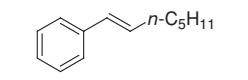


Scheme 4-12 Synthesis of (*E*)- and (*Z*)- heptenyldiisopropylsilanols.

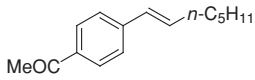
A few notable advantages of organosilanols are: (1) their ability to be synthesized by multiple methods in geometrically homogenous form; (2) their stability and ease of handling; and (3) the ability to modify the spectator group on the silicon to modulate reactivity and/or suppress side reactions. Not surprisingly, the cross-coupling reactions of the silanols are just as rapid and high yielding as the previously reported siletane couplings, albeit with marginally lower stereoselectivities (Scheme 4-13) [26]. Both electron-rich and electron-poor aryl iodides react with equal facility. The cross-coupling of the isopropylsilanols (*E*)-**34** and (*Z*)-**34**, however, afford higher stereoselectivities and display similar reaction times, although in slightly lower yields.

The extension of this method to more highly substituted substrates has also been demonstrated. Substituted alkenylsilanols (*E*)-**36** and (*Z*)-**36**, could be synthesized in high-yielding sequences and undergo cross-coupling with a variety of aryl iodides (Scheme 4-14) [27]. Most of the reactions proceed smoothly using the same mild conditions as previously employed, in spite of the rates being generally lower than observed with silanols (*E*)-**32** and (*Z*)-**32**. Interestingly, (*Z*)-**36** coupled at

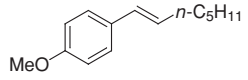




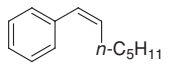
(*E*)-**14**
R = Me: 91%, (97.8/2.2)
R = *i*Pr: 82%, (99.2/0.8)



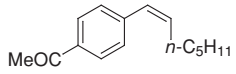
(*E*)-**15**
R = Me: 93%, (96.5/3.5)
R = *i*Pr: 80%, (99.5/0.5)



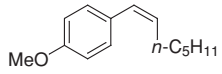
(*E*)-**16**
R = Me: 95%, (97.2/2.8)



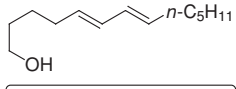
(*Z*)-**14**
R = Me: 90%, (2.7/97.3)
R = *i*Pr: 81%, (0.6/99.4)



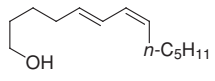
(*Z*)-**15**
R = Me: 92%, (4.8/95.2)
R = *i*Pr: 86%, (1.0/99.0)



(*Z*)-**16**
R = Me: 94%, (2.6/97.4)



(*EE*)-**35**
R = Me: 91%, (95.8/4.2)
R = *i*Pr: 87%, (97.8/2.2)

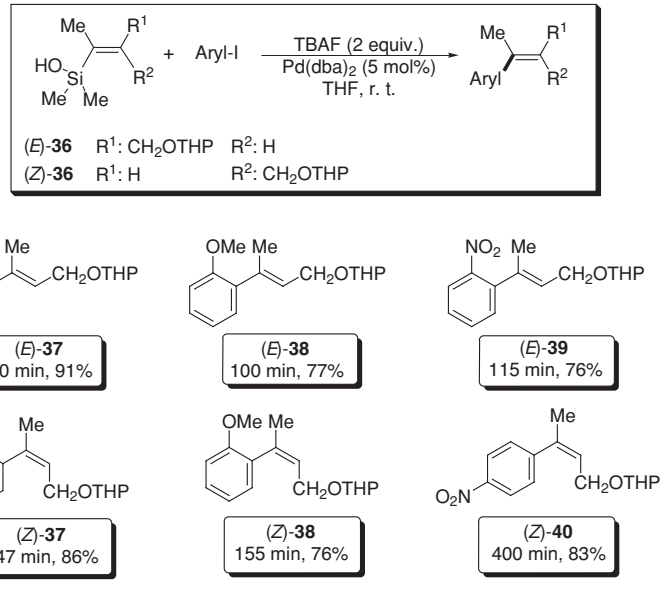


(*EZ*)-**35**
R = Me: 72%, (4.6/95.4)

Scheme 4-13 Cross-coupling reactions of (*E*)- and (*Z*)- alkenylsilanols promoted by TBAF.

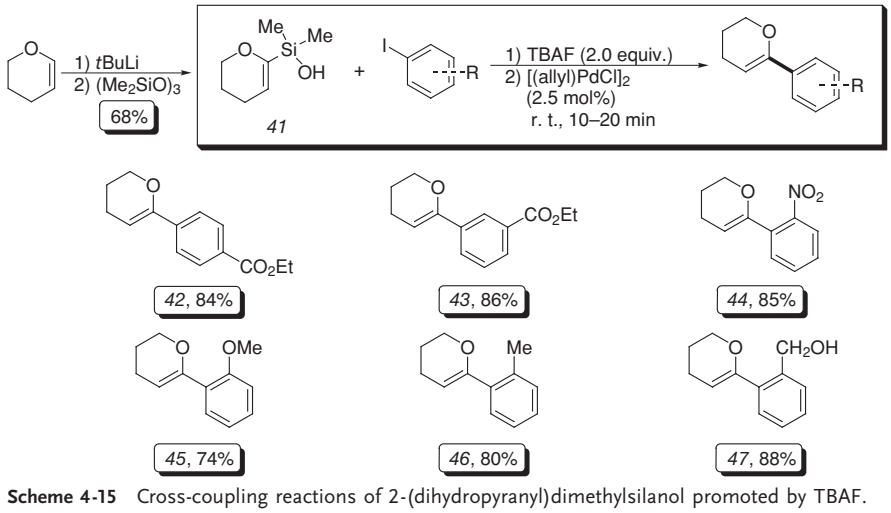
consistently lower rates than (*E*)-**36**. Clearly, increased substitution on the alkenylsilanols attenuates reactivity, but this is significant only in the cases involving the *Z*-isomers. Reactions with (*Z*)-**36** also produce small amounts of dimers arising from homocoupling of the aryl iodide. This problem is overcome by the portionwise addition of the electrophile. In general, these coupling reactions tolerate several functional groups and the rates are generally independent of steric and electronic factors (*cf.* Scheme 4-14 for reaction times). Overall, these reactions highlight the use of (*E*)-**36** and (*Z*)-**36** as useful stereodefined alkenylating agents. In addition, the products represent stereodefined trisubstituted allylic alcohols, the syntheses of which are otherwise not trivial.

Simple alkenyl groups and unsaturated units bearing a pendant heteroatom such as an α-alkoxy group can be effectively transferred from a silanol moiety. Silanols containing α-alkoxyalkenyl groups are readily synthesized from the corresponding enol ethers [28]. For example, 2-(5,6-dihydro-4*H*-pyranyl)dimethylsilanol **41** is produced by lithiation of pyran and trapping with hexamethylcyclotrisiloxane (D_3)

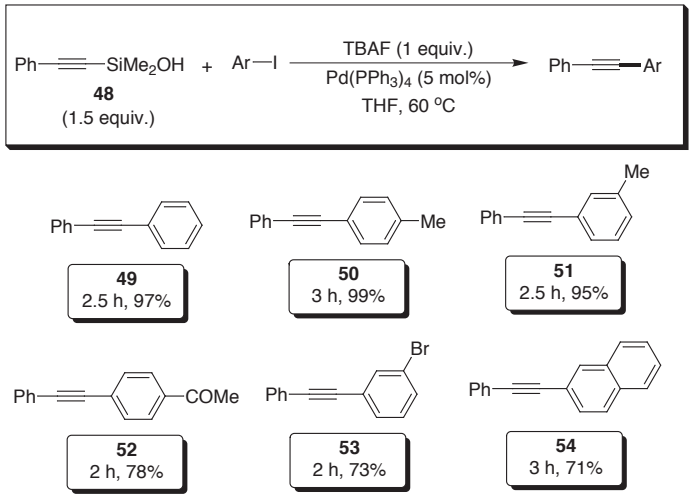


Scheme 4-14 Cross-coupling reactions of hindered silanols promoted by TBAF.

(Scheme 4-15). This silanol undergoes cross-coupling with several aryl and alkenyl iodides with the same facility, mildness, and functional group compatibility as the silanols previously mentioned. In all these cases, though, the catalyst used is $[(allyl)PdCl]_2$ instead of $Pd(dba)_2$, primarily for ease of product purification. The higher efficiency of the silicon- compared to tin-based cross-coupling process is illustrated by the synthesis of **46**. This compound was made previously by a Stille coupling which required 2 h in refluxing acetonitrile to give the same final yield [29].



Scheme 4-15 Cross-coupling reactions of 2-(dihydropyranyl)dimethylsilanol promoted by TBAF.

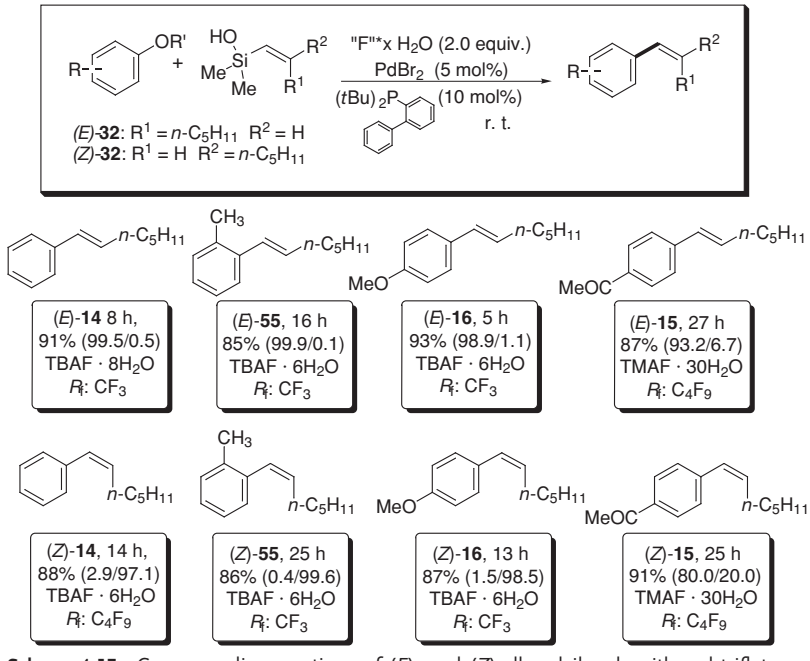


Scheme 4-16 Cross-coupling reactions of alkynylsilanols promoted by TBAF.

The cross-coupling reactions of aryl- and alkenylsilanols are adequate replacements for the analogous Stille and Suzuki reactions. Yet the scope of organosilanol coupling extends beyond this. It has also been shown that the use of alkynylsilanols presents a viable alternative to the classic Sonogoshira-type couplings of alkynes.

The coupling reaction of alkynyltrimethylsilanes using a palladium/copper(I) cocatalyst system has been reported and thoroughly studied [30]. However, the cross-coupling of alkynylsilanols in the presence of TBAF proceeds under still milder conditions (Scheme 4-16) [31]. Dimethyl(phenylethynyl)silanol, **48**, undergoes successful cross-coupling with a variety of aryl iodides. With only one equivalent of TBAF at 60 °C, the reactions are generally high yielding and complete within a few hours. This method is general, in that other alkynylsilanols containing a variety of pendant groups also successfully react in the same fashion.

One of the most appealing aspects of conventional cross-coupling systems is the scope of employable electrophiles. The use of triflates, derived from phenol and enol moieties, in the Stille and Suzuki coupling reactions effectively expanded their scope beyond halides [32]. Similar success has recently been achieved in silanol-cross-coupling. Organotriflates can react with organosilanols when promoted by a nucleophilic fluoride source (Scheme 4-17) [33, 34]. Essential to the success of this reaction is the use of biphenyl(di-*t*-butyl)phosphine as the ligand an palladium [35]. However, the susceptibility of triflates to undergo hydrolysis in the presence of a nucleophilic promoter severely hampers this process. Remarkably, the addition of water attenuates the nucleophilicity of TBAF and TMAF (tetramethylammonium fluoride) such that the triflate (or nonaflate – $ROSO_2n\text{-}C_4F_9$) remains intact, thereby allowing the cross-coupling reaction to proceed at room temperature and in generally high yields [36]. The amount of water added is dictated by the elec-



Scheme 4-17 Cross-coupling reactions of (*E*)- and (*Z*)-alkenylsilanols with aryl triflate and nonaflates promoted by hydrated TBAF.

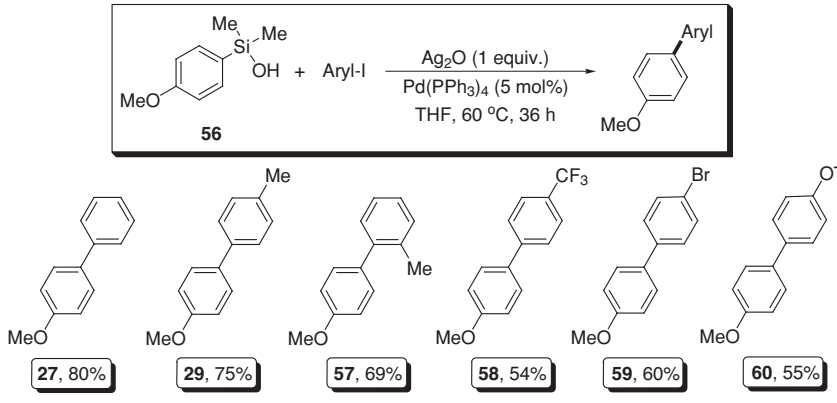
tronic properties of the triflate, with electron-deficient aryl triflates, (*E*)- and (*Z*)-**15**, requiring significantly more water to suppress side-product formation from triflate hydrolysis.

4.2.2.2 **Non-Fluoride-Promoted Coupling**

Despite the success of the TBAF-promoted coupling reactions of organosilanes, it was recognized that certain incompatibilities can arise from the use of a fluoride promoter. For example, the fluoride ion would be incompatible in complex molecule synthesis wherein one of the coupling partners might contain silyl protective groups. In recent years, therefore, many research groups have actively sought an adequate replacement for fluoride as the nucleophilic promoter in silicon based cross-coupling. Through optimization and evaluation, a promoter scope that rivals that of organoboron coupling has been developed.

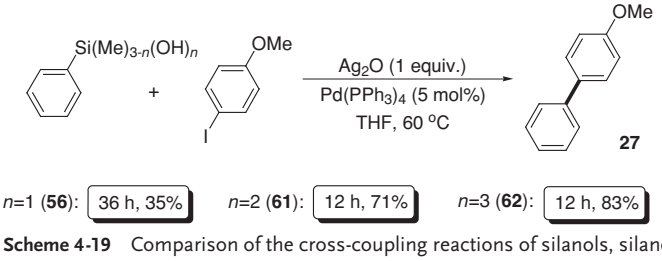
In the first organosilanol cross-coupling system developed by Mori et al., silver(I) oxide was reported to be a highly effective activator that promoted the coupling of aryl silanol **56** to a variety of aryl iodides (Scheme 4-18) [37]. The arylsilanols are prepared by lithiation of an aryl halide followed by trapping with hexamethylcyclotrisiloxane (D3) (cf. Scheme 4-11). The common silicon coupling promoter, TBAF, is ineffective in this method. The ability of silver oxide to promote this coupling is attributed to two different roles. The first is nucleophilic activation of the silane

through association with the oxygen of silver oxide, and the second is the ability of silver to assist in halide abstraction from palladium, thereby aiding transmetallation [38]. Alkenylsilanols are also employed with similar success. The range of aryl iodides compatible under the reaction conditions is good, with electron-poor iodides generally giving much lower yields (**58**). It is noteworthy that the iodide is exclusively preferred as the group for cross-coupling, even in the presence of a bromide and triflate (**59**, **60**).



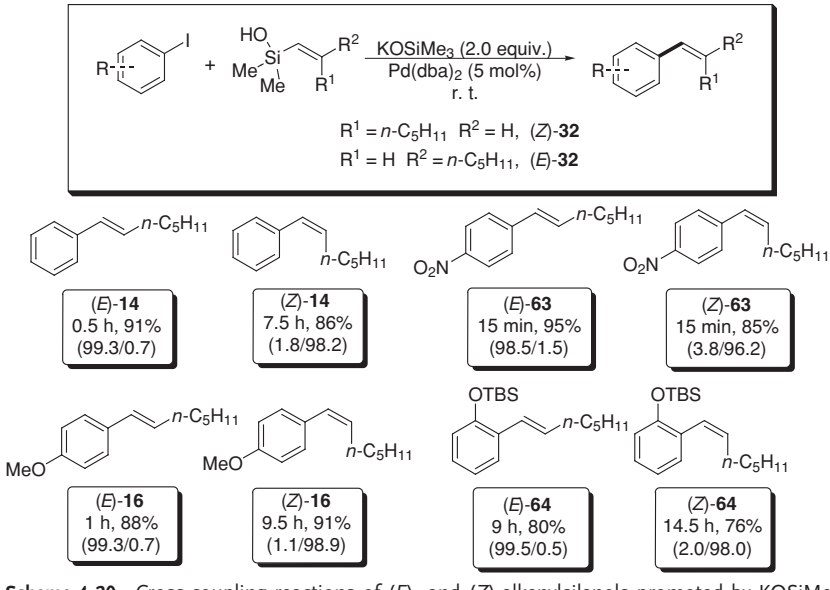
Scheme 4-18 Cross-coupling reactions of aryl silanols promoted by silver(I) oxide.

The long reaction times and elevated temperatures required for this method, however, prompted further investigation into coupling partners other than a simple silanol. In light of the beneficial role of hydroxyl group substitution on silicon for successful cross-coupling, it was hypothesized that a silicon precursor containing more than one hydroxyl group per silicon atom can exhibit even greater reactivity. Aryl- and alkenylsilanediols and -triols are easily synthesized from the corresponding chlorides (through hydrolysis), and undergo similar cross-coupling reactions. The comparison of silanol **56**, silanediol **61**, and silanetriol **62** demonstrates the higher coupling efficiency associated with **61** and **62** relative to the simple silanol (Scheme 4-19). The clean synthesis of such polyols, however, is not always possible. Many liquid silanediols and triols are used directly from the hydrolysis mixture of the corresponding chlorides as purification of these compounds is difficult.



Scheme 4-19 Comparison of the cross-coupling reactions of silanols, silanediols, and silanetriols.

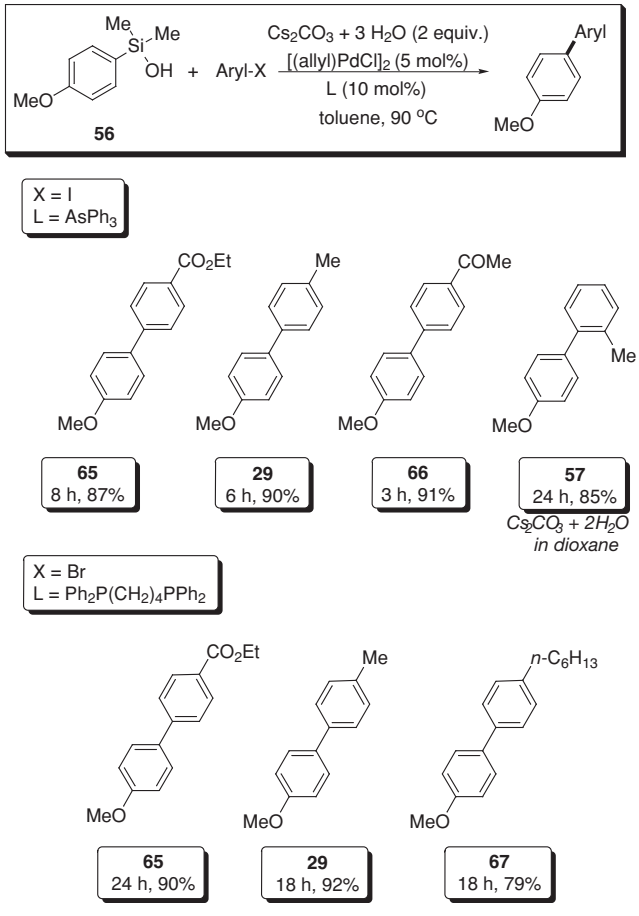
Whereas the use of a stoichiometric amount of silver oxide to promote the coupling reactions of organosilanols avoids the problems associated with fluoride activation, the conditions generally require elevated temperatures and long reaction times. An alternative promoter is another silyloxide, which is believed to be capable of serving both as a base and a nucleophile to generate an active pentacoordinate silicate has been reported. The inexpensive and soluble agent, $KOSiMe_3$, effectively promotes the coupling of both silanols (*E*)-**32** and (*Z*)-**32** at acceptable rates with a variety of aryl iodides at room temperature (Scheme 4-20) [39].



Scheme 4-20 Cross-coupling reactions of (*E*)- and (*Z*)-alkenylsilanols promoted by $KOSiMe_3$.

A survey of coupling partners shows this to be a very general method that tolerates several functionalities and proceeds readily at room temperature. Unlike most TBAF-promoted reactions however, the *Z* isomer of the silanol reacts at a much lower rate than the *E* isomer. In general, electron-deficient aryl iodides couple faster than their electron-rich counterparts. The synthetic potential of this new method of activation is clearly demonstrated in the synthesis of (*E*)- and (*Z*)-**64**. The coupling reaction occurs cleanly in the presence of a TBS-protected alcohol, without any observable deprotection. Thus, not only is the compatibility with silyl protective groups established, the concept of employing the silanol moiety as a prosthetic group for controlled carbon-carbon bond formation and a silanolate as an activator is also achieved through this fluoride-free method.

An alternative to the silver oxide-promoted coupling of arylsilanols has been developed (Scheme 4-21) [40]. In this system, cesium carbonate is the promoter of choice, presumably functioning by deprotonation to generate a cesium silanolate. As in the fluoride-promoted coupling reaction of silanols with triflates, water is essential for the success of this reaction. The added water may increase

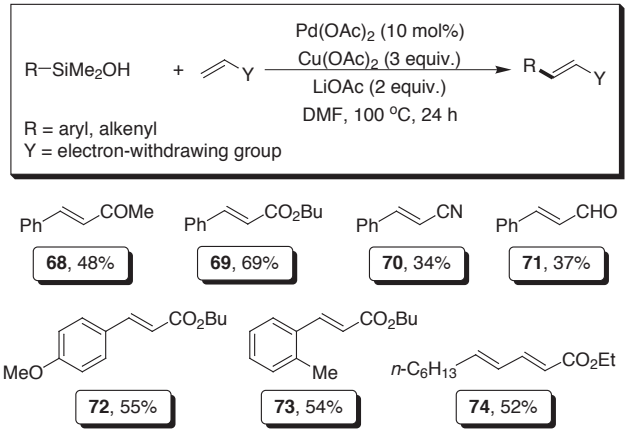


Scheme 4-21 Cross-coupling of arylsilanols promoted by cesium carbonate.

the solubility of the base or disfavore the silanol to disiloxane conversion (the latter being unreactive in this system). The optimal hydration level is determined to be three moles of water per mole of cesium carbonate. $[(Allyl)PdCl]_2$ is the most effective catalyst, with triphenylarsine as the ligand when aryl iodides are used, or diphenylphosphinobutane (dppb) when aryl bromides are employed. The reaction is general, and gives consistent results for a variety of aryl iodides and bromides, with aryl iodides generally coupling at higher rates. Even sterically congested substrates react well under these conditions (**57**) albeit at longer reaction times. In the cross-coupling reaction with iodides, small amounts of homocoupling products of the iodide are formed during the reaction, but these are generally minimal (6 % or less) with proper choice of the catalyst ligand selection.

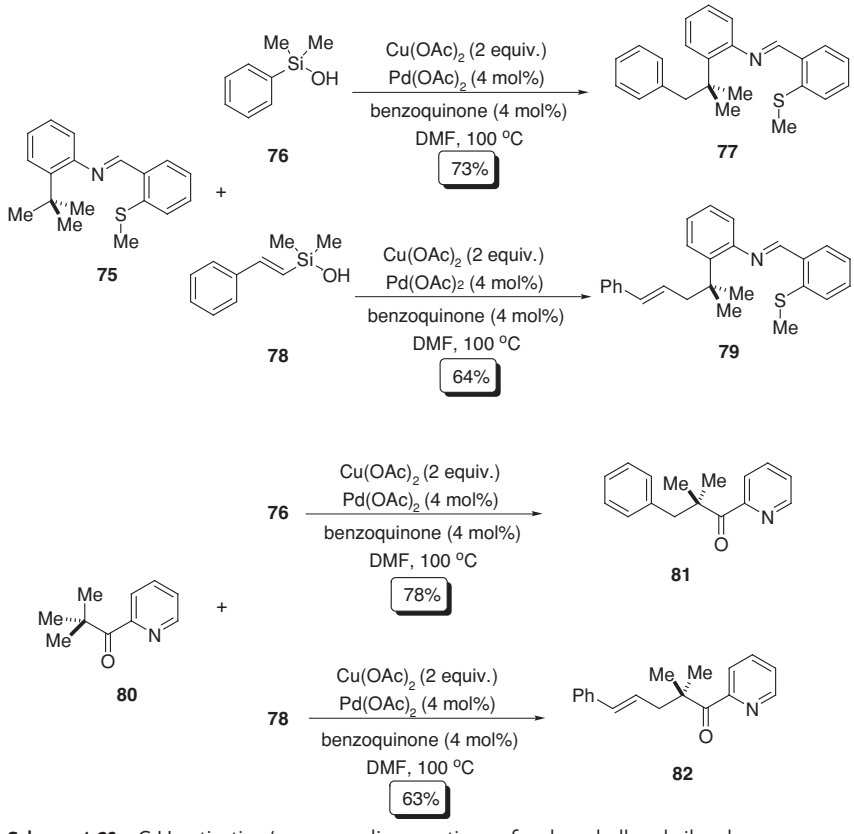
All of the cross-coupling reactions described thus far require a nucleophilic promoter such as TBAF, Ag_2O, or $KOSiMe_3$. In the absence of such a promoter, however, a Heck-type process occurs between aryl- or alkenylsilanols and electron-deficient alkenes (Scheme 4-22) [41]. This system, which employs $Pd(OAc)_2$ (10 mol %)

as the catalyst, involves a silicon-palladium transmetallation as the first step. In addition, $Cu(OAc)_2$ and LiOAc are used to re-oxidize the resultant palladium(0) species, which is a necessary byproduct of the Heck-type process. This halogen-free method works best with silanols; $PhMe_2SiOMe$, $PhSiMe_3$, and $PhMe_2SiCl$ are much less effective than $PhSiMe_2OH$ in direct comparisons. (These comparisons are conducted with a stoichiometric amount of $Pd(OAc)_2$ and therefore without $Cu(OAc)_2$ or LiOAc as stoichiometric oxidants.) It is intriguing to note that phenyltrifluorosilane exhibits similar reactivity to the silanol, thereby demonstrating that a single hydroxyl group on the silicon atom may be as effective as three fluorine atoms in activating the Si-C bond for cleavage.



Scheme 4-22 Mirozoki-Heck reactions of alkenyl- and arylsilanols.

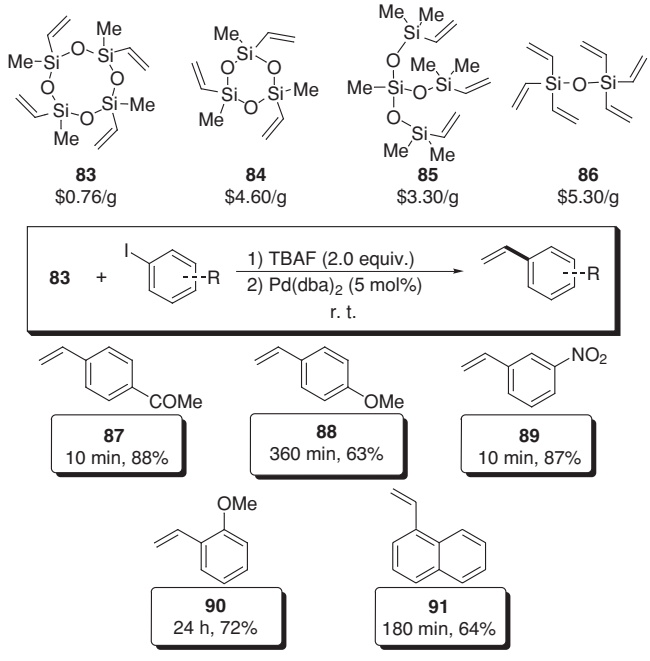
Clearly, the promoter-less coupling discussed previously follows a pathway that is mechanistically distinct from all the other reported palladium-catalyzed silanol cross-couplings, namely, that of a Heck-type process. Another use of organosilanols in coupling reactions that proceed by a unique pathway has been reported by Sames et al. [42] In studies with the ortho-*t*-butylaniline substrate **75** (arising from related work on the synthesis of the teleocidin class of natural products), a novel carbon-carbon bond-forming reaction was developed that involves the cross-coupling reactions with an organosilanol from a C-H bond activation (Scheme 4-23). Sames and colleagues proposed that an imine or pyridine (**80**) directs the site of C-H activation by palladium(II), resulting in an alkylpalladium intermediate which is incapable of *β*-hydride elimination. Interestingly, the resulting transmetallation with the silanol to give the coupling product requires no activation, indicating that the C-H activation step is not the only mechanistically distinct feature of this reaction. Optimal yields are achieved with $Cu(OAc)_2$ (2 equiv.) and benzoquinone (4 mol %) which are used to oxidize the palladium(0) byproduct of this coupling process to regenerate the active palladium(II) species. This coupling works equally well for both aryl- (**76**) and alkenyl-silanols (**78**). Finally, both $PhB(OH)_2$ and $PhSnBu_3$ fail to react under these conditions, thereby highlighting the importance of silicon in this particular system.



Scheme 4-23 C-H activation/cross-coupling reactions of aryl- and alkenyl-silanols.

4.2.3
Organosiloxanes

The ability of an oxygen substituent on the silicon atom to enhance reactivity prompted investigation into other classes of organosilane substrates possessing this structural feature. Di- and polysiloxanes, which constitute dimers of organosilanols and oligomers of silanediols and silanetriols, have been successfully employed in many cross-coupling reactions. The commercial availability of several inexpensive polyvinylsiloxanes makes these reagents ideal for simple vinylation of aryl and alkenyl halides. Three classes of such siloxanes, cyclooligodisiloxanes (**83**, **84**), an orthosiliconate (**85**), and hexavinyldisiloxane (**86**), are suitable for the delivery of vinyl groups (Scheme 4-24) [43]. Polysiloxanes, **83**–**85** all undergo efficient cross-coupling with 4-iodoacetophenone within 10 min. Polysiloxane **84** displays good reactivity and generality with a wide range of aryl and alkenyl electrophiles. Unlike the reactions of alkenylsilanols, this coupling is slower with electron-rich iodides and requires 3.0 equiv. of TBAF for the reaction to



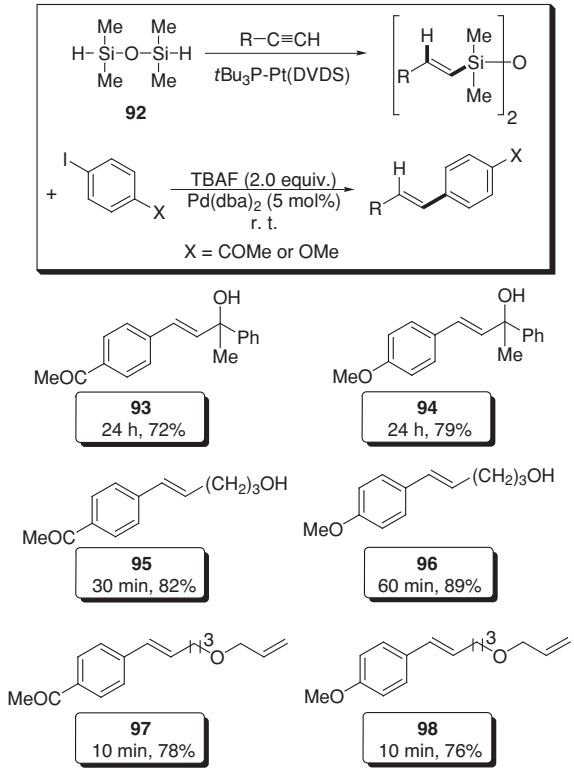
Scheme 4-24 Vinylation of aryl halides with commercially available di- and polyvinylsiloxanes.

go to completion (with **88**, **90**). In addition, steric effects are apparent; reaction times are significantly longer for substrates bearing *ortho* substituents (to form **90** and **91**).

The low cost of the precursors, combined with the high facility of the vinylations, illustrate their superiority over tin-based methods [44]. Although the preparative advantages of commercially available siloxanes are clearly demonstrated, the number of structurally diverse precursors is obviously limited. This shortcoming is addressed through the development of a general method for the custom preparation of alkenyldisiloxanes from simple, readily available starting materials.

The synthesis of alkenyldisiloxanes is achieved in a manner analogous to the synthesis of *E*-alkenylsilanols by the well-established, platinum-catalyzed hydrosilylation of alkynes (Scheme 4-25). In this case, however, a readily available dihydridodisiloxane is employed as the precursor. The combination of the hydrosilylation step with a subsequent, cross-coupling step avoids the need to isolate the intermediate disiloxane. This newly developed "one-pot" hydrosilylation/cross-coupling thus provides hydroarylation products directly from terminal alkynes.

Two general methods that employ this "one-pot" procedure have been developed. The first uses (tBu$_3$P)Pt(0)(DVDS) (DVDS = 1,3-divinyl-1,1,3,3-tetramethyldisiloxane) as the hydrosilylation catalyst in combination with tetramethyldisiloxane (**92**) and a variety of alkynes (Scheme 4-25) [45]. The hydrosilylation and subsequent cross-coupling reaction promoted by TBAF proceeds at room temperature. In addition, despite highly variable reaction times, the yields and stereoselectivities are

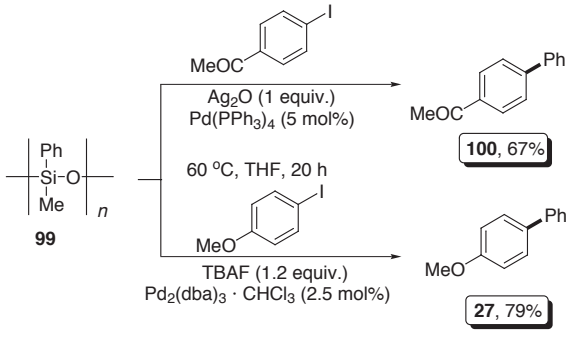


Scheme 4-25 Intermolecular hydrosilylation/cross-coupling of terminal alkynes.

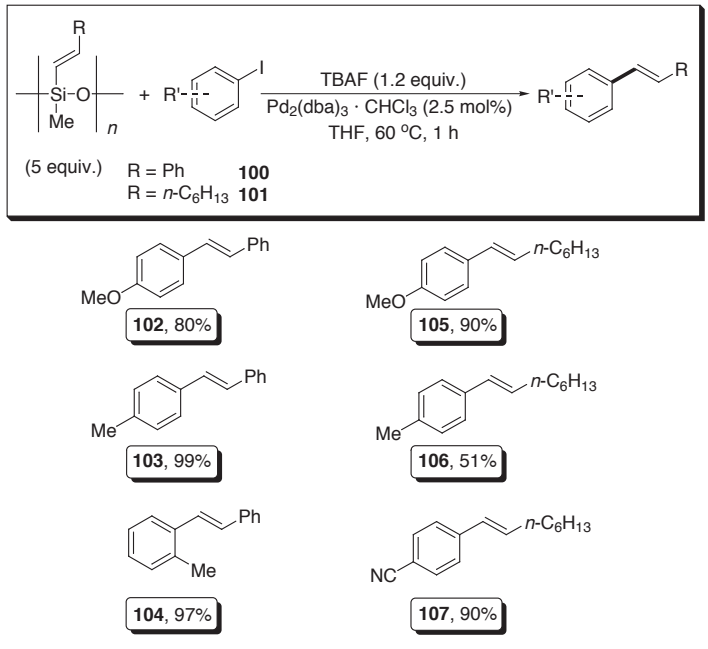
exceptional. The hydrosilylation of alkynes can be cleanly conducted in the presence of a free hydroxyl group (**93**–**96**), and even in the presence of a pendant alkene (**97**, **98**). In all cases, the major isomer is formed with greater than 99 % geometrical purity.

The second general method consists of using various cyclic and non-cyclic polysiloxanes with either TBAF or Ag_2O as the activator [46]. Poly(phenylmethylsiloxane) (**99**) serves as a very convenient phenylating source for biaryl synthesis in the presence of Ag_2O (Scheme 4-26). TBAF is also an effective promoter and works well with a phosphine-free catalyst, $Pd_2(dba)_3 \cdot CHCl_3$. The reaction is general, and comparable in yields to silanol cross-coupling.

In addition, poly(alkenylmethylsiloxanes) can be custom-made in quantitative yields by the hydrosilylation of alkynes with poly(methylhydroxysilane) (PMHS) in the presence of $(n\text{-}Bu_4N)_2PtCl_6$ (Scheme 4-27). The resulting polysiloxanes are stable at room temperature under aerobic conditions for months, and can be used for the subsequent cross-coupling reaction without further purification. The coupling of siloxanes **100** and **101** with several different aryl iodides provides convenient access to products previously synthesized from silanols. Electron-rich (**102**, **105**), electron-deficient (**107**), and even sterically encumbered aryl iodides (**104**)



Scheme 4-26 Phenylation of aryl halides with poly(phenylmethyl)siloxane.



Scheme 4-27 Cross-coupling reactions of aryl halides with poly(alkenylmethyl)siloxanes promoted by TBAF.

react equally well. In general, the use of polysiloxanes in this fashion streamlines intermediate purification steps involved when employing other silicon reagents.

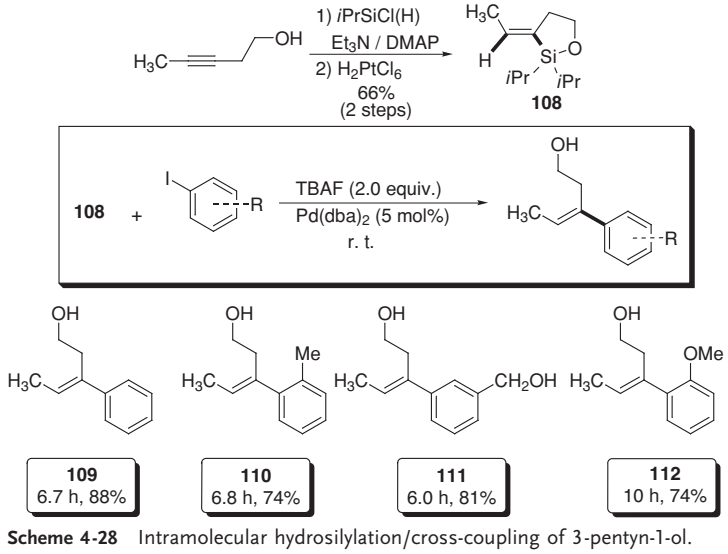
The commercial availability of vinylating reagents in combination with novel one-pot approaches to synthesize coupling products from alkynes, render the use of polysiloxanes in cross-coupling chemistry very attractive. This is particularly applicable to synthesis on a large scale, or where intermediate steps of purification can be cumbersome. This class of organosilane coupling partners clearly shows superiority, both in cost and efficiency, when compared to other non-silicon-based-coupling reactions.

4.2.4
Organosilyl Ethers

The use of alkenylsilyl ethers in palladium-catalyzed cross-coupling reactions has long been known. In fact, only a year after Hiyama's landmark report on the TBAF-promoted coupling reactions of vinyltrimethylsilane, Tamao and Ito capitalized on the use of alkoxy-substituted silanes as viable components for such reactions (*cf.* Scheme 4-4). The generality of the silyl ether coupling added a useful class of organosilicon substrates that are complementary to the fluorosilanes developed by Hiyama et al. These studies showed that other heteroatom-based units, namely alkoxy groups, on the silane could be equally beneficial in rendering the organosilane suitable for cross-coupling.

The main advantage of using silyl ethers in cross-coupling reactions is the ability to incorporate them into molecules by a number of methods. Cyclic silyl ethers, as a class, nicely illustrate this attribute. The well-known hydrosilylation of alkynes to form vinylsilanes can easily be rendered intramolecular by attachment of the silane as, for example, a homopropargyl silyl ether to form an oxasilacyclopentane **108** (Scheme 4-28) [47]. In this structure, the double-bond geometry is defined by the stereochemical course of hydrosilylation and the ether tether defines the location of the silicon atom with respect to the alkene. Thus, the silicon-oxygen bond in this molecule serves to direct the hydrosilylation, as well as to activate the silicon for cross-coupling.

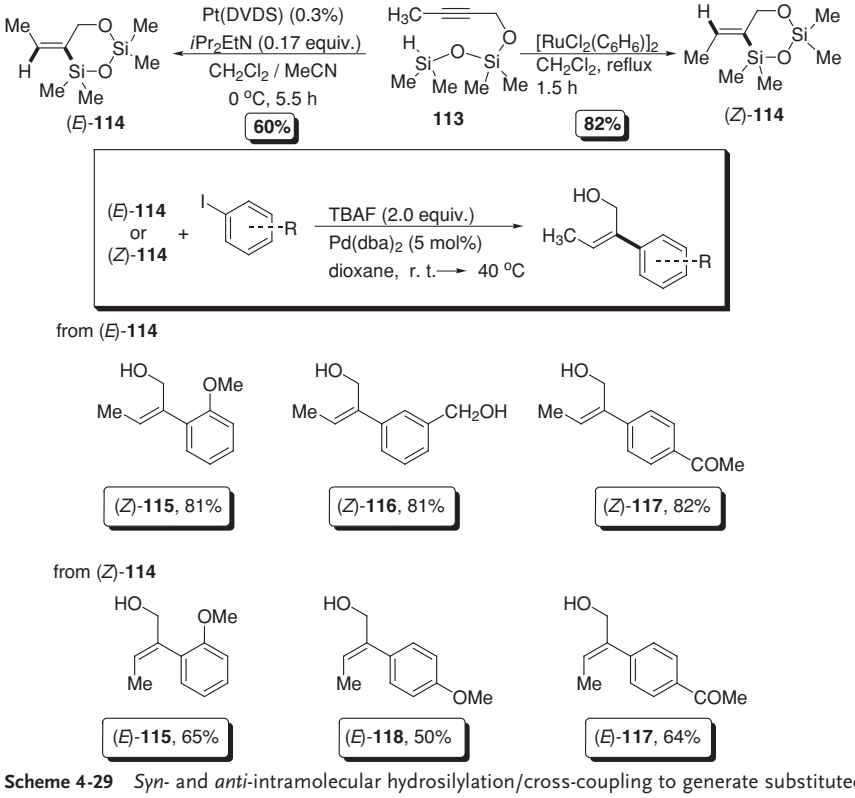
Silyl ether **108** undergoes cross-coupling with a range of aryl iodides (Scheme 4-28). The reaction times are generally longer than those observed with simple alkenylsilanols and disiloxanes, but are similar those of the trisubstituted alkenylsilanols previously described (*cf.* Scheme 4-14). The lower rate of cross-coupling



Scheme 4-28 Intramolecular hydrosilylation/cross-coupling of 3-pentyn-1-ol.

often leads to formation of homocoupling byproducts, which can be minimized by the portionwise addition of the electrophile. Two noteworthy features of these reactions are the absence of any significant electronic or steric effects on the rate of coupling, and the high stereoselectivity of the process. The facile formation and high reactivity of these silicon-containing substrates bodes well for the use of other methods of synthesizing cyclic silyl ethers for incorporation into designed cross-coupling partners.

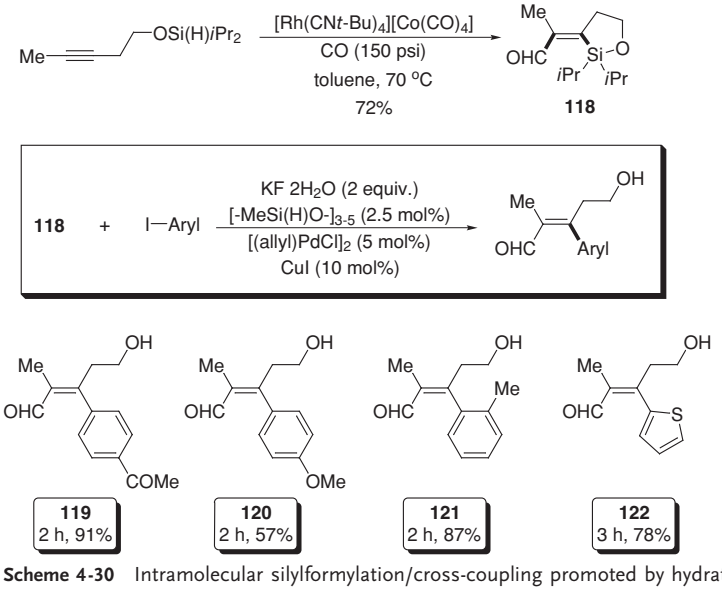
The silyl ether tether used in this example leads to homoallylic alcohols as the products of the coupling reaction. Allylic alcohols, on the other hand, can not be easily accessed by this method, because the tether would have to be shortened by one methylene unit, resulting in the formation of a cyclic silyl ether. In a related system designed to address this limitation, silyloxy-silyl ethers are employed as coupling substrates to allow allylic alcohols to be obtained as coupling products from relatively unstrained cyclic substrates (Scheme 4-29). In this system, procedures for both *syn*- and *anti*-hydrosilylations are optimized, which generate complementary cyclic *E*- and *Z*-silyl ethers as coupling precursors [48]. Disiloxane **113** is used as the precursor to cyclic silyl ether (*E*)-**114** via a platinum-catalyzed hydro-



Scheme 4-29 *Syn*- and *anti*-intramolecular hydrosilylation/cross-coupling to generate substituted allylic alcohols.

silylation. This same precursor generates the corresponding *Z* isomer by an *anti*-hydrosilylation under catalysis by a ruthenium complex. Both of these substrates undergo reaction with a variety of aryl iodides to generate stereodefined trisubstituted allylic alcohols as the products. The reaction of (*E*)-**114** is completely stereoselective, affording only the *Z* products, whereas (*Z*)-**114** gives mostly *E* products (with <3% of the undesired *Z* products). This work highlights the utility of the hydrosilylation methods to access stereodefined silicon-coupling precursors. By harnessing the stereoselectivity of silicon cross-coupling, stereodefined, functionalized allylic alcohols are readily accessed.

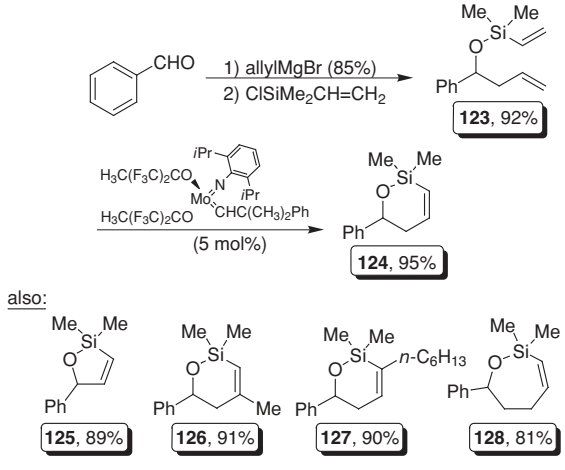
The preceding methods for intramolecular incorporation of a silicon unit all involve the addition of a hydrogen and silicon atom on an alkyne. An alternative constructive incorporation of a silicon moiety is the intramolecular silylformylation reaction [49]. This well-established procedure for the net addition of both a carbon and a silicon group to an alkyne has been successfully developed and employed with silicon (Scheme 4-30) [50]. The rhodium-catalyzed silylformylation of a simple alkyne proceeds under 150 psi of CO to give cyclic silyl ether **118** in 72% yield. This silyl ether undergoes cross-coupling with a variety of aryl iodides in moderate to good yields at room temperature. In all cases, a small (<11%) amount of the iodide homocoupling product is also detected. As in other reported silicon cross-coupling systems, the addition of water to the promoter has a salutary effect on coupling rate. Unlike the cross-coupling of cyclic silyl ethers described above, the rate of coupling of **118** is low at room temperature, most likely due to the electron-withdrawing formyl group. The addition of copper(I) iodide (presumably to enable a preliminary silicon to copper transmetallation) is essential for the coupling to proceed under mild conditions. In addition, small amounts of a hydro-



Scheme 4-30 Intramolecular silylformylation/cross-coupling promoted by hydrated KF.

silane are necessary to initiate and promote the coupling. This was initially discovered by the observation that trace impurities of hydrosilanes in silyl ether **118** were actually necessary for a successful coupling! The role of the hydrosilanes may be to reduce the palladium(II) catalyst to an active palladium(0) species. The final conditions for this unique coupling result from detailed optimization, and illustrate the compatibility of this coupling with aldehydes. This example features the ability of electron-deficient silanes to participate smoothly in cross-coupling reactions.

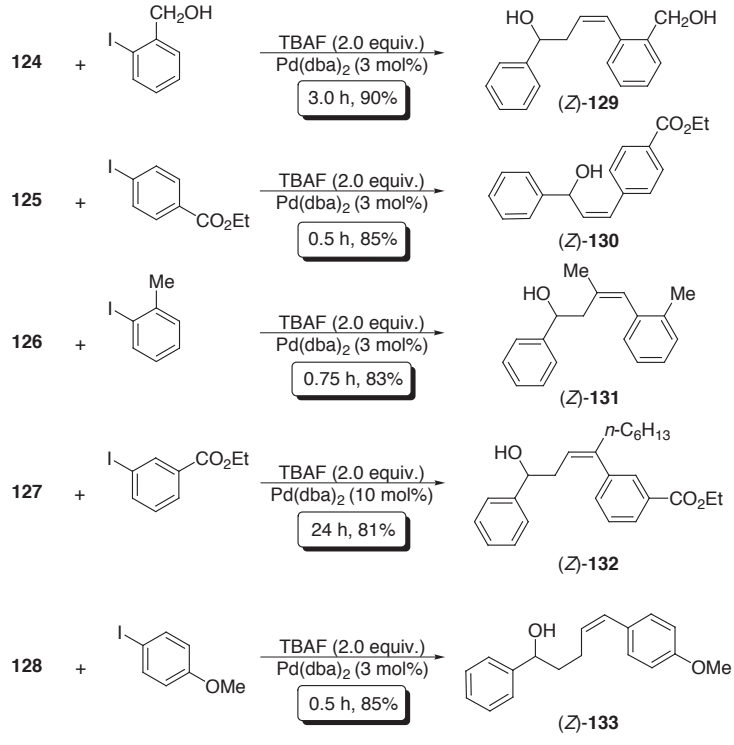
The use of intramolecular hydrosilylation and silylformylation highlights how a pendant functional group (homopropargyl or propargyl alcohol) can be used to install a silicon moiety into a substrate for cross-coupling. This method generally provides an exocyclic alkenyl silyl ether. By employing ring-closing metathesis (RCM) [51], cyclic silyl ethers in which the alkenyl unit resides within the ring can be generated (Scheme 4-31). The olefin geometry in this coupling substrate is fixed in the *Z*-configuration in small- to medium-sized rings. This method offers another route by which *Z*-allylic or -homoallylic alcohols can be obtained by cross-coupling.



Scheme 4-31 Formation of unsaturated, cyclic silyl ethers by ring-closing metathesis.

The power and generality of RCM for the synthesis of carbo- and heterocyclic rings of various sizes has been amply demonstrated in recent years. In this variant, however, the RCM reaction serves to define the olefin geometry and set the stage for inter- or intramolecular cross-coupling. Thus, silyl ethers **124–128** of various ring sizes are first prepared by RCM (Scheme 4-31) [52]. Unfortunately, only the sterically less sensitive and more reactive molybdenum-based catalyst, $[(CF_3)_2MeCO]_2Mo(=CHCMe_2Ph)(=NC_6H_3\text{-}2,6\text{-}i\text{Pr}_2)$, effects the ring closure for these silyl ethers.

The cross-coupling reaction of the cyclic silyl ethers **124–128** with aryl iodides having various functional groups and electronic properties is successful (Scheme 4-32). Aryl halides bearing electron-withdrawing and electron-donating groups exhibit similar reactivity. In addition, the absence of other isomers illustrates

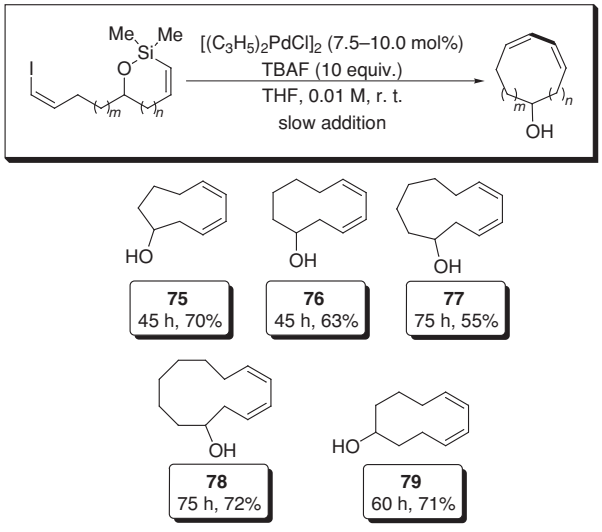


Scheme 4-32 Cross-coupling reaction of unsaturated, cyclic silyl ethers promoted by TBAF.

the high selectivity of the cyclic silyl ether approach in the synthesis of cross-coupling products with *Z*-alkene geometry. This process exhibits an excellent scope with regard to the tether length (that is, silyl ether ring size) and substituents on the alkene, both in the RCM step and the subsequent cross-coupling step. A substituent at the *α*-position of silyl ether **127** retards the rate significantly, but the yields of all these reactions are satisfactory.

An intramolecular version of this process has also been developed [53]. A series of cyclic silyl ether substrates bearing a tethered electrophile undergo the cross-coupling reaction to produce medium-size rings (Scheme 4-33). By this method, 9-, 10-, 11-, and 12-membered cycloalkadienes can easily be synthesized. This is significant because the synthesis of rings of this size – particularly with a 1,3-*cis*-*cis*-diene unit – is challenging due to the unfavorable entropic and enthalpic factors associated with such a transformation [54].

The application of the RCM approach to create a range of cyclic silyl ethers successfully expands the scope of reactions utilizing the temporary silicon tether approach, and the novel concept of heteroatom activation of the silicon from the coupling substrate itself. Thus, in cases where homoallylic alcohols or medium-sized rings are the desired products, the aforementioned methods offer a facile and direct route for their synthesis.



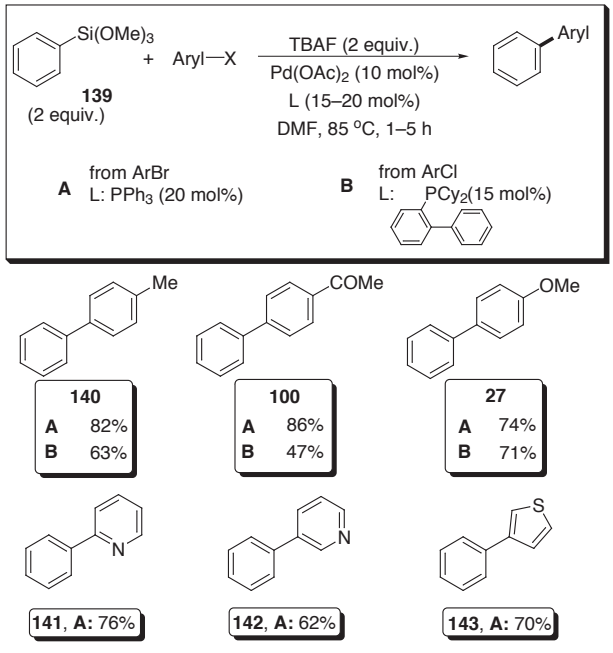
Scheme 4-33 Intramolecular cross-coupling reactions of unsaturated, cyclic silyl ethers promoted by TBAF.

Despite the diversity of organosilyl ether cross-coupling systems, all of the aforementioned examples are similar in one aspect: they employ alkenylsilyl ethers. Arylsilyl ethers (specifically, aryl orthosiliconates), however, have played a significant role in biaryl synthesis.

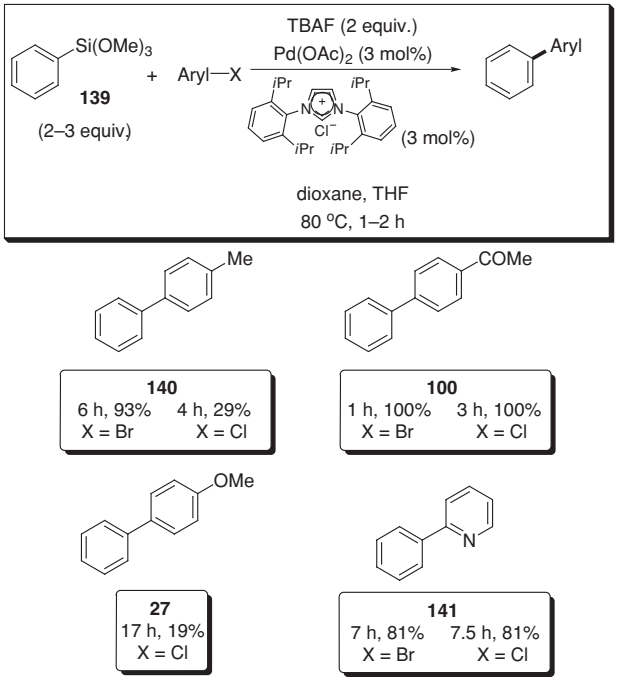
One of the first general studies of arylsilyl ethers in cross-coupling reactions was reported by DeShong et al. [55]. Phenyltrimethoxysilane **139** efficiently reacts with several aryl halides in the presence of $Pd(OAc)_2/PPh_3$ (Scheme 4-34). (If homocoupling of the aryl halide is problematic, the use of tri-*o*-tolylphosphine in place of triphenylphosphine is suggested.) In general, the coupling to aryl bromides is high-yielding for both electron-rich and electron-deficient arenes (**27**, **100**). Heterocyclic bromides are also viable substrates for this reaction (**141**–**143**).

The cross-coupling of arylsilyl ethers with aryl chlorides is also possible, albeit in much lower yield than the corresponding reactions with aryl bromides (B, Scheme 4-34). For this reaction, it is necessary to employ a different phosphine ligand, 2-(dicyclohexylphosphino)biphenyl, which is well known to activate aryl chlorides in other palladium-catalyzed coupling reactions [35]. The reaction of **139** proceeds rapidly in good yields with several different types of aryl halides.

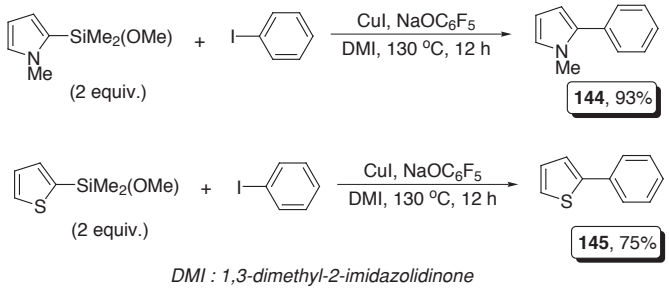
Soon after DeShong's report on the use of aryl orthosiliconates, Nolan et al. reported a modification that employs $Pd(OAc)_2$ and an imidazolium salt as the ligand (Scheme 4-35) [56]. In this system, **139** reacts both with aryl bromides as well as with electron-deficient and heterocyclic aryl chlorides (**100**, **141**). Unfortunately, the coupling to electron-rich aryl chlorides is generally low-yielding (**140**, **27**). The substrate scope is comparable to those of previous reports, and generally, two or more equivalents of silyl ether are needed. A key advantage of this system, however, is the low catalyst loading required (3 mol % of palladium and the ligand).



Scheme 4-34 Cross-coupling reactions of phenyltrimethoxysilane with aryl bromides and chlorides promoted by TBAF.



Scheme 4-35 Cross-coupling reactions of phenyltrimethoxysilane with aryl bromides and chlorides promoted by TBAF.

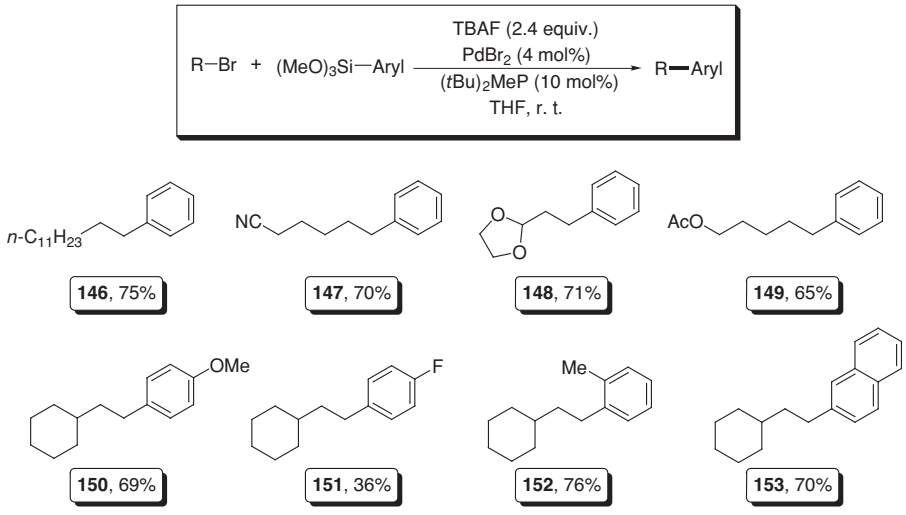


Scheme 4-36 Cross-coupling reactions of phenyltrimethoxysilane with aryl bromides and chlorides promoted by TBAF.

Protiodesilylation of the starting material is occasionally encountered in the coupling reactions of aryl-silanes with a nucleophilic promoter. This side-reaction can be suppressed by the use of a stoichiometric amount of a copper(I) salt to promote the cross-coupling of arylsilyl ethers with iodoarenes (Scheme 4-36) [57]. The preferred salt is $CuOC_6F_5$, generated in situ by mixing CuI and $NaOC_6F_5$, to effectively promote this reaction. Unlike other arylsilyl ether cross-coupling reactions wherein a trialkoxysilane is used, the mono-methoxysilane reacted much more efficiently than either the di- or trimethoxysilane. Despite the harsh conditions used, this is an impressive fluoride- and palladium-free reaction.

Alkyl-alkyl cross-coupling reactions have historically been the most difficult to realize. Among the many obstacles to the effective development of such a system are the lower reactivity of alkyl groups relative to alkenyl and aryl groups, as well as side processes such as *β*-hydride elimination that are accessible with alkyl substrates. Recent reports by Fu et al. have disclosed successful alkyl cross-coupling protocols that employ the Stille [58] and Suzuki [59] reactions. In an analogous fashion, a coupling system with aryl orthosiliconates and alkyl bromides and iodides has also been developed [60]. The optimal conditions employ $PdBr_2$ (4 mol%) and $(t\text{Bu})_2\text{MeP}$ (10 mol%) as the catalyst and ligand respectively in the presence of 2.4 equiv. of TBAF (Scheme 4-37). The coupling takes place at room temperature, and yields are moderate to good in most cases. The substrate scope encompasses a wide range of electrophiles and silanes; electron-deficient orthosiliconates (**151**) provide the lowest yield of coupling product. The reaction is also tolerant of a variety of functional groups, and even sterically demanding substrates (**152**) react under these mild conditions.

The breadth of organosilyl ether cross-coupling now rivals that of organosilanols. There are, however, a few limitations; most notably that some of these systems – particularly in biaryl synthesis – require a large excess of organosilane relative to the electrophile employed. In spite of this, organosilyl ethers are a useful class of substrates because of the ease of synthesis of many of the precursors, as well as their stability and high reactivity.

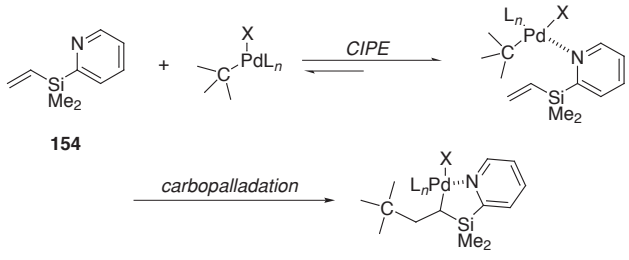


Scheme 4-37 Cross-coupling reactions of phenyltrimethoxysilane with alkyl bromides promoted by TBAF.

4.2.5
Organopyridyl- and Organothiophenylsilanes

All of the aforementioned variants of silicon cross-coupling have highlighted the activating ability of oxygen substitution on the silicon. The advantages of silanols, silyl ethers, and siloxanes over other classes of organosilicon precursors such as chloro- and fluorosilanes is their relative stability, reactivity, and ease and low cost of synthesis. These advantages do not represent infallible systems because all of the aforementioned silane precursors are susceptible to nucleophilic attack, and their stability towards other reactions has not been demonstrated (that is, wherein a silane moiety is installed in a heavily functionalized substrate, and then carried through several functional group manipulations of a multi-step synthesis). Potential incompatibilities of different reaction systems with -SiR_2O- units have prompted investigation into other classes of reactive silane precursors for cross-coupling. Heterocycle-substituted silanes, although not members of the general class of oxygen-substituted silanes, are surrogates of silanols and have revealed new avenues of cross-coupling chemistry previously not available.

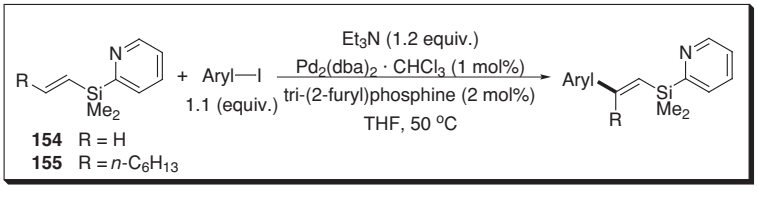
The utility of alkenyl-pyridylsilanes in palladium-catalyzed reactions was first recognized in a slightly different arena. 2-Pyridyldimethyl(vinyl)silane (**154**) (synthesized from the 2-pyridyldimethylsilane and an alkenyllithium reagent) is effective for the Heck reaction with aryl and alkenyl iodides [61]. The process of carbopalladation of vinylsilanes under typical Heck reaction conditions generally leads to silicon-carbon bond cleavage. However, the pyridylsilane **154** is stable under these reaction conditions. It is believed that the nitrogen of the pyridine ring stabilizes the intermediate either by a complex-induced proximity effect

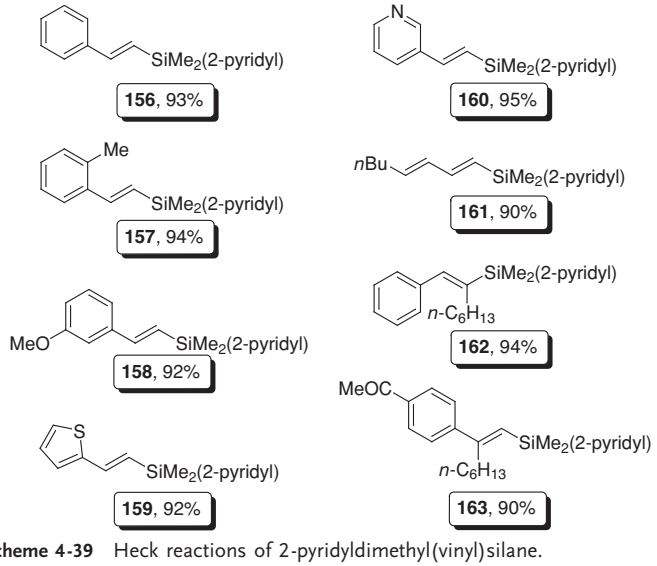


Scheme 4-38 Mechanism of directed carbopalladation of 2-pyridyldimethyl(vinyl)silane.

(CIPE), or by coordinating to the palladium to promote the carbopalladation step (Scheme 4-38) [62].

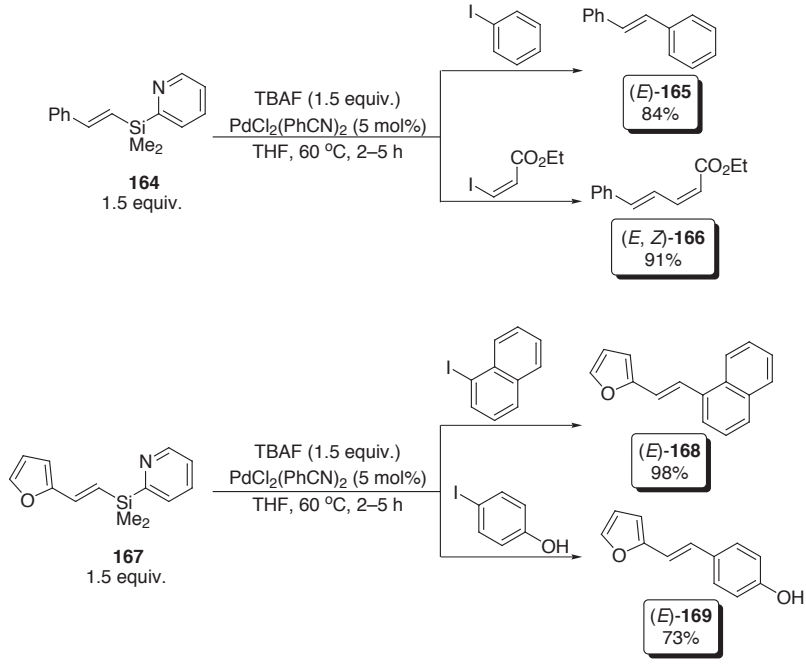
The Heck reaction with a variety of aryl iodides is achieved under mild conditions using Et_3N, and $Pd_2(dba)_3 \cdot CHCl_3$/tri-(2-furyl)phosphine as the catalyst system (Scheme 4-39). In all cases, the yields are exceptional and the preference for the *trans* product is high (99 %). The Heck coupling proceeds with only 1 mol % of the catalyst, even for sterically demanding substrates such as **157**. Most noteworthy, however, is that the coupling to a 1,2-disubstituted vinylsilane proceeds with high regio- and stereoselectivity for the *trans* isomer. This lends strong support to the hypothesis of a CIPE effect of the pendant pyridyl ring.





Scheme 4-39 Heck reactions of 2-pyridyldimethyl(vinyl)silane.

A completely different reaction manifold can be activated by the use of TBAF to promote cross-coupling at the silicon-bearing carbon [63]. Mixing TBAF with pyridyldimethyl(alkenyl)silanes results in the cleavage of the pyridyl group and formation of the corresponding silanol, presumably from the water contained in commercial TBAF · $3H_2O$. Thus, the 2-pyridylsilane also serves as a masked silanol. The TBAF-promoted cross-coupling of several pyridyldimethyl(alkenyl)silanes has been reported, thereby showing that two different coupling pathways are accessible when using this type of silane (Scheme 4-40).

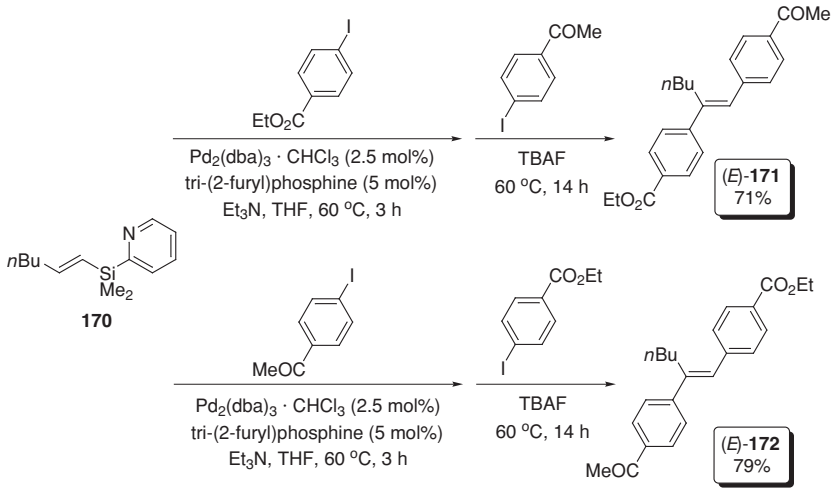


Scheme 4-40 Cross-coupling reactions of 2-pyridyldimethyl(vinyl)silane promoted by TBAF.

The TBAF-promoted coupling of pyridylsilanes to alkenyl and aryl iodides works equally well to form (*E*)-**165** and (*E,Z*)-**166**. As with previously reported coupling reactions of silanols, the reactions employing 2-pyridylsilanes are also compatible with several functional groups, including an ester ((*E,Z*)-**166**) and a phenol ((*E*)-**169**).

The successful implementation of two distinct cross-coupling pathways from a single starting material clearly suggests their combination in a one-pot procedure. The sequential carbometallation/transmetallation/cross-coupling of alkenylpyridyl(butenyl)silane (*E*)-**170** generates, in a complete regio- and stereoselective fashion, two new carbon-carbon bonds (Scheme 4-41). This impressive sequence provides access to extended conjugated systems consisting of trisubstituted alkenes in a simple one-pot/two-step procedure.

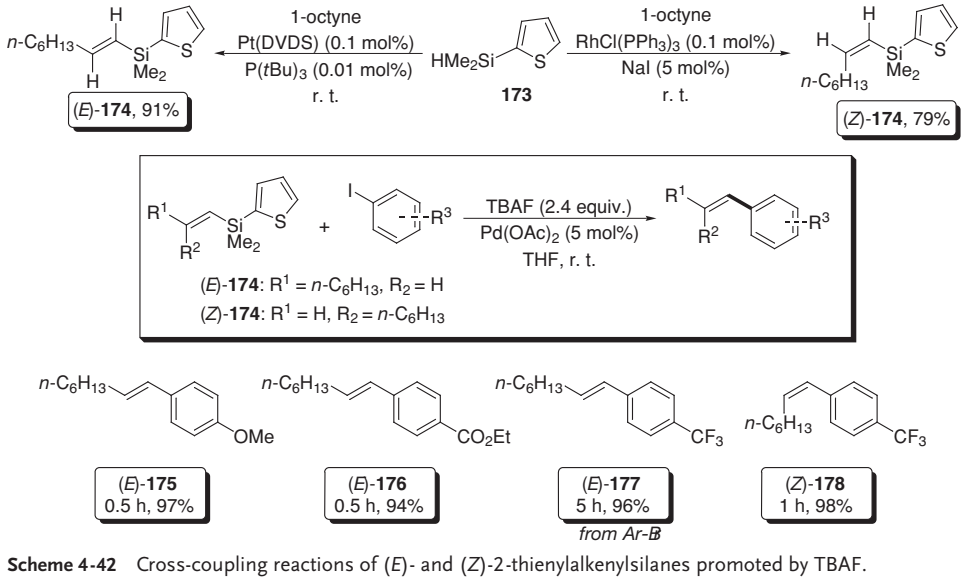
The utility of 2-pyridylsilanes to direct two types of coupling reactions widens the scope of organosilicon-cross-coupling, both experimentally and conceptually, as it



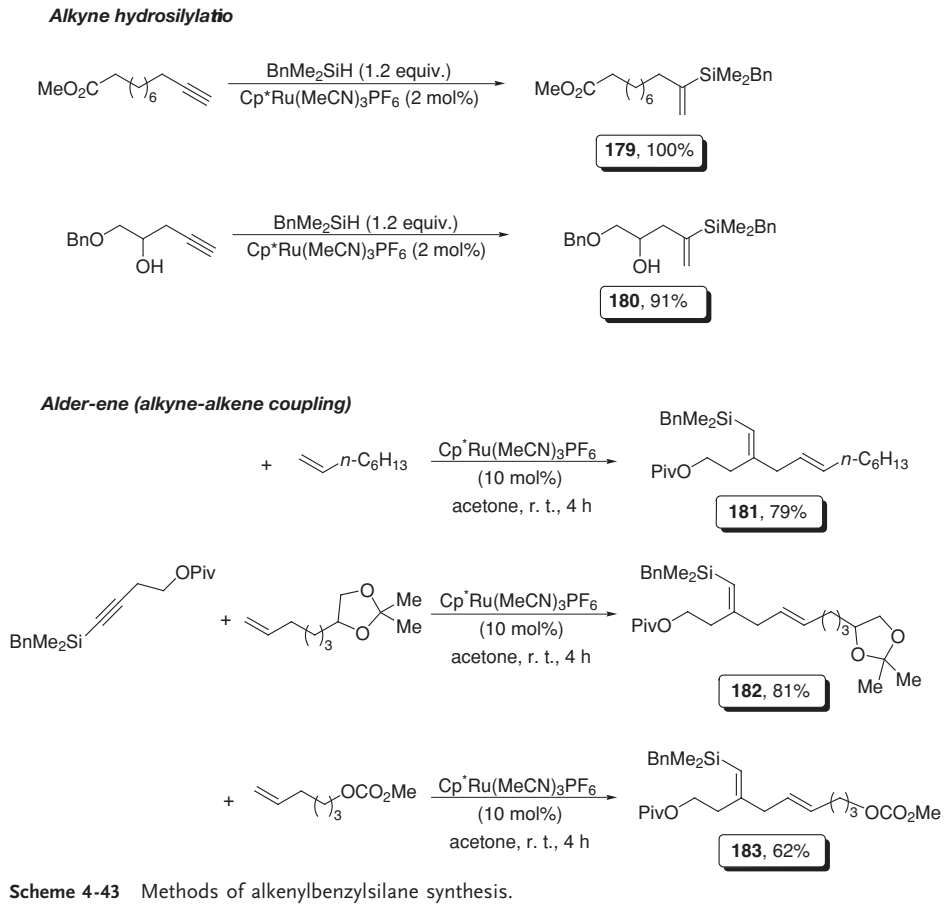
Scheme 4-41 Cascade Heck/cross-coupling of 2-pyridyldimethyl(vinyl)silanes.

represents a new class of organosilanes that are not dependent on the more common methods of simple heteroatom substitution.

Another class of heterocycle-substituted organosilanes that are effective cross-coupling substrates are 2-thienylsilanes (Scheme 4-42) [64]. In a fashion similar to 2-pyridylsilanes, these substrates are believed to form the corresponding silanols in the presence of TBAF · $3H_2O$. Both (*E*)- and (*Z*)-alkenyldimethyl(2-thienyl)silanes (**174**) are readily accessible from **173** by hydrosilylation of alkynes. These substrates undergo room-temperature cross-coupling reactions with several aryl



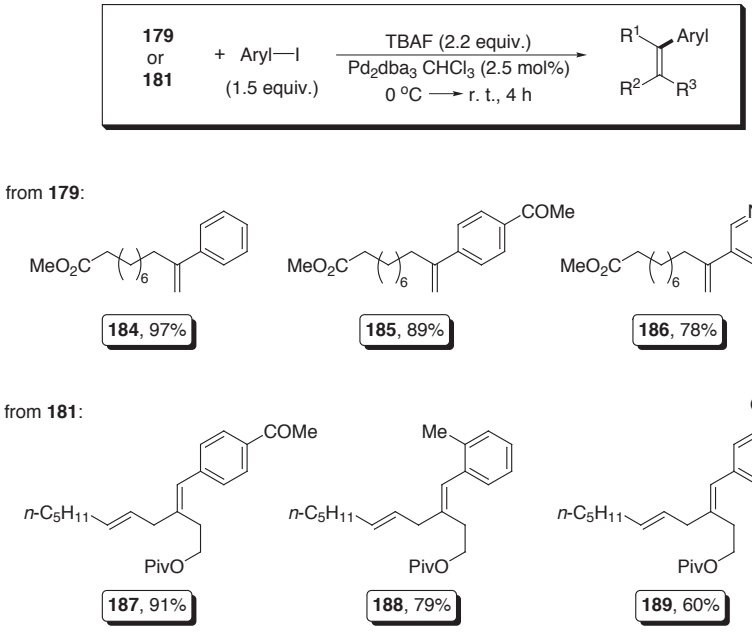
Scheme 4-42 Cross-coupling reactions of (*E*)- and (*Z*)-2-thienylalkenylsilanes promoted by TBAF.



Scheme 4-43 Methods of alkenylbenzylsilane synthesis.

iodides and even aryl bromides. The excellent yields reflect the high efficiency of this procedure.

In addition to heterocyclic silanes, Trost et al. have recently reported the use of another type of silane that can serve as a more robust alternative to the more commonly used classes of oxygen-substituted silanes [65]. The benzyldimethylsilyl unit can also serve as a surrogate for the corresponding silanol because, in the presence of TBAF · $3H_2O$, the benzyl group is rapidly cleaved, presumably generating the corresponding silanol. This moiety is capable of transferring alkenyl groups in a cross-coupling reaction. Another important advantage of the benzyldimethylsilyl group is that it can be installed by either hydrosilylation or Alder-ene reaction (Scheme 4-43). The coupling reaction proceeds at room temperature, is tolerant of a variety of functional groups, and yields stereodefined products in moderate to good yields for a variety of substrates (Scheme 4-44). The robust nature of the benzyldimethylsilyl group is highlighted by its stability to conditions of silyl-protective group removal (*t*-butylphenylsilyl; TBDPS) of a primary alcohol



Scheme 4-44 Cross-coupling of alkenylbenzylsilanes promoted by TBAF.

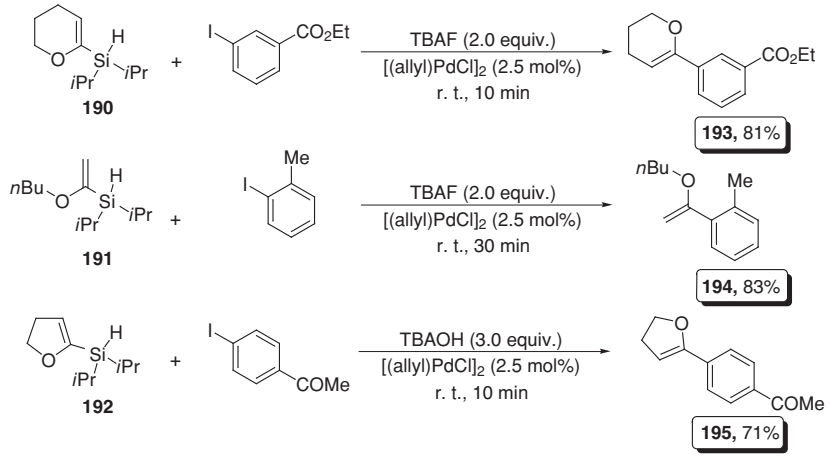
(buffered conditions; TBAF/AcOH). This surrogate of a silanol, together with the heterocyclic silanes, represents a growing class of useful coupling substrates that possesses the high coupling reactivity of oxygen-substituted silanes, but that also displays greater stability and robustness for a broader range of synthetic applications.

4.2.6
Organosilyl Hydrides

Silyl hydrides, like the heterocyclic and benzylic silanes discussed above, are useful surrogates for silanols. During the course of their studies in pyranylsilanol couplings (*cf.* Scheme 4-15), Denmark et al. discovered that hydrosilanes, in the presence of TBAF, couple just as readily as the cognate silanols (Scheme 4-45) [26]. A silanol is most likely generated in situ, by fluoride-catalyzed oxidative hydrolysis which generates hydrogen from the water in TBAF · $3H_2O$ [66].

Unlike silanes **190** and **191**, silyl hydride **192** suffered rapid protiodesilylation in the presence of TBAF, releasing dihydrofuran. Replacement of the TBAF solution with tetrabutylammonium hydroxide solution in MeOH (3.0 equiv.) allows the coupling reaction to proceed smoothly to **195**.

The rapid growth of usable silicon precursors for cross-coupling is a testament to the versatility of this method. There are now several avenues to incorporate different types of active silicon subunits into a molecule. Unlike other conventional



Scheme 4-45 Cross-coupling of silyl hydrides promoted by TBAF and TBAOH.

cross-coupling methods, organosilicon cross-coupling does not reflect one specific type of unit that directs the site of reaction. Rather, a silicon atom with pendant silyloxy, alkoxy, hydroxyl, pyridyl, thienyl, benzyl, or even hydrido groups is a usable and effective cross-coupling subunit. As will be discussed in the following section, however, all of these different precursors may react according to a common mechanism. Indeed, the high reactivity and stereoselectivity exhibited in many of these systems, particularly with fluoride activation, strongly suggests this.

4.3
Mechanistic Studies in Silicon-Based Cross-Coupling Reactions

4.3.1
The Pentacoordinate Silicon

The reigning dogma in the field of silicon-based cross-coupling is the necessity to generate a pentacoordinated siliconate as a prerequisite for a successful coupling. This is not an unreasonable scenario because it is well known that silicon can readily expand its valency [8]. The unique structural and reactivity characteristics of penta- and hexacoordinate silanes have even been documented in thorough reviews. Although there is no direct evidence for an "activation" step preceding a cross-coupling when a tetracoordinate silane is employed in the presence of a nucleophilic promoter, there are ample experimental data available that lend support to this contention [67].

Indirect evidence for an activation step is found in the ability of pre-synthesized, stable, pentacoordinate silanes to transfer an organyl group onto palladium. Two examples are the use of catecholsilanes for alkenyl transfer and the use of TBAT (tetra-*n*-butylammonium triphenyldifluorosilicate) as a phenylating reagent

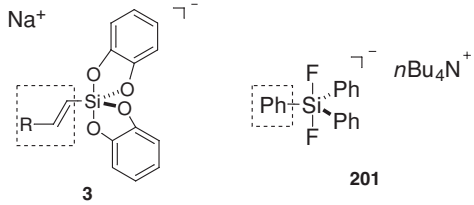
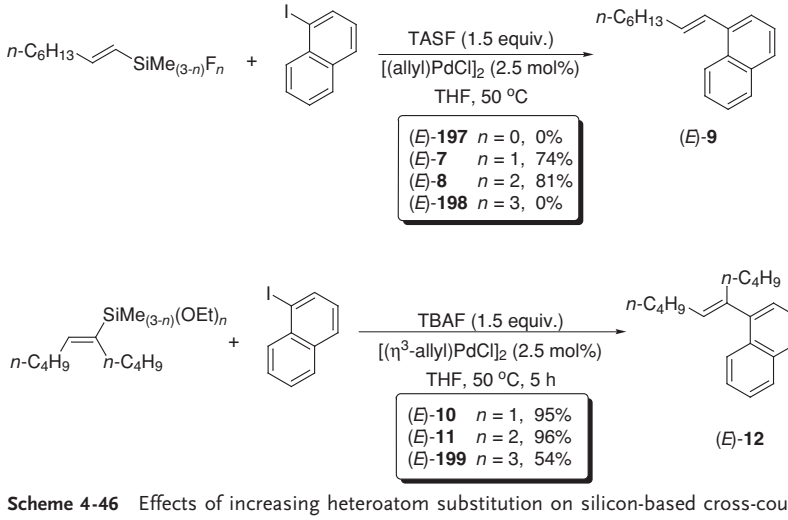


Figure 4-1 Stable pentacoordinate silanes used in cross-coupling reactions.

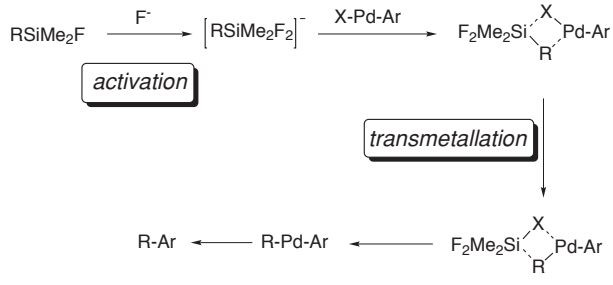
(Figure 4-1) [10, 68]. Yet there are also indications from earlier work with fluoride-activated fluorosilanes of how pentacoordinate silanes could play a role in the reaction.

An early observation in the development of fluorosilane cross-coupling noted the affect of heteroatom substitution at the silicon on the facility of coupling. In the cross-coupling reactions between (1-octenyl)silyl fluorides and 1-iodonaphthalene, it was determined that fluoride substitution on silicon was essential for the reaction to proceed (Scheme 4-46). The reactivity of the silane decreased with increasing numbers of fluoride atoms, however, such that trifluorosilane (*E*)-**198** is completely unreactive [13]. In a related experiment with alkoxysilanes, a similar effect is observed, with trialkoxysilane (*E*)-**199** displaying reduced, albeit not completely attenuated, reactivity [14].



Scheme 4-46 Effects of increasing heteroatom substitution on silicon-based cross-coupling.

These observations were rationalized by the assumption that a pentacoordinate silane is necessary for the cross-coupling. Both mono- and difluorosilanes are efficient fluoride ion acceptors (from TASF), thereby accessing a pentacoordinate state (Scheme 4-47). The remaining coordination site on silicon would presumably be



Scheme 4-47 Proposed mechanism of palladium-catalyzed fluorosilane cross-coupling.

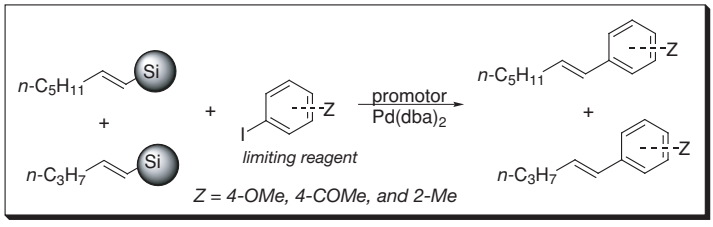
occupied by the halide from the arylpalladium halide complex to allow for a four-centered transmetallation transition state. This last coordination site would not be accessible with a trifluorosilane because it would readily accept two fluoride ions from the promoter, forming an unreactive coordinatively saturated siliconate, and thereby leaving no site for palladium halide complexation.

Despite much speculation over the years and indirect evidence, a clear mechanistic picture, supported by experimental evidence (kinetics, reactive intermediates, calculations), is still lacking. Very recently, however, a number of investigations including quantitative evaluation of substituent effects, rate equation, and spectroscopic identification of intermediates have provided crucial insights into the mechanistic details of these important reactions.

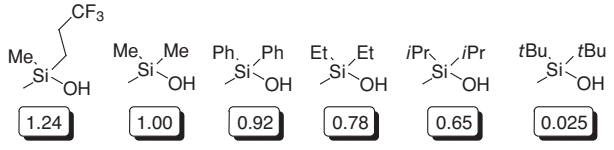
4.3.2 Substituent Steric Effects

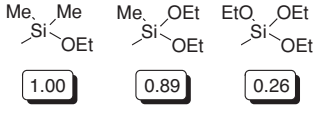
In all of the aforementioned organosilicon cross-coupling systems, only one substituent on silicon is transferred, whereas the remaining are simply "spectator" groups that do not participate directly in the coupling event. This does not mean that they exhibit no influence on the rate or selectivity of cross-coupling. For example, it was noted by Denmark et al. that isopropyl spectator groups significantly reduce the amount of undesired regioisomers in alkenylsilanol coupling compared to methyl groups (*cf.* Scheme 4-13) [69]. This observation prompted a thorough investigation of both steric and electronic effects of silicon substituents on such couplings.

A series of silanols and silyl ethers with varying degrees of heteroatom substitution were synthesized, and their relative efficiencies of coupling to three aryl iodides were elucidated (Scheme 4-48). This was done by running competition experiments of all possible pairwise mixtures of these silanes. To differentiate the coupling products and to evaluate the relative efficiencies of coupling, different transferable groups (pentenyl versus heptenyl) were employed. The choice of these was dictated by the necessity to keep the electronic and steric properties of the transferable group as close as possible, so that these properties of the spectator groups could be evaluated independently. Two methods of activation were also evaluated, with relative rates of coupling of the silane established for both TBAF- and $KOSiMe_3$-

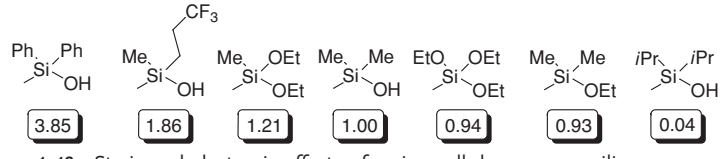


relative efficiency (TBAF promotion):





relative efficincy ($KOSiMe_3$ promotion):



Scheme 4-48 Steric and electronic effects of various alkyl groups on silicon.

promoted couplings. The results of this comprehensive quantitative evaluation proved informative.

Three different aryl iodides were employed (4-$MeOC_6H_4I$, 4-$MeCOC_6H_4I$, and 2-MeC_6H_4I) to evaluate electronic and steric contributions from the coupling partner. Steric and electronic factors on the aryl iodide had no effect on influencing the relative reactivity of the different silanes, regardless of the method of activation.

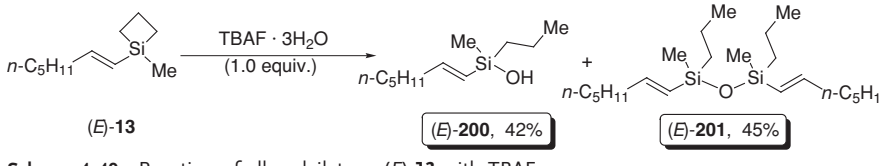
The size of the silicon substituents has little influence on the rate of coupling when TBAF is used as the promoter (for example, similar efficiencies are seen with $SiMe_2OH$, $SiPh_2OH$, $SiEt_2OH$, and $Si(iPr)_2OH$ groups). However, the *t*-butyl-substituted silane is significantly less efficient (Scheme 4-48). The electronic contribution to the rate of coupling is also modest; little difference is observed among $SiMe(CH_2CH_2CF_3)OH$, $SiPh_2OH$, and $SiMe_2OH$ groups. The trend of decreasing efficiency observed for increasing alkoxy-substitution is similar to that noted by Tamao (*cf.* Scheme 4-43). It is also noteworthy that $SiMe_2(OEt)$ and $SiMe_2OH$ groups reacted with similar efficiencies.

In contrast to the TBAF-promoted coupling, the $KOSiMe_3$-promoted reaction reveals dramatically different results. Steric factors have a significant impact on relative efficiencies, with the $Si(iPr)_2OH$ group exhibiting less than a 20-fold lower efficiencies of coupling compared to the $SiMe_2OH$ group. The increased steric demand of the alkyl groups seemingly reduces the efficiency of either activation or transmetallation steps of the coupling mechanism. Once again, as was seen with TBAF-promoted reactions, electronic factors are not insignificant. Interestingly, the silanes with the $SiPh_2OH$ group couple at almost four times more efficiently than those with the $SiMe_2OH$ group. The $SiMe(CH_2CH_2CF_3)OH$ group enhances the rate almost twofold relative to the $SiMe_2OH$ group. The slightly electron-withdrawing group on the silicon can perhaps stabilize any negative charge build-up on the silane when accessing a pentacoordinate state.

The divergence of steric and electronic effects between the two promoters employed clearly suggests the operation of different mechanisms for the two systems. This issue has been addressed through kinetic studies discussed in the following section.

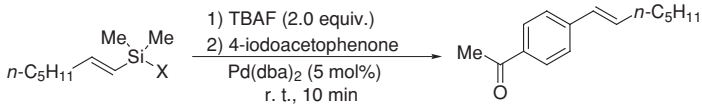
4.3.3
Convergence of Mechanistic Pathways

The high rate, selectivity, and generality of siletane coupling reactions is surprising (see Scheme 4-7). However, the observation of significant heat generation when combining an organosiletane with the TBAF solution provided a key insight [70]. The origin of this exotherm is the siletane ring opening, resulting in the formation of two compounds; silanol (*E*)-**200** and disiloxane (*E*)-**201** (Scheme 4-49). The ring opening of (*E*)-**13** could be understood as the combined action of TBAF and water (from the crystal hydrates in commercial TBAF · $3H_2O$). The heat generated reflects the 26 kcal mol^{-1} of ring strain energy in the siletane [71].



Scheme 4-49 Reaction of alkenylsiletane (*E*)-**13** with TBAF.

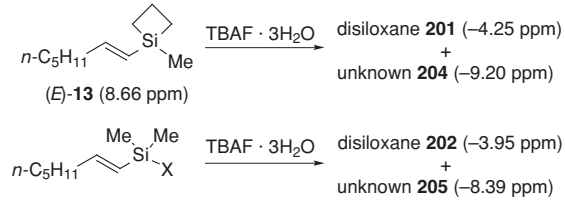
The destruction of the siletane ring upon exposure to TBAF · $3H_2O$ clearly eliminates the hypothesis of strain-release Lewis acidity as the reason behind the facility of this coupling. The crucial question is whether a silanol, disiloxane, or even a related fluorosilane (as developed by Hiyama) is the actual species responsible for the cross-coupling. This question could be addressed by independent synthesis and testing of all three compounds (**32**, **202**, and **203**) – the dimethyl analogs of the three most likely candidates for that putative reactive intermediate. Strikingly, all three are competent coupling partners with 4-iodoacetophenone, and give comparable yields of coupling products after 10 min (Scheme 4-50).



X = OH, (*E*)-**32**	79%
X = OSi(Me)$_2$C$_7$H$_{13}$, (*E*)-**202**	82%
X = F, (*E*)-**203**	78%

Scheme 4-50 Comparison of the cross-coupling reactions of alkenylsilanols, disiloxanes, and fluorosilanes.

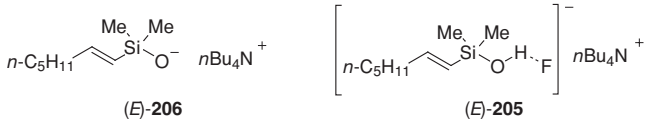
The similarity of reaction rates and yields could be explained by either interconversion of these species to one another, or conversion of each of them to a more advanced, common reactive intermediate. ^{1}H-NMR analysis of a mixture of TBAF with either siletane **13**, silanol **32**, disiloxane **202**, or fluorosilane **203** shows only two species that are formed almost immediately. One is identified as the disiloxane of the corresponding silanol, and the other species an unknown compound **204** (or **205**) containing both silicon and fluorine as determined by ^{29}Si and ^{19}F-NMR (Scheme 4-51). Moreover, the ratio of **204** (**205**) to disiloxane increased with TBAF stoichiometry; under typical conditions for cross-coupling the ratio is heavily in favor (>10:1) of **204** (**205**).



X = OH, (*E*)-**32** (–0.30 ppm)
X = OSi(Me)$_2$C$_7$H$_{13}$, (*E*)-**202** (–3.95 ppm)
X = F, (*E*)-**203** (18.40 ppm)

Scheme 4-51 ^{29}Si-NMR analysis of alkenylsilane/TBAF mixtures.

Attempts to isolate **204** and **205** provide only the silanols **200** or **32**. The sign and magnitude of the ^{29}Si-NMR chemical shift is indicative of tetracoordinate silicon species [72], yet it does not match any of the previously synthesized tetracoordinate silanes. The possibility that **204** and **205** are oligomers was eliminated by a ^{29}Si-NMR crossover experiment [70]. Structural possibilities that remained for **204** and **205** required that they be monomeric and tetracoordinate. The tetrabutylammonium silyloxide salt (*E*)-**206** and a TBAF hydrogen bond complex (*E*)-**205** were proposed (Figure 4-2). The silyloxide salt is ruled out by independent synthesis of the corresponding tetra*methyl*ammonium salt, the ^{29}Si-NMR chemical shift (–26.23 ppm) of which does not correspond to that for **206**. Because compound (*E*)-**205** contains a hydrogen-bonded fluorine atom, ^{19}F-NMR analysis of a sample generated from (*E*)-**32** and TBAF should display the presence of fluorine at a resonance different from that of TBAF. At room temperature, the spectrum displays only a single resonance at –117.7 ppm. Cooling the solution to –95 °C, however,



(*E*)-**206** (*E*)-**205**

Figure 4-2 Tetrabutylammonium silyloxide salt (*E*)-**206** and the TBAF-silanol complex (*E*)-**205**.

allows the observation of two signals, one at –113.2 ppm for TBAF and one at –150.8 ppm, which is very close to the chemical shift for bifluoride (FHF^-) at –148 ppm [73].

Although indirect, all of the available data are consistent with structure (*E*)-**205** (a hydrogen-bonded complex between an organosilanol and TBAF) as the best fit for the reaction component in question. Subsequent kinetic analyses discussed in the following section reveal the role of this intermediate in the cross-coupling pathway.

These mechanistic studies disproved the rationale for the ability of siletanes to couple so mildly, and they uncovered an unexpected intermediate in the reaction pathway.

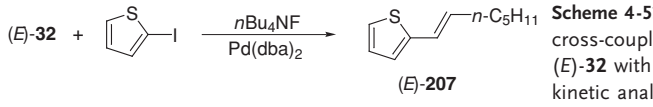
Most significant, however, is that the observation of a common intermediate among silanol-, disiloxane-, and fluorosilane-cross-coupling reactions signifies that these systems, which encompass the vast majority of documented organosilicon cross-coupling systems to date, likely react according to a common mechanism.

4.3.4
Kinetic Analysis and Mechanistic Implications

The kinetics of two organosilanol cross-coupling systems have recently been investigated. In the TBAF-promoted coupling of (*E*)-**32** with 2-iodothiophene, the overall rate equation is as follows [74]:

$$\text{rate} = k_{obs}[\text{SiOH}]^2[\text{TBAF}]^n \quad (1)$$
$$k_{obs} = k[\text{Pd}]^1$$
$$n = 1 \text{ at TBAF/SiOH} < 2 \text{ and } n = -1 \text{ at TBAF/SiOH} > 2$$

The implications of this equation are detailed below in the context of the basic three-step catalytic cycle for palladium-catalyzed cross-coupling reaction [5f] involving: (1) oxidative insertion of palladium(0) into an alkyl halide; (2) transmetallation of the transferable group from the donor moiety onto palladium; and (3) reductive elimination of the resultant organopalladium species to give the coupled product and regenerate the palladium(0) catalyst.



(*E*)-**207**

Scheme 4-52 TBAF-promoted cross-coupling of alkenylsilanol (*E*)-**32** with 2-iodothiophene for kinetic analysis.

The first-order rate-constant dependence on palladium concentration is consistent with a mononuclear palladium entity participating in each turnover of the catalytic cycle. This is similar to the kinetic result obtained for organotin-based cross-couplings [5]. It is noteworthy that the rate dependence on the catalyst concentration, manifested in the rate constant, eliminates the possibility that simple fluoride activation of the silanol (which does not involve palladium) could be turnover limiting.

The zero-order behavior in 2-iodothiophene also finds analogy in the mechanism of organotin cross-coupling [75]. This is interpreted as a rapid and irreversible oxidative insertion step of the palladium(0) under the reaction conditions. The facility of this process has been well documented, and the predominant use of iodides in many of the early reports of cross-coupling chemistry has its origin in this behavior.

Thus, the remaining possibilities are that either transmetallation or product-forming reductive elimination could be the rate-determining step of this reaction. The positive correlation between the rate and silanol concentration strongly supports the conclusion that transmetallation is turnover limiting, as it is in organotin-based coupling reactions. In particular, the unique second-order dependence on silanol concentration indicates that two silicon-based entities participate in the turnover limiting transmetallation step. NMR-spectroscopic studies revealed the rapid formation of a disiloxane from two molecules of silanol in the presence of TBAF. Therefore, this suggested that the second-order dependence is due to such a disiloxane, not a silanol, undergoing transmetallation. The data obtained thus far indicate that oxidative insertion of the palladium into the aryl iodide and disiloxane formation precedes a turnover limiting transmetallation step.

The striking divergence of rate dependence on fluoride concentration provided an interesting insight. A change in slope of this nature is usually indicative of a change in mechanism. Previous ^{29}Si-NMR spectroscopic studies suggested that a hydrogen-bonded silanol-TBAF complex was a thermodynamically stable intermediate formed by the interaction of TBAF $\cdot$ $3H_2O$ with nearly any silafunctionalized precursor (*cf.* Figure 4-2). If such a complex were formed, then the process of conversion to a pentacoordinated fluoride-activated disiloxane would release one molecule of TBAF for every two molecules of complex initially present (Figure 4-3). This mode of transmetallation is consistent with an *inverse* dependence of fluoride on the coupling rate, since one molecule of TBAF must dissociate prior to the rate-determining transmetallation step.

It is crucial to note that a rate equation reveals information regarding the mechanistic pathway from *the lowest energy species to the highest transition state*. Hence, the inverse order dependence of TBAF lends further support to the existence of **205**. There is, however, a region where first-order dependence on TBAF is observed. Three discrete species, (*E*)-**32**, disiloxane **202**, and (*E*)-**205**, are known to be in equilibrium in the reaction mixture (*cf.* Scheme 4-48). It has also been observed that the predominant species in solution is dependent on the TBAF/silanol ratio. At low TBAF equivalents, silicon is mostly in the form of disiloxane. At higher TBAF loadings however, the predominant species becomes (*E*)-**205**.

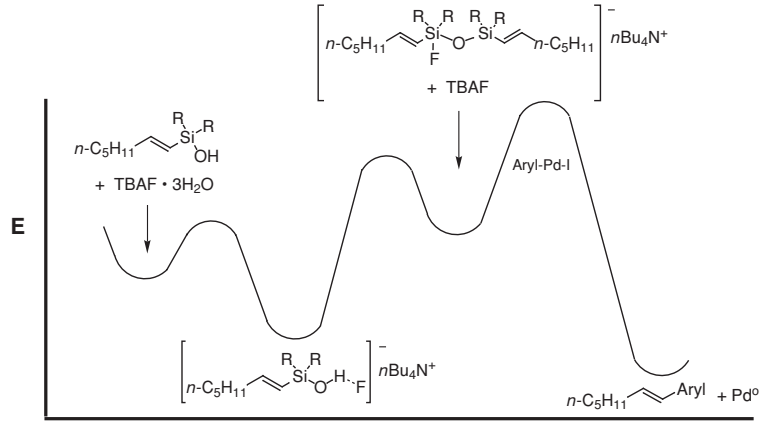


Figure 4-3 Mechanism of TBAF-promoted coupling of (*E*)-**32** with 2-iodothiophene using a TBAF/(*E*)-**32** ratio > 2/1.

Direct formation of disiloxane from (*E*)-**32** and resultant fluoride activation would be consistent with second-order behavior in silanol, and *first*-order behavior in TBAF (Figure 4-4). Hence, the TBAF/silanol ratio in solution dictates whether the prevalent pathway towards transmetallation involves **205**, or not.

It should be emphasized that the results of these kinetic studies do not represent only the TBAF-promoted coupling of alkenylsilanols. Analyzed in the context of the spectroscopic studies and reported observations – which reveal that siletanes, silanols, and fluorosilanes, silyl hydrides, and heterocyclic silanes all form related species when mixed with TBAF – the mechanism deduced by the kinetic studies likely represents the mechanism of cross-coupling of all of these species. These mechan-

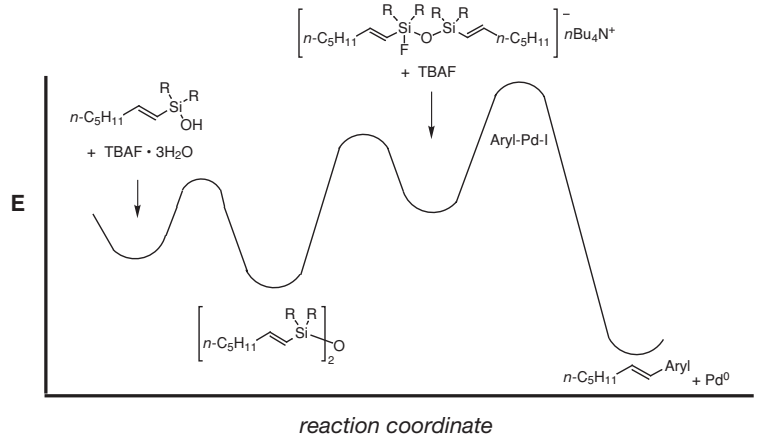
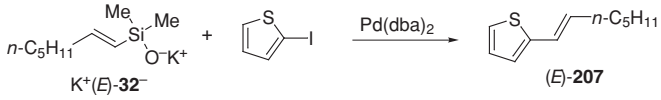


Figure 4-4 Mechanism of TBAF-promoted coupling of (*E*)-**32** with iodothiophene using a TBAF/(*E*)-**32** ratio < 2/1.



Scheme 4-53 Coupling of potassium silanolate (*E*)-**32** with 2-iodothiophene for kinetic analysis.

istic results are therefore relevant to a significant body of work, encompassing everything from the early fluorosilane cross-coupling systems to the more recently developed TBAF-promoted coupling of pyridyl-, thienyl-, and benzylsilanes.

The kinetic analysis of the fluoride-free coupling of silanolate K^+(*E*)-**32**$^-$ to 2-iodothiophene has also been studied in similar detail (Scheme 4-53) [76]. This system is representative of the $KOSiMe_3$-promoted cross-coupling of silanols (*cf.* Scheme 4-20). The derived rate equation is as follows:

$$\begin{aligned} &\text{rate} = k_{obs}[R_3SiOH]^n \\ &k_{obs} = k[Pd]^1 \\ &n = 1 \text{ when } R_3SiOK/Pd < 20/1 \\ &n = 0 \text{ when } R_3SiOK/Pd > 20/1 \end{aligned} \tag{2}$$

The zeroth order rate dependence on 2-iodothiophene and the first-order dependence of the rate constant on palladium concentration are straightforward to interpret. As in the kinetic analysis of the TBAF-promoted system, these data are consistent with a fast and irreversible oxidative insertion of the palladium into the aryl iodide bond. Thus, the oxidative addition step is not interpreted to be the turnover limiting step (TLS) of this coupling.

The results of varying silanolate concentration show two regions with distinct slopes. This can be interpreted either as a change in mechanism, or a switch in the turnover limiting step of the same mechanism. It is immediately apparent that the mechanism diverges from that of TBAF-promoted reaction. A change to zero-order behavior in silanolate is evidence of an *intra*molecular transmetallation step. The proposed mechanism for this fluoride-free system is therefore shown in Figure 4-5.

The region of low silanolate concentration (below 1 equiv. with respect to iodide) shows first-order behavior. This can be interpreted as either turnover limiting formation of **i**; this slope then levels, implicating a zero-order regime at higher concentrations. This lends support to a turnover limiting *intra*molecular transmetallation from **i**. This is due to the fact that the concentration of palladium catalyst (0.05 equiv.) is static throughout the course of the reaction. Therefore, a turnover limiting intramolecular process involving this catalyst should exhibit a rate behavior which is independent of the silanolate concentration.

The analysis of silanolate order with a stoichiometric amount of palladium with respect to 2-iodothiophene also revealed a first-order dependence of reaction rate on silanolate concentration. This critical experiment rules out the possibility that an activated complex involving another molecule of silanolate (with **i** to generate a pentacoordinate silicon) is formed. In this latter case, second-order behavior would have been expected.

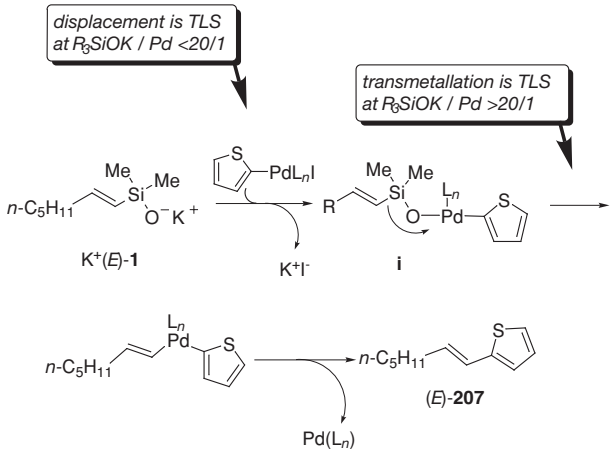


Figure 4-5 Mechanism of fluoride-free silanol cross-coupling.

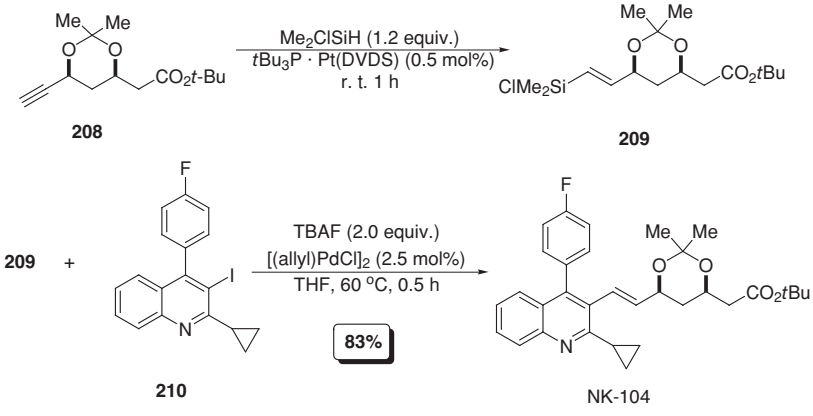
These results are very surprising because the reigning dogma in silicon-based cross-coupling reactions is that transmetallation to an arylpalladium unit requires prior activation as a pentacoordinate siliconate. In fact, the addition of nucleophilic activators in all published organosilane cross-coupling systems is aimed toward such nucleophilic activation. This illustrates the importance of the silicon-oxygen-palladium linkage because it allows for an otherwise unfavorable transformation to occur. The divergence of the mechanism from that of fluoride activation, wherein an intermolecular transmetallation from a fluoride-activated disiloxane is found to be turnover limiting, is remarkable because two equally efficient room temperature coupling systems can operate via different mechanisms.

The combination of spectroscopic studies and kinetic analysis has provided an invaluable insight into the mechanism of silicon-based cross-coupling reactions. Interestingly, several different silicon precursors can operate under a common mechanistic regime. However, a change in the promoter employed causes a change in the mechanism reflecting radically different modes of transmetallation.

4.4
Applications to Total Synthesis

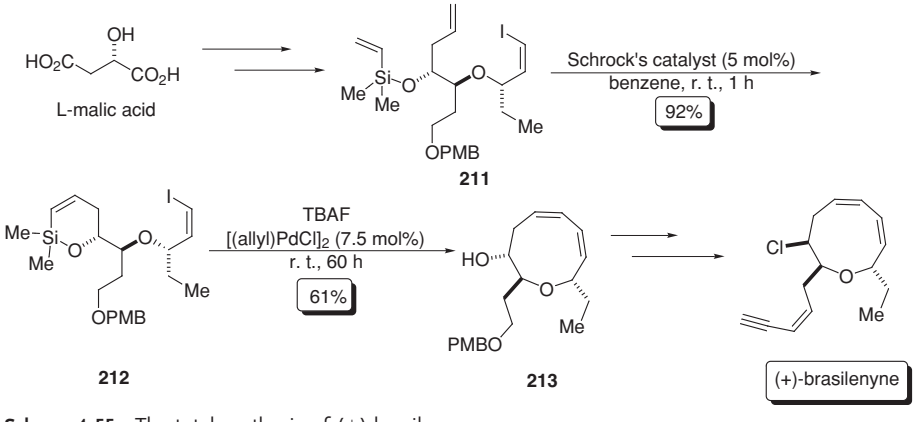
The utility of silicon-cross-coupling has only recently been applied in the synthesis of structurally novel and useful products. Hiyama et al. employed a hydrosilylation/chlorosilane cross-coupling approach (alkenyl-aryl) for the synthesis of NK-104, an artificial HMG-CoA reductase inhibitor (Scheme 4-54) [77].

More recently, the first total synthesis of (+)-brasilenyne, an antifeedant isolated from the sea hare (*Aplysia brasiliana*) by Fenical in 1979, was reported [78]. This report makes novel use of the cyclic silyl ether-generating ring-closing metathesis/cross-coupling sequence. The synthesis of (+)-brasilenyne is achieved from



Scheme 4-54 The total synthesis of NK-104.

L-malic acid in 19 steps and 5.1 % overall yield. The key step, an intramolecular cross-coupling, proceeds at room temperature in 61 % yield to set the unusual 1,3-*cis*-*cis*-diene unit in the nine-membered cyclic ether (Scheme 4-55).



Scheme 4-55 The total synthesis of (+)-brasilenyne.

4.5
Summary and Outlook

The progress achieved in organosilicon cross-coupling over the past five years – particularly in the types of employable silicon precursors for cross-coupling and the methods available to incorporate silicon into organic molecules – reflects the constantly increasing applicability of this method in organic synthesis. The scope of usable substrates and promoters is extensive and rivals – if not surpasses – the range of boron and tin precursors known. Although there has been impress-

ive progress in the expanding the range of unsaturated donors and methods to incorporate silicon into substrates, the development of efficient alkylsilane donors is needed. In addition, the scope of electrophiles is somewhat less thoroughly studied. Future investigations will likely address these current limitations, as well as highlight applicability to more synthetic endeavors. In addition, mechanistic studies have provided valuable information about the cross-coupling reaction pathway taken by different organosilicon substrates under different modes of motivation. Further studies are warranted to obtain relevant insight into systems wherein the current conclusions regarding the mechanism are not directly applicable. Premier among the mechanistic questions is a detailed picture of the transmetallation event from silicon to palladium. Finally, the combination of silicon-based cross-coupling with other valuable transformations such as ring-closing metathesis and C-H activation presage important new directions in this field. The impressive developments of the past five years provide a tantalizing glimpse into the untapped potential of this exciting field of research.

4.6 Experimental Procedures

4.6.1 TBAF-Promoted Palladium-Catalyzed Cross-Coupling Reaction of Alkenylsilanes with Aryl or Alkenyl Halides (Scheme 4-13). (1*E*)-1-Heptenylbenzene (*E*)-14) [26]

Tetrabutylammonium fluoride (631 mg, 2.0 mmol, 2.0 equiv.) was dissolved in anhydrous THF (2 mL) at room temperature under an atmosphere of dry nitrogen. The silanol (201 mg, 1.2 mmol, 1.2 equiv.) was added neat and the mixture stirred for 10 min at room temperature. Iodobenzene (112 mL, 1.0 mmol) was added to the mixture, followed by $Pd(dba)_2$ (29 mg, 0.05 mmol, 0.05 equiv.), and the mixture stirred at room temperature for 10 min. The reaction mixture was then filtered through a short silica gel column (20 g). The plug was washed with diethyl ether (100 mL), and the solvent evaporated. Purification by column chromatography (RP-C18, $MeOH/H_2O$, 9/1) and Kugelrohr distillation afforded 159 mg (91 %) of (*E*)-**14** as a colorless oil.

4.6.2 Palladium-Catalyzed Cross-Coupling of (4-Methoxyphenyl)dimethylsilanol with 4-Substituted Aryl Iodides (Scheme 4-21). 4-Carbethoxy-4′-methoxybiphenyl (65) [40]

Anhydrous cesium carbonate (651 mg, 2.0 mmol, 2.0 equiv.) was suspended in anhydrous toluene (1.0 mL) at room temperature in a 5-mL, round-bottomed flask with a magnetic stir bar and fitted with a reflux condenser and an argon inlet adapter. To this suspension was added dropwise H_2O (108 mL, 6.0 mmol, 6.0 equiv.), and the resulting slurry was stirred for 10 min. Ethyl 4-iodobenzoate (276 mg, 1.0 mmol, 1.0 equiv.), and the arylsilanol (218 mg, 1.2 mmol, 1.2 equiv.) were

then added, followed by $[allylPdCl]_2$ (18.3 mg, 0.05 mmol, 0.05 equiv.), and triphenylarsine (30.6 mg, 0.1 mmol, 0.1 equiv.). The flask was then purged with argon and placed in a 90 °C oil bath for 8 h. The reaction was monitored by GC analysis at certain intervals until completion. Sampling of the reaction was performed by removing 10-mL aliquots of the mixture via a syringe. Each aliquot was filtered through a small plug of silica gel and eluted with 5 mL ethyl acetate. The aliquot was then analyzed by GC. On completion, the reaction was cooled to room temperature, treated with H_2O (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was further purified by column chromatography (SiO_2) (hexane/EtOAc, 20/1) to afford the corresponding product which was further purified by recrystallization (EtOH) to afford 160 mg (87 %) of **65** as a colorless solid.

4.6.3

One-Pot Sequential Hydrosilylation/Cross-Coupling Reaction (Scheme 4-25). (*E*)-5-(4-Methoxyphenyl)-4-penten-1-ol (96) [45]

To a solution of 1,1,3,3-tetramethyldisiloxane (121 mg, 0.90 mmol, 1.8/2 equiv.) in 0.2 mL THF was added tBu$_3$P-Pt(0) complex (25 μL). 4-Pentyn-1-ol (151 mg, 1.8 mmol, 1.8 equiv.) was then slowly added with external cooling with a water bath (the temperature of the reaction mixture was not allowed to exceed 30 °C). The hydrosilylation mixture was stirred at room temperature for 30 min after complete addition of the alkyne. A solution of TBAF (2.0 mL, 1.0 *M* in THF, 2.0 equiv.) was added to above solution. After 10 min, 4-iodoanisole (234 mg, 1.0 mmol, 1.0 equiv.) and $Pd(dba)_2$ (29.0 mg, 5.0 mol %) were added sequentially. A strong exotherm was observed. The reaction was monitored by GC or GC-MS. When the halide had been consumed (60 min), ether (10 mL) was added and the mixture stirred for an additional 5 min. The mixture was filtered through a short column of silica gel, which was then eluted with ether (100 mL). The combined eluates were concentrated by rotary evaporation and vacuum drying to give the crude product; this was purified by silica gel chromatography (pentane/EtOAc, 2/1) to afford 170 mg (89 %) of the product **96**, as colorless solid.

4.6.4

Palladium-Catalyzed Cross-Coupling of Phenyltrimethoxysilane with Aryl Iodides (Scheme 4-34). 4-Acetylbiphenyl (65) [55b]

To a solution of 0.201 mg (1.01 mmol) 4-bromoacetophenone, 24 mg (0.107 mmol) $Pd(OAc)_2$, and 55 mg (0.210 mmol) Ph_3P in 10 mL DMF was added 419 mg (2.11 mmol) phenyltrimethoxysilane. Then, 2.1 mL (2.1 mmol) TBAF solution was added to the reaction mixture via a syringe. The reaction mixture was degassed to remove oxygen by one freeze-pump-thaw cycle. The resulting orange solution was heated at 90 °C, and after 5 h the reaction mixture had turned black. The reaction mixture was heated for a total of 24 h at 90 °C. The resulting black

suspension was quenched by the addition of 50 mL water; the aqueous layer was extracted with 4 × 50 mL Et_2O, and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (30 mm, 14 cm, 0–10 % Et_2O/pentane) gave 171 mg (86 %) of 4-acetylbiphenyl. TLC R_f 0.41 (25 % Et_2O/pentane).

4.6.5

One-Pot Sequential Mizoroki-Heck/Cross-Coupling Reaction (Scheme 4-41). (*E*)-4-[2-(4-Acetylphenyl)-1-butylethenyl]benzoic Acid Ethyl Ester (171) [63a]

To a solution of $Pd(OAc)_2$ (4.3 mg, 0.02 mmol, 10 mol %), tri-2-furylphosphine (5.1 mg, 0.02 mmol, 10 mol %), triethylamine (32.7 mg, 0.32 mmol), and 4-iodobenzoic acid ethyl ester (75.2 mg, 0.27 mmol) in THF (0.9 mL) was added **1** (65.7 mg, 0.30 mmol) under argon, and the reaction mixture was stirred at 60 °C for 3 h. After cooling the reaction mixture to room temperature, 4-iodoacetophenone (48.2 mg, 0.20 mmol) and tetrabutylammonium fluoride (0.46 mmol, 1.0 *M* in THF) were added, and the mixture was stirred at 60 °C for 14 h. The catalyst was removed by filtration through a short silica gel pad (EtOAc). The filtrate was evaporated, and the residue chromatographed on silica gel (hexane/EtOAc = 10/1) to afford **171** (48.6 mg, 71 %) as a colorless oil.

Abbreviations

AcOH	acetic acid
Ag_2O	silver(I) oxide
$[(allyl)PdCl]_2$	allylpalladium(II) chloride dimer
CIPE	complex-induced proximity effect
$Cu(OAc)_2$	copper(II) acetate
$CuOC_6F_5$	copper(I) pentafluorophenoxide
CuI	copper iodide
D3	hexamethylcyclotrisiloxane
dppb	diphenylphosphinobutane
DVDS	1,3-divinyl-1,1,3,3-tetramethyldisiloxane
Et_3N	triethylamine
$KOSiMe_3$	potassium trimethylsilanolate
LiOAc	lithium acetate
$NaOC_6F_5$	sodium pentafluorophenoxide
$(nBu_4N)_2PtCl_6$	bis(tetra-*n*-butylammonium) hexachloroplatinate
$PdBr_2$	palladium bromide
$Pd(dba)_2$	bisdibenzylideneacetone palladium
$Pd_2(dba)_3$	tribenzylideneacetone bispalladium
$Pd(OAc)_2$	palladium(II) acetate
$PhB(OH)_2$	phenylboronic acid
$PhMe_2SiOMe$	dimethylmethoxyphenylsilane

$PhMe_2SiCl$	dimethylchlorophenylsilane
PMHS	poly(methylhydroxysilane)
$PhSiMe_3$	phenyltrimethylsilane
$PhSiMe_2OH$	phenyldimethylsilanol
$PhSnBu_3$	tri-*n*-butylphenyltin
PPh_3	triphenylphosphine
RCM	ring-closing metathesis
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetra-*n*-butylammonium fluoride
TBAT	tetra-*n*-butylammonium triphenyldifluorosilicate
TBDPS	*t*-butylphenylsilyl
TBS	*t*-butyldimethylsilyl
$t(Bu)_2MeP$	bis(di-*t*-butyl)methylphosphine
tBu_3P	tri-*t*-butylphosphine
THF	tetrahydrofuran
TMAF	tetramethylammonium fluoride

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5
Cross-Coupling of Organyl Halides with Alkenes: the Heck Reaction

Stefan Bräse and Armin de Meijere

5.1
Introduction

The carbopalladation of an alkene by an organylpalladium halide is the essential step in one of the major contemporary metal-catalyzed C-C-coupling reactions. About 35 years ago, a Japanese and an American group almost simultaneously designed and executed palladium-mediated coupling reactions of aryl and alkenyl halides with alkenes [1]. In subsequent investigations, Richard Heck and his group developed this reaction into a catalytic transformation and started to demonstrate its usefulness as well as its rather broad scope. The real push to utilize this powerful C–C bond-forming process, however, started only around the mid-1980s, and by now an impressive number of publications has established the meanwhile so-called Heck reaction [2] as an indispensable method in organic synthesis [3]. The applications range from the preparation of hydrocarbons, novel polymers and dyes to new advanced enantioselective syntheses of natural products and biologically active non-natural compounds. The more or less simultaneous developments of mechanistically related variants, namely the Suzuki, Stille, Hiyama, Kumada and Negishi coupling reactions (see Chapters 2, 3, 4, 12 and 15 in this book, respectively) of metallated alkenes and arenes with aryl and alkenyl halides or the metal-catalyzed formation and cycloisomerization of enynes have drawn profit from the improvement of and mechanistic insights into the Heck reaction. This, of course, also applies *vice versa*. Using only a catalytic amount of a palladium(0) complex or a precursor to a palladium species, the Heck reaction can bring about unprecedented structural changes, particularly when conducted intramolecularly. The full potential of this palladium-catalyzed process is still being further explored, as demonstrated by a total of 2400 relevant publications during the past 10 years, and a continuous annual growth in publications of 15 % per year. Therefore, it is appropriate to say that the Heck reaction is one of the true "power tools" in contemporary organic synthesis [4], competing favorably with the Diels-Alder reaction (25 000 references), olefin metathesis (1500 references), Wittig reaction (15 000 references), or Claisen rearrangement (15 000 references).

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In this chapter, an attempt is made to summarize the current state of understanding the basics of the mechanism, to provide an overview over the diverse and sometimes mysterious compositions of applicable catalyst "cocktails", and to review important recent developments and applications of this reaction principle.

5.2 Principles

5.2.1 The Mechanism

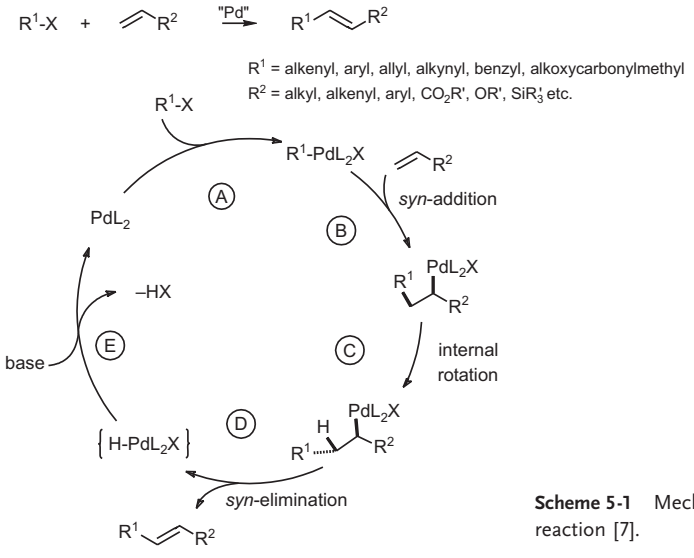
Even at an early stage in the evolution of the Heck reaction into a facile method for the preparation of alkenyl- and aryl-substituted alkenes, reasonable concepts for the mechanism emerged, which could serve at least as working hypotheses. By now, many mechanistic details have been worked out by experimental means such as kinetic [5, 6] and electrochemical measurements under various conditions.

A coordinatively unsaturated 14-electron palladium(0) complex, usually coordinated with weak donor ligands (mostly tertiary phosphanes), has meanwhile been proved to be the catalytically active species [7]. This active complex is always generated *in situ*, e. g., from tetrakis(triphenylphosphane)palladium(0) which exists in an equilibrium with tris(triphenylphosphane)palladium(0) and free triphenylphosphane in solution. The endergonic loss of a second phosphane ligand [8] leads to the catalytically active bis(triphenylphosphane)palladium(0). However, palladium(II) complexes or salts such as bis(triphenylphosphane)palladium dichloride or palladium acetate, which are easily reduced (e. g., by triarylphosphanes, see below) in the reaction medium, are more commonly employed for convenience, as they are inherently stable towards air. The mechanistic situation is a bit more complicated with palladium acetate in that anionic acetoxypalladium species $Pd(PPh_3)_n(AcO^-)$ ($n = 2, 3$) are formed in the presence of acetate ions [7], and these actually participate in the oxidative addition step and the following coupling reaction.

In the first step of the sequence (A in Scheme 5-1), a haloalkene or haloarene is commonly assumed to add oxidatively to the coordinatively unsaturated palladium(0) complex, generating a σ-alkenyl- or σ-arylpalladium(II) complex [9]. As the electrophilicity of this complex is enhanced, it more readily accepts an alkene molecule in its coordination sphere, probably by exchange for another ligand.

If the alkenyl (aryl) residue and alkene ligand on palladium are in a *cis*-orientation, rotation of the alkene can lead to its in-plane coordination, and subsequent *syn*-insertion of the σ-alkenyl- or σ-aryl-palladium bond into the C=C double bond occurs to yield a σ-(β-alkenyl)- or σ-(β-aryl)alkylpalladium complex via a four-centered transition state (B).

In the next step, the product-yielding β-hydride elimination (step D) can occur only after an internal rotation (step C) around the former double bond, as it requires at least one β-hydrogen to be oriented synperiplanar with respect to the



Scheme 5-1 Mechanism of the Heck reaction [7].

halopalladium residue. In some cases, *anti*-elimination was made possible by suitable substrates or conditions, leading to a $E1_{cb}$ mechanism type [10,11]. The subsequent *syn*-elimination yielding an alkene and a hydridopalladium halide is, however, reversible, and therefore the thermodynamically more stable (*E*)-alkene is generally obtained when the coupling reaction is performed with a terminal alkene. Reductive elimination of HX from the hydridopalladium halide, aided by the added base, regenerates the active catalyst and thereby (step E) completes the catalytic cycle.

This mechanism has not been proved in all details, and especially the rate-determining step has not been identified unequivocally in all cases. Frequently, the oxidative addition has been assumed to be rate-determining, however, in certain cases it has been doubted [12] or even disproved experimentally [6].

5.2.2
The Catalysts

Commercially available palladium salts and complexes in the presence of various ligands are most frequently used as catalysts. The first choice is often the air-stable and relatively inexpensive palladium acetate, though several other published variants may be preferable in certain applications. It is commonly assumed that the palladium(II) species is reduced in situ by the solvent, the alkene [13], the amine [14] or the added ligand (frequently a phosphane, which is oxidized to a phosphane oxide) [15]. In some cases, highly dispersed elemental palladium on charcoal can be applied. In the case of alkenyl or aryl bromides, phosphanes are necessary to avoid precipitation of palladium black (*cf.*, however, Section 5.2.4),

whereas iodides have been reported to be less reactive in the presence of phosphanes. Triflates have been found to be more reactive in the presence of chloride ions, as the chloride ligand is more easily removed from palladium than the triflate ion [16]. However, this has also become questionable, because successful coupling reactions of alkenyl triflates have been performed in the absence of chloride ions [17].

It was shown that palladacycles **1** [3c,18] prepared from palladium(II) acetate and tris(*o*-tolyl)- or trimesitylphosphane, are excellent catalysts for the Heck coupling of triflates and halides including certain aryl chlorides. In this case, the possible involvement of oxidation states +II and +IV in the catalytic cycle has been considered [19]. Similarly, other palladacycles such as **2** [20], **3** [21e,h] or **6** [22] have been used in Heck reactions (Figure 5-1) [18,21]. It has been proposed that, at least for NC palladacycles, the reaction proceeds through the classical phosphine-free Pd(0)/Pd(II) catalytic cycle, and that the active catalysts are actually slowly formed palladium clusters [23].

A promising new class of highly active catalysts are palladium complexes of nucleophilic carbenes such as **4**, **5**, or **10** [24–27]. The first example of a successful coupling of the notoriously unreactive chloroarenes was reported by Herrmann et al. [28]. The phosphanes which are used as ligands in many catalyst cocktails for the Heck reaction, undergo P-C cleavage at the higher temperatures required for the coupling of, for example, chlorides. The palladium complexes **10a**,**b** are thermally considerably more stable than palladium complexes with triorganylphosphane ligands. In addition, the Pd^0-carbene complex **10b** has an extremely high activity with long-term stability in the Heck reaction: with only 4×10^{-4} mol %

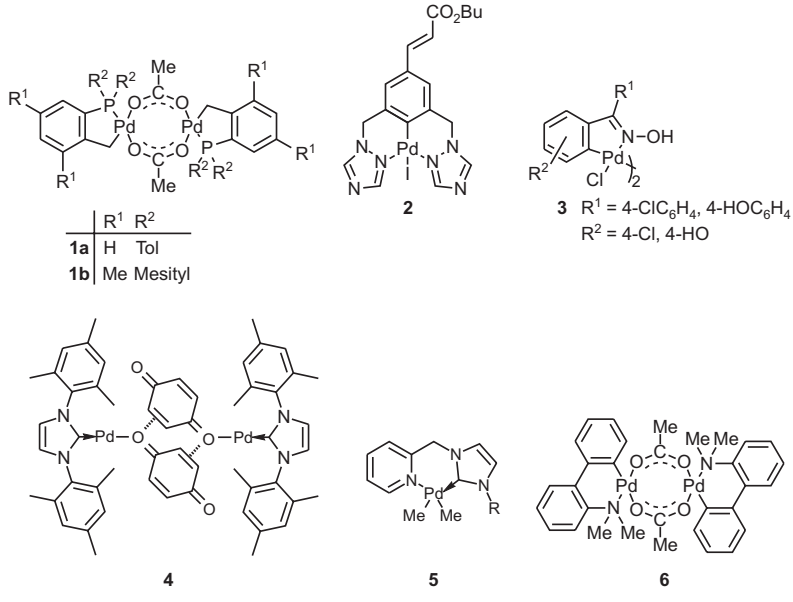
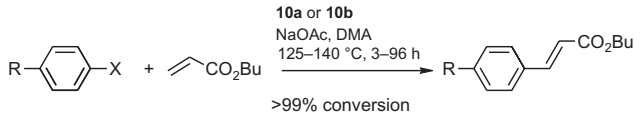
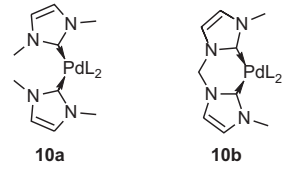


Figure 5-1 Innovative palladium catalysts.



7	X	R	Cat.	mol%	Time [h]
a	Br	COMe	**10a**	4×10^{-4}	43
b	Cl	NO_2	**10a**	0.1	36



10a **10b**

Scheme 5-2 Highly efficient catalysts for the Heck reaction [28].

of catalyst, the bromoarene **7** could be completely converted to the cinnamate **9** in 43 h [28].

Alternatively, sterically highly congested phosphanes such as tBu$_3$P [29], diadamantylalkylphosphanes [30], bulky secondary phosphanes [31] or (bulky) bidentate phosphanes (e. g., dippb or even dppe) [32a–d] are also suitable for coupling of chloroarenes. In particular, polymer-bound ligands [33,34] or inorganic solid-supported palladium metal [33] have been frequently used for the ease of regeneration of the catalyst. With solid-supported palladium catalysts, the reaction proceeds presumably in the liquid phase [35, 36].

In some cases, quite stable palladium(0) complexes such as dibenzylideneacetonepalladium [Pd(dba)$_2$, Pd$_2$(dba)$_3$, or Pd$_2$(dba)$_3 \cdot$ CHCl$_3$] can be utilized advantageously, especially when the substrate is sensitive towards oxidation.

In essence, many palladium(0) precursors which are either conventional or newly designed, such as phosphane-free complexes [37] might be suitable for a successful and efficient carbopalladation reaction. At a higher temperature, many palladium complexes and ligand-free palladium(0) precursors [37] decompose, forming nanoparticles [38]. It has been disputed whether in many cases the nanoparticles having an accurate size are the active catalysts for Heck reactions and other palladium-catalyzed processes [39,40]. Since smaller particles would aggregate at higher concentration, this ought to be the rational for highly active "homeopathic" doses [41] of palladium.

Table 5-1 Various palladium catalysts applied in the Heck reaction[a].

Palladium catalyst	*Apply for*	*Remarks*	*Ref.*
Pd(OAc)$_2$	All systems	Most frequently employed, inexpensive	*Cf.* [3]
Pd(OTfa)$_2$	Coupling of benzoic acids [42]	Air-stable	[43]
PdCl$_2$	Coupling of aryl or vinyl arenecarboxylates [44]	Least expensive Pd salt	[68a]

Table 5-1 (continued)

Palladium catalyst	*Apply for*	*Remarks*	*Ref.*
$[Pd(acac)_2]$	Aryl halides	Air-stable	[36]
$[Pd_2(dba)_3 \cdot CHCl_3]$	Aryl iodides	Limited air stability	[45]
$[Pd_2(dba)_3]$	Alkenyl triflates	Limited air stability	[46,47]
[Pd(dppb)]	Aryl iodides	From $[Pd_2(dba)_3]$ and dppb	[45,46]
Palladacycles **1**	Chloride as leaving group	Air-stable	[19a]
Nucleophilic carbene palladium complexes		Air-stable	[20,24–28]
Palladium on charcoal (Pd/C) [b]	a) Aroyl chlorides as substrates	Inexpensive, highly active	a) [48a]
	b) Diazonium salts		b) [49]
	c) Aryl halides, e. g., chlorides		c) [50,51]
Palladium on other solids (SiO_2, zeolites [52])[b]	Aryl iodides	Air-stable	[36]
Palladium black	Aryl iodides	Air-stable	[36]
$[Pd(PPh_3)_4]$	a) Alkenyl triflates	Air-sensitive	a) [53]
	b) Aryl iodides	Air-sensitive	b) [54,55]
$[Pd(PPh_3)_2(OTfa)_2]$	Aryl iodides	Air-stable	[56]
$[Pd(PPh_3)_2Cl_2]$	Aryl triflates	Air-stable	[57]
$[Pd(PhCN)_2Cl_2]$	Arenesulfonyl chlorides	Air-stable, soluble form of $PdCl_2$	[58]
$[Pd(MeCN)_2Cl_2]$	Aryl bromides, alkenyl triflates	Air-stable, soluble form of $PdCl_2$	[59,60]
Pd-Clusters	Aryl iodides, bromides, chlorides	Air-stable	[61]
Pd-Colloids	Activated aryl bromides	Air-stable	[62a]
Pd-Graphite[b]	Aryl iodides, polycondensation	Air-stable	[56b]
Palladium on:			
a) derivatized polystyrenes	Aryl halides	Air stable	a) [63a–c]
b) derivatized clays		Air stable	b) [63d]
Complexes with polymer-bound ligands		Recycling of ligand/ metal	[64]

[a] For other metals used in Heck-type reactions, see e. g. [65].
[b] In the case of solid-supported palladium catalysts, the reaction proceeds in the liquid phase [35a,36].

Initially, only dipolar aprotic solvents such as dimethylformamide (DMF), *N*-methylpyrrolidinone (NMP), dimethylsulfoxide (DMSO), acetonitrile (MeCN) and anisole were common. However, the presence of water has been found to accelerate certain Heck reactions [66,67], and consequently the development has gone to water-soluble triarylphosphane ligands (e. g., triphenylphosphane-*m*-trisulfonic acid sodium salt (TPPTS) [68a]) with which many alkene arylations superbly succeed in aqueous solvent mixtures [69]. More recently, ionic liquids (molten low melting ammonium salts) [25,27,70–74] and supercritical CO_2 [75] have been found to be superb solvents for Heck reactions. A puzzling finding is that nucleophilic carbenes are formed even in the presence of the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) [76].

Table 5-2 Most common solvents for the Heck reaction.

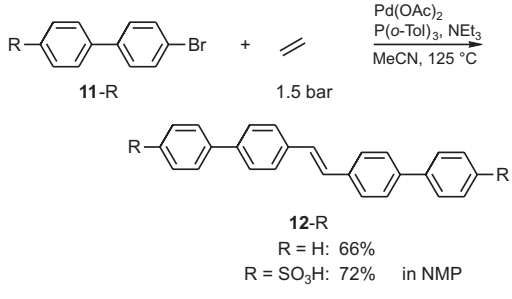
Solvent	*Remarks*	*Example for catalytic systems*	*Ref.*
DMF	Standard solvent	$Pd(OAc)_2$, NEt_3, PPh_3	[3]
DMA	Higher boiling point than DMF	**1a**, base (aryl chloride)	[19a,45,77b]
NMP	More stable at elevated temp. than DMF		[78]
MeCN	Common solvent	[$Pd(PPh_3)_4$], NEt_3 (aryl iodide)	[54]
DMSO		$Pd(OAc)_2$, (*S*)-BINAP, Bu_4NOAc	[79]
MeOH or EtOH	For diazonium salts	Pd/C, 60 °C, 12 h	[49]
*t*BuOH		[$Pd_2(dba)_3$], BINAP, K_2CO_3	[78]
THF		[$Pd(PPh_3)_4$], LiCl, Li_2CO_3 (for alkenyl triflates)	[53]
		[$Pd(OAc)_2$], BINAP, PMP (for aryl triflates)	[80]
Dioxane		$Pd(OAc)_2$, BINAP, K_2CO_3	[78]
Benzene		$Pd(OAc)_2$, NEt_3, Bu_4NBr, r. t., 163 h (aryl iodide)	[81]
Toluene	High boiling, nonpolar	[$Pd(PPh_3)_2(OTfa)_2$], pentamethyl-piperidine (PMP), 110 °C	[56,77a,82]
m-Xylene	High boiling, nonpolar	[$Pd(PhCN)_2Cl_2$], K_2CO_3, $BnOct_3NCl$, 140 °C, 4 h (aryl sulfonylchloride)	[58]
Mesitylene	High boiling, nonpolar	$Pd(OAc)_2$, BINAP, K_2CO_3	[78]
Anisole	High boiling, nonpolar	[$Pd(PPh_3)_4$], KO*t*Bu	[83]
$CHCl_3$			[78]
$ClCH_2CH_2Cl$		[$Pd_2(dba)_3$], (*R*)-BINAP, K_2CO_3, *t*BuOH, 60 °C	[78,83]
NEt_3	Acts as a base	$Pd(OAc)_2$, PPh_3, reflux (aryl iodides)	[84]
*i*PrCN		$Pd(OAc)_2$, $BnEt_3NBr$, KOAc, 90 °C (aryl iodides)	[85]

Table 5-2 (continued)

Solvent	*Remarks*	*Example for catalytic systems*	*Ref.*
H_2O	Neat [86], superheated (260 °C) [87] or in mixtures with e. g., HMPA [66c], DMF [66,67] or MeCN [66d]	$Pd(OAc)_2$, TPPTS, K_2CO_3, DMF/H_2O	[66,68]
No solvent	Alkene acts as solvent	$Pd(OAc)_2$, TBABr, K_2CO_3 (acrylates)	[88]
Molten salts/ ionic liquids	Equivalent to conditions without solvents	$Pd(PPh_3)Cl_2$, TBABr, 100 °C, 6-43 h (aryl halides, acrylates)	[25,70,72]
Supercritical carbon dioxide	Prevents isomerization of the double bond [89]	$Pd(OTfa)_2$, P(2-furyl)$_3$, *i*Pr_2EtN; $Pd(OTfa)_2$ or $Pd(F_6$-acac$)_2$] and fluorinated phosphanes [90]	[91]

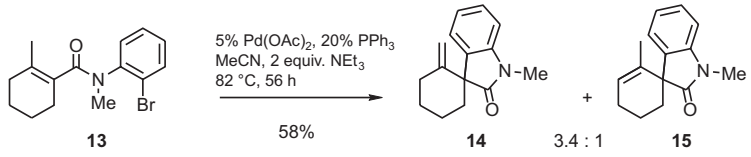
5.2.3 The Alkenes

Usually, monosubstituted or 1,1-disubstituted alkenes were used in the Heck reaction because of their increased reactivity. The coupling of ethylene to a variety of bromoarenes is an elegant approach to substituted styrenes, and the two-fold coupling of ethene can even produce stilbenes such as **12-**SO_3H, which was commonly used as a laser dye, in good yields. The ratio between formed styrene and stilbene depends on the ethylene excess, which can be controlled by the applied pressure (Scheme 5-3) [92]. Oligovinylarenes can be prepared from 1,2- (*cf.* Scheme 5-13), 1,4-dibromoarenes [93,94], 1,3,5-tribromobenzene and 1,2,4,5-tetrabromobenzene [95].



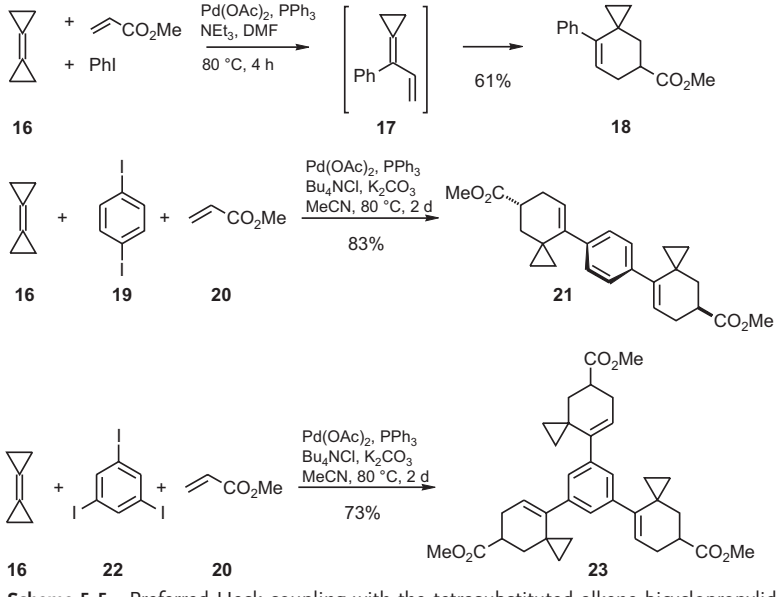
Scheme 5-3 Two-fold Heck coupling with ethene to yield stilbene derivatives [92].

Although Heck reactions with tetrasubstituted alkenes are known, their examples are still rare [96–99]. One trend-setting observation was that tetrasubstituted alkenes with a conjugated carbonyl group have a sufficiently increased reactivity. Such coupling reactions permit a rapid access to skeletons with quaternary carbon centers (Scheme 5-4).

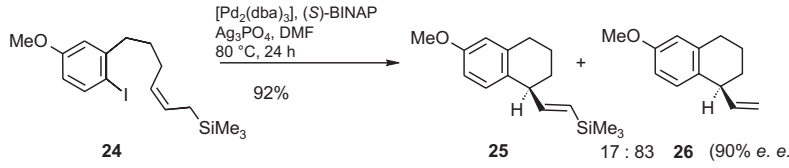


Scheme 5-4 Intramolecular Heck reaction with a tetrasubstituted double bond [98].

On the other hand, methylenecyclopropane derivatives with tetrasubstituted double bonds are outstandingly reactive in intramolecular Heck reactions and the particularly strained bicyclopropylidene (**16**) [100] in its reactivity even surpasses styrene and methyl acrylate, as demonstrated in an interesting cascade reaction of the three partners iodobenzene, bicyclopropylidene (**16**) and methyl acrylate. Even when all three components were mixed with the palladium catalyst in one pot, reaction between iodobenzene and bicyclopropylidene occurs first, and only the reactive diene **17**, which is formed after a cyclopropylcarbinyl- to homoallylpalladium halide rearrangement, traps the acrylate in a Diels-Alder reaction to give the spiro[2.5]octenecarboxylate **18** as the vastly predominating product (Scheme 5-5) [101,102]. This domino Heck-Diels-Alder reaction can be performed two-fold on 1,4-diiodobenzene, three-fold on 1,3,5-tribromo- or 1,3,5-triiodobenzene, and even four-fold on 1,2,4,5-tetraiodobenzene [101b].



Scheme 5-5 Preferred Heck coupling with the tetrasubstituted alkene bicyclopropylidene (**16**): Single, double and triple Heck-Diels-Alder cascade reactions [101,102].



Scheme 5-6 Silane-terminated intramolecular Heck reaction [110].

Early investigations dealing with intermolecular arylations of unsymmetrically donor-substituted alkenes often revealed only poor regioselectivities, especially for acyclic enol ethers. However, suitable conditions have since been developed for both the selective *α*- and *β*-arylation of enol ethers and enamides [103]. While *β*-selectivity is achieved with modified alkenyl ethers (e. g., 2-(diphenylphosphanoethyl) ethenyl ether [104] or [2-(dimethylamino)ethoxy]ethene [105]), selective *α*-coupling can be achieved by using electron-rich aryl halides [106], alkenyl triflates [107], bidentate ligands [103,106,108] and in the presence of silver triflate or thallium(I) acetate [108]. A density functional method using different catalyst models has been used to explain these results [109].

In probing the relative reactivities of alkynes and alkenes, a preference for the addition across the triple-bond has been observed (*cf.* e. g. Scheme 5-18) [101]. When allylsilanes such as **24** were cyclized by an intramolecular Heck reaction, *β*-silyl-group elimination can occur to predominantly give the desilylated **26** along with the silyl-substituted **25** (Scheme 5-6) [110a].

Table 5-3 Various types of alkenes in the Heck reaction, according to substitution pattern.

Alkene	*Type*	*Intermolecular [Ref.]*	*Intramolecular [Ref.]*
Ethene	0	[92,111]	–
1-Substituted	I (α,β) [a]	[2] (β), [57] (β)	[112]
1,1-Substituted	IIG (α,β)	[113] (β), [114] (β)	[115]
1,2-Disubstituted (*E*)	IIE (α,β)	[2] (β), [116] (α), [117,118] (β)	[119a]
1,2-Disubstituted (*Z*)	IIZ (α,β)	[2] (β), [85,118,120]	[121]
Trisubstituted (1,1-*sym*)	IIIS (α,β)	[122]	[119]
Trisubstituted (*E*)	IIIE (α,β)	[123] (β), [124] (β)	[56], [77a,b,d] (α)
Trisubstituted (*Z*)	IIIZ (α,β)	[123] (α)	[45a,56,125] (β), [126] (α)
Tetrasubstituted (*sym*)	IVS (α,β)	[96,101,48c] (α)	[101] (α)
Tetrasubstituted (*E*)	IVE (α,β)		[127]
Tetrasubstituted (*Z*)	IVZ (α,β)		[97b,98,99]

[a] Attack at the more highly substituted end (according to CIP rule) is referred to as α.

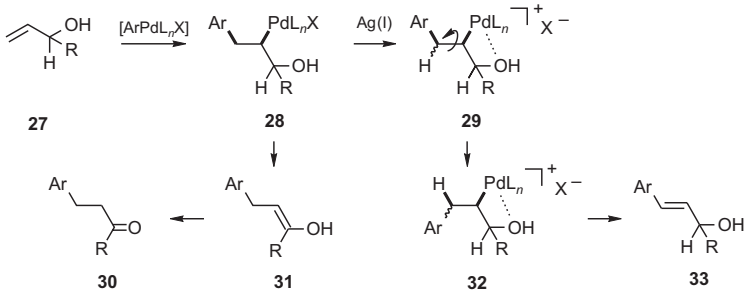
Table 5-4 Various alkenes in the Heck reaction, according to type of substituent.

Substituent	*Preferred site of attack*	*Intermolecular [Ref.] (Type)*	*Intramolecular [Ref.] (Type)*
Alkyl	β	[113] (IIGβ), [123] (IIZα,β)	[115] (IIG)
Alkenyl	β	[128] (Iβ), [129] (Iβ), [130] (Iα)	[131b] (IIEβ), [56] (IIIZα)
Alkylidene (allenes)	central	[132]	[133]
Oxo (ketenes)	α	[48c] (IVSα)	
(Het)aryl	β	[92]	
Carbonyl	β (α)	[93] (Iβ), [19b] (IIGβ)	[56] (IIIZβ), [77a,b,d] (IIIEα)
Nitril	β	[123] (IIIβZ), [66b] (Iβ), (117b) [IIβE]	
SiR_3		[134] (I) (elimination of SiR_3 possible)	
Sn		Stille coupling occurs (see Chapter 3)	
OR	α	[48,104] (Iβ), [105] (Iα,β), [123] (IIIZβ), [135a] (IIZα), [124] (IIIZα), [65] (Iβ) (with vinyl acetate to yield stilbenes), [136] (IIZ), [135b,137] (ketene acetals)	
SR	β	[138a] (Iβ)	[138b,c] (IIIβE) (alkenyl sulfones)
S(O)R	β		[118] (IIβEZ)
NR_2		[139] (Iβ), [140] (IIZα), [141] (IIGβ), [142] (enamides)	[143]
NO_2	β	[144] (IIEβ)	[145]
$B(OR)_2$		[146] (Iβ) (competing Suzuki reaction possible: see Chapter 2)	
PR_2	β	[147] (Iβ) (phosphonates), [148] (Iβ) (phosphane oxides)	
Halide (F)	α	[149] (bromoethene and iodoethene react via insertion)	
M (M = Li, Mg, Zr, Al, etc.)	α	Cross-coupling possible [2]	

5.2.4
Effects of Bases, Ligands, and Additives

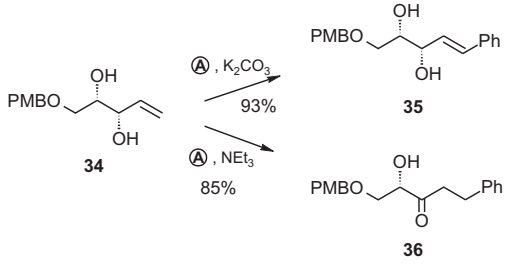
Thus, the regioselectivity of Heck reactions with unsymmetrical alkenes can favorably be manipulated by appropriate variations of the "catalyst cocktail"; for example, the best conditions for the coupling of bromobenzene with *t*-butyl acrylate in the presence of the $Pd[(o\text{Tol})_3P]_2Cl_2$ were found to be with potassium carbonate in ethanol at 80 °C. This is unusual for this kind of catalyst system. The active catalyst is actually believed to be nanodispersed palladium metal generated by reduction of the catalyst precursor by ethanol under basic conditions [150].

The impact of silver(I) and thallium(I) salts [151] on Pd-catalyzed reactions extends beyond just increasing regioselectivities and enhancing reaction rates [152]. Without these additives, the arylation of allyl alcohols **27** afforded aldehydes and ketones **30**, rather than the *β*-arylallyl alcohols **33**. Apparently, the *β*-hydride elimination in the intermediate **28** is faster in the direction leading to enol **31** (Scheme 5-7). Alternatively, *β*-hydride elimination to give the allyl alcohol **33** followed by readdition of the hydridopalladium species to the double bond and subsequent *β*-hydride elimination to give the more stable enol **31** would explain the facts. This type of isomerization consisting of a sequence of β-hydride elimination, readdition and recurring elimination is not restricted to allyl alcohols (*cf.* Schemes 5-28, and 5-29).



Scheme 5-7 Heck reaction with allyl alcohols in the absence and in the presence of silver salts [151,152].

On the other hand, on simple switching from triethylamine to potassium carbonate as the base, the products can also be changed from carbonyl compounds **36** to allyl alcohols **35** [153].



Scheme 5-8 A: Pd(OAc)$_2$, *n*Bu$_3$P, PhI, DMF.

A major achievement was the discovery that Heck reactions are greatly accelerated in the presence of quaternary ammonium salts as phase-transfer catalysts and solid bases ["Jeffery" conditions: Pd(OAc)$_2$, MHCO$_3$ (M = K, Na), *n*Bu$_4$NX (X = Br, Cl), DMSO or DMF] [154]. Under these conditions, iodoarenes and iodoalkenes can be coupled to alkenes at room temperature. The major role of the tetraalkylammonium salts apparently lies in enhancing the regeneration of the zerovalent palladium catalyst [155].

Table 5-5 Some additives and special reaction conditions for the Heck reaction (HR).

Additives and reagents	*Apply for*	*Effect*	*Example [Ref.]*
Bases			
	All types of reactions	Regeneration of Pd^0	[3]
TEA, EDA [48], NEM [48], BDA [48]	Simple HR	Bases	[3]
PMP	Aryl iodides or triflates for trisubstituted dienes	Hindered base	[45,56,80]
Sec. or prim. amines	Dienes	Primary attack resulting in a π-allyl complex	[3]
Dicyclohexylamine or Methyl(dicyclohexylamine)		a) Phosphane-free conditions b) Increase of *e.e.*	a) [156] b) [157]
Proton sponge®	(Enantioselective) HR	Excellent base, increase of *e.e.* and/or yields [77a]	[158]
DABCO	a) Reductive HR b) Acid-sensitive alkenyl triflates c) *anti*-Elimination	Strong base, increase of yield	a) [159] b) [59] c) [11]
K_2CO_3, Na_2CO_3	Spirocyclization	Base	[115]
K_2CO_3		Soluble base in DMF/H_2O	[67]
Cs_2CO_3	Aryl chlorides	With $P(t\text{Bu})_3$	[29]
KO*t*Bu		Strong base	[83]
Cs pivaloate	Biaryl iodides	1,4-Palladium migration	[160]
NaOAc, KOAc	a) Enantioselective HR b) Spirocyclization	a) Stabilization of Pd^0	a) [78] b) [115]
$CaCO_3$	Enantioselective HR	Base, increase of *e.e.* with Ag_3PO_4	[161]
$NaCO_2H/HCO_2H$		Reductive HR	[162]
Reagents			
Boranes (e.g., $NaBPh_4$)		Alkylation (phenylation) through anion capture	[163a]
Stannanes (e.g., $PhSnBu_3$)	Allyl complexes as intermediates	Phenylation through transmetallation	[133]
Bu_3SnH	Stille-Heck cascade on enynes	Hydrostannylation	[164]
Zincates (e.g., PhZnCl)		Alkylation (phenylation) through anion capture	[163a]
$Zn/ZnCl_2$		Alkenylation/arylation through anion capture	[163c]
Zirconates [e.g., (1-hexenyl)$ZrCp_2Cl$]		Alkylation through transmetallation	[165]
KCN		Cyanation through anion capture	[166]

Table 5-5 (continued)

Additives and reagents	*Apply for*	*Effect*	*Example [Ref.]*
CO	Carbonylation	(Reversible) insertion of CO	[167]
[18]-Crown-6	Cyanation reaction	Coordination of the counter ion	[166]
Ligands			
Monodentate phosphanes [PPh_3, P(*o*Tol)$_3$ (TOTP), P(*o*Furyl)$_3$ (TFP) P(C_6F_5)$_3$]	Bromide as leaving groups	Stabilization of Pd^0	[168a] [43]
P(*t*Bu)$_3$ or P(*t*Bu)$_3 \cdot HBF_4$ (air-stable) [169]	Excellent for unreactive aryl bromides		[11,29,170]
Diadamantylalkylphosphanes	Excellent for aryl chlorides		[30]
Secondary phosphanes (HP*t*Bu$_2$, HPAd$_2$)	Excellent for aryl chlorides	Stability towards oxygen, cheaper than tertiary phosphanes	[31]
Chiral phosphanes (see Table 5-8)		Enantioselective HR (Section 5.1.5.)	
Bidentate phosphanes	Alkenyl ethers	Enhanced α-selectivity	[103,104,108]
a) dppm	Biaryl iodide	1,4-Palladium migration	[160]
b) dppe	Aryl bromides	Increased yield	[77c,d,171]
c) dppp	a) Aryl triflates b) Aryl bromides	a) Increased yield with TlOAc, reversed regioselectivity (β) with allyl alcohols b) Increased yield	a) [172] b) [77a,173]
d) dppb	Alkenyl triflates	Increased yield	[45,46]
e) dppf	Aryl triflates	Reversed regioselectivity	[172a]
f) dippb	Aryl chlorides	Enhanced reactivity	[32a]
g) dcpe	Aryl bromides with trisubstituted alkenes	Sterically congested ligand leads to increased yield	[77b]
h) Polymer-bound ligands	Aryl iodides	Recyclable, increased stability	[174]
1,10-Phenanthroline derivatives	Aryl triflates, ~bromides, ~iodides	Stabilization of Pd^0, allows coupling at 40 °C (alkenyl ethers)	[175]
Isoquinoline	Aryl or vinyl arenecarboxylates	Stabilization of Pd^0	[44]
*t*BuOH (cat.)	Enantioselective HR (alkenyl triflates)	Increased yield	[78]
1,2-Diols (cat.) (e. g., pinacol)	Enantioselective HR (alkenyl triflates)	Stabilization of Pd^0, increased yield	[78]

Table 5-5 (continued)

Additives and reagents	*Apply for*	*Effect*	*Example [Ref.]*
$Bu_3N(CH_2CH_2)Br$		Decarbonylative HR of vinyl esters	[176]
Pincer ligands	Aryl halides (chlorides, bromides, iodides)	High turnover number	[20]
Phosphinous acids	Hetaryl halides	Stablilization with palladium complexes	[177]
Salts			
a) LiCl	a) Aryl triflates or arenecarboxylates	a) Increased Pd-OTf bond cleavage, stabilization of Pd^0	a) [16a-c,44,53]
b) LiCl, NaCl, KCl	b) Aryl iodides	b) Increased yield with Pd/C (free NH on alkene necessary)	b) [16d]
NaBr	Alkenyl triflates in HR with asymmetric induction	Prevented counter-ion exchange, increased *e.e.*	[79]
$NiBr_2$/NaI	Aryl chlorides	Increased yield due to in-situ formation of aryl iodides	[32e]
Phase transfer catalysts			
a) Bu_4NX (X = Cl, Br) [TBACl, TBABr], solid base	a) Alkenyl and aryl iodides	a) Coupling at r.t.	a) [154]
b) $BnEt_3NBr$ $BnOct_3NCl$ Pr_4NBr Et_4NCl	b) Various systems	b) Increased yields	b) [85] [58] [178] [163b]
c) TBABr, HDTAB	c) Aryl iodides	c) Molten salts as reaction medium	c) [72]
d) Bu_4NOAc	d) Aryl iodides	d) Solvolysis of highly reactive palladium complexes	d) [7,179]
Me_3SiCl	Carbonylation reaction	Rate enhancement	[167d]
Silver salts			
Ag_2CO_3	Aryl halides Arenecarboxylic acids	Base, suppressed double bond migration [98] Oxidant	[77,180] [42]
Ag_3PO_4	a) Aryl iodides, triflates	a) Base	a) [45]
	b) Aryl bromides	b) No phosphanes needed	b) [127]
$AgNO_3$	a) Alkenyl- and allylsilanes	a) Suppressed desilylation	a) [134,181]
	b) Cyclic alkenes	b) Suppressed double bond migration	b) [98]

Table 5-5 (continued)

Additives and reagents	*Apply for*	*Effect*	*Example [Ref.]*
AgOAc	a) Allyl alcohols b) Terminal aliphatic alkenes	Suppressed double bond migration	a) [152] b) [182]
AgOTf	Asymmetric HR		[161]
Silver-exchanged zeolite	Asymmetric HR, alkenyl iodides	Increased *e. e.*	[183]
Ag_2O	Asymmetric HR	Increased *e. e.*	[184]
Thallium salts			
Tl_2CO_3	Alkenyl halides	Base, suppressed double bond migration	[97b,180]
TlOAc	Aryl halides	Base, suppressed double bond migration	[77c,97b,185]
Others			
Solid support	a) Combinatorial synthesis of libraries b) Macrocyclization	a) Formation of libraries possible b) Prevented dimerization	a) [102,186–190] b) [189]
Molecular sieves	Asymmetric HR	Improved *e. e.*, yield (3Å > 4Å, 5Å)	[191]
High pressure	Alkenyl chlorides and other	Remarkable rate enhancement	[140,192]
Microwave irradiation	Aryl iodides, bromides, and triflates	Dramatic rate enhancement	[74,193–195]

5.2.5 The Leaving Groups

The Heck coupling can be used to bind alkenyl, aryl, allyl [196], benzyl [1b,197], methyl, certain alkyl [48d,198a], alkoxycarbonylmethyl, alkynyl [199], silyl [198b] and carborane [200] fragments to a variety of alkenes. The nature of the leaving group greatly affects the reaction rate: aryl iodides react faster than bromides (e. g., [201]), and aryl chlorides are the least reactive. However, increasingly advanced catalysts (and especially ligands) have been developed in recent years which make the coupling of aryl chlorides possible. The apparent reactivity grading of the halides has been taken to indicate that the oxidative addition of the haloarene (haloalkene) to palladium(0) is the rate-determining step [202]. The order of reactivities has been determined by electrochemical measurements to be: PhI >> $(PhCO)_2O$ > PhOTf > PhBr (> PhCl) [203]. Yet, even the cross-coupling of low-cost chloroarenes using specially designed palladium catalysts, allowing high turnover rates, has been investigated in particular in recent years [19a,40,51,70,204] (see above).

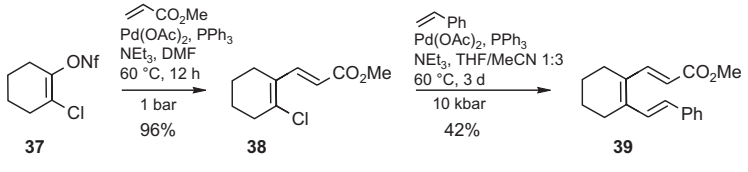
It had been shown previously that chloroarenes can be activated for oxidative addition onto palladium(0) catalysts through the formation of the corresponding tricarbonylchromium complexes [205], as the $(CO)_3Cr$ group exerts a strong elec-

tron-withdrawing effect on the arene moiety [206]. This activation can also be achieved with catalytic amounts of hexacarbonylchromium, since the starting materials and the products are exchanging the tricarbonylchromium fragment at elevated temperatures [205b]. Alternatively, the coupling of chloroarenes can be enhanced by addition of nickel(II) salts which leads to an in-situ conversion of the aryl chlorides to the corresponding iodides [32e].

Heck-type cross-coupling reactions can also be performed with aryldiazonium salts [207–209] (frequently called the Matsuda reaction), *N*-nitroso-*N*-arylacetamides [210] and hypervalent iodo compounds [211] at room temperature.

Alkenyl perfluoroalkanesulfonates have gained importance as substitutes for haloalkenes – at least in laboratory-scale preparations – as they are easily obtained from the corresponding carbonyl compounds [212, 213]. Many successful reactions with alkenyl trifluoromethanesulfonates (alkenyl triflates) took advantage of this leaving group, and alkenyl nonafluorobutanesulfonates have been found to be even more reactive [213]. Even dienediol bisnonaflates can be prepared and coupled [213] (Scheme 5-58). The previously observed inhibition of the overall coupling reaction following facile oxidative addition of an alkenyl triflate to palladium(0) can be prevented by adding lithium chloride to the reaction mixture. Aryl iodides, however, are more reactive than the corresponding triflates (e. g., [43]) [9]. New substitutes for alkenyl triflates are the corresponding tosylates [214] and phosphates, the latter having been successfully applied in the total synthesis of (+)-cytisine [215]. It is noteworthy that in the case of tosylates as coupling partners, an equimolar ratio of palladium(II) acetate and the added phosphine ligand is beneficial. Alkenyl mesylates appear to be less suitable for Heck reactions [214].

The coupling reaction can be accelerated by applying high pressure [6, 140, 192, 216–218]. Starting with the 2-chlorocyclohexenylnonaflate **37** prepared in one step from chlorocyclohexanone [219], the first Heck coupling with methyl acrylate is achieved in 96 % yield at 60 °C and ambient pressure. The chlorine in the product **38** can be substituted by a styryl group at 60 °C and 10 kbar to give the hexatriene **39** (Scheme 5-9) [192].



Scheme 5-9 Acceleration of a Heck reaction by high pressure [6,192,219]. Nf = $C_4F_9SO_2$.

The influence of high pressure on the Heck reactions of selected alkenyl and aryl halides, respectively, i. e. 1-iodocyclohex-1-ene, iodobenzene, bromobenzene, with alkyl acrylates has been investigated and the activation parameters of these reactions determined [6]. Two different catalyst cocktails were used in this study, the classical system [$Pd(OAc)_2$, NEt_3, PPh_3] and the one reported by Herrmann, Beller et al. [19] (**1a**). The temperature-dependent and the pressure-dependent rate coefficients both follow the order: Ph-I/$Pd(OAc)_2$ > 1-iodocyclohexene/$Pd(OAc)_2$ > Ph-I/**1a**

> Ph-Br/**1a**, and the activation enthalpies as well as the activation entropies exhibit the trend 1-iodocyclohexene/$Pd(OAc)_2$ < Ph-I/$Pd(OAc)_2$ < Ph-I/**1a** < Ph-Br/**1a**. The absolute values of the activation volumes, which were ascertained from the pressure-dependent rate coefficients, increase as follows: 1-iodocyclohexene/$Pd(OAc)_2$ < Ph-I/$Pd(OAc)_2$ ≈ Ph-I/**1a** < Ph-Br/**1a**. Under high pressure, the lifetime of the active palladium catalyst and thereby the turnover numbers are greatly enhanced [140].

Some of the latest developments in terms of substrates for Heck reactions are nitrophenyl benzoates [44], acyl benzoates (mixed anhydrides) [220], and substituted benzoic acids [42]. In the latter cases, the leaving groups are carbon dioxide and carbon monoxide, respectively. A variety of alkenes has been coupled with these substrates. Whereas esters and anhydrides presumably react in a catalytic cycle like that of the classical Heck reaction [221], arenecarboxylic acids, when treated with an equimolar amount of a silver salt as reoxidant appear to undergo a nonclassical Heck reaction, as demonstrated by the coupling with 2-cyclohexenone to give a 3-arylcyclohexenone.

New classes of substrates for ruthenium- [222], rhodium- [223] and palladium-catalyzed Heck-type reactions are areneboronic acids [222–225], arylstannanes [226] and arylsilanols [227] which, under oxidative or nonoxidative [224] conditions, undergo coupling with electron-deficient alkenes.

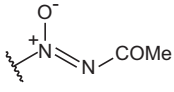
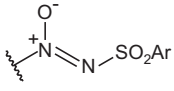
The Heck reaction can also be drastically accelerated under microwave irradiation (typically 3–4 min reaction time at room temperature, compared to a few hours at elevated temperatures). In these cases, DMF [193] or ionic liquids [74] have proved to be excellent solvents.

The Heck reaction is compatible with a variety of substituents, and only strong oxidizing agents such as quinones or TCNE are not tolerated.

Table 5-6 Leaving groups in alkenyl and aryl derivatives[a].

Leaving group	*Remarks*	*Preferred catalytic systems*	*Ref.*
Cl	Least expensive halide, but poor leaving group	a) On arenes: $Pd(OAc)_2$, dippb, NaOAc, DMF, 150 °C, 24 h	a) [19,32a]
		b) On alkenes: 10 kbar	b) [192]
Br	Quite good	$Pd(OAc)_2$, PPh_3, NEt_3, DMF	[3]
I	Excellent, but expensive	$Pd(OAc)_2$, PPh_3, NEt_3, DMF	[3]
COCl	Inexpensive, better than iodides [228]	a) Arylation: $Pd(OAc)_2$, NEM, xylene	a) [48a,c]
		b) Aroylation/acylation: $Pd(OAc)_2$, NEt_3	b) [48b,d]
CO_2H	Very inexpensive, better than iodides	$Pd(OTfa)_2$, Ag_2CO_3, 5 % DMSO/DMF, 120 °C	[42]
$CO_2(CO)R$	Cheap	$PdCl_2$, NaBr, NMP, 160 °C	[220,221]
$CO_2(CO)OtBu$	In situ from acids, cheap	$PdCl_2$, LiCl, γ-picoline	[229]
$CO_2C_6H_4NO_2$	Cheap, salt/base	$PdCl_2$, LiCl, isoquinoline, NMP, 16 h, 160 °C	[44]
$CO_2C(CH_3)=CH_2$	Cheap, salt/base	$PdCl_2$, $Bu_3N(CH_2CH_2OH)Br$, NMP, 16 h, 160 °C	[176]

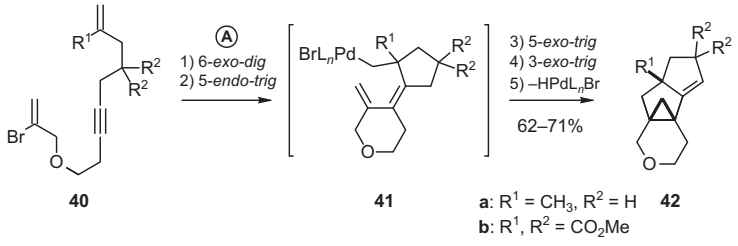
Table 5-6 (continued)

Leaving group	*Remarks*	*Preferred catalytic systems*	*Ref.*
OTf	Sometimes excellent, less reactive than iodides	a) On alkenes: $[Pd(PPh_3)_4]$, LiCl, Li_2CO_3, THF, reflux b) On arenes: $[Pd(PPh_3)_2Cl_2]$, NEt_3, DMF, acrylates, 90 °C	a) [53] b) [57]
ONf	Excellent leaving group	$Pd(OAc)_2$, PPh_3, NEt_3, DMF	[192,213,219, 230]
$OSO(CF_2)_2O$-$(CF_2)_2H$	Excellent leaving group	$[Pd(PPh_3)_2Cl_2]$, NEt_3, DMF, 90 °C	[57b]
$OP(O)Et_2$	Good leaving group	$Pd(OAc)_2$, P(*o*Tol)$_3$, NEt_3, MeCN, 60 °C, 24 h	[215]
OTs		$Pd(OAc)_2$, PPh_3 (1:1), NEt_3, DMF/DMA, 90–105 °C, 30 min–2.5 h	[214]
OH	After in-situ conversion into OSO_2R	$H(CF_2)O(CF_2)_2SO_2F$, $[Pd(PPh_3)_2Cl_2]$, NEt_3, DMF, 80 °C, 24 h	[231]
NH_2	After in-situ conversion into $N\equiv N^+$	$Pd(OAc)_2$, BuONO, AcOH, CH_2Cl_2, 20–30 °C	[232]
$N\equiv N$	Excellent	$[Pd(dba)_2]$, MeCN, 25 °C (alkenylsilanes)	[207]
		$[Pd(dba)_2]$, MeCN, 40 °C, < 1 h (alkenes)	[210]
		$[Pd(PPh_3)_4]$, PhH, 120 °C	[233]
IPh^+X^- (X = BF_4, OTs)	Mild conditions	$Pd(OAc)_2$, DMF, $NaHCO_3$, r. t.	[211]
SO_2Cl		On arenes: $[Pd(PhCN)_2Cl_2]$, K_2CO_3, $BnOct_3NCl$, *m*-xylene, 140 °C, 4 h	[58]
H	Arenes a) regioselectivity as in electrophilic aromatic substitution b) C-H activation c) Carbopalladation of alkynes with phenols	a) $Pd(OAc)_2$, HOAc, AgOAc or $Cu(OAc)_2$, O_2, reflux, 8 h b) $Pd(OAc)_2$, HOAc/toluene, TsOH, benzoquinone, O_2, reflux, 8 h c) $Pd_2(dba)_3$, 10 % NaOAc, HCOOH, 25 °C	a) [234] b) [235] c) [236]
$BiPh_3^+$ BF_4^-	Alkenes	$Pd(OAc)_2$, Na_2CO_3, DMF, r. t., 1.5 h (acrylates)	[237]
HgX (X=Br, Cl)	Toxic!	cat. $PdCl_2$, PhHgCl, $CuCl_2$, THF, r. t.	[238]
XPh_n (X=P, As, Sb, Bi, Te, Se), ArX (X = $B(OH)_2$, Si-Me_2OH, SnR_3)	From XPh_{n+1} to yield styrenes	Stoich. $Pd(OAc)_2$, MeCN, 50 °C, 5 h (acrylates, alkenes); cat. $Pd(OAc)_2$, $Cu(OAc)_2$, CH_2Cl_2, r. t.	[222–227,239, 240]

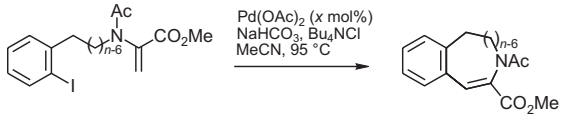
[a] The leaving groups on allyl derivatives may vary: Ac, RO_2CO [167].

5.2.6
Structural Requirements in Intramolecular Cyclizations

For the design of natural products syntheses, a predictability of the regioselectivity is required. However, all ring sizes from three- to nine-membered are attainable, either by *exo-trig* for 3- (Scheme 5-10) to nine- or *endo-trig* cyclizations for six- to nine-membered rings (Scheme 5-11). Applications towards the construction of larger rings (sizes 13–24) have been demonstrated using solid support in combinatorial syntheses (*cf.* Scheme 5-76) [190], by employing slow addition of the substrate and/or the high dilution principle [189].



Scheme 5-10 A 3-*exo-trig* ring closure occurring in a cascade cyclization [241]. A: $Pd(OAc)_2$ (3–5 mol %), PPh_3 (12–20 mol %), Ag_2CO_3, MeCN, 80–130 °C.



43a *n* = 7 *x* = 20 **44a** 54%
b *n* = 8 *x* = 15 **b** 60%
c *n* = 9 *x* = 10 **c** 58%

Scheme 5-11 7-, 8-, and 9-*endo-trig* ring closures [143].

Table 5-7 Examples of ring sizes achieved in intramolecular Heck reactions.

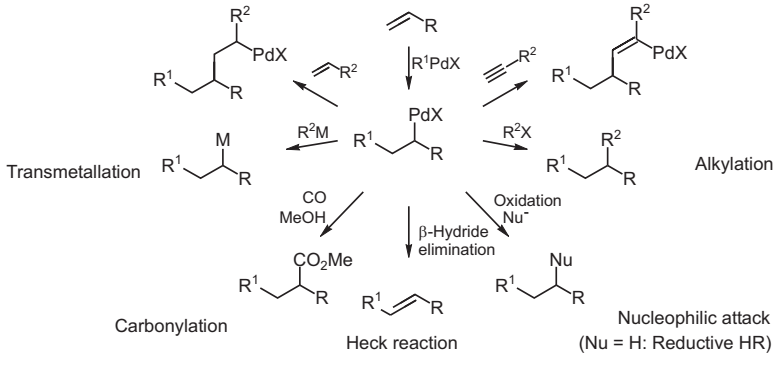
Ring size	*endo-trig (dig) [Ref.]*	*exo-trig (dig) [Ref.]*
3		[241] [a]
4		[213,242,243]
5	[244, 245]	[115,185,243,246–248]
6	[80, 247a, 249]	[115,121,243,247a,250–252]
7	[143, 253–255]	[178,256,257c,258]
8	[143, 250a, 256a, 259]	[257]
9	[143]	[133] [b]
10–15	[260] (12), [133] (13)	[133] (11,12) [b], [164] (12–15) [c]
16–19	[261] (16), [262] (16, 18)	[133] (18) [b], [164] (16,17) [c]
>19	[133] (21), [262] (20, 22), [189] (20–24), [55] (20)	[55] (19)

[a] The formation of three-membered rings is reversible: *Cf.* ref. [250c].
[b] With allenes as alkenes.
[c] Heck-Stille cascade.

5.3
Cascade Reactions and Multiple Couplings

Cascade reactions provide valuable avenues especially for the construction of various carbo- and heterooligocyclic systems with three, four or more annelated rings [263]. The Heck reaction has been employed successfully in various inter-inter-, intra-inter- as well as all-intramolecular reaction cascades [3d].

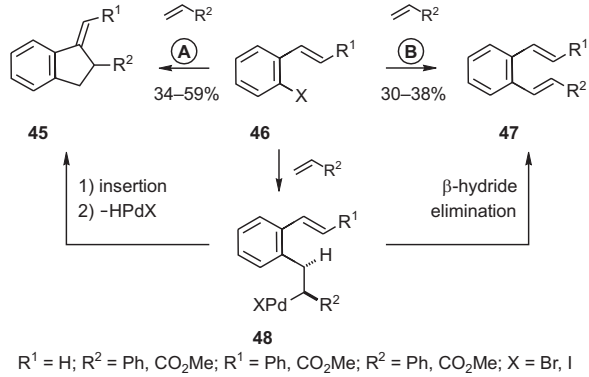
In the insertion step of the Heck reaction (see Scheme 5-1) a new metal-carbon bond is formed which, in principle, can undergo any of the typical reactions of a σ-M-C bond (Scheme 5-12), if the β-hydride elimination is not too fast. When the β-hydride elimination is totally suppressed, the alkylpalladium species can undergo a number of reactions with the formation of new C-C bonds. With an appropriate choice of substrates, these transformations can occur as a sequence of events in a single synthetic operation.



Scheme 5-12 Reaction modes of alkylpalladium species [3].

5.3.1
Heck Cascades Involving C_{sp^2} Centers

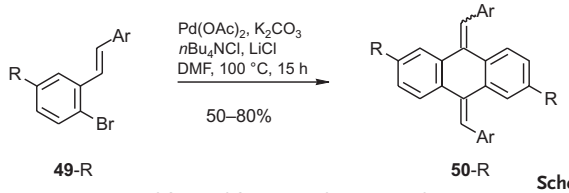
For example, *ortho*-bromostyrenes **46** (X = Br), under palladium catalysis, yield substituted indanes **45**. In this case, careful variation of the conditions is necessary to prevent the β-hydride elimination in the alkylpalladium intermediate **48** to yield *o*-dialkenylarenes **47** (Scheme 5-13) [93]. This reaction mode plays a dominant role in the attempted six-fold Heck coupling of hexabromobenzene with styrenes yielding complex mixtures of various isomers of the six-fold coupling product. The analogous six-fold Suzuki and Stille coupling reactions with alkenylboronates and alkenylstannanes, respectively, gave the corresponding pure hexakisalkenylbenzene derivatives in high yields [264, 265]. Even an eight-fold Suzuki coupling of octabromonaphthalene with an alkenylboronate has recently been achieved [265].



R^1 = H; R^2 = Ph, CO_2Me; R^1 = Ph, CO_2Me; R^2 = Ph, CO_2Me; X = Br, I

Scheme 5-13 A short reaction cascade forming indanes or dialkenylarenes [93]. Ⓐ: $Pd(OAc)_2$, NMP, $KHCO_3$ or K_2CO_3, LiCl + Bu_4NBr or Bu_4NCl. Ⓑ: $Pd(OAc)_2$, NEt_3, PAr_3, DMF or NMP.

The analogous *o*-bromostilbenes **49**-R, under Jeffery conditions, undergo dimerization with cyclization to give 9,10-bis(arylmethylene)dihydroanthracenes **50**-R in high yields (Scheme 5-14).

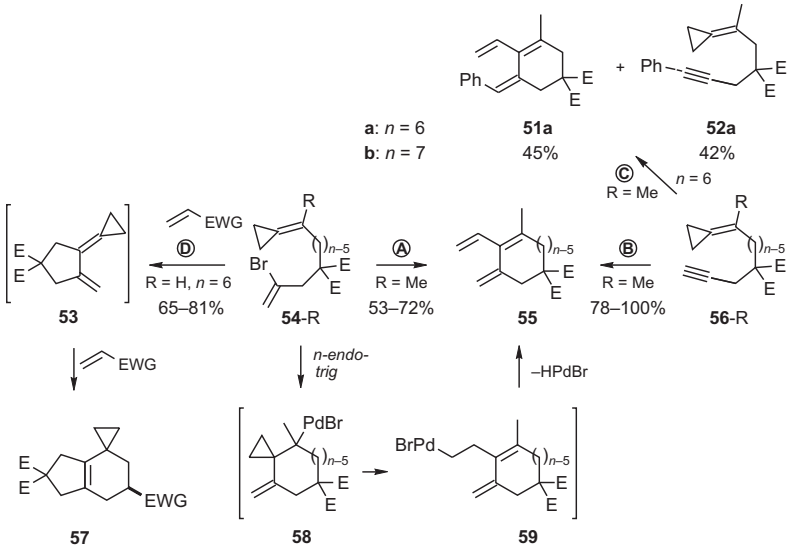


49-R **50**-R

R = H, CO_2Me, CO_2Et; Ar = C_6H_5, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-MeO_2C-C_6H_4 etc.

Scheme 5-14 Dimerization of *o*-bromostilbenes to yield 9,10-bis(arylmethylene)dihydroanthracenes [266].

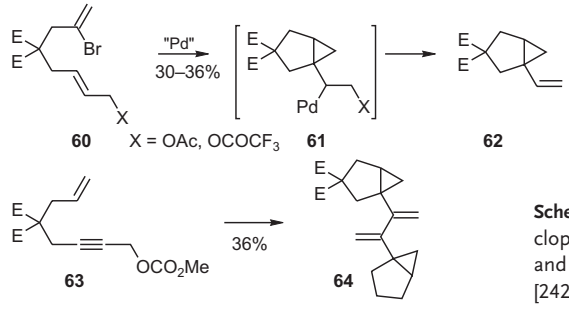
In trying to elucidate scope and limitations of a recently developed domino sequence consisting of an intramolecular and a subsequent intermolecular Heck Diels-Alder reaction [119], 2-bromo-1,6-dienes of type **54** with methylenecyclopropane end groups (Scheme 5-15, Scheme 5-19) have been used successfully. When R = H, such compounds react in the usual way to give 1,2-dimethylenecycloalkanes **53**, which undergo cycloaddition with dienophiles like methyl acrylate to yield products of type **57** (Scheme 5-15) [119a]. However, when the double bond in **54** is tetrasubstituted, e. g., when R = Me, a sequence of (*n*–1)-*exo-trig*, 3-*exo-trig* and two consecutive cyclopropylcarbinyl to homoallylpalladium rearrangements, overall formally an *n-endo-trig* cyclization with a subsequent cyclopropylcarbinyl- to homoallylpalladium rearrangement, occurs to yield dendralenes of type **55** [101a]. Under the conditions of the cycloisomerization reaction [267] (see below, Section 5.1.4.), the 1,6- **56a**-Me and 1,7-enyne **56b**-Me gave the dendralenes **55a** (n = 6) and **55b** (n = 7) in 78 and 100 % yield, respectively. In the presence of iodobenzene under Heck conditions the enyne **56a**-Me gave the (*Z*)-phenyl-substituted dendralene **51a** (45 %) together with the phenyl-substituted enyne **52a** (42 %).



EWG = CO_2Et, CN, COMe; E = CO_2Me or CO_2Et

Scheme 5-15 A Heck reaction cascade forming cross-conjugated trienes [101,119a]. Ⓐ: $Pd(OAc)_2$, PPh_3, DMF, 80 °C. Ⓑ: $[Pd_2(dba)_3 \cdot CHCl_3]$, TOTP, HOAc, C_6H_6, 20 °C. Ⓒ: $Pd(OAc)_2$, PPh_3, PhI, DMF, 80 °C. Ⓓ: $Pd(OAc)_2$, Ag_2CO_3, PPh_3, MeCN, 90 °C, 45 min.

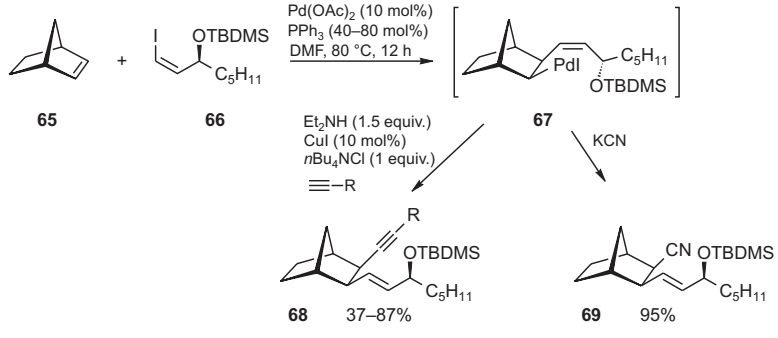
Starting from 1,6-octadienes **60** with two leaving groups in the 2- and 8-position, the palladium-catalyzed transformation proceeds by a sequence of 5-*exo-trig* and 3-*exo-trig* cyclization eventually leading to bicyclic vinylcyclopropanes **62** by elimination of a palladium salt from the intermediate **61** (Scheme 5-16) [268, *cf.* 242, 269]. Starting from propargyl carbonates **63** with a pentenyl tether, the vinylcyclopropane derivative **62** could be obtained in 68 % yield, when the catalyst cocktail contained 2 equiv. of sodium formate and 1 equiv. of Et_4NBr. Without the latter being present, the interesting dehydrodimer **64** was formed in 36 % yield. Heteroring-annelated vinylcyclopropane derivatives similar to **62** were also obtained by the domino cyclization-anion capture methodology as reported by Grigg et al. [270].



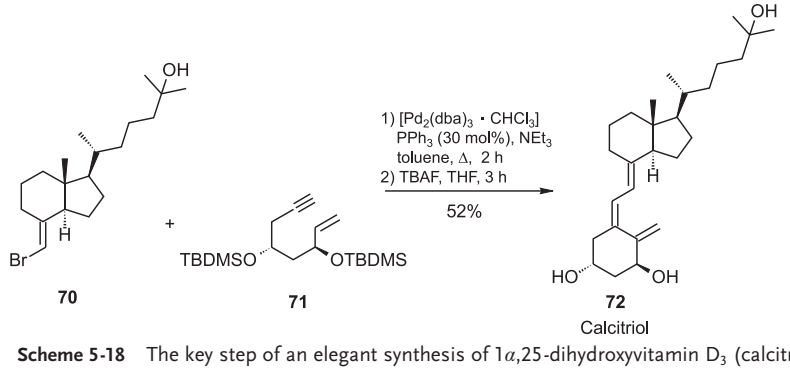
Scheme 5-16 Formation of vinylcyclopropanes by a domino of 5-*exo-trig* and 3-*exo-trig* cyclizations. E = CO_2Et [242, 268, 269].

5.3.2
Heck-Reaction Cascades Involving C_{sp^2} and C_{sp} Centers

The palladium-catalyzed domino assembly of norbornene (**65**), the *cis*-alkenyl iodide **66** and a terminal alkyne or cyanide reported by Torii, Okumoto et al. [271], provides an example for a sequence of oxidative addition, intermolecular double bond insertion, and interception of a copper acetylide or potassium cyanide. These reactions with acetylenes have been performed in good yields in the presence of diethylamine, tetra-*n*-butylammonium chloride, and catalytic amounts of palladium acetate, triphenylphosphane, and copper(I) iodide. Remarkably, they are characterized by complete inversion of the *cis*-configuration of the alkenyl iodide and a high degree of discrimination for the enantiotopic ends of the double bond in norbornene. To account for that, intermediate formation of a cyclopropylcarbinylpalladium species by 3-*exo-trig* cyclization in **67** and subsequent cycloreversion to a new homoallylpalladium intermediate as the direct precursor to **68** and **69** has been assumed. Thus, the products **68** and **69** are formed virtually with complete stereoselectivity (Scheme 5-17).



Scheme 5-17 Three-component couplings with norbornene as one partner [271].



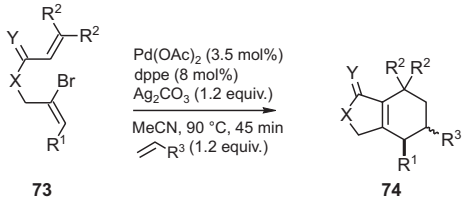
Scheme 5-18 The key step of an elegant synthesis of 1α,25-dihydroxyvitamin D_3 (calcitriol) [272].

Purely intramolecular cascade reactions using triple bonds as a kind of relais station are well known (Schemes 5-10, 5-16, 5-20, 5-21, 5-22, and 5-24). An inter-intramolecular variant was developed as an elegant access to calcitriol (**72**) (Scheme 5-18) [272].

5.3.3 Cascades Consisting of Heck and Subsequent Cycloaddition or Electrocyclization Reactions

5.3.3.1 Heck-Diels-Alder Cascades

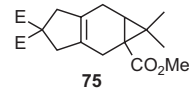
An interesting possibility for the construction of bicyclic systems containing one six-membered ring arises when an intramolecular Heck reaction or palladium-catalyzed enyne cycloisomerization [267] to give a vicinal exodimethylenecycloalkane is immediately followed by a Diels-Alder reaction (Scheme 5-15, Scheme 5-19). This sequence is normally conducted in two steps, but may also be performed in a one-pot procedure without isolating the intermediate diene, by adding the external dienophile right after the palladium-catalyzed cyclization has occurred [119]. This intra-intermolecular sequence consisting of a Heck and a Diels-Alder reaction can also be performed with the dienophile being present in the mixture from the beginning, as long as the dienophile is not a strong oxidant (like benzoquinone or TCNE) that would oxidize the catalyst [119]. In addition to common dienophiles and diene starters, three-membered strained cyclopropene and methylenecyclopropane derivatives have also been used leading to spiro- and bicyclic systems like **57** (Scheme 5-15), **75** or **76** (Scheme 5-19, Procedure 5.10.4), respectively [119a]. Even



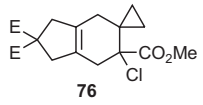
73 **74**

X	Y	R^1	R^2	R^3	%
O	H_2	Me	H	CO_2Me	55[a]
OCH–N	H_2	H	H	CO_2Me	62
Bn–N	H_2	H	H	CO_2Me	46
Ac–N	H_2	H	H	CO_2tBu	63
p-NO_2–$C_6H_4SO_2$–N	H_2	H	H	CO_2tBu	72
Bn–N	O	Me	H	CO_2Me	51[b]
$C(CO_2Et)_2$	H_2	H	–$(CH_2)_2$–	CO_2Me	93

[a] Mixture of regioisomers and diastereomers, *cis*-2,3-(*quasi-ortho*) predominating (67%). – [b] Mixture of regioisomers and diastereomers, *cis*-2,3-disubstituted one predominating (71%).



75

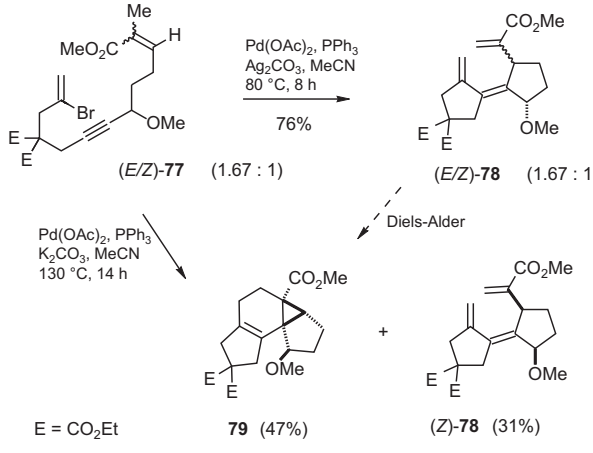


76

Scheme 5-19 Intra-intermolecular domino Heck-Diels-Alder reactions [119,273].

heteroatom containing 2-bromo-1,6-dienes **73** react smoothly in the presence of dienophiles to give heterocycles as well as **74** in good yields (X = O, NR, Scheme 5-19) [119,273]. Palladium-catalyzed 1,6-enyne cycloisomerizations [267] (see below, Section 5.1.4.) can also be adopted for this one-pot procedure. However, it should be kept in mind that homologous bromodienes can be cyclized, whereas the corresponding cycloisomerization of homologous 1,7- or higher eneynes fails (*cf.* Scheme 5-15, the enyne **56a**-H gave no diene **56**).

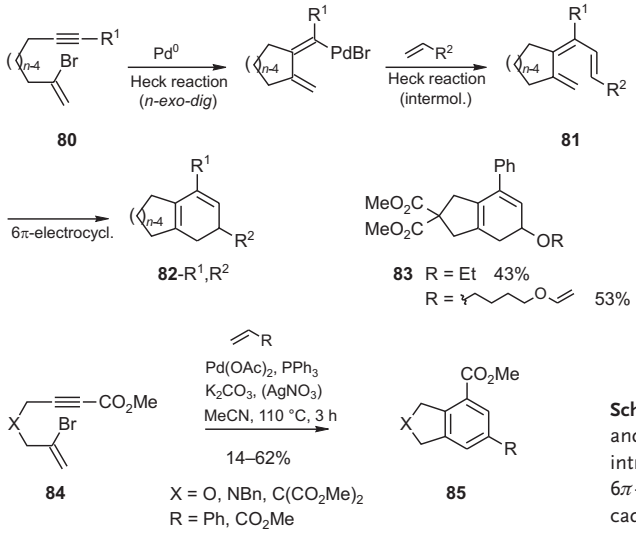
An interesting sequence of two consecutive Heck-type cyclizations and a subsequent Diels-Alder addition was observed, when the methoxycarbonyl-substituted 2-bromotrideca-1,11-dien-6-yne (*E/Z*)-**77** was treated with a typical palladium catalyst [274]. The cyclization of dienyne **77** at 80 °C gave two diastereomeric trienes (*E/Z*)-**78**. At higher temperature (130 °C), an intramolecular Diels-Alder reaction of only the (*E*)-isomer (*E*)-**78** occurred to give the tetracyclic **79**, whereas (*Z*)-**78** remained as such, probably due to steric interference of the methoxycarbonyl group.



Scheme 5-20 A cascade of two intramolecular Heck and a Diels-Alder reaction [274].

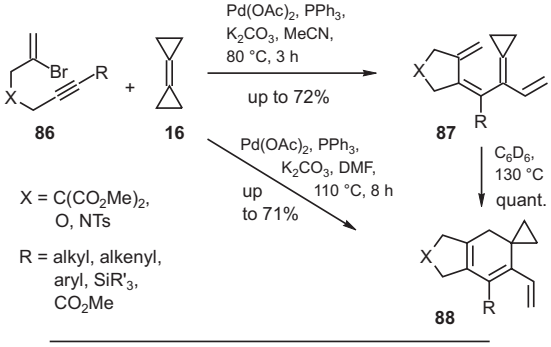
5.3.3.2 Heck-6π-Electrocyclization Cascades

While inter- and intramolecular Diels-Alder reactions normally require electron-deficient dienophiles, the 6π-electrocyclization proceeds with a large variety of substituents on a hexatriene. In one such approach, the intramolecular Heck-type reaction of a 2-bromo-1-en-(ω–1)-yne **80** is used as a trigger to initiate an intermolecular Heck coupling with an alkene to form the conjugated 1,3,5-hexatriene **81** which eventually cyclizes in a 6π-electrocyclic process (Scheme 5-21) [275]. In many cases, aromatization of the primarily formed cyclohexadiene **82** occurs to yield carbo- and heterobicyclic compounds of type **85** [275a]. But with alkyl ethenyl ethers, the cyclohexadienes **83** can be obtained in moderate yields [275b].



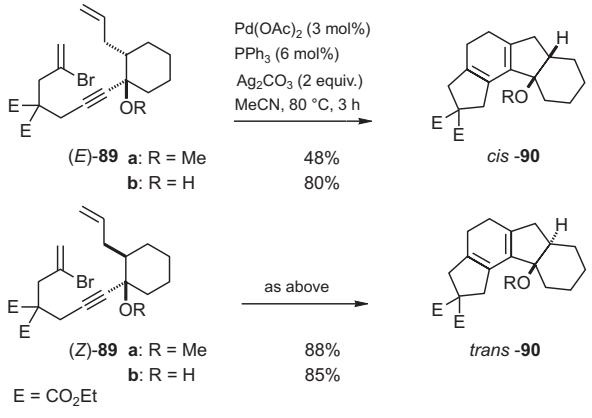
Scheme 5-21 The principle and some examples of an intra-intermolecular Heck-6π-electrocyclization cascade [275].

With a 2-bromo-1,6-enyne **86** as a starter and the more reactive bicyclopropylidene (**16**) as an interceptor, the sequential action proceeds with a cyclopropylmethyl- to homoallylpalladium rearrangement and subsequent β-hydride elimination to yield cross-conjugated tetraenes **87**. The latter undergo 6π-electrocyclization at elevated temperature (130 °C) to furnish the spirocyclopropanated biyclononadiene derivatives **88** (Scheme 5-22) [276].



86	X	R	**87** (%)	**88** (%)
a	$C(CO_2Me)_2$	*t*Bu	66	56
b	$C(CO_2Me)_2$	$SiMe_2$*t*Bu	72	65
c	$C(CO_2Me)_2$	Ph	38	49
d	O	$SiMe_2$*t*Bu	34	41
e	O	Ph	54	71
f	NTs	Ph	–	44

Scheme 5-22 Intra-intermolecular Heck reaction cascade of enynes **86** and bicyclopropylidene (**16**).



(*E*)-**89** **a**: R = Me 48%
b: R = H 80%

cis -**90**

(*Z*)-**89** **a**: R = Me 88%
b: R = H 85%

E = CO_2Et

trans -**90**

Scheme 5-23 Intra-intramolecular Heck-6π-electrocyclization cascades [274].

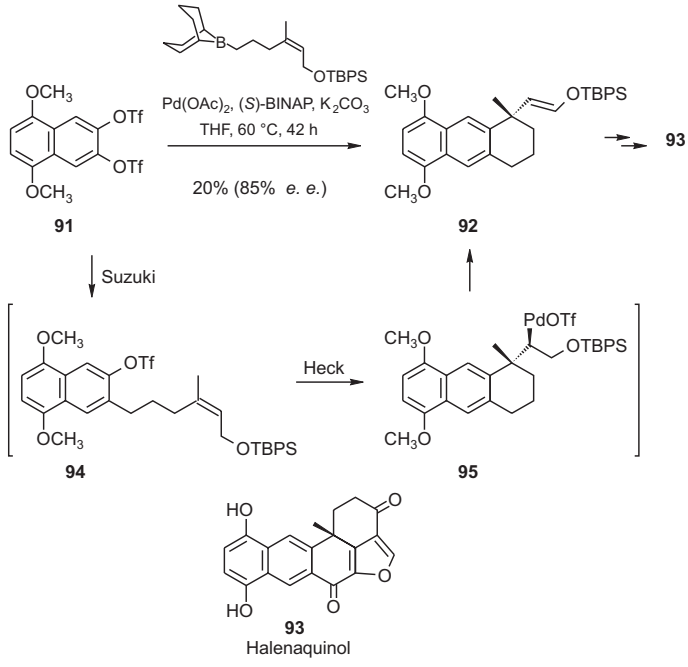
For the construction of highly condensed oligocyclic skeletons, the cascade consisting of two intramolecular Heck-type reactions and a 6π-electrocyclization as performed with the 2-bromododeca-1,11-dien-6-ynes (*E*)- and (*Z*)-**89** to yield tetracycles *cis*- and *trans*-**90**, respectively, is particularly elegant (Scheme 5-23) [274].

5.3.4
Heck Reactions Combined with other Cross-Coupling Processes

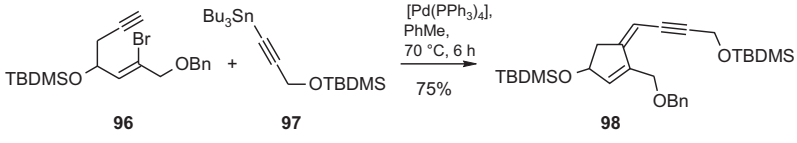
The first reported cascade consisting of a Suzuki cross-coupling and an asymmetric Heck reaction [277] was applied in an elegant access to halenaquinone, the oxidation product of halenaquinol **93**, a marine natural product which possesses antibiotic, cardiotonic, and protein kinase inhibitory activities. Starting from the dihydroxynaphthalene bis-triflate **91**, the intermolecular Suzuki coupling with the appropriately substituted borane to give the monotriflate **93** is followed by an enantioselective intramolecular Heck-type 6-*exo-trig* cyclization to give **92** as the precursor to **93** (Scheme 5-24).

Another intriguing cascade of an intramolecular Heck-type followed by an intermolecular Stille coupling produces the dienyne **98** starting from the enyne **96** and the stannane **97** [278] (Scheme 5-25). The reversed sequence of a Stille-type followed by a Heck reaction has also been applied. It is also possible to terminate such a sequence after transmetallation from a zincate [163a,c], either added to the reaction mixture [163a] or generated in situ from an iodoalkene [163c].

A newly developed cascade reaction for the construction of highly functionalized cyclohexadiene systems starts from 2-bromocyclohexenol triflates like **99**, which are readily accessible from the corresponding α-bromoketones (*cf.* Scheme 5-9) [279]. Such bromoenol triflates undergo a perfectly chemoselective Stille coupling

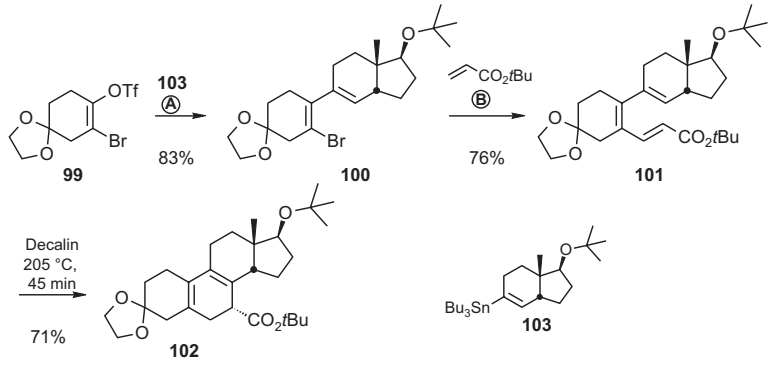


Scheme 5-24 An inter-intramolecular Suzuki-Heck cascade [277].



Scheme 5-25 An intra-intermolecular Heck-Stille cascade [278].

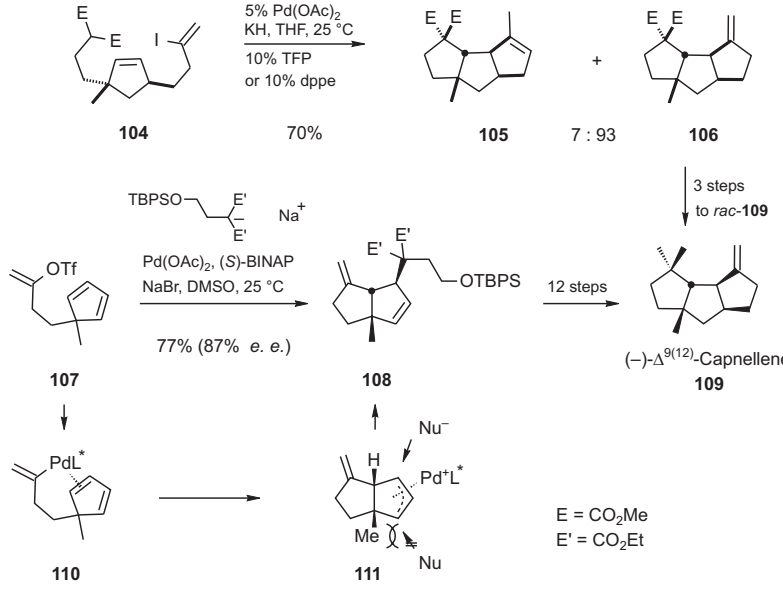
with an alkenylstannane such as **103** replacing the triflate leaving group only, to give a 1-bromo-1,3-butadiene derivative such as **100**, and this subsequently performs a Heck coupling with, for example, an alkyl acrylate to complete a 1,3,5-hexatriene system such as **101**. The latter, upon heating in decalin at 205 °C, undergoes a completely diastereoselective 6π-electrocyclization to furnish the tetracyclic system **102**, a protected steroid analogue with a cyclohexadiene B-ring, yet with a *cis*-junction of the C and D rings. The analogous tetracyclic compound with a *trans*-C,D-junction has been prepared along the same route starting with the corresponding *trans*-configured analogue of **103** [279b] (Scheme 5-26).



Scheme 5-26 An inter-intermolecular two pot Stille-Heck cascade for the assembly of tri- and tetracyclic systems [279b]. **A**: $Pd_2(dba)_3 \cdot CHCl_3$, LiCl, CuI, $AsPh_3$, NMP, 65 °C, 4.5 h. **B**: Palladacycle **1a** from $Pd(OAc)_2$ + $P(o\text{Tol})_3$, Bu_4NOAc, DMF/MeCN/H_2O (5:5:1), 120 °C, 16 h.

5.3.5
Palladium-Catalyzed Reactions Involving Nucleophilic Substrates

The σ-complexes generated by oxidative addition of haloarenes and haloalkenes to palladium(0) are electrophilic at the metal-substituted center, and can therefore react with nucleophiles other than alkenes, especially with enolate and homoeno-



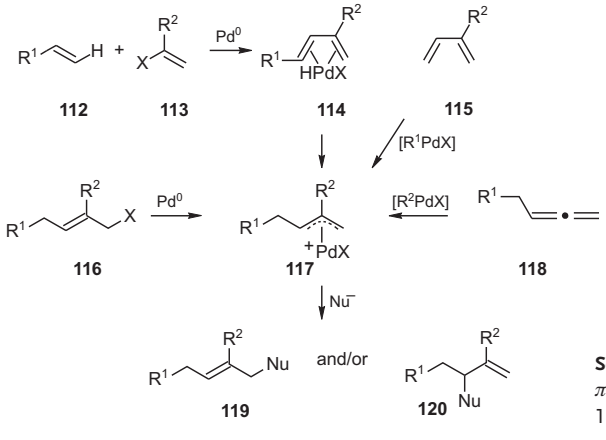
Scheme 5-27 A synthesis of capnellene (**109**) employing an enantioselective intramolecular Heck and anion capture process [79a,168a].

late ions to form new C-C bonds [280,281]. This reaction mode has been termed "anion capture" [282].

With this notion in mind, an elegant synthesis of the sesquiterpene (±)-$\Delta^{9(12)}$-capnellene *rac*-**109** was developed (Scheme 5-27). Thus, biscyclization of the cyclopentene derivative **104** gave the tricycle **106** (with **105** as a byproduct) which was converted to the target molecule **109** in three further steps [168a]. The enantiomerically pure product (–)-**109** was obtained starting from **107** employing an enantioselective coupling with an appropriately substituted sodiomalonate [79a]. After insertion of the palladium into the carbon–oxygen bond of the trienyl triflate **107**, the (*S*)-BINAP ligand on the palladium led to selective coordination to one of the enantiotopic double bonds with subsequent cyclization to give the intermediate π-allyl complex **111**. This was regio- and stereoselectively trapped by the nucleophile. Further elaboration of **108** gave the natural product in good optical purity.

Palladium-catalyzed substitutions of allylic esters **116**, which proceed via intermediate π-allylpalladium complexes such as **117**, are well established [283]. In contrast, the reactions proceeding through π-allylpalladium intermediates, generated by addition of the palladium σ-complex intermediates from haloarenes, haloalkenes, or corresponding triflates, to allene and substituted allenes **118** (Scheme 5-28), have scarcely been tapped [132].

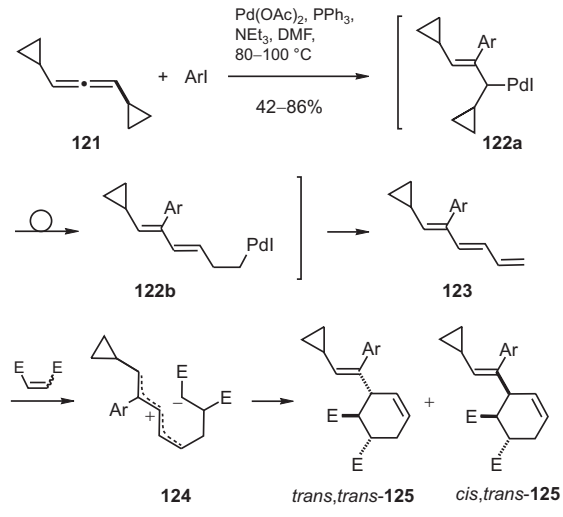
The σ-allylpalladium intermediate **122a**, which must be formed upon coupling of 1,3-dicyclopropyl-1,2-propadiene (**121**), with e. g., iodobenzene under palladium catalysis, rapidly undergoes rearrangement to the homoallylpalladium species **122b** and subsequent β-hydride elimination to yield the 1,3,5-hexatriene **123**.



Scheme 5-28 Formation of π-allyl complexes from 1,3-dienes and allenes.

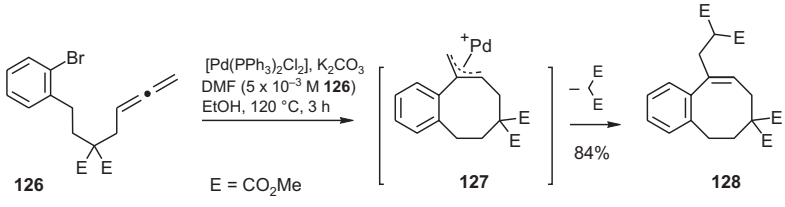
This in turn undergoes [4+2] cycloaddition with an added dienophile to furnish the 3-(2-cyclopropyl-1-phenyl)cyclohexene derivatives **125** as a mixture of *trans,-trans-* and *cis,trans*-diastereomers (Scheme 5-29).

Negishi et al. demonstrated the carbopalladation mode of an allene to be feasible for an intramolecular approach to medium and large rings [133]. The new C-C bond is formed at the central carbon atom of the allene moiety to give a π-allyl-



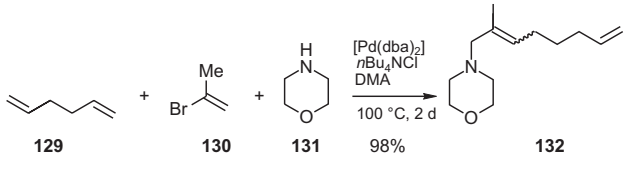
Scheme 5-29 A three-component reaction with 1,3-dicyclopropyl-1,2-propadiene, an aryl iodide and a dienophile.

palladium complex, which in turn can be trapped by a variety of nucleophiles (arylstannanes to give arylated products, malonates, phenols, amines, etc.) (Scheme 5-30). The yields are remarkably good without using sophisticated nucleophile delivery techniques.

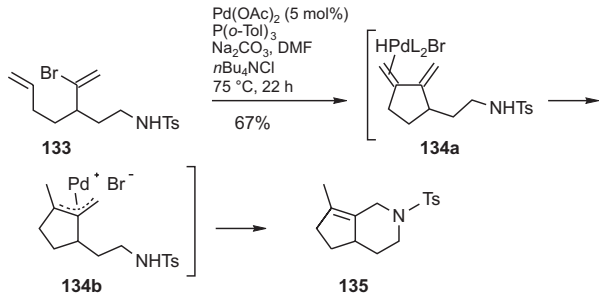


Scheme 5-30 Intramolecular carbopalladation of an allene with subsequent nucleophilic trapping of the π-allylpalladium intermediate [133].

Early findings by Heck et al. revealed that coupling reactions of haloalkenes **113** with alkenes **112** in the presence of secondary amines gave allylamines [128a, 284] (Scheme 5-28: **119/120**; Nu = NR_2). Based on this observation, inter-inter- as well as intra-intramolecular cascade reactions [285] (Scheme 5-31), the latter ones leading to a variety of bicycles [286] (Scheme 5-32), were developed.

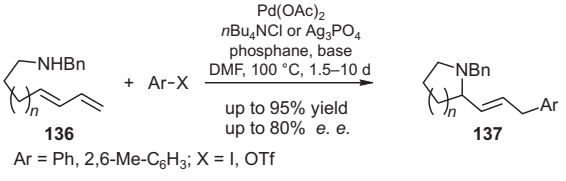


Scheme 5-31 An inter-intermolecular three-component reaction [285a].



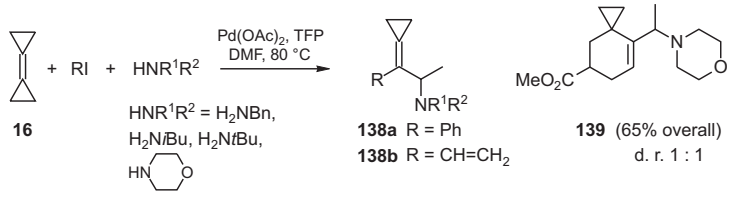
Scheme 5-32 An intra-intramolecular cascade reaction leading to heterobicycles [286b].

Pyrrolidine derivatives **137** are accessible by a cascade carbopalladation of a diene **136** and intramolecular trapping of the intermediate π-allylpalladium complex by a secondary amine moiety. In this case, an efficient enantiocontrol has been achieved using chiral phosphane ligands (Scheme 5-33) [287].



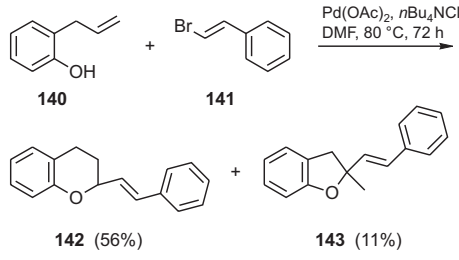
Scheme 5-33 Asymmetric synthesis of pyrrolidines [287].

Similar three-component reactions can also be carried out with bicyclopropylidene (**16**) as an alkene partner. After carbopalladation with, for example, phenylpalladium iodide across its double bond, rapid ring opening of the resulting (1-cyclopropylcyclopropyl)palladium to a 3-cyclopropylidene-3-phenylpropylpalladium species occurs; subsequent rearrangement to a π-allylpalladium and its trapping with a primary or secondary amine then yields an allylamine **138a** with a cyclopropylidene end group (Scheme 5-34) [288]. Similarly, this three-component reaction with bicyclopropylidene (**16**) has been performed with *o*-iodobenzyl alcohol to give a cyclopropylidene-substituted benzodihydropyran derivative. It is interesting to note, that even an *ortho*-positioned amide nitrogen is nucleophilic enough for an



Scheme 5-34 A three-component reaction involving bicyclopropylidene (**16**) leading to 1-aryl- and 1-vinyl-substituted 1-cyclopropylidene-2-propylamines **138** [288].

intramolecular attack [288]. This transformation is related to the three-component reaction leading to 1′-arylallylidenecyclopropane derivatives (see Scheme 5-5) [101]. With vinyl iodide as a coupling partner in this new three-component reaction, aminoethyl-substituted allylidenecyclopropanes **138b** can be prepared in up to 75 % yield, and these can be further transformed by [4+2] cycloadditions, e. g., to **139** [289].

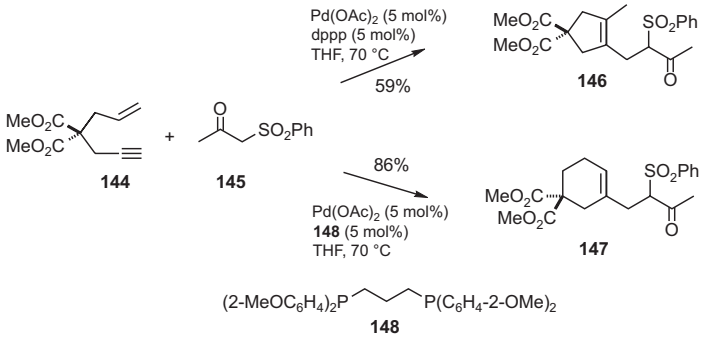


Scheme 5-35 Intramolecular termination of carbopalladation cascades by oxygen nucleophiles [290].

Since hydroxy groups do not interfere with palladium catalysts, the termination of carbopalladation cascades by oxygen nucleophiles has been employed in various cases. As discussed above, the palladium-catalyzed couplings of alkenyl halides with alkenes can give rise to the formation of π-allylpalladium complexes which can then be attacked by internal nucleophiles including hydroxy groups to yield various oxacyclic systems (Scheme 5-35) [290].

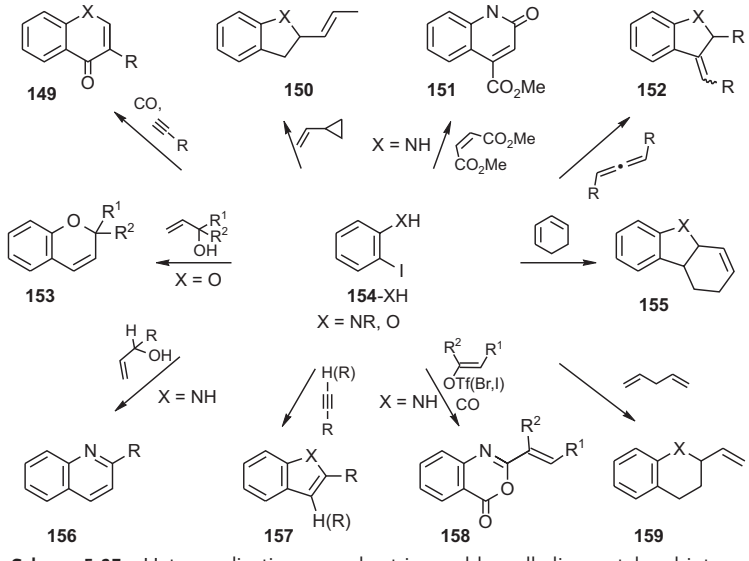
An analogous sequence of an enyne cycloisomerization and subsequent coupling with a stabilized enolate has been employed (Scheme 5-36) [291]. In this case, variation of the appropriate ligand (e. g., switching from dppp to the 1,3-bis(diarylphosphano)propane derivative **148**) for the palladium can lead to different ring sizes.

Given the tremendous variety of naturally occurring heterocyclic compounds, the development of elegant and efficient routes to the appropriately substituted ring systems is a formidable task. *o*-Amino- and *o*-hydroxysubstituted iodoarenes like



Scheme 5-36 An intra-intermolecular cascade reaction involving a stabilized enolate.

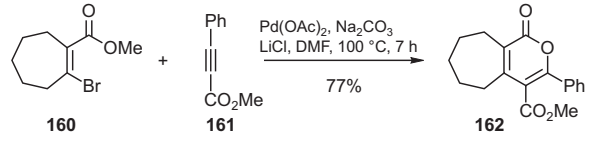
154-XH (X = O, NR) can undergo a vast array of reactions with 1,2-, 1,3- and 1,4-dienes as well as ethenylcyclopropanes, when treated with an appropriate palladium catalyst [120,132d,f,292]. Several of these reactions which lead to substituted dihydrobenzofurans and dihydroindoles **150**, **152**, **155**, **159**, also proceed via intermediate π-allylpalladium complexes (Scheme 5-37).



Scheme 5-37 Heterocyclization cascades triggered by palladium-catalyzed intermolecular coupling reactions [292].

o-Iodoamino- and *o*-iodohydroxyarenes like **154**-XH also react with various alkynes [293], alkenes [294], and enol triflates with or without incorporation of carbon monoxide to yield versatile heterocyclic compounds (Scheme 5-37).

α,β-Unsaturated or *α*-aryl esters with a *β*- or *ortho*-leaving group (bromo, iodo, trifluorosulfonyloxy) undergo coupling with alkynes to give 2-pyrone or isocoumarine derivatives, respectively, in good yields (Scheme 5-38) [295].



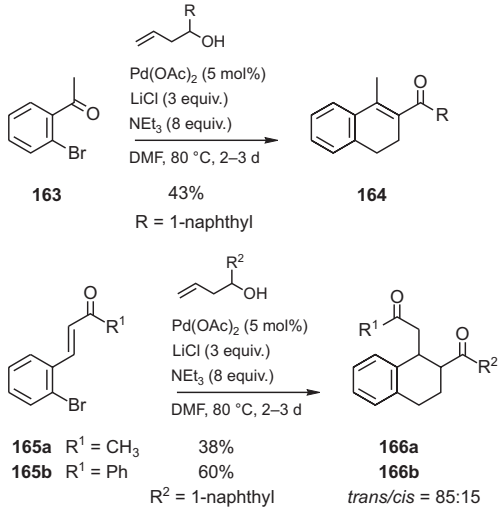
Scheme 5-38 Isocoumarines by Heck-type reactions [295].

5.3.6
Heck-Aldol and Heck-Michael Cascades

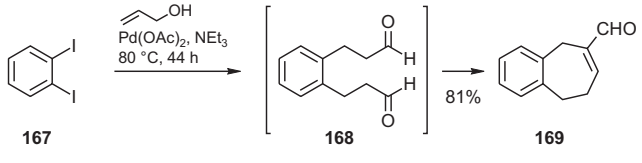
The intermolecular coupling of homoallyl alcohols with *o*-bromoacetophenone (**163**) or *o*-bromostyryl ketones **165** gave dihydro- **164** and tetrahydronaphthalene derivatives **166** in a sequence of Heck and aldol or Heck and Michael reactions (Scheme 5-39, Scheme 5-40) [296]. After addition of the initially formed arylpalladium species to the homoallyl alcohols, elimination/isomerization yield carbonyl compounds which, under the reaction conditions, undergo intramolecular aldol reactions or Michael additions.

The two-fold coupling product of 1,2-diiodobenzene (**167**) with allyl alcohol, a 1,8-dicarbaldehyde **168**, readily underwent an intramolecular aldol condensation under the reaction conditions to yield 5,6-benzocycloheptenecarbaldehyde (**169**) (Scheme 5-40) [297].

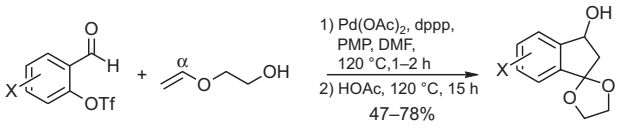
Monoprotected 3-hydroxyindan-1-ones **172** have been prepared in moderate to good yields by a new domino Heck-Aldol annelation reaction involving salicylaldehyde triflates and commercially available 2-hydroxyethyl vinyl ether (Scheme 5-41). In this one-pot transformation, which proceeds in the presence of a palladium catalyst with a bidentate ligand, two new rings are formed [298].



Scheme 5-39 Sequences of a Heck and an aldol condensation reaction as well as a Michael reaction [296].



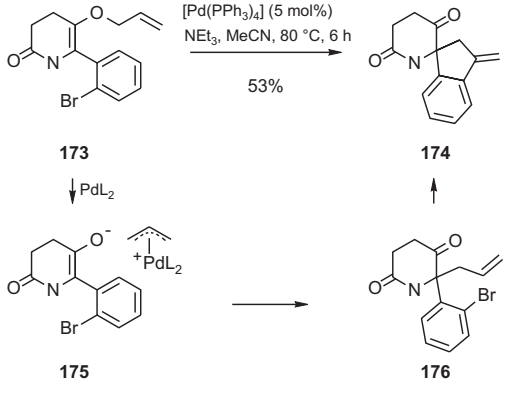
Scheme 5-40 A sequence of a two-fold Heck and an intramolecular aldol reaction [297].



170 **171** **172**

Scheme 5-41 Synthesis of monoprotected hydroxyindanones [298].

An interesting new mode was discovered in the reaction of the enol ether **173** under Heck-type conditions. In the presence of both $[Pd(PPh_3)_4]$ and a base, the allyl alkenyl ether **173** underwent a Pd^0-catalyzed 1,3-allyl shift and an intramolecular Heck arylation to give the spiroindane **174** (Scheme 5-42). Mechanistic investigations suggest that the 1,3-allyl shift proceeds by first forming the π-allylpalladium enolate intermediate **175** which by recombination yields **176**, and this in turn undergoes a 5-*exo-trig* cyclization [299].



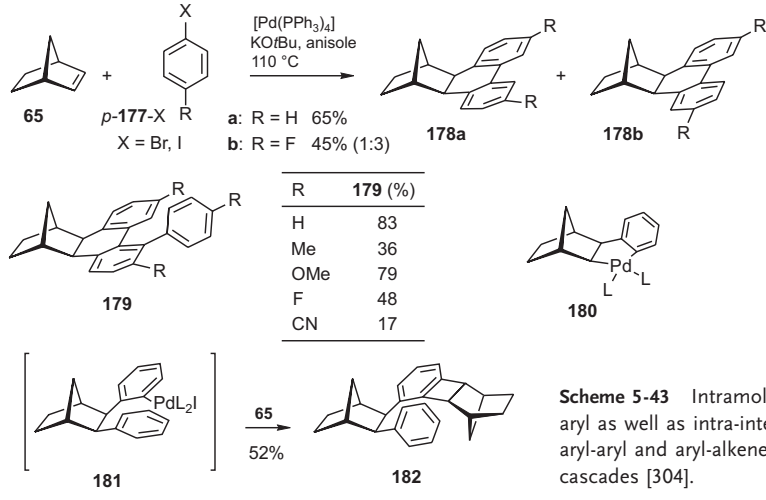
173 **174** **175** **176**

Scheme 5-42 A domino reaction consisting of a 1,3-allyl shift and a Heck arylation [298].

5.3.7
C-H Activation in Heck-Type Processes

Cascade reactions are often triggered when a *syn-β*-hydride elimination cannot take place, e. g., in a cycloalkyl- or neopentylpalladium intermediate. Such systems then seek an alternative reaction mode, in particular, C-H activation often plays a major role [300, 301].

In such situations, even the insertion into aryl C-H bonds can occur, for example, in the coupling of aryl halides **177**-X with norbornene (**65**). Thus, upon reaction of iodo- or bromoarenes **177**-X with norbornene (**65**) (in the presence of $[Pd(PPh_3)_4]$, KO*t*Bu, and anisole at 110 °C), Catellani and Chiusoli et al. obtained the norbornane-annelated 9,10-dihydrophenanthrenes **178a** and **178b** (Scheme 5-43) [83,302]. However, under different reaction conditions $[Pd(OAc)_2$, K_2CO_3,



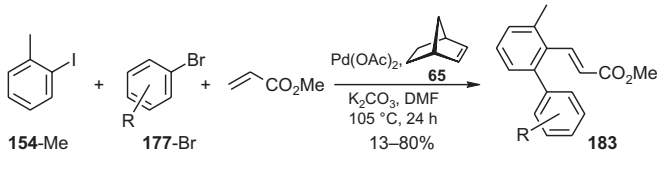
R	179 (%)
H	83
Me	36
OMe	79
F	48
CN	17

Scheme 5-43 Intramolecular aryl-aryl as well as intra-intermolecular aryl-aryl and aryl-alkene coupling cascades [304].

nBu_4NBr, DMF, 80 °C] the norbornane-annelated 4-aryl-9,10-dihydrophenanthrenes **179** were formed almost exclusively, apparently from three molecules of **177**-Br and one molecule of norbornene (**65**) [303]. The diversion of these two reactions is likely to occur only after the first three identical steps. *ortho*-C-H activation must occur twice in the formation of **179**.

Under yet another set of conditions [$Pd(PPh_3)_4$, K_2CO_3, DMF, 80 °C], intermediate **181** – which is formed via a palladacycle intermediate **180** and is common to the formation of **178a,b** and **179** – reacts with norbornene (**65**) to afford the benzocyclobutene derivative **182** [304]. In recent years, Catellani et al. have developed this chemistry of palladium-catalyzed coupling reactions involving norbornene, aryl halides, halostyrenes, alkenes, amines, carbon monoxide each combination under appropriate conditions selectively leading to one of a multitude of interesting oligofunctionalized aromatic compounds. During the course of this work, these authors have gathered conclusive evidence for rigorous mechanistic rationalizations for the results presented in Scheme 5-43 and the new developments [305].

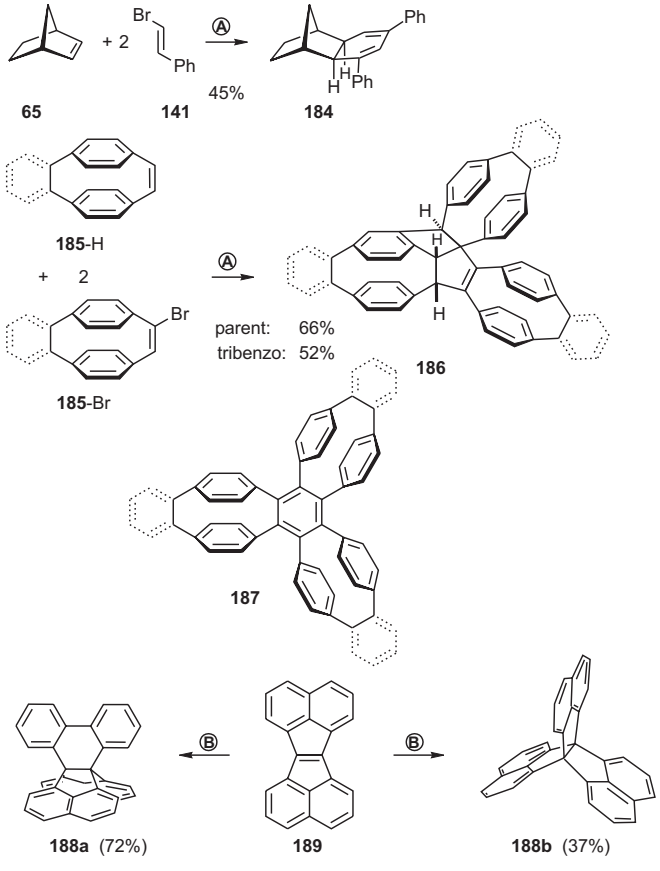
A new three-component reaction incorporating an aryl iodide, an aryl bromide and an acrylate to give *ortho*-aryl-substituted cinnamates **183**, recently also developed by Catellani et al. [306] (Scheme 5-44) proceeds only in the presence of nor-



Scheme 5-44 A three-component coupling cascade coupling an aryl iodide, an aryl bromide and an acrylate involving norbornene as a co-catalyst [306].

bornene and involves an intermediate norbornylpalladium complex and palladation of an arene ring.

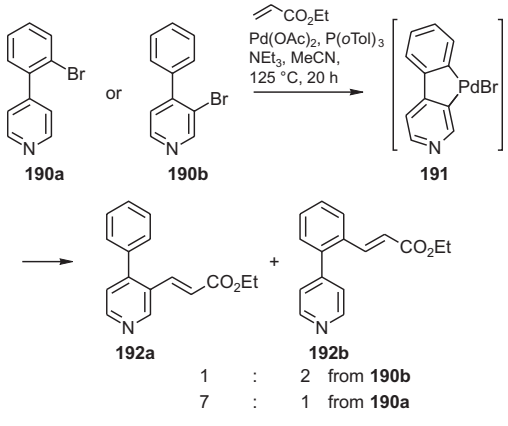
The same type of inter-intramolecular coupling cascade with formation of a six-membered ring as in **178**/**179** can be performed under Jeffery conditions [$Pd(OAc)_2$, K_2CO_3, Bu_4NBr, DMF, 80 °C] with norbornene (**65**) and haloalkenes such as β-bromostyrene yielding **184** (45 % isolated) (Scheme 5-45) [303d]. The same reaction between [2.2]paracyclophan-1-ene **185**-H and its 1-bromo derivative **185**-Br or the benzo analogues benzo-**185**-H and benzo-**185**-Br, however, apparently follows a different mode, most probably via a palladacycle intermediate [307] to give tris[2.2]paracyclophane-annelated bicyclo[3.3.0]octa-2,6-diene **186** or tribenzo-**186** in remarkable yields of 66 and 52 %, respectively [303e]. The latter is an interesting $C_{60}H_{38}$ hydrocarbon, however, the more interesting D_{3h}-symmetric $C_{60}H_{36}$ hydrocarbon tribenzo-**187** just like the parent trifoliaphane **187** could be



Scheme 5-45 Inter-intramolecular alkenyl-alkene and aryl-alkene coupling cascades involving C-H activation [96,303d,e]. Ⓐ: $Pd(OAc)_2$, K_2CO_3, $n$$Bu_4NBr$, DMF, 80 °C, 24 h. Ⓑ: Like Ⓐ, but 100 °C for 7 and 21 days, respectively.

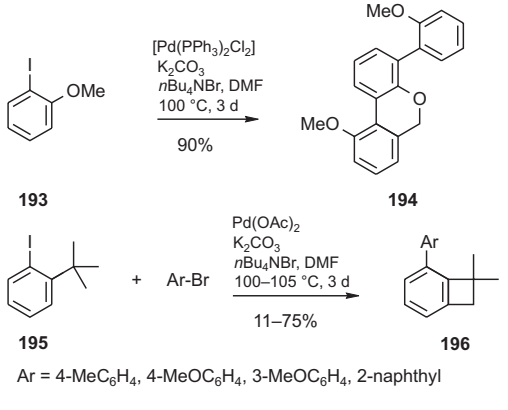
obtained in remarkably good yields (69 and 48 % overall) by palladium-catalyzed two-fold coupling of 1,2-dibromo-9,10-benzo[2.2]paracyclophane-1-ene with 9,10-benzo[2.2]paracyclophane-1-magnesium bromide – or the corresponding parent [2.2]paracyclophane derivatives – leading to a 1,3,5-hexatriene with one central and two terminal [2.2]paracyclophane units, which underwent 6π-electrocyclization under the coupling conditions and formal oxidation upon subsequent treatment with bromine [308].

The formation of the interesting propellanes **188a**,**b** with their hexaarylethane substructures from the hexacyclic hydrocarbon **189** with a central tetrasubstituted, but strained double bond, and iodobenzene or 1-iodonaphthalene under palladium catalysis, as reported by Dyker et al. [96] also proceeds via palladacycle intermediates.



Scheme 5-46 Formal translocations of coupled groups occurring via palladacycles [309].

Palladacycles are presumably also involved in the observed formal translocation of the attached group during Heck-type coupling of unsymmetrically substituted 2-bromobiaryls (Scheme 5-46). It is puzzling that these relocations are more or less restricted to 4-aryl-3-bromopyridines as well as 4-(2′-bromoaryl)pyridines [309] and can be switched "on" and "off" using different catalysts [160].

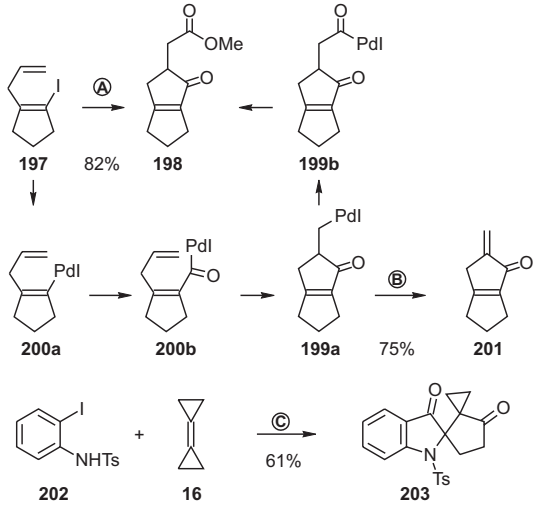


Scheme 5-47 C-H activation on *ortho*-methoxy and *ortho-tert*-butyl groups in the formation of biaryls [310].

An unusual C-H activation on *ortho*-methoxy groups was observed by Dyker et al. in the reaction of methoxyiodoarenes like **193** leading elegantly to 6*H*-dibenzo[*b*,*d*] pyrans like **194** (Scheme 5-47) [310,311]. Under the same conditions, 2-*tert*-butyliodobenzene (**195**) with various aryl halides gave the benzocyclobutene derivatives **196**, the formation of which also involves an alkyl C-H activation [310e].

5.3.8
Heck Reactions with Subsequent Incorporation of Carbon Monoxide

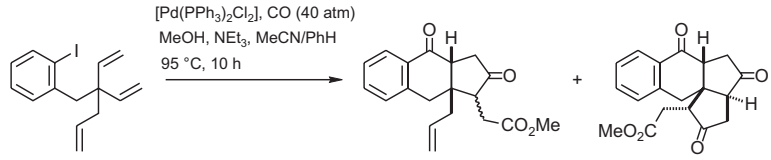
Aryl-, alkenyl- and alkynylpalladium species readily undergo carbonylation reactions because carbon monoxide as a loosely bound ligand can reversibly insert into any palladium-carbon bond [167]. Thus, 2-allyl-1-iodocyclopentene (**197**), under palladium catalysis, reacts with carbon monoxide in two modes, depending on the excess of carbon monoxide and the catalyst cocktail [167a]. With a slight excess (1.1 atm of CO) in the presence of $[Pd(PPh_3)_4]$ in tetrahydrofuran, **197** cyclized with one CO insertion to yield 3-methylenebicyclo[3.3.0]oct-1(5)-en-2-one (**203**), and under 40 atm of CO with $[Pd(PPh_3)_2Cl_2]$ in benzene/acetonitrile/methanol, gave methyl 2-{3′-(2′-oxobicyclo[3.3.0]oct-1′(5′)-enyl)}acetate (**198**) after two CO insertions (Scheme 5-48).



Scheme 5-48 Heck-carbonylation cascades [167a,311]. Ⓐ: $[Pd(PPh_3)_2Cl_2]$, 40 atm CO, NEt_3, C_6H_6/MeCN/MeOH, 100 °C, 24 h. Ⓑ: $[Pd(PPh_3)_4]$, 1.1 atm CO, NEt_3, THF, 60 °C, 24 h. Ⓒ: $[Pd(PPh_3)_4]$, 2–3 atm CO, K_2CO_3, nBu$_4$NBr, MeCN, 70–80 °C, 20 h.

The intermolecular Heck cross-coupling of *o*-iodo-*N*-tosylaniline (**202**) with bicyclopropylidene (**16**) also proceeds with incorporation of two molecules of carbon monoxide to yield the interesting spiroheterocycle **203**, and thus constitutes a formal four-component queuing cascade [312].

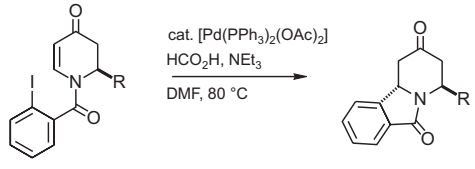
Even more impressive is the carbonylative cascade starting from the trienyliodobenzene derivative **204** [167b]. Under appropriate conditions, even the tetracycle **206** with incorporation of four CO, was formed, albeit in low yield



Scheme 5-49 Intramolecular cross-coupling cascade with four-fold carbon monoxide insertion [167b].

(Scheme 5-49). This is quite remarkable, as it involves the formation of seven new carbon–carbon bonds in a single operation.

Heck reactions with subsequent reduction ("hydride-ion capture") [159,162,313] also have become valuable methods for the construction of various carbo- and heterocyclic skeletons. Such a reaction comes about, when the *syn*-addition of an aryl- or alkenylpalladium species onto a multiple bond leads to an intermediate which does not or cannot undergo a rapid *syn*-β-hydride elimination (Scheme 5-50) [162].



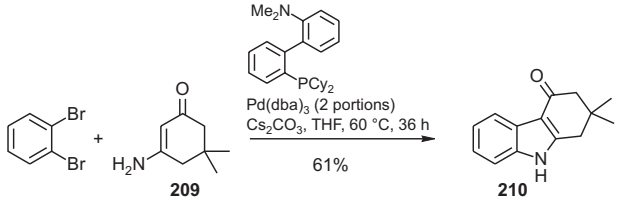
Scheme 5-50 Reductive intramolecular Heck coupling reactions leading to heterocycles [162].

5.3.9
The Heck Coupling in Combination with other Reactions

Since the Heck reaction is quite robust to the presence of various electrophilic and nucleophilic functional groups and reagents, its combination with other reaction types is very appealing. The one-pot performance of a Heck reaction and a catalytic hydrogenation is definitely one of the most useful approaches to β-aryl-substituted esters and nitriles (see Section 5.8).

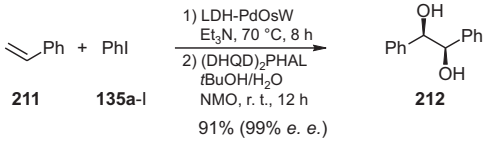
The Hartwig-Buchwald arylation of amines can also be favorably combined with the Heck reaction [314]. For example, the intramolecular palladium-catalyzed *N*-arylation of immobilized dehydrohalophenylalaninate was found to proceed smoothly to form indolecarboxylates. The method was successfully combined with the Heck reaction to constitute a one-pot indole synthesis in the form of a palladium-catalyzed cascade C,N-arylation reaction [315] (Scheme 5-51).

An interesting combination is that of a Heck coupling with an enantioselective dihydroxylation reaction. To achieve this, a bifunctional catalyst consisting of active palladium and osmium species anchored on silica gel through a mercaptopropyl



Scheme 5-51 Hartwig-Buchwald-Heck cascade [314].

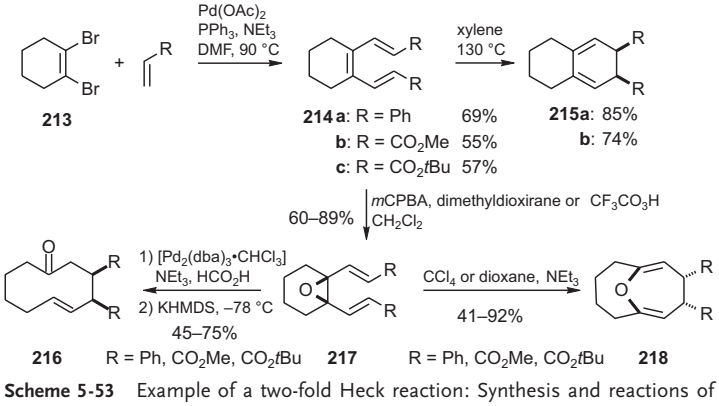
spacer and a cinchona alkaloid, respectively, was prepared and applied using *N*-methylmorpholine *N*-oxide as a co-oxidant. This domino process of alkene formation and subsequent dihydroxylation afforded diols of type **212** in excellent yields and high enantiomeric excesses [316] (Scheme 5-52).



Scheme 5-52 A domino of Heck coupling with subsequent asymmetric *cis*-dihydroxylation [316].

5.3.10
Multiple Heck Couplings

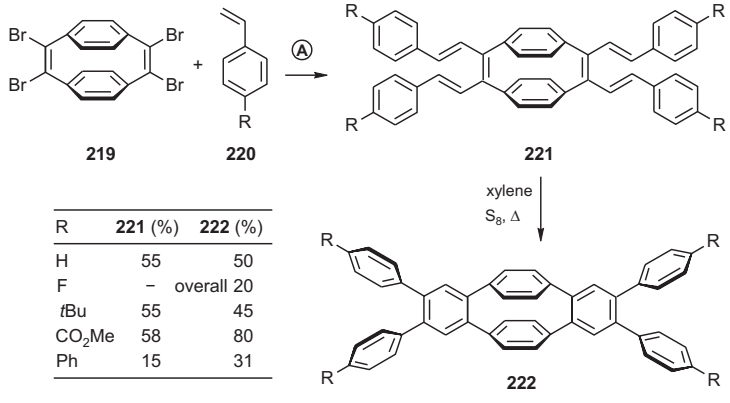
The feasibility of multiple couplings had already been demonstrated by Heck himself [1, 317]. Such reactions have later been improved [318] and further developed to conveniently prepare starting materials for various carbo- and heterocyclic frameworks [318, 319]. For example, the two-fold coupling of 1,2-dihalocycloalkenes yields (*E,Z,E*)-1,3,5-hexatrienes **214** [318] which readily undergo 6π-electrocyclization to yield ring-annelated cyclohexa-1,3-dienes. The trienes **214**, however, can also be used as precursors for larger rings; for example, the epoxides **217**, easily



Scheme 5-53 Example of a two-fold Heck reaction: Synthesis and reactions of (*E,Z,E*)-1,3,5-hexatrienes **214** [219,320,321].

accessible by treatment of the hexatrienes **214** with peracids or dimethyldioxirane, rearrange smoothly to the bridgehead-bridgehead dienes **218** [320]. Alternatively, palladium(0)-catalyzed reduction of the diethenylepoxides **217** leads to 1,5-hexadien-3-ols which readily undergo an anionic oxy-Cope rearrangement to give the ring-enlarged ketones **216** diastereoselectively (Scheme 5-53) [219,321].

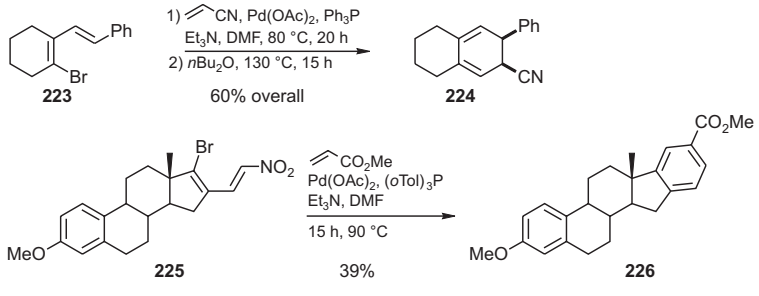
The strategy of a vicinal two-fold Heck reaction was applied on tetrabromo[2.2]paracyclophanediene **219**. After its four-fold coupling with styrene (**220**-H) or substituted styrenes **220**-R, the products **221** can be 6π-electrocyclized with subsequent aromatization (*cf.* Scheme 5-21) to the benzoannelated [2.2]paracyclophanedienes **222**, molecules with eight orthogonal biphenyl moieties (Scheme 5-54) [322a].



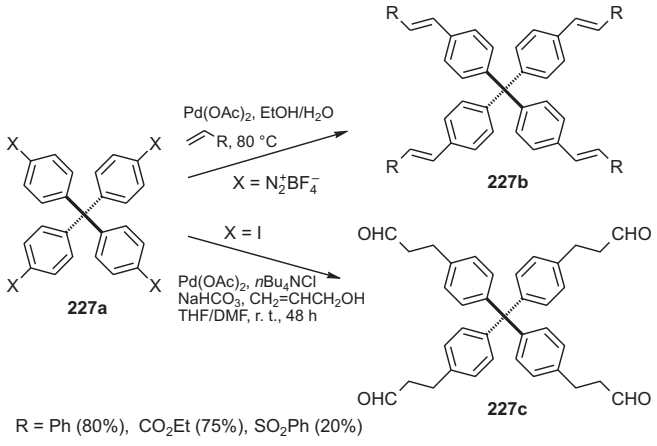
R	**221** (%)	**222** (%)
H	55	50
F	–	overall 20
*t*Bu	55	45
CO_2Me	58	80
Ph	15	31

Scheme 5-54 Construction of 1:2,9:10-dibenzoannelated [2.2]paracyclophanedienes with alternatingly orthogonal π-systems using a four-fold Heck reaction as the key step. Ⓐ: $Pd(OAc)_2$, K_2CO_3, nBu$_4$NBr, DMF, 70 °C, 3 days [322a,b].

The Heck-reaction/6π-electrocyclization sequence can also be performed on 2-alkenyl-1-halocycloalkenes leading to unsymmetrically substituted cyclohexadiene-annelated ring systems or their dehydrogenation products such as the 2-nitroethenyl steroid **225** (Scheme 5-55) [323].



Scheme 5-55 Heck reaction-6π-electrocyclization cascades and its application to the synthesis of modified steroids [219,323].



Scheme 5-56 Four-fold-Heck reactions with tetraarylmethane derivatives [325].

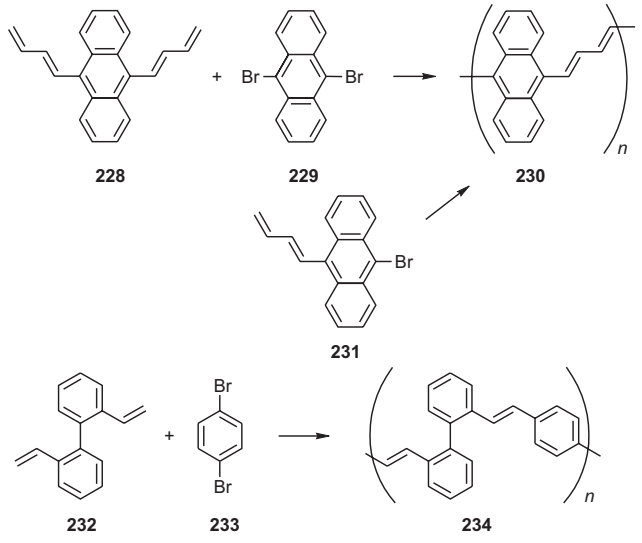
Double and even triple Heck-Diels-Alder cascade reactions involving 1,4-diiodo- or 1,3,5-triiodobenzene, respectively, and bicyclopropylidene (**16**) have been accomplished (*cf.* Scheme 5-5) [101b]. The efficiency of these sequences, in which each carbopalladation across the highly strained alkene is followed by a cyclopropylmethyl to homoallyl rearrangement with concomitant β-hydride elimination to yield an allylidenecyclopropane which subsequently undergoes a smooth [4+2] cycloaddition (see above, Scheme 5-5), is quite remarkable [101b].

2,5-Dihalothiophenes are also excellent substrates for two-fold Heck couplings, even with 1,1-dimethylallene, the products of which can subsequently undergo a twofold Diels-Alder reaction [324]. Even four-fold Heck reactions applying a tetradiazonium salt with a tetraphenylmethane framework have been demonstrated with various alkenes to yield the corresponding four-fold coupled tetraarylmethane derivatives (Scheme 5-56) [325].

Multiple palladium-catalyzed couplings, for example, of dihaloarenes with dialkenylarenes, have also been used to prepare new types of oligomers with extended π-systems [326–328], some of which have liquid crystalline properties [329,330]. For example, 9,10-dibromoanthracene (**229**) and 9,10-bisbutadienylanthracene (**228**) gave oligomers **230** with an average degree of polymerization of $n = 12$ (Scheme 5-57). These oligomers can also be constructed from the bifunctional monomer **231**. The analogous coupling of 2,2′-diethenylbiphenyl (**232**) with *p*-dibromobenzene (**233**) led to oligomeric stilbenes **234** with an average degree of polymerization of $n = 15$.

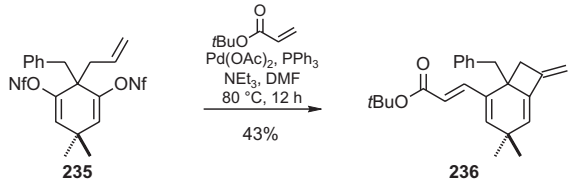
For good yields in such vicinal multifold couplings, it may be essential to use the protocol of Jeffery [154, 155]. Employing this, the three- and even four-fold vicinal couplings of oligohaloarenes can be achieved without problems [219,318b,d]. Recently, multifold Heck couplings were performed on bisporphyrins [331].

The treatment of the dienediol bisnonaflate **235** containing an (ω−1)-alkenyl substituent with the typical Heck catalyst cocktail in the presence of an external



Scheme 5-57 Formation of oligomers with extended π-systems by palladium-catalyzed cross-coupling of dihaloarenes with dialkenylarenes.

alkene such as an acrylate gives rise to the formation of the bicyclic tetraene **236** by an intramolecular followed by an intermolecular Heck coupling (Scheme 5-58) [213]. This reaction can be performed using chiral catalysts to achieve asymmetric induction with up to 30 % *e. e.* (*cf.* Scheme 5-69).

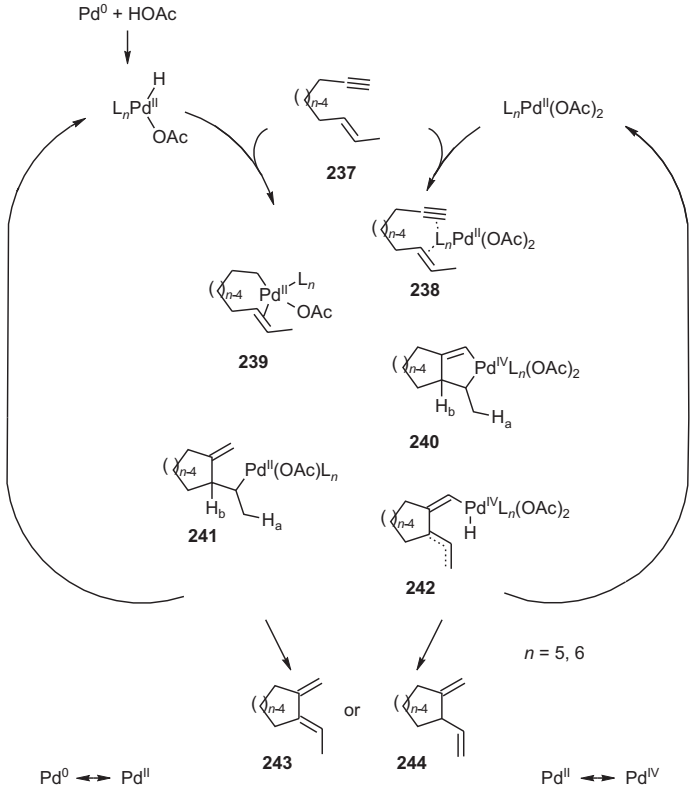


Scheme 5-58 An intra-intermolecular Heck reaction cascade [213].

5.4 Related Palladium-Catalyzed Reactions

The palladium-catalyzed cross-coupling reactions of boronates as well as boranes (Suzuki coupling) and stannanes (Stille coupling) which are mechanistically related to the Heck reaction in the initial oxidative addition step, are discussed in Chapters 2 and 3.

During the mid-1980s, Trost et al. [267] developed an ingeniously simple palladium-catalyzed cycloisomerization of enynes. The atom economy [332] of this reaction equals that of the Diels-Alder reaction. The cycloisomerization



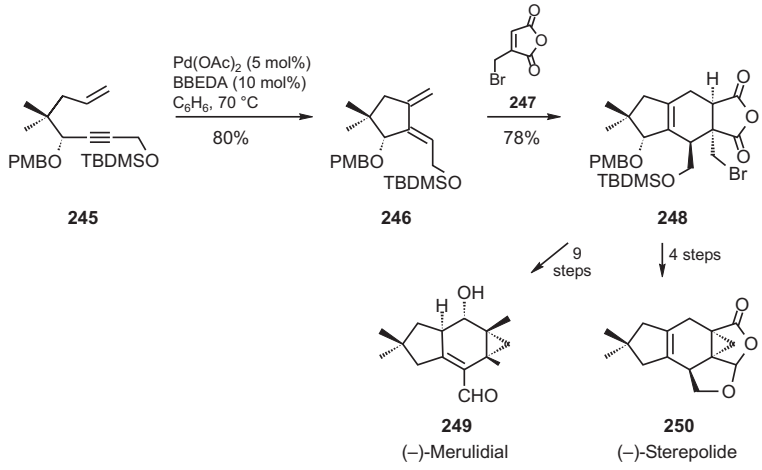
Scheme 5-59 Mechanistic aspects of the palladium-catalyzed enyne cycloisomerizations [267,332].

of 1,6- and 1,7-enynes **237** ($n = 5, 6$) to 1,2-dimethylenecycloalkanes **243** (or 1-ethenyl-2-methylenecycloalkanes **244**) is performed by using either palladium(II) acetate and ligands like triarylphosphanes, triarylstibanes, chiral phosphanes (to yield nonracemic products, *cf.* e. g. [267g]) or BBEDA [267] or palladium(0) complexes, ligands, and acetic acid or other carboxylic acids including chiral ones [267f]. The catalytic cycle may involve both Pd^0/Pd^{II} or Pd^{II}/Pd^{IV} oxidation states (Scheme 5-59).

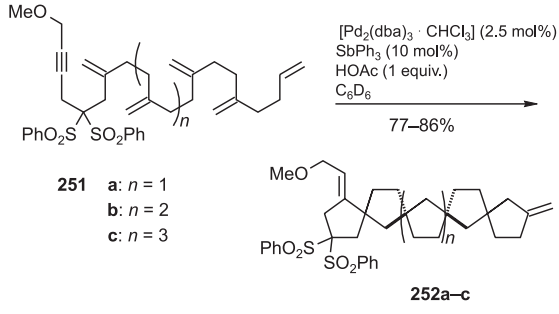
This reaction has been applied as a key step in the synthesis of a number of natural products, for example, (–)-merulidial (**249**) and (−)-sterepolide (**250**) (Scheme 5-60) [333].

It has also been extended to remarkable cascade reactions such as the "Pd-zipper" converting oligoenynes **251** to dialkylideneoligospiranes **252** (Scheme 5-61) [334].

Thus, the heptaenyne **251c** can be cyclized to give the hexaspiro compound **252c** as a 3:1 mixture of only two out of 32 possible diastereomers in outstandingly good yield. This is one of the most impressive examples for selectivity in ring-forming reactions in view of the fact that the σ-alkenylpalladium complex formed from **251c**, has the choice between six electronically equivalent double bonds.



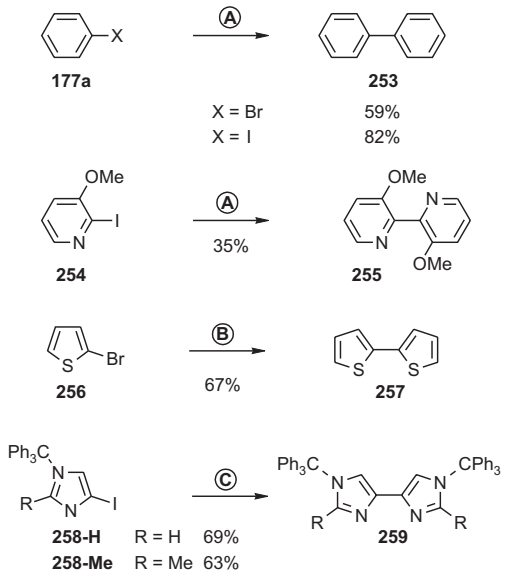
Scheme 5-60 Synthesis of natural products applying a cycloisomerization reaction as a key step [333].



Scheme 5-61 A palladium-driven zipper-type sequential reaction [334].

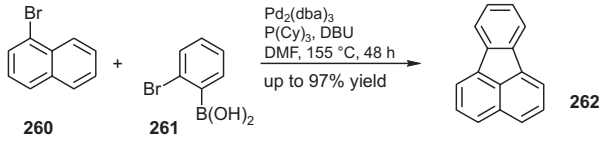
Although comparable with the Heck reaction in terms of the catalytic cocktail, the recently developed conversions of aryl bromides to arylamines (Hartwig-Buchwald reactions) proceed by a different mechanism (see Chapter 13).

Surprisingly, haloarenes such as iodobenzene (**177a**-I) or 2-bromothiophene (**256**) can undergo reductive dimerization under Heck conditions without adding a special reducing agent (Scheme 5-62). Generally, the biaryls and heterobiaryls are formed in good yields [335], and under appropriate conditions [335a–c] it is not necessary to add triphenylarsane as claimed in this context [335e]. The formation of biaryls as side-products in Heck reactions is frequently observed especially with iodoarenes when unreactive alkene components are employed [96, 101]. Another possible side reaction is the reduction of the aryl or alkenyl halide to the corresponding hydrocarbon [317b]. However, these byproducts usually were found only in cases of highly reactive catalyst cocktails and thus rarely caused a serious problem.



Scheme 5-62 Ⓐ: Reductive homocoupling of aryl halides under palladium catalysis. 1 mol % $Pd(OAc)_2$, K_2CO_3, nBu_4NBr, NMP, 150 °C, 48 h. Ⓑ: As in Ⓐ, but at 20 °C. Ⓒ: $[Pd(PPh_3)_4]$, Et_3N, DMF, 110 °C, 48 h [335].

Under palladium catalysis, *o*-bromobenzeneboronic acid (**261**) can be coupled with 1-bromonaphthalene (**260**) (Scheme 5-63) or other oligocyclic bromoarenes containing peri-positioned hydrogens to furnish indeno-annelated polycyclic aromatic hydrocarbons **262** in a single operation in moderate to very good yields [336].



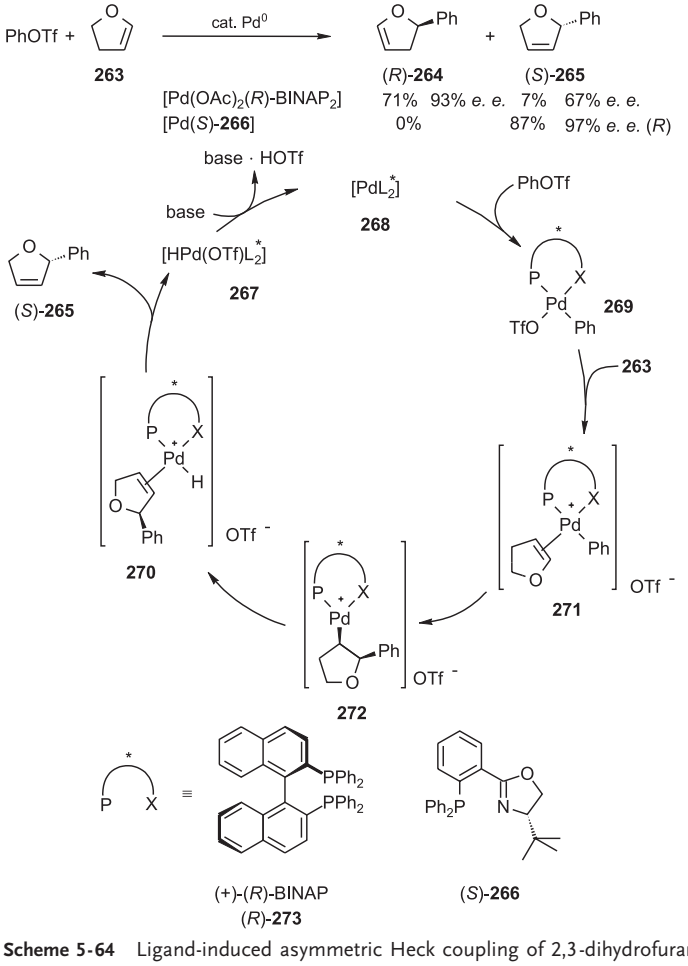
Scheme 5-63 A Heck-Suzuki domino arylation sequence leading to indeno-annelated polycyclic aromatic hydrocarbons [336].

5.5 Enantioselective Heck-Type Reactions

Asymmetric synthesis has become the most relevant route to enantiomerically pure compounds, and transition metal-induced reactions are increasingly important in the array of methods for the enantioselective construction of new asymmetric centers. Catalytic processes, in which chiral information is transferred from a small fraction of a chiral auxiliary in the catalyst to a large fraction of the prochiral substrate, are rapidly developing into extremely valuable methods. Among the established methods, however, are only a few for the catalytic enantioselective formation of carbon-carbon bonds. An ordinary Heck reaction – that is,

the coupling of an aryl or alkenyl derivative with an alkene – does not form a new center of chirality. With cyclic alkenes, however, the stereoselective *syn*-β-hydride elimination after the *syn*-addition of the organopalladium species to the double bond, leads to the formation of non-conjugated dienes [337]. With chiral ligands on the palladium catalyst, the new stereogenic center can be formed in an enantioselective way [338].

A model reaction is the asymmetric arylation of dihydrofuran **263** [339,340] (Scheme 5-64). Whereas coupling of **263** with iodoarenes gave only low enantiomeric excesses in the presence of the C_2-symmetric ligand (*R*)-2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl [(*R*)-BINAP, (*R*)-**273**)], its coupling with phenyl triflate, however, afforded (*R*)-2-phenyl-2,3-dihydrofuran [(*R*)-**264**] in up to 71 % yield with up to 93 % enantiomeric excess. In the reaction with iodobenzene, the BINAP ligand apparently reversibly dissociates from the intermediate phenylpalla-



Scheme 5-64 Ligand-induced asymmetric Heck coupling of 2,3-dihydrofuran [340–347].

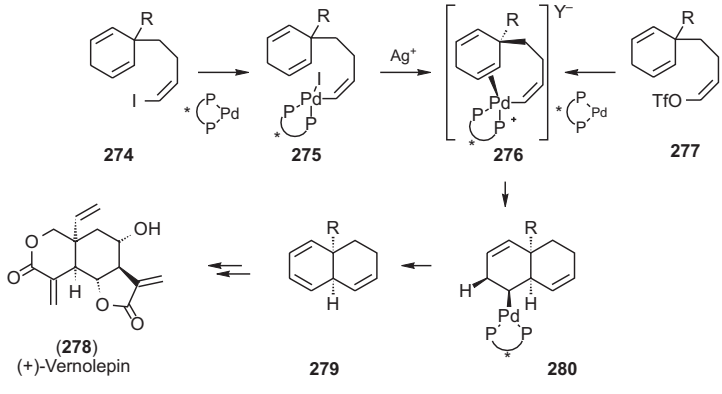
dium iodide complex to a certain extent. In contrast, when phenyl triflate is employed in the coupling, the labile triflate ligand dissociates more easily from the intermediate **269**, thus generating the cationic complex **271**. In this, the BINAP ligand is much more tightly bound, and asymmetric induction is possible during the addition step leading to **272**.

Quite interestingly, the minor product 2-phenyl-2,5-dihydrofuran (**265**) has the opposite configuration, i. e. (*S*)-**265**, compared to that of (*R*)-**264**. However, this compound is produced with a significantly lower enantiomeric excess. It is possible that this is caused by a kinetic resolution effect in the alkene complex **270**; the π-bound hydridopalladium moiety in complex **270** could add again to the double bond. An influence of the used base is also noteworthy, and the highest enantiomeric excess was achieved with 1,8-bis(bisdimethylamino)naphthalene ("proton sponge").

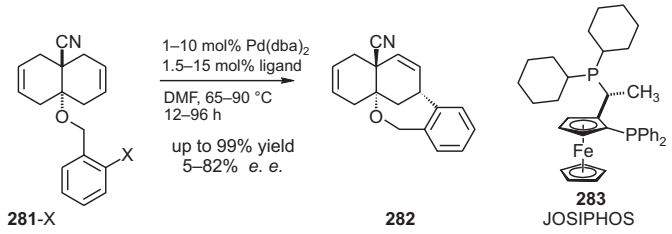
A different case arose with the use of the *tert*-butyldihydrooxazole **266** as a ligand on palladium [341]. In this case, a rapid dissociation of the complex **270** gives only **265** with an especially high enantiomeric excess.

The enormous potential of intramolecular Heck reactions has been demonstrated impressively in elegant syntheses of even the most complicated natural product skeletons. The intramolecular Heck reaction on the non-chiral iodoalkenes **274** and the corresponding alkenyl triflates **277** with their pairs of enantiotopic double bonds in the cyclohexa-1,4-diene moieties, applying catalysts with chiral ligands, gave tetrahydronaphthalenes **279**, or hydrindanes from precursors such as **274**, **277** or corresponding precursors with one less carbon in the tether [183f], with excellent enantioselectivities. Complementary to the asymmetrically induced intermolecular arylation with triflates (Scheme 5-64), reasonable asymmetric inductions in intramolecular reactions were also achieved with iodides upon the addition of silver salts to promote the formation of cationic intermediates such as **276** [45b,78,183] (Scheme 5-65).

Other asymmetric intramolecular Heck reactions using two enantiotopic double bonds gave similarly good results [157,342]. The desymmetrization of the 2-substi-



Scheme 5-65 Intramolecular asymmetric Heck reactions.

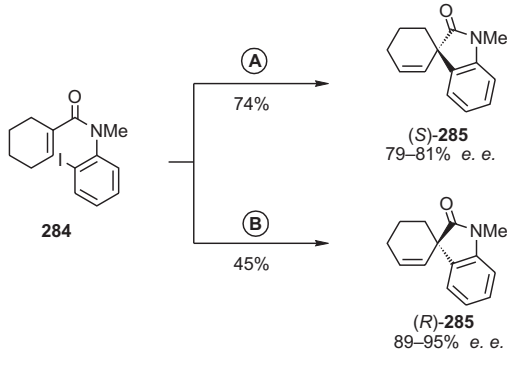


281-X **282** **283** JOSIPHOS

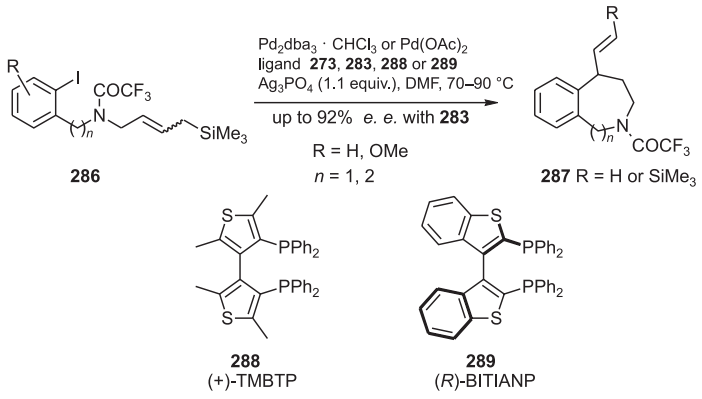
Scheme 5-66 Intramolecular differentiation of enantiotopic double bonds [342].

tuted benzyloxyhexahydronaphthalene derivative **281**-X gave the tetracycle **282** with good enantioselectivities [342] (Scheme 5-66). Thus, the Heck reaction with iodides **281**-I, bromide **281**-Br and triflate **281**-OTf under different conditions led to the formation of **282** with different results. The usual ligands for asymmetric Heck reactions, BINAP or the oxazoline **266** led to very low enantioselection or no conversion at all. Other ligands, e. g., PHANEPHOS, were either not active or produced products with a low stereoinduction. The use of the hydrogenation catalyst JOSIPHOS **283** gave remarkably high enantiomeric excesses (up to 83 % *e. e.*). In addition, the use of the **282**-Br gave a higher enantiomeric with decreased yield than the use of **281**-I. The addition of 3 equiv. of LiCl to **281**-I led to an almost racemic product. The change from a bromide to a triflate or nonaflate leaving group gave neither a significant change in yield nor in enantiomeric excess. The use of a silver salt, which is known to have positive effects on conversion rates and stereoinduction, had no significant influence on the product ratio but made work-up more difficult. Other bases than Et_3N had no beneficial effects in this reaction.

The asymmetric induction in the formation of **282** stems from a differentiation of two enantiotopic double bonds in the same molecule. The intramolecular discrimination between the two enantiofaces of the same double bond (*cf.* Scheme 5-64 for the intermolecular version) has also been achieved, for example, with the asymmetric construction of quaternary carbon centers in the preparation of spirooxindoles **285** from **284** (Scheme 5-67). It is particularly noteworthy that either



Scheme 5-67 Enantioselective synthesis of spiroindoles (*S*)- and (*R*)-**285** by intramolecular Heck coupling. Ⓐ: 5 % $[Pd_2(dba)_3]$, 10 % (*R*)-BINAP, 2 equiv. Ag_2CO_3, DMA, 60–80 °C. Ⓑ: 10 % $[Pd_2(dba)_3]$, 20 % (*R*)-BINAP, 5 equiv. 1,2,2,6,6-pentamethylpiperidine, DMA, 80–100 °C [184].



Scheme 5-68 Intramolecular asymmetric Heck reactions [345].

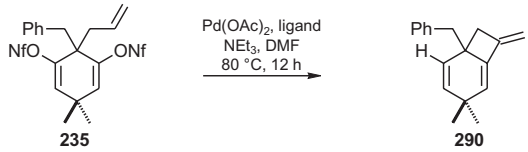
of the two product enantiomers could be obtained selectively by careful adaptation of the reaction conditions, yet with exactly the same enantiomer of the chiral phosphane ligand [184].

This methodology has been utilized by Overman et al. in their elegant total syntheses of various natural products, such as quadrigemine C [343], psycholeine [343] and other molecules of this type (see Table 5-9).

It has been shown that one of the main disadvantages of the Heck reaction, namely the low selectivity in the elimination of the L_nPd-H species to form the double bond in the last step of the catalytic cycle, can be overcome by using allylsilanes as terminating alkenes. This allowed the selective formation of tertiary stereogenic centers starting from acyclic alkenes for the first time (see Scheme 5-6). However, the use of this procedure for the synthesis of chiral heterocyclic compounds such as benzazepines and tetrahydroisoquinolines **286** with BINAP (**273**) as a ligand was rather disappointing in view to its low enantioselectivity [110a]. By contrast, employing the novel chiral ligands **288** and **289** [344], Tietze et al. were able to obtain the heterocycles **287** with up to 92% *e.e.* (Scheme 5-68) [345].

Asymmetrically induced Heck reactions can also be performed with substrates containing two enantiotopic leaving groups. Starting from dimedone, novel cyclohexa-1,4-diene-1,5-diol bis(nonafluorobutanesulfonates) such as **235** have been prepared and cyclized under palladium catalysis to cleanly give bicyclo[4.2.0]octadienes **290** and bicyclo[4.2.0]octenones, respectively, by an unprecedented 4-*exo-trig* process (Scheme 5-69, *cf.* Scheme 5-58). In the presence of a chiral phosphane ligand, the products could be obtained with modest enantiomeric excesses (up to 52% *e.e.*) [213].

These and other enantioselective Heck reactions [346] were performed with a variety of chiral ligands (Table 5-8 and Figure 5-2). Particularly high enantioselectivities could so far be achieved with BINAP (accessible in both enantiomeric forms), oxazoline derivatives (preferably the bulky **266**), PHANEPHOS **304** or TMBTP as ligand. The latter is easily obtained as the (*S*)-enantiomer.



235 290

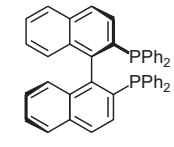
Ligand	Yield (%)	*e. e.* (%)
(+)-BINAP (**273**)	57	27
PHANEPHOS (**304**)	23	37
*t*Bu-Oxazoline (**266**)	25	52

Scheme 5-69 A 4-*exo-trig* cyclization with intramolecular differentiation of enantiotopic leaving groups [213].

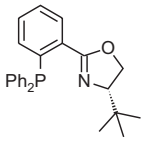
Table 5-8 Some chiral ligands used in asymmetric Heck reactions [347] (see Figure 5-2).

Ligand	*Ref.*	*Example (Type[a], e. e., yield)*
BINAP (**273**)	[348a]	[159] (A, 11, 70), [45a] (B, 95, 84), [78] (B, 95, 78), [349] (B, 95, 62)
Tol-BINAP (Tol-**273**)		[343] (B, 90, 62)
*t*Bu-Oxazoline (**266**)	[347]	[347] (C, 153, 145)
JOSIPHOS“,4> (**283**)		[342] (B, 83, 65)
(+)-TMBTP (**288**)		[345] (B, 92, 73)
(*R*)-BITIANP (**289**)		[345] (B, 91, 67), [344] (C, 90, 85)
Norphos (**291**)	[350]	[159] (A, 43, 94)
BCPM (**292b**)	[347]	[78c] (B, 30, 17)
BPPM (**292a**)	[347]	[159] (A, 63, 23), [79c] (B, 58, 61)
BPPFA (**293**)	[347]	[79c] (B, 26, 68), [183b] (B, 45, 79)
BPPFOAc (**294**)	[347]	[183b] (B, 52, 62)
BPPFOH (**295**)	[351]	[183] (B, 94, 86)
MOD-DIOP (**296b**)	[347]	[159] (A, 7, 54), [183b] (B, 43, 32)
(*R,R*)-DIOP (**296a**)	[348b]	[78c] (B, 5, 17), [79c] (B, 11, 63)
Ms-Valphos (**297**)	[159]	[159] (A, 74, 81)
Ms-Phenophos (**298**)	[159]	[159] (A, 60, 89)
Ms-*t*-Leuphos (**299**)	[159]	[159] (A, 62, 75)
PMO-Ms-Valphos (**300**)	[159]	[159] (A, 63, 85)
PCl-Ms-Valphos (**301**)	[159]	[159] (A, 68, 94)
Bs-Valphos (**302**)	[159]	[159] (A, 61, 66)
NMe-Ms-Valphos (**303**)	[159]	[159] (A, 5, 62)
PHANEPHOS (**304**)		See Scheme 5-69
Pyridine **305**		[352] (C, 97, 99)
Oxazolineferrocenes **306**		[353] (C, 98, 99), [354] (C, 97, 76)
Phosphinamide **307**		[157] (B, 96, 70–75)
(*R*)-MeO–BIPHEP (**308**)		[345] (B, 28, 56)
(+)-BIPI ligands (**309**)		[355] (B, 87, 50)

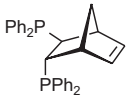
[a] A: Reductive, intermolecular; B: intramolecular; C: intermolecular.



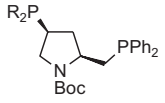
(*R*)-**273**
(+)-(*R*)-BINAP



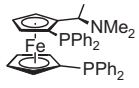
266



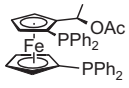
291
(+)-Norphos



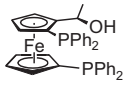
(–)-(*S*,*S*)-BPPM (**292a**) (R = Ph)
(–)-(*S*,*S*)-BCPM (**292b**) (R = *c*-Hex)



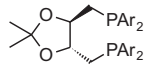
293
(–)-(*R*,*S*)-BPPFA



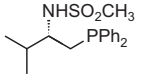
294
(–)-(*R*,*S*)-BPPFOAc



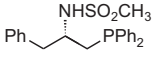
295
(–)-(*R*,*S*)-BPPFOH



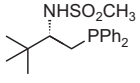
(*R*,*R*)-DIOP (**296a**) (Ar = Ph)
(*R*,*R*)-MOD-DIOP (**296b**)
(Ar = 3,5-Me_2-4-$MeOC_6H_2$)



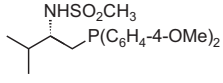
297
Ms-Valphos



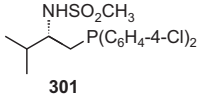
298
Ms-Phenophos



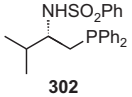
299
Ms-*t*-Leuphos



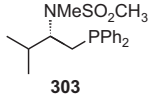
300
PMO-Ms-Valphos



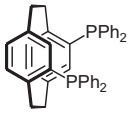
301
PCl-Ms-Valphos



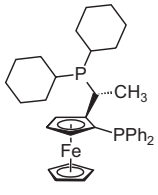
302
Bs-Valphos



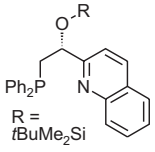
303
NMe-Ms-Valphos



304
PHANEPHOS



283
JOSIPHOS



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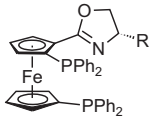
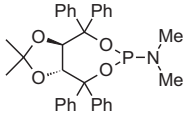


(S,S_p)-**306a** R = *i*Pr
(S,S_p)-**306b** R = Bn
(S,S_p)-**306c** R = *t*Bu



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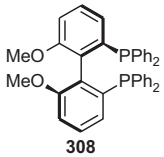
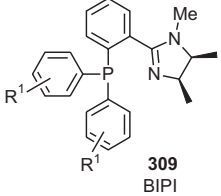


308
(*R*)-MeO-BIPHEP



309
BIPI

Figure 5-2 Some chiral ligands used in asymmetric Heck reactions (see Table 5-8).

5.6
Syntheses of Heterocycles, Natural Products and other Biologically Active Compounds Applying Heck Reactions

Since most biologically active compounds – both natural and non-natural products – contain heterocyclic substructures, intramolecular C-C bond-forming processes including Heck reactions have been applied to accomplish heterocyclization [356, 357].

Nitrogen heterocycles such as β- and γ-carbolines [358,359], isoquinolines [360, 361], indoles [245], oxindoles [80], pyrrolidines [273], and indolo[2,1-b]isoquinolin-7(5H)-ones [362], indolizidinones [363], quinolizidinones [363] and benzoazepinones [363] have been prepared using Heck reactions as the heterocycle-forming step (Figure 5-3; see also Scheme 5-37).

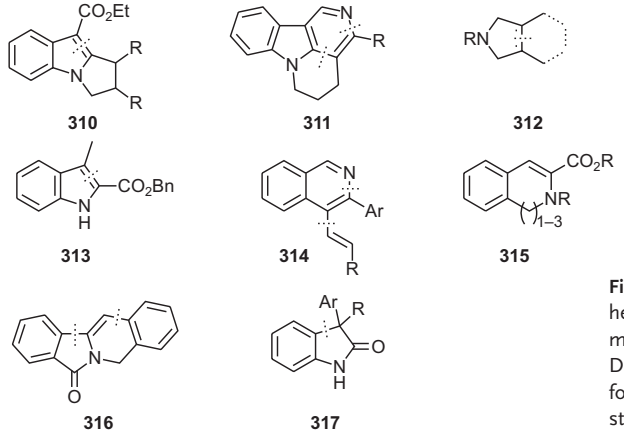
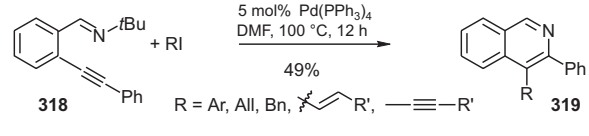


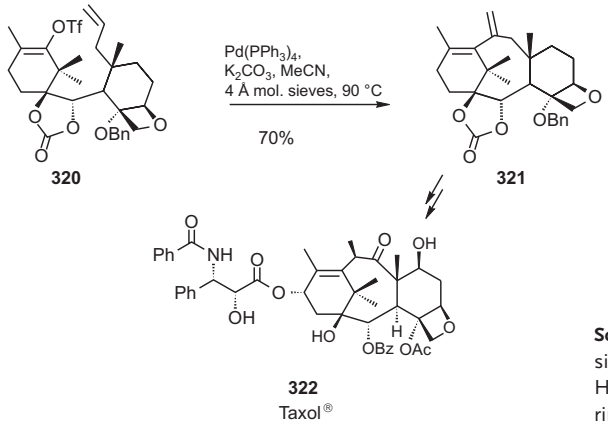
Figure 5-3 Examples for heterocycles formed by intramolecular Heck reactions. Dashed lines indicate bonds formed in the cross-coupling step.

The palladium-catalyzed cross-coupling of readily available *N-tert*-butyl-2-(1-alkynyl)benzaldimines **318** with aryl, allyl, benzyl, alkenyl, as well as alkynyl halides, provides a valuable new route to 3,4-disubstituted isoquinolines with aryl, allyl, benzyl, 1′-alkenyl, and 1′-alkynyl substituents, respectively, in the 4-position (Scheme 5-70). This transformation involves a carbopalladation of the triple bond in **318** with concomitant attack by the imine moiety and subsequent loss of the *tert*-butyl group as isobutene [361].

Applications of the Heck reaction in natural product syntheses were rather limited during the first 20 years, despite the great potential of this reaction for the arylation and alkenylation of alkenes on a wide scope. However, during the past 15 years, efficient syntheses of natural products and non-natural biologically active



Scheme 5-70 Synthesis of isoquinolines by an inter-intramolecular Heck-type coupling cascade [361].



Scheme 5-71 A total synthesis of taxol employing the Heck reaction as a key step for ring closure [257].

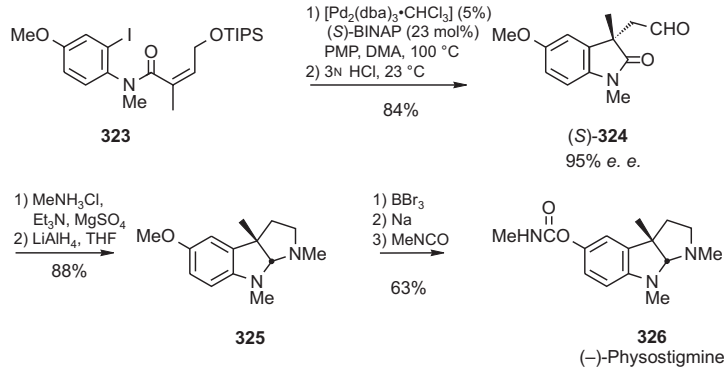
compounds employing the Heck reaction as one of the key steps were accomplished in large numbers [338c].

One of the most remarkable applications is the one reported for the construction of the skeleton of taxol (**322**) [364] by an 8-*exo-trig* cyclization of the enol triflate **320** [257a,b] (Scheme 5-71). The ring closure of the eight-membered ring to complete the rigid and compact tricyclic system is not trivial [125]. The application of a metal such as palladium probably brings in a certain template effect by precoordination of the freely rotating allyl group in **320** and thereby an association with the sterically congested trimethylcyclohexene moiety in the molecule.

Since the Heck reaction tolerates a variety of functionalities, extensive use of protecting groups is not necessary, and thus many highly functionalized target molecules can be assembled in just a few highly efficient steps. The frequently employed elevated reaction temperatures which may be detrimental to the yield, can be avoided, if necessary, by an appropriate choice of special additives and/or leaving groups (*cf.* Sections 5.2.4. and 5.2.5.)

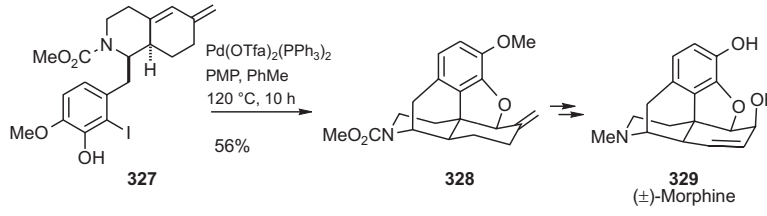
Overman et al. have demonstrated the feasibility of a chiral ligand to achieve asymmetric induction in an elegant enantioselective synthesis of (+)- and (−)-physostigmine (**326**) (Scheme 5-72) [45a]. An intramolecular Heck reaction of the aryl iodide **323** proceeds smoothly, even though a trisubstituted double bond is being attached by the aryl moiety. This methodology thus allows one to construct quaternary carbon centers in a stereoselective manner [80,365].

A new total synthesis of morphine **329** employing a palladium-catalyzed coupling as a key step started from the hydroisoquinoline derivative **327** to give dihydrocodeinone **328** (Scheme 5-73). This transformation constitutes a cascade of an intramolecular Heck carbopalladation and subsequent heterocyclization. The initially formed arylpalladium iodide species attacks the bridgehead position of the diene functionality in **327** to form a π-allylpalladium complex which is trapped by the internal nucleophilic phenol moiety (*cf.* Scheme 5-28).



Scheme 5-72 A total synthesis of physostigmine **326** employing a Heck reaction with ligand-induced π-enantiofacial differentiation [45a].

Since the starting diene **327** can be prepared in both enantiomeric forms employing an asymmetric reduction of a ketone, this sequence allows one to prepare both the natural morphine and its unnatural enantiomer.



Scheme 5-73 A total synthesis of morphine **329** employing a Heck reaction [56].

Table 5-9 Syntheses of important natural products and biologically active compounds applying the Heck reaction.

Natural product	*Reaction type*	*Ref.*
Variety of natural and unnatural amino acids	Different approaches	*Cf.* [366]
Aflatoxin B1 **347**	Intramol. reductive HR of an aryl bromide	[60]
Anthramycin methyl ester	Intermol. HR of an alkenyl triflate	[59]
(±)-Aphidicolin	Intramol. HR of an alkenyl bromide	[367]
Argemonine	Intramol. HR of an aryl halide	[368]
Artepillin	Intermol. HR of an aryl iodide	[369]
Asperazine	Intramol. HR of an aryl iodide	[370]
(±)-Aurantioclavine	Intermol. HR of an aryl iodide	[371]
2-Azachrysenes	Intermol. HR of an aryl iodide	[372]
Aziridinomitosene model	Intramol. HR of an aryl bromide	[245]

Table 5-9 (continued)

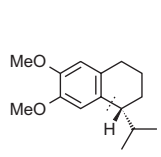
Natural product	*Reaction type*	*Ref.*
Baclofen and homobaclofen	Intermol. HR of an aryldiazonium salt	[373]
Balanol **351** analogue	Intramol. HR of an aryl iodide	[374]
2-Benzazepine analogue	Intermol. HR of an aryl bromide	[375]
Bisabolone sesquiterpenes	Intramol. HR of an aryl iodide	[340a]
(±)-7-epi-*β*-Bulnesene	Intramol. HR of an alkenyl iodide	[254]
(−)-Callystatin **356**	Intermol. HR of an alkenyl iodide	[182]
(*S*)-Camptothecin **337**	Intramol. HR of a hetaryl halide	[376,377]
(−)-$\Delta^{9(12)}$-Capnellene **109**	Asymm. intramol. HR with subsequent π-allylpalladium trapping	[79a,168a]
Carbomycin B model	Intramol. HR of an alkenyl iodide	[261]
(±)-CC-1065 (CPI) **338**	Intermol. HR of an aryl iodide	[378]
(−)-Cephalotaxin	Intermol. HR of an alkenyl iodide or bromide	[379]
Chanoclavine	Intramol. HR of an aryl bromide	[380]
Chelerythrine	Intramol. Heck-type biaryl synthesis	[381]
(±)-Clavicipitic methyl esters	Intermol. HR of an aryl bromide	[382]
(−)-Codonopsinine	Intermol. HR of an aryldiazonium salt	[209]
(+)-δ-Coniceine	Asymm. intramol. HR of an alkenyl iodide	[183a,b]
CP-122,288	Intermol. HR of an aryl bromide	[383]
CP-225,917 and CP-263,114	Intramol. HR of an iodofuran	[258]
(*R,R*)-Crinan **339**	Intramol. HR of an aryl halide	[250b]
Cyathin diterpenoid model	Intramol. HR of an alkenyl triflate	[384]
(±)-Cytisine	Intramol. HR of an alkenyl triflate or phosphate	[215]
Deethylhomocatharanthine	Asymm. intramol. HR with subsequent π-allylpalladium trapping	[259b]
(±)-Dehydrolennoxamine	Intramol. HR of an aryl iodide	[385]
(±)-Dehydrotubifoline **340**	Intramol. HR of an alkenyl halide	[386]
(+)-7-Demethyl-2-methoxy-calamene **330**	Asymm. intramol. HR of an alkenyl iodide	[110b,387]
Diazonamide model	Intramol. HR of an aryl iodide	[260]
(+)-1,2-Diepilentiginosine and (+)-lentiginosine **333**	Asymm. intramol. HR of an alkenyl iodide	[388]
(+)-1α,25-Dihydroxyvitamin D_3 **72**)	Intramol. HR of an alkenyl halide or triflate	[272,389–391]
(±)-Duocarmycin SA **341**	Intramol. HR of a hetaryl bromide	[392]
Dynemycin A intermediate	Intramol. HR of an aryl bromide	[393]
Ecteinascidin 743	Intramol. HR. of an aryl iodide	[394]
(±)-Epibatidine and (±)-homoepibatidine	Reductive intermol. HR of a hetaryl iodide	[395]
(±)-6a-Epipretazettine and (±)-tazettine **346**	Intermol. HR of an aryl iodide	[396]

Table 5-9 (continued)

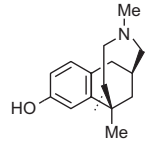
Natural product	*Reaction type*	*Ref.*
(−)-Eptazocine **331**	Asymm. intermol. HR of an aryl triflate	[125]
Ergot alkaloids (seco-C/D ring analogues)	Intramol. HR of hetaryl halides	[397]
(±)-FR 900482 **342**	Intramol. HR of an aryl iodide	[54]
Furaquinocin A, B, E **358a–c**	Intramol. reductive HR of an aryl iodide	[398]
G-2N, G-2A	Intermol. HR of an aryl bromide	[43]
(−)-Galanthamine **350**	Intermol. HR of an aryl bromide	[77]
(±)-Gelsemine	Intramol. HR of an aryl halide	[127c]
(+)-Gelsedine	Intramol. HR of an aryl bromide	[399]
(−)- Gephyrotoxin 209D **332**	Asymm. intramol. HR of an alkenyl iodide	[388]
Halenaquinone and halenaquinol **93**	Asymm. intermol. HR-Suzuki cascade	[277]
6-epi-(–)-Hamigeran B **352**	Intramol. HR of an aryl triflates	[400]
Herbertenediol **349** and mastigophorenes A	Intermol. HR of an aryliodide	[126]
Hodgkinsine **354**	Asymm. intramol. HR	[401]
Idiospermuline	Intramol. HR	[402]
Iejimalides (subunit)	Intermol. HR of an alkenyl bromide	[114]
Indolizidine derivatives: (+)-5-epiindolizidine 167B and indolizidine 223AB	Asymm. intramol. HR of an alkenyl iodide	[183,403]
Infractine	Intermol. HR of a hetaryl triflate	[404]
β-Ionone	Intermol. HR of an alkenyl triflate	[405]
Irisquinone and maesanin	Intermol. HR of an aryl bromide	[406a]
Lamellarin-G-trimethyl ether	Intramol. HR of an aryl bromide	[405b]
Laposiodiplodin	Intermol. HR of an aryl triflate	[407]
(−)-Laurequinone	Intramol. HR of an aryl iodide	[408]
LTD_4 Antagonists L-699,392 and L-708,738	Intermol. HR of aryl iodides	[409]
Lycoramine	Intramol. HR of an aryl iodide	[179]
(+)-γ-Lycorane and 2-epimer	Intermol. HR of an aryl bromide	[410,411]
(+)-Lycoricidine **343**	Intramol. HR of an aryl halide	[171,412–414]
(±)-Magallasine	Intramol. HR of an aryl bromide	[185]
(±)-Maritidine **357**	Intramol. HR of an aryl iodide	[415]
(±)-Maxonine	Intramol. HR of an aryl bromide	[416]
7-Methoxymitosene	Intramol. HR of an aryl bromide	[417]
(−)- and (+)-Morphine **329** and dihydrocodeinone	Intramol. HR of an aryl iodide with subsequent π-allylpalladium trapping	[56]
(±)-Munduserone	Intramol. HR of an aryl iodide	[418]
Nabumetone	Intermol. HR of an aryl bromide	[419]

Table 5-9 (continued)

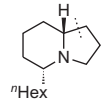
Natural product	*Reaction type*	*Ref.*
Neocarcinostatin chromophore model	Intramol. HR of an alkenyl bromide	[278]
Ningalin C	Intermol. HR of an aryl bromide	[420]
Nor- and homo-DDATHF	Intermol. HR of an aryl iodide	[421]
(−)-Oppositol **334** and (−)-prepinnaterpene **335**	Asymm. intramol. HR of an alkenyl triflate	[183]
(±)-Oxerine	Intramol. HR of an hetaryl bromide	[248]
Pellitorine	Intermol. HR of an alkenyl iodide	[88]
Perophoramidine	Intramol. HR of an aryl iodide	[422]
(+)- and (−)-Physostigmine **326**	Asymm. intramol. HR of an alkenyl iodide	[45]
Phthoxazolin A	Intermol. HR of an alkenyl iodide	[423]
(+)-Phorbol	Intramol. HR of an alkenyl iodide	[424]
Plicatin B	Intermol. HR of an aryl bromide	[425]
Podophyllotoxin (derivative)	Intermol. HR of an aryl bromide	[426]
Prostaglandin analogue (Beraprost intermediate)	Intermol. HR of an benzyl halide	[197f]
Psycholeine	Intramol. asymm. HR of an aryl triflate	[343]
Quadrigemine C	Intramol. asymm. HR of an aryl triflate	[343]
(+)-Ratjadone	Intermol. HR of an alkenyl iodide	[182]
Saponaceolide	Intramol. HR of an alkenyl bromide	[427]
Scopadulcic acid A and B **344**	Intramol. HR of an aryl iodide	[428]
Steroid and D-homosteroid backbone	Intermol. HR of an alkenyl bromide	[429] (*Cf.* [46])
Steroid model	Intermol. HR of an alkenyl triflate	[430]
Streptonigrin quinoline-5,8-quinone moiety	Intermol. HR of an aryl iodide	[431]
Strychnine **345**	Intermol. HR of an alkenyl iodide	[432b,433]
2-Styrylbenzoic acid	Intermol. HR of an aryl iodide	[372]
Suberenol	Intermol. HR of an aryl bromide	[434]
(±)-Tabersonine and (±)-Δ^{18}-dehydrotabersonine **359**	Intramol. reductive HR	[435]
(±)-Tangutorine **348**	Intermol. HR of an aryl bromide	[436]
Taxol **322**	Intramol. HR of an aryl iodide/ triflate	[257a,b]
(±)-*cis*-Trikentrin A	Intermol. HR of an aryl bromide	[117]
(−)-Tubofoline	Intramol. HR of an aryl bromide	[433]
(+)-Vernolepin **278**	Asymm. intramol. HR of a alkenyl triflate	[78]
(±)-Wortmanin	Intramol. HR of an aryl triflate	[437]
(+)-Xestoquinone **336**	(Asymm.) Intramol. HR of an aryl triflate (bromide)	[438]
(+)-Zearalenone **360**	Intermol. HR of an aryl triflate	[407]
Zoanthenol	Intramol. HR of an aryl triflate	[439]



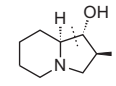
330 [110b,387]
7-Demethyl-2-methoxy-calamene



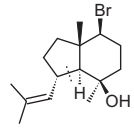
331 [125]
(–)-Eptazocine



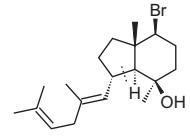
332 [388]
(–)-Gephyrotoxin 209D



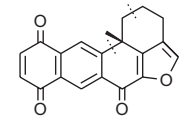
333 [388]
(+)-Lentiginosine



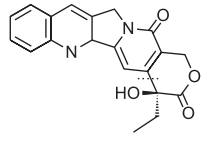
334 [183]
(–)-Oppositol



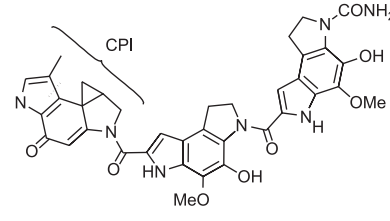
335 [183]
(–)-Prepinnaterpene



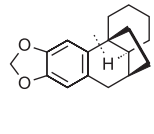
336 [438]
(+)-Xestoquinone



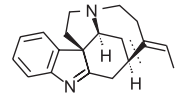
337 [376,377]
(*S*)-(+)-Camptothecin



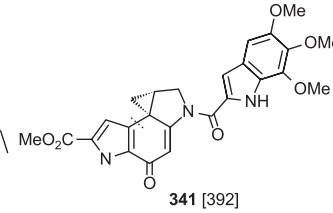
338 [378]
(+)-CC-1065 (CPI)



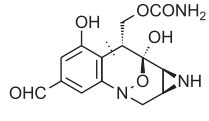
339 [250b]
(*R*,*R*)-Crinan



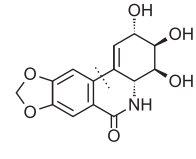
340 [386]
(±)-Dehydrotubifoline



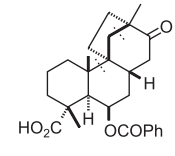
341 [392]
Duocarmycin SA



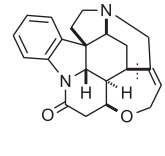
342 [54]
FR 900482



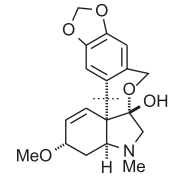
343 [171,412–414]
(+)-Lycoricidine



344 [428]
(±)-Scopadulcic acid B



345 [432b,433]
(±)-Strychnine



346 [396]
(±)-Tazettine

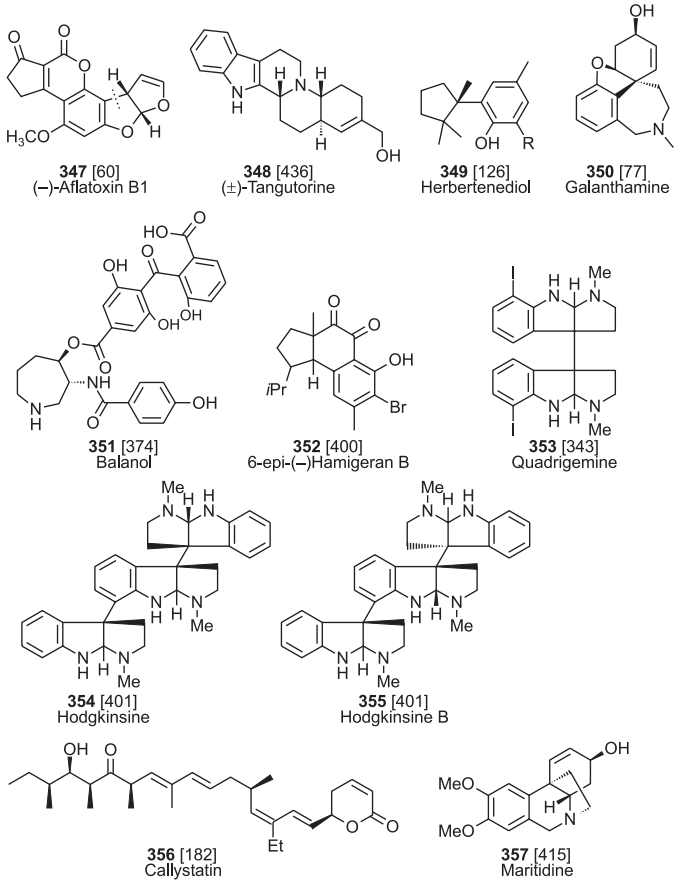
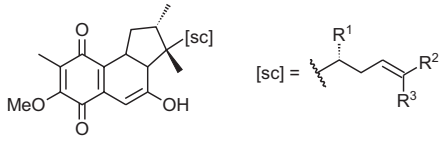


Figure 5-4 Some biologically active compounds prepared applying Heck reactions with asymmetric induction. (The dashed lines indicate bonds formed by palladium-catalyzed coupling.)

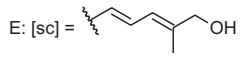
5.7
Carbopalladation Reactions in Solid-Phase Syntheses

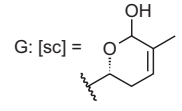
Starting with the preparation of oligopeptides and oligosaccharides, initiated by Merrifield in 1963 [440], solid-phase organic synthesis (SPOS) has more recently become a cornerstone in the combinatorial generation of libraries of "drug-like" small organic molecules [441]. Hence, during the past decade several research groups in academia and industry have made extreme efforts to adopt transformations, which were originally developed for liquid-phase operations, to be carried out on a solid support. As a result of this, multiple parallel synthesis in a combinatorial manner has emerged as an indispensable routine to speed up the discovery of biologically active compounds for medicinal and agrochemical applications. In this context, palladium-catalyzed transformations are among the most versatile tools

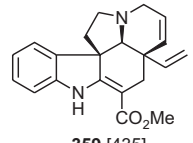


358a,b,c [398] Furaquinocin A, B, E

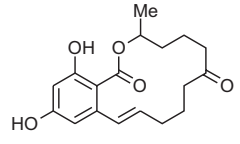
Furaquinocin	R^1	R^2	R^3
A	OH	Me	CH_2OH
B	OH	CH_2OH	Me
C	H	Me	Me
D	OH	Me	Me
F	H	CH_2OH	Me
H	OH	CH_2OH	CO_2OH







359 [435]
(±)-Δ^{18}-Dehydrotabersonine



360 [407]
(*S*)-Zearalenone

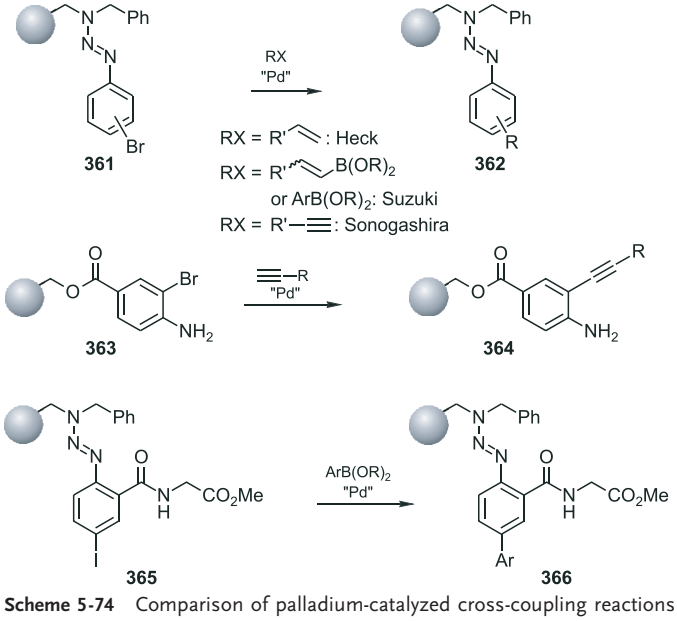
Figure 5-5 Some biologically active compounds prepared applying Heck reactions.

due to their tolerance of a variety of functional groups and their potential applicability to build up complex structures in a minimum number of operational steps. The advantages of solid-phase transformations such as the avoidance of tedious work-up procedures are particularly valuable for palladium-catalyzed homogeneous reactions, because the soluble palladium catalyst can be easily removed by washing processes. A quasi high-dilution effect, high yields by employing excess of reagent, amenability to automatization and the non-interference of various functionalities in the building blocks on solid supports are additional benefits of solid-phase chemistry. The Heck reaction is one of the most efficient transformations for C-C bond connections on the solid phase. Over the past few years, this reaction has become one of the most powerful tools to bring about complex structural changes, particularly when conducted intramolecularly. Due to the mild conditions employed and the tolerance of many functional groups, the Heck reaction has been successfully adapted on a broad scope to organic synthesis on the solid phase [442].

Heck reactions on solid supports have been extensively applied due to the easy accessibility of starting materials such as polymer-bound haloalkenes or haloarenes and alkenes. The most frequently used reaction conditions are either the standard Heck conditions [$Pd(OAc)_2$, PPh_3 or $P(o\text{Tol})_3$, DMF, 80 to 100 °C, 2 to 24 h] [3] or the protocol developed by Jeffery [$Pd(OAc)_2$, PPh_3, Bu_4NCl, K_2CO_3, DMF, 20 to 80 °C] [155]. The yields obtained under Jeffery conditions were frequently enhanced

by the addition of 10% of water to the reaction mixture. In some cases, $Pd_2(dba)_3 \cdot CHCl_3$ was found to be far more effective than $Pd(OAc)_2$ [443]. The Heck reaction was performed on immobilized aryl halides, mostly iodides, or aryliodonium salts with soluble alkenes [102,186,187,444–451] or on immobilized alkenes with soluble aryl halides [187,452–457]. When performed on the same type of resin and with the same catalyst system, the immobilization of the aryl iodide appears to be more beneficial than that of the alkene [187].

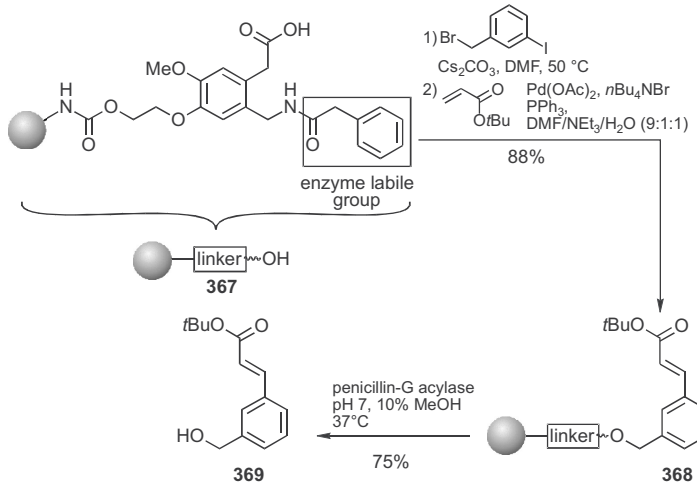
Although all types of triazene-linked haloarenes underwent Heck, Suzuki and Sonogashira reactions without any problems, the Suzuki reactions failed with *ortho*-halo-substituted anilines [458] (Scheme 5-74).



Scheme 5-74 Comparison of palladium-catalyzed cross-coupling reactions with polymer-bound aryl halides, attached on different linkers [458].

An enzyme-labile, so-called safety catch linker **367** was used successfully in various palladium-catalyzed cross-coupling reactions [459]. The linker **367**, which releases a hydroxy or an amino functionality upon enzymatic cleavage of its phenylacetamide moiety and subsequent rapid lactam formation, was attached to a soluble POE 6000 polymer, and its free phenyl acetic acid moiety was transformed to a *m*-iodobenzyl ester. The thus immobilized *m*-iodobenzyl alcohol was Heck-coupled with *tert*-butyl acrylate, and the coupling product **369** was cleaved off the solid support with penicillin G acylase under very mild conditions (pH 7, 37 °C) (Scheme 5-75).

The main advantage of carrying out intramolecular Heck reactions on a solid support is the virtual high dilution of the starting material, leading to a significant increase of the yield. The first use of this principle was reported in 1995 for the



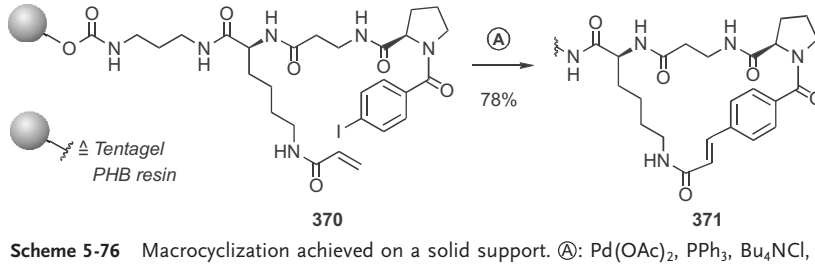
Scheme 5-75 Heck reaction of an iodoarene anchored on an enzyme-labile safety catch linker [459].

synthesis of 20- to 24-membered macrocyclic ring systems **371** (Scheme 5-76) [189].

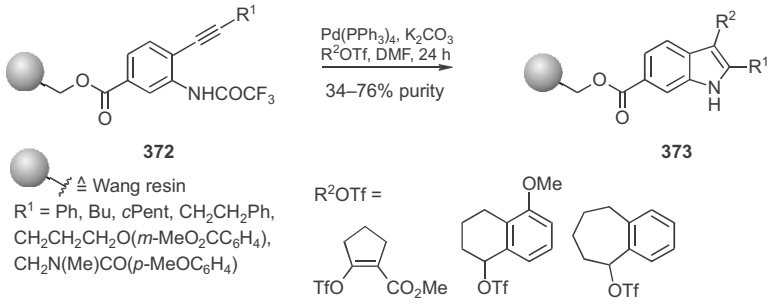
Similarly, a 20-membered ring of a tetrapeptide derivative containing a 3-substituted cinnamic acid template was closed on a solid support [460]. This methodology was also applied in the synthesis of a small library (15 examples) of cyclic RGD mimics having a diverse array of amino acids, with a variety of ring sizes [461].

Besides the preparation of macrocycles, cyclizations to give heteroatom-containing five-, six- and seven-membered rings have been investigated [188, 462–466]. Thus, the construction of indoles, benzofurans, dihydroisoquinolines and benzazepines has been reported. Starting from aryl iodides with appropriate alkenyl or, under reductive conditions, alkynyl ethers, smooth cyclizations occur under standard conditions.

Intermolecular carbopalladation of a triple bond as in **372** by an in-situ formed organopalladium triflate and subsequent intramolecular nucleophilic trapping



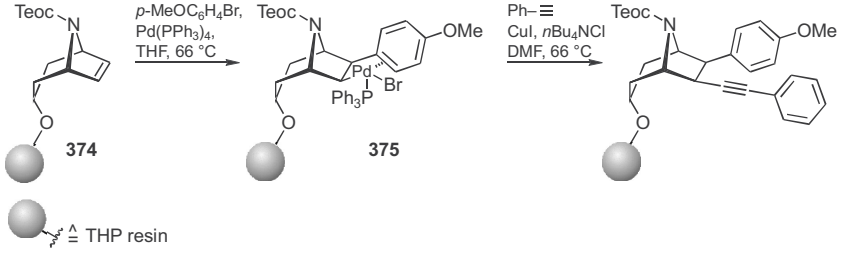
Scheme 5-76 Macrocyclization achieved on a solid support. Ⓐ: $Pd(OAc)_2$, PPh_3, Bu_4NCl, DMF/Et_3N/H_2O (9:1:1), r.t., 15 h [189].



Scheme 5-77 Intermolecular carbometallation and subsequent cyclization of *o*-alkynylaniline derivatives [467].

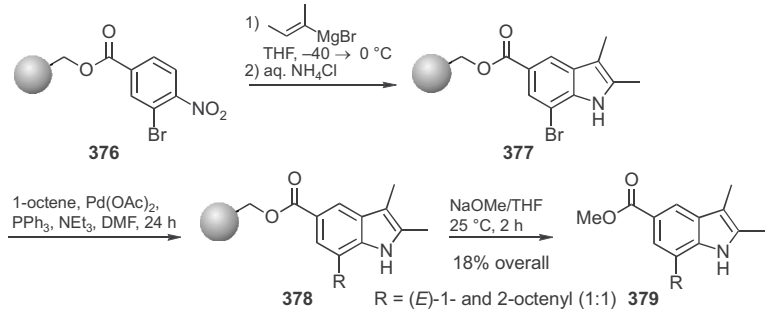
gives rise to indoles **373** (Scheme 5-77) [467]. The versatility of this approach derives from the fact that the triflate may be varied in a wide range.

An interesting sequential reaction, consisting of an intermolecular alkene carbometallation and subsequent intermolecular alkyne cross-coupling, has been reported (Scheme 5-78) [468]. Starting from an immobilized tropane framework **374**, stoichiometric carbopalladation yields a stable organopalladium intermediate **375** which, in the presence of copper(I) iodide, undergoes coupling with an added terminal acetylene.



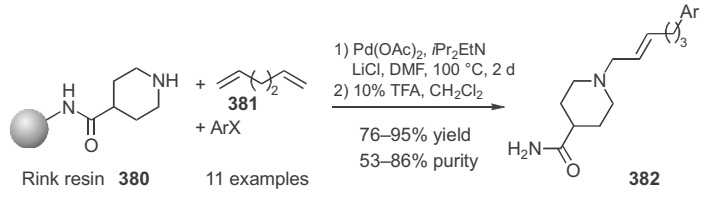
Scheme 5-78 Carbometallation on the tropane framework [468].

In order to demonstrate an application of halo-substituted indoles formed by reaction of a nitroarene with a Grignard reagent (the so-called Bartoli reaction) on solid supports, a subsequent Heck reaction was performed [469]. First, the resin-bound *o*-bromonitrobenzene **376** was converted to the resin-bound bromoindole **377** with 2-butenyl-2-magnesium bromide. Subsequent reaction of **377** with 1-octene under optimized Heck conditions ($Pd(OAc)_2$, PPh_3, NEt_3, DMF, 24 h, 105 °C) provided the resin-bound coupling products **378** which, upon cleavage under basic conditions [470] furnished the alkenylated indoles **379** as a mixture of two regioisomers ((*E*)-1-octenyl and 2-octenyl) [442] in a 1:1 ratio in 18 % overall yield with a purity of 96 % (Scheme 5-79).



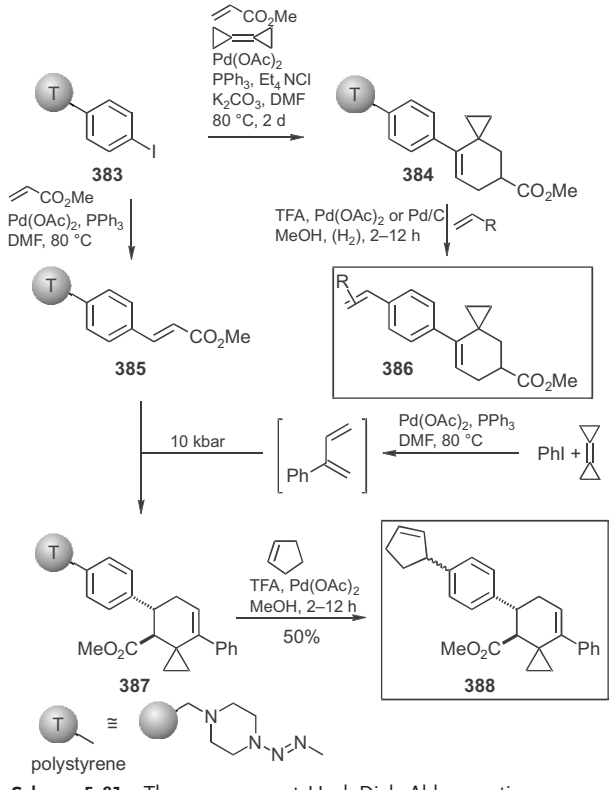
Scheme 5-79 Bartoli and subsequent Heck reaction [468].

Multi-component reactions (MCR) are particularly feasible for combinatorial synthesis. The advantage of conducting an MCR on a solid support lies in the ease of removal of non-polymer-bound reagents and impurities. A three-component reaction yielding highly diverse products using an aryl halide, a non-conjugated diene **381**, and an appropriate nucleophile (mostly an amine), has been carried out using immobilized amines on a solid phase **380** (Scheme 5-80) [455]. The advantage of this procedure in comparison with the use of immobilized aryl halides is that any possible byproducts formed from aryl halides, such as simple Heck-coupling products, remain in solution and can be removed by washing processes. The yields of this three-component reaction are quite good, and the purities of the obtained products **382** are moderate to good. The diversity in using different starting materials (11 different aryl halides and five different resin-bound amines) makes it a very attractive approach to a library of compounds of type **382**.



Scheme 5-80 Couplings of a solid-supported piperidine with 1,5-hexadiene and aryl halides [455].

The reactions of bicyclopropylidene (**16**) with aryl halides under Heck conditions give rise to the formation of 1-arylallylidenecyclopropanes, which in turn can react with dienophiles in a Diels-Alder mode (see Scheme 5-5). This new three-component reaction has also been conducted on a solid support using the versatile triazene T1 linker (Scheme 5-81) [102,471]. Heck coupling of an immobilized iodoarene **383** with bicyclopropylidene (**16**) in the presence of an acrylate forms a polymer-bound 4-arylspirooctenecarboxylate **384**. Alternatively, the iodoarene **383** could first be transformed into a polymer-bound cinnamate **385** by palla-

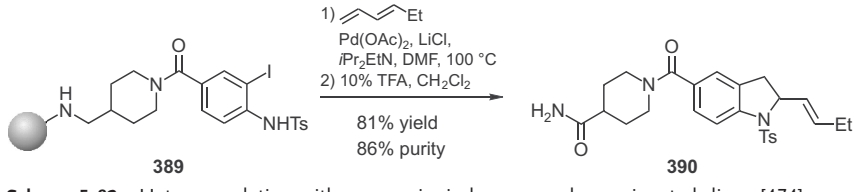


Scheme 5-81 Three-component Heck-Diels-Alder reactions on a solid support [101b].

dium-catalyzed coupling with an acrylate. The polymer-bound cinnamate can then act as a dienophile for the Heck-coupling products of bicyclopropylidene and aryl iodides to give the polymer-bound spirooctene derivatives of type **387**. The latter transformation was conducted under high pressure, which facilitates both the Heck coupling and the Diels-Alder reaction. The triazene moieties upon cleavage with acid first yield diazonium salts, which in turn can be involved in Heck reactions with various alkenes to give the additionally substituted spirooctenes **386** and **388** in good yields and excellent purities. When palladium on charcoal is employed for this transformation, the same catalyst may also serve for a subsequent catalytic hydrogenation of the double bond in the alkene-coupled product [101b,471].

The cross-coupling of aryl iodides containing a potentially nucleophilic *ortho* substituent (amino or hydroxy) with alkynes provides an elegant and straightforward access to substituted indoles and benzofurans (for reviews, see Refs. [472,473]). This sequential reaction, involving the carbometallation of a triple bond and subsequent nucleophilic displacement of the metal, has frequently been used to prepare benzoannelated heterocycles, and various reaction conditions have been reported [474–484]. While terminal alkynes were mostly coupled in the presence

of a copper co-catalyst [480–482], internal alkynes were successfully converted under copper-free conditions [483, 484]. In most cases, the more sterically demanding group on the triple bond (*t*Bu, $SiMe_3$ > Ph > CO_2Et, Et, CH_2CH_2R, Me) will be found in the 2-position of the indole or benzofuran, thus the substitution pattern in the product can be predicted. Since trimethylsilyl substituents are readily removable from the indole core, trimethylsilylalkynes serve as surrogates for terminal alkynes; however, they react with the opposite regioselectivity [483,484]. The nitrogen atom of the iodoaniline may either be unprotected, acylated or even attached in the form of an aminal to a solid support [483]. The coupling of 1,3- and 1,4-dienes with aryl halides having a nucleophilic *ortho* substituent such as an amino or hydroxy group was developed in the liquid phase by Larock et al., and is one of the most versatile heteroannelation reactions. Similarly, the reaction of an immobilized aminoiodoarene on a solid support with a 1,3-butadiene or 1,4-pentadienes led to the formation of polymer-bound dihydroindoles, dihydrobenzofurans, tetrahydroquinolines and tetrahydrobenzopyrans, respectively, which were cleaved off by treatment with trifluoroacetic acid [474] (Scheme 5-82).

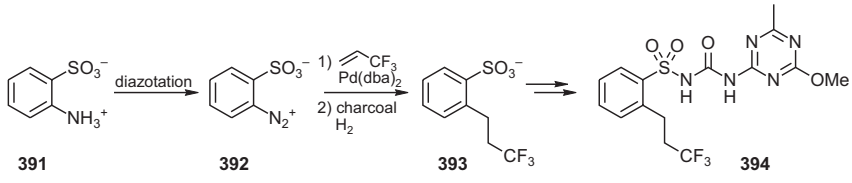


Scheme 5-82 Heteroannelation with an *o*-aminoiodoarene and a conjugated diene [474].

5.8
The Heck Reaction in Fine Chemicals Syntheses

The Heck reaction is well-suited for the production of fine chemicals [485,486]. In most cases, heterogeneous palladium catalysts have been used for this purpose. Yet, as of October 1998, the second-largest plant using Heck chemistry had an output of only 20 metric tons per year [487]. Five or more commercial products have recently been produced on a scale of more than tons per year. Sodium 2-(3,3,3-trifluoropropyl)benzenesulfonate, a key intermediate for the sulfonylurea herbicide Prosulfuron®, was prepared in the Central Research Laboratories of Ciba-Geigy by the three-step sequence of diazotation, Matsuda arylation with the 2-sulfonatobenzenediazonium salt of 3,3,3-trifluoropropene and subsequent hydrogenation [207]. Various attempts to find a classical synthetic method such as a Friedel-Crafts alkylation of benzenesulfonic acid, all failed. A process was developed starting with 2-aminobenzenesulfonic acid and ending with sodium 2-(3,3,3-trifluoropropyl) benzenesulfonate without isolation of the diazonium or alkene intermediates, producing only 2 kg of waste per kg product over all three consecutive synthetic steps. The yield over these three steps is 93 %, i. e., an average of 98 % per step. The solvent had to be compatible with three different chemical reactions, had to

have high dissolving power for trifluoropropene, and had to be easily regenerated. Pentan-1-ol showed all of these properties to a high degree. The cost and separation of the Pd catalyst was another crucial factor. After careful optimization of the reaction conditions, catalyst loading for the arylation could be lowered to 0.5–1.5 % and the catalyst precursor $Pd(dba)_2$ was prepared from readily available $PdCl_2$. The most crucial idea, however, was to add charcoal after completion of the arylation reaction, in order to produce in situ a heterogeneous hydrogenation catalyst that on the one hand is able to catalyze the hydrogenation of the C=C double bond and on the other hand allows the palladium to be efficiently recovered from the reaction mixture by simple filtration. By linking homogeneous and heterogeneous catalysis, and by using a one-pot procedure for three consecutive steps, it was possible to develop an economically and ecologically feasible process for the production of Prosulfuron **394** (Scheme 5-83) [488].



Scheme 5-83 An industrial process for the synthesis of Prosulfuron® [488].

The sunscreen agent 2-ethylhexyl *p*-methoxycinnamate has been produced on a pilot plant scale by a Heck cross-coupling of *p*-methoxyphenyl iodide with 2-ethylhexyl acrylate using palladium on charcoal as a catalyst [489]. Naproxen, a member of the arylacetic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs), is produced by the Albemarle Corporation by a Heck reaction of 2-bromo-6-methoxynaphthalene with ethylene, followed by carbonylation of the product [490]. Monomers for coatings are produced by a Heck coupling on 2-bromobenzocyclobutene [491]. A key step in the production of montelukast sodium (Singulair®), a leukotriene receptor antagonist for the treatment of asthma in children and adults, also makes use of the Heck reaction by way of coupling an allyl alcohol with methyl 2-iodobenzoate to give a (2-arylethyl) alkyl ketone.

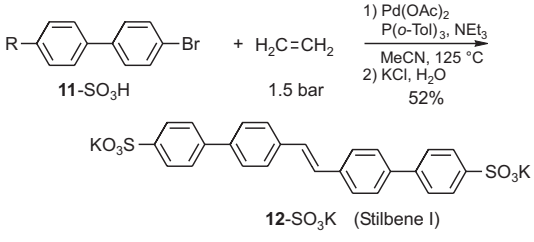
The high cost of palladium has greatly stimulated the development of more active palladium catalysts, in particular for the production of fine chemicals. Along these lines, ligandless catalysts, which are suitable for reactive substrates, were used on production scale. Palladacycles (e. g., the one prepared by heating palladium acetate with tris-*o*-tolylphosphane) are much more stable than simple palladium phosphane complexes and can be used at higher temperatures. The same effect has been achieved with so-called pincer ligands. Bulky ligands lead to coordinatively unsaturated palladium complexes, which are highly active for the Heck reaction. The reuse of palladium catalysts plays a pivotal role to cut costs. While the immobilization of catalysts by solid-supported ligands due to leaching and reduced activity is less attractive, ligandless palladium catalysts for the Heck reaction can be precipitated permanently on carriers.

5.9
Conclusions

By now, a more or less well-experimentally corroborated mechanism of the palladium-catalyzed arylation and alkenylation of alkenes – the so-called Heck reaction – has been established, although the individual steps are far from being completely understood. The ever-growing insight into the factors controlling these reactions has contributed significantly to the rapidly proceeding and ever-increasing development and improvements of the methods. Numerous related procedures have emerged from the classic Heck reaction. Chemoselective, regioselective and stereoselective couplings are now possible with the appropriate catalyst cocktail. Indeed, even ligand-controlled enantioselective intramolecular couplings of highly functionalized aryl and alkenyl derivatives with unsymmetrical and oligosubstituted alkenes, cycloalkenes, and unsaturated heterocycles are possible. Two-, three- and even multifold couplings proceed with astonishing yields, both inter- and intramolecularly. The vast number of applications of the Heck reaction in the synthesis of natural and non-natural biologically active compounds as well as theoretically interesting molecules, as a key C-C-bond-forming step provides convincing evidence for its importance as a real power tool in modern organic synthesis.

5.10
Experimental Procedures

5.10.1
Dipotassium (*E*)-4,4′-Diphenylstilbene-4″,4‴-disulfonate (Stilbene I) (12-SO_3K)



11-SO_3H **12**-SO_3K (Stilbene I)

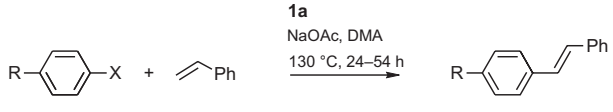
Typical procedure for the Heck reaction of aryl bromides with ethene [92]: A 1-L glass autoclave was charged with a magnetic stirring bar as well as a mixture of 4′-bromobiphenyl-4-sulfonic acid (**11**-SO_3H) (172 g, 0.55 mol), sodium 3-(diphenylphosphanyl)benzenesulfonate (3.78 g, 10.4 mmol), and demineralized water (174 mL). The autoclave was cooled with ice-water, while triethylamine (189 mL, 1.36 mol) was added slowly with manual stirring until the solids had dissolved. The solution was purged with nitrogen for 10 min under stirring at r.t., $Pd(OAc)_2$ (1.24 g, 5.5 mmol) was added, the autoclave was closed with its nitrogen atmosphere, filled

with ethene up to a pressure of 1.4–1.5 bar with intensive magnetic stirring for 10 min, and the ethene pressure was then released under a well-working hood. This cycle of filling with 1.4–1.5 bar of ethene and releasing was repeated twice, and finally the autoclave was filled with ethene to a pressure of 1.4–1.5 bar, then heated at 100 °C in an oil bath with vigorous stirring. During the first 24 h, ethene had to be added every 2–3 h, but later every 12 h. After 72 h the autoclave was cooled to r. t., and the remaining ethene blown off with care. The reaction mixture was transferred into a 1-L flask, and the autoclave washed with small amounts of water and methanol. The solvent was removed under reduced pressure (20 Torr) in a rotary evaporator at 60–80 °C, the warm residue was dissolved in 1.5 L methanol, and 20 g powdered charcoal was added. After 10 min under reflux, the solution was filtered twice through the same filter. Methanol was evaporated under reduced pressure, and the warm residue dissolved again in 300 mL methanol. To this solution were added carefully 300 mL acetone and *ca*. 250 mL triethylamine, and the clear solution was cooled to between –20 and –30 °C. The triethylammonium salt of the stilbene crystallized together with a small amount of triethylammonium hydrobromide; this was filtered off after 30 min and washed with 100 mL of a cooled (–30 °C) methanol:acetone mixture (1:1). The solid was recrystallized twice from a methanol:acetone:triethylamine mixture (3:3:2, more triethylamine led to the formation of an oil), and dried in a rotary evaporator at 70 °C under reduced pressure (20 Torr) to give 119.9 g of the bis(triethylammonium) salt **12**-$SO_3H \cdot NEt_3$ as a light yellow hygroscopic powder.

To a solution of this salt in 500 mL hot demineralized water was added dropwise with swirling 200 mL of a saturated aqueous solution of potassium chloride. The mixture was kept at r. t. for 30 min and filtered. The solid was washed with 20 mL saturated potassium chloride and twice with 50 mL water, dried, then treated for 10 min with 400 mL boiling-hot water, and re-filtered while hot. (At this stage the solid should be slightly yellow or colorless, otherwise this procedure has to be repeated.) The product was washed with 100 mL cold methanol, 100 mL acetone and 100 mL pentane and dried at r. t. *in vacuo* (20 Torr), then at 80–100 °C (0.01 Torr) to yield 81.5 g (52 % based on consumed starting material) of Stilbene I (**12**-SO_3K) as a colorless or slightly yellow powder.

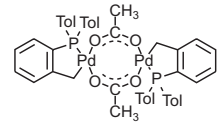
5.10.2
***trans*-4-Acetylstilbene (395a)**

General procedure for the coupling of styrenes with bromo- and chloroarenes [19]: In a 100-mL three-necked flask equipped with a reflux condenser, stirring bar and internal thermometer were placed under a stream of nitrogen bromoacetophenone (**7a**-Br) (5.0 g, 25 mmol) [or 4-chloroacetophenone (**7a**-Cl) (3.3 mL, 3.9 g, 25 mmol) plus nBu$_4$NBr (1.64 g, 5 mmol)], styrene (4.3 mL, 3.9 g, 37 mmol), 2,6-di-*tert*-butylphenol (20 mg, as a radical scavenger), NaOAc (2.5 g, 30 mmol), and *N,N*-dimethylacetamide (50 mL). To the well-stirred suspension was added 12 mg (0.1 mol %) of the palladacycle **1a**, and the mixture was heated at 130 °C for 24 h (54 h with chloroacetophenone). After the reaction mixture had cooled



7-X **395**

	X	R	Yield (%)
a	Br	$COCH_3$	89
a	Cl	$COCH_3$	69
c	Br	F	93
d	Br	Me	65
e	Br	OMe	69
f	Cl	CN	48



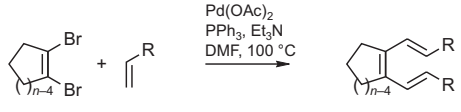
1a

to r. t., it was poured into ice-water (200 mL). The precipitate was collected on a filter, carefully washed with water, and recrystallized from acetone:water to yield 4.9 g (89 %) of **395a** (3.8 g, 69 % from chloroacetophenone **7a**-Cl).

The same procedure can be applied for *trans*-4-fluorostilbene (**395c**) (93 %), *trans*-4-methylstilbene (**395d**) (65 %), *trans*-4-methoxystilbene (**395e**) (69 %), *trans*-4-fluoro-4′-methoxystilbene (85 %), *trans*-4,4′-dimethoxystilbene (30 %) from the corresponding bromoarenes and *trans*-4-cyanostilbene (**395f**) (48 %) from 4-chlorobenzonitrile (**7f**-Cl).

5.10.3

Methyl 3-(*E*)-{2-[2-(*E*)-methoxycarbonylethenyl]cyclopent-1-enyl}acrylate (397b)



396 *n* = 5
213 *n* = 6

a: R = Ph
b: R = CO_2Me
c: R = CO_2tBu

397
214

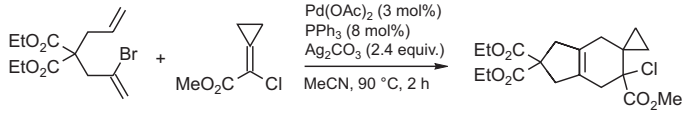
Typical procedure for the Heck reaction of dibromoalkenes with alkenes [219, 318]: A mixture consisting of 1,2-dibromocyclopentene (**396**) (1.30 g, 5.75 mmol), methyl acrylate (2.48 g, 28.8 mmol), NEt_3 (3.2 mL, 23 mmol), and DMF (60 mL) was placed in a thick-walled Pyrex® bottle [492] equipped with a magnetic stirring bar. The solution was purged with nitrogen, then $Pd(OAc)_2$ (129 mg, 0.575 mmol) and PPh_3 (377 mg, 1.44 mmol) were added. After heating with stirring at 100 °C for 35 h and cooling to r. t., the mixture was added to CH_2Cl_2 (200 mL) and washed five times with water (80 mL each). The aqueous layer was extracted back once with CH_2Cl_2 (100 mL) and the combined organic layers

were dried with $MgSO_4$. The solvent was evaporated *in vacuo* and the residue purified by column chromatography on silica gel (column 3 × 30 cm, petroleum ether:EtOAc, 4:1) to yield 980 mg (72 %) of **397b**.

The same procedure can be applied for the two-fold coupling of 1,2-dibromocyclopentene (**396**) as well as 1,2-dibromocyclohexene (**213**) with other acrylates, styrene and substituted styrenes. For the coupling with ethenylsilanes, far better yields were obtained from 1,2-diiodocycloalkenes [493].

5.10.4

Diethyl 4′-Chloro-4′-methoxycarbonylspiro[cyclopropane-1,3′-bicyclo[4.3.0]non-1′(6′)-ene]-8′,8′-dicarboxylate (76)



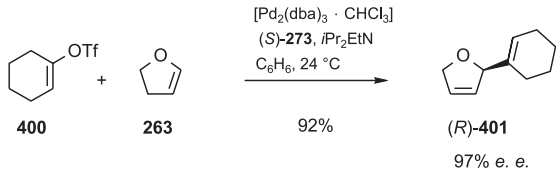
398 **399** 74% **76**

General procedure for a domino Heck-Diels-Alder reaction [119]: To a solution of diethyl allyl(2-bromallyl)malonate (**398**) [494] (640 mg, 2.01 mmol) in acetonitrile (16 mL) in a screw-capped Pyrex® bottle were added $Pd(OAc)_2$ (14 mg, 3 mol %), PPh_3 (42 mg, 8 mol %), silver carbonate (665 mg, 2.41 mmol), and methyl 2-chloro-2-cyclopropylideneacetate (**399**) (354 mg, 2.41 mmol) [495]. The solution was purged with argon, and then stirred in the sealed bottle at 90 °C bath temperature for 2 h. The reaction mixture was cooled to r. t. and filtered through a bed of charcoal and Celite, and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (25 g, column 1.5 × 30 cm, light petroleum:ether, 4:1) to give 572 mg (74 %) of **76**.

5.10.5

(*R*)-2-Cyclohexenyl-2,5-dihydrofuran (401)

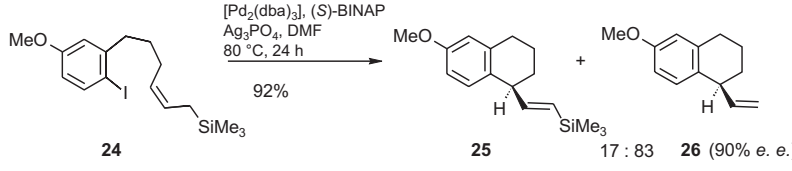
General procedure for an intermolecular enantioselective Heck reaction [341]: $[Pd_2(dba)_3 \cdot CHCl_3]$ (77.5 mg, 0.067 mmol) and (–)-(*S*)-**273** (104.6 mg, 0.270 mmol) were placed under argon in an ampoule equipped with a magnetic stirring bar and a Young valve and treated with a solution of 1-cyclohexenyl triflate (**400**) (1.048 g, 4.55 mmol) and *n*-tridecane (424 mg, 2.3 mmol) as internal standard in Ar-saturated benzene (10 mL), followed by 2,3-dihydrofuran (**263**) (1.35 mL, 17.9 mmol), *N*,*N*-diisopropylethylamine (1.57 mL, 9.17 mmol), and Ar-saturated benzene (40 mL). The ampoule was sealed under argon and the mixture stirred at 24 °C (red solution, precipitation of *N*,*N*-diisopropylethylammonium triflate) until the reaction was complete according to GC analysis. The reaction mixture was diluted



with pentane (*ca.* 150 mL), and the resulting red suspension was filtered through a 2-cm layer of silica gel ($\phi = 7$ cm). Further elution with Et_2O and concentration gave a red oil which was purified by flash chromatography (silica gel, 4 × 25 cm, *n*-pentane:CH_2Cl_2, 1:1) followed by Kugelrohr distillation (125 °C, 12 kPa) to afford 269 mg (92 %) of **401**.

5.10.6

6-Methoxy-1-(*S*)-ethenyl-1,2,3,4-tetrahydronaphthalene (26)

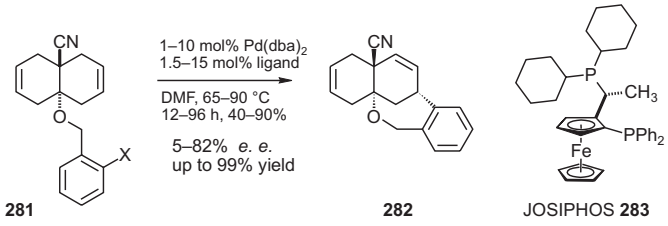


General procedure for a silane-terminated intramolecular enantioselective Heck reaction [110a,b]: A mixture of $[Pd_2(dba)_3 \cdot CHCl_3]$ (0.025 mmol, 2.5 mol %) and (*S*)-BINAP (0.07 mmol, 7 mol %) in degassed DMF (0.1 *M*) was slowly heated to 55 °C under argon with vigorous stirring to attain a homogeneous system (10 min). Then, Ag_3PO_4 (1.1 mmol) and 1-iodo-4-methoxy-2-[6-(*Z*)-trimethylsilylhex-4-enyl]benzene (**24**) (1.0 mmol) were added, and the reaction mixture was heated at 80 °C for about 48 h. After completion of the reaction (TLC), the mixture was diluted with diethyl ether, filtered through silica gel, and washed with water. The organic phase was separated and the aqueous phase extracted with diethyl ether (2 × 20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography using petroleum ether:diethyl ether (150:1) to afford 92 % of a mixture of **25** and **26** as a colorless oil (90 % *e. e.*).

5.10.7

10,11-Benzo-13-oxatricyclo[7.4.1.0^{1,6}]tetradeca-3,7-diene-6-carbonitrile (282)

General procedure for an enantioselective Heck reaction by desymmetrization: In a dry reaction vessel with a magnetic stirring bar was placed 50–100 mg of a substituted



281 **282** JOSIPHOS **283**

tetrahydro-4*H*-naphthaline-4a-carbonitrile **281** with 10 mol % palladium dibenzylidene-acetone and 3 equiv. of a phosphane ligand. The vessel was closed, and the air in it was totally replaced by argon. To the reaction mixture was added 15 mL of anhydrous DMF and 3 equiv. of triethylamine, and this mixture was heated at 65–75 °C for 12–48 h. The reaction was monitored by TLC. When all of the starting material was consumed, the reaction mixture was allowed to cool to ambient temperature and then mixed with 50 mL water. The aqueous phase was extracted with diethyl ether (2 × 50 mL), the combined organic phases were dried over $MgSO_4$, and the diethyl ether was removed in a rotary evaporator. The crude product was purified by chromatography on silica gel. The enantiomeric excess was determined by HPLC or GC on chiral stationary phases.

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Abbreviations and Acronyms

Ac	Acetyl
acac	Acetylacetonate
BBEDA	1,2-Bisbenzylideneaminoethene
BDA	Benzyldimethylamine
BINAP	2,2′-Bis(diphenylphosphanyl)-1,1′-binaphthalene (**272a**)
Bn	Benzyl
BPPFA	*N,N*-Dimethyl[1,2-bis(diphenylphosphanyl)ferrocenyl]ethylamine (**293**)
BPPFOH	*N,N*-Dimethyl[1,2-bis(diphenylphosphanyl)ferrocenyl]ethanol (**295**)
BPPFOAc	*N,N*-Dimethyl[1,2-bis(diphenylphosphanyl)ferrocenyl]ethyl acetate (**294**)
BPPM	*tert*-Butyl (*S,S*)-4-diphenylphosphano-2-diphenylphosphanomethyl-1-pyrrolidinecarboxylate (**292a**)
BCPM	*tert*-Butyl (*S,S*)-4-dicyclohexylphosphano-2-diphenylphosphanomethyl-1-pyrrolidinecarboxylate (**292b**)
BOC	*tert*-Butoxycarbonyl
Cy	Cyclohexyl
Cp	Cyclopentadienyl
DABCO	Diaza[2.2.2]bicyclooctane
DBU	Diazabicycloundecane
dcpe	1,2-Bis(dicyclohexylphosphano)ethane
dba	Dibenzylideneacetone
DMF	*N,N*-Dimethylformamide
DMA (DMAC)	*N,N*-Dimethylacetamide
DMSO	Dimethylsulfoxide
DIOP	2,3-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphanyl)butane (**296a**)
dippb	1,4-Bis(diisopropylphosphano)butane
dppb	1,4-Bis(diphenylphosphano)butane
dppe (DIPHOS)	1,2-Bis(diphenylphosphano)ethane
dppf	1,1′-Bis(diphenylphosphano)ferrocene
dppp	1,3-Bis(diphenylphosphano)propane
EDA	ethyldiisopropylamine
e. e.	Enantiomeric excess
HDTBPB	Hexadecyltributylphosphonium bromide
HMPA	Hexamethylphosphoric acid triamide
HR	Heck reaction
KHMDS	Potassium hexamethyldisilylamide
*m*CPBA	*meta*-Chloroperbenzoic acid
MCR	Multi-component reaction
NEM	*N*-Ethylmorpholine
Nf	Nonafluorobutanesulfonyl

NMP	*N*-Methylpyrrolidone
Norphos	2,3-Bis(diphenylphosphanyl)bicyclo[2.2.1]hept-5-ene (**291**)
PHAL	1,4-Phthalazindiyl diether
PHANEPHOS	13,15-Bis(diphenylphosphanyl)tricyclo[8.2.2.2^{4,7}]hexadeca-1(13),4(16),5,7(15),10(14),11-hexaene
PMB (MPM)	*p*-Methoxybenzyl
PMP	2,2,5,5,6-Pentamethylpiperidine
Proton sponge®	1,8-Bis(dimethylamino)naphthalene
PTC	Phase-transfer catalysis (catalyst)
r. t.	room temperature
TBABr	Tetrabutylammonium bromide
TBACl	Tetrabutylammonium chloride
TBAF	Tetrabutylammonium fluoride
TBDMS (TBS)	*tert*-Butyldimethylsilyl
TBPS (TBDPS)	*tert*-Butyldiphenylsilyl
TCNE	Tetracyanoethene
TEA	Triethylamine
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
Tfa	Trifluoroacetyl
TFA	Trifluoroacetic acid
TFP	Tris(*o*-furyl)phosphane
THF	Tetrahydrofuran
TIPS	Trisisopropylsilyl
Ts	Tosyl (*p*-tolylsulfonyl)
Tol	Tolyl
TOTP (POT)	Tris(*o*-tolyl)phosphane
TPPTS	Triphenylphosphane *m*-trissulfonate sodium salt

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6
Cross-Coupling Reactions to sp Carbon Atoms

Jeremiah A. Marsden and Michael M. Haley

6.1
Introduction

Alkyne cross-coupling reactions have seen incredible growth over the past quarter century, proving their worth as an important tool for organic synthesis. Examples of the varied applications for alkyne couplings include the preparation of pharmaceuticals, complex natural products, and advanced materials such as molecular wires and sensors. The rigidity and electron-rich nature of the alkyne moiety are not only structurally appealing but also provide a point of unsaturation for further derivatization and/or transformation. Of the many synthetic advancements made since the initial cross-coupling of an alkynylcopper and a haloarene by Stephens and Castro four decades ago, one of the most important has been the utilization of palladium as a catalyst. Pd is currently favored in the vast majority of modern sp cross-couplings. The Pd-catalyzed reaction of a terminal alkyne with its coupling partner in the presence of a Cu co-catalyst and an amine base is the most widely used cross-coupling technique, and is known as the Sonogashira reaction. Over the past 15–20 years, countless derivations have been seen with respect to the alkyne, with a greater emphasis on the use of alkynylmetal reagents. While arguably no single alkynylmetal shows superiority, each has shown its worth in specific examples, and for more demanding cross-couplings, more reactive alkynylmetals are often necessary. Numerous reviews have been written on the subject of cross-coupling to sp carbon atoms [1]; nevertheless, our goal is to cover the major developments in the field, to describe recent examples of sp couplings, and to highlight sophisticated, new modifications to the methodology.

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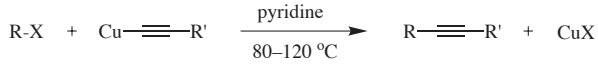
6.2
Alkynylcopper Reagents

6.2.1
Stephens-Castro Reaction

The first example of cross-coupling between sp and sp^2 carbon atoms was reported in 1963 by Stephens and Castro [2]. The reaction involves the formation of an internal acetylene from a copper(I) acetylide and a phenyl or vinyl halide (Scheme 6-1). By heating *para* or *ortho*-substituted iodoarenes with cuprous phenylacetylide in a solution of pyridine, the original preparation provided a variety of substituted tolanes in 75–99 % yield. It was found that nucleophilic substituents *ortho* to the halogen might induce cyclization, affording heterocycles such as indoles, benzofurans, and phthalides [2b, 3]. The authors also noticed that with more electron-donating groups on the haloarenes, increased temperatures were necessary to effect cross-coupling. This trend in reactivity is valid for all alkynyl cross-couplings. Hence, phenyl and vinyl halides possessing highly electron-withdrawing substituents are the most reactive. In further studies the reaction proved applicable to bromo- and chloroarenes as well as iodoarenes, with the trend in reactivity being I > Br > Cl [4]. The utility of the reaction for the preparation of haloolefins [5] as well as halogen-substituted heterocycles such as furans, thiophenes [6], and pyrazoles [7] has also been reported.

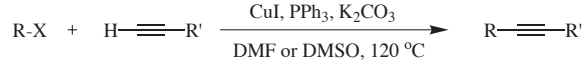


R = aryl, alkenyl R' = aryl, alkyl X = I, Br

Scheme 6-1

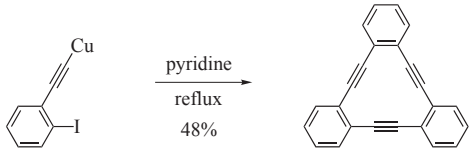
A modification to the original Stephens-Castro protocol involves generation of the alkynylcopper moiety in situ from the corresponding terminal acetylene, thus avoiding isolation of the relatively unstable (and sometimes explosive) Cu-acetylide. This alteration has been shown to work at 120 °C either with a stoichiometric amount of CuI in HMPA [8], or with a catalytic 2:1 ratio of CuI and PPh_3 employing K_2CO_3 as a base in the reaction [9] (Scheme 6-2).

Because of the discovery of simple and more efficient catalytic sp cross-coupling procedures, the Stephens-Castro reaction is not widely used today, but a few recent examples have been reported [7, 10–13]. One illustration is the synthesis of the anti-aromatic dehydrobenzo[12]annulene (DBA) **1** (Scheme 6-3) [12]. Cyclotrimeri-



R = aryl, vinyl R' = aryl, alkyl X = I, Br

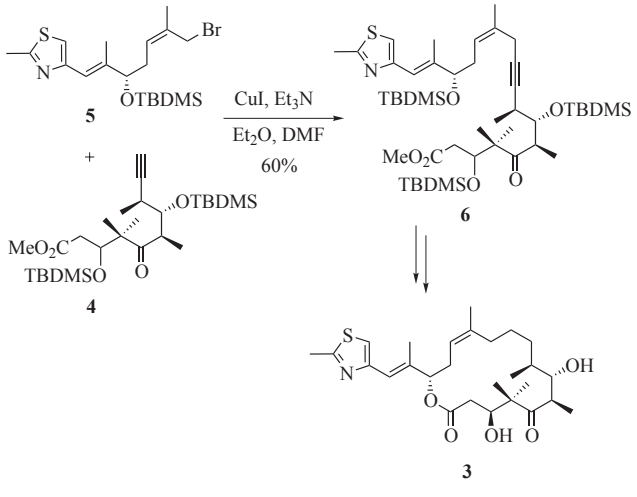
Scheme 6-2



2 1 **Scheme 6-3**

zation of **2**, which incorporates both the Cu-acetylide and halogen substituents in a single reagent, gave annulene **1** in modest 48 % yield.

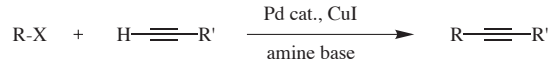
Another recent, noteworthy example of a modified Stephens-Castro hetero-coupling was a key step in the total synthesis of epothilone D (**3**), a natural product with reported anti-cancer properties (Scheme 6-4) [13]. The alkynylcopper was generated in situ from terminal alkyne **4** using Et_3N and CuI. The resultant Cu-acetylide was then cross-coupled with allyl bromide **5**, yielding dienyne **6**. This reaction was unusual in that the coupling partner was an allyl halide.



Scheme 6-4

6.2.2
Sonogashira Reaction

The most significant contribution to the field of alkyne cross-coupling was the innovation of palladium as a catalyst. Developments made by three separate groups in 1975 demonstrated its importance to the protocol. The groups of Cassar and Heck showed independently that aryl and vinyl halides cross-couple with terminal acetylenes using a Pd-complex and a base. These procedures resembled an alkyne extension of the well-known Heck reaction [14]. Later that year, Sonogashira and Hagihara found that the reaction proceeded more smoothly and under milder con-

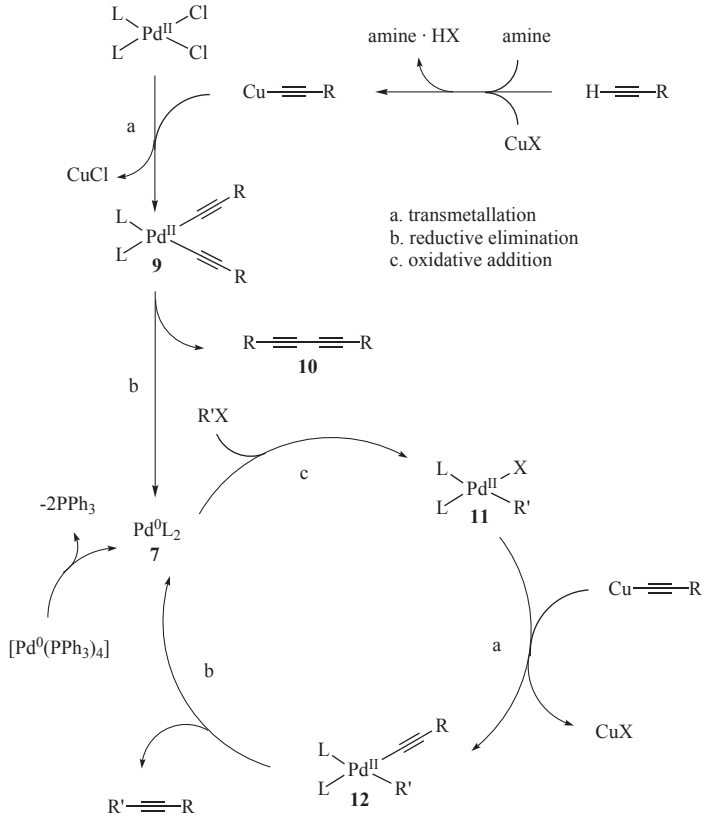


R = aryl, vinyl R' = aryl, alkenyl, alkyl, SiR_3 X = I, Br, OTf **Scheme 6-5**

ditions by employing CuI as a co-catalyst with an amine base as solvent/reactant (Scheme 6-5) [15]. This latter development is akin to a Pd-catalyzed Stephens-Castro cross-coupling, and is now referred to as the Sonogashira reaction. This procedure is currently the most commonly used method for alkyne cross-coupling due to the simplicity of starting material preparation, mild coupling conditions, and the ability to tolerate a large variety of functional groups. A tremendous number of modifications have been reported to improve yields, to create even milder coupling conditions for unactivated organic electrophiles, and to overcome some of the limitations of the reaction such as formation of homo-coupled byproducts and difficulties with the cross-coupling of alkynes bearing electron-withdrawing groups. The most widely investigated element of the reaction is the Pd catalyst. In recent years, a significant number of refined, highly active catalysts have been reported, which allow for milder reaction conditions and the ability to cross-couple in difficult situations (vide infra).

6.2.2.1 Mechanism

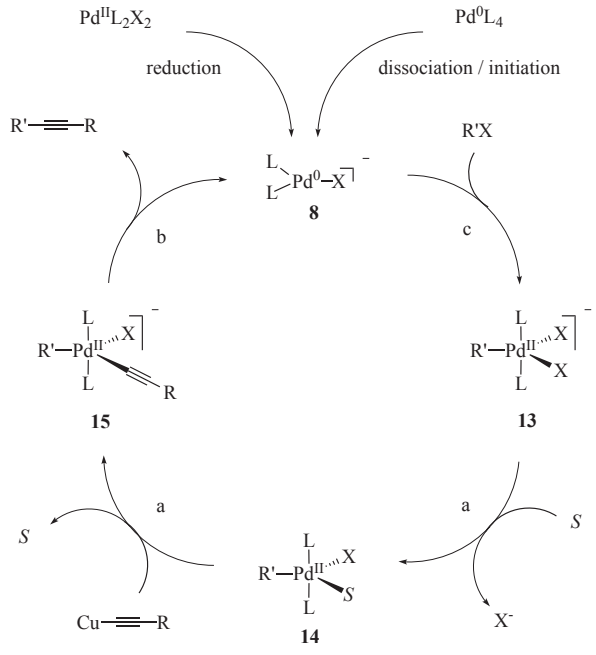
The traditionally accepted mechanistic pathway of the Sonogashira reaction is similar to that originally proposed by Sonogashira and Hagihara (Scheme 6-6a) [15]; however, there has been evidence from recent studies of cross-coupling reactions that suggest a more complex mechanism involving a pentacoordinated anionic Pd species (Scheme 6-6b) [16]. Typically 2–5 mol % Pd is used along with generally twice this amount of CuI co-catalyst. In many cases a smaller amount of Pd can be utilized, and the reaction can also proceed without CuI. The classical and most widely used catalysts for the reaction are $[Pd[II](PPh_3)_2Cl_2]$ and $[Pd[0](PPh_3)_4]$. The active catalytic complex is still the subject of some debate, but is classically thought be the coordinatively unsaturated 14-electron $[Pd[0]L_2]$ (**7**) [15]. In the presence of anions and halides, however, new results point to anionic $[(Pd[0]L_2X)^-]$ (**8**) as the active catalytic species [16]. In the 'textbook' catalytic cycle $[Pd(PPh_3)_2]$ is thought to form by dissociation of two PPh_3 ligands from $[Pd(PPh_3)_4]$ (Scheme 6-6a). Alternatively, generation of **7** from Pd[II] proceeds via transmetallation of an alkynyl copper, which is generated by the reaction of the amine base and CuI, followed by reductive elimination of the dialkynylPd[II] species **9** to give **7** and 1,3-butadiyne **10**. Compound **10**, which is formed by the reduction of the Pd[II] complex, is also a common by-product that plagues Sonogashira reactions, and sometimes is the major acetylene-containing product. Although this dimerization is often detected even when a Pd[0] catalyst is used, it can be minimized by the careful purging of oxygen from the solvents and by running the reaction under an inert atmosphere. If desired, however, diyne **10** can be prepared catalytically and in



Scheme 6-6a

high yields if no organic electrophile is present and if a suitable oxidant is employed [17]. Upon formation of the active Pd[0] catalyst **7**, oxidative addition of the aryl or vinyl halide occurs providing Pd[II] complex **11**. This step is critical for the catalytic process, and a number of new catalysts have been designed for its enhancement. Transmetallation with the Cu-acetylide next gives **12**, and finally reductive elimination follows to afford the cross-coupled product as well as to regenerate the active catalyst.

Amatore and Jutand have more recently established that halides from ArX and Pd[0] precursors may play a more crucial role in the catalytic cycle and that the main intermediate Pd[0] complex may actually be the halide-ligated anionic $[(Pd[0]L_2X)^-]$ (**8**) (Scheme 6-6b) [16]. This active Pd species is similarly formed by reduction from $Pd[II]L_2Cl_2$ by transmetallation/reductive elimination steps followed by association of one of its initially attached chloride ions. From $Pd[0]L_4$, **8** is produced by dissociation of two phosphine ligands followed by association of X^- presumably from R′X generated after one complete standard catalytic cycle (Scheme 6-6a) or from CuI present in solution. Oxidative addition of a vinyl or



Scheme 6-6 b

aryl halide next gives the pentacoordinated Pd[II] species **13**, which is in fast uphill equilibrium with the neutral solvent-coordinated complex R′PdX*S*L$_2$ (**14**). Addition of the copper acetylide to this species completes the transmetallation process and gives the anionic complex **15** in which R and the acetylene are adjacent and in good position for reductive elimination providing the alkyne product and the active Pd complex **8**.

There are many variables that dictate the overall efficiency of the catalytic cycle, including ligand(s), amine base, copper salt, solvent, other "additives", and the electronic and steric characteristics of the organic electrophile and alkyne. Electron-deficient organohalides are again more reactive to cross-coupling than electron-rich, while the opposite is true for the alkyne [18]. The general reactivity order of the sp^2 species is vinyl iodide ≥ vinyl triflate > vinyl bromide > vinyl chloride > aryl iodide > aryl triflate ≥ aryl bromide >> aryl chloride [1]. Aryl iodides are the most commonly used organohalides under Sonogashira conditions, and usually react at room temperature. Until only recently, cross-coupling to unactivated aryl bromides typically required temperatures in excess of 80 °C. In the past ten years, a large amount of research has been devoted to the design of highly active catalysts, allowing milder reaction conditions and the ability to cross-couple to aryl bromides at room temperature as well as to typically inert aryl chlorides.

6.2.2.2 **Sonogashira Catalysts**

The majority of cross-couplings proceed smoothly using the standard $[Pd(PPh_3)_2Cl_2]$ or $[Pd(PPh_3)_4]$ catalysts. There is usually little difference in the reactivity between these two catalysts, but in the authors' experience, freshly prepared $[Pd(PPh_3)_4]$ has shown modest improvements in yield and shorter reaction times for bromoarenes than $[Pd(PPh_3)_2Cl_2]$. Freshly prepared $[Pd(PPh_3)_4]$ is a bright-yellow crystalline solid, which darkens over time and with exposure to air and temperatures above 0 °C, decreasing catalyst reactivity in many cases [19]. $[Pd(PPh_3)_4]$ is commercially available, though the quality of material varies greatly among chemical suppliers. Another advantage of $[Pd(PPh_3)_4]$ is that the reductive elimination step required of $[Pd(PPh_3)_2Cl_2]$ to form **7** is avoided, so very little or none of dimer **10** is formed (Scheme 6-6a). $[Pd(PPh_3)_2Cl_2]$ has the benefit of air and temperature stability and is less expensive than $[Pd(PPh_3)_4]$, yet will always produce at least an equivalent amount of **10**. Relevant examples of the Sonogashira cross-coupling with a variety of different compounds and conditions via these catalysts are shown in Table 6-1.

In more demanding situations, highly active or specialized catalysts are often needed. The bulk of recent research in this area has focused on new ligands for the Pd center, typically to facilitate oxidative-addition of the haloarene component to the Pd center. While a large variety of phosphine ligands have received the most attention, there have been many other recent developments using carbene and amine ligands. Nevertheless, the majority of Sonogashira cross-couplings reported in the last ten years still utilize the original $[Pd(PPh_3)_2Cl_2]$ or $[Pd(PPh_3)_4]$ catalysts with typically excellent results.

In the small-scale organic laboratory, homogeneous catalysts are the simplest systems to use, and usually produce very good results. However, from an industrial standpoint and for larger scale needs, it is desirable to recover the expensive Pd metal and/or to have high catalyst turnover numbers (TON). For these reasons, a number of groups have focused their research on heterogeneous catalyst systems such as polymer-, alumina-, silica-, or carbon-bound complexes in order to recover the valuable catalysts. Air-stable Pd[0] complexes are also of interest, as well as aqueous-phase catalysts and Cu- and amine-free reactions. The following sections will provide an overview on many of the recent advancements in these two fields.

Homogeneous catalyst developments

The most commonly utilized ligands for Pd complexes in the Sonogashira reaction are phosphines. Of the phosphines, PPh_3 is the most universally used because it is relatively inexpensive and works well in the majority of cases. Nonetheless, other Pd catalysts with bidentate ligands, such as $[Pd(dppe)Cl_2]$, $[Pd(dppp)Cl_2]$, and $[Pd(dppf)Cl_2]$, have also been employed. More recent work in the field has focused on electron-rich and/or bulky phosphine ligands as these have been shown to facilitate oxidative-addition to aryl halides. This step is essential for alkyne cross-coupling to occur with deactivated bromoarenes and chloroarenes. This greater reactivity also translates into use of milder conditions for thermally sensitive com-

Table 6-1 Examples of Sonogashira reactions using $[Pd(PPh_3)_2Cl_2]$ or $[Pd(PPh_3)_4]$ catalysts.

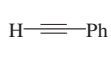
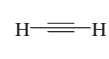
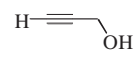
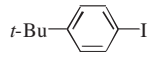
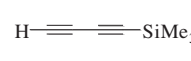
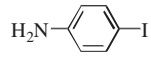
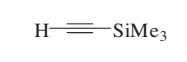
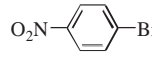
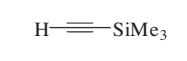
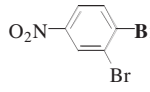
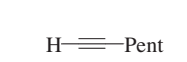
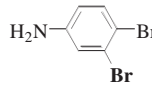
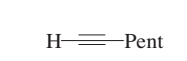
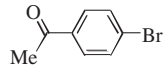
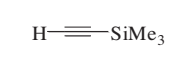
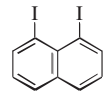
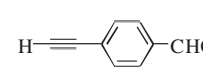
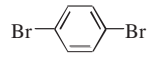
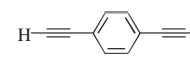
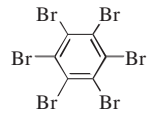
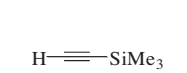
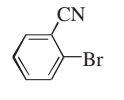
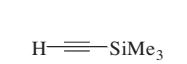
Catalyst	*RX*	*Alkyne*	*Conditions*	*Yield (%)*	*Ref.*
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_2NH r.t., 3 h	85	[15a]
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_2NH r.t., 6 h	90	[15a]
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_2NH r.t., 3 h	80	[15a]
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_3N, 60 °C	95	[20]
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_3N, 40 °C	83	[21]
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_3N, r.t.	92	[21]
$[Pd(PPh_3)_4]$ $CuBr_2$			Et_3N, r.t., 5 h	92	[18a]
$[Pd(PPh_3)_4]$ $CuBr_2$			Et_3N, 90 °C 38 h	70	[18a]
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_3N, r.t.	80	[21]
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_2NH 80 °C, 10 h	35	[22]
$[Pd(PPh_3)_4]$ CuI			Et_3N, PhMe 110 °C, 2 h	79	[23]
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_3N 100 °C, 72 h	28	[24]
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_3N 120 °C, 20 h	61	[25]

Table 6-1 (continued)

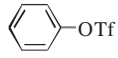
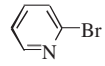
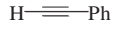
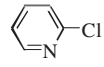
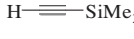
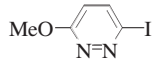
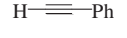
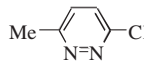
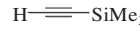
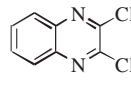
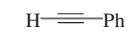
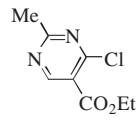
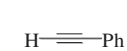
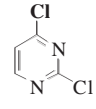
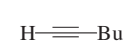
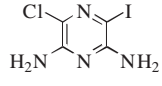
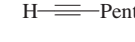
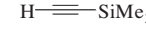
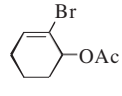
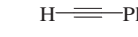
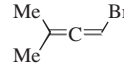
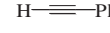
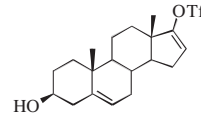
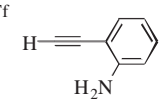
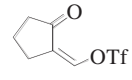
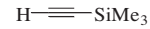
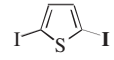
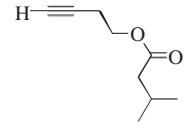
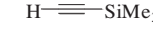
Catalyst	*RX*	*Alkyne*	*Conditions*	*Yield (%)*	*Ref.*
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_3N, DMF 90 °C, 3 h	91	[26]
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_2NH r.t., 3 h	99	[15a]
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_3N 120 °C, 12 h	80	[27]
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_3N, THF r.t., 8 h	67	[28]
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_3N 100 °C 6 h	84	[27]
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_3N DMSO r.t., 6 h	71	[29]
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_3N r.t., 24 h	75	[30]
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_3N r.t., 20 h	55	[31]
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_2NH r.t., 18 h	63	[32]
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_3N, r.t.	85	[33]
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_2NH r.t., 3 h	91	[15a]
$[Pd(PPh_3)_4]$ CuI			Et_2NH, r.t.	32	[34]
$[Pd(PPh_3)_4]$			NMP, 80 °C 45 min	42	[35]

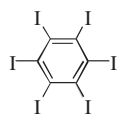
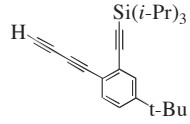
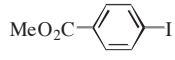
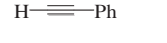
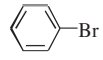
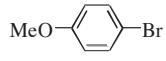
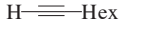
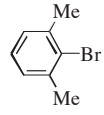
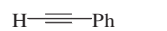
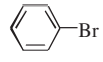
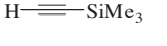
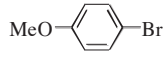
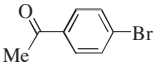
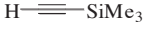
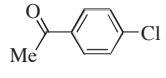
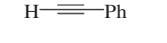
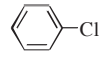
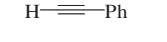
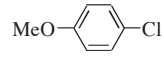
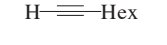
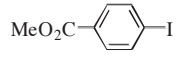
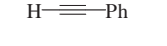
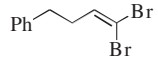
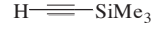
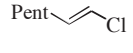
Table 6-1 (continued)

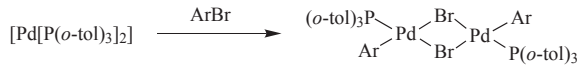
Catalyst	*RX*	*Alkyne*	*Conditions*	*Yield (%)*	*Ref.*
$[Pd(PPh_3)_4]$ CuI			Et_2NH, r.t.	78	[36]
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_3N, PPh_3 90 °C, 4 h	68	[37]
$[Pd(PPh_3)_4]$ CuI			$BuNH_2$ PhH, r.t., 6 h	90	[38]
$[Pd(PPh_3)_2Cl_2]$ CuI			Et_2NH r.t., 4 h	86	[39]
$[Pd(PPh_3)_4]$ CuI			Et_3N MeCN, 0 °C 40 min.	35	[40]
$[Pd(PPh_3)_4]$ CuI			Et_3N, PhH 80 °C, 6 h	50	[41]
$[Pd(PPh_3)_4]$ CuI			piperidine PPh_3 110 °C, 2 h	>75	[42]
$[Pd(PPh_3)_4]$ CuI			piperidine PPh_3 110 °C, 2 h	>75	[42]

pounds. Table 6-2 illustrates several of the newly developed catalytic systems using bulky phosphines such as $P(t\text{Bu})_3$, PCy_3, and $(1\text{-Ad})_2PBn$. The catalysts are most often generated in situ by combining two equivalents of phosphine with a weakly ligated Pd source such as $Pd(OAc)_2$, $[PdCl_2(PhCN)_2]$, or $[Pd_2(dba)_3]$. To avoid the coordinating properties of some of these precatalysts, Pd compounds such as $Na_2[PdCl_4]$ and $PdCl_2$ have also been examined. Similar to other previously known, bulky phosphines (e.g., $P(o\text{tol})_3$), the coupling reaction has been shown to proceed through a monoligated Pd[0]L complex [43]. For example, oxidative addition using $[Pd[P(o\text{tol})_3]_2]$ gives the dimeric arylpalladium species **16** (Scheme 6-7).

A few examples of the Sonogashira reaction in aqueous media have been reported [50, 51]. The main advantages of this approach are the ease of product iso-

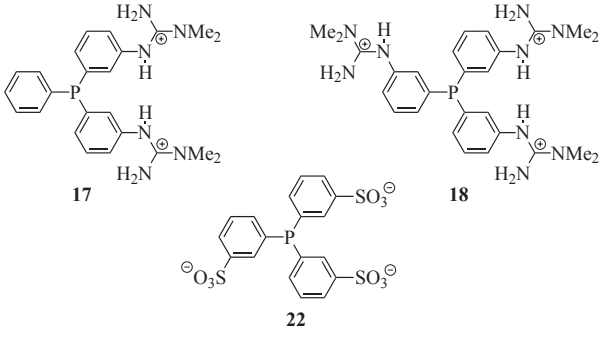
Table 6-2 Examples of highly active phosphine ligands in the Sonogashira reaction.

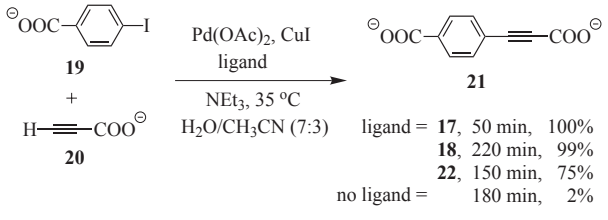
Catalyst	*RX*	*Alkyne*	*Conditions*	*Yield (%)*	*Ref.*
$[Pd[P(o\text{-tol})_3]_2]$ CuI			Et_3N, NMP 60 °C	30	[20]
$[Pd[P(o\text{-tol})_3]_2]$ CuI			*i*-Pr_2NEt DMF, TBAI –20 °C	39	[44]
$[Pd(PhCN)_2Cl_2]$ $P(t\text{-Bu})_3$, CuI			*i*-Pr_2NH dioxane, r.t.	94	[45a]
$[Pd(PhCN)_2Cl_2]$ $P(t\text{-Bu})_3$, CuI			*i*-Pr_2NH dioxane, r.t.	93	[45a]
$[Pd(PhCN)_2Cl_2]$ $P(t\text{-Bu})_3$, CuI			*i*-Pr_2NH dioxane, r.t.	63	[45a]
$[Pd_2(dba)_3]$, $P(t\text{-Bu})_3$			Et_3N, r.t.	92	[46]
$[Pd_2(dba)_3]$, $P(t\text{-Bu})_3$			Et_3N, r.t.	51	[46]
$[Pd_2(dba)_3]$, $P(t\text{-Bu})_3$			Et_3N, r.t.	100	[46]
Na_2PdCl_4, CuI $(1\text{-Ad})_2PBn{\cdot}HBr$			Na_2CO_3 PhMe, 100 °C	90	[47]
Na_2PdCl_4, CuI $(1\text{-Ad})_2PBn{\cdot}HBr$			Na_2CO_3 PhMe, 120 °C	76	[47]
Na_2PdCl_4, CuI $(1\text{-Ad})_2PBn{\cdot}HBr$			Na_2CO_3 PhMe, 120 °C	54	[47]
$[Pd_2(dba)_3]$, CuI $P(2,4,6\text{-}Me_3C_6H_2)_3$			*i*-Pr_2NEt DMF, TBAI –20 °C	98	[44]
$[Pd(dppf)Cl_2]$, CuI			*i*-Pr_2NH PhH, r.t.	68	[48]
$[Pd(MeCN)_2Cl_2]$, CuI			piperidine, r.t.	90	[49]
$PdCl_2$, $AsPh_3$, CuI			piperidine, r.t.	75	[49]



16 **Scheme 6-7**

lation and recovery of catalyst, which is important from an industrial standpoint. Using guanidino phosphines **17** and **18**, reaction between two anionic species has been carried out (Scheme 6-8) [51a]. Under basic conditions in H_2O/MeCN (7:3), *p*-iodobenzoate (**19**) cross-coupled with propiolate ion (**20**) to furnish phenylacetylene **21** in nearly quantitative yield. Identical conditions with the well-known and industrially-used water-soluble phosphine tppts (**22**) or with only $Pd(OAc)_2$ gave inferior results.

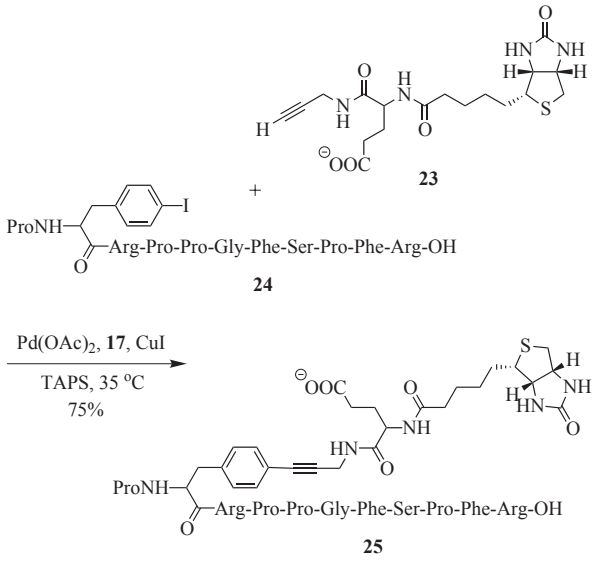




Scheme 6-8

Using water-soluble phosphine ligands for cross-coupling to biologically relevant substrates is another area under investigation, as the mild aqueous conditions can protect the fragile tertiary structure of the compounds. Schmidtchen et al. have recently proved this methodology applicable to the synthesis of a conjugated peptide-biotin derivative (Scheme 6-9) [51b]. Biotinylglutamoylpropargylamide (**23**), a water-soluble biotin derivative, was cross-coupled with Pro(*p*-I-Phe)-bradykinin (**24**), a multifunctional, free and unprotected peptide in aqueous 3-[tris(hydroxymethyl)methylamino]-1-propanesulfonic acid (TAPS) buffer (pH 8.3) using ligand **17** with $Pd(OAc)_2$ to give **25** in 75 % yield. The native structure and function of the protein remained intact under these mild reaction conditions.

N-Heterocyclic carbene (NHC) ligands have received considerable attention recently as "phosphine mimics" in Sonogashira and numerous other metal-mediated



Scheme 6-9

reactions. Because of the large steric bulk and electron-rich character of the ligand, NHCs show great promise in highly active catalyst systems. The primary advantage of NHC ligands is that they do not easily dissociate from the metal center and have a strong σ-donor character. Although initial studies required elevated temperatures and activated bromoarenes, some recent examples have demonstrated efficient cross-coupling through milder conditions and with deactivated bromoarenes (Table 6-3).

Catalytic activity in the Sonogashira reaction has also been demonstrated by a variety of palladacycles (Table 6-4). Herrmann reported using only 0.1 mol % of an sp^3-metallated phosphine palladacycle with no CuI co-catalyst to cross-couple alkynes with bromoarenes at 90 °C [57]. This catalyst proved to be very robust at high temperatures, and showed high TONs. Oxime palladacycles by Nájera et al. displayed reasonable cross-coupling yields with iodo- and bromoarenes at elevated temperatures, again without the use of CuI or an amine base [58]. The Nájera group has also demonstrated similar reactivity with a di-(2-pyridyl)methylamine-based palladacycle, which is water-soluble and capable of cross-coupling in aqueous media [59]. Eberhard's phosphinito pincer palladacycle exhibited catalysis with chloroarenes at high temperature (160 °C). Although yields were poor, replacement of CuI with $ZnCl_2$ [60], resembling an in-situ Negishi cross-coupling, improved yields considerably.

Heterogeneous catalyst developments

The advantages that heterogeneous catalytic systems display for cross-coupling reactions have drawn a great deal of recent interest. The most obvious benefit is the ease of separation and thus recovery of the solid-supported Pd catalyst. The expen-

Table 6-3 Examples of *N*-heterocyclic carbene ligands in the Sonogashira reaction.

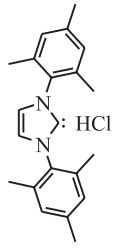
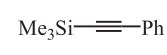
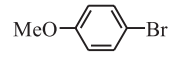
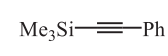
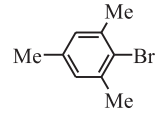
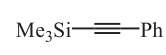
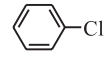
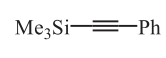
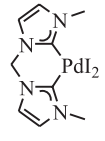
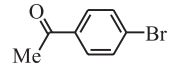
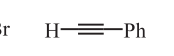
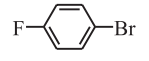
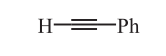
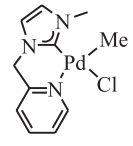
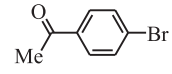
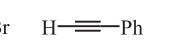
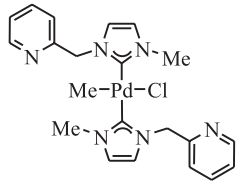
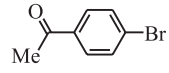
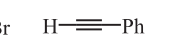
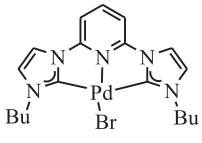
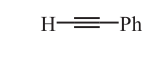
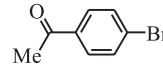
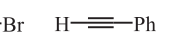
Catalyst	*RX*	*Alkyne*	*Conditions*	*Yield (%)*	*Ref.*
$Pd(OAc)_2$, 			Cs_2CO_3 DMA 80 °C, 0.5 h	91	[52]
			Cs_2CO_3 DMA 80 °C, 0.5 h	82	[52]
			Cs_2CO_3 DMA 80 °C, 1 h	82	[52]
			Cs_2CO_3 DMA 80 °C, 1 h	51	[52]
			Et_3N 90°C, 48 h	76	[53]
			Et_3N 90°C, 48 h	71	[53]
			Et_3N 90°C, 48 h	54	[54]
			Et_3N 90°C, 48 h	39	[54]
			CuI pyrrolidine 87 °C, 1 h	92	[55]
			CuI pyrrolidine 87 °C, 19 h	10	[55]

Table 6-3 (continued)

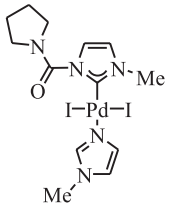
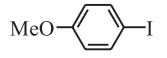
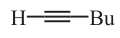
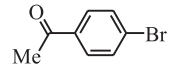
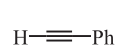
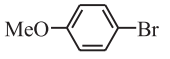
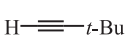
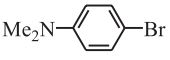
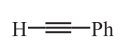
Catalyst	RX	Alkyne	Conditions	Yield (%)	Ref.
			PPh_3, CuI Et_3N, DMF r.t.	91	[56]
			PPh_3, CuI Et_3N, DMF 80 °C	99	[56]
			PPh_3, CuI Cs_2CO_3 DMF, 80 °C	97	[56]
			PPh_3, CuI Cs_2CO_3 DMF, 80 °C	95	[56]

Table 6-4 Examples of palladacycles in the Sonogashira reaction.

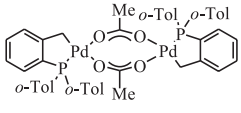
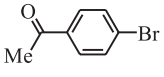
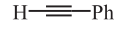
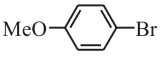
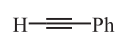
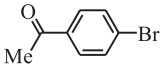
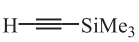
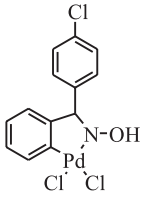
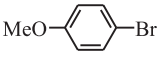
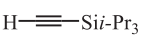
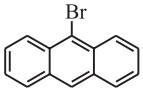
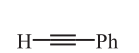
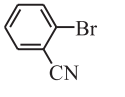
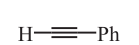
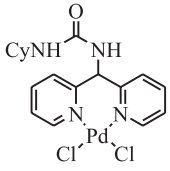
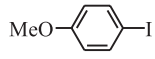
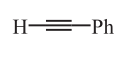
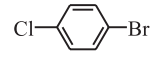
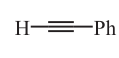
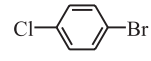
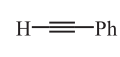
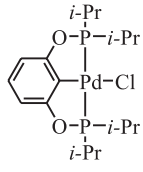
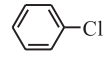
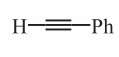
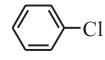
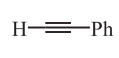
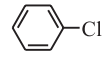
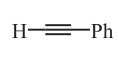
Catalyst	RX	Alkyne	Conditions	Yield (%)	Ref.
			Et_3N 90 °C, 5 h	99	[57]
			Et_3N 90 °C, 24 h	80	[57]
			Et_3N 90 °C, 7 h	0	[57]
			NMP TBAOAc 130 °C, 1 h	85	[58]
			NMP TBAOAc 110 °C, 1 h	81	[58]
			NMP TBAOAc 110 °C, 1 h	96	[58]

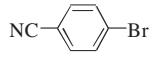
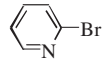
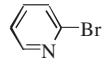
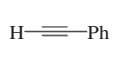
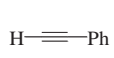
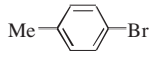
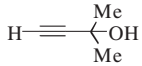
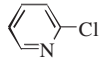
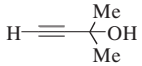
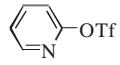
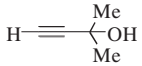
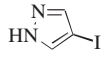
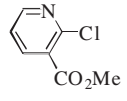
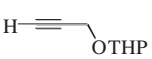
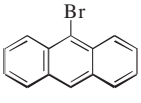
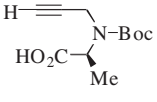
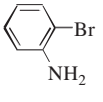
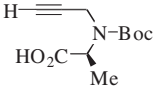
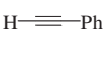
Table 6-4 (continued)

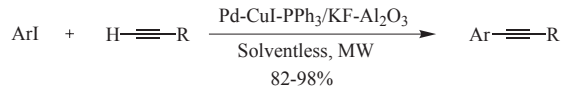
Catalyst	*RX*	*Alkyne*	*Conditions*	*Yield (%)*	*Ref.*
			NMP TBAOAc 110 °C, 7 h	96	[59]
			NMP TBAOAc 110 °C, 2 h	69	[59]
			H_2O pyrrolidine 100 °C, 4 h	96	[59]
			CuI, Et_3N 160 °C, 24 h	0	[60]
			CuI Cs_2CO_3 160 °C, 24 h	14	[60]
			$ZnCl_2$ Cs_2CO_3 160 °C, 24 h	61	[60]

sive catalyst can be reused in these types of systems, which is advantageous for industrial or large-scale applications. In most cases there is also no need for catalyst ligands, which can often be air-sensitive and difficult to handle. Typical heterogeneous systems are supported on either an activated solid or a polymer matrix. In some instances, solid-supported Pd catalysts exhibit greater air and temperature stability over traditional homogeneous Pd complexes.

There have been several reports of the Sonogashira reaction using Pd/C as the metal source. These reactions displayed yields and conditions comparable to, and in some cases, better than standard Pd catalysts (Table 6-5). Most of these procedures still use an amine base, CuI as co-catalyst, and inexpensive PPh_3 as ligand. While Pd/C is heterogeneous, the active catalyst is most likely homogeneous PPh_3-ligated Pd[0] formed by Pd leaching from the solid support. In fact, $[Pd(PPh_3)_4]$ can be isolated when the reaction conditions are repeated in the absence of any aryl halide or acetylene [61]. This active catalytic system requires only a small amount of Pd leached into the solution to proceed (1.8 % observed by atomic absorption measurements), which allows for recovery and reuse of the Pd/C without significant loss of bound Pd metal [62]. Upon recycling of the Pd/C, cross-coupling indeed occurred, although the catalytic activity decreased with each successive use. Pd/C has also been used to cross-couple iodobenzene with phenylacetylene in the absence of PPh_3 and CuI [63].

Table 6-5 Examples of Pd/C in the Sonogashira reaction.

Catalyst	*RX*	*Alkyne*	*Conditions*	*Yield (%)*	*Ref.*
Pd/C, PPh_3 CuI			Et_3N, MeCN 80 °C, 3 h	59	[61]
Pd/C, PPh_3 CuI			Et_3N, MeCN 80 °C, 3 h	67	[61]
$Pd(OH)_2$/C PPh_3, CuI			K_2CO_3 DME, H_2O 80 °C, 21 h	71	[64]
Pd/C, PPh_3 CuI			Et_3N, MeCN 80 °C, 3 h	53	[61]
Pd/C, PPh_3 CuI			*i*-Pr_2NH DMA, H_2O 80 °C, 24 h	51	[62]
Pd/C, PPh_3 CuI			*i*-Pr_2NH DMA, H_2O 80 °C, 24 h	51	[62]
Pd/C, PPh_3 CuI			K_2CO_3 DME, H_2O 80 °C, 16 h	95	[65]
Pd/C, PPh_3 CuI			K_2CO_3 DME, H_2O 80 °C, 16 h	85	[65]
Pd/C, PPh_3 CuI			K_2CO_3 DME, 80 °C 16 h	83	[66]
Pd/C, PPh_3 CuI			K_2CO_3 DME, H_2O 80 °C, 6 h	81	[67]
Pd/C, PPh_3 CuI			K_2CO_3 DME, H_2O 80 °C, 6 h	18	[67]
Pd/C			NMP pyrrolidine 100 °C, 6 h	80	[63]



Scheme 6-10

Microwave irradiation has also been reported to increase activity and shorten reaction times for sp carbon cross-couplings [68]. Kabalka et al. reported a novel solid-state method for the Sonogashira reaction of iodoarenes using alumina and microwave irradiation [69]. Pd powder was mixed with a commercially available alumina/KF mixture along with CuI and PPh_3. This solventless, reusable, catalytic system exhibited cross-coupling between a variety of iodoarenes and alkynes in good to excellent yields with very short reaction times and in an open flask in the microwave (Scheme 6-10). Also, since alumina absorbs little microwave energy, the increase in temperature of the reaction mixture was minor. This work effectively demonstrates a novel, air-stable, environmentally friendly adaptation to the Sonogashira reaction.

Heterogeneous polymer-supported catalysts have also attracted considerable interest. Catalysts such as **26** containing a triazene-bound Pd on a Merrifield resin [70] and **27** containing a phosphine-bound Pd on a PS-PEG resin [71] have both shown catalytic activity for the cross-coupling of iodoarenes with alkynes at moderate temperatures (Figure 6-1). MeOPEG-supported bulky and/or electron-rich phosphines such as **28** and **29** have also shown efficient cross-coupling to bromoarenes and chlorobenzene [72]. These catalysts share the benefits of the above mentioned heterogeneous complexes.

Another interesting polymeric catalyst active in the Sonogashira reaction was formed by ring-opening metathesis polymerization [73]. The bis(pyrimidine)-based Pd-bound polymer **30** was made by ROMP of norbornene **31** using the cat-

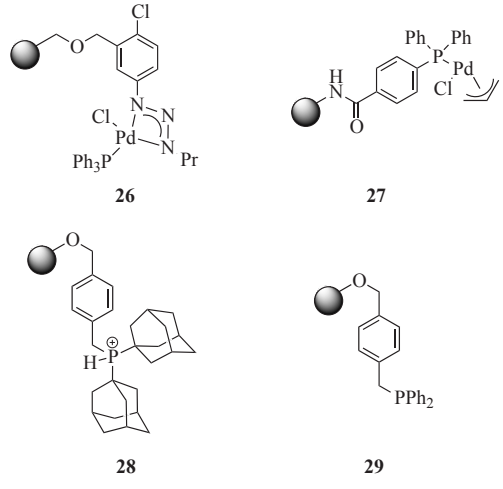
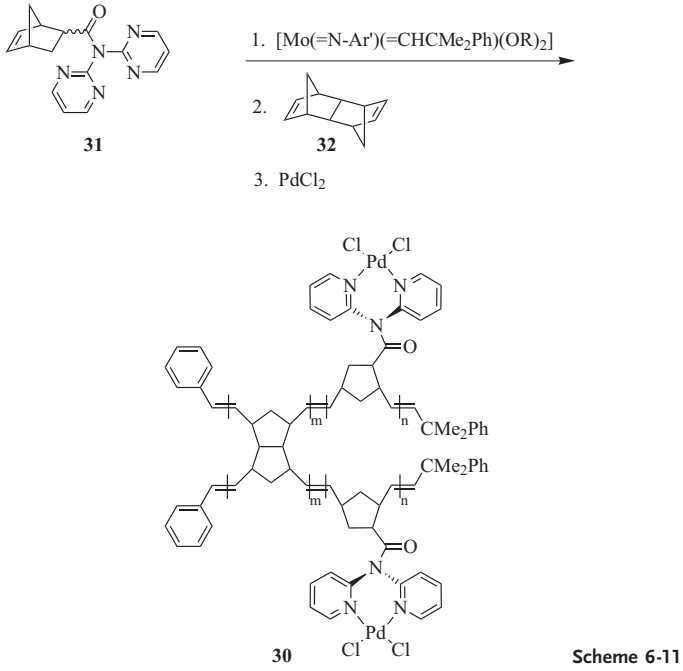


Figure 6-1 Polymer-supported catalysts and ligands.



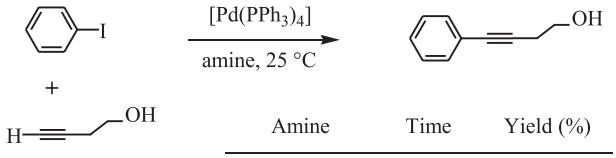
Scheme 6-11

alyst [Mo(=N-Ar′)(=CHCMe$_2$Ph)(OR)$_2$] with diene **32** as a cross-linker and PdCl$_2$ as the source of Pd (Scheme 6-11). This reaction yielded polymer particles with a mean diameter of 20–40 μm that catalyze cross-coupling of phenylacetylene with iodo-, bromo-, and chlorobenzene at 65 °C in 98 %, 68 %, and 65 % yields, respectively, with an extremely low catalyst loadings (0.004–0.007 mol % Pd) and no need for CuI as co-catalyst.

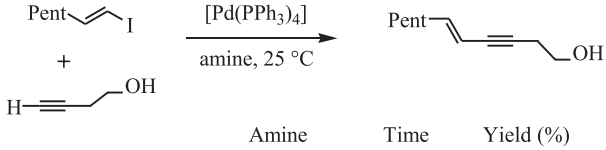
6.2.2.3 **Amine Bases**

The amine base is another crucial element of the Sonogashira reaction. Et$_3$N, Et$_2$NH, and *i*Pr$_2$NH are the most widely used bases, and show good results in most circumstances, although success can be highly substrate-dependent. Stronger bases such as piperidine and pyrrolidine are also commonly used, and frequently show a notable increase in reaction rate. This may be rationalized by assuming that the acetylide is the active alkyne coupling partner. Linstrumelle has reported that stronger bases considerably increase yield and reaction rate when no CuI co-catalyst is used in the reaction [74] (Table 6-6). Another study describes the reaction rate decreasing in the order of BuNH$_2$ > Et$_3$N > *i*Pr$_2$NH > Et$_2$NH > K$_2$CO$_3$ for the cross-coupling of trimethylsilylacetylene (TMSA) with iodopyridone **33** (Scheme 6-12) [75]. Brandsma describes better results using *i*Pr$_2$NH over piperidine and Et$_3$N in other instances [1c]. Hünig's base (*i*Pr$_2$NEt) has also produced excellent results for cross-couplings in many cases [76]. Since reactivities can

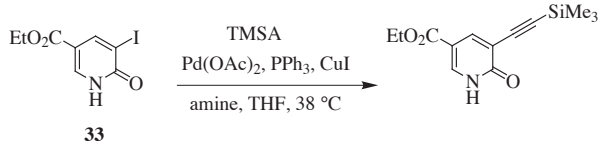
Table 6-6 Amine bases in the Sonogashira reaction.



Amine	Time	Yield (%)
Et_3N	22 h	0
i-Pr_2NH	26 h	2
Et_2NH	24 h	0
$BuNH_2$	25 h	85
piperidine	6 h	76
pyrrolidine	2.5 h	93



Amine	Time	Yield (%)
Et_3N	72 h	0
i-Pr_2NH	72 h	3
Et_2NH	26 h	33
$BuNH_2$	23 h	85
morpholine	8 h	35
piperidine	1 h	76
pyrrolidine	0.25 h	93



33

Scheme 6-12

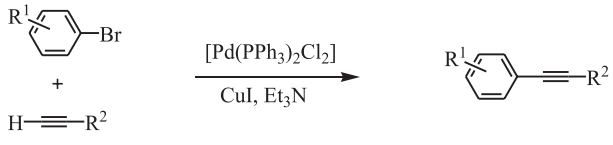
vary by substrate and conditions to such an extent, employing the proper amine is usually a matter of preference and should be tailored by experience along with trial and error.

6.2.2.4 **Solvents and Additives**

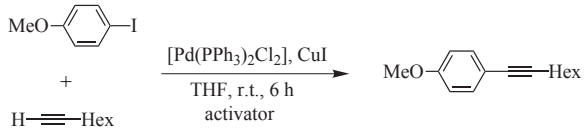
In the original Sonogashira protocol, the amine base functioned not only as a reactant but also as the solvent. Later reports describe reaction rate and yield improvements using a mixture of amine with other solvents, most notably THF. A detailed report by Krause compares yields and reaction times with and without THF (Table 6-7) [77]. With THF as a co-solvent, yields were typically higher than with only Et_3N, and reaction conditions were milder. The authors also found it unnecessary to degas the solvent if a slow addition of the alkyne is performed, as shown by the very low yield of byproduct **10**. Several other groups have also used THF as a co-solvent with beneficial results [1c, 28, 78]. Other common co-solvents include DMF [26, 44, 56, 79], NMP [20, 35, 58, 59], benzene [34, 41, 48, 80], and toluene [23, 47, 81]. To the best of the authors' present knowledge, there is no detailed explanation for reaction improvements due to solvent effects, although in many cases an increase in the solubility of catalysts, reactants, and products seems to be a major factor.

The use of various additives has been explored in the Sonogashira reaction with hopes to increase yield and reaction rate. Ammonium and silver salts have shown the most promise for this purpose. Mori et al. found that by using two equivalents of either TBAF or TBAOH, activation of the cross-coupling with either electron-

Table 6-7 Yield improvements using THF.



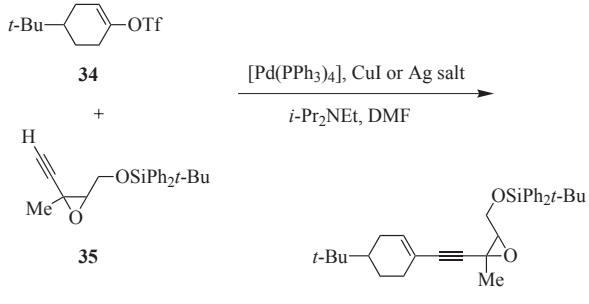
		THF co-solvent		No THF co-solvent	
R^1	R^2	Conditions	Yield (%)	Conditions	Yield (%)
4-CHO	$SiMe_3$	25 °C, 1 h	99	90 °C, 2 h	99
4-COMe	$SiMe_3$	25 °C, 1 h	92	25 °C, 4 h	80
2-CO_2Me	$SiMe_3$	25 °C, 16 h	88	80 °C, 3 h	81
3-CO_2Me	$SiMe_3$	25 °C, 16 h	87	100 °C, 16 h	70
4-CO_2Me	$SiMe_3$	25 °C, 16 h	88	100 °C, 4 h	69
4-COMe	Bu	25 °C, 16 h	91	140 °C, 2 h	73
4-COMe	Ph	25 °C, 16 h	87	90 °C, 3 h	83
4-CHO	Ph	25 °C, 16 h	82	100 °C, 1 h	66



Activator: Bu_4NF (77%), Et_3N (14%), piperidine (20%), Et_2NH (33%), *i*-Pr_2NH (15%) **Scheme 6-13**

withdrawing or -donating substituted iodoarenes occurred, providing excellent yields in short reaction times [82]. The reaction of 1-octyne with *p*-iodoanisole gave the cross-coupled product in much higher yield than with standard amine bases (Scheme 6-13). Using TBAOH as an activator, room temperature cross-coupling to bromoarenes was also possible. TBAI is an essential additive for the low-temperature cross-couplings (–20 °C) described by Yamaguchi, while other amine salts such as TOAI, TEAI, and BTEACl were less effective [44]. TBAOAc has also been used to accelerate the reaction using a palladacycle as catalyst [58]. BTEACl has been reported to facilitate the reaction by acting as a phase transfer catalyst in aqueous NaOH and benzene under otherwise typical Sonogashira conditions [34].

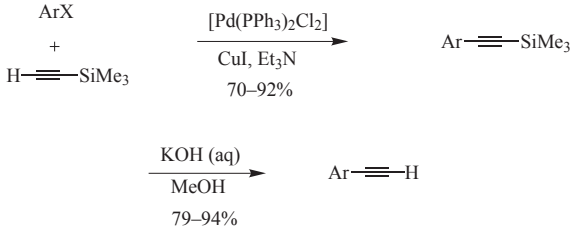
Mori has also reported the use of Ag_2O in place of CuI, but only with modest results [82b]. In another paper, silver salts such as AgI, $AgNO_3$, Ag_2CO_3, and AgOTf, when substituted for CuI, improved cross-coupling yields of vinyltriflates (**34**) with epoxide-bearing alkynes (**35**) (Scheme 6-14) [83]. The proportions of the reagents also had a crucial affect on the yield, with 10 mol % $[Pd(PPh_3)_4]$ and 20 mol % AgI providing the best results.



CuI (20–54%), Ag salt (40–78%) **Scheme 6-14**

6.2.2.5 Silane Protecting Groups and In-Situ Protodesilylation/Alkynylation

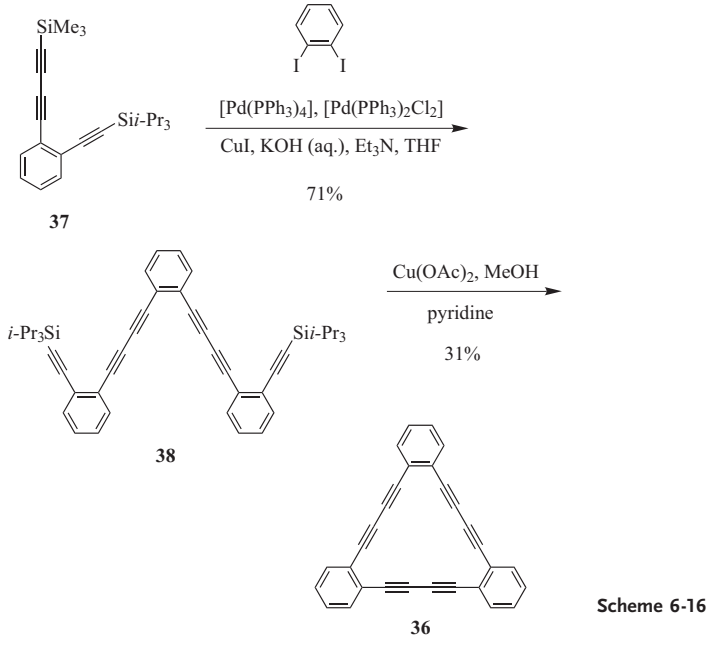
Trialkylsilanes are commonly used as protecting groups for terminal alkynes as many alkynylsilanes are commercially available, such as TMSA, triethylsilylacetylene (TESA), and triisopropylsilylacetylene (TIPSA). TMSA can easily be cross-coupled with haloarenes using the Sonogashira reaction and deprotected at will by treatment with aqueous or methanolic KOH or K_2CO_3, or with a fluoride source such as KF or TBAF, to give the terminal acetylene (Scheme 6-15) [21]. An additional haloarene can then be cross-coupled to form symmetrical or asymmetrical internal alkynes. Iterative Sonogashira syntheses by this route require systematic silane deprotection/cross-coupling to afford larger phenylacetylene and ethynylene systems [84]. There have been recent reports, however, of increased overall yields for deprotection/cross-coupling by removing the TMS group in situ with aqueous or methanolic KOH or K_2CO_3 under otherwise standard cross-coupling conditions [85]. Since the deprotection of the TMS group has a similar reaction rate to the cross-coupling sequence, the amount of free alkyne in solution is minimized, thereby reducing the formation of homo-coupled diyne byproduct. Alkynylsilanes can also be used for direct cross-coupling to haloarenes (see Section 6.6).



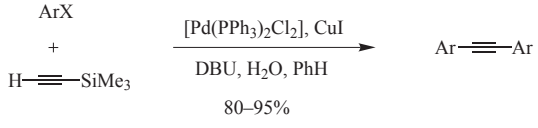
Scheme 6-15

The more bulky TIPS group requires a fluoride ion for deprotection as it is inert to the basic conditions used for removal of TMS and TES groups. Larger or more complex phenylacetylenes and nanoarchitectures can be made by using a combination of silane protecting groups with different reactivities, such as TIPS and TMS. One pertinent example by Haley et al. is the synthesis of DBA **36** (Scheme 6-16) [86]. The TMS group on triyne **37** is selectively deprotected by aqueous KOH and then cross-coupled in situ to diiodobenzene, forming polyyne **38**. This two-step process avoids the handling of the terminal phenylbutadiyne, which exhibits low stability in concentrated solution or in the neat state. The TIPS group is then later removed by TBAF, and the resultant phenylacetylene is intramolecularly homo-coupled under Glaser conditions [87] to afford the annulene.

Another report of an in-situ protodesilylation/alkynylation technique allows formation of symmetrical or asymmetrical diphenylacetylenes from TMSA and haloarenes by a one-pot procedure [88]. In the reaction for symmetrical compounds, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) first performs the typical role of an amine base to give the silylethynylarene cross-coupled product, then promotes deprotection of the TMS moiety and further cross-coupling of the resultant



Scheme 6-16

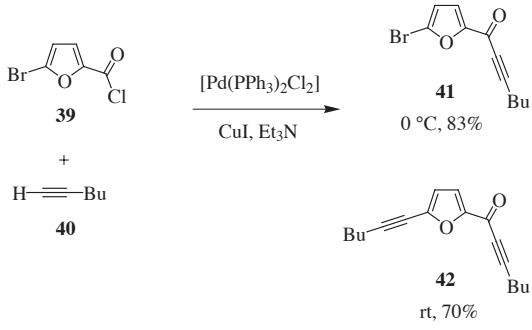


Scheme 6-17

terminal alkyne to a second equivalent of haloarene (Scheme 6-17). Unsymmetrical systems were also formed in one pot by an initial cross-coupling without DBU to give the silylethynylarene, followed by subsequent addition of DBU and a different haloarene. Deprotection as above and a second alkynylation sequence furnished the unsymmetrical diarylacetylenes in very good overall yields.

6.2.2.6 **Acyl Chloride Cross-Coupling**

Terminal alkynes also combine efficiently with a variety of acyl chlorides under typical Sonogashira conditions to form alkynylketones [89]. The cross-coupling can proceed with or without Pd catalysts, and gives good yields in their absence [90]. Microwave irradiation using doped KF/Al_2O_3 has been shown to greatly accelerate the reaction [91]. Crisp and coworkers effectively demonstrated the selectivity of this cross-coupling using a 2-furoyl chloride (**39**) (Scheme 6-18) [92]. With only one equivalent of alkyne **40**, and by keeping the reaction temperature at 0 °C, coupling selectively occurred at the acyl halide to give monoyne **41**, retaining the 5-bromo functionality. By using an excess of alkyne and running the reaction at room temperature, cross-coupling occurred at both positions giving diyne **42**.

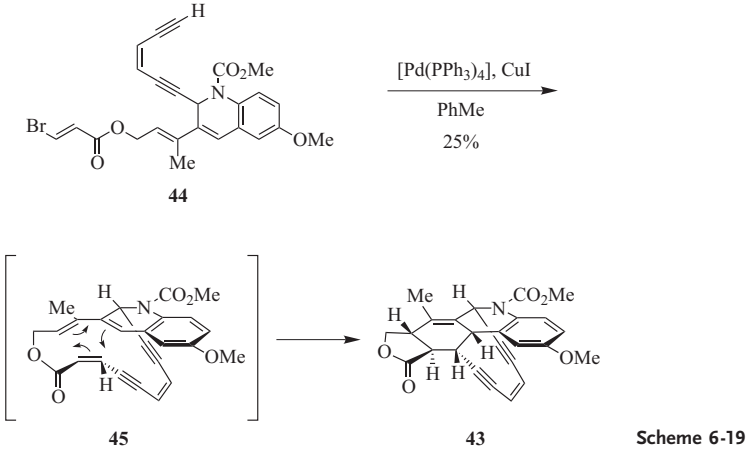


Scheme 6-18

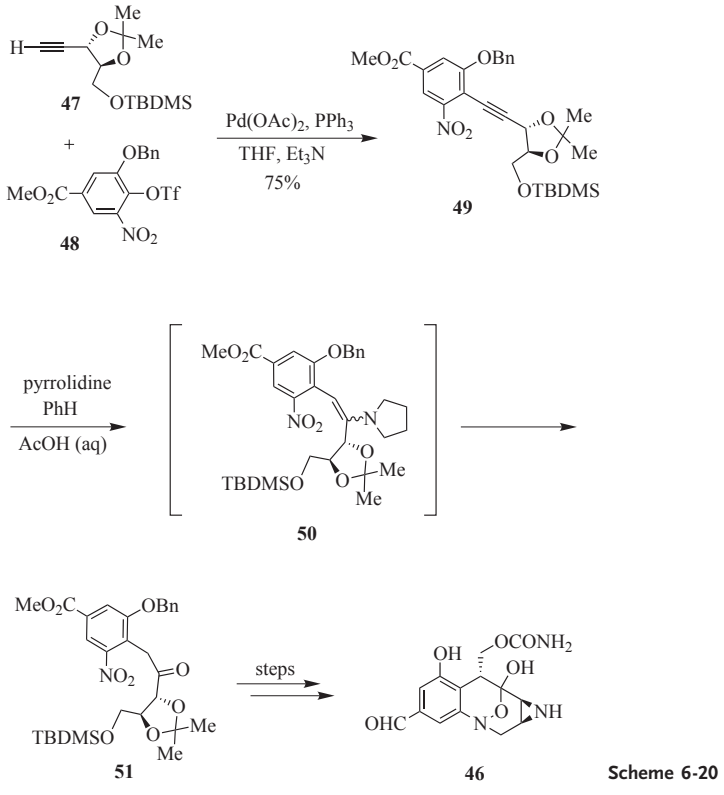
6.2.2.7 Applications of the Sonogashira Reaction

There are numerous applications to the Sonogashira reaction, ranging from the synthesis of natural products to the construction of non-natural, technologically advanced materials. An arylalkyne not only provides a rigid molecular framework for unique structural shape and geometry, but also provides a point of unsaturation which can be utilized in further synthetic transformations.

Many natural products contain alkyne moieties, and the Sonogashira reaction has often been used in their syntheses. Enediynes are an important class of anticancer antibiotics [93]. The active functionality is the 1,5-diyne-3-ene core, which has the ability to generate sp^2 carbon radicals that cleave DNA through a Bergman cyclization [94]. This enediyne functionality is commonly constructed using the Sonogashira protocol, which is elegantly exemplified in the construction of dynemicin A system **43** by Schreiber et al. [95]. Intramolecular cross-coupling of **44** gave tricyclic intermediate **45**, which sets the conjugated 1,3-diene up for a transannular Diels-Alder reaction with the *trans*-enoate moiety, providing **43** in one step (Scheme 6-19). Three rings and four contiguous stereocenters are formed in this remarkable one-pot reaction.



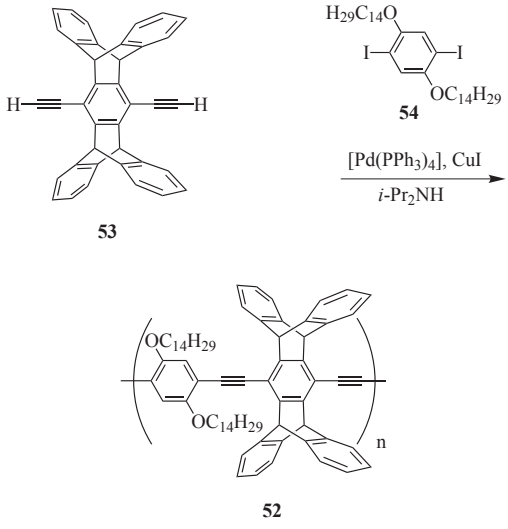
Scheme 6-19



Scheme 6-20

Another recent example of a natural product synthesis utilizes Sonogashira cross-coupling for the attachment of two major units in the synthesis of antitumor antibiotic FR900482 (**46**), isolated from *Streptomyces sandaenisis* (Scheme 6-20) [96]. Acetylene **47** was cross-coupled with triflate **48** to give **49**. In this example, the alkyne functionality is not retained throughout the synthesis. Instead, conjugate addition of pyrrolidine to the *o*-nitroarylacetylene (**49**) afforded intermediate **50**, which formed ketone **51** after hydrolysis with $AcOH/H_2O$. This precursor was then converted to the natural product **46** after several additional transformations.

Alkyne cross-coupling is widely used for construction of conjugated materials with potential utilization in electronic and photonic devices as well as many other technologically applicable materials [85, 97]. Because of the extensive conjugation in phenylacetylene and polyyne oligomers and polymers, these systems often act as organic semiconductors. Applications for such materials include nonlinear optics, polarizers for liquid crystal displays, light-emitting diodes, and detection of explosives. A very unique poly(phenyleneethynylene) (PPE) sensor (**52**) was prepared by polymerization through Sonogashira cross-coupling of diethynylpentiptycene (**53**) with diiodoarene **54** (Scheme 6-21) [98]. A thin film of the resultant

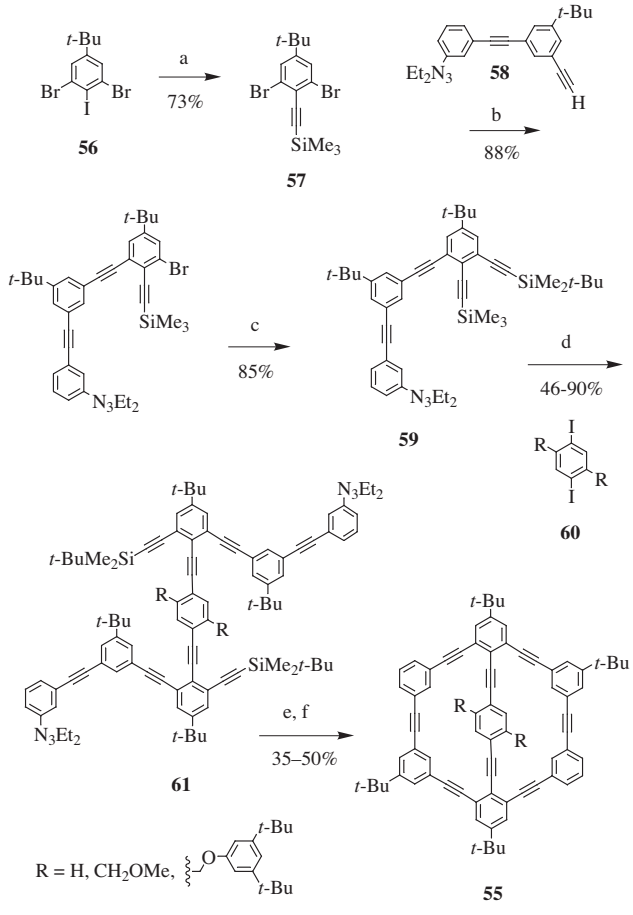


Scheme 6-21

highly porous, shape-persistent polymer could detect trace amounts of 2,4,6-trinitrotoluene (TNT) by fluorescence quenching.

Alkyne cross-coupling is also an important tool in the assembly of unique nanoarchitectures used as molecular devices. In an elaborate synthesis comprised mainly of Sonogashira reactions, the Moore group constructed macrocycle **55**, which acts as a "molecular turnstile" based on the rigid outer framework and the rotation of the central spindle (Scheme 6-22) [99]. Starting from trihaloarene intermediate **56**, the first alkyne was cross-coupled to the more labile iodo position, giving **57**. The second alkyne (**58**) was then attached to only one bromo position by careful control of stoichiometry. A third Sonogashira reaction to the remaining bromoarene afforded intermediate **59**. Selective deprotection of the TMS group and subsequent cross-couplings to diiodoarene **60** afforded precursor **61**, which formed the final assembly after further silane deprotection, triazene to iodide conversion, and intramolecular Sonogashira hetero-coupling. This reaction sequence exemplifies strategic control of alkyne cross-coupling by bromoarene reactivity, selective protodesilylation, and use of the triazene functionality as a masked iodoarene.

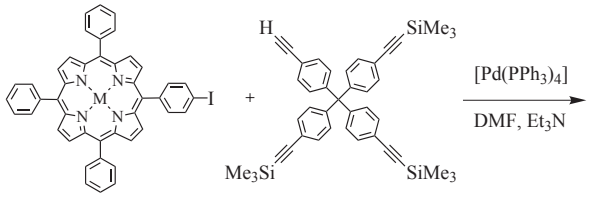
The Sonogashira reaction is frequently used for linking porphyrin units together to create larger multi-porphyrin rods, stacks, or other "light-harvesting" assemblies. An interesting example is the synthesis of "tripodaphyrin" **62**, which consists of porphyrins connected to a central methane unit by phenylacetylene rods (Scheme 6-23) [100]. Iodoporphyrin **63** and tetraarylmethane **64** were connected to give **65**. Next, the silanes were removed *via* base, and the resultant alkynes attached to the porphyrin-terminated iodoarene **66**, giving the final tetrahedral scaffold **62**.



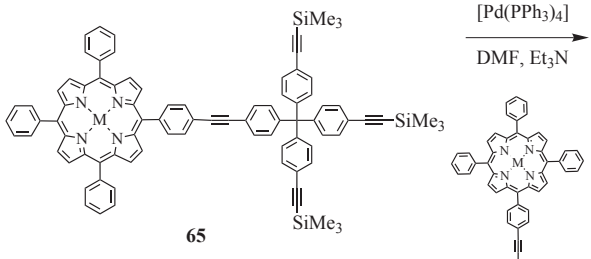
(a) TMSA, $[Pd(dba)_2]$, CuI, PPh_3, NEt_3, 12 h, 75 °C. (b) $[Pd(dba)_2]$, CuI, PPh_3, NEt_3, 12 h, 75 °C. (c) (*tert*-Butyldimethylsilyl)acetylene, $[Pd(dba)_2]$, CuI, PPh_3, NEt_3, 12 h, 75 °C. (d) i] MeOH, Na_2CO_3, 30 min, rt; ii] **60**, $[Pd(dba)_2]$, CuI, PPh_3, NEt_3, 12 h, 75 °C. (e) MeI, 12 h, 120 °C. (f) i] TBAF, THF; ii] $[Pd(dba)_2]$, CuI, PPh_3, NEt_3, 12 h, 75 °C.

Scheme 6-22

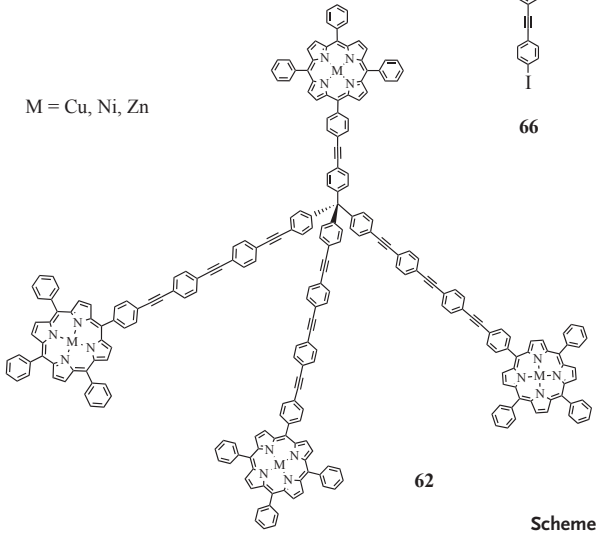
An unusual cross-coupling under Sonogashira conditions occurs between an alkyne and a halocubane. Instead of the expected alkynylcubane products, the reaction of a variety of substituted iodocubanes **67** with alkyl or phenylacetylenes **68** gave substituted alkynylcyclooctatetraenes **69** in modest yields [101] (Scheme 6-24). Synthesis of the alkynylcubanes is only possible through an alternate route starting from cubyl methyl ketones [101].



63 **64**

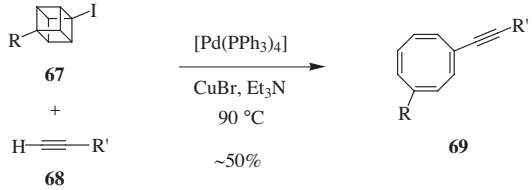


65 **66**



62

Scheme 6-23

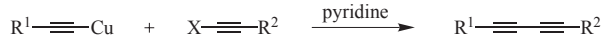


Scheme 6-24

6.2.3
Cadiot-Chodkiewicz Reaction

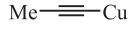
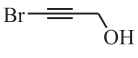
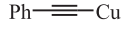
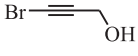
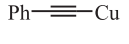
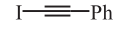
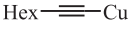
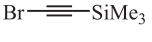
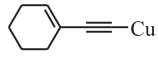
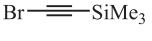
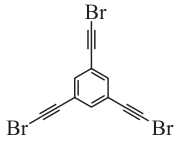
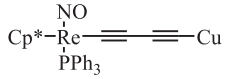
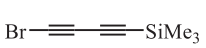
Alkynylcopper species can cross-couple to haloalkynes with or without Pd catalysts to give conjugated 1,3-butadiynes. Many natural products and novel materials contain butadiyne or longer linear alkyne units. Either symmetric or asymmetric polyynes can be made in this manner, yet this procedure is most useful for asymmetric hetero-couplings, whereas the Cu-mediated homo-coupling of alkynes by Glaser or Hay conditions [87] is useful for symmetrical couplings. This latter route, however, gives mixtures of products if dissimilar alkynes are used. As before, the alkynylcopper can either be isolated initially or generated in situ from the terminal alkyne.

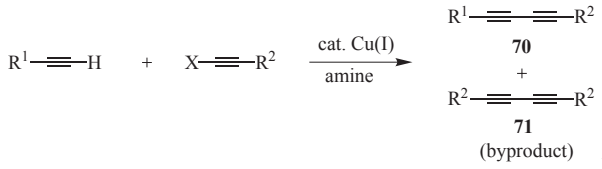
The cross-coupling of an alkynylcopper with a haloalkyne takes place in a pyridine solution at room temperature, and is typically an exothermic reaction forming 1,3-diynes (Scheme 6-25). This reaction is analogous to the Stephens-Castro reaction, and a few examples have been reported and are highlighted in Table 6-8. Although there are cases in which the use of a cuprous acetylide rather than a terminal acetylene is preferred, the use of a terminal acetylene is much easier and, as described below, more commonly used [102].



Scheme 6-25

Table 6-8 Examples of Cadiot-Chodkiewicz cross-couplings between alkynylcopper reagents and haloalkynes.

Alkynylcopper	*Haloalkyne*	*Yield (%)*	*Ref.*
		60	[102]
		65	[102]
		96	[102]
		83	[103]
		85	[103]
		43	[104]
		77	[105]



Scheme 6-26

The reaction between a terminal alkyne and a haloalkyne using a catalytic amount of Cu[I] salt in an amine base was reported in 1957, and is known as the Cadiot-Chodkiewicz reaction (Scheme 6-26) [106]. A small amount of $NH_2OH \cdot HCl$ is also often added as a reducing agent. The unsymmetrical 1,3-butadiyne **70** is the major product from the reaction, although the symmetrical diyne **71** is also observed as a common side product due to homo-coupling of the haloalkyne. This byproduct is minimized by using catalytic copper salt, using the proper amine base, and adding the bromoalkyne slowly to the reaction. Table 6-9 gives re-

Table 6-9 Examples of recent Cadiot-Chodkiewicz reactions.

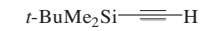
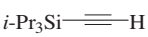
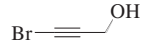
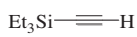
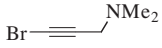
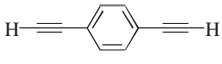
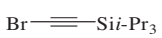
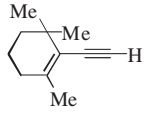
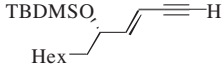
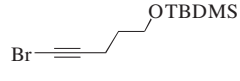
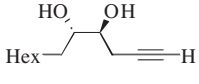
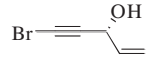
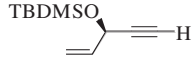
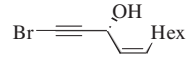
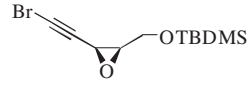
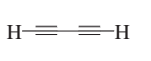
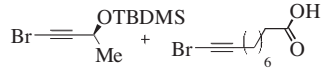
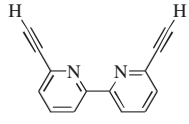
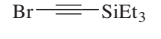
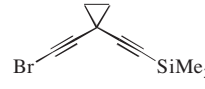
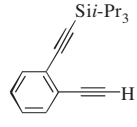
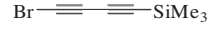
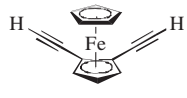
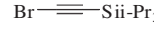
Terminal Alkyne	*Haloalkyne*	*Conditions*	*Yield (%)*	*Ref.*
		CuCl $NH_2OH{\cdot}HCl$ $BuNH_2$, H_2O	82	[107]
		CuCl $NH_2OH{\cdot}HCl$ $BuNH_2$, H_2O	91	[107]
		CuCl $NH_2OH{\cdot}HCl$ $BuNH_2$, H_2O	92	[107]
		CuCl $NH_2OH{\cdot}HCl$ $EtNH_2$, DMF	30	[108]
		CuCl, $EtNH_2$ MeOH	38	[109]
		CuI pyrrolidine	88	[110]
		CuCl $NH_2OH{\cdot}HCl$ $EtNH_2$, MeOH	63	[111]

Table 6-9 (continued)

Terminal Alkyne	*Haloalkyne*	*Conditions*	*Yield (%)*	*Ref.*
		CuCl $NH_2OH{\cdot}HCl$ $EtNH_2$, MeOH H_2O	64	[112]
		CuCl $NH_2OH{\cdot}HCl$ $EtNH_2$, MeOH 0°C	91	[113]
		CuCl $NH_2OH{\cdot}HCl$ $EtNH_2$, MeOH (mixture of pdts)	30	[114]
		CuCl $NH_2OH{\cdot}HCl$ $EtNH_2$, THF	84	[115]
		a) MeLi, THF CuCl, 0 °C b) pyridine	75	[116]
		a) BuLi, THF –78 °C b) CuBr, pyridine	62	[117]
		a) BuLi, THF –78 °C b) CuI, $PrNH_2$	63	[118]

cent pertinent examples, while more classical examples can be found in the original review by Cadiot and Chodkiewicz [106c].

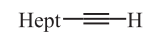
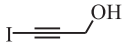
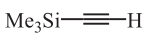
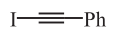
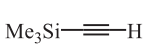
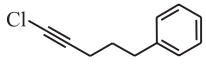
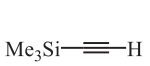
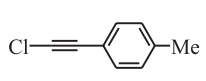
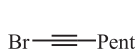
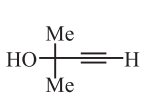
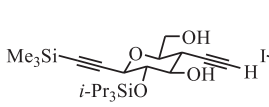
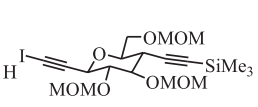
1-Bromoalkynes give the best results for the procedure, but iodo and chloro derivatives have also been used. 1-Iodoalkynes are more strongly oxidizing toward the copper ion, and often favor byproduct **71**. 1-Chloroalkynes have a lower reactivity, although there are instances of chloroalkynol cross-couplings [106]. The reactivity of the terminal alkyne is similar to that described for the Sonogashira reaction.

Generally, arylacetylenes provide better results than alkylacetylenes. Less acidic alkynes have also been shown to produce larger quantities of **71** [119].

The amine base has a large effect on the efficiency of the reaction. Typically, reactivity decreases as follows: cyclic secondary > primary > secondary > tertiary [106c, 119]. Pyrrolidine has demonstrated some of the highest cross-coupling yields, and can even affect the cross-coupling of 1-iodoacetylenes and less acidic alkylacetylenes. Co-solvents can be employed to facilitate solubility if needed, and commonly include MeOH, EtOH, THF, DMF, and NMP.

Pd co-catalysts have recently been incorporated into the Cadiot–Chodkiewicz reaction and give modest yield improvements and demonstrate efficient hetero-coupling of 1-iodoalkynes and 1-chloroalkynes (Table 6-10). In most cases, very little homo-coupling was observed by this variation of the protocol. Rigorous exclusion of oxygen was found unnecessary. A considerable amount of homo-coupled byproduct was observed for the Pd-catalyzed cross-coupling of ethynylsaccharides, however [120].

Table 6-10 Examples of Pd catalysts in the Cadiot–Chodkiewicz reaction.

Catalyst	*Terminal Alkyne*	*Haloalkyne*	*Yield (%)*	*Ref.*
$[Pd(PPh_3)_2Cl_2]$ CuI			73	[121]
$[Pd(PPh_3)_2Cl_2]$ CuI			91	[121]
$[Pd(PPh_3)_2Cl_2]$ CuI			100	[122]
$[Pd(PPh_3)_2Cl_2]$ CuI			38	[122]
$[Pd(PPh_3)_2Cl_2]$ CuI			82	[119]
$Pd(OAc)_2$ tppts			57	[123]
$[Pd(PPh_3)_4]$ CuI			64	[120]

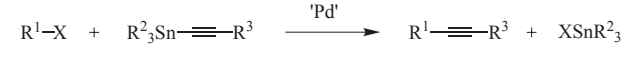
6.3
Alkynyltin Reagents

6.3.1
Stille Reaction

The cross-coupling of an organic electrophile with an organotin reagent is commonly known as the Stille reaction. Many comprehensive reviews have been written on the subject [124]. Organostannanes possess some beneficial properties that other similar organometallics do not. They tolerate a variety of functional groups that are often reactive to other organometals, eliminating the need for protective groups, and they are typically water- and air-stable, allowing trouble-free isolation and storage. Many organostannane reagents are also commercially available. One drawback to these compounds, however, is their high toxicity, so care should be used in their handling. Tin reagents containing more alkyl groups and smaller alkyl chains show an increased toxicity [125]. For this reason, Bu_3SnR is more often used than Me_3SnR. A common problem with Bu_3SnR, however, is the difficulty in the removal of Bu_3SnX formed in the reaction as it is soluble in most common organic solvents, has low volatility, elutes with nonpolar solvents, and tends to "streak" heavily under column chromatography. Me_3SnX, on the other hand, is water-soluble and rather volatile, thus allowing easy removal.

Although the first Pd-catalyzed organotin hetero-couplings were published in the late 1970s [126], other than a few scattered examples, work focusing on the cross-coupling of alkynyltins was not reported until the mid 1980s [127]. Alkynyltins are the most reactive organotin reagents, which make them particularly useful for cross-coupling [128]. In many instances where the preparatively simpler Sonogashira reaction is not successful, alkynylmetal couplings such as the Stille reaction give better results, such as with alkynes substituted with electron-withdrawing groups [129]. Base-sensitive compounds, which may degrade under the conditions used in the Sonogashira coupling, are often safe with the Stille reaction's neutral conditions. For example, cyclopentadienyl and other organometallic halides that are frequently sensitive to amine bases effectively cross-couple using this methodology. The Stille reaction also often gives superior results for the cross-coupling of organotriflates.

The general protocol for alkynylstannane cross-coupling is outlined in Scheme 6-27, where the organic electrophile and tin alkyne react to form acetylene using a Pd catalyst. The mechanism is analogous to the Sonogashira cross-coupling, lacking generation of the metal-alkyne (see Scheme 6-6a). Both oxidative-addition of the organic electrophile to the Pd catalyst and the final reductive-elimination are



R^1 = aryl, vinyl, acyl R^2 = Me, Bu R^3 = aryl, vinyl, alkyl, etc. **Scheme 6-27**

thought to be faster than transmetallation [130] which, though still not well understood, has been determined as the rate-limiting step [128].

Preparation of alkynyltin reagents is typically achieved by lithiation of the corresponding terminal acetylene or by formation of the alkynyl Grignard reagent, followed by transmetallation with trialkyltin chloride [127, 131]. This can be done in the same pot before addition of the organic electrophile, or the typically stable alkynylstannane can be isolated beforehand. Alternatively, the alkynyltin species can be generated by reacting a terminal acetylene with $R_3SnNR'_2$ (R = Me, Bu; R′ = Me,Et) [127]. Facile exchange of the trialkyltin with the terminal hydrogen atom occurs; the resultant volatile amine is removed in vacuo and the residual alkynyltin can then be reacted immediately.

The reactivity order for organic electrophiles is analogous to the Sonogashira reaction (see Section 6.2.2.1), although organotriflates are in many cases more reactive than organobromides if a suitable additive such as LiCl is added. The cross-coupling of alkynylstannanes works well with vinyl- and aryl halides as well as many interesting heteroaryl halides and organometallic halides. Table 6-11 illustrates examples of typical Stille reactions involving alkynyltins. A comprehensive list of examples following the Stille protocol can be found in a 1997 review by Farina [124b].

Typical catalysts used in the Stille cross-coupling are $[Pd(PPh_3)_2Cl_2]$, $[Pd(PPh_3)_4]$, $[BnPdCl(PPh_3)_2]$, and $[Pd(MeCN)_2Cl_2]$. Various other catalysts and ligands have also been employed, as shown in Table 6-11. Such catalysts include $[Pd(dppf)Cl_2]$, $[Pd_2(dba)_3]$, $[Pd(dppb)Cl_2]$, or $[Pd(dppp)Cl_2]$. It has been reported that excess PPh_3 actually slows down the coupling process, suggesting that coordinatively unsaturated "$[Pd(PPh_3)_2]$" acts as the active catalyst, and unique Pd(II) species have been used to facilitate its generation in situ [156]. To expand on this principle the "ligandless catalyst" systems such as $[(\eta^3\text{-}C_3H_5PdCl)_2]$, $[Pd(MeCN)_2Cl_2]$, and $LiPdCl_3$ have shown higher TON values and cross-couplings at milder temperatures than the typical Pd catalysts by generation of $RPd(solvent)_2$ type complexes in situ [157].

A number of newer catalyst systems have provided dramatic rate improvements in the Stille reaction of alkynyltins with haloarenes. These include Farina's tri(2-furyl)phosphine used in conjunction with $[Pd_2(dba)_3]$ or other Pd sources, as well as $AsPh_3$, which show rates of up to 10^3 times those of PPh_3 [158]. A recently described system is iminophosphine-Pd catalyst **72** prepared in two steps from 2-diphenylphosphinobenzaldehyde (Scheme 6-28) [159]. Remarkable yield improvements were seen over using tri(2-furyl)phosphine, dppp, or PPh_3 as ligands for the cross-coupling of alkynyltin **73** with iodoarene **74**. Fu has also recently disclosed that $P(t\text{Bu})_3$ with $[Pd_2(dba)_3]$ efficiently catalyzes the reaction between alkynylstannanes and aryl bromides at room temperature [160].

Table 6-11 Examples of Stille alkynyltin cross-couplings with organohalides.

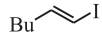
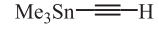
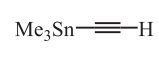
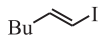
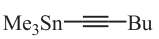
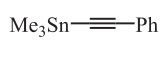
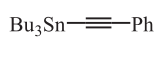
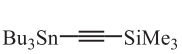
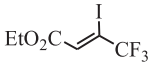
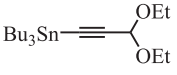
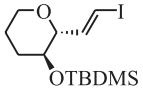
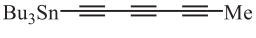
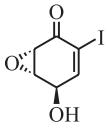
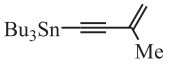
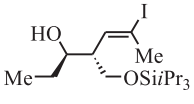
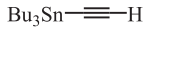
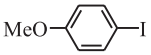
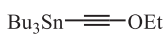
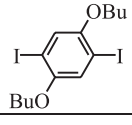
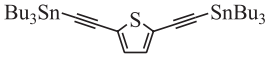
Organohalide	*Alkynylstannane*	*Conditions*	*Yield (%)*	*Ref.*
		$[Pd(PPh_3)_4]$ Et_2O, r.t., 22 h	50	[127]
		$[Pd(PPh_3)_4]$ THF, r.t., 24 h	90	[127]
		$[Pd(MeCN)_2Cl_2]$ DMF, –50 °C 0.05 h	88	[127]
		$[Pd(PPh_3)_4]$ THF, r.t., 10 h	90	[127]
		$[Pd(PPh_3)_2Cl_2]$ THF, r.t., 50 h	92	[127]
		$[Pd(PPh_3)_4]$ PhH, 55 °C, 9 h	77	[132]
		$[Pd(MeCN)_2Cl_2]$ DMF, r.t.	78	[133]
		$[Pd(PPh_3)_2Cl_2]$ THF, r.t.	95	[134]
		$[Pd(PPh_3)_2Cl_2]$ CuI, THF, r.t. 2 h	74	[135]
		$[Pd(PPh_3)_4]$ THF, 50 °C, 1 h	91	[136]
		$[Pd(PPh_3)_2Cl_2]$ Et_4NCl, DMF r.t., 1.5 h	60	[129b]
		$[Pd(PPh_3)_4]$ THF, 80 °C 24 h	94	[137]

Table 6-11 (continued)

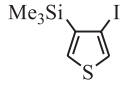
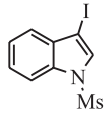
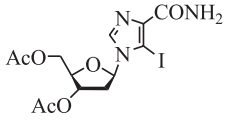
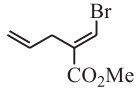
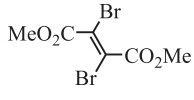
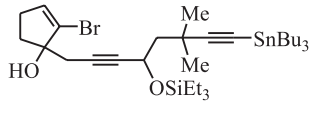
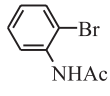
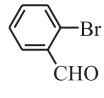
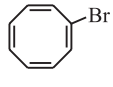
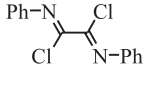
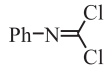
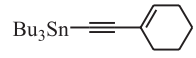
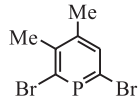
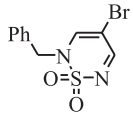
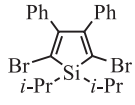
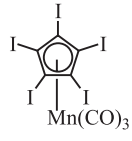
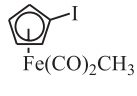
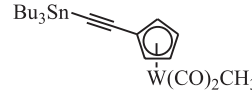
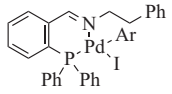
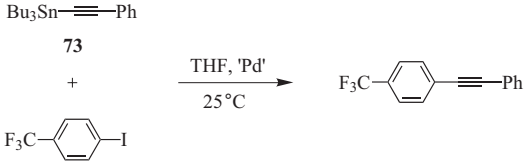
Organohalide	*Alkynylstannane*	*Conditions*	*Yield (%)*	*Ref.*
	$Bu_3Sn{\equiv}SnBu_3$	$[Pd(PPh_3)_4]$ dioxane, Et_3N 90 °C, 8 h	56	[138]
	$Bu_3Sn{\equiv}OEt$	$[Pd(PPh_3)_2Cl_2]$ Et_4NCl, DMF 50 °C, 2 h	60	[139]
	$Bu_3Sn{\equiv}SiMe_3$	$[Pd(PhCN)_2Cl_2]$ MeCN, 100 °C	69	[140]
	$Bu_3Sn{\equiv}Ph$	$[Pd(MeCN)_2Cl_2]$ $P(2\text{-furyl})_3$ PhMe, 80 °C 24 h	88	[141]
	$Bu_3Sn{\equiv}Ph$	$[Pd(PPh_3)_2Cl_2]$ THF, 25 °C 72 h	92	[142]
	$Bu_3Sn{\equiv}SnBu_3$	$[Pd(PPh_3)_4]$ THF, 50 °C 86 h	72	[143]
	$Bu_3Sn{\equiv}Bu$	$[Pd(PPh_3)_4]$ PhMe, 100 °C 2 h	84	[144]
	$Bu_3Sn{\equiv}{-}_2SiMe_3$	$[Pd(PPh_3)_2Cl_2]$ PhMe, 110 °C 2 h	91	[145]
	$Bu_3Sn{\equiv}SnBu_3$	$[Pd_2(dba)_3]$ $P(2\text{-furyl})_3$, THF r.t., 3 h	55	[146]
	$Bu_3Sn{\equiv}Ph$	$[Pd_2(dba)_3]$ $AsPh_3$, PhMe 50 °C, 5 h	50	[147]

Table 6-11 (continued)

Organohalide	*Alkynylstannane*	*Conditions*	*Yield (%)*	*Ref.*
		$[Pd(PPh_3)_2Cl_2]$ PhH, 70 °C, 5 h	74	[148]
	Bu_3Sn—≡—Ph	$[Pd(PPh_3)_4]$ DCE, 20 °C, 2 h	70	[149]
	Me_3Sn—≡—Ph	$[Pd_2(dba)_3]$ PPh_3, THF 85 °C, 3 h	85	[150]
	Bu_3Sn—≡—Ph	$[Pd(PPh_3)_2Cl_2]$ DCE, 50 °C	30	[151]
	Me_3Sn—≡—Ph	$[Pd(PPh_3)_2Cl_2]$ THF, 60 °C 12 h	100	[152]
	Me_3Sn—≡—Me	$[Pd(MeCN)_2Cl_2]$ DMF, 20 °C 40 h	38	[153]
		$[Pd(MeCN)_2Cl_2]$ DMF, 25 °C 8-12 h	85	[154]
	Bu_3Sn—≡—Ph	$[Pd(PPh_3)_4]$ THF,75 °C 20 h	51	[155]



72



73 + 74

Catalyst	Yield
72	90%
$P(2\text{-furyl})_3$, $[(\eta^3\text{-}C_3H_5PdCl)_2]$	57%
dppp, $[(\eta^3\text{-}C_3H_5PdCl)_2]$	34%
PPh_3, $[(\eta^3\text{-}C_3H_5PdCl)_2]$	1%

Scheme 6-28

6.3.2
Organotriflates in the Stille Reaction

Organotriflates are important electrophiles in Stille reactions due to their simple preparation from readily available phenols and ketones. Examples of alkynyltin cross-couplings with organotriflates are listed in Table 6-12. The addition of Li salts is typically necessary for a reaction to occur, with at least one equivalent of LiCl giving the best results. It is hypothesized that the LiCl provides chloride as a ligand for the Pd catalyst to facilitate the transmetallation step of the reaction [161]. Vinyl and aryl triflates readily react under somewhat mild conditions in solvents such as THF, NMP, dioxane, and DMF. The use of $P(2\text{-furyl})_3$, $P(o\text{tol})_3$, and $AsPh_3$ ligands with $[Pd_2(dba)_3]$ have increased product yields respectably [162]. Whereas the first two ligands required the use of LiCl, this additive was unnecessary with $AsPh_3$, which gave good yields in its absence. When polar solvents such as NMP are used, LiCl is again often unnecessary [124b]. Many other additives have been used in the Stille procedure and have shown modest improvements in cross-coupling rate and yield, and include stoichiometric $ZnCl_2$ [158b], CuO [171], Ag_2O [171], Et_4NCl [129b, 139], and catalytic CuI [172]. Transmetallation of the metal ions with the Sn species or ligation of the halides to the catalyst is theorized as the rate-improving process.

Alkynylstannanes can cross-couple with a variety of other functional groups through the Stille reaction (Table 6-13). Coupling to acyl chlorides is a well-known procedure under Stille conditions, and alkynylketones are afforded in respectable yields. Other reports include alkynyltin cross-couplings with α-haloethers, alkenyl(phenyl)iodonium salts, alkynyl halides, and allyl halides. Alkynylstannanes have also been shown to cross-couple with iron halides through Stille conditions effectively forming iron-carbon bonds.

Table 6-12 Examples of Stille alkynyltin cross-couplings with organotriflates.

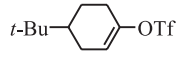
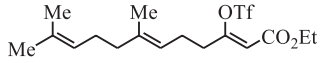
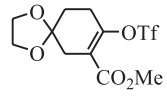
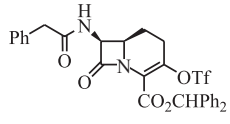
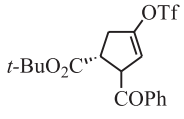
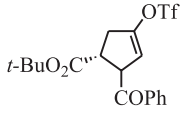
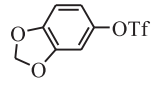
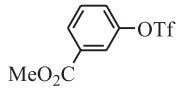
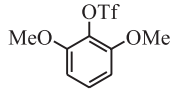
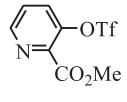
Organotriflate	*Alkynylstannane*	*Conditions*	*Yield (%)*	*Ref.*
	$Me_3Sn{-}{\equiv}{-}SiMe_3$	$[Pd(PPh_3)_4]$, LiCl THF, 60 °C, 41 h	90	[161c]
	$Bu_3Sn{-}{\equiv}{-}H$	$[Pd(PhCN)_2Cl_2]$ $AsPh_3$, CuI, NMP r.t., 18 h	31	[163]
	$Bu_3Sn{-}{\equiv}{-}Pr$	$[Pd(PPh_3)_4]$, LiCl THF, 60 °C	98	[164]
	$Bu_3Sn{-}{\equiv}{-}Me$	$[Pd_2(dba)_3]$ $P(2\text{-furyl})_3$, $ZnCl_2$ NMP, 25 °C, 16 h	50	[158b]
	$Bu_3Sn{-}{\equiv}{-}SiMe_3$	$[Pd(PPh_3)_4]$, LiCl THF, 60 °C	0	[165]
	$Bu_3Sn{-}{\equiv}{-}SiMe_3$	$[Pd_2(dba)_3]$ $P(2\text{-furyl})_3$, $ZnCl_2$ NMP, Et_2O, r.t. 16 h	49	[165]
	$Bu_3Sn{-}{\equiv}{-}H$	$[Pd(PPh_3)_4]$, LiCl dioxane, 98 °C 4 h	73	[161a]
	$Bu_3Sn{-}{\equiv}{-}Bu$	$[Pd(PPh_3)_4]$, LiCl dioxane, 100 °C 3 h	88	[144]
	$Bu_3Sn{-}{\equiv}{-}Ph$	$[Pd(PPh_3)_2Cl_2]$ dppf, LiCl, DMF 120 °C, 5 h	50	[166]
	$Bu_3Sn{-}{\equiv}{-}SiMe_3$	$[Pd(PPh_3)_4]$, LiCl dioxane, 80 °C	83	[167]

Table 6-12 (continued)

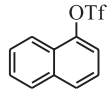
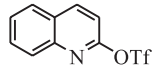
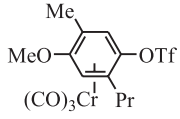
Organotriflate	*Alkynylstannane*	*Conditions*	*Yield (%)*	*Ref.*
	Bu_3Sn—≡—Ph	$[Pd_2(dba)_3]$ PPh_3, LiCl THF, 60 °C, 16 h	75	[168]
	Bu_3Sn—≡—Ph	$[Pd(PPh_3)_2Cl_2]$ LiCl, dioxane 90 °C, 24 h	65	[169]
	Bu_3Sn—≡—$SiMe_3$	$[Pd(PPh_3)_4]$, LiCl THF, 65 °C, 37 h	79	[170]

Table 6-13 Unusual alkynyl Stille cross-couplings

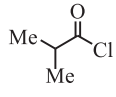
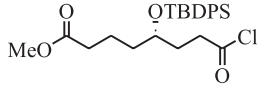
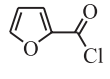
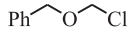
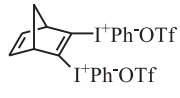
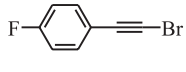
Electrophile	*Stannane*	*Conditions*	*Yield (%)*	*Ref.*
	Bu_3Sn—≡—Ph	$[Pd(PPh)_2Cl_2]$ DCE, 84 °C, 2 h	77	[173]
	Me_3Sn—≡—Oct	$[Pd(PPh)_2Cl_2]$ DCE, 84 °C, 0.5 h	82	[174]
	Bu_3Sn—≡—Bu	$[Pd(PhCN)_2Cl_2]$ PPh_3, $CHCl_3$, r.t., 6 h	52	[91]
	Bu_3Sn—≡—Ph	$[Pd(PPh_3)_4]$, PhH 80 °C, 6 h	73	[175]
	Bu_3Sn—≡—Ph	$[PdBn(PPh_3)_2Cl]$, CuI DMF, r.t., 0.5 h	92	[176]
	Me_3Sn—≡—Ph	$[Pd_2(dba)_3]$, PPh_3 CsF, 18-crown-6 PhMe, 110 °C, 4 h	52	[177]

Table 6-13 (continued)

Electrophile	*Stannane*	*Conditions*	*Yield (%)*	*Ref.*
Bu—≡—I	Bu_3Sn, *i*-PrO, O	[BnPd(PPh_3)$_2$Cl] CuI, DMF, r.t.	57	[172b]
Cl	Me_3Sn—≡—Ph	[$Pd_2(dba)_3$], PPh_3 THF, 50 °C, 19 h	12	[178]
Fe—I, OC, CO	Me_3Sn—≡—≡—H	[Pd(MeCN)$_2$$Cl_2$] THF, r.t.	57	[179]

6.3.3 Applications of the Stille Reaction

The use of alkynylmetals such as alkynylstannanes is an excellent method for the preparation of functionalized terminal acetylenes, which is difficult through the Sonogashira reaction and usually requires protection/deprotection steps [21, 84]. Since the alkynyltin is the reactive sp species under Stille conditions, cross-coupling occurs solely at this position and not at the terminal acetylene (Figure 6-2). Protection/deprotection steps can be avoided under Sonogashira conditions by using acetylene gas, but a mixture of further cross-coupling and alkyne dimerization products are seen, given that the terminal acetylene is the reactive species under these conditions [180]. Ethynyltributylstannane is also a commercially available material, so its preparation is unnecessary.

Due to its mild coupling conditions and excellent chemoselectivity, the Stille reaction has often been used for the synthesis of natural products. A remarkable application of this nature was reported by Danishefsky in the synthesis of a dynemicin A system **75** (Scheme 6-29) [181]. After a number of failed Sonogashira reactions of the terminal acetylene precursor **76**, iodination of **76** and subsequent

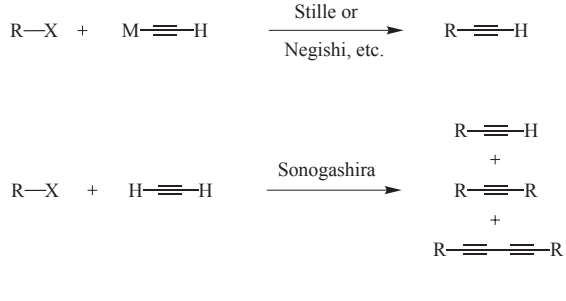
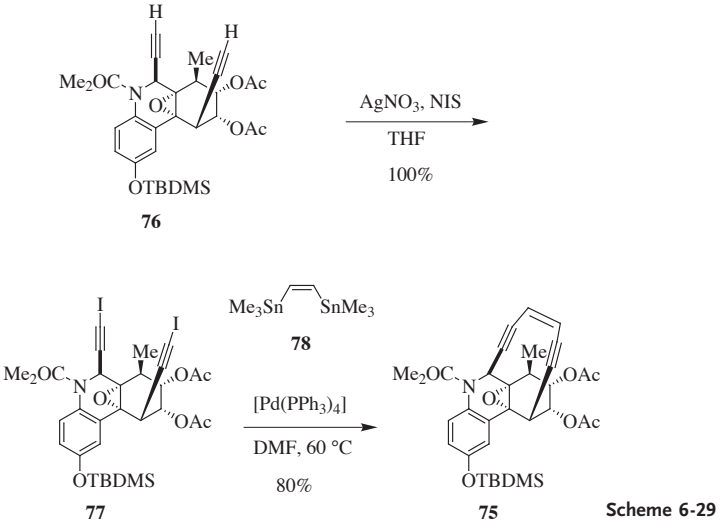


Figure 6-2 Preparation of functionalized terminal acetylenes.



Scheme 6-29

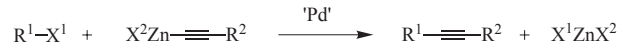
cross-coupling of iodoalkyne **77** with bis-stannylethylene **78** furnished an 80 % yield of **75**. This route has proven to be a very resourceful method for construction of cyclic enediyne systems.

6.4 Alkynylzinc Reagents

6.4.1 The Negishi Protocol

Alkynylzinc reagents typically show a higher intrinsic reactivity for cross-coupling than alkynylstannanes, although the Sn derivatives show comparable reactivity under newer sophisticated procedures. Alkynylzinc protocols, however, are still less commonly used than either Sonogashira or Stille procedures. Although Zn reagents display a higher nucleophilicity than Sn ones, reasonably good chemoselectivity is still observed [182]. Zn reagents are also easy to remove from the reaction mixture due to their high water solubility. Like alkynylstannanes, alkynylzincs can easily be used to provide terminal alkynes without the need for protection/deprotection steps (Figure 6-2) [180]. A major drawback to Zn reagents is their high water and air sensitivity, which prevents isolation and storage and necessitates strictly anhydrous conditions for their use. Alkynylzinc reagents, nevertheless, remain a powerful tool for C-C bond formation.

During the late 1970s, the Negishi group experimented with the Pd- and Ni-catalyzed cross-coupling of a variety of organometal reagents [183]. During this course of study, they found that alkynylzincs gave superior product yields and increased



R^1 = aryl, vinyl, acyl R^2 = aryl, vinyl, alkyl, etc.

X^1 = I, Br, Cl, OTf X^2 = Br, Cl

Scheme 6-30

reaction rates over other alkynylmetals. Pd catalysts were also found superior to Ni. The cross-coupling of organozinc reagents with organic electrophiles is now commonly referred to as the Negishi reaction. Al and Zr couplings are also often associated with Negishi and will be discussed in a later section. Several reviews have been written on the subject since its initial discovery [184]. Negishi established the applicability of Zn to alkyne cross-coupling early on with a variety of substituted alkynylzinc reagents, which cross-coupled efficiently with aryl or vinyl halides yielding the hetero-coupled products in good yields and with high selectivity [185] (Scheme 6-30).

Alkynylzinc reagents are normally prepared in situ before the addition of catalyst and organic electrophile from their alkynyllithium or alkynyl Grignard precursors with anhydrous $ZnBr_2$ or $ZnCl_2$ at low temperature [184e]. Again, the most typical Pd catalysts are $[Pd(PPh_3)_4]$ and $[Pd(PPh_3)_2Cl_2]$, although in the case of the latter, early reports often called upon reducing agents such as iBu$_2$AlH for in-situ generation of the active Pd[0] catalyst. Other Pd catalysts showing higher activity are $[Pd(dppf)Cl_2]$, [Pd(DPEphos)Cl_2], and $[Pd[P(2\text{-furyl})_3]_2Cl_2]$. Pd catalysts were shown to possess a slightly lower cross-coupling reactivity than Ni catalysts; however, they displayed remarkable improvements in yield and selectivity [184]. The catalytic cycle for the Negishi reaction is analogous to that of the Stille, which proceeds through the standard cycle of oxidative-addition of the organic electrophile, followed by transmetallation of the alkynylzinc species, and a final reductive elimination to give the cross-coupled product (see Scheme 6-6).

The Negishi protocol should be considered over other alkynyl cross-couplings in demanding situations where other methods have failed. In cases involving electron-withdrawing groups conjugated with the alkyne, alkynylzinc reagents have been reported to proceed where typical Sonogashira procedures falter [184e]; however, a two- to three-fold excess of the alkynylzinc reagent is often needed to effectively afford cross-coupling. Although early papers reported the cross-coupling to proceed with only vinyl and aryl iodides or activated bromides, more recent procedures include efficient cross-couplings with unactivated bromides, vinyl- and aryl chlorides, acyl chlorides, triflates, and nonaflates. Also, addition of $ZnCl_2$ as a co-catalyst has been shown effectively to cross-couple aryl halides with terminal alkynes [60, 186]. A variety of representative alkynylzinc cross-couplings is shown in Table 6-14.

An exceptional example of the difference in reactivity between the Sonogashira cross-coupling of terminal alkynes and the cross-coupling of alkynylzinc reagents was recently demonstrated by Tobe in the synthesis of hexaethynylarene **79**

Table 6-14 Examples of Negishi alkynylzinc cross-couplings.

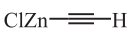
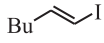
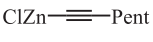
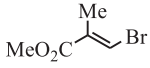
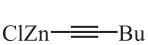
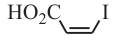
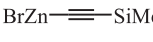
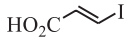
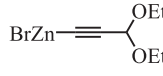
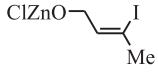
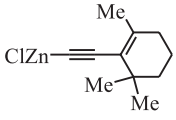
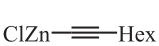
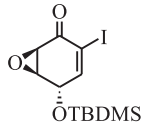
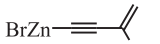
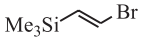
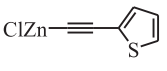
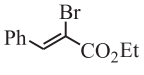
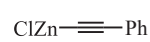
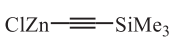
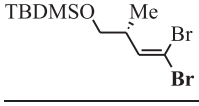
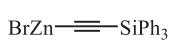
RX	*Alkynylzinc*	*Conditions*	*Yield (%)*	*Ref.*
		$[Pd(PPh_3)_4]$, THF 25 °C	65	[185a]
		$[Pd(PPh_3)_4]$, THF 25 °C	76	[185a]
		$[Pd(PPh_3)_4]$, THF 25 °C	65	[185a]
		$[Pd(MeCN)_2Cl_2]$ DMF, Et_2O, r.t., 12 h	88	[187]
		$[Pd(MeCN)_2Cl_2]$ DMF, Et_2O, r.t., 12 h	71	[187]
		$[Pd(PPh_3)_2Cl_2]$, BuLi DMF, 70 °C, 5 h	68	[188]
		$[Pd(PPh_3)_4]$, THF 20 °C, 24 h	62	[189]
		$[Pd(dba)_2]$ $P(2\text{-furyl})_3$, DMF r.t., 1 h	73	[190]
		$[Pd(PPh_3)_4]$, THF 0 °C, 15 h	87	[191]
		$[Pd(PPh_3)_4]$, THF 60 °C	88	[192]
		$[Pd(DPEphos)Cl_2]$ THF, 0 °C, 1 h	84	[193]
		$[Pd(DPEphos)Cl_2]$ THF, 0 °C, 6 h	99	[193]

Table 6-14 (continued)

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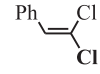
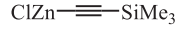
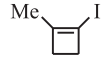
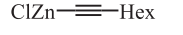
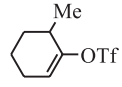
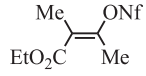
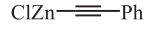
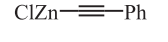
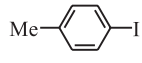
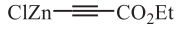
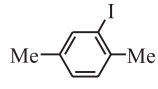
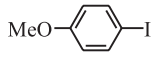
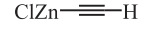
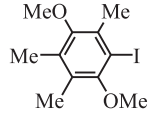
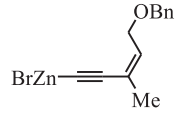
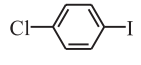
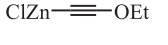
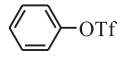
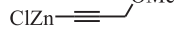
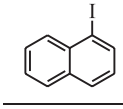
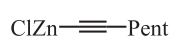
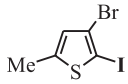
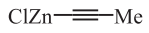
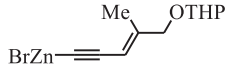
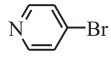
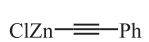
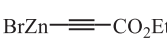
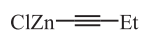
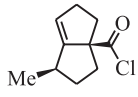
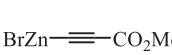
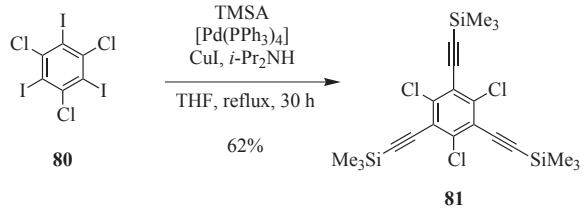
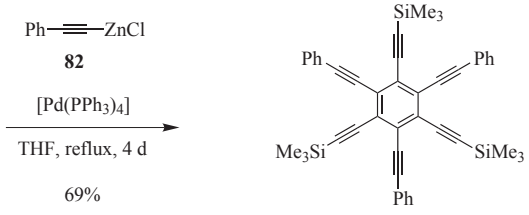
		$[Pd(dppf)Cl_2]$, THF r.t., 6 h	84	[193]
		$[Pd(PPh_3)_4]$, THF r.t., 1 h	78	[194]
		$[Pd(PPh_3)_4]$, THF r.t., 1 h	83	[195]
		$[Pd(dba)_2]$, dppf THF, 65 °C, 22 h	85	[196]
		$[Pd(PPh_3)_4]$, THF r.t., 0.5 h	74	[185b]
		$[Pd(PPh_3)_2Cl_2]$, THF 50 °C, 3 h	67	[129a]
		$[Pd(PPh_3)_4]$, THF r.t., 3 h	83	[180]
		$[Pd(PPh_3)_4]$, THF r.t., 1 h	56	[185b]
		$[Pd(PPh_3)_4]$, THF 50 °C, 7 h	70	[197]
		$[Pd(PPh_3)_2Cl_2]$, PPh_3 BuLi, THF, r.t., 4 h	65	[198]
		$[Pd(PPh_3)_4]$, LiCl THF, DMF 70 °C, 12 h	67	[199]
		$[Pd(PPh_3)_4]$, THF 50 °C, 4 h	80	[200]

Table 6-14 (continued)

RX	*Alkynylzinc*	*Conditions*	*Yield (%)*	*Ref.*
		$[Pd(PPh_3)_2Cl_2]$ *i*-Bu_2AlH, THF r.t., 2 h	70	[185b]
		$Pd(OAc)_2$, PPh_3 THF, r.t., 3 h	68	[201]
		$[Pd(PPh_3)_4]$, THF r.t., 1 h	82	[202]
		$[Pd(PPh_3)_4]$, THF 60 °C, 12 h	84	[203]
		$[Pd(PPh_3)_4]$, THF r.t., 1 h	82	[195]
		$[Pd(PPh_3)_4]$, THF r.t., 10 min	84	[202]
		$[Pd(PPh_3)_4]$, THF r.t., 4 h	72	[204]
		$[Pd(PPh_3)_4]$, THF r.t., 1 h	86	[195]

(Scheme 6-31) [205]. The initial Sonogashira coupling of TMSA in refluxing THF occurred at the more reactive iodo positions of arene **80**, with no coupling observed at the chloro positions. The slightly electron-withdrawing character of the alkyne groups in the product **81** was enough to activate the C-Cl bond so that cross-coupling was possible through Negishi conditions using 20 equiv. of alkynylzinc **82**. After four days in refluxing THF, hexaethynylarene **79** was isolated in 43 % overall yield for the two steps. It should be noted however, that the Sonogashira cross-coupling using 5.2 equiv. of phenylacetylene with arene **80** did give 33 % yield of tetra-coupled product after two days under reflux.

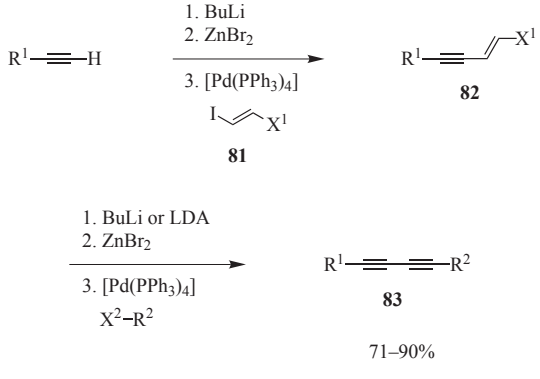




Scheme 6-31

6.4.2
Alternative 1,3-Butadiyne Synthesis

The Negishi group has also employed organozinc chemistry for an alternative synthesis of various conjugated 1,3-diynes [206]. The method involves initial cross-coupling of an in-situ-generated alkynylzinc to the iodo position of (*E*)-dihaloethene **81** (Scheme 6-32) [206a]. Treatment of the resultant haloalkene **82** with base (BuLi for $X^1 = Cl$, LDA for $X^1 = Br$) followed by $ZnBr_2$ and addition of an organic electrophile with $[Pd(PPh_3)_4]$ induces a second cross-coupling to give diyne **83**. This



R^1 = aryl, alkenyl, alkyl, etc. R^2 = aryl, alkenyl X = Br, Cl

Scheme 6-32

method has the benefit of allowing no possibility for homo-coupled products such as commonly seen under Cadiot-Chodkiewicz conditions (see Scheme 6-26) [106].

6.5 Alkynylboron Reagents

6.5.1 The Suzuki Reaction

The cross-coupling of organoboron reagents with organic electrophiles in the presence of a base and Pd catalyst is commonly known as the Suzuki reaction, and has been established as a powerful tool for C-C bond formation over the past 20 years [207]. Organoboron reagents show a number of advantageous properties over other organometals [208]. Like organozincs, organoborons have a much lower toxicity than organostannane reagents. In addition, they have the advantage of water and air stability, so that isolation and storage is possible. Organoboron reagents tolerate many functional groups, show insignificant effects due to steric hindrance, and are easily separable from the reaction mixture.

Alkynylboranes are stronger Lewis acids than alkyl-, alkenyl-, or arylboranes, and thus have been used for a number of synthetic transformations such as enantioselective addition to enones [209] and aldehydes [210] to give propargylic alcohols, Diels-Alder cycloadditions [211], enyne [212] and enynone [213] synthesis, and precursors to vinylboronates [207]. However, because alkynylboranes are easily hydrolyzed, they have been utilized far less in cross-coupling reactions because of the base necessary for the transformation. Nevertheless, there have been a few recent reports describing alkynylboron reagents which give cross-coupled products and are stable under cross-coupling conditions. These reagents include alkynylborates, alkynylborinates, alkynylboronic esters, and alkynyltrifluoroborates.

6.5.2 9-Alkynyl-9-BBN Cross-Couplings

Until recently, there had been only one report in 1979 of the successful use of alkynylboron reagents in cross-coupling reactions (Table 6-15) [183]. Some 16 years later, the groups of Soderquist [214] and Fürstner [215] independently reported that alkynylborates prepared from 9-methoxy-9-borabicyclo[3.3.1]nonane (9-OMe-9-BBN) effectively cross-couple with a variety of bromoalkenes and -arenes using a Pd catalyst under base-free conditions. Suzuki had previously described success with the cross-coupling of 9-alkyl and 9-alkenyl-9-BBN derivatives prepared by hydroboration of alkenes and alkynes under basic conditions [207]. The active nucleophile is most likely the borate formed from reaction of the borane and base. Soderquist and Fürstner avoided using basic conditions and the formation of the unstable alkynylborane by generating the more stable alkynylborate **84** in situ from alkynylmetals and 9-OMe-9-BBN (**85**) (Scheme 6-33). Addition of

Table 6-15 Examples of Suzuki alkynylboron cross-couplings.

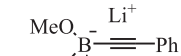
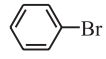
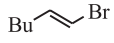
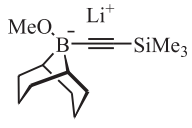
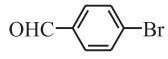
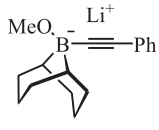
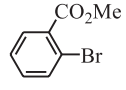
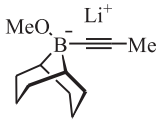
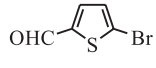
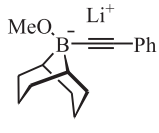
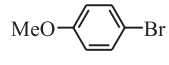
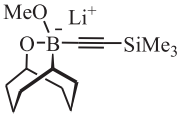
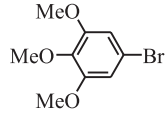
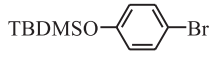
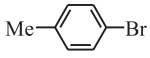
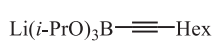
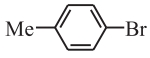
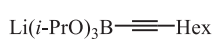
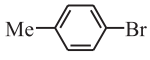
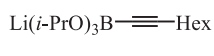
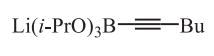
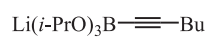
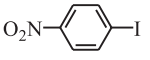
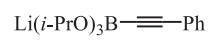
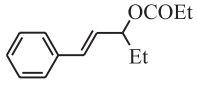
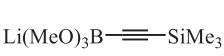
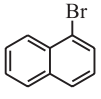
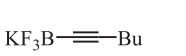
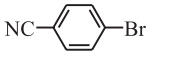
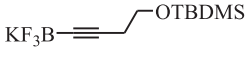
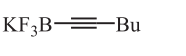
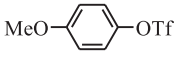
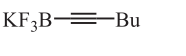
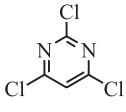
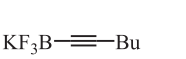
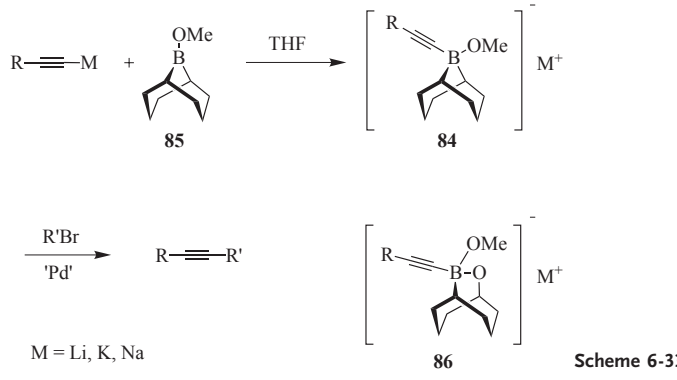
RX	*Alkynylboron*	*Conditions*	*Yield (%)*	*Ref.*
		$[Pd(PPh_3)_2Cl_2]$ *i*-Bu_2AlH, THF 60 °C, 1 h	92	[183]
		$[Pd(PPh_3)_4]$, THF 60 °C	94	[214]
		$[Pd(PPh_3)_4]$, THF 60 °C	55	[214]
		$[Pd(dppf)Cl_2]$, THF 60 °C	77	[215]
		$[Pd(dppf)Cl_2]$, THF 60 °C	87	[215]
		$[Pd(dppf)Cl_2]$, THF 60 °C	68	[215]
		$[Pd(PPh_3)_4]$, THF 60 °C	62	[216]
		$[Pd(dppf)Cl_2]$, THF 60 °C	77	[217]
		$[Pd(dppf)Cl_2]$, THF 60 °C	56	[217]

Table 6-15 (continued)

RX	*Alkynylboron*	*Conditions*	*Yield (%)*	*Ref.*
		$[Pd(PPh_3)_4]$ DME/THF (10/1) 60 °C, 5 h	98	[218]
		$[Pd(PPh_3)_4]$, THF 60 °C, 5 h	30	[218]
		$[Pd(PPh_3)_4]$, DME 60 °C, 5 h	0	[218]
		$[Pd(PPh_3)_2Cl_2]$ DMF, 60 °C, 4 h	47	[219]
		$[Pd(PPh_3)_2Cl_2]$, CuI DMF, 60 °C, 4 h	93	[219]
		$[Pd(PPh_3)_4]$, CuI DMF, 60 °C, 15 h	98	[219]
		$[Ni(dppe)Cl_2]$, THF 60 °C, 12 h	93	[220]
		$[Pd(dppf)Cl_2]$, THF H_2O, Cs_2CO_3 60 °C, 12 h	87	[221]
		$[Pd(dppf)Cl_2]$, THF H_2O, Cs_2CO_3 60 °C, 12 h	88	[221]
		$[Pd(dppf)Cl_2]$, THF H_2O, Cs_2CO_3 60 °C, 12 h	78	[221]
		$[Pd(dppf)Cl_2]$, THF Cs_2CO_3 60 °C, 12 h	78	[221]
		$[Pd(dppf)Cl_2]$, THF H_2O, Cs_2CO_3 60 °C, 12 h	70	[221]

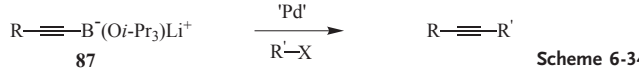


Scheme 6-33

$[Pd(PPh_3)_4]$ or $[Pd(dppf)Cl_2]$ and a variety of bromoalkenes or arenes gave the cross-coupled products in moderate yields (Table 6-15). The cross-coupling proceeds mechanistically by the characteristic pathway of oxidative-addition, transmetallation, and reductive-elimination affording the product while regenerating the active catalyst. Soderquist and coworkers have also developed alkynylborinates **86**, designed for cross-coupling, which allow easier isolation than their 9-BBN counterparts **84** [216].

6.5.3
Alkynyl(trialkoxy)borate Cross-Couplings

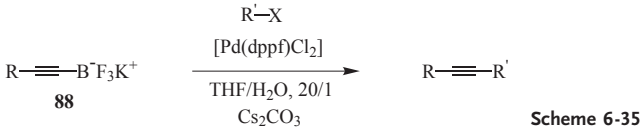
There have been a few reports of the successful Suzuki cross-coupling of alkynylboronic esters and alkynyl(trialkoxy)borates. Fürstner and coworkers have cross-coupled ethynyl(trimethoxy)borates with a variety of haloarenes in moderate yields using $Pd(dppf)Cl_2$ in refluxing THF (Table 6-15) [217]. The Colobert group later described the in-situ formation of alkynyl(triisopropoxy)borates (**87**) from alkynyllithium precursors, that cross-coupled with a variety of bromoarenes and alkenes using $Pd(PPh_3)_4$ to give the internal acetylene products (Scheme 6-34; Table 6-15) [218]. The group found the reaction to be quite solvent-dependent, with a 10:1 ratio of DME/THF affording the best results. The analogous alkynylboronic ester isolated beforehand gave poorer yields. Oh and Jung similarly reported the cross-coupling of **87** with bromo- and iodoarenes (Scheme 6-34) [219]. They found that the lithium alkynyl(triisopropoxy)borates were quite stable upon work-up and refrigerated storage for several months. Interestingly, they discovered that CuI as a co-catalyst with $[Pd(PPh_3)_4]$ in DMF increased product yields (Table 6-15). Alkynyl(trimethoxy)borates have also been reacted with allyl carbonates by the Deng group using $[Ni(dppe)Cl_2]$ as catalyst (Table 6-15) [220].



Scheme 6-34

6.5.4
Alkynyltrifluoroborate Cross-couplings

More recently, Molander et al. have reported that potassium alkynyltrifluoroborates **88** give moderate to good yields of hetero-coupled products with an array of aryl- and heteroaryl halides and triflates (Scheme 6-35) [221]. Compounds based on **88** are prepared by reacting alkynyllithium reagents with 1.5 equiv. $B(OMe)_3$, followed by addition of 6 equiv. KHF_2. These alkynylborates have the advantage of air and moisture stability as well as increased atom economy. Careful control of solvent, base, and catalyst was found necessary for the reaction with a 20:1 ratio of $THF:H_2O$, 3 equiv. Cs_2CO_3, and 9 mol% $[Pd(dppf)Cl_2]$ giving the best yields of cross-coupled product (Scheme 6-35). Interestingly, these authors found the reactivity order for the cross-coupling to be OTf > Br > I ≈ Cl, which is quite different from most cross-coupling reactions.



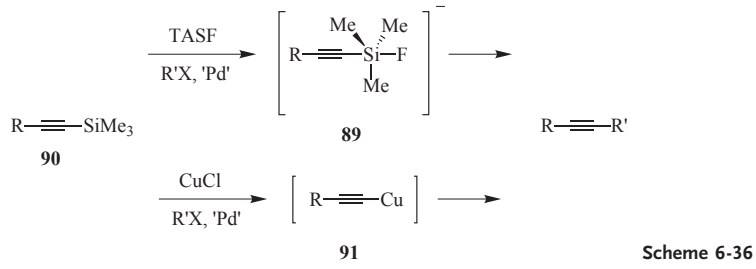
Scheme 6-35

6.6
Alkynylsilicon Reagents

6.6.1
Alkynylsilane Cross-Couplings

Organosilicon reagents are readily available, inexpensive, and robust. Their use in acetylene chemistry has classically been limited to protective groups for terminal acetylenes (see Section 6.2.2.5). Indeed, alkynylsilanes are stable to the amine base used in the Sonogashira reaction, and will not react under normal Pd-mediated cross-coupling conditions due to the low polarization of the C-Si bond. However, this bond can be activated by fluoride ion to effect cross-coupling [222]. Alkynylsilanes have also been reported to efficiently cross-couple in the presence of additives such as Cu and Ag salts. The unique ability of alkynylsilanes to serve both as a protective group and a cross-coupling reagent make them powerful tools for the synthesis of unsymmetrical diarylacetylenes and extended π-electronic molecules. The standard three-step process for making these systems using Sonogashira chemistry involving cross-coupling of TMSA, followed by protodesilylation, then a final cross-coupling can be circumvented by this route, and one-pot reactions are also possible.

Much of the organosilicon cross-coupling chemistry has been developed by Hiyama, who reported the activation of alkenyl, allyl, and alkynyltrimethylsilanes by fluoride ion in 1988 [223]. A slight excess of tris(diethylamino)sulfonium



Scheme 6-36

difluorotrimethylsilicate (TASF) provides a fluoride ion which forms pentacoordinated silicate **89** from alkynylsilane **90**. This new silicate easily undergoes transmetallation with Pd catalysts (Scheme 6-36). Cross-coupling occurs with an assortment of haloarenes and alkenes in excellent yields (Table 6-16). This methodology has the benefits of mild reaction conditions, low or no detectable diyne byproduct, and good stereospecificity and regioselectivity.

More recently, alkynylsilanes were reported to cross-couple with aryl, alkenyl, and alkynylhalides and triflates with catalytic CuCl and $[Pd(PPh_3)_4]$ in DMF [224]. Instead of activation of the alkynylsilane by fluoride ion, transmetallation with Cu to form Cu-acetylide **91** is considered the activation step (Scheme 6-36). Compound **91** then reacts as in the Sonogashira reaction, and consequently has been referred to as the "sila-Sonogashira-Hagihara" coupling. A number of internal acetylenes were constructed by this tactic (Table 6-16). Hosomi has actually isolated many of the Cu-acetylides formed from alkynylsilanes and CuCl, and has subsequently applied these intermediates in the cross-coupling with acid chlorides [225]. The reaction is also applicable to the synthesis of 1,3-diynes from aryl(chloro)ethynes, which often fail under Cadiot-Chodkiewicz conditions [226]. Higher yields were achieved in the absence of Pd catalyst for this procedure. By using CuCl, Et_3N, or Bu_3N, and by substituting 1,3-dimethylimidazolidin-2-one (DMI) for DMF, Marshall et al. were able to cross-couple alkynylsilanes with vinyl and aryl halides [227]. They reported that, again, in the absence of Pd catalysts, higher yields were obtained, with no homo-coupled alkyne as is seen in the presence of Pd catalysts.

The cross-coupling of alkynylsilanes has also been achieved using Ag salts, as demonstrated by Mori utilizing bis(TMS)alkynes with iodoarenes, Ag_2O, and $[Pd(PPh_3)_4]$ (Table 6-16) [228]. Using a combination of AgI and TBAF with $[Pd(PPh_3)_4]$, Pale and co-workers were able to cross-couple a variety of alkynylsilanes with vinyl triflates [229]. Silanes as bulky as TIPS efficiently reacted with the vinyl triflates. Similarly, alkynylsilanols have been reported to hetero-couple with iodoarenes using TBAF or Ag_2O as additives [230]. The Nolan group has also used their imidazolium ligands (see Table 6-3) to afford cross-coupling between TMS-acetylenes and bromo- and chloroarenes [231].

Table 6-16 Exaamples of organosilicon cross-couplings.

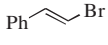
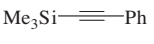
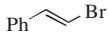
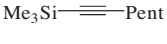
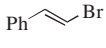
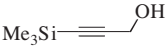
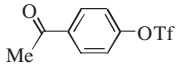
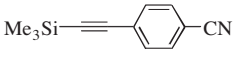
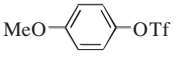
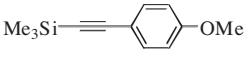
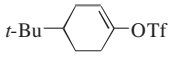
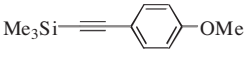
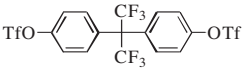
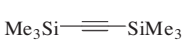
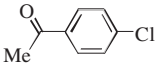
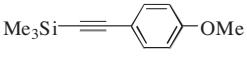
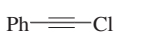
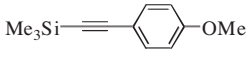
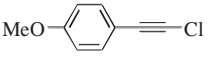
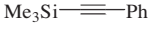
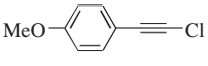
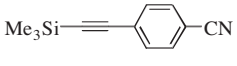
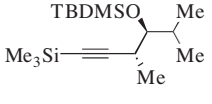
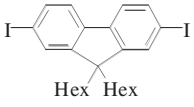
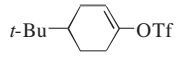
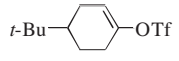
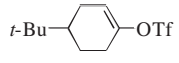
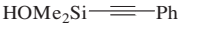
RX	*Organosilicon*	*Conditions*	*Yield (%)*	*Ref.*
		TASF $[\eta^3\text{-}C_3H_5PdCl)_2]$ THF	83	[223]
		TASF $[\eta^3\text{-}C_3H_5PdCl)_2]$ THF	86	[223]
		TASF $[\eta^3\text{-}C_3H_5PdCl)_2]$ THF	84	[223]
		CuCl $[Pd(PPh_3)_4]$, DMF 80 °C, 24 h	52	[232]
		CuCl $[Pd(PPh_3)_4]$, DMF 80 °C, 24 h	49	[224]
		CuCl $[Pd(PPh_3)_4]$, DMF 80 °C, 24 h	90	[232]
		CuCl $[Pd(PPh_3)_4]$, DMF 80 °C, 16 h	63	[233]
		CuCl $[Pd(dppb)Cl_2]$, DMF 120 °C, 12 h	56	[224]
		CuCl DMF, 80 °C, 48 h	65	[226]
		CuCl DMF, 80 °C, 48 h	56	[226]
		CuCl DMF, 80 °C, 48 h	61	[226]
		CuCl DMI, 80 °C, 8 h	85	[225]
		CuCl DMI, Bu_3N 120 °C, 19 h	94	[227]

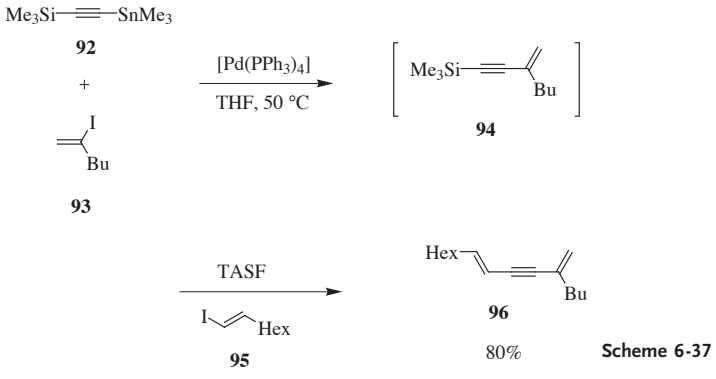
Table 6-16 (continued)

RX	*Organosilicon*	*Conditions*	*Yield (%)*	*Ref.*
		Ag_2O $[Pd(PPh_3)_4]$, THF 60 °C, 5 h	99	[228]
		AgI, TBAF $[Pd(PPh_3)_4]$, H_2O DMF, r.t., 21 h	87	[229]
		AgI, TBAF $[Pd(PPh_3)_4]$, H_2O DMF, r.t., 24 h	75	[229]
		AgI, TBAF $[Pd(PPh_3)_4]$, H_2O DMF, r.t., 24 h	75	[229]
		Ag_2O $[Pd(PPh_3)_4]$, THF 60 °C, 2 h	78	[230]
		TBAF $[Pd(PPh_3)_4]$, THF 60 °C, 2 h	90	[230]

6.6.2
One-Pot Two-Fold Cross-Couplings

The significance of the alkynylsilicon methodology is most aptly demonstrated in one-pot reactions that would typically require two cross-coupling steps along with a silane deprotection step. Sequential Sonogashira and CuCl activated cross-coupling was reported by Nishihara and Hiyama [224]. This procedure is similar to the method described previously using DBU as a base for silane deprotection (see Scheme 6-17) [87]. Both cross-couplings proceed through Sonogashira conditions, with a Cu-acetylide generated in each case.

In another one-pot reaction, sequential Stille and TSAF activated cross-coupling were reported by Hiyama [234]. This procedure lacks any copper or amine base, so is truly unlike the Sonogashira cross-coupling. Initial Stille coupling occurred at the trimethylstannyl group of **92** with vinyliodide **93** giving intermediate **94** in which the trimethylsilyl group is still intact (Scheme 6-37). Addition of TASF and the second vinyliodide (**95**) then furnished asymmetrical alkyne **96** through the above-mentioned silicate cross-coupling. An assortment of functionalized dienynes was constructed by this method.



Scheme 6-37

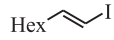
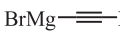
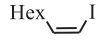
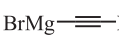
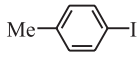
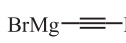
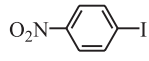
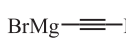
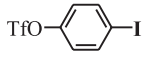
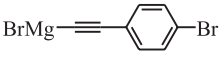
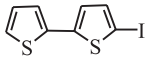
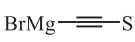
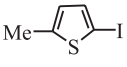
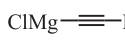
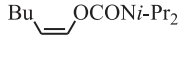
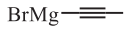
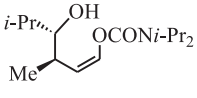
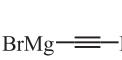
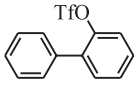
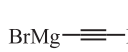
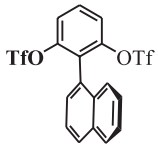
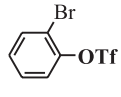
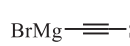
6.7 Alkynylmagnesium Reagents

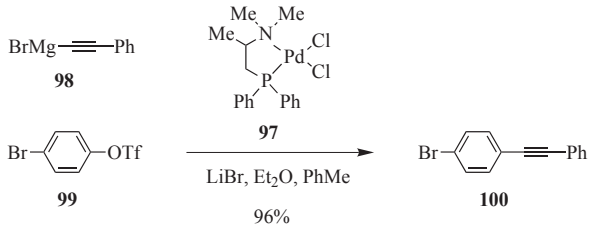
Alkynylmagnesium and alkynyllithium reagents are typically used for the preparation of other alkynylmetals such as alkynylstannanes, -zincs, and -borons. Alkynylmagnesium reagents do however show a moderate reactivity for cross-coupling, and in many cases their direct cross-coupling can be attempted before conversion to further alkynylmetals such as alkynylzinc or tin. On the other hand, alkynyllithium reagents are generally not applicable to metal-mediated cross-couplings. Due to their high nucleophilicity, poisoning of the catalyst is typically seen and palladate complexes such as $[Li_2Pd(C{\equiv}CR)_4]$ have been observed [235].

The Pd-catalyzed cross-coupling of alkynyl Grignard reagents was reported as early as 1978 by the groups of Linstrumelle [236] and Negishi [183]. These reagents effectively cross-couple with vinyl and aryl iodides at room temperature, displaying an intrinsic reactivity which is nearly as high as other alkynylmetals such as those containing Zn or Sn. The Hayashi group has recently reported alkynyl Grignard reagents which efficiently cross-couple with aryltriflates in high yields at room temperature [237]. The main drawback to alkynylmagnesium reagents is their low chemoselectivity. Due to their high nucleophilicity, they show poor compatibility with groups such as carbonyl and nitro; therefore, their general use in cross-coupling reactions is somewhat limited. Alkynylmagnesium reagents do possess the benefits that they are often commercially available, or are otherwise easily prepared. Terminal alkyne synthesis is possible *via* this route, and the magnesium salt can be easily removed from the reaction.

The cross-coupling of alkynyl Grignard reagents with vinyl iodides can be achieved in good yield at room temperature using $[Pd(PPh_3)_4]$ as a catalyst (Table 6-17) [236]. Stereoselectivities in this report were all greater than 97 %. Lower – though still acceptable – yields were reported when the cross-coupling was attempted with aryl iodides at room temperature with the same catalyst [180, 183]. This procedure has also been successfully employed with iodothiophenes for the synthesis of antifungal and nematicidal agents [238]. Furthermore, using a Ni catalyst

Table 6-17 Examples of alkynylmagnesium cross-couplings.

RX	*Alkynylmagnesium*	*Conditions*	*Yield (%)*	*Ref.*
		$[Pd(PPh_3)_4]$, THF, r.t.	83	[236]
		$[Pd(PPh_3)_4]$, THF, r.t.	80	[236]
		$[Pd(PPh_3)_4]$, THF r.t., 24 h	49	[183]
		$[Pd(PPh_3)_4]$, THF r.t., 1 h	86	[180]
		$[Pd(PPh_3)_4]$, THF 0 °C, 12 h	0	[180]
		$[Pd(alaphos)Cl_2]$ Et_2O, PhMe 30 °C, 2 h	91	[237]
		$[Pd(PPh_3)_4]$, THF PhH, 60 °C, 5 h	65	[238]
		$[Pd(PPh_3)_4]$, THF, r.t.	35	[240]
		$[Ni(PPh_3)_2Cl_2]$, PhH 70 °C, 168 h	80	[239]
		$[Ni(PPh_3)_2Cl_2]$, PhH 70 °C, 21 h	78	[239]
		$[Pd(alaphos)Cl_2]$ LiBr, Et_2O, PhMe 30 °C, 6 h	93	[241]
		$[Pd(alaphos)Cl_2]$ LiBr, Et_2O, PhMe 30 °C, 4 h	91	[242]
		$[Pd(alaphos)Cl_2]$ LiBr, Et_2O, PhMe 30 °C, 4 h	91	[237]



Scheme 6-38

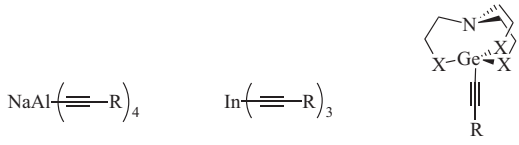
$[Ni(PPh_3)_2Cl_2]$, a unique cross-coupling of alkynylmagnesium reagents with vinylcarbamates was reported to give enyne products in moderate yields [239].

More recently, excellent yields were reported in the cross-coupling of alkynyl Grignard reagents with aryltriflates [237]. A catalyst screening was performed by Hayashi with an array of phosphine and β-(dimethylaminoalkyl)phosphine-ligated Pd catalysts [241]. Whereas typical phosphine ligands gave very low yields, near-quantitative yields for alkynylmagnesium cross-couplings were achieved with dichloro[(2-dimethylamino)propyldiphenylphosphine]palladium ($[PdCl_2$(alaphos)], **97**) (Scheme 6-38). Using this catalyst, the cross-coupling of Mg-acetylides is highly selective for aryltriflates over aryl bromides. Phenylethynylmagnesium bromide (**98**) cross-coupled selectively at the triflate position of 4-bromophenyl triflate (**99**) giving **100** in 96 % yield. Addition of 1 equiv. LiBr was found to give a slight increase in yield. High yields of the cross-coupled product were also obtained with sterically hindered aryl triflates and iodoarenes with the reactivity order established I > OTf > Br (Table 6-17).

The cross-coupling of alkynylmagnesiums with haloalkynes to give unsymmetrical butadiynes was reported in 1954 [243]. Alkynyl Grignard reagents in an Et_2O solution reacted with 1-iodoalkynes with either catalytic CuCl or CoCl to give the hetero-coupled diynes in low to moderate yields.

6.8 Other Alkynylmetals

Superior alternatives or reactions complementary to the widely used Sonogashira and related alkynylmetal cross-couplings have long been a synthetic goal, with hopes to overcome some of the intrinsic problems of the previously mentioned reactions and to provide a secondary coupling procedure for less-reactive electrophiles. Therefore, a variety of other alkynylmetal reagents have been investigated for potential cross-coupling capability. A screening of alkynylmetals in 1978 by Negishi suggested that the most applicable metals may be limited to Zn, Sn, B and, to a lesser extent, Al [183]. During the past 25 years, significant developments in ligands, catalysts, and reaction conditions, among other variables, have enabled efficient cross-coupling of several other alkynylmetals.



101 **102** **103a**, X = CH_2 **103b**, X = O

Figure 6-3 Other active alkynylmetals.

Like boron, Group 13 organometallics such as alkynylaluminum reagents have shown some promise for cross-coupling ability. In 1980, Oshima reported moderate yields from the cross-coupling of alkynylaluminum reagents of the form [RC≡C$AlEt_2$] with enol phosphates catalyzed by [$Pd(PPh_3)_4$] (Table 6-18) [244]. A few years later, the same group described similar reagents providing alkynylketones from acyl chlorides in an analogous procedure [245]. More recently, Blum and Molander reported high yields from the cross-coupling of sodium tetraalkynylaluminates (**101**) with aryl bromides (Figure 6-3) [246]. The aluminates were easily prepared from terminal alkynes and $NaAlH_4$ and were usually air- and moisture-stable solids, although isolation was not necessary. In-situ generation of **101** effectively gave cross-coupled products from a variety of aryl bromides catalyzed by [$Pd(PPh_3)_2Cl_2$] in refluxing THF or DME. The reaction is chemoselective for the bromo functionality, leaving triflates, carbonyl, and other sensitive groups untouched. Homo-dimerization of the alkyne, which typically plagues the Sonogashira reaction, was also not observed.

Sarandeses has recently described another Group 13 organometallic species, trialkynylindium (**102**), that efficiently cross-couples with aryl iodides, activated aryl bromides and triflates, vinyl triflates, benzyl bromides, and acyl chlorides (Table 6-18) [247]. The trialkynylindium species is prepared in situ from the corresponding alkynyllithium or Grignard reagent and $InCl_3$. All three of the groups attached to the In center are transferable to the electrophile, so that only 0.34 equiv. of [$(RC{\equiv}C)_3In$] is required in the reaction. In most cases, excellent yields of cross-coupled products are achieved with only 1 mol% [$Pd(PPh_3)_2Cl_2$] or [$Pd(PPh_3)_4$] catalyst, whereas more demanding electrophiles demonstrate better yields using [Pd(dppf)Cl_2].

Similar to alkynylsilicon, alkynylgermanium reagents are unreactive to cross-coupling without some form of activation. In order to activate tetracoordinated germane, Kosugi et al. prepared 1-aza-5-germa-5-alkynylbicyclo[3.3.3]undecane **103a** [248]. Transannular coordination of the nitrogen to germanium was hoped to activate the organocarbagermatrane for cross-coupling. These alkynylgermanium reagents were prepared by hydrozirconation of triallylamine followed by transmetallation with $GeCl_4$ and further reaction of the resultant complex with alkynyllithium or Grignard reagents. Compound **103a** (R = Ph) did indeed give a moderate yield of cross-coupled product with 4-bromotoluene catalyzed by [$Pd_2(dba)_3$] and $PPh(o\text{tol})_2$, although elevated temperatures were required (Table 6-18). Expanding on this concept, Faller later reported alkynylgermatranes **103b** to cross-couple with

Table 6-18 Examples of other alkynylmetal cross-couplings.

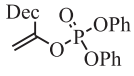
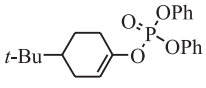
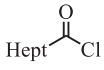
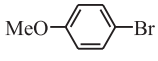
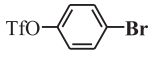
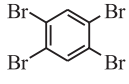
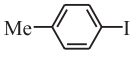
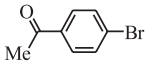
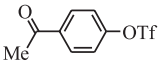
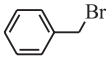
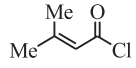
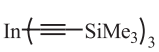
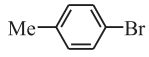
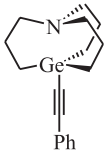
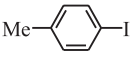
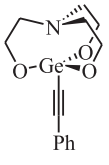
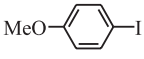
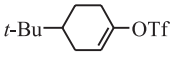
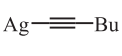
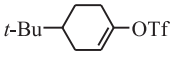
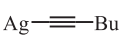
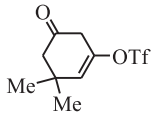
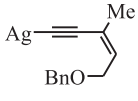
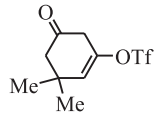
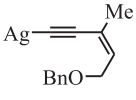
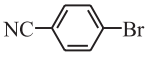
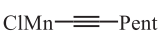
RX	*Alkynylmetal*	*Conditions*	*Yield (%)*	*Ref.*
	$LiBu_3Al$—≡—Pent	$[Pd(PPh_3)_4]$, THF 60 °C, 24 h	38	[183]
	Et_2Al—≡—Pent	$[Pd(PPh_3)_4]$, THF 25 °C, 2 h	57	[244]
	Et_2Al—≡—Ph	$[Pd(PPh_3)_4]$, THF 25 °C, 6 h	70	[244]
	Et_2Al—≡—Bu	$[Pd(PPh_3)_4]$, THF 25 °C	67	[245]
	$NaAl(≡—Ph)_4$	$[Pd(PPh_3)_2Cl_2]$, DME 90 °C, 12 h	86	[246]
	$NaAl(≡—Ph)_4$	$[Pd(PPh_3)_2Cl_2]$, DME 90 °C, 12 h	76	[246]
	$NaAl(≡—SiMe_3)_4$	$[Pd(PPh_3)_2Cl_2]$, DME 90 °C	81	[246]
	$NaAl(≡—Ph)_4$	$[Pd(PPh_3)_2Cl_2]$, DME 90 °C	92	[246]
	$In(≡—SiMe_3)_3$	$[Pd(PPh_3)_2Cl_2]$, THF 60 °C, 1 h	93	[247]
	$In(≡—Ph)_3$	$[Pd(PPh_3)_2Cl_2]$, THF 60 °C, 1 h	94	[247]
	$In(≡—SiMe_3)_3$	$[Pd(PPh_3)_2Cl_2]$, THF 60 °C, 1 h	91	[247]
	$In(≡—SiMe_3)_3$	$[Pd(dppf)Cl_2]$, THF 60 °C, 2.5 h	94	[247]

Table 6-18 (continued)

RX	*Alkynylmetal*	*Conditions*	*Yield (%)*	*Ref.*
		$[Pd(PPh_3)_4]$, THF 60 °C, 3 h	90	[247]
		$[Pd_2(dba)_3]$ $PPh(o\text{-tol})_2$, THF 120 °C, 24 h	67	[248]
		$[Pd(dba)_2]$ 2-P(*t*-Bu)$_2$-biphenyl Bu_4NF, THF, 60 °C	91	[249]
		$[Pd(dba)_2]$ 2-P(*t*-Bu)$_2$-biphenyl Bu_4NF, THF, 60 °C	68	[249]
		0.1 equiv $[Pd(PPh_3)_4]$ DMF, r.t., 24 h	30	[250]
		0.5 equiv $[Pd(PPh_3)_4]$ DMF, r.t., 5 min	98	[250]
		0.5 equiv $[Pd(PPh_3)_4]$ DMF, r.t., 70 min	44	[250]
		0.5 equiv $[Pd(PPh_3)_4]$ MeCN, r.t., 15 min	77	[250]
		$[Pd(dppp)Cl_2]$, THF DME, 0 °C, 24 h	91	[251]

iodoarenes if the complexes were activated toward transmetallation by TBAF [249]. The alkynylgermatranes were readily prepared from the corresponding alkynylgermanium trichlorides. The best yields of hetero-coupled products with a variety of substituted iodoarenes were achieved using the bulky 2-P(tBu)$_2$-biphenyl ligand with [Pd(dba)$_2$] in refluxing THF with no detection of homo-coupled product. No iodogermatrane was observed in the reaction mixture, while fluorogermatrane and free iodide were, suggesting that either reductive elimination of a GeI complex was not taking place or that a fluoride displaced the iodide after reductive-elimination.

Alkynylsilver reagents have been reported to cross-couple with organotriflates. As mentioned earlier, Ag_2O and AgI salts in combination with terminal alkynes or alkynylsilanes and Pd catalysts (see Sections 6.2.2.4 and 6.6.1) gave moderate yields of cross-coupled products [83, 228–230]. Pale has furthermore noted the generation of Ag-acetylides beforehand, and their reaction to form cross-coupled products with vinyl triflates, albeit in low to moderate yields (Table 6-18) [250]; however, by using a large amount of [Pd(PPh$_3$)$_4$] (0.5 equiv.), yields were improved by 68 %. Yields were also very solvent-dependent and varied greatly by coupling reagents.

Alkynylmanganese reagents, similar in form to [RC≡CMgX] and [RC≡CZnX], have also given high yields of cross-coupled product with an activated arylbromide (Table 6-18) [251]. Among the variety of catalysts tried, [Pd(dppp)Cl$_2$] was the only catalyst to give good yields in the reaction. The group also observed a reversal of typical cross-coupling reactivity (for the Ar-Ar cross-coupling), in that iodoarenes were less reactive than bromoarenes.

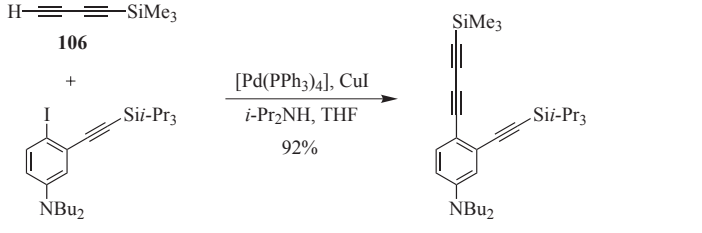
6.9 Concluding Remarks

After a slow start, cross-coupling reactions to sp carbon atoms have experienced rapid development over the past quarter-century. The key discovery in 1975 was the use of palladium complexes to catalyze the reaction between a terminal acetylene and a haloarene. Since then, important advances have been made each decade, with the 1980s and early 1990s devoted to exploration of alkynylmetal species, and the late 1990s/early 2000s dedicated towards preparation of "hotter" catalysts possessing bulky, electron-rich ligands. What will the next 25 years hold for this field? It is difficult to predict, especially as we still do not fully understand the mechanistic pathway(s) of the Sonogashira chemistry discovered over 25 years ago. One thing is certain however: the modern synthetic methods described within this chapter have helped to revolutionize the construction of sp-containing carbon-carbon bonds in molecules, making the preparation of complex natural products, important pharmaceuticals, and advanced organic materials a much simpler process.

6.10
Experimental Procedures

6.10.1
N,*N*-Dibutyl-3-[(triisopropylsilyl)ethynyl]-4-[4-(trimethylsilyl)-1,3-butadiynyl]aniline (**104**)

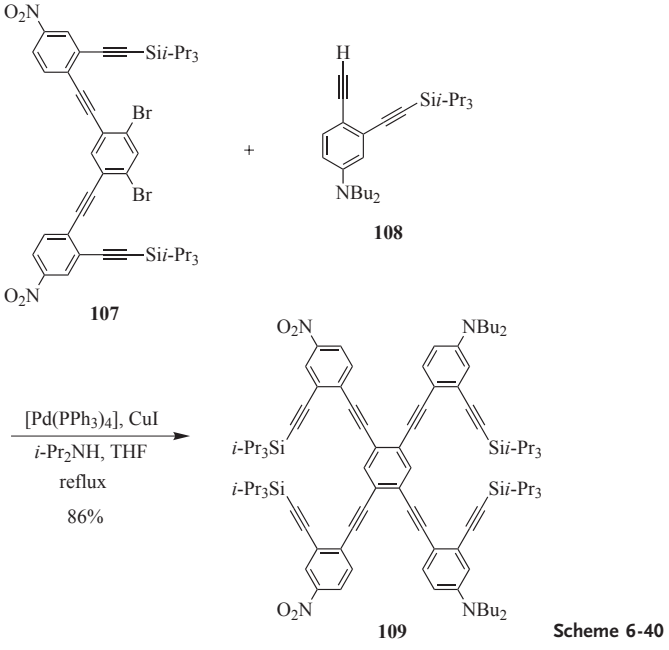
A typical procedure for the Sonogashira cross-coupling of a terminal alkyne with an iodoarene is depicted in Scheme 6-39 [252]. A round-bottomed flask was charged with iodoarene **105** (5.11 g, 10 mmol), *i*Pr_2NH (100 mL), and THF (50 mL). After degassing the solution by bubbling Ar for 30 min, (trimethylsilyl)-butadiyne (**106**) (1.34 g, 11 mmol), [$Pd(PPh_3)_4$] (210 mg, 0.30 mmol), and CuI (114 mg, 0.60 mmol) were added and the reaction stirred under a N_2 atmosphere at room temperature for 12 h. Upon completion, the mixture was concentrated in vacuo and then diluted with CH_2Cl_2 (200 mL). This crude solution was filtered through a thin cake of silica gel using CH_2Cl_2 and the solvent was removed in vacuo. The resultant residue was purified by column chromatography on silica gel (10:1 hexanes/CH_2Cl_2) to yield **104** (4.63 g, 92 %) as a yellow oil.



Scheme 6-39

6.10.2
Sonogashira Cross-Coupling of a Terminal Alkyne with a Bromoarene

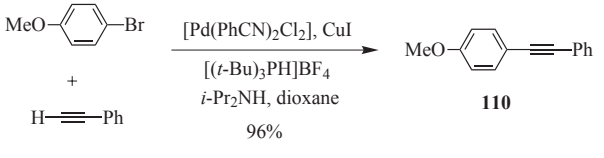
Scheme 6-40 illustrates a typical procedure for the Sonogashira reaction between a terminal alkyne and a bromoarene [253]. A round-bottomed flask was charged with dibromoarene **107** (587 mg, 0.66 mmol), terminal alkyne **108** (655 mg, 1.7 mmol), *i*Pr_2NH (50 mL), and THF (50 mL). After the solution was degassed by three freeze-pump-thaw cycles, [$Pd(PPh_3)_4$] (38 mg, 0.03 mmol) and CuI (13 mg, 0.06 mmol) were added and the reaction mixture was heated at reflux under a N_2 atmosphere for 16 h. Upon completion, the reaction was cooled, concentrated in vacuo, and diluted with CH_2Cl_2 (200 mL). The crude mixture was filtered through a thin cake of silica gel using CH_2Cl_2 and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (3:1 hexanes/CH_2Cl_2) to yield **109** (857 mg, 86 %) as a red gum.



Scheme 6-40

6.10.3
4-Methoxytolane (110)

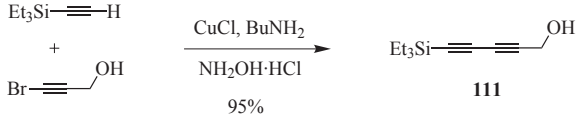
A general procedure for the room-temperature cross-coupling of a terminal alkyne with a bromoarene using a highly active catalyst system is shown in Scheme 6-41 [45b]. A Schlenk tube was charged with $[Pd(PhCN)_2Cl_2]$ (12 mg, 0.03 mmol), CuI (3.9 mg, 0.02 mmol) and $[(t\text{Bu})_3PH]BF_4$ (19 mg, 0.065 mmol), evacuated and refilled with Ar (five cycles). Dioxane (1.0 mL), $i\text{Pr}_2\text{NH}$ (166 mg, 1.2 mmol), 4-bromoanisole (127 mg, 1.0 mmol), and phenylacetylene (127 mg, 1.2 mmol) were added, and the Schlenk tube was sealed and stirred at room temperature for 2 h. Upon completion, the reaction mixture was diluted with EtOAc (5 mL), filtered through a thin cake of silica gel using EtOAc, and purified by column chromatography on silica gel (1% Et_2O in hexanes) affording **110** (201 mg, 96%) as a brown solid.



Scheme 6-41

6.10.4
5-Triethylsilylpenta-2,4-diyn-1-ol (111)

Scheme 6-42 represents a general procedure for the Cadiot-Chodkiewicz reaction between a terminal alkyne and a 1-bromoalkyne [107]. A flask was charged with CuCl (6.0 mg, 0.06 mmol) and 30 % aqueous $BuNH_2$ (2.5 mL), forming a blue solution. A few crystals of $NH_2OH \cdot HCl$ were added to form a colorless solution containing Cu(I) salt. TESA (505 mg, 3.6 mmol) was added to the solution, and the yellow acetylide suspension was immediately cooled with an ice bath. 3-Bromo-2-propyn-1-ol (**112**) (405 mg, 3.0 mmol) was added and the ice bath removed. The reaction mixture was stirred at room temperature for 30 min, and more $NH_2OH \cdot HCl$ was added throughout to prevent the formation of a green or blue solution. Upon completion, the product was extracted with Et_2O (3 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (9:1 hexanes/EtOAc) to give **111** (552 mg, 95 %) as a light yellow oil.

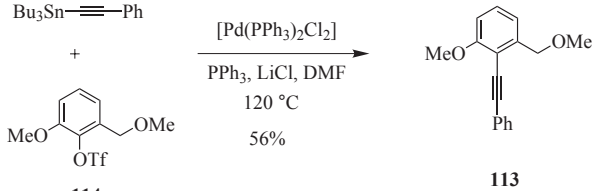


112 **111**

Scheme 6-42

6.10.5
1-Methoxy-3-(methoxymethyl)-2-(phenylethynyl)benzene (113)

A general Stille cross-coupling between an alkynylstannane and an aryl triflate is shown in Scheme 6-43 [166]. A round-bottomed flask was charged with triflate **114** (150 mg, 0.50 mmol), LiCl (171 mg, 4.2 mmol), PPh_3 (79 mg, 0.30 mmol), $[Pd(PPh_3)_2Cl_2]$ (37 mg, 0.06 mmol), and DMF (4.5 mL). Tributyl(phenylethynyl)-stannane (587 mg, 1.5 mmol) was added in two portions along with a crystal of inhibitor (2,6-di-*t*-butyl-4-methylphenol). The reaction mixture was heated at 120 °C under an Ar atmosphere for 5.5 h. Upon completion, the reaction mixture was cooled and diluted with H_2O (25 mL) and Et_2O (25 mL). The organic phase was washed with 1.5 N HCl (6 × 20 mL), saturated KF solution (5 × 20 mL), and dried (Na_2SO_4). The solvent was removed in vacuo and the resultant residue suspended



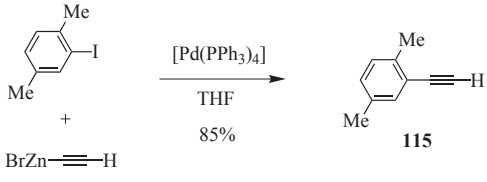
114 **113**

Scheme 6-43

in EtOAc and filtered. The crude material was purified by column chromatography on silica gel (hexanes/EtOAc) to yield **113** (71 mg, 56 %) as an oil.

6.10.6
2-Ethynyl-*p*-xylene (115)

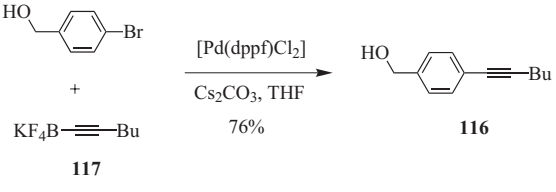
A representative cross-coupling procedure of an alkynylzinc with an iodoarene by the Negishi protocol is shown in Scheme 6-44 [180]. A solution of [HC≡CZnBr] was prepared by the reaction of [HC≡CMgBr] (6.0 mL, 0.5 M solution in THF, 3.0 mmol) with dry $ZnBr_2$ (675 mg, 3.0 mmol) dissolved in 5 mL THF in a flame-dried, 50-mL round-bottomed flask. 2-Iodo-*p*-xylene (464 mg, 2.0 mmol) and [$Pd(PPh_3)_4$] (115 mg, 0.1 mmol) were added under an Ar atmosphere, and the reaction mixture was stirred at room temperature for 3 h. Upon completion, the reaction was quenched with aqueous NaCl, extracted with Et_2O, dried ($MgSO_4$), and concentrated in vacuo. Purification by column chromatography on silica gel (hexanes) afforded **115** [254] (220 mg, 85 %).



Scheme 6-44

6.10.7
4-(1-Hexyn-1-yl)benzyl alcohol (116)

A representative Suzuki cross-coupling of a potassium trifluoroborate with a bromoarene is shown in Scheme 6-45 [221]. Potassium (1-hexyne-1-yl)trifluoroborate (**117**) (94 mg, 0.50 mmol), 4-bromobenzyl alcohol (94 mg, 0.50 mmol), [$Pd(dppf)Cl_2$] · CH_2Cl_2 (36 mg, 0.045 mmol), and Cs_2CO_3 (489 mg, 1.5 mmol) were added to a flask containing THF (5 mL) and degassed H_2O (0.25 mL) under Ar. The reaction mixture was heated at reflux for 12 h to completion, cooled, and diluted with H_2O (10 mL). The solution was extracted with Et_2O, the organic layer washed with 1 M HCl and brine, and then dried ($MgSO_4$). The solvent was removed under vacuum and the residue purified by column chromatography on silica gel (3:1 hexanes/EtOAc) to give **116** (71 mg, 76 %) as a colorless oil.

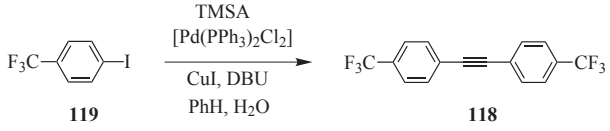


117 **116**

Scheme 6-45

6.10.8
4,4′-Bis(trifluoromethyl)tolane (118)

Scheme 6-46 demonstrates a general procedure for the synthesis of symmetrical bisarylethynes by from iodoarenes and TMSA [88]. A flame-dried, round-bottomed flask was purged with Ar and charged with $[Pd(PPh_3)_2Cl_2]$ (16.8 mg, 0.048 mmol), CuI (15.2 mg, 0.080 mmol), and iodoarene **119** (218 mg, 0.80 mmol). The flask was sealed with a rubber septum and dry, Ar-sparged benzene (4.0 mL) and DBU (718 μL, 4.8 mmol) were added by syringe and the solution was purged by bubbling Ar. Ice-chilled TMSA (57 μL, 0.40 mmol) and distilled H_2O (5.8 μL, 0.32 mmol) were then added and the reaction mixture stirred in the dark for 18 h. Upon completion, the reaction mixture was diluted with Et_2O and H_2O (50 mL each), the organic phase washed with 10 % aqueous HCl (3 × 75 mL) and saturated aqueous NaCl (75 mL), and dried ($MgSO_4$). The solvent was removed in vacuo and the crude product purified by column chromatography on silica gel (hexanes) to provide **118** (116 mg, 93 %).

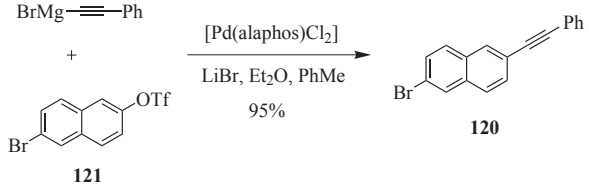


119 **118**

Scheme 6-46

6.10.9
2-Bromo-6-(phenylethynyl)naphthalene (120)

Scheme 6-47 shows a representative procedure for the cross-coupling of alkynylmagnesium reagents with aryltriflates using a novel Pd catalyst [237]. To a mixture of triflate **121** (71 mg, 0.20 mmol), dichloro[(2-dimethylamino)propyldiphenylphosphine]palladium ([Pd(alaphos)Cl_2], **97**) (4.4 mg, 0.010 mmol), and LiBr (17.2 mg, 0.20 mmol) in Et_2O (1 mL) was added (phenylethynyl)magnesium bromide (290 μL, 1.4 M, 0.4 mmol) in 2:1 Et_2O/PhMe (3 mL) at room temperature. The reaction mixture was stirred at 30 °C for 30 min to completion, quenched with H_2O, and extracted with Et_2O (100 mL). The organic phase was washed with saturated aqueous



121 **120**

Scheme 6-47

NaCl (2 × 20 mL), dried ($MgSO_4$), and concentrated under vacuum. The crude material was purified by preparative TLC (silica gel, 3:1 hexanes/benzene) to give **120** (57 mg, 95 %).

Acknowledgments

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Abbreviations and Acronyms

Ad	adamantyl
alaphos	(2-dimethylamino)propyldiphenylphosphine
BBN	borabicyclo[3.3.1]nonane
Boc	*tert*-butoxycarbonyl
BTEACl	benzyltriethylammonium chloride
Cp*	pentamethylcyclopentadienyl
Cy	cyclohexyl
dba	dibenzylideneacetone
DBA	dehydrobenzoannulene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DMA	*N,N*-dimethylacetamide
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMI	1,3-dimethylimidazolidin-2-one
DMSO	dimethylsulfoxide
DPEphos	Bis(2-diphenylphosphinophenyl) ether
dppb	bis(diphenylphosphino)butane
dppe	bis(diphenylphosphino)ethane
dppf	bis(diphenylphosphino)ferrocene
dppp	bis(diphenylphosphino)propane
HMPA	hexamethylphosphoric acid triamide
LDA	lithium diisopropylamide
MOM	methoxymethyl
MW	microwave
Nf	nonafluorobutanesulfonyl (nonaflyl)
NHC	*N*-heterocyclic carbene

NIS	*N*-iodosuccinimide
NMP	*N*-methylpyrrolidinone
OTf	trifluoromethanesulfonate
*o*tol	*ortho*-tolyl
PEG	polyethylene glycol
PPE	poly(phenyleneethynylene)
PS	polystyrene
ROMP	ring-opening metathesis polymerization
r. t.	room temperature
TAPS	3-[tris(hydroxymethyl)methylamino]-1-propanesulfonic acid
TASF	tris(diethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBAOAc	tetrabutylammonium acetate
TBAOH	tetrabutylammonium hydroxide
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TEAI	tetraethylammonium iodide
TESA	triethylsilylacetylene
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TIPSA	triisopropylsilylacetylene
TMS	trimethylsilyl
TMSA	trimethylsilylacetylene
TOAI	tetraoctylammonium iodide
TON	turn-over-number
tppts	triphenylphosphine trisulfonate trisodium salt

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7
Carbometallation Reactions

Ilan Marek, Nicka Chinkov, and Daniella Banon-Tenne

7.1
Introduction

Since the first carbometallation reaction was discovered in the pioneering studies of Ziegler and Bähr, and published in *Berichte der Deutschen Chemischen Gesellschaft* in 1928 [1] (see Figure 7-1), an ever increasing number of additions of organometallics to carbon-carbon multiple bonds has been reported. Excellent reviews and chapters have been published in this field [2], but during the past decade consider-

39. K. Ziegler und K. Bähr: Über den vermutlichen Mechanismus der Polymerisationen durch Alkalimetalle (Vorläufige Mitteilung).

[Aus d. Chem. Institut d. Universität Heidelberg.]
(Eingegangen am 9. Dezember 1927.)

Die polymerisierende Wirkung der Alkalimetalle auf ungesättigte Kohlenwasserstoffe ist seit langem bekannt. Butadien-Kohlenwasserstoffe liefern mit diesen Agenzien die verschiedenen Abarten von „Natrium-Kautschuk", über die in den Laboratorien der Technik viel gearbeitet worden ist, wie die umfangreiche Patentliteratur[1]) auf diesem Gebiet beweist, und von denen wir seit den Arbeiten von Harries[2]) wissen, daß sie nach einem anderen Polymerisationsprinzip als der Natur-Kautschuk oder die Wärme-Polymerisate der Butadiene aufgebaut sein müssen. Die Kenntnis weiterer derartiger Polymerisationen verdanken wir W. Schlenk. Er zeigte, daß Styrol[3]) und 1-Phenyl-butadien[4]) durch Natriumpulver in ätherischer Lösung in hochmolekulare Substanzen übergeführt werden.

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[3]) G. Jantzsch, Journ. prakt. Chem. [2] **115**, 14 [1927].
[1]) vergl. z. B. Matthews und Strange, Dtsch. Reichs-Pat. 249868; Frdl. Teerfarb.-Fabrikat. **10**, 1051; Bad. Anilin- u. Soda-Fabrik, Dtsch. Reichs-Pat.*) 255786, 287787; Frdl. Teerfarb.-Fabrikat. **11**, 831, **12**, 571. — Farbwerke vorm. Fr. Bayer & Co., Dtsch. Reichs-Pat. 280959; Frdl. Teerfarb.-Fabrikat. **11**, 832.
[2]) A. **383**, 213 [1911]. [3]) B. **47**, 476 [1914].
[4]) Houben-Weyl, 2. Aufl., Bd. 4, S. 971.

Figure 7-1 Facsimile of the original paper by Ziegler and Bähr in *Berichte der Deutschen Chemischen Gesellschaft*, 1928.

Metal-Catalyzed Cross-Coupling Reactions, 2nd Edition. Edited by Armin de Meijere, François Diederich

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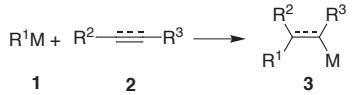
able progress has been made and new families of organometallic derivatives have been found to be useful for the carbometallation reactions.

A carbometallation reaction is defined by the addition of a carbon-metal bond of an organometallic **1** across a carbon-carbon multiple bond **2**, leading to a new organometallic **3**, in which the newly formed carbon-metal bond can be used for further transformations (Scheme 7-1).



Scheme 7-1
Definition of the carbometallation reaction.

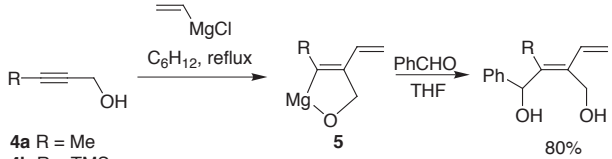
To be synthetically useful, the newly formed organometallic **3** must have a reactivity different from that of **1** in order to avoid the polymerization of the carbometallated product. Therefore, the carbometallation ability of 1 must be higher than that of **3** at the exception of intramolecular carbometallation reactions.

By no means does this chapter aim at cataloguing all the examples recently published, but will rather focus on the most prominent recent advances in this field, both from our own and from other groups (from 1997 until the present time, since previous carbometallation reactions were reported in the first edition) [3].

7.2
Carbometallation Reactions of Alkynes

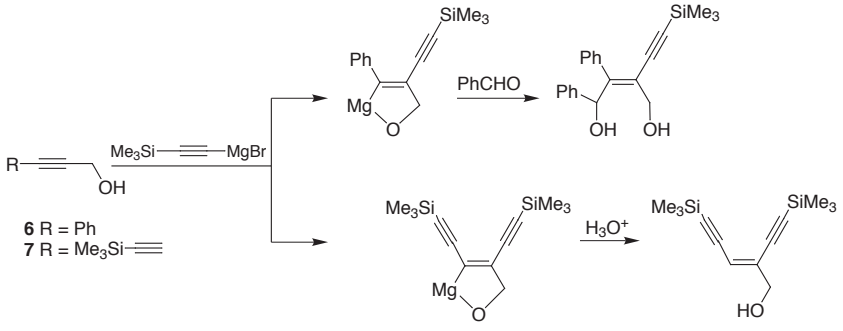
7.2.1
Intermolecular Carbometallation Reactions

The past few years have seen an impressive number of successful intermolecular carbometallation reactions of alkynes, which were previously largely restricted to the carbocupration reactions [2a]. As an illustrative example, the addition of vinyl and alkynyl Grignard reagents to propargyl alcohols **4** was reinvestigated and found to be a powerful method for the preparation of metallated dienes in a single-pot operation [4]. This reaction proceeds *via* the intermediate magnesium chelate **5** (Scheme 7-2).



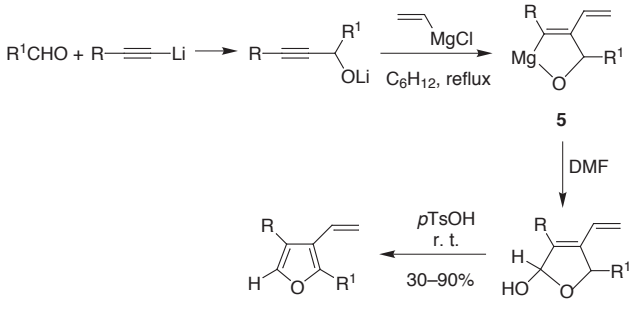
Scheme 7-2 Addition of vinylmagnesium chloride to propargyl alcohols [4].

This addition, formally resulting from an *anti*-addition of the Grignard reagent [5], is in contrast to the normal *syn*-addition usually observed [2]. This carbometallation reaction was extended to the synthesis of enynes by addition of trimethylsilylethynylmagnesium chloride to various slightly activated propargyl alcohols, such as **6** and **7** (Scheme 7-3).



Scheme 7-3 Preparation of enynes by carbomagnesiation of propargyl alcohols [4].

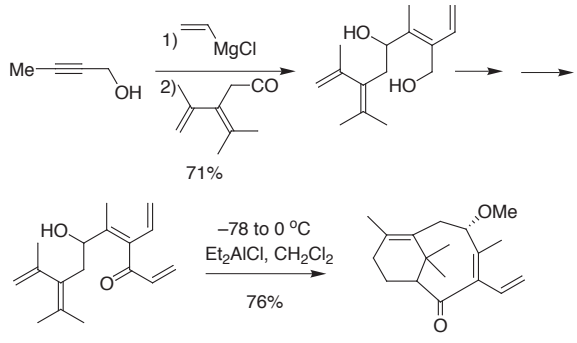
The versatility and scope of this carbometallation was illustrated by the synthesis of substituted furans, when the intermediate **5** was reacted with dimethylformamide (Scheme 7-4) [6].



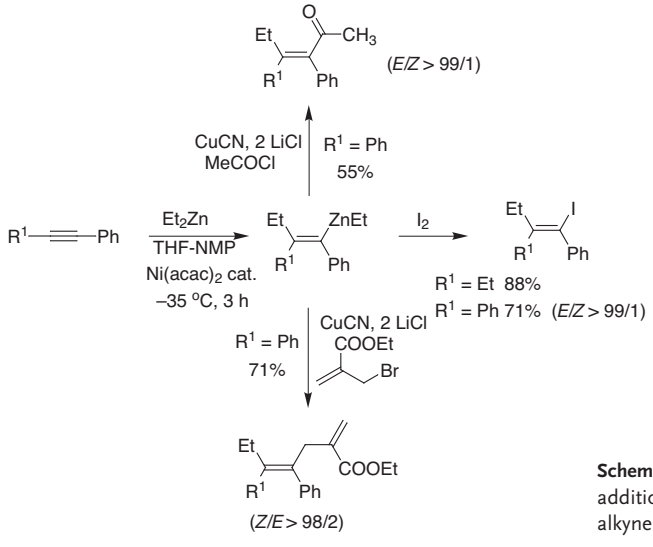
Scheme 7-4 Synthesis of oligosubstituted furans by carbomagnesiation of propargyl alcohols and subsequent reaction with DMF [6].

Although the chemical yields were modest in some cases, the sequence led directly to the trisubstituted furans, in which four new bonds were created during the reaction. This magnesium-mediated carbometallation reaction has been extended to more complex systems in a straightforward manner, such as the A-B ring building blocks of the taxanes (Scheme 7-5) [7].

An alternative to this magnesium-mediated carbometallation of alkynes is the nickel-catalyzed addition of dialkylzincs to alkynes [8]. Remarkably, this addition proceeds with complete *syn*-stereoselectivity and excellent regioselectivity (Scheme 7-6).

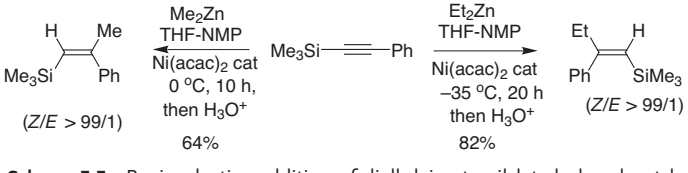


Scheme 7-5 Application of the carbomagnesiation reaction of 2-butyn-1-ol [7].



Scheme 7-6 Nickel-catalyzed addition of diethylzinc to alkynes [8].

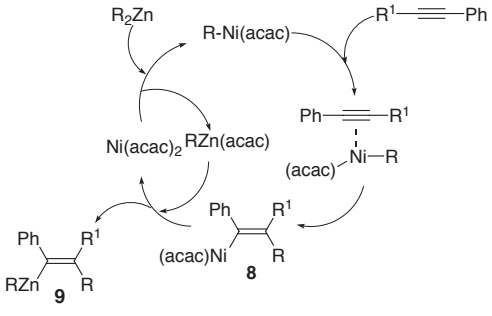
Interestingly, not only dialkylzinc, but also diphenylzinc can be added to substituted phenylacetylenes. With silylated phenylacetylene, the opposite regioisomer is obtained selectively, i. e., the organic group adds at the α-position to the phenyl ring (Scheme 7-7) [9].



Scheme 7-7 Regioselective addition of dialkylzinc to silylated phenylacetylene [9].

It should be noted, that the successful introduction of methyl and phenyl groups on the alkyne overcomes the main limitation of the carbocupration reaction [2a]. The carbozincation can also be efficiently applied to alkynes bearing heterocyclic substituents. Thus, 2-thienyl-5-pyrimidinyl-, 2-pyridyl-substituted alkynes add diethyl- or diphenylzinc with complete regio- and stereoselectivity; this affords, after quenching with electrophiles, tri- or tetrasubstituted alkenes in good overall yields [9].

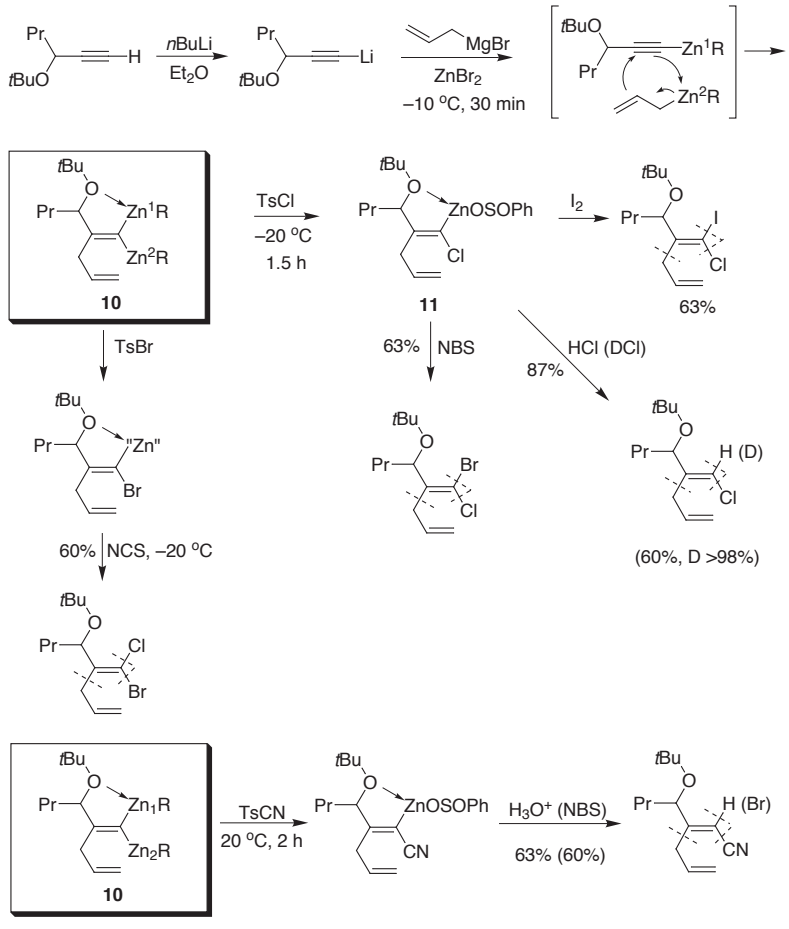
The mechanism of the carbozincation can best be rationalized by assuming that the zinc reagent R_2Zn undergoes a transmetallation with $Ni(acac)_2$ to generate an alkylnickel species, RNi(acac). Then, after complexation with the substituted phenylacetylene, a carbonickelation occurs affording the alkenylnickel intermediate **8** (Scheme 7-8). By a subsequent transmetallation reaction with RZn(acac), the carbozincation product **9** is obtained and the catalyst is regenerated.



Scheme 7-8 Mechanism of the nickel-catalyzed carbozincation of an alkyne [9].

The synthesis of diastereomerically pure oligosubstituted alkenes in a one-pot operation was recently investigated by using the formation of sp^2 *gem*-bismetallic compounds [10]. If an internal chelation by a Lewis-base functional group is possible, the difference in reactivity of the two carbon-metal bonds toward two different electrophiles leads to a unique geometrical isomer of the alkene (Scheme 7-9).

The internal chelation of the oxygen atom to the metal residue Zn^1R in **10** decreases the reactivity of the latter toward the first electrophile (such as phenylsulfonyl halide or phenylsulfonyl cyanide), and thus the nonchelated metal Zn^2R reacts preferentially with this electrophile (Scheme 7-9) [11]. The reactivity of the remaining metal Zn^1R can be increased by transmetallation with an organocuprate [10]. Recent computational studies have established that only zinc was present in the bismetallic structure [12]. In the case of halozinc carbenoids (as **11** in Scheme 7-9), the alkylation of Zn^1R requires higher temperatures and the corresponding zinc carbenoid undergoes an interesting Fritsch-Buttenberg-Wiechell (FBW) rearrangement [13]. Indeed, chlorocarbenoids can act as common nucleophiles, as electrophiles toward organometallic nucleophiles [14], but also as a source of alkyne *via* the FBW rearrangement (Scheme 7-10).



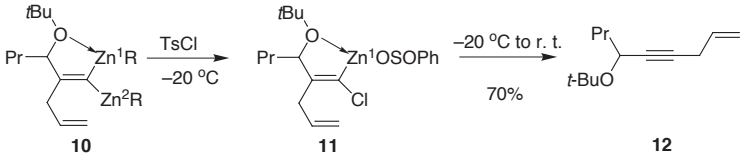
Scheme 7-9 Formation of oligosubstituted alkenes *via* sp^2 *gem*-bismetallic compounds [10,11].

LG = leaving group

Scheme 7-10 The Fritsch-Buttenberg-Wiechell (FBW) rearrangement of sp^2 carbenoids [13].

This rearrangement, known in the literature since 1894 [13], is used as an efficient synthetic approach to alkynes, when the migrating group (R^1 or R^2) is a hydrogen [15], a heteroatom [16] or an aryl moiety [17]. However, when R^1 or R^2 is an alkyl group, the yields of alkynes are very low (<10 %) due to competitive C-H insertion reactions [18].

However, in the alkylidene zinc carbenoid **11**, generated from the 1,1-dizincoalkene **10**, rearranges cleanly in 70 % yield, just by warming the reaction mixture to room temperature, into the disubstituted alkyne **12** (Scheme 7-11) [19].

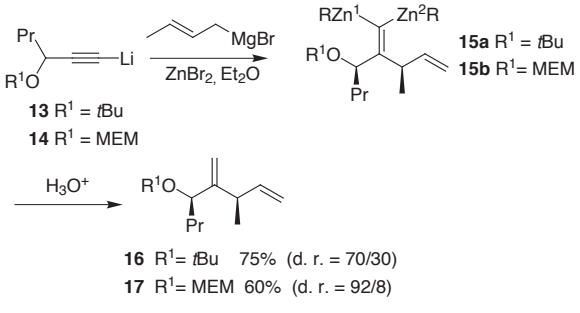


10 **11** **12**

Scheme 7-11 Formation of a disubstituted alkyne from an alkylidenezinc carbenoid [19].

The diastereoselectivity of the carbometallation step [20] was investigated by the addition of a substituted allylorganometallic, such as crotyl zinc bromide (prepared *in situ* by the addition of crotylmagnesium bromide to zinc bromide) across the secondary metallated propargylic ether (Scheme 7-12) [19].

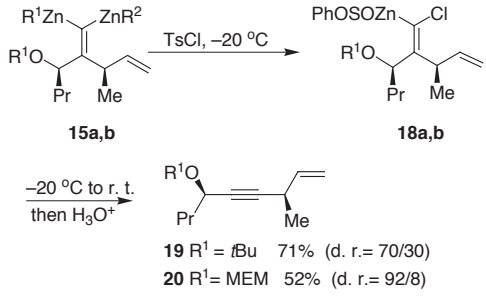
Whilst a moderate stereoselectivity is observed for the crotylmetallation of **13** (formation of **16** after hydrolysis with a diastereomeric ratio of 70:30), the replacement of the *tert*-butoxy by a methoxy ethoxymethoxy group (OMEM), as in **14**, raises the diastereoselectivity to 92:8 with a 60 % yield of **17** (Scheme 7-12). By this carbometallation strategy, two stereogenic centers and a bismetallated exomethylene moiety were created with a rather good diastereoselectivity.



Scheme 7-12 Diastereoselective crotylmetallation of metallated propargylic ethers [19].

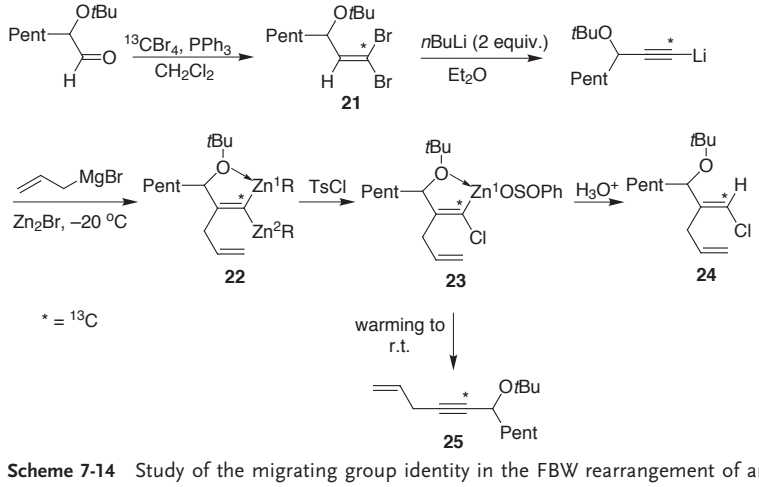
The question of the fate of a chiral sp^3 carbon center as a migrating group in the FBW rearrangement was then raised. To answer this question, **15a**,**b** were treated with $PhSO_2Cl$, as described above (see Scheme 7-9), and the resulting carbenoids **18a**,**b** (Scheme 7-13) were warmed to room temperature. A clean rearrangement took place to lead to the enyne ethers **19** and **20** with the same diastereoselectivity as was obtained for the intermediate **15a**,**b** [19].

Starting from **15b** (R^1 = MEM), the obtained ether **20** displays a 92:8 diastereomeric ratio, similar to the hydrolyzed product **17** (Scheme 7-12). From this study it can be concluded, that the migration occurs with complete retention of configuration of the migrating group. Moreover, by chemical correlations, it was also shown



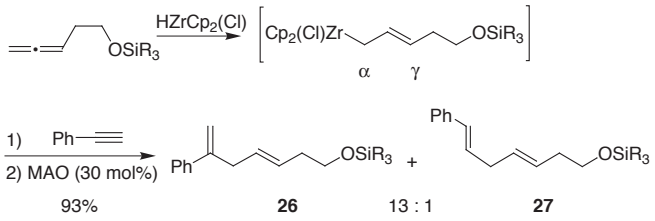
Scheme 7-13 Stereoselective migration of a chiral sp^3 carbon center [19].

that the FBW rearrangement occurs *via* the zinc carbenoids with complete retention of configuration at the migrating atom. The last question which had to be addressed was the identity of the migrating carbon. To examine further the migration of an *α*-heterosubstituted alkyl *versus* an allyl group, the labeled **21** was prepared from *α-tert*-butoxyheptanal and $^{13}CBr_4$ (Scheme 7-14). Then, **21** was converted into 1-lithio-3-*tert*-butoxy-1-octyne by a first FBW rearrangement and was submitted *in situ* to the carbometallation procedure to afford the vinylidene *gem*-bismetallic species **22**. By selective chlorination (see Scheme 7-9), the corresponding chlorocarbenoid **23** was formed (as demonstrated by its hydrolyzed product **24**) and by just warming the mixture to room temperature, the second FBW rearrangement occurred. A ^{13}C-NMR study disclosed that only the enyne **25** was formed, indicating the exclusive migration of that alkoxymethyne moiety which was located *trans* to the chlorine in **23** (Scheme 7-14) [21].



Scheme 7-14 Study of the migrating group identity in the FBW rearrangement of an sp^2-zinc carbenoid [21].

However, this FBW rearrangement for zinc carbenoids strongly depends on the migrating abilities of the groups, whatever the configuration of the carbenoid. Selective migrations of the alkoxymethyne moiety were observed only in specific cases [21].

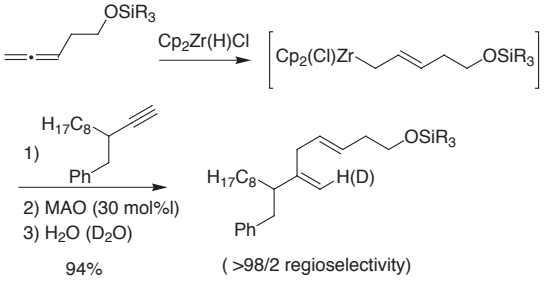


Scheme 7-15 Regioselective allylmetallation of a 1-alkyne in the presence of MAO [22].

The allylmetallation of alkynes can also proceed with activated allylzirconocene derivatives. The allylzirconium species, generated by hydrozirconation of allenes, undergo regioselective *α*-addition to 1-alkynes in the presence of organoaluminum reagents, among which methylaluminoxane (MAO) is particularly effective (Scheme 7-15) [22]. Two regioisomers **26** and **27** were obtained in a ratio of 13:1.

MAO presumably abstracts the chlorine atom from the zirconium to form an allylzirconocene cation, which coordinates the alkyne triple bond. The subsequent migratory insertion is regioselective, as it is found that the new bond is mainly formed between the *α*-carbon of the allylzirconium species and the internal carbon of the terminal alkyne.

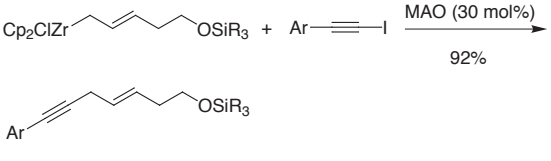
The regioselectivity of the reaction can be increased with the steric bulk of the alkyne substituents (compare Schemes 7.15 and 7.16).



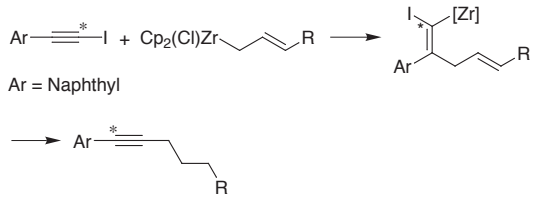
Scheme 7-16 Example of an allylzirconation at the internal carbon of a terminal alkyne [22].

When 1-iodoalkynes are reacted with allylzirconocene chloride in the presence of a catalytic amount of MAO, disubstituted alkynes are formed (Scheme 7-17) [23].

Although, at first sight, this might appear to be a simple substitution reaction, the alkyne is, in fact, formed by a carbometallation reaction followed by a FBW rearrangement of a zirconocene carbenoid intermediate. Evidence was provided



Scheme 7-17 MAO-catalyzed formation of disubstituted alkynes [23].

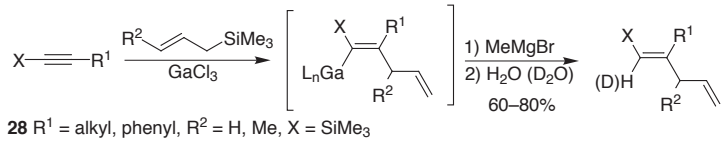


Scheme 7-18 Mechanistic study of the MAO-catalyzed formation of a disubstituted alkyne [23].

by an experiment with a ^{13}C-labeled iodoalkyne, showing that the naphthyl group migrates during the reaction sequence (Scheme 7-18) [23].

Allylgallation reactions of silylalkynes or 1-alkynes were also found to take place upon treatment of allylsilanes with $GaCl_3$ at room temperature (Scheme 7-19) [24].

Although silylalkynes undergo self-dimerization in the presence of $GaCl_3$ [25], the regioselective cross-coupling reaction with allylsilanes is more rapid. Primary and secondary aliphatic alkynes as well as aromatic alkynes, react similarly.



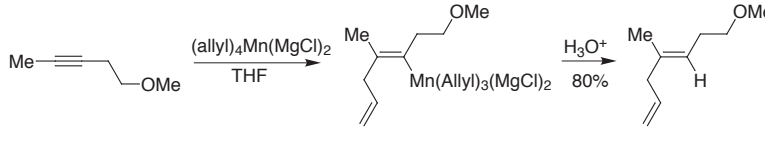
28 R^1 = alkyl, phenyl, R^2 = H, Me, X = $SiMe_3$
29 R^1 = alkyl, phenyl, R^2 = H, Me, X = H

Scheme 7-19 Allylgallations of alkyne derivatives [24].

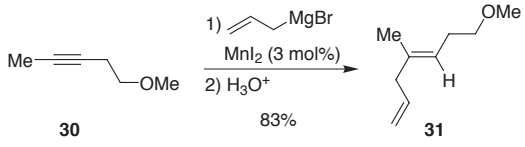
Unactivated terminal alkynes undergo efficient hydroallylation in a Markovnikov sense upon treatment with allyl bromide and indium metal in THF at room temperature, and subsequent hydrolysis [26].

Triallylmanganate and tetraallylmanganate also add to the triple bond of propargyl and homopropargyl alcohols and derivatives to give monoallylated products. Among several stoichiometric reagents such as allylmanganese chloride [(allyl)MnCl)], diallylmanganese [$(allyl)_2Mn$], triallylmanganate [$(allyl)_3MnMgCl$] and tetraallylmanganate [$(allyl)_4Mn(MgCl)_2$] with the methyl ether of 3-pentyn-1-ol, tetraallylmanganate proved to be the best reagent in terms of yield (80 % after hydrolysis; Scheme 7-20) [27].

The allylmanganation of alkynes is oxygen-assisted, and classical dialkylalkynes such as 6-dodecyne were completely recovered even after heating the mixture in refluxing THF for 10 h.



Scheme 7-20 Allylmanganation of a homopropargylic ether [27].

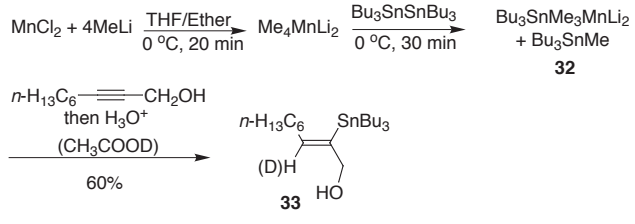


Scheme 7-21 Mangano-catalyzed allylmagnesiation of a homopropargyl ether [27].

The treatment of allylic alcohols with a triallylmanganate also gave the allylated products in good yields (particularly when HMPA was added as a co-solvent) [27]. However, the large excess of allyl groups necessary for the allylmanganation reaction (three to four allyl moieties for one Mn salt), represents a major drawback of this method. Hence, the mangano-catalyzed allylmagnesiation reaction was successfully developed [27]. Treatment of an ethereal solution of the homopropargyl ether **30** with 1.5 equiv. allylmagnesium bromide in the presence of 3 mol % MnI_2 for 3 h led to the monoallylated product **31** in 83 % yield after hydrolysis.

The intermediary alkenylmagnesium compound could be trapped by electrophiles such as allyl bromide or aldehydes. The *syn* addition of the allylmetal derivative was also confirmed.

The transmetallation reactions between hexabutylditin and organomanganate complexes were found to give the stannylmanganate derivative **32** (Scheme 7-22). The resulting reactive mixed manganate [$Bu_3Sn(Me)_3MnLi_2$] has proved to have high *trans*-addition selectivity toward propargyl alcohols and gave the corresponding *Z*-alkenylstannane **33** in 60 % yield after hydrolysis. Deuterolysis of the reaction mixture afforded the corresponding deuterated product **33** (Scheme 7-22) [28].

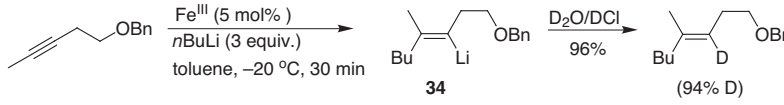


Scheme 7-22 Selective *trans*-addition of a stannylmanganate [28].

Though the intermediary stannylmanganate was successfully trapped with CH_3COOD, it could not be coupled with various other electrophiles, such as allyl bromide; the only product that could be obtained was the methylated form (probably from a reductive elimination with one of the methyl groups attached to the manganese atom).

Silylmagnesiation [29] and phenylmagnesiation [30] of alkynes, catalyzed by manganese(II) chloride, regio- and stereoselectively lead to the carbometallated product by a *syn* addition.

The intermolecular carbolithiation reaction of alkynes is limited practically, as the vinyllithium intermediates produced tend to isomerize easily. However, a major improvement was recently found in that iron can catalyze the regio- and stereoselective carbolithiation reaction of alkynes. Indeed, homopropargyl ethers react with butyllithium and a catalytic amount of $FeCl_3$ in Et_2O or toluene to



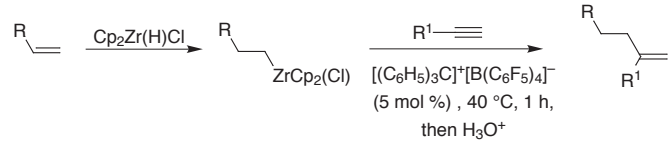
Scheme 7-23 Iron-catalyzed regio- and stereoselective carbolithiation of a homopropargyl ether [31].

yield e. g. **34** as a single isomer and in excellent yield, as determined by its deuterolysis product (Scheme 7-23) [31].

The postulated vinyllithium intermediate **34** further reacted with electrophiles, such as chlorosilanes, aromatic and aliphatic aldehydes, and even ketones to give the tetrasubstituted functionalized alkenes as single isomers.

Recent computations have shown that the addition of *tert*-butyllithium (*t*BuLi) to trichlorovinylsilane in the presence of alkynes leads to the corresponding silaheterocycles in a carbometallation-elimination sequence [32].

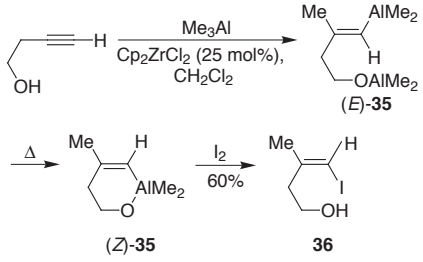
Several other metals can promote the carbometallation reactions of alkynes, such as triphenylcarbenium tetrakis(pentafluorophenyl)borate (Scheme 7-24) [33]. $[(C_6H_5)_3C]^+[B(C_6F_5)_4]^-$ was found to be the catalyst of choice for the alkylzirconation of alkynes, whereas the allylzirconation of 1-alkynes was promoted by the addition of methylaluminoxane (MAO) (see Scheme 7-15).



Scheme 7-24 Alkylzirconation of alkynes, promoted by $[(C_6H_5)_3C]^+[B(C_6F_5)_4]^-$ [33].

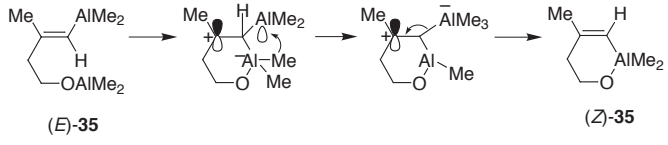
Various alkyl groups on the alkylzirconium and alkyne can be combined, and the regioselectivity is usually in favor of the branched products (Scheme 7-24). The reaction was proved to be applicable to internal alkynes, giving trisubstituted alkenes in high yields [34]. Carbozirconations, as the great majority of the synthetically useful carbometallation reactions of alkynes, are *syn*-addition processes. However, a novel strategy for achieving a net *anti*-carbometallation of homopropargyl alcohols, and even some higher homologues, was disclosed. Specifically, treatment of 3-butyn-1-ol with Me_3Al and 25 % of Cp_2ZrCl_2 in CH_2Cl_2 at 23 °C produced the expected *syn*-methylalumination product **35** [35]. Upon refluxing the reaction mixture for 72 h, a complete reversal of the stereochemistry from >98 % *E* to >98 % *Z* took place to produce, after iodinolysis, a 60 % yield of vinyliodide **36** (Scheme 7-25) [35].

Similarly, 1- and 2-methyl-substituted homopropargyl alcohols were converted to their Z isomers upon heating under reflux for 72 h. It is important to note that, in the absence of the homopropargyl hydroxyl group, the *E* to *Z* isomerization does



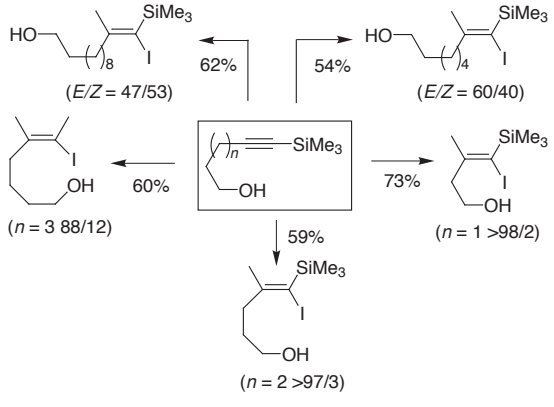
Scheme 7-25 Isomerization of carbometallated products [35].

not occur. The isomerization of (*E*)-**35** must therefore be chelation-controlled, and an alternative Lewis acid-induced chelation-controlled reaction mode was postulated (Scheme 7-26).



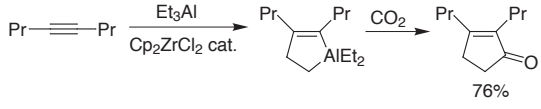
Scheme 7-26 Lewis acid-induced, chelation-controlled mode of *E* to *Z* isomerization [35].

Substitution of the terminal alkynyl hydrogen by a Si or a Ge group not only accelerates the stereoisomerization, but also expands the scope of the reaction: a series of ω-(trimethylsilyl)alkynols was treated under these carbometallation-isomerization conditions and the *E*/*Z* ratio was found to be dependent on the length of the alkyl chain tethers (Scheme 7-27) [36].



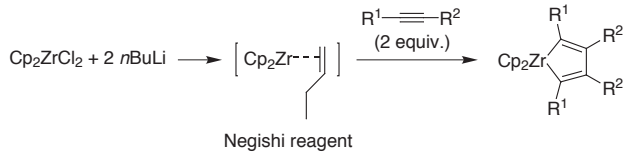
Scheme 7-27 Isomerization of ω-(trimethylsilyl)alkynols as a function of the chain length between the triple bond and the hydroxy group [36].

These results reinforce the view that the high *E*/*Z* ratios observed with the C_4 and C_5 ω-alkynols must be chelation-controlled and involve the formation of six- and seven-membered rings, respectively. This strategy was recently used for the synthesis of stereo- and regio-defined isoprenoids, containing 1,5-diene moieties [37]. The available data clearly indicate that the Zr-catalyzed carboalumination is multi-mechanistic and that the mechanism strongly depends on a number of parameters, such as the nature of R of R_3Al, the number and nature of other substituents and the solvent used [38]. Moreover, it has recently been shown that the reaction with Et_3Al and Cp_2ZrCl_2 proceeds *via* cyclic intermediates and produces cyclic products (Scheme 7-28) [39].



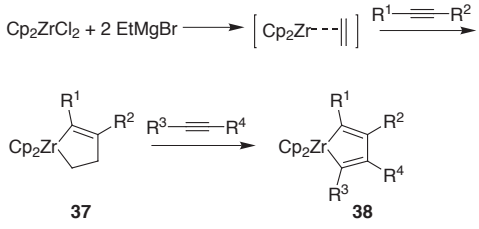
Scheme 7-28 Zr-catalyzed ethylalumination of alkynes [39].

During the past decade, carbometallation reactions with dialkylzirconocene complexes have undergone a tremendous evolution. These achievements have triggered an avalanche of interest and many elegant applications described in the literature corroborate the notion that zirconocene-based syntheses of complex targets may clearly outperform more conventional approaches. In this chapter, only basic knowledge will be provided, and readers interested in this field will find a comprehensive overview in a recently published book [40]. In situ-generated dialkylzirconocenes such as $Cp_2Zr(n\text{Bu})_2$, Cp_2ZrEt_2 and $Cp_2Zr(t\text{Bu})(i\text{Bu})$ are thermolyzed to afford zirconocene-alkene complexes. In the cases of $Cp_2Zr(n\text{Bu})_2$ and $Cp_2Zr(t\text{Bu})(i\text{Bu})$, the generated Cp_2Zr-alkene complexes tend to act as a "Cp_2Zr" equivalent, since the initially generated alkene is often replaced by another π-bond-containing compound. In the presence of alkynes, complexes of the latter can be formed (Scheme 7-29) [41].



Scheme 7-29 Formation of zirconacyclopentadienes *via* zirconocene-alkene reagents [41].

On the other hand, Cp_2Zr(ethylene), generated from Cp_2ZrEt_2, can serve as a building block, as the ethylene moiety is often incorporated in the final organic products [41]. Moreover, Cp_2Zr(ethylene) is also a very useful reagent for the pre-



Scheme 7-30 Preparation of unsymmetrical zirconacyclopentadienes by use of the Cp_2Zr(ethylene) reagent [41].

paration of unsymmetrical zirconacyclopentadienes, as two different alkynes can be coupled selectively *via* zirconacyclopentenes **37** (Scheme 7-30).

The regiochemistry of the alkyne can be controlled by the nature of the substituents. With a trimethylsilyl-substituted alkyne, the trimethylsilyl groups are placed in *α*-positions of zirconacyclopentadienes with excellent selectivity. With a phenyl-substituted alkyne, regioselective reactions are usually observed, although in some cases, a mixture of isomers may be formed (Figure 7-2) [41].

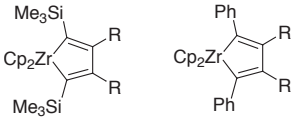


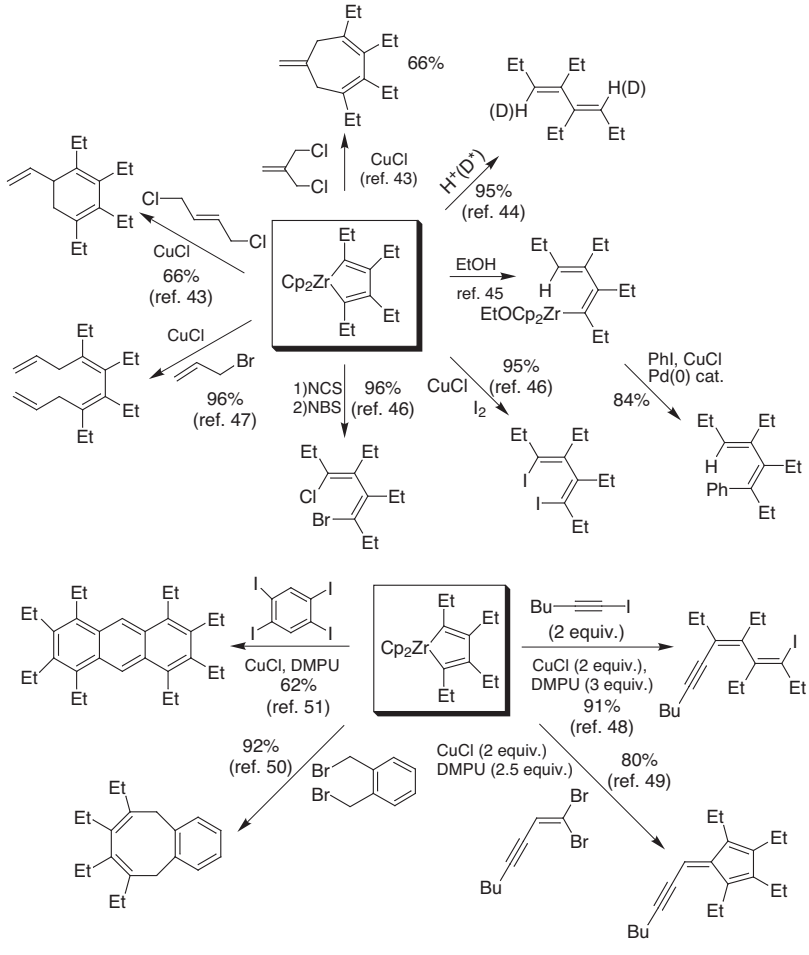
Figure 7-2 Regioselective formation of zirconacyclopentadienes.

Zirconacyclopentadienes **38** as well as zirconacyclopentenes **37** react selectively with electrophiles, with or without a transmetallation step, to give, in a single-pot operation, functionalized dienes (Scheme 7-31) [42].

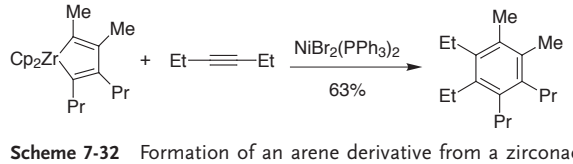
The reaction of a zirconacyclopentadiene with a third alkyne leads, in the presence of a stoichiometric amount of $NiBr_2(PPh_3)_2$, to a single hexasubstituted benzene derivative (Scheme 7-32) [52].

Zirconacyclopentenes also react selectively with electrophiles, with loss of ethylene, to give functionalized molecules (Scheme 7-33).

As for low-valent zirconocene complexes, the generation of divalent titanium complexes and their utilization for intermolecular carbometallation reactions of alkynes has also attracted considerable interest over the past few years. Major aspects have been summarized in a recent monograph [40], and only a few representative examples will be described in this chapter. Several divalent titanium complexes have been widely used for this purpose and among these complexes, (η^2-propene)Ti(O*i*Pr)$_2$ **39**, readily prepared from Ti(O*i*Pr)$_4$ and 2 equiv. of isopropylmagnesium halide has been found recently to be of significant practical value. Synthetically useful reactions, mediated by **39** can be classified into two categories: (1) the generation of titanium-alkyne complexes and further synthetic applications

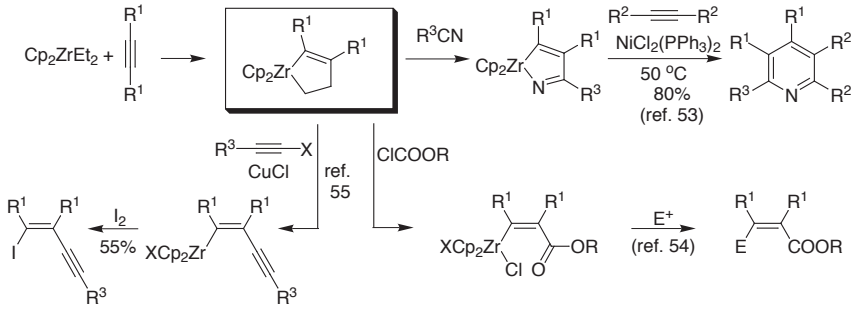


Scheme 7-31 Selective reactions of zirconacyclopentadienes with different electrophiles.

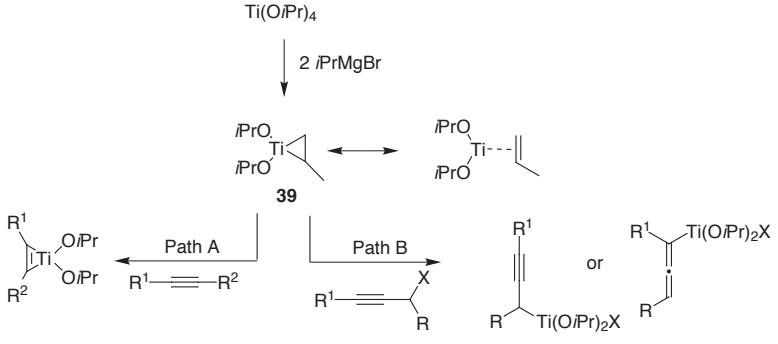


Scheme 7-32 Formation of an arene derivative from a zirconacyclopentadiene, promoted by a nickel reagent [52].

(Scheme 7-34, path A), including the intramolecular nucleophilic acyl substitution reaction of unsaturated esters; and (2) the generation of propargyl- or allenyltitaniums and their use as propargylating (or alternatively allenylating) reagents (Scheme 7-34, path B).

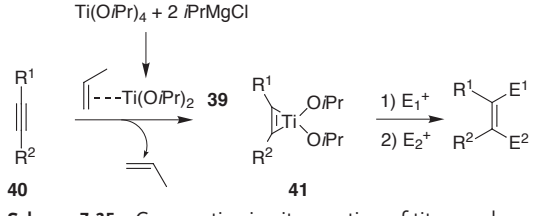


Scheme 7-33 Reactions of zirconacyclopentenes with different electrophiles.



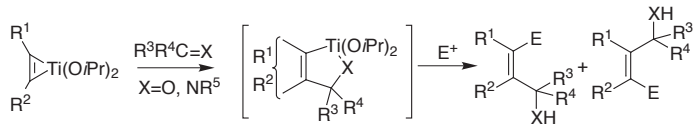
Scheme 7-34 Synthetic utilities of the divalent titanium-propene complex.

Most of the cases described in path A of Scheme 7-34 referred to the treatment of an internal alkyne **40** with **39** to give the corresponding titanacyclopropene **41**, which reacts *in situ* with a variety of electrophiles, including two different electrophiles in consecutive order (Scheme 7-35).



Scheme 7-35 Consecutive in-situ reaction of titanacyclopropene with two different electrophiles.

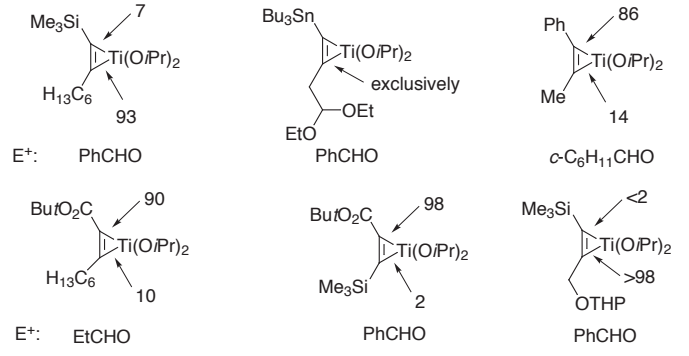
Hydrolysis (deuteriolysis) of the titanium-alkyne complex **41** provides the corresponding alkene (1,2-deuterioalkene) exclusively with the *cis* configuration, thus providing a convenient one-pot method for preparing *cis*-1,2-dideuterioalkenes from acetylenic derivatives [56].



Scheme 7-36 Reaction of titanium-alkyne complexes with carbonyl compounds [57,58].

The titanium-alkyne complexes react with aldehydes, ketones [57] and imines [58] to afford oxa- and azatitanacycles, respectively (Scheme 7-36).

The titanium-carbon bond remaining in the oxa- and azatitanacycle intermediates can react with one more electrophile (E^+). For a titanium complex arising from any unsymmetrical alkyne, the reaction may form two regioisomers. Representative examples for the reactivity of unsymmetrical alkyne are given in Scheme 7-37 [40].

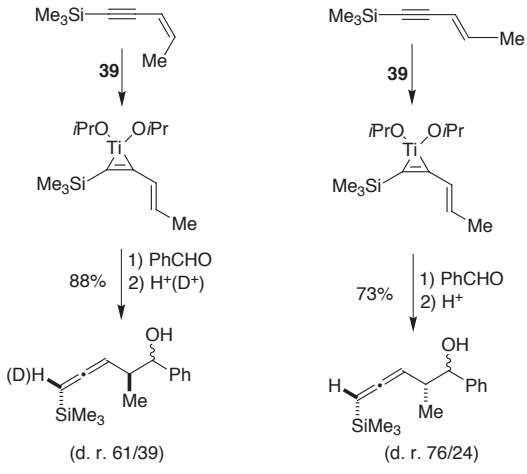


Scheme 7-37 Regioselectivities for the reactions of various alkyne complexes with electrophiles.

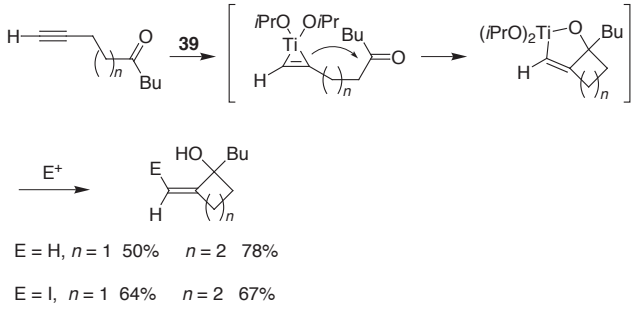
The titanium-alkyne complexes generated from an *E*- or *Z*-enyne and **39** react with aldehydes, ketones, and imines at the remote olefinic carbon in a regioselective and stereoselective manner to give the corresponding allenyltitanium compounds which, upon hydrolysis, afford allenes regio- and stereoselectively (Scheme 7-38) [59].

Although terminal alkynes *per se* do not form stable titanium-alkyne complexes in reactions with **39**, terminal alkynes having a keto carbonyl group at the γ- or δ-position in reactions with **39** and subsequently with electrophiles form 2-methylenecyclobutanols and -cyclopentanols apparently *via* titanium complexes of the respective alkynes (Scheme 7-39) [60].

In addition to the above electrophiles, the alkyne-titanium complexes react regioselectively with other acetylenes, providing the corresponding titanacyclopentadienes [61]. Especially noteworthy is the highly regioselective cross-coupling reaction of unsymmetrical and terminal acetylenes, which is illustrated in Scheme 7-40 [62].



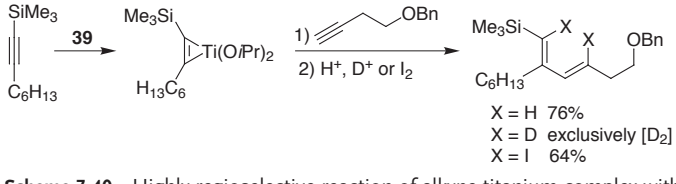
Scheme 7-38 Regio- and stereoselective formation of allenyltitanium compounds [59].



E = H, $n = 1$ 50% $n = 2$ 78%

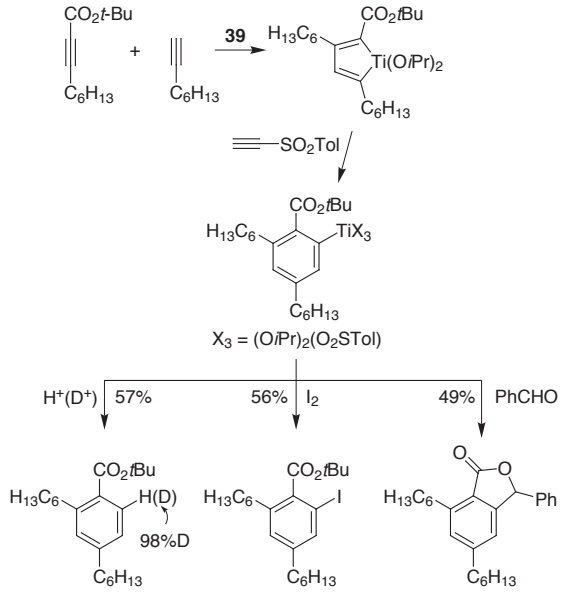
E = I, $n = 1$ 64% $n = 2$ 67%

Scheme 7-39 Intramolecular carbotitanation of carbonyl-substituted terminal alkynes [60].



X = H 76%
X = D exclusively [D_2]
X = I 64%

Scheme 7-40 Highly regioselective reaction of alkyne-titanium complex with a terminal acetylene [62].



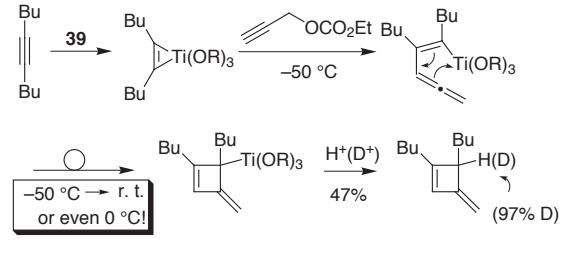
Scheme 7-41 Chemo- and regioselective formation of an aryltitanium compound and its further reactions with electrophiles [63].

Titanacyclopentadiene intermediates, generated from two unsymmetrical acetylenes, have been shown to react with ethynyl *p*-tolylsulfone to afford an aryltitanium compound (Scheme 7-41) [63].

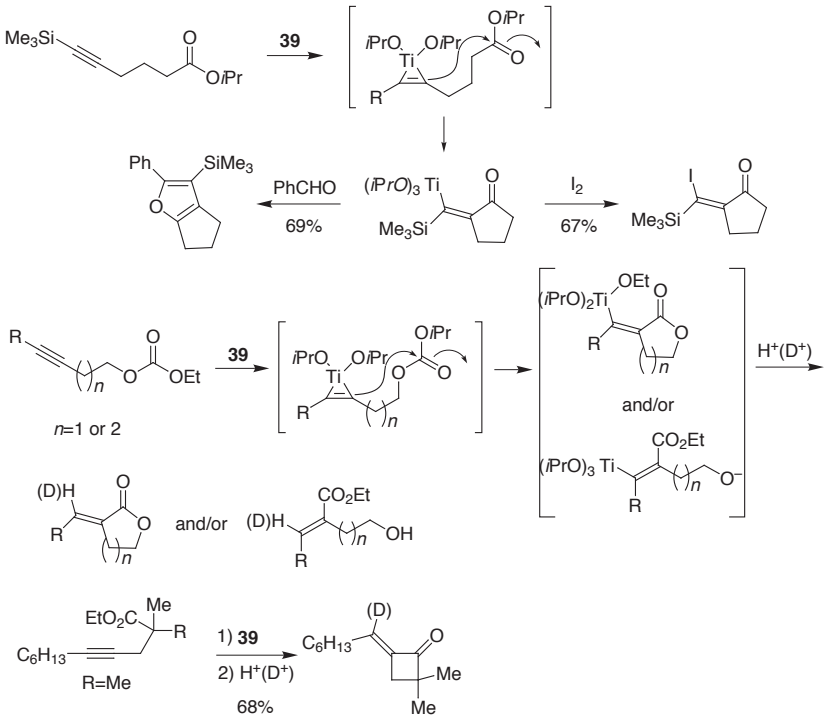
It should be noted that the reaction achieved a highly chemo- and regioselective trimerization of three different unsymmetrical alkynes. The reaction also opens up, for the first time, a direct synthesis of aryltitanium compounds from three acetylenes and a metal constituent.

Titanium-alkyne complexes react with propargyl carbonates *via* a regioselectively formed titanacycle, with subsequent *β*-elimination. The reaction, therefore, provides a convenient method for the preparation of titanated vinylallenes, which undergo facile, unidirectional electrocyclization to give cyclobutene derivatives under extremely mild reaction conditions (Scheme 7-42) [64].

The *π*-alkynyltitanium intermediates, shown in the schemes described above, have a highly strained titanacyclopropene structure, and the relief of the strain



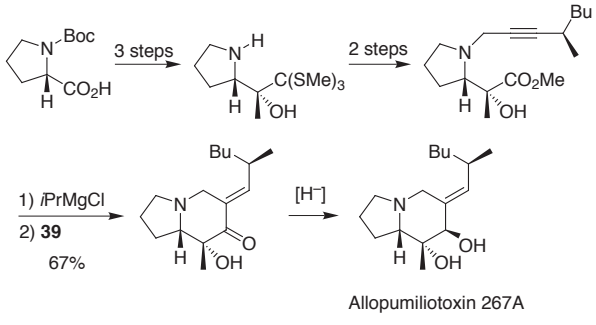
Scheme 7-42 Formation of cyclobutene derivative *via* a titanated vinylallene [64].



Scheme 7-43 Preparation of functionalized metallated carbocycles by intramolecular nucleophilic acyl substitution [65].

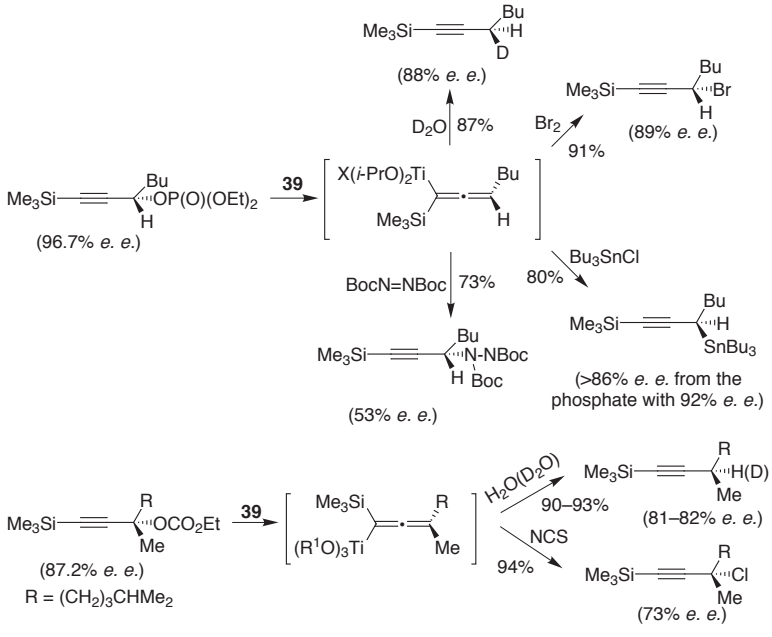
by an intramolecular nucleophilic acyl substitution reaction is a powerful method for the preparation of functionalized metallated carbocycles (Scheme 7-43) [65].

An elegant application was recently reported with the synthesis of allopumiliotoxin 267A; this is one component of the toxic skin secretion of certain neotropical frogs, and displays significant cardiotoxic activity (Scheme 7-44) [66].



Scheme 7-44 Synthesis of allopumiliotoxin 267A, achieved by intramolecular nucleophilic acyl substitution [66].

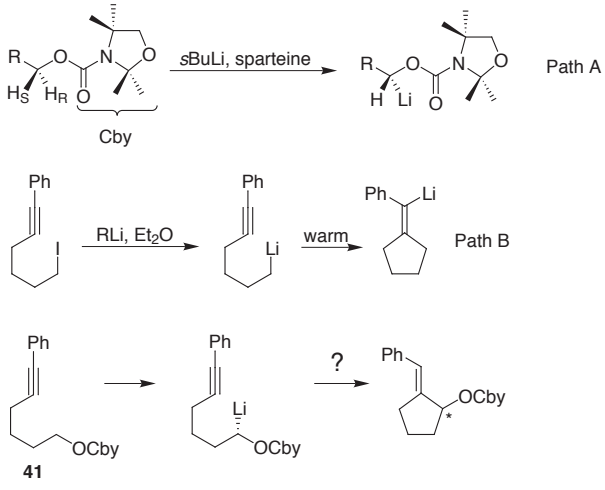
The titanium-propene complex **39** reacts with propargyl alcohol derivatives to provide synthetically useful propargyl- or allenyltitanium compounds. The reaction of **39** with secondary propargyl phosphates and tertiary propargyl carbonates (Scheme 7-45) proceeds with excellent stereoselectivity, and although the sense of stereoselectivity differs in the two cases, it provides a practical and general method for synthesizing enantiomerically enriched chiral allenyltitaniums, starting from easily accessible optically active propargyl alcohol derivatives [67].



Scheme 7-45 Stereoselective reactions of enantioenriched, homochiral allenyltitanium intermediates [67].

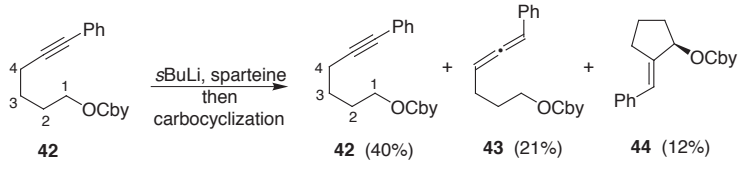
7.2.2
Intramolecular Carbometallation Reactions

The enantioselective deprotonation of carbamate esters from primary alkanols with the chiral base *s*-butyllithium/(–)-sparteine and the subsequent stereoselective electrophilic substitution of the carbanionic intermediate by external electrophiles represents a powerful tool for the synthesis of enantioenriched secondary alkanols [68]. An extension of this method is the employment of carbon-carbon multiple bonds as internal electrophiles, corresponding to an intramolecular carbolithiation. Therefore, the combination of the concepts of enantioselective deprotonation (path A, Scheme 7-46) and intramolecular carbolithiation (path B, Scheme 7-46) has led to an increasing interest in the synthetic community [69].



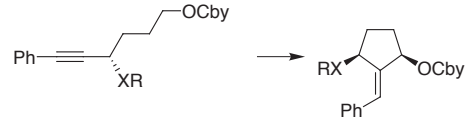
Scheme 7-46 Enantioselective deprotonation and intramolecular carbolithiation as a new tool for the formation of enantioenriched carbocyclic compounds [68,69].

When 6-phenyl-5-hexynyl carbamate **42** was deprotonated enantioselectively with *s*-BuLi/sparteine at –78 °C, followed by the carbocyclization step, a mixture of the starting material **42**, the allene **43**, and the desired cyclopentane **44** was obtained in moderate yield (Scheme 7-47).



Scheme 7-47 First attempt to combine the deprotonation and cyclization steps in one substrate [69].

The low yield of **44** is due to the relatively high acidity of the propargylic protons at C4 competing with the kinetic acidity of the activated protons at C1 *α* to the carbamate moiety. However, following previous observations [70], the blocking of the deprotonation in the propargylic position could be achieved by the introduction of a large substituent, such as *N,N*-dibenzylamino, trityloxy, or silyloxy groups and with the use of a sterically hindered base, such as *s*BuLi/sparteine. Therefore, racemic and chiral **45**, **46** and **47** were prepared for this study [71] (Scheme 7-48).

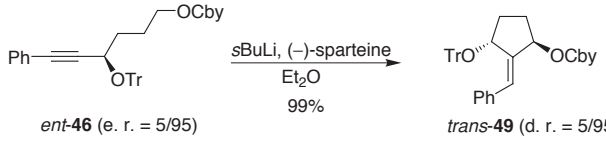


45 XR = NBn_2 (e. r. = 99/1)
46 XR = OTr (e. r. = 95/5)
47 XR = TBDMS (e. r. = 95/5)

48 70% (d. r. = > 99/1
49 88% (d. r. = 95/5)
50 82% (d. r. = 95/5)

Scheme 7-48 Enantioselective deprotonation and carbocyclization of *α*-substituted alkynylalkyl carbamates [71].

The enantioselective deprotonation of chiral **45**–**47** and the carbocyclization reaction were performed using the above-mentioned conditions, and the corresponding *cis*-2,5-disubstituted alkylidenecyclopentanes **48**–**50** were obtained in diastereomerically pure form as single products in good yields (see Scheme 7-48). The diastereomeric ratios of the functionalized cyclopentanes **48**–**50** directly corresponded to the enantiomeric ratios (e. r. = 99:1 to 95.5 for **45**, **46** and **47**, respectively) of each individual cyclization precursor **45**, **46**, and **47** [71]. Nevertheless, since only the (*S*)-configured precursors were cyclized in the presence of the chiral ligand (–)-sparteine, the enantiomeric (*R*)-configured precursor *ent*-**46** was also prepared and submitted to this enantioselective deprotonation-carbometallation sequence (Scheme 7-49).



Scheme 7-49 Enantioselective deprotonation-carbometallation sequence applied to the (*R*)-enantiomer of **46** (see Scheme 7-48) [71].

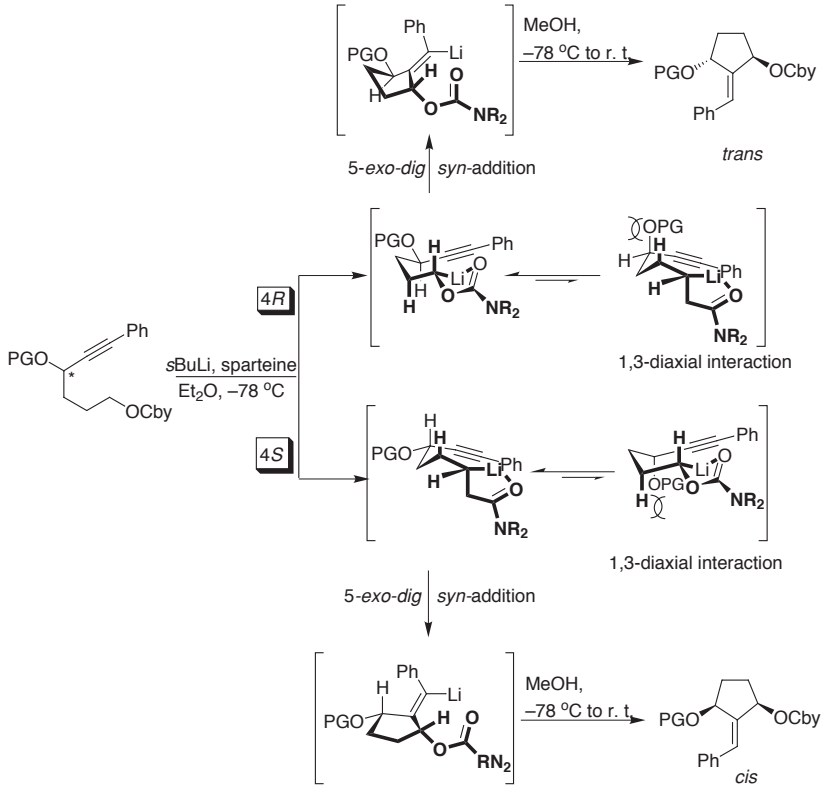
Under these standard conditions, the *trans*-disubstituted benzylidene cyclopentane **49** was obtained in quantitative yield. Thus, the chiral base *s*BuLi/sparteine selectively abstracts the *pro-S*-proton independently of the configuration of the propargylic stereocenter. The very high diastereoselectivity observed was rationalized with a chair-like transition state, in which 1,3-diaxial interactions play a primordial role (Scheme 7-50).

When this enantioselective deprotonation-carbometallation protocol was applied to trimethylsilyl-substituted alkyne derivatives such as **51**, the *cis*-2,5-disubstituted methylenecyclopentane derivative **52** was obtained in 70 % yield with a d. r. >95/5 (e. r. of **51** = 99/1). Thus, **52** is formed by an intramolecular reaction of the vinyllithium on the carbamic ester group (OCby) (Scheme 7-51).

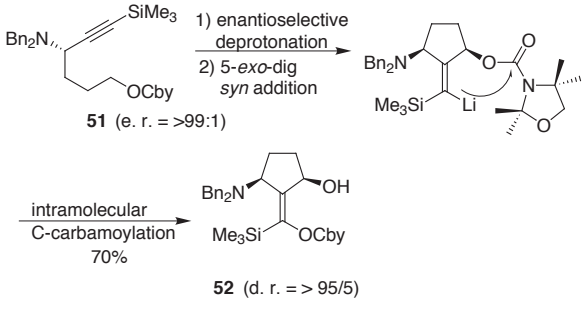
The 5-*exo-dig* carbocyclization reaction of alkynylalkylcarbamates was also performed on enantiomerically enriched α-lithiated 4-substituted 5-hexynyl carbamate **53**. Indeed, the lithiodestannylation of **53** (1*S*,4*R*,*S*) with *n*BuLi at low temperature, followed by the asymmetric 5-*exo-dig* ring closure provided the *cis*- and *trans*-cyclization products in a ratio of 50:50 after substitution with different electrophiles (Scheme 7-52) [72].

All *cis*- and *trans*-2,5-disubstituted methylenecyclopentane derivatives **55** to **57** were isolated with high enantiomeric excesses, and the two diastereomers were easily separated by flash chromatography. 5-*Exo-dig* cyclization usually proceeds in a *syn*-addition across the alkyne, but in this case, a formal *anti*-addition was observed.

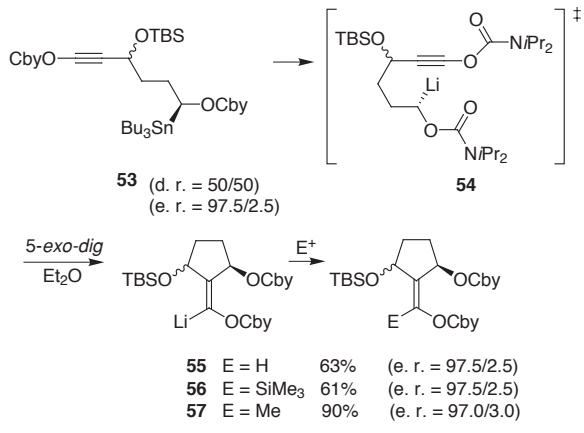
In light of the facile 5-*exo-dig* cyclization of simple acetylenic alkyllithiums [3], the 5-*exo*-cyclization of a tethered benzynylalkyllithium was investigated [73].



Scheme 7-50 Mechanism of the carbocyclization [71].



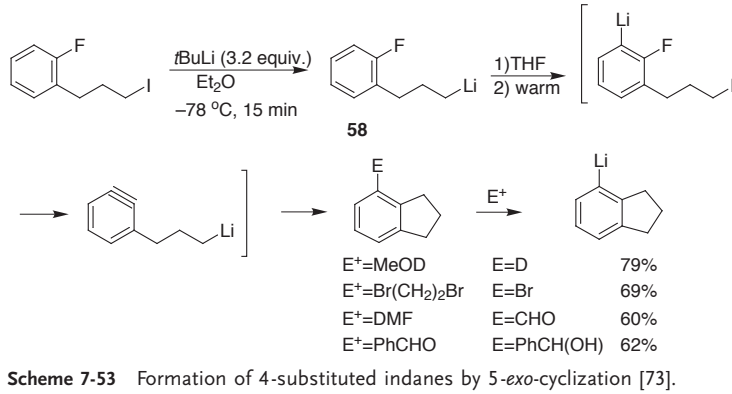
Scheme 7-51 Deprotonation-carbamoylation sequence of a TMS-substituted alkyne.



Scheme 7-52 The 5-*exo-dig* carbocyclization of an enantiomerically enriched α-lithiated carbamate [72].

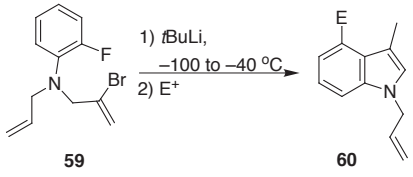
This new five-step, one-pot synthetic sequence was used for the preparation of 4-substituted indanes by cyclization of the tethered 3-benzynylpropyllithium derivative (Scheme 7-53).

The rapid lithium-iodine exchange on 3-(2′-fluorophenyl)propyl iodide was easily accomplished by the classical procedure [74], and in order to avoid the self-lithiation by intermolecular proton transfer between two molecules of 3-(2-fluorophenyl)propyllithium **58**, an equimolar quantity of THF was added in the second step. Thus, the hydrogen-lithium exchange occurs to give the *ortho*-lithiated product, and by loss of LiF, the tethered benzenylpropyllithium was formed. A 5-*exo-dig*-cyclization gives the corresponding 4-indanyllithium (Scheme 7-53). Isomerically pure 3-substituted benzocyclobutenes or 5-substituted tetralins were obtained from the corresponding α-(2-fluorophenyl)ω-iodoalkane involving the same five-step, one-pot procedure with the 4- or 6-*exo*-cyclization of a tethered benzenylalkyllithium [73]. An extension of this methodology was recently described for the preparation of regioselectively substituted functionalized heterocyclic derivatives [75].



Scheme 7-53 Formation of 4-substituted indanes by 5-*exo*-cyclization [73].

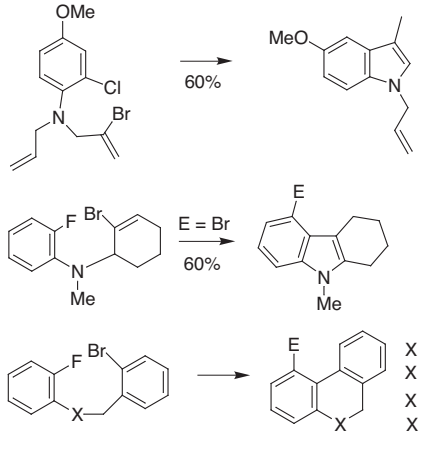
The reaction of *N*-(2-bromoallyl)-*N*-methyl-2-fluoroaniline **59** with an excess of *tert*-butyllithium in THF at low temperature and further treatment with different electrophiles gave the 4-functionalized 1,3-dimethylindoles **60** in moderate to good yields (Scheme 7-54).



E = H	70%
E = Bu_3Sn	52%
E = Me_3Si	50%
E = PhS	50%
E = Br	50%

Scheme 7-54 Synthesis of functionalized indoles by 5-*exo*-*dig*-cyclization [75].

The mechanism can be formulated as a sequence of: (1) halogen-metal exchange with formation of *N*-(2)-lithioallylamines; (2) ortho-metallation with respect to the fluorine with the additional equivalents of *t*BuLi; (3) elimination of LiF to produce the benzyne intermediate; (4) carbocyclization to give the C(4)-lithiated 3-methyleneindoline derivative; (5) functionalization with different electrophiles; and (6) isomerization of the indoline to the functionalized indole on work-up. Several other heterocycles were prepared by this methodology (Scheme 7-55) [76].

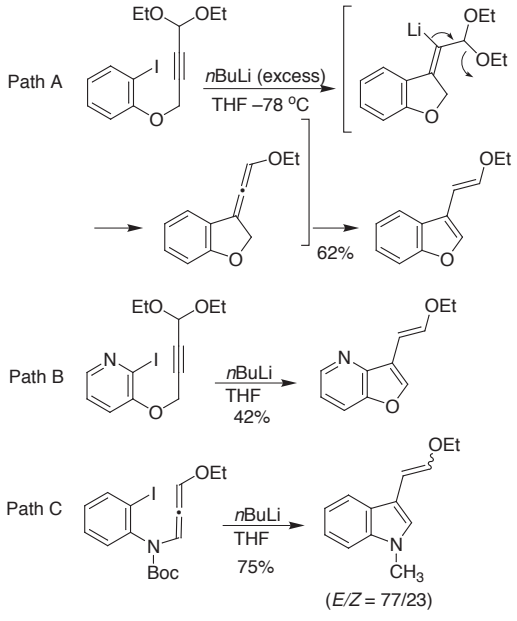


X = NMe	E = Br	68%
X = N(allyl)	E = Br	73%
X = O	E = Br	61%
X = S	E = H	80%

Scheme 7-55 Formation of different heterocycles by a five-step, one-pot procedure [76].

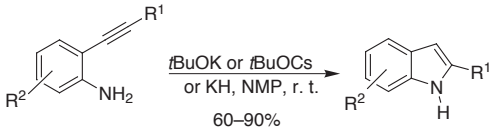
3-Vinylbenzofuranes, 3-vinylfuropyridines and 3-vinylindoles were also easily prepared by a 5-*exo*-*dig*-cyclization reaction followed by a lithium-ethoxide elimination (Scheme 7-56; paths A and B) [77].

The putative exocyclic allene rearranged in this basic medium to 3-vinylbenzofuran and 3-vinylfuropyridines. When the same sequence was applied to the propargyl aldehyde acetal of *N*-Boc-2-iodoanilinyl residue at the other propylic positions, a complex mixture of products was obtained. On the other hand, the desired ring closure could be effected on the corresponding alkoxyallene (Scheme 7-56, path C) in 75 % yield, but gave a mixture of two diasteromers [77].



Scheme 7-56 5-*exo-dig*-cyclizations leading to substituted benzofurans, furopyridines and indoles [77].

2-Substituted indoles could also be prepared by cyclization of heteroatomic nucleophiles adding to triple bonds, mediated by a potassium or a cesium base in *N*-methylpyrrolidinone (NMP; Scheme 7-57).

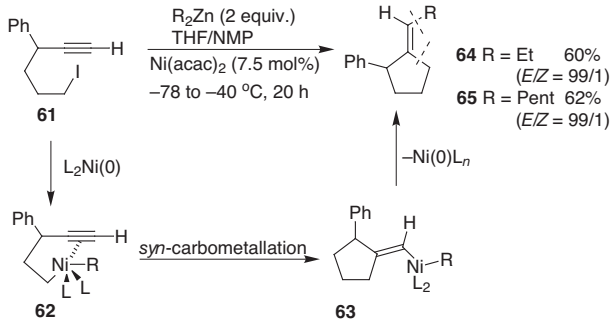


Scheme 7-57 Preparation of 2-substituted indoles, promoted by potassium or cesium base [78].

The scope of this reaction is broad, since R^1 can be an alkyl, aryl, H, hydroxyl, acetal, additional amino, alkynyl and even a nitro group, whereas R^2 can be alkyl, halide or trifluoromethyl groups [78].

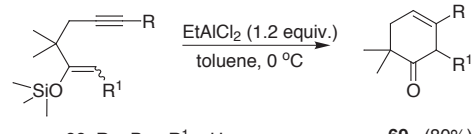
The addition of dialkylzinc to ω-iodoalkynes in the presence of catalytic amounts of $Ni(acac)_2$ in THF/NMP mixtures leads to the cyclic products in moderate yields as single diastereomers (Scheme 7-58) [9].

These results may be explained by assuming that diethylzinc reacts with $Ni(acac)_2$ generating a nickel(0) species, which undergoes an oxidative addition to **61**, providing a nickel(II) complex **62**, which coordinates to the triple bond. After *syn*-carbonickelation, leading to the alkenylnickel **63**, a reductive elimination occurs, furnishing the products **64** and **65**, respectively.



Scheme 7-58 Ni-catalyzed stereo- and regioselective cyclization of ω-iodoalkynes [9].

Most of the intramolecular carbometallations of alkynes are derived from sp^3-organometallic derivatives and only few examples of carbocyclizations of silyl enol ethers were reported [79]. These reactions proceed through electrophilic activation of the alkyne by the Lewis acid, enabling it to react with the modestly nucleophilic silyl enol ether moiety. Therefore, the carbocyclization of butyl- **66** and phenyl-substituted **67**,**68** alkynylalkyl silyl enol ethers proceeded smoothly to give the β,γ-unsaturated ketones **69**–**71** in 80 %, 75 % and 76 % yields, respectively (Scheme 7-59) [80].



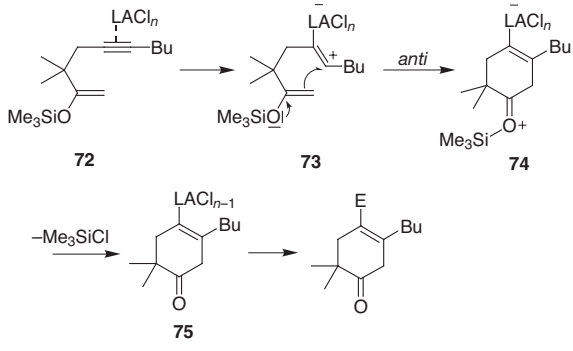
66 R = Bu, R^1 = H
67 R = Ph, R^1 = H
68 R = Ph, R^1 = Me

69 (80%)
70 (75%)
71 (76%)

Scheme 7-59 Formation of β,γ-unsaturated ketones by carbocyclization of silyl enol ethers [80].

It should be pointed out that in all cases the carbocyclizations proceeded exclusively in an *endo*-fashion, and no traces of the *exo*-cyclization were detected. To explain the observed results, it has been suggested that the coordination of the Lewis acid to the triple bond of **72** would form zwitterionic intermediate **73** (Scheme 7-60). The vinyl cation moiety of **73** would then react with the double bond of the silyl enol ether moiety at the most nucleophilic terminal position in an *anti*-fashion affording the *endo*-cyclization product **74**. The elimination of TMSCl from **74** would then form the vinyl metal derivative **75**, which can be trapped with different electrophiles (Scheme 7-60) [80].

Intramolecular carbozirconation [40] and carbotitanation [40] reactions were recently described in detail, and will not be addressed in this chapter.



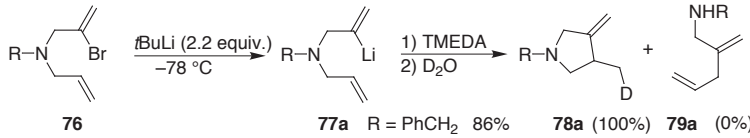
Scheme 7-60 A mechanistic rationalization of the *endo*-cyclization product formation [80]. LA = Lewis-acidic center.

7.3 Carbometallation Reactions of Alkenes

7.3.1 Intramolecular Carbometallation Reactions

The formation of ring systems by intramolecular carbometallation of alkenes is usually easier for the formation of five than for six-membered rings. However, recent reports have shown that the cyclization of *N*-allyl-*N*-(2-lithioallyl)amines proceeds *via* 5-*exo*- or 6-*endo*-carbocyclization according to the substituents bound to the nitrogen atom.

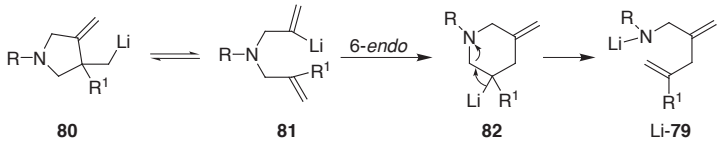
Treatment of *N*-allyl-*N*-(2-bromoallyl)amines **76** with 2 equiv. of *t*BuLi at –78 °C afforded the vinyllithium derivatives **77a**,**b**, which undergo the intramolecular addition at 0 °C in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (Scheme 7-61). When the reaction was carried out with **77a**, methylenepyrrolidine **78a** was obtained as the only product after deuterolysis. However, the reaction of **77b** under the same conditions, led only to minor amounts of pyrrolidine derivative **78b** rather than to the 2-methylene-4-pentenylamine 79b [81].



Scheme 7-61 Carbocyclization of *N*-allyl-*N*-(2-bromoallyl)amines [81].

Products **79** can be obtained by a 6-*endo-trig*-cyclization *via* the organolithium compounds **82**, which immediately undergo a *β*-elimination to give the lithium amides Li-**79**, which furnish **79** after hydrolysis (Scheme 7-62).

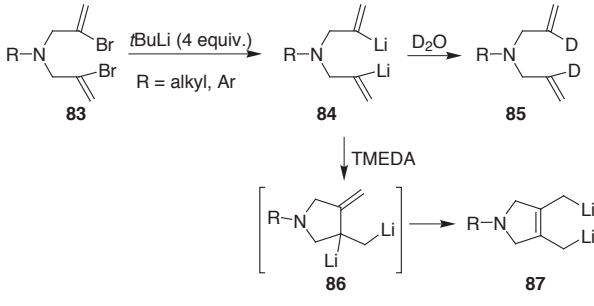
In order to explain these results, a simple reversion of the kinetically favored 5-*exo*-product **80** to the starting vinyllithium **81** was suggested, followed by a 6-*endo*-



Scheme 7-62 Reversibility of the carbometallating cyclization.

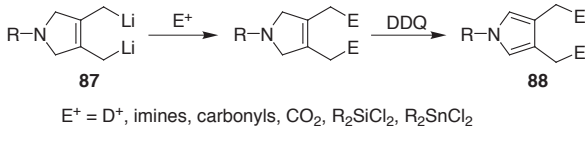
closure and an irreversible β-elimination of the functionalized organolithium **82**. To gain more insight into this reversible carbocyclization, D_2O was added to **81** (R = Ph, R^1= Me) after 40 min at 0 °C, and a 3:2 mixture of deuterated compounds corresponding to intermediates **81** and **80** was obtained. However, when the mixture was stirred at 0 C for 2 h, followed by quenching with D_2O and further hydrolysis, the amide **79** (R = Ph, R^1 = Me) was the only compound detected. This result shows that the initial 5-*exo-trig*-cyclization is reversible in this particular case.

When **81** is treated with CuCN, the corresponding vinylcopper undergoes preferentially the 5-*exo-trig*-cyclization, whatever the nature of the substituent on the nitrogen atom [82]. Interestingly, treatment of *N,N*-bis-(2-bromoallyl)amines **83** with 4 equiv. of *t*BuLi in Et_2O at –78 °C gave the dianion **84**, characterized by deuterolysis to yield the dideuterated amines **85** (Scheme 7-63). The dianion **84** afforded 3,4-bis-(lithiomethyl)dihydropyrrole **86** after addition of TMEDA. This unusual carbometallation could be explained by assuming first an intramolecular carbolithiation of one vinyl moiety by the other one, affording methylenepyrrolidine derivatives **86**. These intermediates could undergo an allylic rearrangement to give the dilithiated compounds **87** [83].



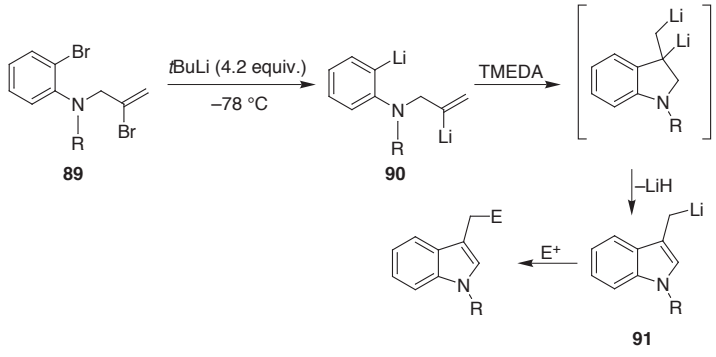
Scheme 7-63 Unusual carbometallation of *N,N*-bis-(2-bromoallyl) amines [83].

The synthetic scope of this new carbocyclization can be extended to the preparation of 3,4-difunctionalized pyrroles **88** (Scheme 7-64) [83b].



Scheme 7-64 Preparation of 3,4-difunctionalized pyrroles by carbocyclization of **83** [83b].

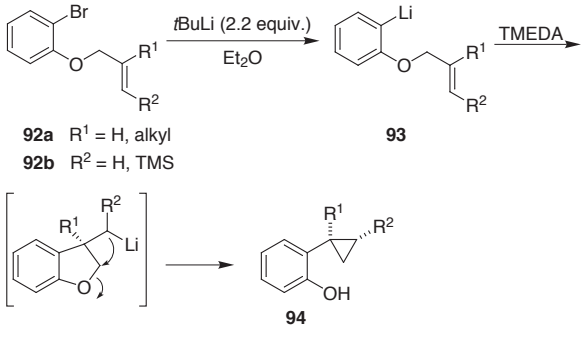
When the same concept is used on 2-bromo-*N*-(2-bromoallyl)anilines **89**, the dianions **90** also undergo the carbocyclization reaction, in the presence of TMEDA, to give the corresponding indoles **91** [83]. The formation of the indole nucleus is also explained by the carbometallation of the vinyllithium moiety by the aryllithium in the dianions **90** (Scheme 7-65).



Scheme 7-65 Preparation of indole derivatives by carbocyclization of 2-bromo-*N*-(2-bromoallyl) anilines [83].

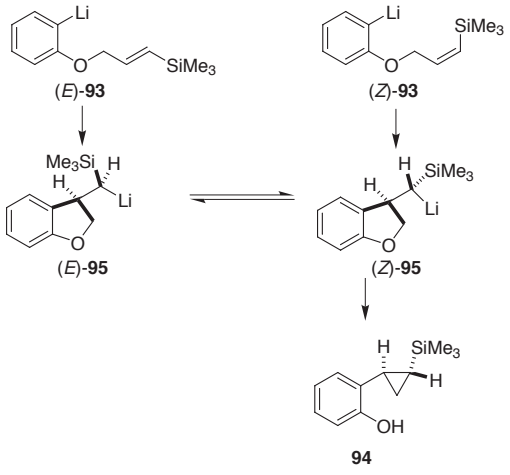
In this particular case, since an allylic rearrangement could involve the loss of aromaticity, elimination of lithium hydride takes place affording 3-(lithiomethyl)indole **91**.

When allyl-*o*-bromoaryl ethers **92** are treated with *t*BuLi in Et_2O, the corresponding organolithiums **93** undergo a carbometallation reaction followed by a 1,3-elimination giving the cyclopropanes **94** (Scheme 7-66) [84].



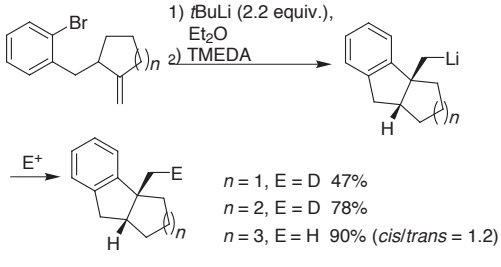
Scheme 7-66 Carbometallation reaction of allyl-*o*-bromoaryl ethers followed by a 1,3-elimination [84].

High *trans*-diastereoselectivity is observed for **94** when substituted alkenes such as *E*-**92b** or *Z*-**92b** are used as starting materials (R^1 = H, R^2 = $SiMe_3$). Moreover, both organolithium compounds *E*-**93** and *Z*-**93** led to the same *trans*-1,2-disubstituted cyclopropane **94** by epimerization of the sp^3-organolithium compound **95**, before the 1,3-elimination (Scheme 7-67) [84].



Scheme 7-67 Epimerization of the sp^3-organolithium leads to high *trans*-diastereoselectivity [84].

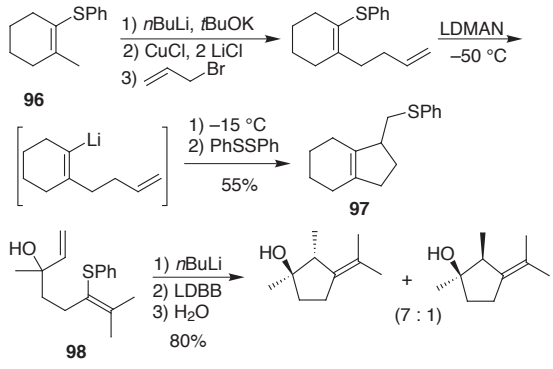
When the reaction is performed in the presence of a chiral diamine such as (–)-sparteine instead of achiral TMEDA, moderate to good enantiomeric excesses were obtained for the cyclopropane (particularly when non-polar solvents were used; for instance in toluene, the enantiomeric excess reached 80 %). The creation of racemic quaternary center by the cyclization of various stable aryllithiums was recently studied and, although kinetically slow, this reaction is thermodynamically a favorable process. This cyclization affords diastereomerically pure *cis*-fused products when the methylenecycloalkane has a five- or six-membered ring, but is virtually nonstereoselective when the methylenecycloalkane has a seven-membered ring (Scheme 7-68) [85a].



Scheme 7-68 Carbocyclization of 2-(2-*o*-bromobenzyl)methylenecycloalkanes [85a].

Aryllithiums, prepared by bromine-lithium exchange from chiral 2-(*o*-bromo phenyl)-substituted perhydro-1,3-benzoxazines, also participate in the intramolecular 6-*exo*-carbocyclization with unactivated double bonds attached to the nitrogen substituent of the heterocycle [85b].

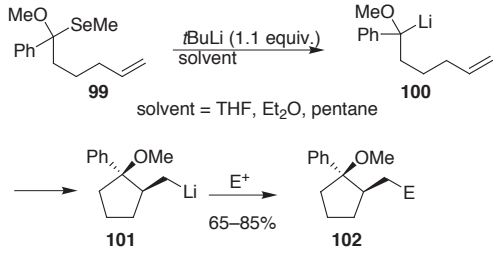
Reductive lithiation of phenyl thioethers greatly extends the versatility of the cyclizations of sp^2-organolithium compounds; when aromatic radical anions



Scheme 7-69 Reductive lithiation of phenyl thioethers [86].

such as lithium 1-dimethylaminonaphtalenide (LDMAN) or 4,4′-di-*tert*-butylbiphenylide (LDBB) react with vinyl phenyl thioether **96**, the corresponding vinyllithium is quantitatively obtained. This then undergoes the carbolithiation reaction to give the cyclopentenylmethyllithium precursor of **97**, which is itself readily produced from **96** (Scheme 7-69) [86].

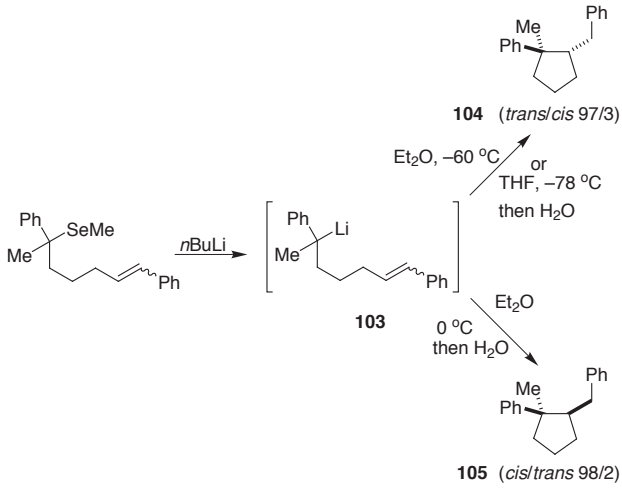
When the alkene linkage is *exo* to the five-membered ring, such as in the cyclization of **98**, an excellent diastereoselectivty is observed [86]. 1-Methoxy-4-phenylalkenyllithiums **100** bearing a ω-double bond, possess a high propensity to produce stereoselectively the carbocyclized product. Trapping the reaction mixture with an electrophile leads, after treatment with acid, to the *cis*-difunctionalized cyclopentyl derivative **102** (Scheme 7-70) [87].



Scheme 7-70 Cyclization of 1-methoxy-1-methylseleno-1-phenylhex-5-ene [87].

This carbocyclization can also be achieved by using a substoichiometric amount of *t*BuLi, since the carbocyclization product **101** can react with **99** to give back the initial 1-methoxy-benzyllithium **100** and thus **102** (E = SeMe). This reaction has also been extended successfully to the homologous 1-methoxy-1-methylseleno-1-phenylhept-6-ene which cyclizes to a six-membered ring with complete stereocontrol [87].

The ω-styrenylbenzyllithium **103** provides, after carbocyclization, 1-aryl-2-benzylcyclopentanes with very high stereocontrol; the *trans*-product **104** is produced when the reaction is carried out in THF at –78 °C or in Et_2O at –60 °C, whereas its *cis*-



Scheme 7-71 Stereoselective carbocyclization of an ω-styrenylbenzyllithium [88].

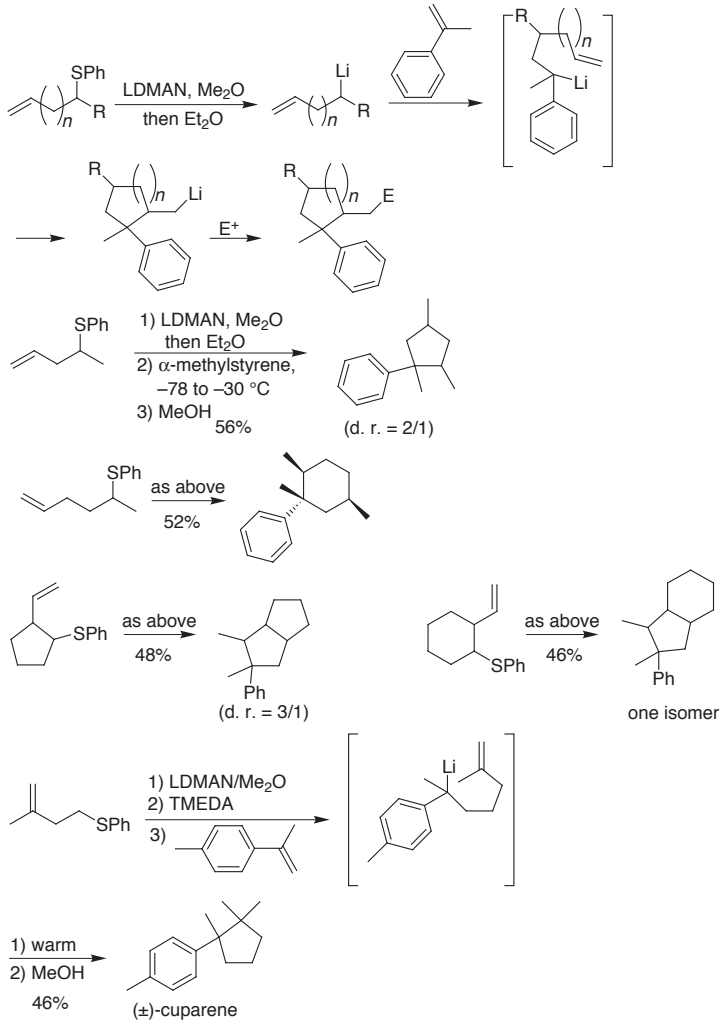
diastereomer **105** is generated when the reaction is carried out in ether at 0 °C (Scheme 7-71) [88].

This reaction occurs under kinetic control. The stereochemistry of the intramolecular carbolithiation reaction of vinyl sulfides with benzylic organolithium compounds has been found to be stereoselective with regard to the formation of the new carbon-carbon bond, and non-stereoselective with regard to the formation of the new carbon-lithium bond [89].

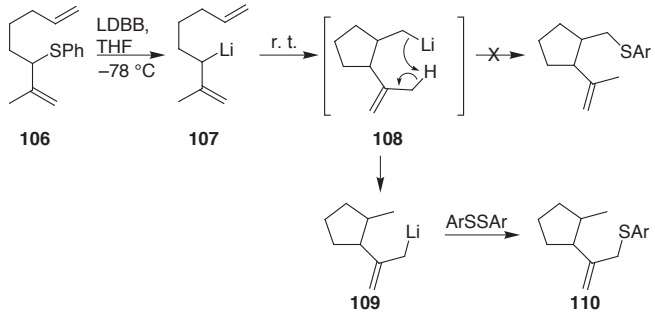
An alternative and potentially useful method for the production of benzyllithiums should be the addition of organolithiums to styrene. Although the anionic polymerization of styrene and its derivatives upon treatment with organolithiums is a well-known process, it was found to be solvent-dependent [90, 91]. Therefore, homo- and bishomoallyllithiums, prepared by reductive lithiation of the corresponding phenyl thioethers in Et_2O with LDMAN [92], are added to α-methylstyrene and give the corresponding cyclic product *via* sequential intermolecular/intramolecular carbolithiation reactions. These addition/cyclization reactions lead to a large family of diversely substituted cyclopentyl- and cyclohexylmethyllithiums in a single-pot operation (Scheme 7-72) [92].

Recent reinvestigations of the lithium-ene cyclization have provided evidence of misassignment of structure in the previously reported case [93]. Indeed, it could be shown that the cyclization of methylallyllithium **107** (generated by reductive lithiation of **106** using LDBB) occurred completely at ambient temperature to give, in 77 % yield after reaction with bis-(*p*-methoxyphenyl)-disulfide, the cyclic thioether **110**, which was not obtained from an electrophilic capture of **108** but from the rearranged allyllithium **109** (Scheme 7-73) [94].

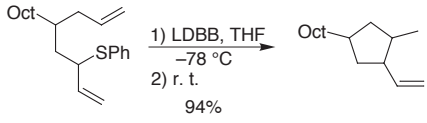
This result indicates that this lithium-ene cyclization is a thermodynamically favorable process. However, when the same reaction was applied to non-substituted allyllithiums, the cyclized organolithium could not be trapped by an external



Scheme 7-72 Domino-addition-cyclization reactions of homoallyl phenyl sulfides [92].



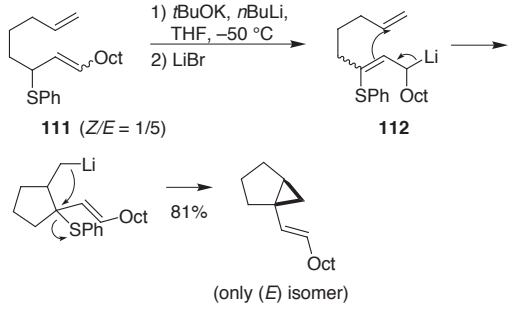
Scheme 7-73 Lithium-ene cyclization of α-methyl allyl sulfides [94].



Scheme 7-74 Lithium-ene cyclization of an allyllithium without an α-methyl substituent [94].

electrophile in THF, as it removed a proton from the solvent and furnished, with an excellent yield, the cyclized product (Scheme 7-74).

This cyclization occurs at low temperatures (as compared to the magnesium-ene cyclization) but, due to the greater basicity of the resulting organolithium, the cyclized organolithium readily abstracts a proton, either in an intramolecular manner to produce an allyllithium, if an allylic methyl group is nearby (Scheme 7-73), or intermolecularly from THF (Scheme 7-74) [94]. On the other hand, if a leaving group is present in the molecule, the cyclized organolithium can undergo an elimination reaction [95]. A typical example is the deprotonation and cyclization of the allylic thioether **111**. A transmetallation step with LiBr is first necessary to lead to the allyllithium **112**, which undergoes the lithium-ene cyclization followed by the intramolecular displacement of the thiophenoxylate ion [96]. Ring-annelated vinylcyclopropanes are easily prepared using this methodology (Scheme 7-75).



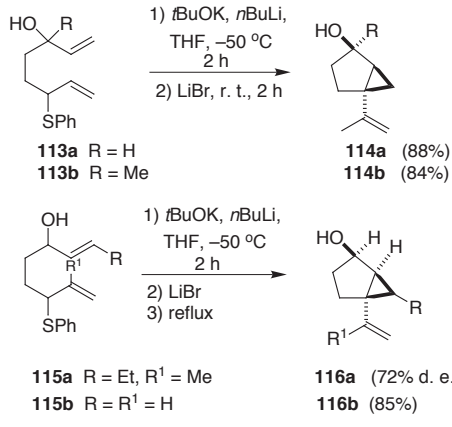
Scheme 7-75 Preparation of ring-annelated vinylcyclopropanes by an intramolecular lithium-ene cyclization [96].

Six-membered rings are also easily prepared by this sequence of lithium-ene cyclization and 1,3-elimination.

To provide one more functionality, an allylic hydroxyl group was introduced into the enophile such as in **113a**,**b** and in **115a**,**b** (Scheme 7-76).

Not only were the cyclizations of **113a**,**b** and **115a**,**b** greatly facilitated by the oxyanionic group, but they also proceeded in high yields and were completely stereoselective, even in the case of **115b**, in which a α,β-disubstituted alkene was used [95].

If activation by allylic oxyanionic groups proves to be general in intramolecular carbometallation, the latter would obviously become very useful. Therefore, the magnesium-ene cyclization in the presence of an allylic oxyanionic group was studied [97]. The conjugate base of **117** was subjected to reductive lithiation by LDMAN



113a R = H
113b R = Me

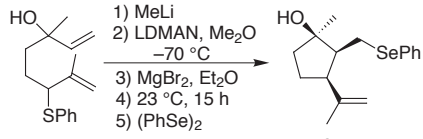
114a (88%)
114b (84%)

115a R = Et, R^1 = Me
115b R = R^1 = H

116a (72% d. e. 100%)
116b (85%)

Scheme 7-76 Lithium-ene cyclization of functionalized allyl phenyl thioethers [95].

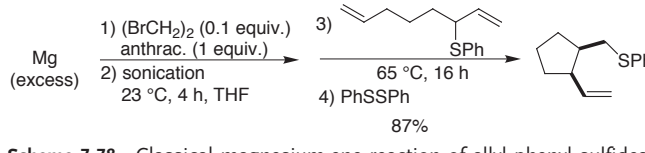
in dimethyl ether as shown above (Scheme 7-72), and then transmetallated with $MgBr_2$ in diethyl ether. The cyclic product was formed at room temperature, and trapped with an electrophile such as diphenyl diselenide, to give **118** in 64 % yield (Scheme 7-77) [97].



117 64% **118**

Scheme 7-77 Magnesium-ene cyclization of functionalized allylsulfides [97].

However, it has been determined that significant stereochemical inhomogeneity had occurred, which was attributed to the presence of lithium salt in the reaction mixture [94]. The reductive magnesiation of allyl phenyl sulfides was therefore developed and tested first in a classical magnesium-ene reaction (Scheme 7-78).

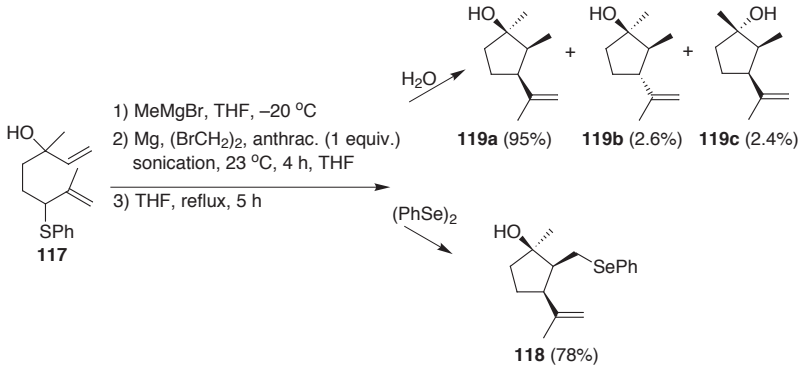


87%

Scheme 7-78 Classical magnesium-ene reaction of allyl phenyl sulfides [94].

This positive result led the authors to attempt the reductive magnesiation of **117** in the absence of lithium ions, hoping to maximize the degree of *cis*-stereoselectivity and to minimize proton transfer from the solvent to the cyclized organometallic.

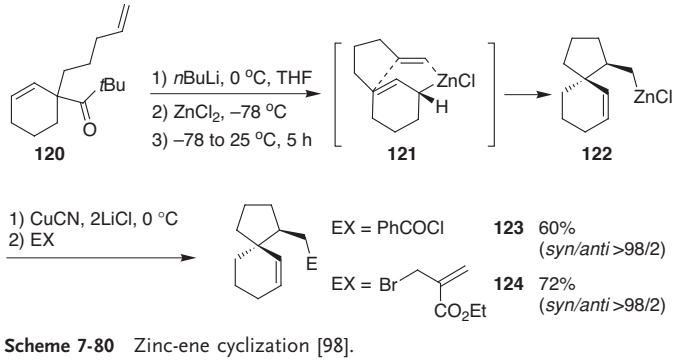
The alcohol **117** was deprotonated with MeMgBr in THF, and the conjugated base was subjected to reductive magnesiation in the presence of 1 equiv. of anthracene under reflux (Scheme 7-79).



Scheme 7-79 Reductive magnesiation of functionalized allylsulfide in the absence of lithium ions [97].

The results indicate that the absence of lithium ions did indeed increase the stereoselectivity; the all-*cis*-configured alcohol **119a** accounted for 95 % of the cyclization products. Moreover, the proton transfer from the solvent was suppressed; **118** could be isolated in 78 % yield, when the cyclized organometallic was trapped with diphenyl diselenide (only 3 % of the protonated product **119** was detected) [97].

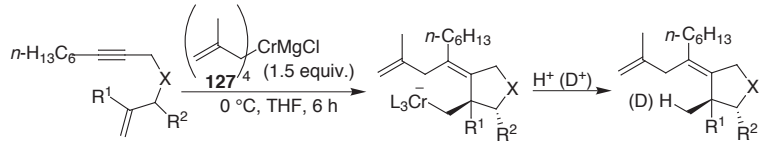
Zinc-ene cyclizations have also been used as key steps in natural products synthesis, but their applications were limited due to the difficulties encountered in the preparation of the starting allylic metal reagents. The use of homoallylic alcohols as masked allylzinc reagents allows now a straightforward preparation of precursors for the zinc-ene reaction (Scheme 7-80) [98].



Scheme 7-80 Zinc-ene cyclization [98].

When the 3-(5-pent-1-enyl)cyclohexenyl *tert*-butyl ketone **120** was treated with *n*-butyllithium at 0 °C in THF, the corresponding tertiary lithium alcoholate was formed and, after cooling to –78 °C, zinc chloride was added. The zinc alcoholate subsequently underwent a fragmentation reaction upon slow warming to room temperature, to give the allylzinc intermediate **121**, which reacted with the remote double bond. The cyclic product **122** is first transmetallated with CuCN, 2 LiCl, and then treated with benzoyl chloride or ethyl 2-(bromomethyl)acrylate, to give 1-substituted spiro[4.5]dec-6-ene derivatives **123** and **124** in 60 % and 72 % yields, respectively. Only one diastereomer was obtained in each case [98].

The methylallylchromate species, easily generated by mixing chromium trichloride and methylallylmagnesium chloride in a 1:4 molar ratio, were added to allyl non-2-yn-1-yl ethers **125a–c** or amine **126** in THF at 0 °C (Scheme 7-81) [99].



125a $R^1 = R^2 = H$, X = O
125b R^1 = Me, R^2 = H, X = O
125c R^1 = H, R^2 = Me, X = O
126 $R^1 = R^2 = H$, X = N

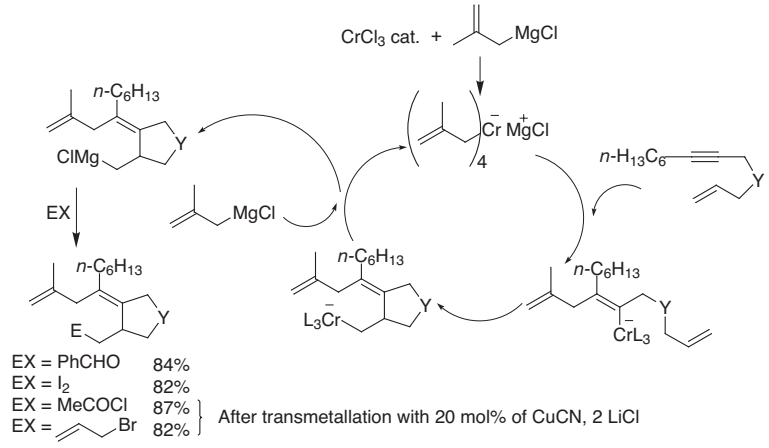
128a (90%)
128b (91%)
128c (81%)
129 (67%)

Scheme 7-81 Carbocyclization with a chloromagnesium tetra(methylallyl)chromate reagent [99].

The addition of DCl/D_2O afforded the labeled product with 90 % deuterium incorporation at the methyl group. It has been proved to be crucial to employ the ate-type chromium reagent **127** for successful cyclization, since trimethylallylchromium afforded **128a** in only 12 % yield. The reaction of **125b** provided **128b** as a single diastereomer. The amount of chromium chloride can also be reduced to 2 mol % if the reaction is performed in THF at 40 °C; **128a** is thus obtained in 80 % yield after hydrolysis, but can also be trapped with different electrophiles (Scheme 7-82).

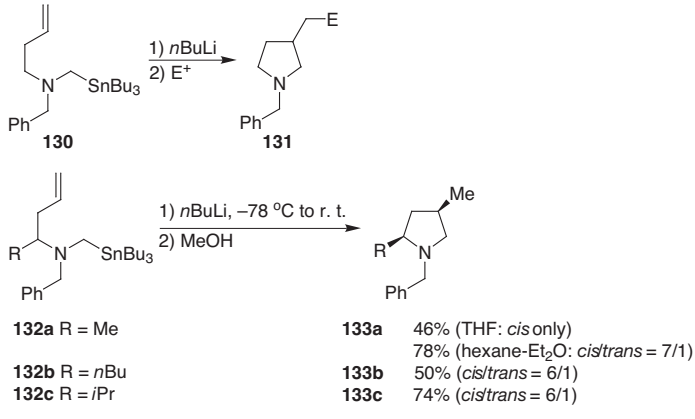
As described above (see Scheme 7-20), homopropargylic alcohols and derivatives react with a tetraallylmanganate or triallylmanganate to provide monoallylated products in good yields with high regio- and stereoselectivities. When the electrophile was an enophile moiety present in the same carbon skeleton, a 5-*exo*-*trig*-cyclization led to the corresponding carbocycle in only 27 % yield [27]. However, when the same reaction was applied to diynes, carbometallated products were obtained according to the nature of the substrate [100].

As reported in the first edition of this book, (α-aminomethyl)lithiums, generated by tin-lithium exchange from the stannane **130**, react intramolecularly with an unactivated alkene to give the substituted pyrrolidine derivative **131** [3]. More recently, the versatility of this anionic cyclization was extended by preparing oligosubstituted pyrrolidines and by exploring the stereoselectivity of the cyclization. Therefore, treatment of the stannanes **132a**,**b**,**c** with 2 equiv. of *n*BuLi in THF, gave



Scheme 7-82 Carbocyclization of 1,6-enynes with α-methylallylmagnesium chloride and a catalytic amount of chromium trichloride.

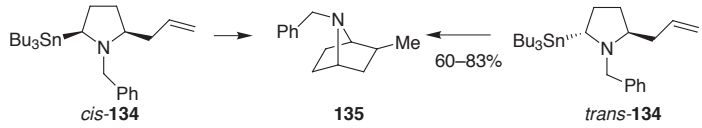
the pyrrolidines **133a**,**b**,**c** after quenching with methanol. Only the *cis*-isomer of **133a** was isolated under these conditions (Scheme 7-83) [101].



Scheme 7-83 Preparation of substituted pyrrolidines by intramolecular carbocyclization of (aminomethyl)lithiums across unactivated alkenes [101].

In contrast, **132b**,**c** did not undergo transmetallation under these conditions. The transmetallation was achieved only in a mixture of hexane-Et_2O as solvent at room temperature. Under these new conditions, all three stannanes **132a**,**b**,**c** cyclized in good yields and with a preference for the *cis*-isomer of the 2,4-disubstituted *N*-benzyl pyrrolidines **133a**,**b**,**c**.

When *cis*-**134** and *trans*-**134** were transmetallated using *n*BuLi (4 equiv.) in hexane-Et_2O-THF (4/1/1) as solvent (–78 °C to room temperature), both isomers led to the same *exo*-2-methyl-7-azabicyclo[2.2.1]heptane **135**. As only the *exo*-isomer **135**

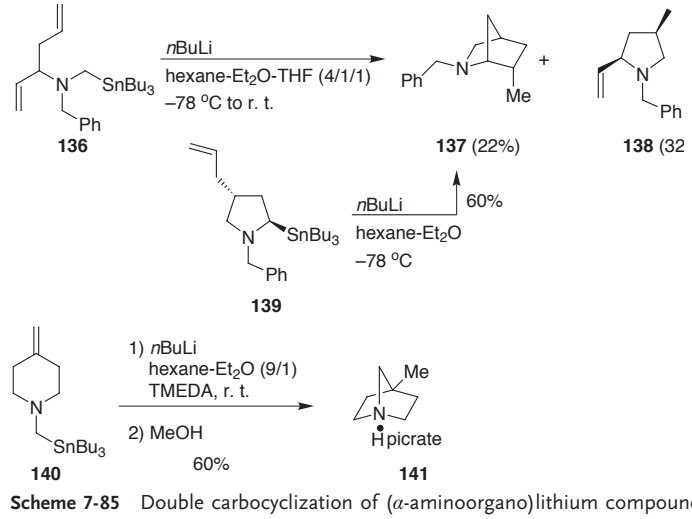


Scheme 7-84 Preparation of *exo*-7-methyl-7-azabicyclo[2.1.1]heptane [102].

was isolated, the organolithium species derived from the *trans*-isomer **134** must have epimerized to the *cis*-isomer before cyclization (Scheme 7-84) [102].

Transmetallation of the stannane **136** in the same mixture of solvents (hexane-Et_2O-THF) led first to the α-amino-organolithium compound and then to the cyclic products at room temperature. Two major products, the desired bicyclic amine **137** (22 %) and the pyrrolidine **138** (32 %) were isolated using these reaction conditions. The product **138** arises from the monocyclization reaction, and variation of the conditions did not improve this result. It appears that, although monocyclization to the pyrrolidine ring occurs easily, the second cyclization is slow and the organolithium species can abstract a proton from THF, which prevents the intermediate from undergoing the second cyclization (Scheme 7-85) [103].

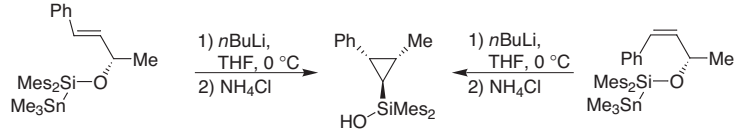
Because of the poor yield achieved in the preparation of the ring system **137**, an alternative route utilizing **139** as starting material was studied. Under modified conditions, the desired 2-azabicyclo[2.2.1]heptane **137** was obtained in 60 % yield, by the expected tin-lithium exchange-epimerization-cyclization sequence. Moreover, it appears that the cyclization of **139** favors a boat-shaped transition state. Finally, when the same sequence was applied to **140**, followed by addition of TMEDA, the picrate salt of 4-methyl-1-azabicyclo[2.2.1]heptane **141** was obtained in 60 % yield [103].



Scheme 7-85 Double carbocyclization of (α-aminoorgano)lithium compounds [103].

Several different intramolecular carbolithiations of chiral (*α*-aminoorgano)-lithium species were described and the enantioselectivities of this process were correlated with the size of the rings created [104].

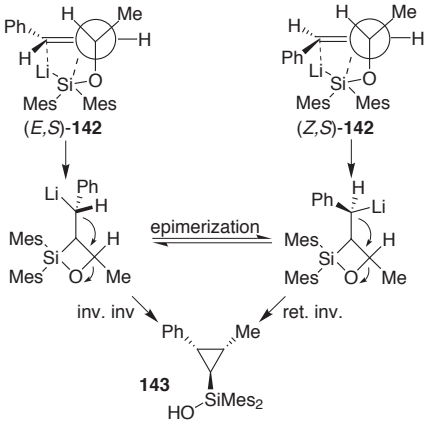
Recently, the intramolecular reaction of silyllithium reagents with alkenes was reported as a new route to cyclopropylsilanes [105]. Moreover, when enantioenriched (*E*-*S*)-**142** (98 % *e. e.*) was treated with *n*BuLi in THF at 0 °C, the corresponding silylcyclopropane **143** was obtained in 79 % yield with 98 % *e. e.*. Under the same reaction conditions, (*Z*,*S*)-**142** gave the same stereoisomer **143** with identical yield and enantiomeric excess (Scheme 7-86) [106].



(*E*,*S*)-**142** (98% *e. e*) **143** (98% *e. e*) (*Z*,*S*)-**142** (98% *e. e*)

Scheme 7-86 Synthesis of cyclopropylsilane by intramolecular reactions of silyllithium reagents with alkenes [105, 106].

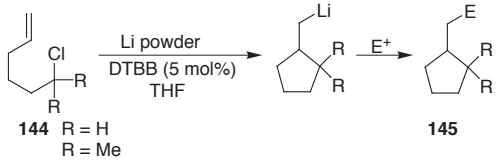
The stereochemical course could be rationalized by an intramolecular *syn*-lithiosilylation followed by a cyclopropanation reaction of the configurationally labile benzylic organolithium in the oxasilacyclobutanes (Scheme 7-87). The cyclopropanation step takes place from a conformation avoiding steric interaction between the phenyl residue and the mesityl groups.



Scheme 7-87 Rationalization of the stereochemical course in the synthesis of a cyclopropylsilane [106].

Low-temperature lithium-iodine exchange between a primary alkyl iodide and 2 equiv. *t*BuLi in a solvent system containing diethyl ether affords the corresponding primary alkyllithium irreversibly, and in virtually quantitative yield [107]. This clean exchange therefore led to the development of the intramolecular carbolithiation reactions of saturated alkyllithium derivatives [3]. When the exchange is con-

ducted using a less reactive organolithium, an equilibrium favoring the more stable organolithium is rapidly established [108]. Therefore, the isomerization of 6-iodo-1-hexene to (iodomethyl)cyclopentane in a variety of solvents with either MeLi or PhLi, was achieved [109]. This transformation, originally supposed to be mediated by a reversible lithium-iodine exchange process, in fact involves a radical-mediated atom transfer process [110]. The same trend was found for unsaturated secondary and tertiary alkyl iodides [111]. When 6-chloro-1-hexene **144** was treated with lithium powder and a catalytic amount of 4,4′-di-*tert*-butylbiphenylide (DTBB, 5 mol %) in THF at –30 °C, the corresponding cyclopentyl derivative **145** was obtained in excellent yield (Scheme 7-88).



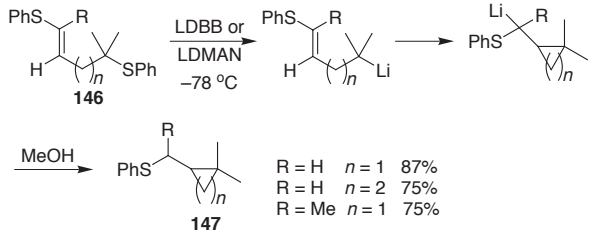
144 R = H
R = Me

145

Scheme 7-88 Carbocyclization reaction of 6-chloro-1-hexene and trapping with electrophiles [112].

When the reaction was applied to the tertiary derivative **144** (R = Me), it was found that either in Barbier conditions at 0 °C (76 %), or at –30 °C in a two-step process (75 %), the expected cyclic product **145** (R = Me) was the only one isolated after reaction with 3-pentanone [112].

Reductive lithiation of 1,4- or 1,5-bis(phenylthio)-1-alkenes with a stoichiometric amount of aromatic radical-anion, results in replacement with a lithium atom of only that phenylthio group which is attached to the sp^3-carbon atom. The resulting carbanion executes an intramolecular nucleophilic addition to the vinyl sulfide group at –78 °C, leading to a phenylthio-substituted cyclopropyl- or cyclobutylcarbinyllithium (Scheme 7-89) [113].



146

147

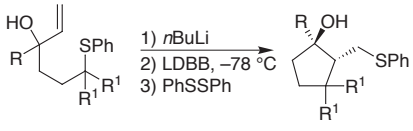
R = H n = 1 87%
R = H n = 2 75%
R = Me n = 1 75%

Scheme 7-89 Reductive lithiation of 1,4- or 1,5-bis-(phenylthio)-1-alkenes [113].

The effect of an alkyl group placed at the terminal alkene carbon atom on the ease of the cyclization was studied for 1,4- or 1,5-bis(phenylthio)-1-alkenes **146** (R = Me, n = 1 and 2). Both uncyclized (6 %) and cyclized products (75 %) were present in the reaction mixture. The methyl substituent at the double bond thus slows down the carbocyclization in comparison to **146** (R = H, n = 1). When a pri-

mary rather than a more reactive tertiary carbanion was used in the cyclization to a four-membered ring, the ring closure was also less favorable [113].

As discussed above [95, 97] (Schemes 7-76 and 7-79), an allylic oxyanion group greatly accelerates the lithium-ene cyclization. The same activation was found for unconjugated alkyllithiums since the cyclization of primary as well as tertiary alkyllithiums occurs in THF at –78 °C (Scheme 7-90).

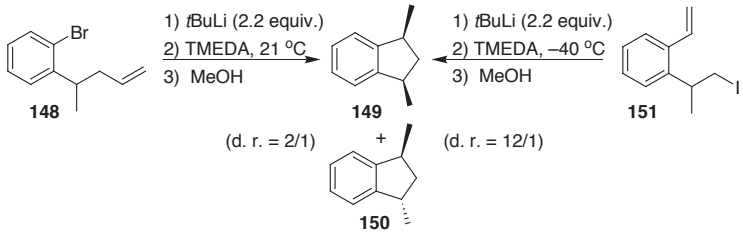


R	R^1	%
H	H	73
Me	H	81
H	Me	86
Me	Me	80

Scheme 7-90 Lithium-ene cyclization of unconjugated alkyllithiums [95].

Moreover, a single isomer was isolated in all these four cases (oxygen function and function derived from the CH_2Li group are on opposite sides of the cyclopentane ring) [95]. Even cyclobutanols can be prepared by this method.

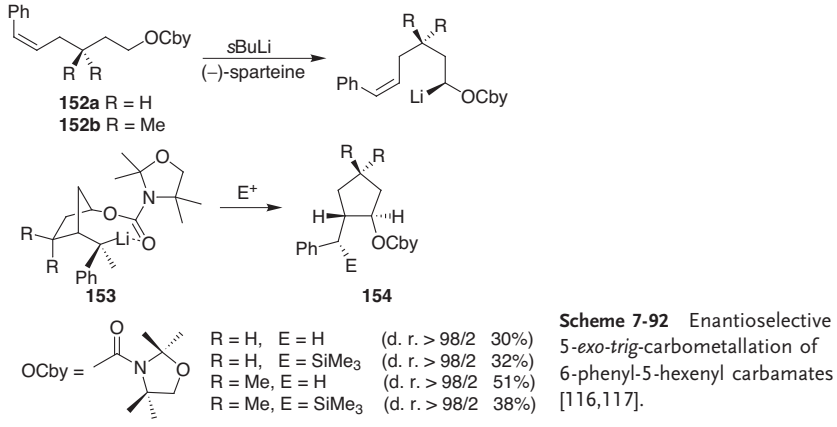
High stereoselectivity in the carbocyclization reaction can also be achieved by a judicious choice of starting materials; whereas **148** led to **149** and **150** in a 2:1 ratio, 2-(2-iodo-1-methyl)-styrene **151** reacted with a much better diastereoselectivity (12:1) and gave an excellent yield (Scheme 7-91) [114].



Scheme 7-91 Stereoselective carbocyclization reaction [114].

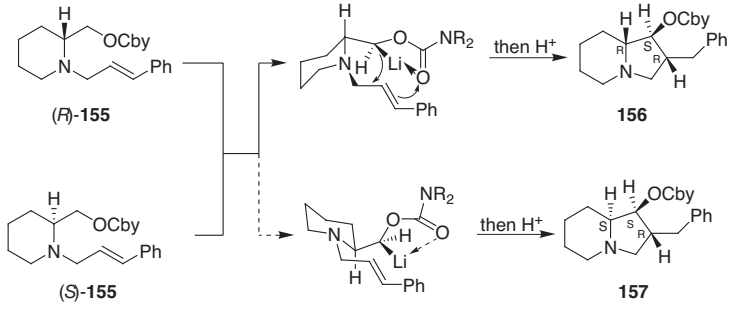
A wide variety of (*S*)-configurated (*α*-carbamoyloxy)alkyllithium derivatives are accessible by (–)-sparteine-mediated deprotonation [115]. Therefore, 6-phenyl-5-hexenyl carbamates **152a**,**b** could be regioselectively deprotonated, and then stereoselectively undergo nucleophilic cycloalkylation to form the appropriate cyclopentanol derivatives. The cyclization shows complete 5-*exo*-*trig* selectivity and leads with high diastereoselectivity to the *trans*-1,2-disubstituted cyclopentanes **154** *via* intermediates **153** (Scheme 7-92) [116].

When the electrophilic attack at the benzylic carbanionic center proceeds on the (*E*)-isomer of **152a**,**b**, the same product **154** is obtained. Therefore, the resulting **153** is presumably thermodynamically more stable due to the equatorial position of the phenyl substituent within the bicyclic chelate [117]. These sequential enantioselective deprotonation-carbocyclization reactions have been extended to the pre-



Scheme 7-92 Enantioselective 5-*exo-trig*-carbometallation of 6-phenyl-5-hexenyl carbamates [116,117].

paration of heterocycles. As the (–)-sparteine-mediated deprotonation of racemic 2-(carbamoyloxy)methyl-*N*-cinnamylpiperidine **155** is an efficient method to obtain enantioenriched (α-carbamoyl)alkyllithium by kinetic resolution, the subsequent diastereoselective anionic 5-*exo-trig*-cyclization was studied (Scheme 7-93).

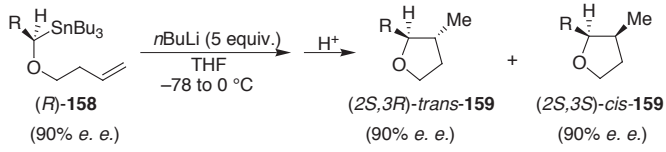


Scheme 7-93 Diastereoselective anionic 5-*exo-trig*-cyclization of racemic 2-(carbamoyloxy)methyl-*N*-cinnamylpiperidine [118].

The use of 0.80 equiv. of (–)-sparteine, 0.75 equiv. of *s*-BuLi with a reaction time of 22 h gave **156** in a yield of 86 % (based on *rac*-**155**) with high diastereoselectivity and an enantiomeric excess of 95 %. Under these conditions, (*S*)-(–)-**155** was recovered in 46 % yield and 63 % *e.e.* [118]. These optimized conditions were used for trapping the intermediate benzylic anion with different electrophiles [118].

When enantio-defined stannane (*R*)-**158** was treated with *n*BuLi (5 equiv.) in THF at –78 °C, followed by hydrolysis, a 7/1 mixture of two retention products (2*S*,3*R*)-*trans*-**159** and (2*S*,3*S*)-*cis*-**159** was obtained (Scheme 7-94).

The stereochemical outcome provides conclusive proof that this cyclization proceeds with complete retention of configuration at the Li-bearing carbanion center,



(*R*)-**158** (90% *e. e.*) (*2S,3R*)-*trans*-**159** (90% *e. e.*) (*2S,3S*)-*cis*-**159** (90% *e. e.*)

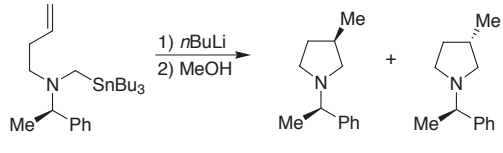
Scheme 7-94 Carbocyclization of an enantio-defined stannane [119].

since the Sn to Li transmetallation proceeds with complete retention of configuration [119].

The formation of enantioenriched indene-derived bicyclic alcohols and tricyclic cyclopropanes *via* (–)-sparteine-mediated deprotonation of a racemic 3-(indenyl)-alkylcarbamate was also reported [120]. Several other cycloalkylation reactions by (–)-sparteine-mediated deprotonation, which were also reported, are mechanistically more related to S_N2' processes and will therefore not be described in this chapter [121].

Returning to the preparation of substituted pyrrolidines by cyclization of (α-amino)organolithium species onto unactivated alkenes, the influence of a chiral ligand attached to the nitrogen was investigated [101].

Transmetallation and cyclization using *n*BuLi was effective in either THF or hexane-Et_2O, and resulted in good yields of the corresponding pyrrolidines, but with low to moderate diastereomeric excesses (58 % maximum) (Scheme 7-95) [122].

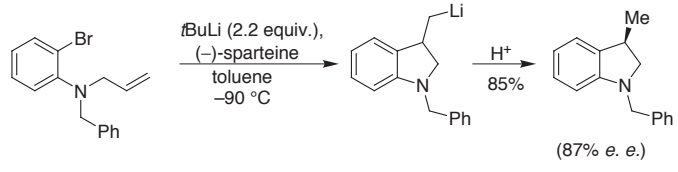


(*R*)-**160** **161a** **161b**

Scheme 7-95 Transmetallation and cyclization of pyrrolidine derivatives [122].

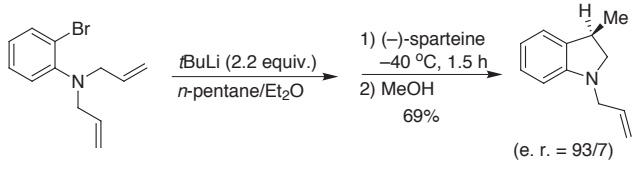
Similarly, the cyclization of the stannane **130** (see Scheme 7-83) in the presence of (–)-sparteine led to the pyrrolidine with low enantiomeric excess [122].

As it had been recently reported that (–)-sparteine can serve as a promoter for the enantioselective carbolithiation of cinnamyl derivatives by adding organolithium compounds [123], the enantioselective intramolecular carbolithiation of 2-(*N*-allyl-*N*-benzyl)aryllithiums in the presence of the chiral diamine (–)-sparteine was studied [124]. When toluene was used as solvent, a high enantioselectivity was achieved at low temperature (Scheme 7-96).



Scheme 7-96 Enantioselective carbolithiation of 2-(*N*-allyl-*N*-benzyl)aryllithiums [124].

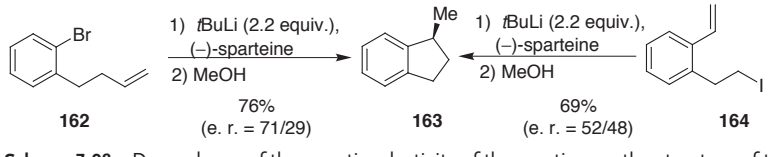
A variety of aryl-substituted *N*-allyl-*N*-benzyl-2-bromoanilines was tested under these conditions, and good yields and enantiomeric excesses were uniformly obtained (4-OBn: 80 % with 87 % *e.e.*; 5-OBn: 86 % with 88 % *e.e.*; 4-Me: 90 % with 89 % *e.e.*; 4-F: 80 % with 90 % *e.e.*). Independently, the enantioselective carbolithiation of 2-(*N*,*N*-diallylamino)phenyllithium was also investigated, and the same results were obtained; at low temperature in a mixture of pentane-Et_2O as solvent, 1-allyl-3-methylindoline was obtained in 69 % yield with an enantiomeric ratio of 93/7 (Scheme 7-97) [125].



Scheme 7-97 Enantioselective carbolithiation of 2-(*N*,*N*-diallylamino)phenyllithium [125].

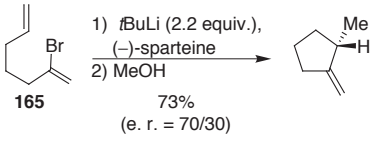
It should be noted that at least 2 equiv. of (–)-sparteine must be added to the reaction mixture to effect rapid enantioselective cyclization of the aryllithium. The generation of the aryllithium by lithium-bromine exchange is accompanied by the formation of a full equiv. of LiBr, and this salt effectively removes a full equiv. of the diamine ligand by preferential complexation with (–)-sparteine, as initially reported for the enantioselective carbolithiation of styrenyl derivatives [123].

The enantioselectivity of the reaction is strongly dependent on the structure of the starting material. When 2-bromo-1-(3-butenyl)benzene **162** is submitted to the sequence bromine-lithium exchange and enantioselective carbolithiation, the protonation of the resulting (1-indanyl)methyllithium product gave a 76 % yield of (*S*)-(–)-1-methylindane **163** with an *e.e.* of 42 %. However, when the same experimental conditions were applied to 1-(2-iodoethyl)-2-vinyl benzene **164**, the cycloisomerization led to the same methylindane in 69 % yield but only with 4 % *e.e.* (Scheme 7-98) [125].



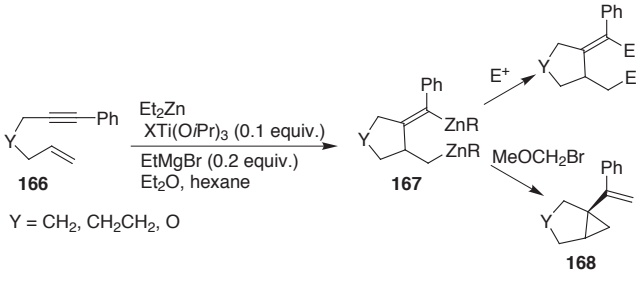
Scheme 7-98 Dependence of the enantioselectivity of the reaction on the structure of the starting material [125].

The cyclization of even simpler substrates may be conducted in an enantioselective fashion in the presence of (–)-sparteine. As illustrated below, the vinyllithium of **165** undergoes a moderately enantioselective cyclization when stirred at 0 °C (*e.e.* = 40 %) (Scheme 7-99) [125].



Scheme 7-99 Enantioselective cyclization of the vinyllithium derived from **165** [125].

Despite a recent surge of publications on Ti(II)- and Zr(II)-promoted carbon-carbon bond formation involving alkenes and alkynes, which have recently been reviewed in a monograph [40], those that are catalytic in titanium were rare. However, a novel trimetallic reagent system consisting of Et_2Zn, $XTi(OiPr)_3$ (0.1 equiv.) and an alkylmagnesium halide (0.2 equiv.), such as EtMgBr or *i*PrMgCl, reacts with various enynes **166** to produce the corresponding cyclic organozinc derivatives **167**. Reactions of **167** with electrophiles provide the corresponding functionalized products, while treatment of **167** with bromomethyl methyl ether provides in good yields the corresponding 1-alkenylbicyclo[*n*.1.0]alkenes **168**, in which *n* is 3 or 4 (Scheme 7-100) [126].



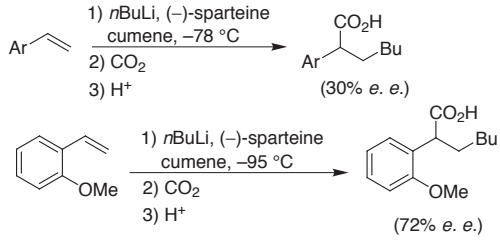
Scheme 7-100 Carbocyclization of nonconjugated enynes [126].

7.3.2
Intermolecular Carbometallation Reactions

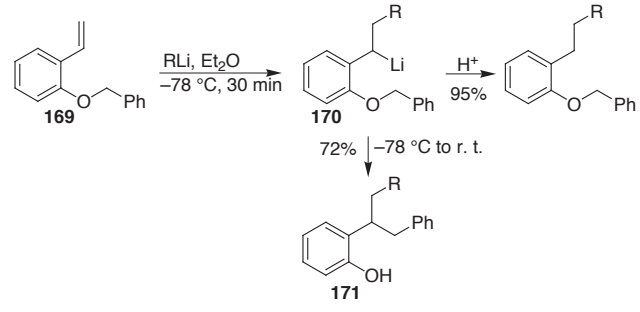
Organolithium addition to styrene and its derivatives, followed by electrophilic trapping, has also been investigated in the presence of (–)-sparteine. With styrene, enantiomeric excesses of up to 30 % were observed, whereas with 2-substituted styrenes, *n*BuLi addition followed by carboxylation gave a range of 2-arylheptanoic acids with *e. e.* values up to 72 % (Scheme 7-101) [127].

When 2-benzyloxystyrene **169** was treated with an organolithium derivative, the carbometallation occurred readily at low temperature. However, by warming the reaction mixture to room temperature before work-up, the new product **171**, apparently arising by C-benzylation in the intermediate organolithium **170** by an intramolecular process, was obtained in 72 % yield (Scheme 7-102) [91].

The same trend was observed with *o*-allyloxy compounds but not with the *o*-methoxy analogue. (*o*-Vinylphenyl)oxazolines **172a**,**b** also react with alkyllithiums

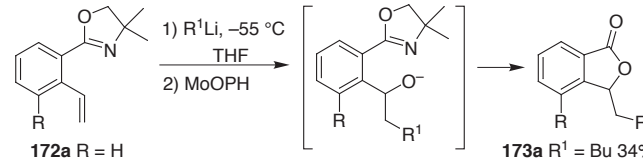


Scheme 7-101 Addition of organolithium compounds to styrene and its derivatives [127].



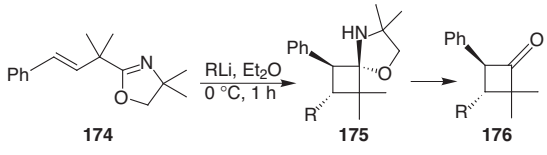
Scheme 7-102 Carbometallation of 2-benzyloxystyrene [91].

to give the benzylic organolithium derivative which, after oxidation with MoOPH and subsequent acidic hydrolysis with aqueous oxalic acid afforded phthalides **173** (Scheme 7-103) [128].



Scheme 7-103 Synthesis of phthalides by carbometallation of *o*-vinyloxazolines [128].

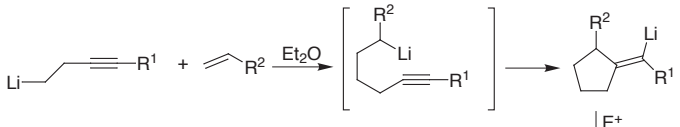
It is noteworthy that the addition of LiBr improves the yield of the reaction. When the oxazoline is closer to the reacting center such as in 2-(3-phenyl-2-propen-1-yl)oxazoline **174**, a cascade carbolithiation-cyclization sequence leads to the corresponding substituted cyclobutanones **176** (Scheme 7-104) [129].



R	%
*n*Bu	76
*t*Bu	90
Me	47
Ph	37

Scheme 7-104 Preparation of cyclobutanones by a cascade carbolithiation-cyclization sequence [129].

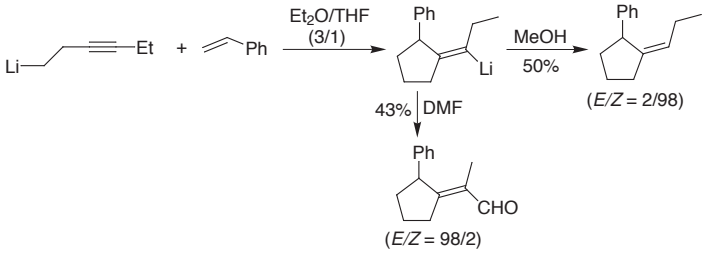
The lower yields of **176** with R = Me and Ph are attributed to the formation of side-products arising under the more forcing conditions required for the reaction (room temperature, overnight). Encouraged by these results, a new cascade intermolecular-intramolecular carbolithiation was designed. This procedure employs organolithium reagents as difunctional, conjunctive reagents and presents a versatile anionic formal [3+2] cycloaddition approach to substituted cyclopentanes (Scheme 7-105) [130].



R^1	R^2	E	%	*E/Z*
Et	Ph	H	61	97/3
Et	Ph	CHO	48	97/3
Ph	Ph	H	53	70/30
Ph	SPh	H	62	100/0

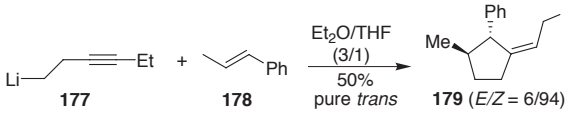
Scheme 7-105 A versatile anionic formal [3+2] cycloaddition approach to substituted cyclopentanes [130].

The formation of (*E*)-configured alkylidenecyclopentane (Scheme 7-105) (when E = H) is consistent with the accepted *syn*-carbolithiation mechanism. However, when a mixture of diethyl ether and THF (3/1) was employed, the corresponding *Z*-isomer was surprisingly obtained as the major product (Scheme 7-106).



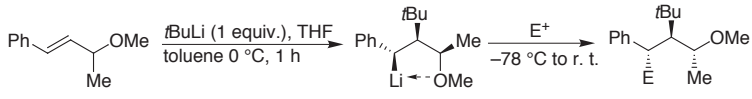
Scheme 7-106 Effect of the solvent on the stereochemical outcome of the formal [3+2] cycloaddition [130].

These reactions can also be carried out with nonterminal alkenes (Scheme 7-107). Thus, reaction of the homopropargyllithium reagent **177** with (*E*)-*β*-methylstyrene **178** in diethyl ether/THF, followed by protonation, produced the cyclized adduct **179** in 50 % yield as a single diastereomer with a *trans*-relationship between the substituents on the carbocycle (Scheme 7-107) [130].



Scheme 7-107 An intermolecular-intramolecular carbolithiation of disubstituted alkenes with a homopropargyllithium reagent [130].

The high diastereoselectivity observed for the reaction between benzylic organolithium derivatives and electrophiles has been addressed for cinnamyl alcohols [131] as well as for secondary and tertiary cinnamyl amines [132]. However, the diastereoselectivity in the carbolithiation of cinnamylmethylether with either *t*BuLi, benzyllithium or alkyllithium was only recently investigated and found to be quite good, as proved by the products obtained upon subsequent treatment with three different electrophiles [133], confirming earlier results [132]. The selectivity in the addition of *t*BuLi to α-methylcinnamyl methyl ether **180** was examined using the conditions developed for the carbolithiation of primary cinnamyl ethers (Scheme 7-108).

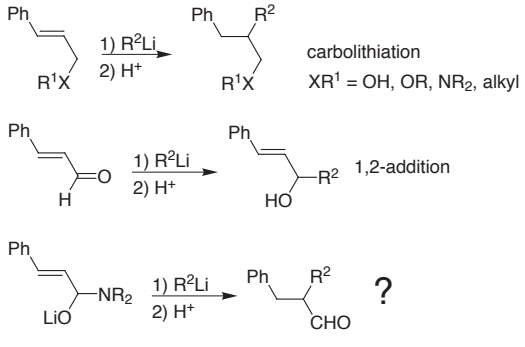


180 **181** **182**

Scheme 7-108 Selective addition of *t*BuLi to α-methylcinnamyl methyl ether [132,133].

After hydrolysis (E = H), a single diastereoisomer of **182** was found. Deuteration, carboxylation and thiomethylation gave diastereomeric ratios similar to those observed in the reaction of the primary cinnamyl methyl ether.

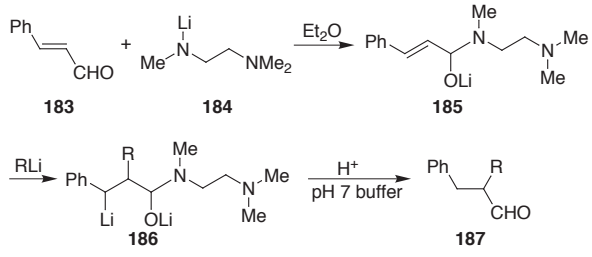
As the carbolithiation of cinnamyl derivatives proceeds efficiently [134], whereas the addition of alkyllithiums to cinnamaldehydes led only to 1,2-adduct (addition to the aldehyde), the in-situ transformation of the aldehyde into a good chelating group such as an α-aminoalkoxide was considered (Scheme 7-109) [135].



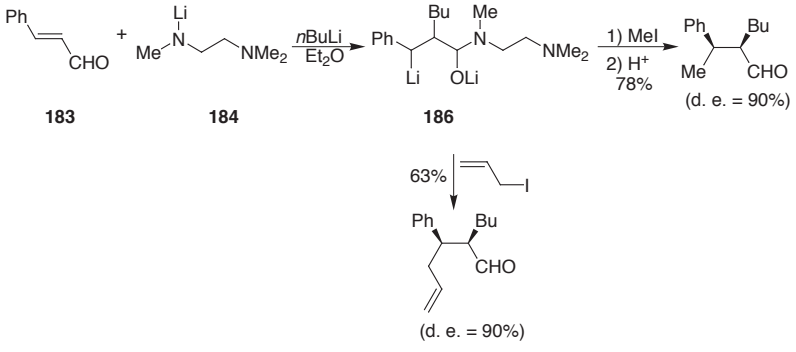
Scheme 7-109 Carbolithiation of cinnamyl derivatives *vs.* 1,2-addition of alkyllithiums [135].

When *N*,*N*,*N*′-trimethylethanediamine **184** was added to cinnamaldehyde **183** in diethyl ether at –40 °C, followed by warming to 0 °C, the corresponding lithium α-aminoalkoxide **185** was obtained. Further addition of *n*BuLi led to an addition product **186**, as seen from hydrolysis to the alkylated aldehyde **187**.

Various organolithium reagents with primary (except MeLi), secondary, and tertiary alkyl groups can be used as well as a salt-free vinyllithium reagent. When electrophiles are added to **186**, excellent diastereoselectivies are observed.

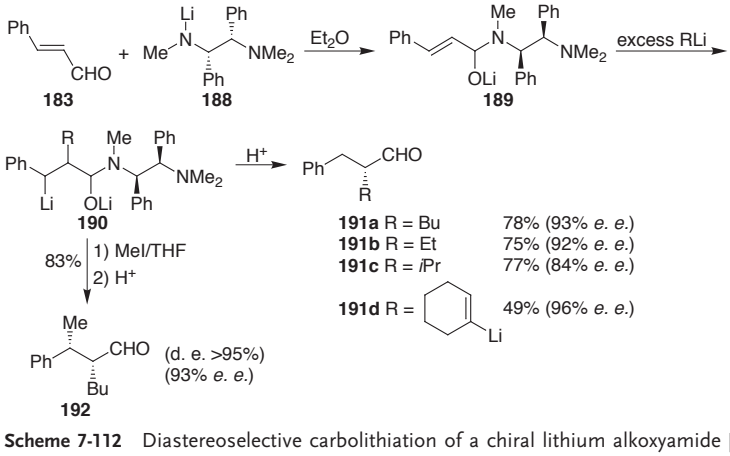


Scheme 7-110 Preparation of α-alkylated aldehydes by a cascade addition of *N*,*N*,*N*′-trimethylethylenediamine to cinnamaldehyde followed by a carbolithiation reaction [135].



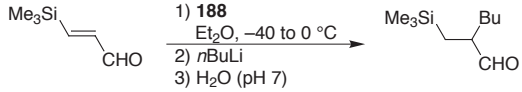
Scheme 7-111 Stereoselective reaction of benzylic organolithiums [135].

When chiral *N*,*N*,*N*′-trimethyl-1,2-diphenylethylenediamine **188** was used to convert cinnamaldehyde to the corresponding lithium alkoxyamide **189**, a regio- and diastereoselective carbolithiation reaction with added alkyllithium occurred in Et_2O to give, after mild hydrolysis, the expected aldehydes, with excellent enantiomeric excesses (Scheme 7-112) [136].



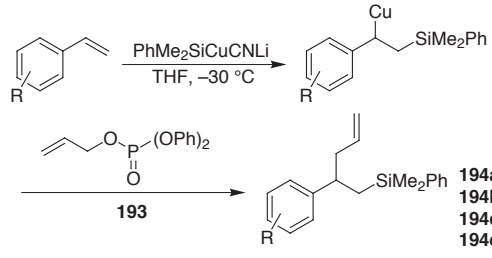
Scheme 7-112 Diastereoselective carbolithiation of a chiral lithium alkoxyamide [136].

When methyl iodide is added to **190**, the aldehyde **192** is obtained in good yield and with good diastereo- and enantiomeric excesses. The phenyl group present in the starting cinnamaldehyde was not compulsory, and could be replaced by other anion-stabilizing residues such as trimethylsilyl groups. Therefore, *β*-trimethylsilylacrolein can be submitted to the amidation-carbolithiation sequence, and leads to the carbometallated product with 92 % *e. e.* of unknown absolute configuration in 82 % yield (Scheme 7-113) [136].



Scheme 7-113 Enantioselective amidation-carbolithiation sequence carried out on *β*-trimethylsilylacrolein [136].

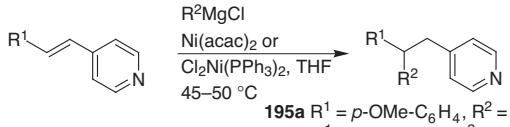
Reaction of styrene derivatives with the silylcuprate reagent $PhMe_2SiCuCNLi$ proceeds smoothly at –30 °C to give an organocopper intermediate, which was trapped by allyl diphenyl phosphate **193** to give **194a** in 73 % yield (R = H) (Scheme 7-114) [137].



Scheme 7-114 Silylcupration of styrene derivatives with lithium cyano(dimethylphenylsilyl)-cuprate [137].

Although this silylcupration of substituted styrenes and subsequent carbocupration by the adducts of allyl diphenyl phosphate afforded products **194b–d** in moderate yields, styrenes substituted at the double bond (such as *α*-methylstyrene, (*E*)-*β*-methylstyrene, indene and (*E*)-stilbene) were not sufficiently reactive enough to give any product.

Alkyl, aryl and vinyl Grignard reagents were added to substituted 4-vinylpyridines under $Ni(acac)_2$ catalysis to give the carbometallated products **195a–c** in good yield (Scheme 7-115) [138].

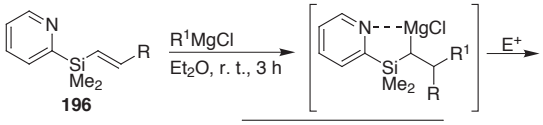


Scheme 7-115 Carbometallation of substituted 4-vinylpyridines with Grignard reagents [138].

Phenylzincate reagents also add to vinylpyridine in the presence of $Ni(acac)_2$. Higher temperatures are usually required and, as a consequence, significant amounts of biphenyl are produced, necessitating the use of more than 2 equiv. $Ph_3ZnMgCl$ [138].

As reported in the first edition, the additions of organolithium and organomagnesium derivatives to vinylsilanes are well known and used for the generation of useful α-silylcarbanions [3]. However, various limitations were associated with these carbometallation reactions such as: (1) activating groups on silicon are usually needed for the addition; (2) substitutions at the silicon atom are often observed as side reactions; and (3) primary alkyl Grignard reagents are not applicable in the reaction. Therefore, a new removable directing group was necessary for the carbometallation reaction of vinylsilanes, and 2-pyridyldimethylvinylsilane **196** was found to be an excellent candidate.

When **196** was treated with primary, secondary, phenyl and allyl Grignard reagents in ether, the electrophilic trapping products **197a–g** derived from the corresponding α-silylorganomagnesium compounds were isolated in excellent yields (Scheme 7-116) [139].



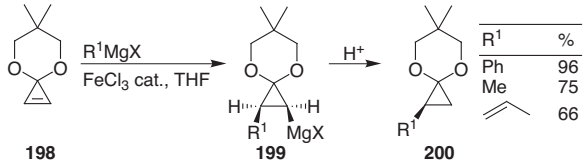
	R	R^1	E	%
197a	H	*n*Bu	H	91
197b	H	*i*Pr	H	93
197c	H	Ph	H	73
197d	H	allyl	H	94
197e	*n*Bu	*n*Bu	H	91
197f	H	*n*Bu	allyl	93
197g	*n*Bu	*n*Bu	allyl	90

Scheme 7-116 Carbometallation reaction of 2-pyridyldimethylvinylsilane with Grignard reagents [139].

Compared to reactions with vinylsilanes described in the first edition, these reactions clearly indicate the enhanced reactivity of **196**. It was assumed that this carbometallation was facilitated by a template effect between **196** and RMgX. This assumption was further supported by the observation of a dramatic solvent effect: weakly coordinating solvents such as ether favor this reaction, whereas strongly coordinating solvents such as THF disfavor it.

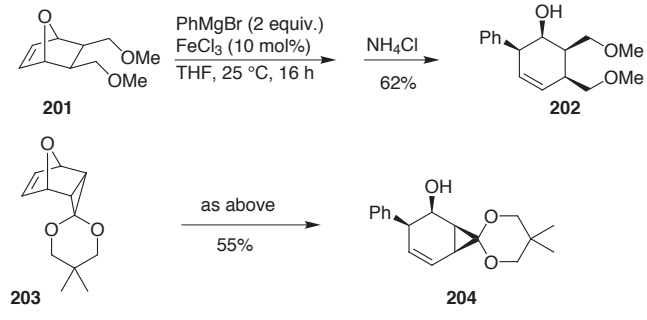
Although addition of Grignard reagents to the cyclopropenone acetal **198** did not take place at low temperature, and gave a complex mixture at higher temperature, the addition of a catalytic amount of $FeCl_3$ (3–5 mol %) promoted the addition (Scheme 7-117) [140].

The reactions of phenyl, vinyl and alkyl Grignard reagents under these conditions, and subsequent protonation, afforded the substituted cyclopropanone acetals **200** in excellent yields. The intermediate **199** can also be trapped with carbon electrophiles, and the configuration of the final product was always *cis* (due to the *syn*-carbometallation).



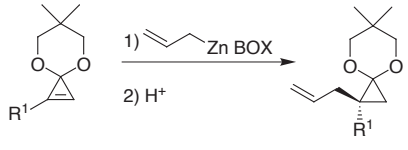
Scheme 7-117 Addition of Grignard reagents to a cyclopropenone acetal in the presence of a catalytic amount of $FeCl_3$ [140].

Organozinc reagents also took part in the iron-catalyzed reaction of **198** under similar conditions. The reaction with diethylzinc and diphenylzinc at –25 °C proceeded under iron catalysis conditions to give **200** with R^1 = Et and $R^1 = C_6H_5$ in 73 and 91 % yield, respectively [140]. The iron catalysis also operated in alkylative ring-opening reactions of 7-oxabicyclo[2.2.1]heptane derivatives **201** and **203** (Scheme 7-118). The addition of PhMgBr to **201** and **203** took place at ambient temperature to give the corresponding substituted cyclohexenols **202** and **204** in 62 and 55 % yield, respectively.



Scheme 7-118 Iron-catalyzed alkylative ring-opening reactions of 7-oxabicyclo[2.2.1]-heptane derivatives [140].

Exploration of the possibility to perform this type of reaction in an enantiocontrolled mode led to a new ternary catalytic system. Addition of dialkylzinc to **198** proceeded with 89–92 % *e.e.* in the presence of (*R*)-*p*-Tol-Binap (7.5 mol %), $FeCl_3$ (5 mol %) and TMEDA in toluene/tetrahydropyran solution.



205a R^1 = Et
205b R^1 = Ph

206a 95% (>98% *e. e.*)
206b 98% (>98% *e. e.*)

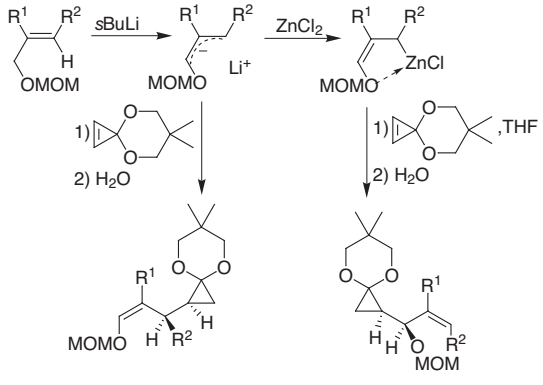
BOX = anionic bisoxazoline ligand from (*S*)-(+)-2-phenylglycine

Scheme 7-119 Preparation of chiral cyclopropanone acetals bearing a quaternary chiral center by an enantioselective allylzincation reaction [141].

Chiral cyclopropanone acetals containing a quaternary center of chirality were prepared by enantioselective allylzincation reaction of substituted cyclopropenone acetals **205a** (R^1 = Et) and **205b** (R^1 = Ph). Addition of a chiral allylzinc reagent

bearing the anionic bisoxazoline ligand derived from (*S*)-(+)-2-phenylglycinol (BOX) gave the corresponding 2,2-disubstituted cyclopropanone acetals in excellent yields with high enantioselectivities (Scheme 7-119) [141].

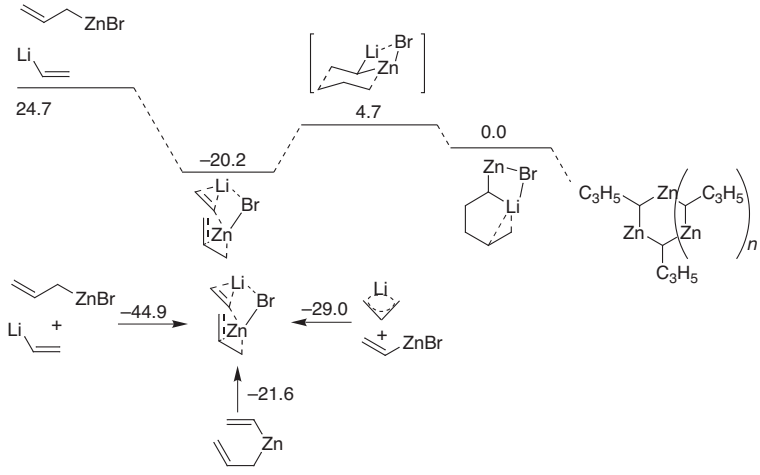
The additions of substituted (alkoxyalkyl)lithium and zinc reagents to cyclopropenone acetal **198** also takes place smoothly, but the pathway of product formation depends on the metal [142]. The (alkoxyalkyl)zinc reagents add to the cyclopropenone in such a manner that the α-carbon attached to the alkoxy group becomes bound to the alkene. The regioselectivity of the (alkoxyallyl)zincation depends on the allyl substituents, yet the diastereoselectivity for the newly formed carbon-carbon bond was excellent and the configuration of the double bond in the product was always exclusively *cis* (Scheme 7-120).



Scheme 7-120 Addition of substituted (alkoxyalkyl)lithium and zinc reagents to cyclopropenone acetal [142].

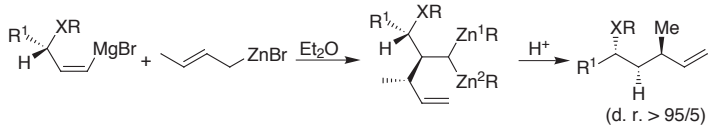
On the other hand, the regioselectivity of the (alkoxyallyl)lithiation depends on the substituents R^1 and R^2, while the diastereoselectivity remains high throughout (>97 %) [142]. Theoretical studies supported this conjecture by revealing that a (hydroxylallyl)lithium species of π-allylmetal nature can react with the cyclopropenone acetal *via* two [2+2]-type four-centered transition states of similar energies, leading to α- and γ-adducts, while the zinc species of σ-allylmetal nature reacts *via* a single [2+4]-type six-centered transition state leading to an α-adduct [143].

Allylindianation of homoallyl alcohols (easily prepared by treatment of allylindium sesquihalides with conjugated aldehydes and ketones) gives *via* a domino carbometallation-elimination sequence the vinylcyclopropanes in yields of 40–60 % [144, 145]. Much better yields and selectivities were found in the allylmetallation of various vinyl Grignard reagents. Indeed, very high diastereoselection was obtained during the addition of a vinylzinc bromide to a (*Z*)- or (*E*)- vinylmetal reagent, and the results were extensively discussed in several chapters and reviews [3, 146–148]. More recent theoretical calculations have led to a better understanding of the reaction [12]. The allylzinc bromide and the vinyllithium reagent first form a very stable complex due to a square-planar arrangement of the Li-C-Zn-Br atoms. This – via a transition state – leads to a higher-energy lithio-zinca adduct, which gives the trimer or tetramer of a 1,1-dizinca compound [12b,c] (Scheme 7-121). These calculations clearly show that, whatever the initial reagents are, the initial stable complex is formed exothermally.



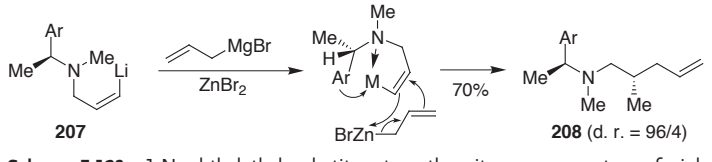
Scheme 7-121 Energetic process and different exothermal approaches to the initial complex of the carbometallation reaction (values in kcal mol^{-1}) [12].

Also of interest is the fact that the crotylzinc reagent, which is prone to metallotropy, reacts preferentially in a *cisoid* form. Therefore, when the vinylmetal partner is heterosubstituted (XR = OR, NR_2, SR) at its allylic position, an excellent facial selectivity is observed; the incoming crotyl moiety reacts on the face *anti* to the R^1 group (Scheme 7-122) [20c].



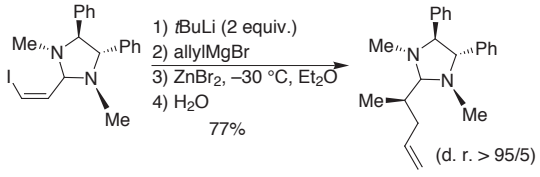
Scheme 7-122 Crotylzinc bromide reacts with a α-heterosubstituted alkenylmagnesium bromide with an excellent facial selectivity.

When the allylic carbon of the 2-vinylmetal partner is primary, profound selectivity was induced by the introduction of a chiral appendage. Thus, a 1-naphthyl ethyl substituent on the nitrogen in **207** promotes a facial preference, which is also attributed to a π-stacking between the aryl group and the vinylmetal, and a diastereomeric ratio of 96/4 was obtained for **208** (Scheme 7-123) [149].



207 **208** (d. r. = 96/4)

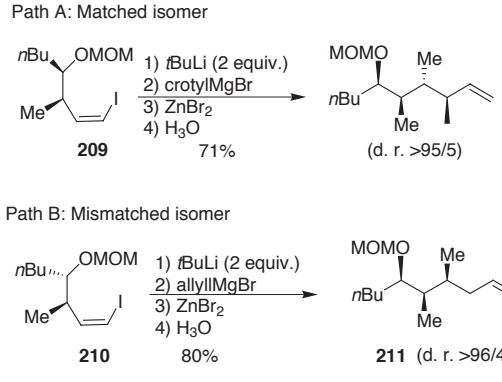
Scheme 7-123 1-Naphthylethyl substituent on the nitrogen promotes a facial selectivity [149].



Scheme 7-124 Derivatization of (*Z*)-*β*-iodoacrolein to a C_2-symmetric amine followed by enantioselective allylmetallation [151].

In the same way, (*Z*)-β-iodoacrolein can be derivatized to a C_2-symmetric amine [150] and submitted to the allylmetallation reaction. A single isomer was obtained (Scheme 7-124) [151].

In vinyllithiums derived from homoallylic ethers, the chiral center is more remote (*γ* to the metal), but still excellent asymmetric induction is observed [152]. Now, if the secondary homoallylic ether has a substituent in the allylic position, either *syn* or *anti* to the homoallylic substituent, a matched or mismatched diastereomer is created in the carbometallation reaction. As expected, the matched isomer **209** undergoes the crotylmetallation diastereoselectively *anti* to both substituents (path A, Scheme 7-125). More surprisingly, the mismatched isomer **210** is also diastereoselectively carbometallated with allylzinc bromide to give the product **211** with a diastereomeric ratio of 96/4. After chemical correlations, it has been found that the allyl group adds *syn* to the allylic methyl substituent and *anti* to the homoallylic butyl group (path B, Scheme 7-125).

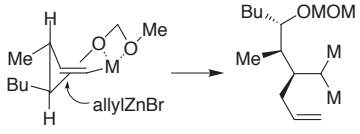


Scheme 7-125 Matched and mismatched allylmetallation of vinylmetals [152].

This unexpected result has been further rationalized by the addition of the allylzinc halide *anti* to the butyl group *via* a six-membered heterocyclic transition structure which behaves like an analogous six-membered carbon cycle. The allylzinc adds axially, *anti* to the *pseudo*-equatorial *n*-butyl group (Scheme 7-126) [153].

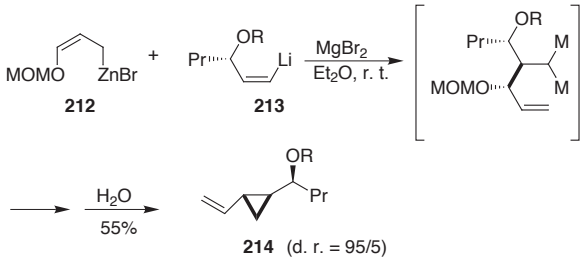
This mechanistic interpretation applies to cases in which the allylic and homoallylic substituents belong to a cyclohexane [153].

When a metallated allyl ethyl ether is transmetallated to the allylzinc derivative **212**, and this is in turn added to the *γ*-alkoxyvinyllithium **213**, in the presence of



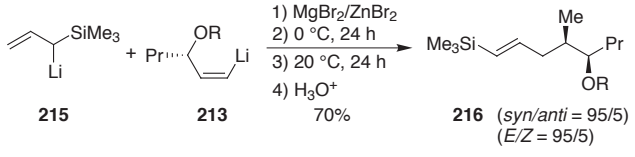
Scheme 7-126 Addition of the allylzinc halide *anti* to the butyl group in a six-membered heterocyclic transition structure [153].

excess magnesium bromide, carbometallation occurs diastereoselectively, and is succeeded by an elimination reaction to give the *trans*-2-vinyl-substituted secondary cyclopropylcarbinols **214** having three well-defined stereocenters with *syn*-configuration (Scheme 7-127) [154].



Scheme 7-127 Addition-elimination sequence of metallated allyl ether to a γ-alkoxyvinyllithium [154].

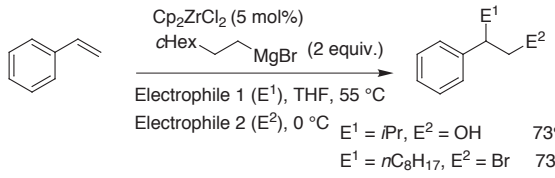
The lithiated allylsilane **215** is also an interesting precursor for carbometallations as the resulting carbon-silicon bond can be used for further functionalization. When **215** is added to **213**, also in the presence of an excess of $ZnBr_2$ and $MgBr_2$ to speed up the reaction, the *syn*-isomer **216** is formed in 70 % yield (Scheme 7-128) [155].



Scheme 7-128 Addition of metallated allylsilane to a γ-alkoxyvinyllithium [155].

Taking advantage of this methodology, a new approach to serricornin has been developed [155].

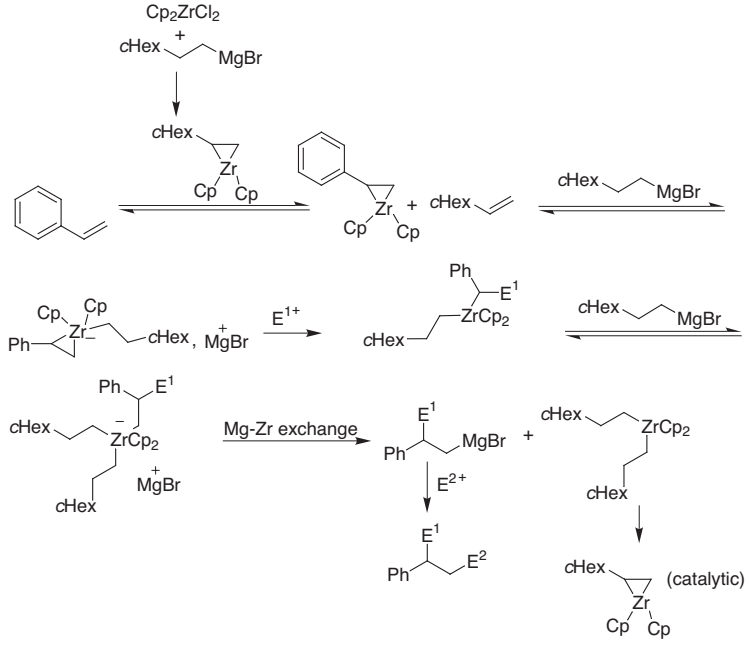
The development of zirconium-catalyzed carbomagnesiation of terminal and cyclic disubstituted allylic alcohols and ethers found new applications in recent years [156]. However, despite the demonstrated utility of catalytic carbomagnesiation in stereoselective synthesis, a number of limitations remain. A notable shortcoming is that alkyl Grignard reagents other than ethylmagnesium halides are less efficient or even fail to participate in catalytic carbomagnesiation. To address this problem,



Scheme 7-129 Electrophilic zirconium-catalyzed carbomagnesiation of styrene [157].

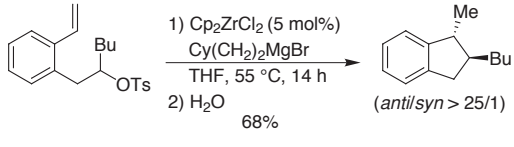
an efficient electrophilic zirconium-catalyzed carbomagnesiation was developed (Scheme 7-129) [157].

The mechanism of this zirconium-catalyzed electrophilic carbomagnesiation can be rationalized (see Scheme 7-130) [158].



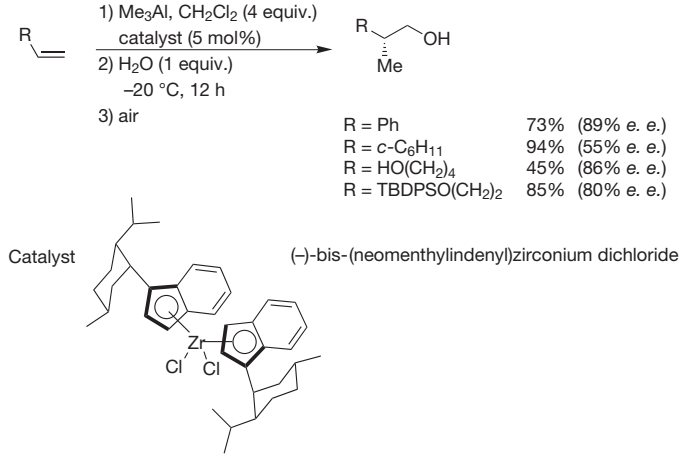
Scheme 7-130 Proposed mechanism for the zirconium-catalyzed electrophilic carbomagnesiation of alkenes [158].

A potential advantage of the Zr-catalyzed electrophilic alkylation is that it may be carried out in an intramolecular manner, which would provide a unique catalytic route to carbo- and heterocyclic structures (Scheme 7-131) [159].



Scheme 7-131 An intramolecular Zr-catalyzed electrophilic alkylation [159].

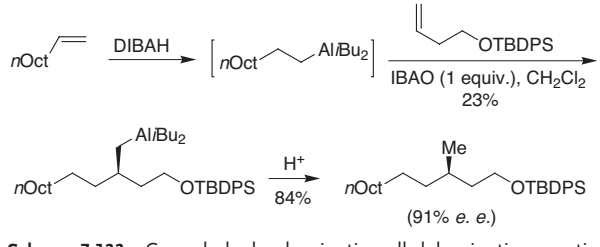
The Zr-catalyzed enantioselective alkylalumination of mono-substituted alkenes led to the carbometallated product with moderate to good enantioselectivities [160]. This catalyzed reaction was found to be greatly accelerated by the presence of water and therefore methylalumination of terminal alkenes has been achieved in good yields, and with good to high enantioselectivities (Scheme 7-132) [161].



Scheme 7-132 Zirconium-catalyzed enantioselective alkylalumination of mono-substituted alkenes [161].

An even broader approach based on the cascade hydroalumination-alkylalumination reactions of alkenes was reported (Scheme 7-133) [162].

Isobutylaluminoxane (IBAO), generated by treating iBu$_3$Al with H_2O (1 equiv.) also significantly accelerates the Zr-catalyzed carbometallation, but it does not significantly affect the enantioselectivity of the reaction. The improvement in *e. e.* from 80 to 90–93 % is almost entirely a result of the shift from methylalumination to isobutylalumination rather than due to the aluminoxanes.

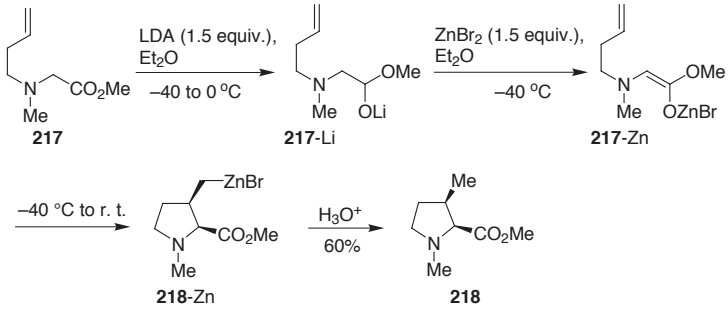


Scheme 7-133 Cascade hydroalumination-alkylalumination reactions of alkenes [162].

7.4
Zinc-Enolate Carbometallation Reactions

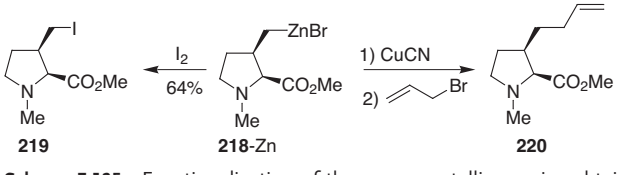
Zinc-induced additions of enolate derivatives across unactivated double bonds constitutes one of the most recent fields of research in the area of carbometallation. Therefore, a specific subchapter will describe the recent achievements in the intra- and intermolecular carbometallation with zinc-enolate derivatives.

The first intramolecular carbometallation reaction with a metal enolate of an unfunctionalized or nonstrained double bond was reported only in 1997 [163]. *N*-Methyl-*N*-(but-3-enyl)glycinate methyl ester **217** was cleanly metallated by treatment with 1.5 equiv. LDA in Et_2O at −40 °C, but after several hours of stirring at room temperature no cyclization of the corresponding lithium aminoenolate **217**-Li was observed. However, addition of 1.5 equiv. zinc bromide salt to **217**-Li led to the zinc aminoenolate **217**-Zn, resulting in a virtually quantitative 5-*exo*-*trig*-cyclization after 1 h at room temperature to give the cyclic product **218**-Zn (Scheme 7-134).



Scheme 7-134 First carbocyclization of a zinc aminoenolate [163].

Hydrolysis of the reaction mixture afforded **218** in 70 % isolated yield as a single diastereomer with *cis*-configuration. The formation of a new functionalized organometallic species was checked by iodinolysis and by reaction with allyl bromide after transmetallation of the resulting organozinc bromide to an organocopper reagent [164] (Scheme 7-135).



Scheme 7-135 Functionalization of the organometallic species obtained after intramolecular carbozincation by a zinc enolate [164].

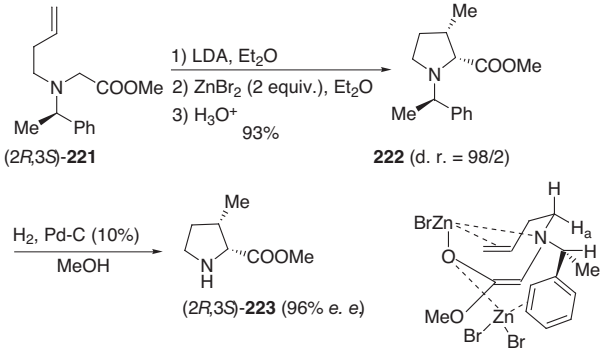
As the (*Z*)-configuration of the zinc enolate is imposed by an intramolecular Zn-N chelation [165], the relative *cis*-configuration of **218**-Zn was attributed to a

217-Zn **218**-Zn

Scheme 7-136 Mechanistic interpretation for the *cis* stereoselectivity [166].

chair-like transition state, in which the zinc (*Z*)-α-aminoenolate was in the plane parallel to that of the olefinic residue [166] (Scheme 7-136).

By this simple strategy, several tri- and tetra-substituted pyrrolidines were easily prepared and the diastereoselectivity of the carbocyclization was studied in detail [167]. When the *N*-(*R*)-1-(phenylethyl)-*N*-(but-3-enyl)glutamate methyl ester **221** was submitted to this metallation-transmetallation-cyclization sequence, the chiral cyclic organozinc bromide was diastereoselectively formed and after hydrolysis, the chiral *β*-methylproline derivative **222** was obtained as a virtually pure *cis*-diastereomer (d. r. = 98/2) in 93 % yield (Scheme 7-137) [167].



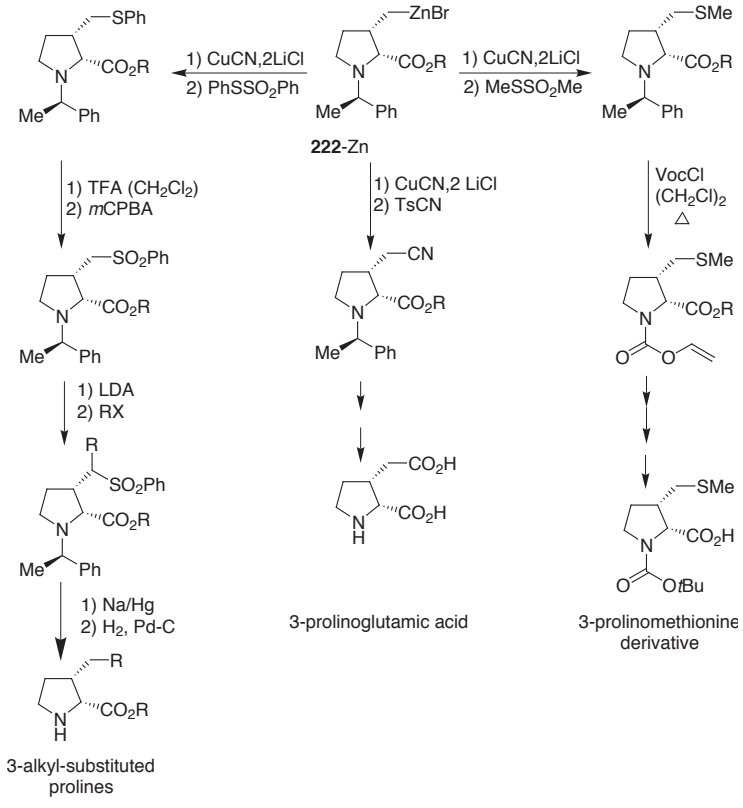
(2*R*,3*S*)-**221** **222** (d. r. = 98/2)

(2*R*,3*S*)-**223** (96% *e. e*)

Scheme 7-137 Carbometallating cyclization of lithium *N*-(*R*)-1-(phenylethyl)-*N*-(but-3-enyl)glutamic acid methyl ester enolate [167].

After hydrogenolysis, the secondary amine **223** was obtained with 96 % *e. e.* [163b]. Interestingly, the enantioselectivity of this carbocyclization fell to 50 % when the reaction was performed with only 1 equiv. zinc salt. Moreover, when the aromatic ring of the chiral inductor was replaced by a cyclohexyl ring, no diastereoselection was observed. In view of these results, the authors have postulated a *π*-chelation between the aromatic ring and the zinc aminoenolate in the transition state (see Scheme 7-137). As some *π*-chelations between organozinc derivatives and unsaturated systems are well known in the literature [168], the excess of zinc salt, which is necessary for the high diastereoselection, should act as a tether between the aromatic ring and the zinc aminoenolate, as depicted in Scheme 7-137. Therefore, the chiral inductor adopts a position in which the methyl group bound to the chiral center has a lowered eclipsing strain with the two hydrogens in the *α*-position, when one face of the carbon-carbon double bond is concerned rather than the other.

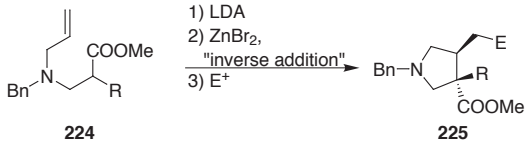
Several modified chiral amino-acids used as probes in structure-activity relationship studies of biologically active peptides, such as 3-prolinomethionines [169], 3-prolinoglutamic acid and 3-alkyl-substituted prolines [170] were easily prepared by this methodology (Scheme 7-138).



Scheme 7-138 Synthetic applications of the zinc aminoenolate carbocyclization [170].

The zinc aminoenolate carbocyclization has also been applied to solid-phase organic synthesis, allowing the preparation of libraries of 3-substituted proline derivatives [171].

When this metallation-transmetallation-cyclization was tested on the analogous *β*-(*N*-allyl)-amino ester, a reverse addition (dropwise addition of the lithium enolate to an ethereal zinc bromide solution) led to a smooth carbocyclization reaction to give, after hydrolysis or reaction with different electrophiles, the corresponding substituted methyl pyrrolidine-3-carboxylates in good yields (Scheme 7-139) [172].

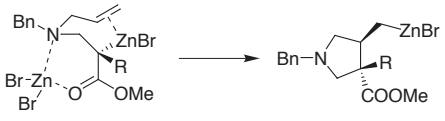


224 **225**

R = H	E = H	50%	(d. r. = 87/13)
R = Me	E = H	75%	(d. r. >99/1)
R = Me	E = I	68%	(d. r. >99/1)
R = Me	E = PhS	67%	(d. r. >99/1)

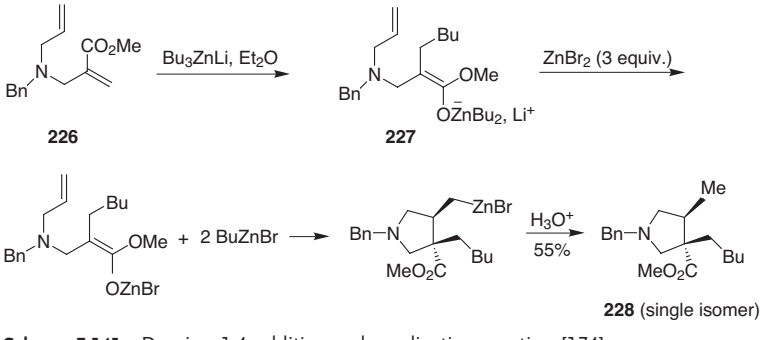
Scheme 7-139 Preparation of substituted pyrrolidine-3-carboxylates [172].

Surprisingly, the stereoselectivity of the carbocyclization in these cases is different from that of the cyclization of *α*-(*N*-homoallyl)amino ester enolates described above in Scheme 7-136. A reasonable explanation for the zinc-enolate cyclization of the *β*-amino ester could involve a carbon-centered enolate, as for the simple Reformatsky reagent [173], rather than an oxygen-centered enolate, as proposed in the case of an *α*-amino ester. Therefore, the group R should adopt a *pseudo*-equatorial position and the methoxycarbonyl group a *pseudo*-axial position, on the basis of their steric hindrance and a possible additional chelation with an external zinc species complexed to the nitrogen atom (Scheme 7-140).



Scheme 7-140 Mechanistic interpretation for the preparation of methylpyrrolidine-3-carboxylates [172].

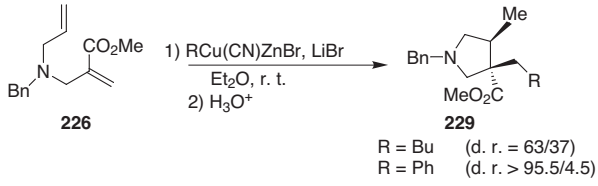
An alternative and elegant method for the preparation of substituted pyrrolidines was recently published and consists of a domino 1,4-addition-carbocyclization on different Michael acceptors, such as **226**, with a mixed copper-zinc reagent or with a triorganozincate-zinc salt combination [174]. Indeed, the 1,4-addition of triorganozincate reagents to *α*,*β*-unsaturated esters **226** led to the corresponding lithium enolzincate **227**, which underwent a subsequent carbocyclization reaction by treatment with $ZnBr_2$ (3 equiv.) to give, after hydrolysis, the methylpyrrolidine-3-carboxylate **228** in 55 % yield as a single diastereomer (Scheme 7-141).



Scheme 7-141 Domino 1,4-addition-carbocyclization reaction [174].

Even more interestingly, the reaction with RCu(CN)ZnBr,LiBr (prepared from *n*BuLi or PhLi and a mixture of $ZnBr_2$ and CuCN in diethyl ether) easily gave the cyclic product in good yield, with moderate to excellent stereoselectivities depending on the nature of the R group (Scheme 7-142) [174].

The diastereoselectivity can be improved either by using an excess of zinc salt during the preparation of the organocuprate, *n*BuCu(CN)ZnBr, LiBr (d. r. 93/7),

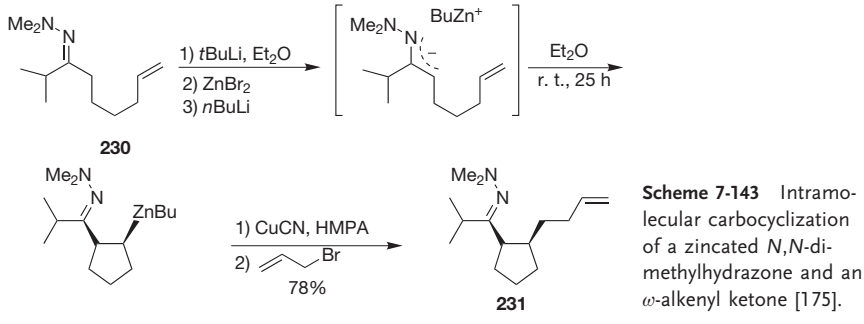


Scheme 7-142 Domino 1,4-addition-carbocyclization with zinc organocuprate derivatives [174].

or by using aryl- or vinyl-organometallic reagents (such as PhCu(CN)ZnBr, LiBr). In all cases, the carbometallated product can be functionalized with various electrophiles [174].

N,N-dimethylhydrazones of ω-alkenyl ketones also undergo carbocyclization upon deprotonation and transmetallation into BuZn(II) cation (see Scheme 7-143) [175].

However, the diastereoselectivity of this carbocyclization (*cis*/*trans* = 88/12) is lower than the diastereoselectivity of the intramolecular carbometallation of the zinc enolate, described above (see Scheme 7-135; d. r. >99/1).

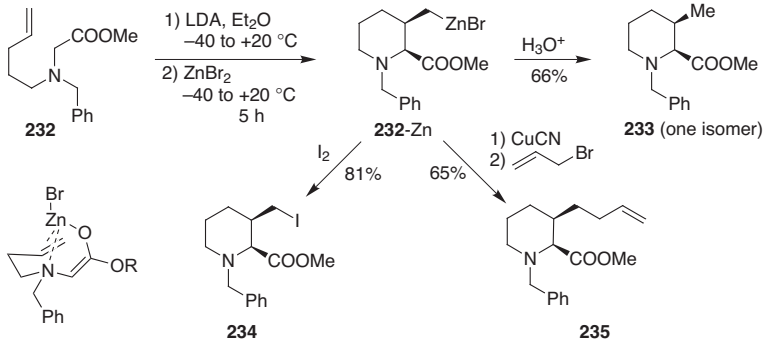


Scheme 7-143 Intramolecular carbocyclization of a zincated *N,N*-dimethylhydrazone and an ω-alkenyl ketone [175].

A 6-*exo*-*trig*-cyclization of a 6-heptenylmetal to a (cyclohexylmethyl)metal is usually much slower than the analogous 5-*exo*-*trig*-cyclization, and therefore fewer examples are known for this transformation [2,3,134]. However, cyclization of the zincaminoenolate has been successfully applied to the formation of six-membered rings, as a new access to oligosubstituted piperidine derivatives (Scheme 7-144) [176].

After metallation in Et_2O and transmetallation with zinc bromide, the corresponding (*Z*-)-zincaminoenolate cyclizes at room temperature to give the metallated piperidines **232**-Zn.

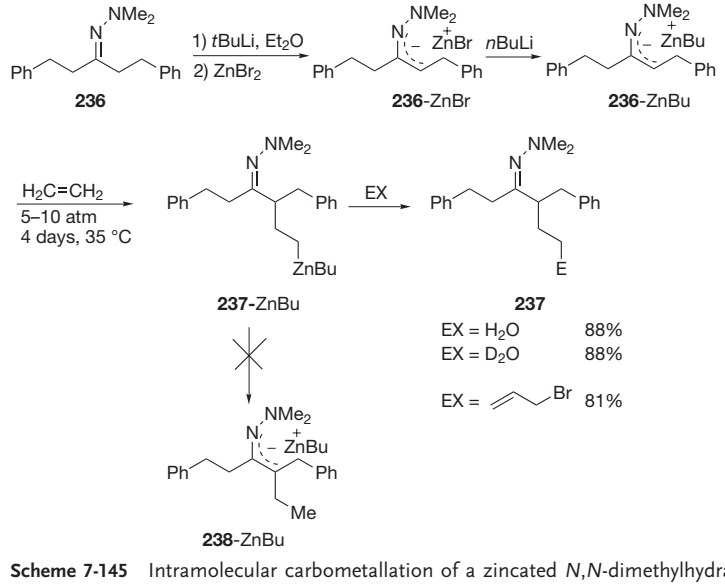
Hydrolysis, iodinolysis or allylation of the reaction mixture after an eventual transmetallation step, afforded the functionalized piperidines **233** to **235** in 66, 81, and 65 % yields, respectively. In all cases, only the *cis*-isomer was detected. The stereoselectivity has been explained by a chair-like transition state in which the electrophilic double bond occupies a *pseudo*-axial position (the zinc (*Z*)-α-aminoenolate and the double bond are *gauche* to each other), as depicted in Scheme 7-144 [176].



Scheme 7-144 Formation of functionalized piperidines by 6-*exo*-*trig*-carbocyclization [176].

The study of the stereochemical influence of substituents on the starting linear substrates on the carbocyclization reaction has been performed in detail, and the stereochemical outcome of this carbocyclization has been found to be mainly controlled by the presence or absence of a substituent in the homoallylic position [176].

Although much slower, the 6-*exo*-*trig*-cyclization of an *α*-zincated ketone hydrazone led to the cyclic derivative in good yield with a diastereoselectivity of 91/9 [175]. The addition reaction of an *α*-zinc hydrazone to, e. g., unsubstituted ethylene, was performed under pressure for four days at 35 °C, and led to the carbometallated intermediate **237**-ZnBu which, upon hydrolysis (or deuterolysis) gave the product **237** in 88 % yield (Scheme 7-145) [177].

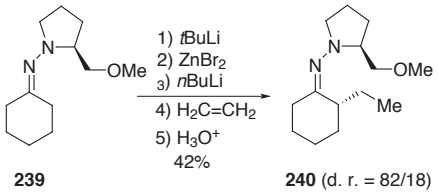


Scheme 7-145 Intramolecular carbometallation of a zincated *N*,*N*-dimethylhydrazone [177].

The α-zinchydrazone **237**-ZnBu does not isomerize to the more stable isomer such as **238**-ZnBu. Here again, the use of the substituted species **236**-ZnBu is critical, as under the same reaction conditions **236**-ZnBr afforded **237** in lower yields (22 %) [177]. The trapping of **237**-ZnBu with carbon electrophiles provided a one-pot, three-component coupling reaction.

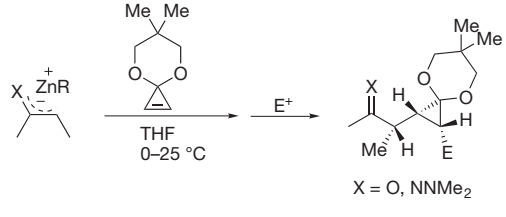
Aliphatic olefins such as 1-octene as well as aromatic olefins (styrene, *p*-methoxystyrene and *o*-trifluoromethylstyrene) also took part, albeit slowly, and gave lower yields. On the other hand, vinylsilane [178] and vinylstannane [179] reacted readily with α-zincated hydrazones, to give the carbometallated products.

The SAMP-hydrazone [177], which was prepared from cyclohexanone and the enantiomerically pure SAMP-hydrazine, also reacted with excess ethylene to form the allylated product in moderate yield and with a d. r. of 82/18 (Scheme 7-146).



Scheme 7-146 Diastereoselective carbocyclization of α-zincated SAMP-hydrazone [177].

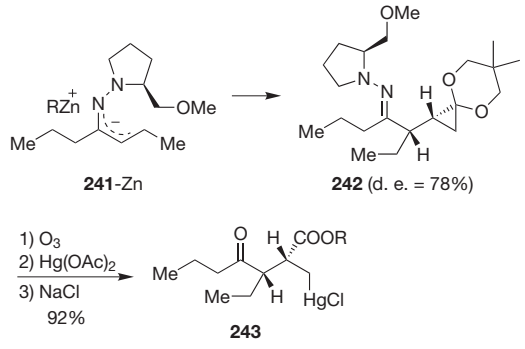
Zinc enolates and α-zincated hydrazones react with the cyclopropenone acetal in a highly diastereoselective manner, to give a β-cyclopropanonyl-carbonyl derivative (Scheme 7-147) [180].



Scheme 7-147 Preparation of β-cyclopropanonyl-carbonyl derivatives [180].

This carbometallation reaction takes place in a *cis*-manner with a generally high level of 1,2-diastereoselectivity for the newly formed C-C bond. The reaction with an enantiomerically pure hydrazone can be useful in synthetic terms, as the level of selectivity is between 87 and 98 % (Scheme 7-148).

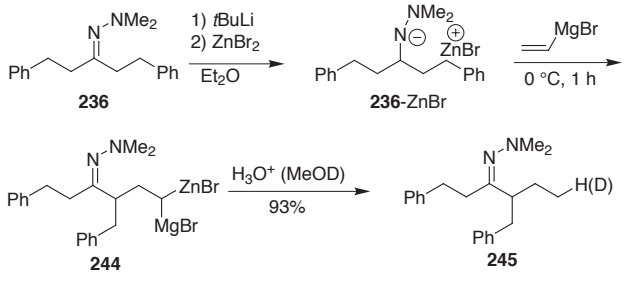
Not unexpectedly for the intermolecular carbometallation reactions, unactivated alkenes are rather poor electrophiles towards enolates, and good yields are obtained only with slightly activated [178, 179] or strained alkenes [180]. On the other hand, the addition of delocalized organometallics such as allyl- or propargylzinc derivatives to vinylmagnesium halide, proceeds very smoothly at low temperature [10].



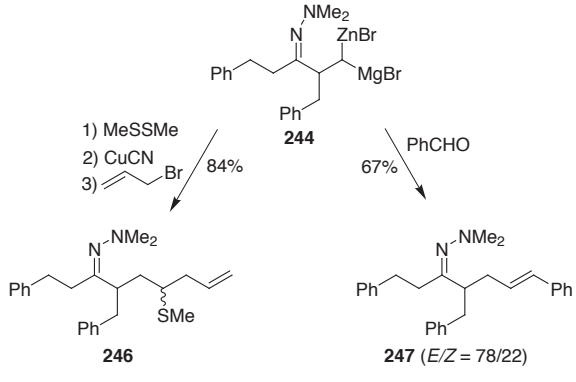
Scheme 7-148 Enantioselective carbometallation of a cyclopropenone acetal [180].

A similar pattern was found for the reaction between the zincated hydrazone **236**-ZnBr and a vinyl-Grignard reagent, which easily takes place at 0 °C within 1 h, to give the bismetallated hydrazone intermediate **244** in near-quantitative yield (Scheme 7-149) [181].

The bismetallated species **244** can also react either with benzaldehyde to give the olefination product **247**, or with two different electrophiles, such as MeSSMe followed by allyl bromide to furnish **246** (Scheme 7-150).



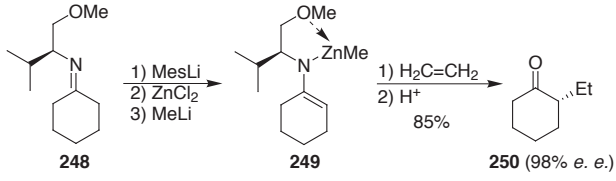
Scheme 7-149 Carbometallation of vinylmagnesium bromide with a zincated hydrazone.



Scheme 7-150 Reactivity of the bismetallated species **244** towards electrophiles [181].

Substituted vinyl Grignard reagents have so far been found to react very sluggishly with the α-metallated *N,N*-dimethylhydrazones.

When the enantiomerically pure cyclohexanone imine **248**, prepared by condensation of cyclohexanone and the methyl ether of (*S*)-valinol, was first deprotonated with 1 equiv. mesityllithium at 0°C in ether, transmetallated with $ZnCl_2$, and the resulting intermediate finally treated with methyllithium, the corresponding chiral zinc enamide **249** was formed. The diethyl ether was then replaced with hexane, and the reaction mixture stirred under an ethylene atmosphere (20 atm) at 40 °C for 24 h. After hydrolysis, 2-ethylcyclohexanone **250** was obtained in good yield and with high enantiomeric excess (Scheme 7-151) [182].

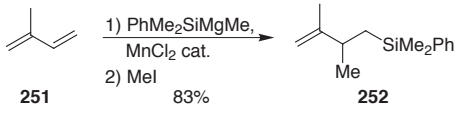


248 **249** **250** (98% *e. e.*)

Scheme 7-151 Carbometallation of ethene with a chiral zinc enamide [182].

7.5
Carbometallation Reactions of Dienes and Enynes

The treatment of isoprene **251** with $PhMe_2SiMgMe$ in the presence of a catalytic amount of manganese dichloride, followed by the addition of iodomethane, afforded 4-(dimethylphenylsilyl)-2,3-dimethyl-1-butene **252** as the main product. The same type of reaction was achieved with 1,3-butadiene, as well as 2,3-dimethyl-1,3-butadiene (Scheme 7-152) [183].

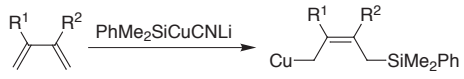


251 83% **252**

Scheme 7-152 Preparation of 4-(dimethylphenylsilyl)-2,3-dimethyl-1-butene [183].

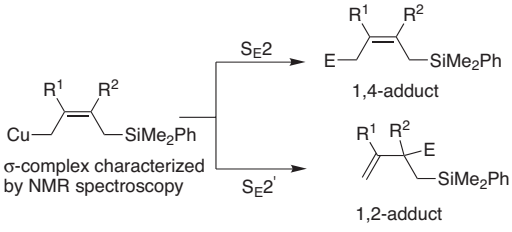
The organometallics $PhMe_2SiLi$ and $PhMe_2SiMgMe$ did not react with isoprene in the absence of manganese(II) chloride. On the other hand, silylcupration reactions of 1,3-dienes with the cyanocuprate reagent $PhMe_2SiCuCNLi$ produced a σ-(silyl-(*Z*)-alken-1-yl)copper complex, obtained from an overall 1,4-silylcupration across the 1,3-diene system (Scheme 7-153) [184].

The regioselectivity of this copper intermediate reacting with electrophiles depends heavily on the nature of the electrophile. Indeed, different electrophiles



253a $R^1 = R^2 = H$
253b $R^1 = Me$, $R^2 = H$
253c $R^1 = R^2 = Me$

Scheme 7-153 Silylcupration reactions of 1,3-dienes with a cyanocuprate reagent [184].

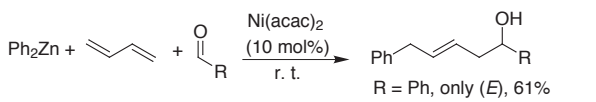


Scheme 7-154 The regioselectivity of the copper intermediate depends strongly on the nature of the electrophile [184].

can give different regiochemistries, i. e. S_E2 or S_E2' substitution products (Scheme 7-154).

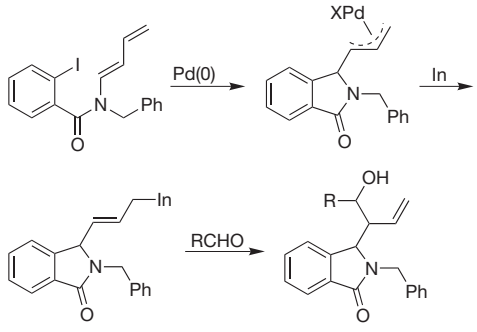
With carbon dioxide as electrophile, the 1,2-addition product was formed exclusively. With water and acetyl chloride, mixtures of 1,2- and 1,4-addition products were obtained, with the ratio between them being independent of the reaction temperature. However, with allyl phosphate or methyl iodide as quenching electrophiles, 1,4-adducts were usually obtained.

A single isomer was obtained in each case when diphenylzinc, in the presence of 10 mol % $Ni(acac)_2$, was reacted with 1,3-butadiene and an aldehyde at room temperature (Scheme 7-155) [185].



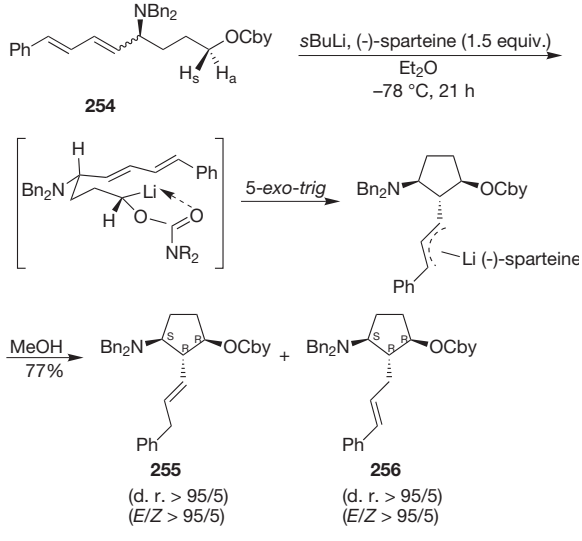
Scheme 7-155 Reaction of Ph_2Zn in the presence of 10 mol% $Ni(acac)_2$ with 1,3-butadiene and aldehydes [185].

The same stereoselectivities were observed for the reactions with isoprene. As described above, allylation of carbonyl compounds is nowadays an important synthetic transformation, and indium has emerged as a new partner in these reactions. In this respect, a new diastereo- and regioselective bismetallic cascade reaction involving the palladium-catalyzed cyclization of an aryl iodide with attack on a proximate 1,3-diene unit to generate a π-allylpalladium(II) complex was developed [186]. Subsequent transmetallation with indium furnished a nucleophilic allylindium species which then underwent Barbier-type addition to aldehydes, affording homoallylic alcohols with three contiguous stereogenic centers (Scheme 7-156) [187].



Scheme 7-156 Preparation of homoallylic alcohols with three contiguous stereogenic centers [187].

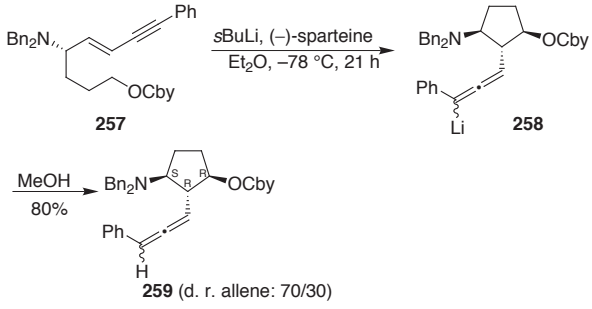
Enantioenriched organolithium derivatives, generated by the asymmetric deprotonation of a carbamate **254** with the chiral base *s*BuLi/(–)-sparteine, undergo smooth intramolecular conjugate addition reactions to dienes, in high yields (Scheme 7-157) [188].



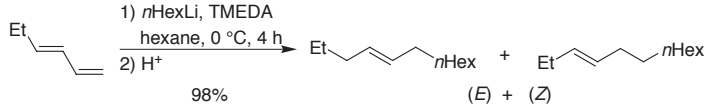
Scheme 7-157 Intramolecular conjugate addition reactions of an enantioenriched organolithium to dienes [188].

In close analogy, the enynyl-substituted carbamate **257**, upon treatment with *s*BuLi in the presence of (–)-sparteine, cleanly cyclized to the allenyllithium **258**. However, quenching with MeOH gave a mixture of two diastereomeric allenes **259** in high yield (Scheme 7-158) [188].

Even non-activated dienes such as hexa-1,3-diene, can be carbometallated with *n*-hexyllithium in the presence of TMEDA in hexane to afford a mixture of regio- and stereoisomers of 3- and 4-dodecenes (Scheme 7-159) [189]. In Et_2O as solvent, only polymers were formed.



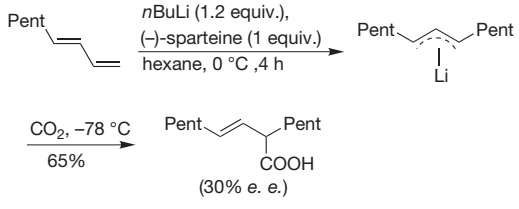
Scheme 7-158 Enantioselective carbocyclization of enynes [188].



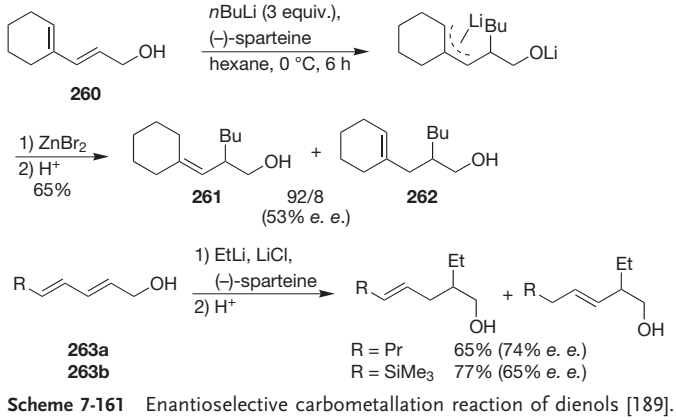
Scheme 7-159 Carbometallation of nonactivated dienes [189].

Starting from nona-1,3-diene, the addition of *n*BuLi, in the presence of (–)-sparteine led to a symmetrical allyllithium, the carboxylation of which gave the corresponding acid with 30 % *e. e.* (Scheme 7-160) [189].

When dienols were used as starting materials, higher enantiomeric excesses were achieved (see Scheme 7-161).



Scheme 7-160 Enantioselective carbometallation reaction of nona-1,3-diene [189].

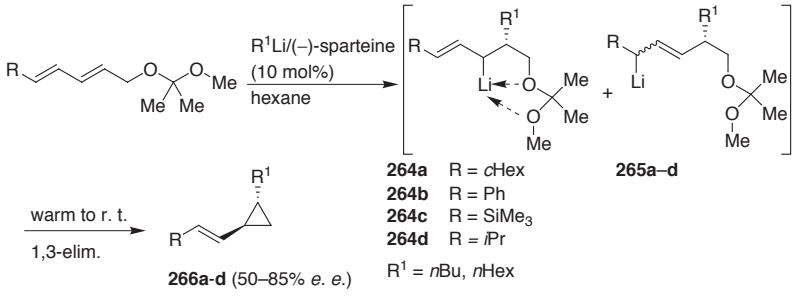


Scheme 7-161 Enantioselective carbometallation reaction of dienols [189].

When **260** was submitted to the enantioselective carbometallation reaction, followed by acidic hydrolysis of the allyllithium intermediate, two isomeric alkenes **261** and **262** were obtained in a ratio of 70/30, with an *e.e.* of 53 %. When $ZnBr_2$ was added to the allyllithium prior to hydrolysis, the regioselectivity of the protonation **261**/**262** was raised to 92/8.

Dienes **263a**,**b** also undergo such carbometallation reaction with good enantiomeric excesses [189].

This concept was used for the catalytic enantioselective synthesis of vinylcyclopropanes (Scheme 7-162) [190].



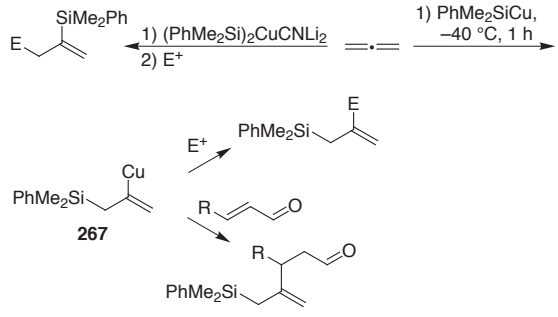
Scheme 7-162 Catalytic enantioselective synthesis of vinylcyclopropanes [190].

Indeed, the addition of alkyllithiums (R^1 = *n*Bu, *n*Hex) in hexane in the presence of 10 mol % (−)-sparteine at −10 °C led to the allylic organolithium derivatives **266a–d** as mixtures of *cis*- and *trans*-diastereoisomers. Once the carbolithiation step is over, a rapid warming of the reaction mixture to room temperature leads to the formation of the vinylcyclopropanes with moderate to good enantiomeric excesses.

7.6 Carbometallation Reactions of Allenes

Silylcupration of allenes has emerged as a new tool for the synthesis of allyl- and vinylsilanes [191], and the scope of the reaction as well as its synthetic applications have recently been reviewed [192]. Addition of the silicon-copper bond across one of the double bonds of allenes occurs *syn*-stereospecifically, and the adducts, by reaction with electrophiles, lead to a large variety of functionalized molecules. More recently, it has been shown that phenyldimethylsilylcopper, prepared from phenyldimethylsilyllithium and CuCN, reacts with 1,2-propadiene with the opposite regiochemistry compared to that of the corresponding higher-order silylcuprate reagent (Scheme 7-163) [193].

When **267** was treated with an α,β-unsaturated aldehyde or ketone in the presence of $BF_3 \cdot Et_2O$, the corresponding oxoallylsilanes were obtained in good yields [194–196]. When phenyldimethysilylcopper was added to 1- and 1,1-disubstituted



Scheme 7-163 Regiochemistry of the reaction of phenyldimethylsilylcopper versus the corresponding higher-order silylcuprate reagent [193–197].

allenes, the corresponding vinylcopper was also obtained and found to undergo S_N2' reactions with allyl phosphates [197].

7.7 Conclusions

The importance of the carbometallation reactions in organic synthesis has been recognized during the past two decades, but more particularly in the past few years. The ever-growing number of new methodologies for the 1,2-dialkyl-functionalization of nonactivated carbon–carbon double and triple bonds attests to this interest. Excellent stereoselectivities are achieved in the creation of (*E*)- or (*Z*)-vinylmetals from alkynes, and in the preparation of *erythro* or *threo* structures from alkenes. However, the enantioselective transformation of alkenes into chiral 1,2-dialkyl-substituted alkanes continues to be one of the most difficult challenges in synthetic organic chemistry, and there is no doubt that during the next few years several new enantioselective carbometallation reactions of alkenes will be developed.

7.8 Experimental Procedures

7.8.1 **(*E*)-2-Allyl-1-bromo-3-(*tert*-butoxy)-1-chlorohex-1-ene** (Scheme 7-9)

To a cooled (0 °C) solution of 3-(*tert*-butoxy)hex-l-yne (309 mg, 2 mmol) in anhydrous Et_2O (10 mL) was added dropwise *n*BuLi (1.6 *M* solution in hexane, 1.6 mL, 2.6 mmol, 1.3 equiv.). The mixture was allowed to warm to room temperature. After an additional stirring, a pale yellow suspension was obtained. To this solution was added dropwise at –30 °C a solution of allylmagnesium bromide (1.38 *M* solution in Et_2O, 1.9 mL, 2.6 mmol, 1.3 equiv.; the solution turned gray) and at –10 °C a solution of $ZnBr_2$ (1 *M* solution in Et_2O, 2.6 mL, 2.6 mmol, 1.3 equiv.). The resulting solution mixture was stirred at –10 °C for 0.5 h, and a

yellow solution of **10** was obtained. The mixture was then cooled to –50 °C, and a solution of TsBr (0.94 mL, 4 mmol, 2 equiv.) in Et_2O (10 mL) was added. After an additional 15 min of stirring at this temperature, a solution of NCS (0.55 g, 4 mmol, 2 equiv.) in CH_2Cl_2 (20 mL) was added. After 2 h of stirring at –30 °C, the mixture was hydrolyzed with a 1 N solution of HCl. The mixture was then allowed to warm to room temperature. The aqueous layer was extracted with Et_2O (2 × 20 mL). The combined extracts were stirred for 4 h in the presence of aqueous Na_2S. The new aqueous layer was extracted with Et_2O (2 × 10 mL). After the usual work-up, flash chromatography of the crude product on silica gel (eluent: cyclohexane) yielded 70 mg (60 %) of the title compound.

7.8.2

(*E*)-4-Methyl-3-deuterio-3-octenyl benzyl ether (Scheme 7-23)

A flask was charged with a solution of $Fe(acac)_3$ in toluene (0.025 *M*, 0.025 mmol, 1.0 mL), toluene (4 mL) and substrate (0.5 mmol) and then cooled to –40 °C. A solution of *n*BuLi in hexane (1.5 *M*, 1.5 mmol) was added to the mixture. The reaction temperature was immediately raised to –20 °C, and the mixture was stirred at –20 °C for 2 h. The reaction was quenched with DCl/D_2O. The reaction mixture was diluted with saturated NH_4Cl solution. After extraction with ether (3 × 10 mL), washing the combined organic layer with saturated $NaHCO_3$, drying over $MgSO_4$ and evaporation of the solvents, the residue was subjected to chromatography on silica gel (eluent, hexane:ethyl acetate, 30:1) to furnish the pure product in 96 % yield.

7.8.3

Carbocyclization of 3,7-dimethyl-6-phenylithio-1,7-octadien-3-ol 117 to the trisubstituted cyclopentanol 118 (Scheme 7-77)

To a stirred solution of 3,7-dimethyl-6-phenylithio-1,7-octadien-3-ol **117** (1.1 g, 4.2 mmol) in anhydrous ether (15 mL) kept at –78 °C, was added via syringe MeLi (1.1 *M* in ether, 4.2 mL, 4.6 mmol). After 10 min, the reaction mixture was cannulated into an LDMAN solution [formed with polished lithium (80 mg, 11.5 mmol), *N*,*N*-dimethyl-l-naphthylamine (2.06 g, 12 mmol) and anhydrous Me_2O (20 mL) for 5 h at –70 °C with stirring] at –70 °C. After 10 min, a solution of anhydrous $MgBr_2$ (20 mmol in 60 mL of ether [taken from a solution formed by stirring Mg (1.2 g, 50 mmol) with 1,2-dibromoethane (5.64 g, 30 mmol) in refluxing ether (90 mL) for 4 h] was added via syringe. After 1 h at –30 °C, the reaction mixture was warmed to and maintained at room temperature for 1.5 h. Diphenyl diselenide (2.81 g, 9 mmol) was added, and the mixture was stirred for 2 h before water (60 mL) was added. The separated organic phase was washed with 1 N aqueous NaOH (2 × 60 mL) and water (60 mL), and then dried over anhydrous K_2CO_3. Evaporation of the solvents and column chromatography (eluent, hexane:ethyl acetate, 7:1, 0.5 % NEt_3) gave the cyclized selenide **118** (380 mg, 64 %) as an oil.

7.8.4

(–)-(1*R*,2*R*)-2-[(1*S*)-1-Phenyl-1-(trimethylsilyl)methyl]cyclopentyl-2,2,4,4-tetramethyl-1,3-oxazolidine-3-carboxylate 154 (Scheme 7-92)

At –78 °C, a solution of **152a** (331 mg, 1 mmol) in Et_2O (3 mL) was treated with *s*BuLi (1.15 mL, 1.5 mmol, 1.5 equiv., 1.3 *M*) in the presence of (–)-sparteine (352 mg, 1.5 mmol, 1.5 equiv.). The mixture was stirred at this temperature for 2 h. Me_3SiCl (0.32 mL, 1.5 mmol, 1.5 equiv.) was then added at this temperature. The mixture was stirred for an additional 5 h at –78 °C before warming to ambient temperature and quenching the reaction with H_2O (5 mL). The crude product was purified by flash chromatography (eluent, ether:hexane, 1:10), yielding **154** with E = $SiMe_3$ (129 mg, 32 %, d. r. 98/2).

7.8.5

(2S*,3R*)-1,3-Dimethyl-2-methoxycarbonyl-*N*-methylpyrrolidine 218 (Scheme 7-134)

A solution of **217** (157 mg, 1 mmol) in anhydrous ether was cooled to –40 °C while LDA (2 *M* in THF/heptane, 1.5 mmol, 0.75 mL) was added dropwise. The reaction mixture was then allowed to warm to 0 °C for 10 min and cooled to –40 °C while zinc bromide (1 *M* in ether, 1.5 mL, 1.5 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature for 30 min. The cyclized product **218**-Zn was then cooled to 0 °C while a solution of NH_4Cl/NH_4OH (2/1) was added slowly. Ether was added, and the mixture was stirred for at least 3 h with a few crystals of $Na_2S.9H_2O$, in order to remove traces of zinc salts. The layers were separated, the aqueous being extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified by chromatography on silica gel (eluent, dichloromethane:methanol, 90:10) to give 109 mg (70 %) of the title compound **218**.

7.8.6

Methyl-(3*R,4*S**)-1,3-dibenzyl-4-methylpyrrolidine-3-carboxylate 229** (Scheme 7-142)

An ethereal solution of zinc bromide (4 mL, 1 N in Et_2O, 4 mmol) and subsequently a solution of PhLi · LiBr (3.2 mL, 1.27 N in Et_2O, 4 mmol) were added dropwise to a suspension of copper cyanide (360 mg, 4 mmol) in Et_2O (7 mL) at –10 °C. The reaction mixture was stirred at 0 °C for 1 h, and a solution of methyl-2-[(*N*-allyl-*N*-benzylamino)methyl]acrylate **226** (490 mg, 2 mmol) in Et_2O was added dropwise at 0 °C. The cold bath was removed, and the biphasic mixture was stirred at room temperature for 2 h. The reaction was quenched with an aqueous solution of NH_4Cl/NH_4OH (2/1). The layers were separated, the aqueous one being extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvents evaporated under reduced pressure. The residue was purified by chromatography on silica gel (eluent, cyclohexane:ethyl acetate, 8:2) to give **142** (356 mg, 55 %) as a yellow oil.

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8
Palladium-Catalyzed 1,4-Additions to Conjugated Dienes

Jan-E. Bäckvall

8.1
Introduction

Additions to nonactivated olefins and dienes are important reactions in organic synthesis [1]. Although cycloadditions may be used for additions to double bonds, the most common way to achieve such reactions is to activate the olefin with an electrophilic reagent. Electrophilic activation of the olefin or diene followed by a nucleophilic attack at one of the sp^2 carbons leads to a 1,2- or 1,4-addition. More recently, transition metals have been employed for the electrophilic activation of the double bond [2]. In particular, palladium(II) salts are known to activate carbon-carbon double bonds towards nucleophilic attack [3], and this is the basis for the Wacker process for industrial oxidation of ethylene to acetaldehyde [4]. In this process the key step is the nucleophilic attack by water on a π-ethylenepalladium complex.

Addition to conjugated dienes constitutes a special class of reactions, and in these it is of great importance to control the regioselectivity towards 1,2- or 1,4-addition. With classical electrophilic reagents it is difficult to control the regioselectivity, and mixtures of 1,2- and 1,4-regioisomers are often formed. With the use of transition metals, highly regioselective additions to conjugated dienes can be obtained [5]. From a synthetic point of view, it is of great importance if these additions are catalytic with respect to the metal. One metal that has been used successfully in this respect is palladium, and several reviews have been produced which include palladium-catalyzed additions to conjugated dienes [5–10]. This chapter will deal with palladium-catalyzed reactions leading to selective bis-couplings in the 1- and 4-position of 1,3-dienes.

Palladium-catalyzed 1,4-additions to conjugated dienes can be divided into two classes: (1) nonoxidation reactions; and (2) oxidation reactions. In the former type of reaction, a palladium(0) catalyst is employed, and the first step in the catalytic cycle is often an activation of one of the reactants by its oxidative addition to Pd(0). In the second type of reaction, a palladium(II) complex is the active catalyst, and this oxidizes the substrate diene under formation of Pd(0). Reoxidation of Pd(0) to Pd(II) by an oxidant regenerates the active catalyst.

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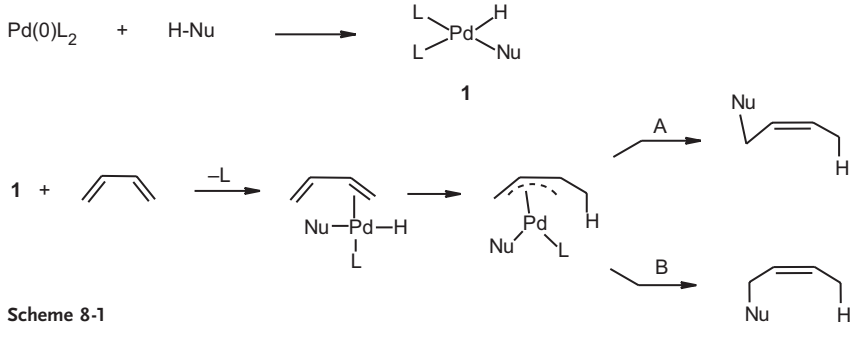
8.2
Palladium(0)-Catalyzed Reactions

These reactions are nonoxidation reactions, and can be divided into several subclasses. The active catalyst is a palladium(0) complex, such as $Pd(PPh_3)_4$, or some analogous phosphine complex. Such palladium(0) phosphine complexes may also be generated in situ from $Pd(0)(dba)_2$ (dba = dibenzylidenacetone) + phosphine or from $Pd(OAc)_2$ + phosphine. In the latter case, Pd(II) is reduced to Pd(0) by the phosphine [11]. A common feature of the palladium(0)-catalyzed additions to conjugated dienes is that they begin with an oxidative addition of a species such as H-Nu or RX to palladium(0) to give a palladium(II) hydride complex or an organometallic R-Pd(II) complex, respectively. These complexes subsequently react with the conjugated diene in a migratory insertion reaction to give an intermediate π-allylpalladium complex.

8.2.1
Addition of H-Nu

This reaction constitutes a special type of process in which a hydrogen and a nucleophile are added across the diene, with formation of a carbon-hydrogen bond in the 1-position and a carbon-Nu bond in the 4-position. Some examples of such reactions are hydrosilylation [12–18], hydrostannation [19, 20], hydroamination [21, 22], and addition of active methylene compounds [21a, 23, 24]. These reactions are initiated by an oxidative addition of H-Nu to the palladium(0) catalyst, which produces a palladium hydride species **1** where the nucleophile is coordinated to the metal (Scheme 8-1). The mechanism commonly accepted for these reactions involves insertion of the double bond into the palladium-hydride bond (hydride addition to the diene), which gives a π-allylpalladium intermediate. Now, depending on the nature of the nucleophile (Nu), the attack on the π-allyl complex may occur either by external *trans*-attack (Scheme 8-1; path A) or via a *cis*-migration from palladium to carbon (path B).



Scheme 8-1

8.2.1.1 1,4-Hydrosilylation

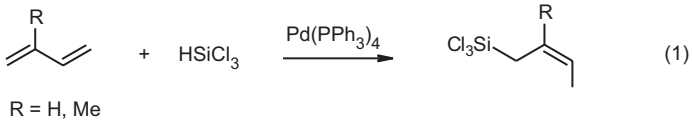
Palladium-catalyzed hydrosilylation of terminal 1,3-dienes proceeds with high 1,4-regioselectivity. For example, both butadiene and isoprene react with $HSiCl_3$ in the presence of $Pd(PPh_3)_4$ to give the 1,4-hydrosilylation product (Eq. (1)) [12].

Hydrosilylation of cyclic dienes also worked well to give allylic silanes. Thus, palladium-catalyzed hydrosilylation of 1,3-cyclopentadiene and 1,3-cyclohexadiene afforded the corresponding allylsilanes in good yields [13, 14].

Early studies on palladium-catalyzed asymmetric hydrosilylation of cyclic conjugated dienes employing menthyl-, neomenthyl-diphenylphosphine, and ferrocenylaminophosphine ligands gave low enantiomeric excesses of the corresponding allylsilane [13].

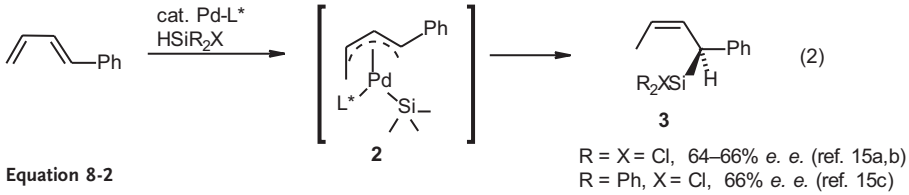
Different ligands have been employed in the asymmetric hydrosilylation of (*E*)-1-phenylbutadiene to give the allylsilane **3** via intermediate **2** [15]. The use of a chiral ferrocenylphosphine ligand gave 64–66 % *e.e.* [15a,b], whereas the use of a chiral binaphthol derivative furnished **3** in 66 % *e.e.* [15c]. Interestingly, the 1,4-addition product **3** had (*Z*)-configuration. This is a common phenomenon in palladium-catalyzed hydrosilylation. The configuration of the product from butadiene in Eq. (1) (R=H) had later been determined and shown to be exclusively *Z* [16]. In accordance with these findings, palladium-catalyzed hydrosilylation of 1-vinyl-1-cyclohexene with $HsiMeCl_2$ gave (*Z*)-1-ethylidene-2-(dichloromethylsilyl) cyclohexane [17].

The high selectivity for formation of (*Z*)-alkenes in palladium-catalyzed hydrosilylation can be attributed to the formation of a *cisoid* complex of type **2** (Eq. (2)) which, after hydride addition, undergoes a reductive elimination which is faster than *syn-anti* isomerization [5].



R = H, Me

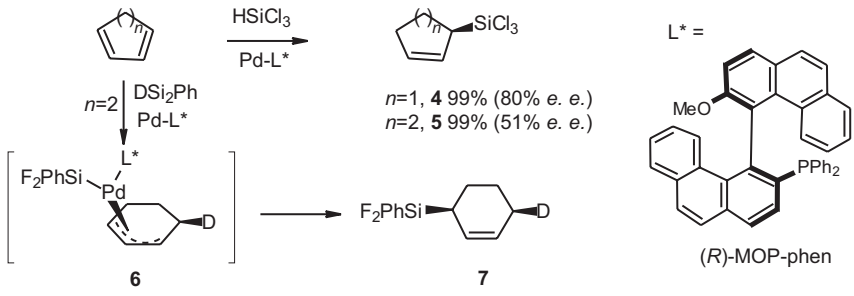
Equation 8-1



R = X = Cl, 64–66% *e. e.* (ref. 15a,b)
R = Ph, X = Cl, 66% *e. e.* (ref. 15c)

Equation 8-2

A significant improvement was accomplished in the asymmetric palladium-catalyzed 1,4-hydrosilylation of cyclic 1,3-dienes with the use of the chiral ligand (*R*)-MOP-phen (Scheme 8-2) [18]. Thus, hydrosilylation of cyclopentadiene gave **4** in 99 % yield with an enantiomeric excess of 80 %, which is the highest reported

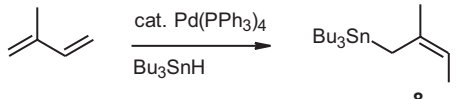


Scheme 8-2

e. e. value for Pd-catalyzed hydrosilylation of 1,3-dienes. With 1,3-cyclohexadiene, the yield of the allylsilane **5** was high, but the *e. e.* was moderate. In the latter study [18], it was demonstrated that the hydrosilylation of cyclic dienes is indeed a 1,4-*syn*-addition. Reaction of 1,3-cyclohexadiene with $DSiF_3Ph$ in the presence of the catalyst afforded exclusively 1-deuterio-4-(phenyldifluorosilyl-2-cyclohexene (**7**). This is consistent with a fast reductive elimination (*vide supra*) from the π-allyl intermediate **6** to give **7** before isomerization by a so-called apparent π-allyl rotation occurs [25].

8.2.1.2 1,4-Hydrostannation

The reaction of isoprene with tributyltin hydride in the presence of catalytic amounts of $Pd(PPh_3)_4$ gave the 1,4-hydrostannation product **8** with high regio- and stereoselectivity (Eq. (3)) [19]. The *Z* configuration can be explained in the same way as for the hydrosilylation (cf. Eq. (2)).

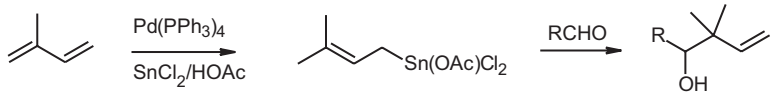


(3)

8

Equation 8-3

Palladium-catalyzed hydrostannation of isoprene was used for the in-situ generation of allylstannane **9**, which was trapped by an aldehyde to give the alcohol **10** (Eq. (4)) [20]. It was suggested that an intermediate $HPdSn(OAc)Cl_2$ is formed. The authors proposed two mechanisms for the hydrostannation: one according to Scheme 8-1, where Nu = $Sn(OAc)Cl_2$; and another where the double bond inserts into the palladium-tin bond, followed by reductive elimination from a π-allylpalladium hydride.



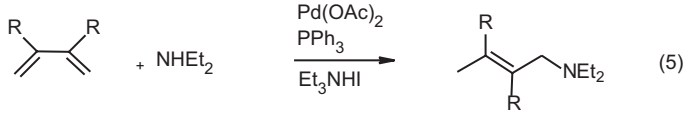
(4)

Equation 8-4 **9** **10**

8.2.1.3 **1,4-Hydroamination**

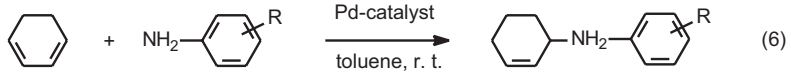
Palladium-catalyzed 1,4-hydroamination of conjugated dienes is usually accompanied by large amounts of 2:1 telomerization products [21, 22]. It was shown that the use of an amine hydrochloride as a co-catalyst increased the selectivity for the 1,4-hydroamination product [23]. Thus, butadiene and 2,3-dimethylbutadiene produced a fair yield in the palladium-catalyzed 1,4-hydroamination (Eq. (5)).

High-yielding palladium-catalyzed 1,4-hydroaminations of 1,3-dienes with anilines have more recently been reported by two groups (Eq. (6)) [26].



R = H 45%
R = Me 67%

Equation 8-5



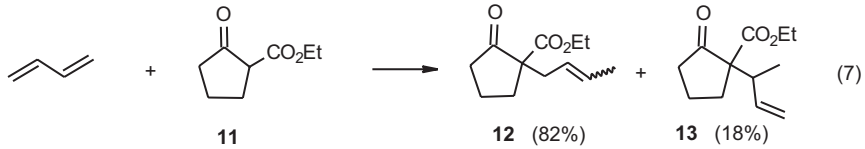
78–99%

Equation 8-6

The reaction also works well with acyclic dienes to give hydroamination products in high yields. In one of the studies, trifluoroacetic acid was used in catalytic amounts to increase the rate of the reaction [26a]. In the latter study, the use of chiral ligands in the hydroamination of 1,3-cyclohexadiene afforded products with up to 95 % *e.e.*.

8.2.1.4 **Addition of Active Methylene Compounds**

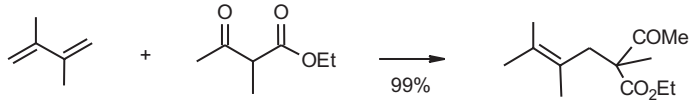
The palladium(0)-catalyzed reaction of 1,3-dienes with active methylene compounds to give 1,4-addition of a hydrogen atom and a stabilized carbanion is complicated by the formation of 2:1 telomerization products [27]. It was found by Hata et al. [21a] that bidentate phosphines such as 1,2-(diphenylphosphino)ethane favor formation of the 1:1 adduct. More recent studies by Jolly have shown that the use of more σ-donating bidentate phosphines on palladium gave high selectivity for 1:1 adduct [23]. For example, 1,3-butadiene reacted with **11** to give the 1,4-addition product **12** in 82 % yield, together with 18 % of the 1,2-addition product **13** (Eq. (7)).



11 **12** (82%) **13** (18%)

(E/Z = 9/1)

Equation 8-7

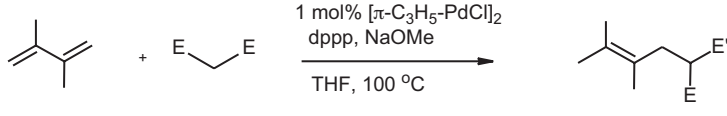


(8)

Equation 8-8 **14**

The reaction of 2,3-dimethylbutadiene with 2-methylacetylacetate **14** gave an excellent yield of a single 1,4-addition product (Eq. (8)). It was suggested that the reaction proceeds via a π-allylpalladium intermediate formed by Pd-H addition to the diene, followed by nucleophilic attack by the carbanion (cf. Scheme 8-1). It is likely that the reaction proceeds via path A (Scheme 8-1); that is, via an external nucleophilic attack by the carbanion.

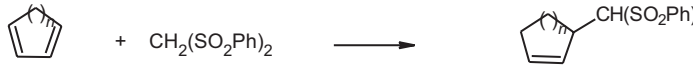
In a related study, Trost and Zhi [24] showed that the use of 1,3-(diphenylphosphino)propane (dppp) as a ligand on palladium also led to a high selectivity for 1,4-addition of active methylene compounds to 1,3-dienes. For example, 2,3-dimethylbutadiene gave an excellent yield with a number of active methylene compounds (Eq. (9)). Interestingly, the reaction temperature is of importance for the 1,4-selectivity. Thus, in the reaction of $(PhSO_2)_2CH_2$ with isoprene employing the Pd(0)-dppp system, the ratio between the desired 1,4-addition product and the telomerization product was 73:27 at 70 °C, but this increased to 95:5 at 100 °C. Cyclic dienes also gave excellent yields of the 1,4-addition products (Eq. (10)).



(9)

E = E' = SO_2Ph 95%
E = SO_2Ph, E' = CO_2Me 92%
E = CH_3CO, E' = CO_2Me 99%

Equation 8-9



(10)

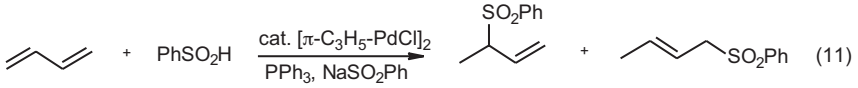
n = 1 95%
n = 2 92%

Equation 8-10

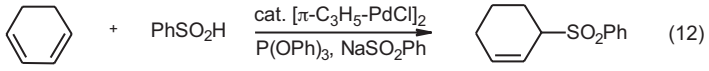
8.2.1.5 **1,4-Hydrosulfonation**

Palladium-catalyzed addition of phenylsulfinic acid to butadiene and isoprene gave mainly 1,2-addition products. From butadiene, 1,2- to 1,4-addition products in a 4:1 ratio were obtained in high yield (Eq. (11)) [28]. It was later shown that the 1,2-addition product is the kinetic product and that prolonged reaction time increased the amount of 1,4-addition product [28b].

1,3-Cyclohexadiene afforded the allylsulfone **15** in 90 % yield in a similar hydrosulfonation reaction (Eq. (12)) [29]. In this case, it was necessary to employ triphe-



Equation 8-11 95% 4 : 1



90%

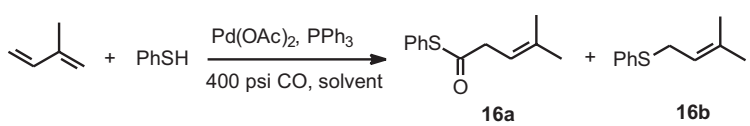
Equation 8-12 **15**

nylphosphite as the ligand, since the use of triphenylphosphine led to a slow reaction and resulted in only a modest yield of **15**.

The use of $PhSO_2Na$ in the palladium(0)-catalyzed ($Pd(PPh_3)_4$) reaction of isoprene in DMF afforded exclusively the 1,4-addition product in 94 % yield [30]. The regioisomer obtained was the 1-phenylsulfonyl-3-methyl-2-butene.

8.2.1.6 1,4-Hydrosulfenation and 1,4-Hydrothiocarbonylation

Palladium-catalyzed reaction of isoprene with thiophenol in the presence of CO gave, depending on the solvent, either a thiocarbonylation product (**16a)** or a product in which a 1,4-addition of sulfur and a hydrogen had occurred (**16b**) [31]. The reaction was optimized for the formation of the thiocarbonylation product (in CH_2Cl_2) to give 1,4-addition products in good yields.

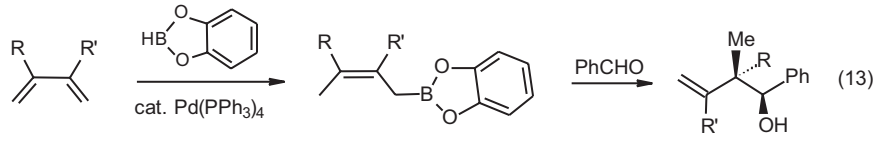


16a **16b**

entry	solvent	time (h)	isolated yield (%) 16a	16b
1	THF	48	27	52
2	CH_3CN	60	0	78
3	Benzene	60	trace	64
4	DME	48	47	18
5	Et_2O	48	64	20
6	CH_2Cl_2	60	83	0

8.2.1.7 1,4-Hydroboration

Palladium-catalyzed hydroboration of acyclic conjugated dienes gave 1,4-addition products with high regioselectivities [32]. Catecholborane reacted with a number of 1,3-dienes in the presence of $Pd(PPh_3)_4$ to give allylic boronates, which were quenched by benzaldehyde to give homoallylic alcohols **17** as single diastereoisomers in each case (Eq. (13)). Isolation of the 1,4-hydroboration adducts from



R=H, R'=H **17a** 81%
R=H, R'=Me **b** 89%
R=R'=Me **c** 81%

Equation 8-13

butadiene and isoprene in 87 and 90% yields was carried out in an independent experiment, and it was shown that the allylic boronates were exclusively (*E*)-configuration. A mechanism according to Scheme 8-1 (Nu = -B(cathecol)) was suggested for the 1,4-hydroboration step.

8.2.1.8 **1,4-Hydrocyanation**

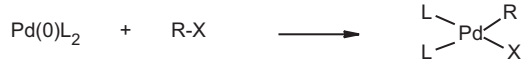
Palladium-catalyzed hydrocyanation of olefins has been reported [33]. However, the corresponding reaction with conjugated dienes have not been explicitly mentioned. The analogous nickel-catalyzed hydrocyanation of conjugated dienes has been described [34], and is the basis for the commercial adiponitrile process. In this case, it has been shown [35] that the overall addition of HCN to the 1,3-diene occurs with *cis* stereoselectivity, consistent with path B in Scheme 8-1.

8.2.2
1,4-Coupling with a Carbanion Equivalent and Another Nucleophile

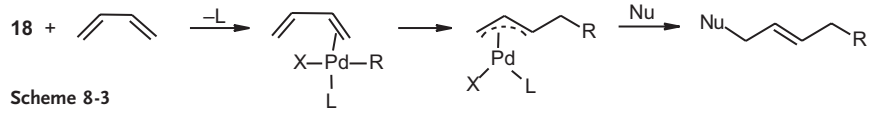
The addition of a nonstabilized carbon nucleophile and another nucleophile to a conjugated diene has similarities to the addition of H-Nu (*cf.* Section 8.2.1). The formation of RPdX (**18**) by oxidative addition of RX and Pd(0) corresponds to the generation of a palladium-hydride species in the H-Nu addition (Scheme 8-3).

Insertion of the diene into the Pd-R bond produces a π-allylpalladium intermediate which reacts with the nucleophile to give the 1,4-addition product. The R group in these reactions is typically an aryl or a vinyl, and the X group in RX is in most cases a halide or a triflate.

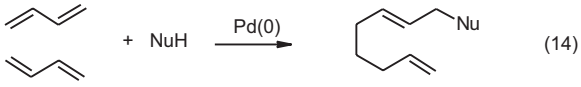
Although 2:1 telomerization reactions can be considered as a special case of 1,4-addition to a conjugated diene by a carbon and a nucleophile (Eq. (14)),



18



Scheme 8-3



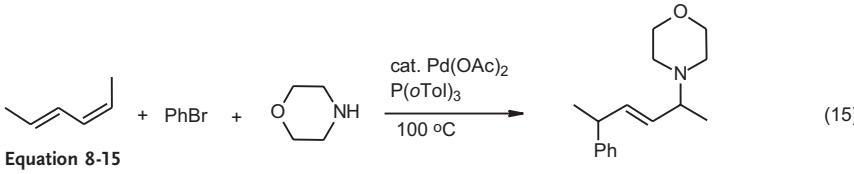
(14)

Equation 8-14

these reactions will not be covered in this chapter, and the reader is advised to consult refs. [8] and [27] for further details on this matter. An intramolecular version of this reaction will be discussed in Section 8.2.2.3.

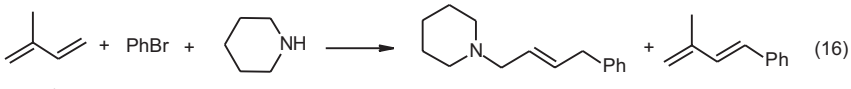
8.2.2.1 **1,4-Carboamination**

The palladium-catalyzed 1,4-addition of a carbon and a nitrogen function to conjugated dienes has been achieved by the use of a free amine to trap the π-allyl intermediate obtained by carbopalladation of the diene (cf. Scheme 8-3) [36, 37]. In these reactions, it is necessary to use phosphines in order to facilitate the nucleophilic attack on the intermediate π-allylpalladium complex. In the absence of phosphine, mainly elimination to diene occurs. It was found that various aryl bromides and amines react with conjugated dienes in the presence of $Pd(OAc)_2$/triarylphosphine (which generates a Pd(0)-phosphine complex in situ [11]) to give 1,4-carboamination products. Morpholine and piperidine gave good results, but the use of diethylamine gave mainly elimination to a diene. A few representative examples are given in Eqs. (15) and (16).



(15)

Equation 8-15

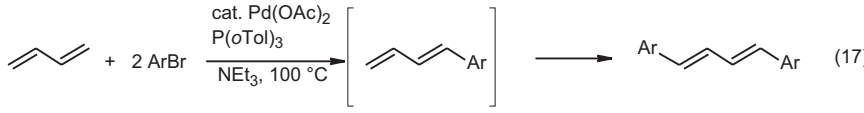


(16)

Equation 8-16

The elimination to a diene is a competing pathway in all these reactions. If triethylamine is employed as the amine, and/or the 1,3-diene has an electron-withdrawing group in the 1-position, then diene formation predominates. For example, (*E*,*E*)-2,4-pentadienoic acid reacted with aryl bromides in the presence of triethylamine and the palladium catalyst to give (*E*,*E*)-5-aryl-2,4-pentadienoic acid in good yield. The propensity for elimination to a diene was later developed into a 1,4-diarylation of 1,3-dienes (Eq. (17)) [38]. This is formally a palladium-catalyzed 1,4-addition of two carbon functions to the 1,3-diene, but it occurs in two steps and can be considered as a two-fold Heck arylation.

The 1,4-carboamination has been extended to the use of vinyl bromides [39–41]. The use of morpholine or piperidine as the external nucleophile led to a 1,4-addi-



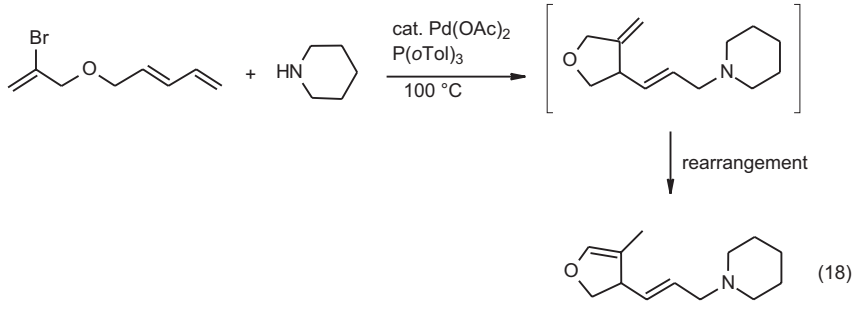
Ar = *p*-Ac-C_6H_4 77%
Ar = *p*-NO_2-C_6H_4 69%

Equation 8-17

tion to the 1,3-diene via a π-allylpalladium intermediate. An example that leads to a carbocyclization via a vinylpalladation is shown in Eq. (18).

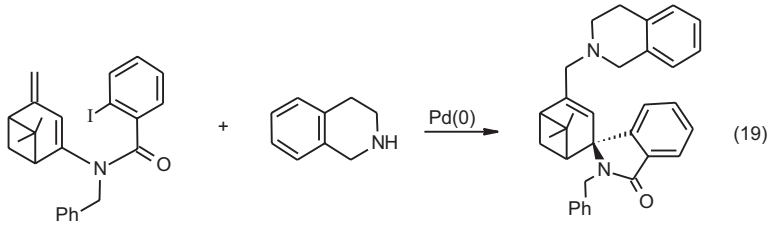
Analogous reactions in which the vinylpalladium is generated from arylpalladation of an acetylene (ArI + Pd(0)), intramolecular insertion of a diene and subsequent amine attack were reported by Xie and Lu [42].

Related palladium-catalyzed 1,4-additions of a carbon and an amine via a carbocyclization of **19** was reported by Grigg et al. (Eq. (19)) [43, 44]. In this case, the spirocyclic compound **20** was formed.



Equation 8-18

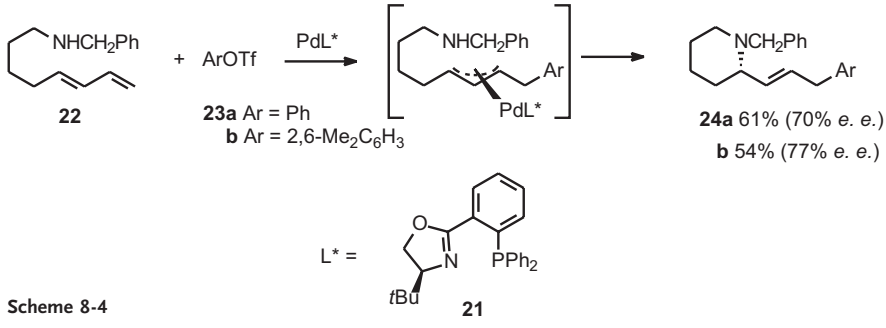
41%



19 **20**

Equation 8-19

The reaction has also been applied in another intramolecular version in which a cyclization occurs in the amination step (Scheme 8-4) [45]. With the use of chiral ligands, an enantioselectivity of up to 80 % *e.e.* was obtained. For example, with ligand **21**, the dieneamine **22** and aryl triflates **23a** and **23b** gave the corresponding products, **24a** and **24b** in 70 and 77 % *e.e.*, respectively.



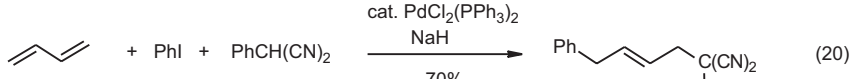
Scheme 8-4

8.2.2.2 1,4-Addition of a Carbon Nucleophile (Aryl or Vinyl) and a Stabilized Carbanion

The use of a stabilized carbanion as an external nucleophile in the arylation or vinylation of conjugated dienes leads to a 1,4-addition of two carbon atoms. This was first demonstrated by Dieck et al. [40] in 1983, who showed that 1-bromo-2-methylpropene and sodium dimethyl malonate reacted with isoprene in the presence of a palladium catalyst to give a 1,4-adduct in moderate yield (22 %).

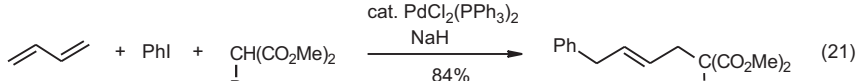
This type of reaction was later studied in more detail using various aryl halides instead of vinyl halides [46]. The reactions were run with 1,3-butadiene employing several different stabilized carbon nucleophiles. Some examples are given in Eqs. (20) and (21).

Cyclization reactions by coupling of an aryl group and a stabilized carbon nucleophile to the 1,4-positions of a diene were reported by Grigg et al. [43]. The reaction proceeds via a spirocyclic π-allyl intermediate. Diethyl malonate and dicyanomethane were used as the stabilized carbanion carbon nucleophiles. In one example, the spirocyclic compound **25** was obtained from **19** in 60 % yield (Eq. (22)).



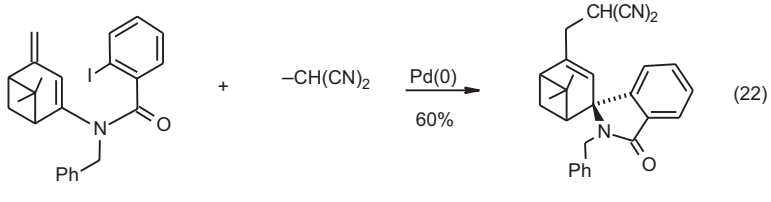
(20)

Equation 8-20



(21)

Equation 8-21



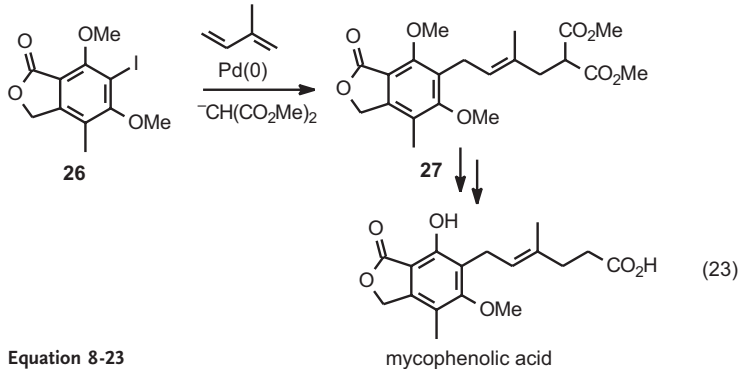
(22)

19 25

Equation 8-22

Mycophenolic acid was synthesized by a three-component coupling between lactone **26**, isoprene and dimethyl malonate (Eq. (23)) [47]. The reaction proceeds by the usual mechanism, with oxidative addition of the aryl halide to Pd(0) and subsequent insertion of isoprene into the Pd-aryl bond to give a π-allyl complex followed by nucleophilic attack by the malonate carbanion. Compound **27** was subsequently transformed to mycophenolic acid.

Related reactions of nonconjugated dienes (e. g., 1,4-dienes) underwent a similar coupling reaction with aryl iodides and stabilized carbon nucleophiles [48]. In these reactions, the initial arylpalladium adduct isomerizes to a π-allylpalladium complex which is attacked by the carbon nucleophile.



(23)

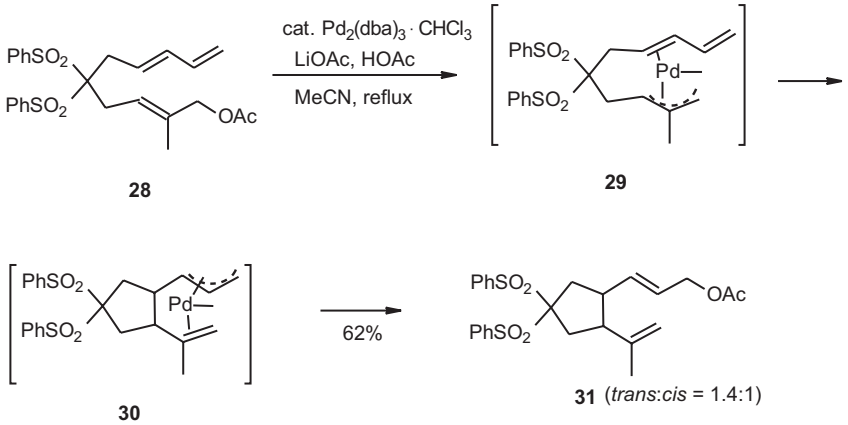
Equation 8-23

8.2.2.3 1,4-Addition of Carbon and Oxygen

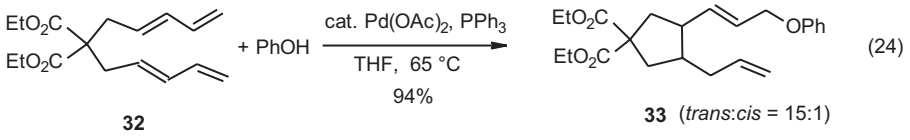
Intramolecular reactions of allylic acetates with conjugated dienes catalyzed by Pd(0) lead to a 1,4-addition of a carbon and an oxygen to the diene. The reaction, which is formally an isomerization, involves two different π-allyl complexes (Scheme 8-5) [49]. Reaction of **28** in the presence of the Pd(0) catalyst $Pd_2(dba)_3 \cdot CHCl3$ (dba = dibenzylidenacetone) and LiOAc/HOAc in acetonitrile under reflux produces the cyclized isomer **31** in 62 % yield. The double bond had exclusively (*E*)-configuration, while the configuration on the ring was a mixture of *cis* and *trans*. Oxidative addition of the allylic acetate to the Pd(0) species gives the intermediate π-allyl complex **29**. Subsequent insertion of a diene double bond into the allyl-palladium bond produces another π-allyl intermediate **30**, which is subsequently attacked by acetate to give the product **31**.

In a related reaction, tetraenes **32** underwent carbocyclization to give allylic ethers **33** (Eq. (**24**)) [50]. The reaction can be considered as an intramolecular telomerization reaction, and leads to the 1,4-addition of a carbon and an oxygen nucleophile to one of the dienes. The reaction involves a π-allyl intermediate, which is subsequently attacked by the oxygen nucleophile.

The use of the terminally hydroxy-substituted tetraene substrate **34** in this reaction made it possible to determine the stereochemistry of the overall 1,4-addition of the carbon and oxygen functions to the diene (Eq. (24)) [51]. Palladium-catalyzed reaction of **34** in THF under reflux afforded product **36** in which a net *anti*



Scheme 8-5



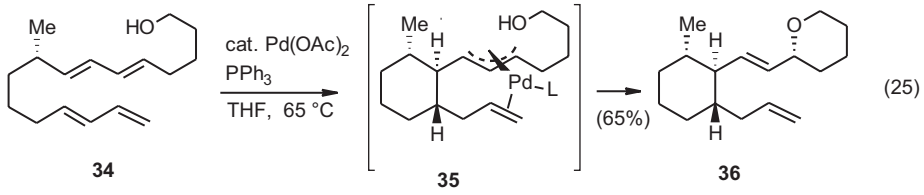
Equation 8-24

1,4-addition had occurred. The stereochemistry was consistent with an intermediate π-allyl complex **35**, in which carbon and palladium have added to the upper diene in a *syn* fashion. Intramolecular attack by the hydroxy group from the face opposite to that of palladium would give the product observed. In this reaction, an interesting 1,2-stereoinduction by the methyl group occurred.

In a reaction similar to those detailed in Eqs. (19) and (22), Grigg et al. [43, 44] also employed lithium acetate as an oxygen nucleophile in place of the amine and stabilized carbon nucleophile, respectively, as presented in these equations. This led to a 1,4-addition of carbon and oxygen to the conjugated diene.

Palladium(0)-catalyzed reactions of allenic dienes **37** in acetic acid afforded allylic acetates **38** (Scheme 8-6) [52]. This reaction is reminiscent of telomerizations, and a mechanism via a palladacycle rearranging to a π-allyl complex was inferred as being likely. A pathway via a palladium hydride can, however, not be excluded.

Larock et al. [53] have studied the palladium-catalyzed arylation of 1,3-dienes followed by intramolecular attack by an oxygen nucleophile. *o*-Iodophenols and *o*-iodobenzyl alcohol were used as substrates. These reactions, which essentially are annelation reactions, lead to a 1,2-addition to the conjugated dienes, and will not be discussed further here. Amides were also used as nucleophiles in these reactions.



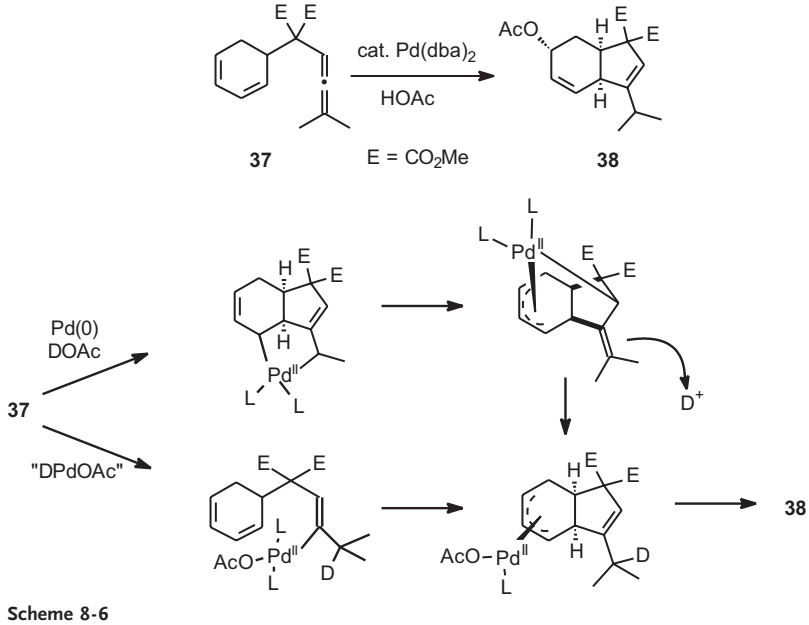
34 35 36

Equation 8-25

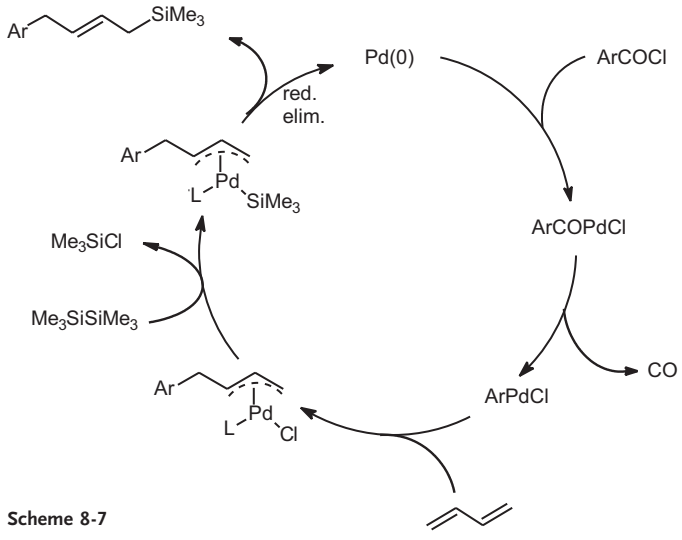
8.2.2.4 **1,4-Carbosilylation**

In the previous section, the hydrosilylation of conjugated dienes was discussed. The analogous 1,4-addition of a carbon and silicon unit instead of a hydrogen and silicon was developed using an acid chloride and an organodisilane in a Pd(0)-catalyzed reaction [54]. The acid chloride undergoes a decarbonylation, and this results in an overall 1,4-addition of the remaining carbon unit and silicon to the conjugated diene. Three different dienes, 1,3-butadiene, isoprene and 2,3-dimethylbutadiene were employed. Some examples are given in Eqs. (26)–(28), and the proposed mechanism is shown in Scheme 8-7. Attempts to use an aryl iodide as a direct source for the arylpalladation intermediate gave poor results; for example, iodobenzene gave only 8 % yield with butadiene and $Me_3SiSiMe_3$. The corresponding reaction with bromobenzene furnished 40 % of the desired 1,4-addition product.

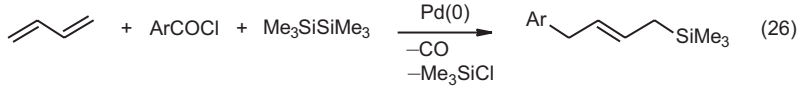
In the proposed mechanism, the ArPdCl generated by decarbonylation of the σ-acylpalladium complex reacts with the diene to give a π-allylpalladium inter-



Scheme 8-6



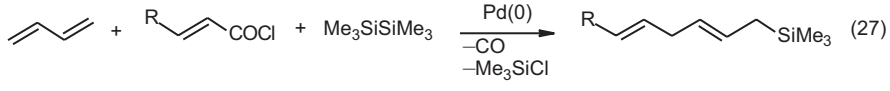
Scheme 8-7



(26)

Ar	%	Ar	%
Ph	86	p-$NO_2C_6H_4$	51
p-MeC_6H_4	77	p-AcC_6H_4	92
p-$ClCC_6H_4$	80	a-naphthyl	95

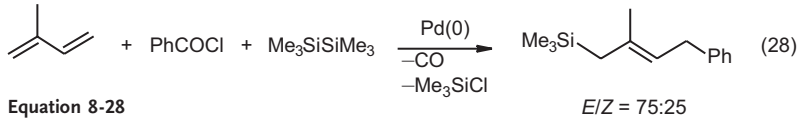
Equation 8-26



(27)

R	%
Ph	94
cHex	78
n-C_6H_{13}	72

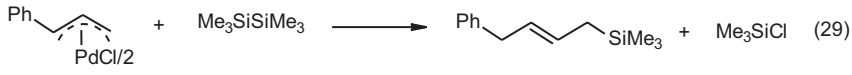
Equation 8-27



(28)

E/*Z* = 75:25

Equation 8-28



39

Equation 8-29

mediate. Reaction of this intermediate with the disilane replaces the chloride by trimethylsilane, and subsequent reductive elimination gives the product. In mechanistic studies, the chlorodimer **39** corresponding to the π-allylpalladium chloride intermediate in Scheme 8-7 was prepared and allowed to react with $Me_3SiSiMe_3$. This led to Me_3SiCl (characterized by ^{29}Si NMR) and 1-phenyl-4-trimethylsilyl-2-butene (Eq. (29)).

It was also demonstrated that organosilylstannanes can be used as the trimethylsilyl anion source. In this case, the acid chlorides gave poor results and it was found that aryl iodides were suitable substrates. Reaction of 1,3-butadiene with PhI and $Bu_3SnSiMe_3$ gave the 1,4-carbosilylation product in 50 % yield as an *E*/*Z* mixture of 84:16. The use of phenyl triflate as the aryl source did not give the desired 1,4-addition product, but afforded the 2:1 telomerization product from two molecules of diene and one trimethylsilyl group in good yield.

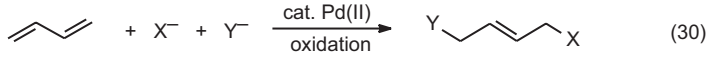
8.3 Palladium(II)-Catalyzed Reactions

Palladium(II)-catalyzed 1,4-additions to conjugated dienes also involve the formation of a π-allylpalladium intermediate. All known reactions of this type are oxidation reactions.

8.3.1 1,4-Addition of Two Nucleophiles

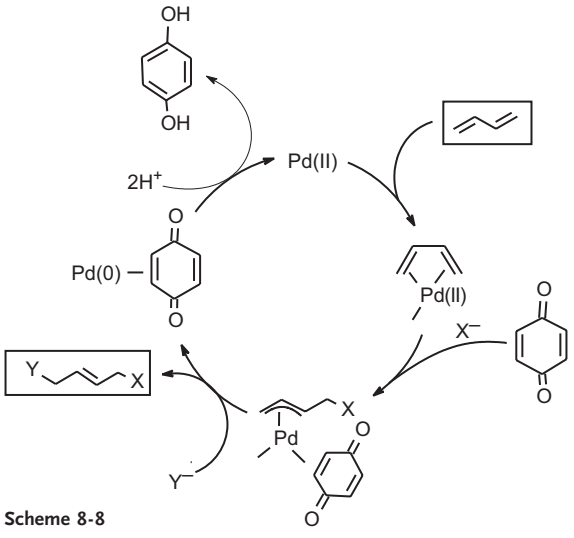
The 1,4-addition of two nucleophiles to 1,3-dienes is an oxidation reaction, and involves nucleophilic attacks on π-diene- and π-allyl-palladium complexes. The principle and mechanism of this reaction are given in Eq. (30) and Scheme 8-8, and the reaction is exemplified with *p*-benzoquinone as the oxidant.

The nucleophilic attack on the π-diene complex occurs in the 1-position of the diene, and produces a π-allylpalladium complex. The second nucleophile then attacks the π-allylpalladium intermediate in a regio- and stereoselective manner to produce the 1,4-oxidation product and Pd(0). Coordination of *p*-benzoquinone



X = OAc,O_2CR, OR
Y = Cl, OAc, O_2CR, OR

Equation 8-30



Scheme 8-8

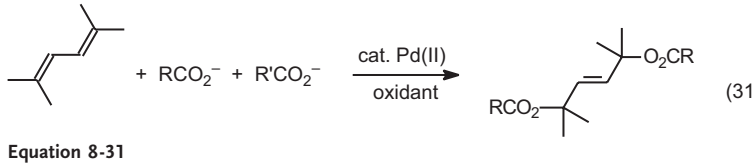
to palladium in the π-allylpalladium intermediate induces the nucleophilic attack. The Pd(0)-benzoquinone formed in the process undergoes an intramolecular redox reaction to give Pd(II) and hydroquinone. Depending on the nature of the nucleophile, the second attack may occur either in a *trans*-mode by a free nucleophile, or in a *cis*-fashion by a coordinated nucleophile. Different oxidants have been tried in an attempt to obtain catalytic conversions, though 1,4-benzoquinones have been mostly used as they are associated with high stereo- and regioselectivity. Another advantage with benzoquinone as the oxidant is that the corresponding hydroquinone obtained can be reoxidized by air or molecular oxygen (*vide infra*). In the latter case, the quinone is used in catalytic amounts only. The principles for such aerobic oxidations are discussed below.

8.3.1.1 1,4-Diacyloxylation

In the 1,4-diacyloxylation, two carboxylate anions are added in a 1,4-fashion to a conjugated diene in an oxidative process involving the removal of two electrons. The catalyst employed is a palladium(II) salt, usually $Pd(OAc)_2$. The 1,4-diacyloxylation may be an intermolecular or an intramolecular process. In the latter case the result is a lactonization. In most cases the stereochemistry of the 1,4-addition of the two carboxylates to the 1,3-diene can be controlled to give either a 1,4-*cis* or 1,4-*trans* adduct.

Intermolecular 1,4-diacyloxylation

In the intermolecular 1,4-diacylaoxylation, two carboxylate anions react with the diene in the presence of a palladium(II) catalyst and an oxidant, according to Eq. (31).



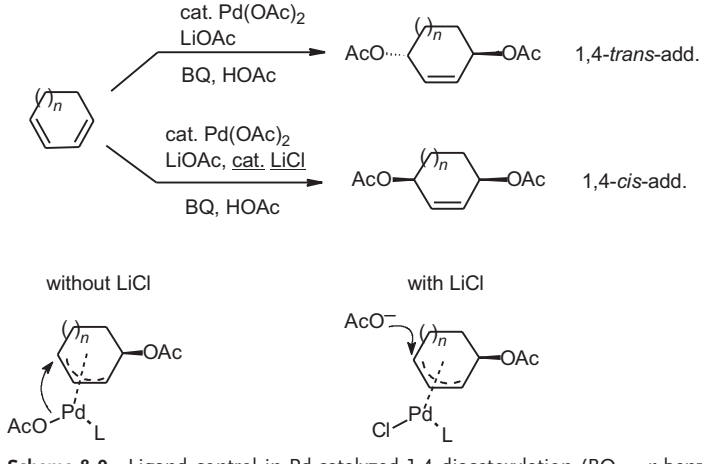
(31)

Equation 8-31

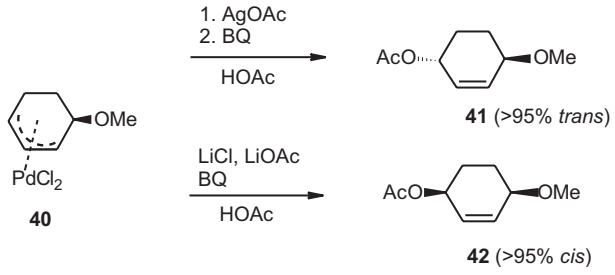
One example of such a reaction was reported in 1971 by Brown and Davidson [55], who studied oxidation reactions of 1,3- and 1,4-cyclohexadiene. These authors observed that reaction of 1,3-cyclohexadiene with *p*-benzoquinone in acetic acid in the presence of catalytic amounts of $Pd(OAc)_2$ produced 1,4-diacetoxy-2-cyclohexene of unknown configuration. At the time, Brown and Davidson were uncertain about the mechanism, and suggested possible involvement of radicals. A related palladium-catalyzed 1,4-diacetoxylation of butadiene employing O_2 as an oxidant and a heterogeneous Pd-Te catalyst has been developed and commercialized by Mitsubishi Chemicals [56].

In 1981, a stereoselective palladium-catalyzed 1,4-diacetoxylation of conjugated dienes was reported [57–59]. By ligand control, it was possible to direct the reaction to either 1,4-*trans*- or 1,4-*cis*-diacetoxylation (Scheme 8-9).

The crucial ligand which dramatically changes the stereochemical outcome of the reaction is Cl^-. Thus, in the absence of chloride ligands, a 1,4-*trans*-diacetoxylation occurs, whereas in the presence of a catalytic amount of chloride ions a 1,4-*cis*-diacetoxylation takes place. An explanation of these results is that, in the absence of chloride ions, the counterion to palladium is acetate, which can migrate from the metal to carbon. Addition of lithium chloride, even in catalytic amounts, results in displacement of the acetate on palladium by chloride due to the very strong palladium chloride bond. In this case only external *trans*-attack by the acetate will be possible. This mechanism has been confirmed by mechanistic studies on isolated π-allylpalladium complexes [60]. Thus, it was found that treatment of complex **40**



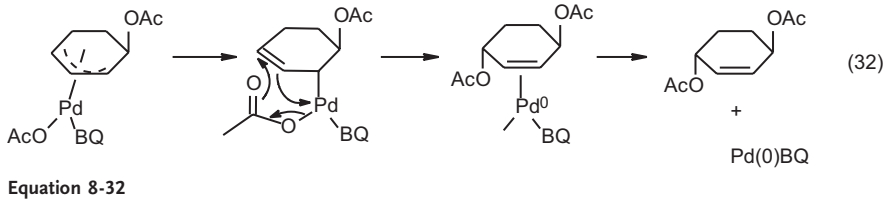
Scheme 8-9 Ligand control in Pd-catalyzed 1,4-diacetoxylation (BQ = *p*-benzoquinone).



Scheme 8-10 Stereocontrolled acetate attack on π-allylpalladium complexes.

with silver acetate and subsequent reaction with *p*-benzoquinone (BQ) in acetic acid afforded allylic acetate **41** with *trans*-configuration via a *cis*-migration (Scheme 8-10). Treatment of complex **40** with BQ in acetic acid gave the *cis* product **42** by external *trans*-attack.

The migration of acetate from palladium to carbon most likely proceeds via a σ-allylpalladium complex (Eq. (32)) [57b, 61]. In such a process, it is not the oxygen coordinated to palladium that attacks the allyl carbon, but rather the carbonyl oxygen [60]. A migration reaction of this type is most likely a frontier orbital-controlled process, and this requires a reasonably high energy of the filled orbital that interacts with the π^* of the π-system of the ring [62]. The filled orbital of the carbonyl oxygen has a much higher energy than the orbital of the palladium-oxygen bond [60, 62, 63]. Thus, attack by the oxygen coordinated to palladium is unlikely.

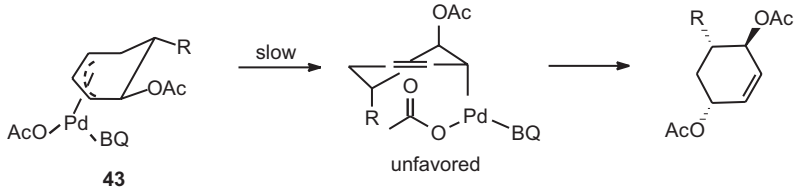


(32)

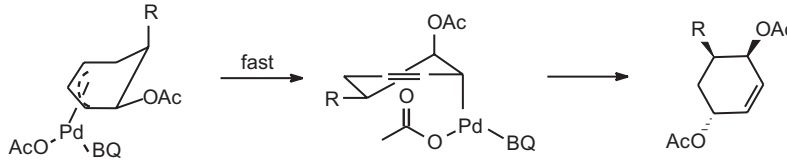
Equation 8-32

The σ-allyl mechanism was supported by the fact that the π-allyl complex **43** is quite unreactive with respect to *cis*-migration, whereas complex **44** reacts rapidly in the same process (Scheme 8-11) [61]. The low reactivity of the π-allyl complex **43** can be explained by the unfavored conversion of this isomer to its σ-allyl complex because of the change of the substituent R from an equatorial to an axial position. For complex **44**, on the other hand, formation of the σ-allyl complex should be facile because the R group will become equatorial in this complex.

A number of dienes undergo the 1,4-diacetoxylation. For example, 6-, 7-, and 8-membered rings work well, but cyclopentadiene gave a moderate yield of diacetoxylation product due to competing Diels-Alder reaction between cyclopentadiene and *p*-benzoquinone. For 6-substituted 1,3-cycloheptadienes, a high diastereoselec-



43

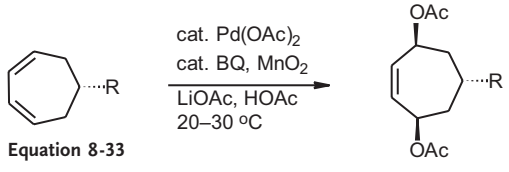


44

Scheme 8-11

tivity was obtained with the two acetates adding *anti* with respect to the 6-substituent (Eq. (33)) [57b].

Although acyclic dienes in general gave lower yields than the cyclic ones, the 1,4-stereocontrol obtained for internal conjugated dienes is of synthetic interest. For example, (*E,E*)- and (*E,Z*)-2,4-hexadiene was stereoselectively transformed to the *d,l*- and *meso*-1,4-diacetate, respectively (*vide infra*).

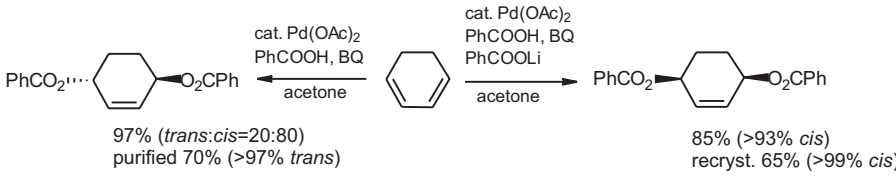


(33)

Equation 8-33

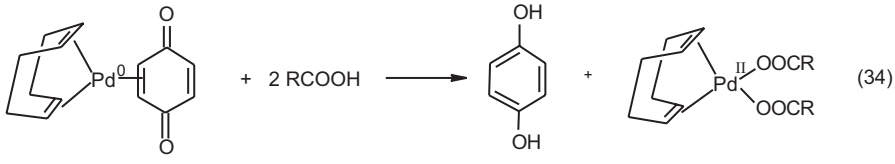
The reaction was also performed in acetone in the presence of 5–10 equivalents of a carboxylic acid [58]. In this way, solid carboxylic acids can be used. A number of different dicarboxylates were prepared in this manner from acetic acid, trifluoroacetic acid, pivalic acid, and benzoic acid. An example where the *cis*- and *trans*-1,4-dibenzoates from 1,3-cyclohexadiene was obtained stereoselectively is shown in Scheme 8-12.

The catalytic cycle of the palladium-catalyzed diacyloxylation follows the cycle depicted in Scheme 8-8 ($X^- = RCOO^-$, $Y^- = R'COO^-$). The coordination of a quinone in the π-allylpalladium intermediate was demonstrated by NMR studies,



Scheme 8-12

including T1 measurements [64]. Attack by the second nucleophile results in the formation of the 1,4-addition product and a palladium(0)-benzoquinone complex. In an independent mechanistic study it was shown that such Pd(0)-benzoquinone complexes, which are stable under neutral conditions (pH 7), react with weak acids to give hydroquinone and the palladium(II) salt of the acid (Eq. (34)) [65].

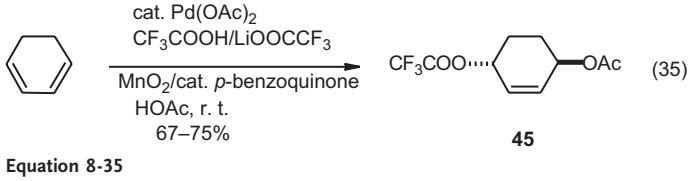


(34)

Equation 8-34

In the catalytic cycle of the palladium-benzoquinone-based 1,4-oxidation of 1,3-dienes, benzoquinone is reduced to hydroquinone. The diacetoxylation reaction is conveniently performed with *p*-benzoquinone in catalytic amounts employing MnO_2 as the stoichiometric oxidant. In this process, the hydroquinone formed in each cycle (*cf.* Scheme 8-8) is reoxidized to *p*-benzoquinone by MnO_2. For example, the catalytic reaction of 1,3-cyclohexadiene using catalytic amounts of both $Pd(OAc)_2$ and *p*-benzoquinone with stoichiometric amounts of MnO_2 in acetic acid in the presence of lithium acetate afforded a 93% yield of *trans*-1,4-diacetoxy-2-cyclohexene (>91% *trans*) [57]. The corresponding reaction in the presence of lithium chloride gave *cis*-1,4-diacetoxy-2-cyclohexene in 79% yield (>96% *cis*).

A 1,4-acetoxytrifluoroacetoxylation of 1,3-dienes was achieved in the presence of trifluoroacetic acid and lithium trifluoroacetate [66]. For cyclic dienes the relative yield of unsymmetrical 1,4-addition product is high (94–95% or better). For example, palladium-catalyzed oxidation of 1,3-cyclohexadiene under these conditions gave **45** in 67–75% yield (Eq. (35)). The reaction was recently improved and also extended to 1,4-alkoxy-trifluoroacetoxylation [60b].

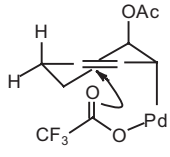


(35)

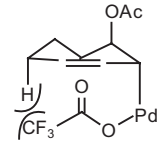
45

Equation 8-35

The reaction proceeds via the same *trans*-4-acetoxy-(η^3-(1,2,3)-cyclohexenyl)palladium complex (**46**) as that involved in the 1,4-diacetoxylation (*cf.* Scheme 8-9). The reaction is performed under conditions favoring *cis*-migration from palladium to carbon in the π-allylpalladium intermediate (absence of strongly coordinating ligands such as Cl^-). At this low pH, the only counterion to palladium will be trifluoroacetate (acetate anions will be protonated by the trifluoroacetic acid). As a consequence, the migrating carboxylate will be trifluoroacetate, which explains the formation of the unsymmetrical product. The migration via the σ-allyl complex is depicted in Figure 8-1. In the seven-membered ring (**47**), a *cis*-migration is unfavored due to steric interactions between the allylic pseudoaxial proton and the CF_3 group in the σ-allyl complex. Accordingly, 1,3-cycloheptadiene did not give the *trans*-adduct under the conditions used for the six-membered ring (*cf.* Eq. (35)), but afforded 58 % *cis*-1-acetoxy-4-trifluoroacetoxy-2-cycloheptene (>96 % *cis*) via external attack by CF3COO$^-$.



46
migration facile

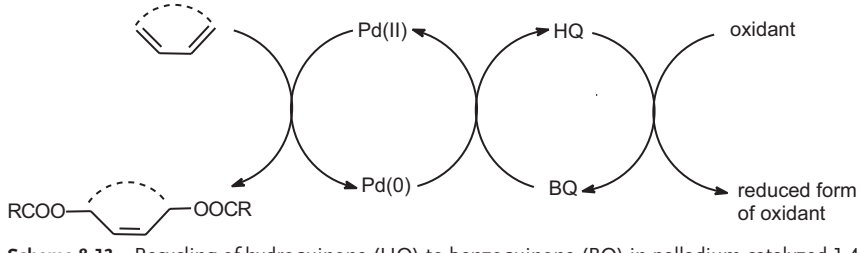


47
migration unfavored

Figure 8-1 Migration of trifluoroacetate in σ-allylpalladium complexes.

The use of *p*-benzoquinone (BQ) in catalytic amounts (as mentioned above), together with a stoichiometric oxidant, makes the 1,4-diacyloxylation more synthetically useful. The principle of the reaction is shown in Scheme 8-13.

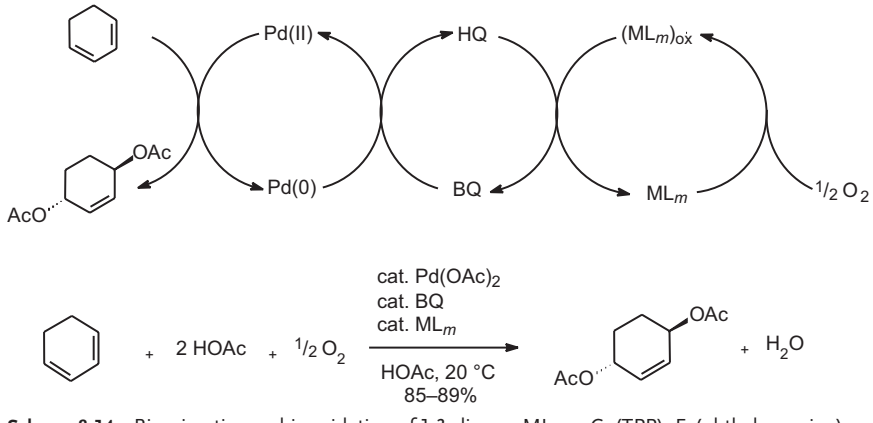
In one procedure, as mentioned above, MnO_2 was employed as the oxidant to reoxidize the hydroquinone to benzoquinone. In another study, it was shown that the hydroquinone can be recycled electrochemicallly by anodic oxidation [67]. The reaction is carried out in acetic acid with $LiClO_4$ as electrolyte with catalytic amounts of both $Pd(OAc)_2$ and *p*-benzoquinone employing a membrane-separated cell.



Scheme 8-13 Recycling of hydroquinone (HQ) to benzoquinone (BQ) in palladium-catalyzed 1,4-oxidation of 1,3-dienes.

A reoxidation of the catalytic amounts of hydroquinone (HQ) to benzoquinone (BQ) in Scheme 8-13 by molecular oxygen was realized by the use of an oxygen-activating metal macrocyclic complex as co-catalyst [59, 68–71]. This leads to a mild biomimetic aerobic oxidation which is now based on a triple catalytic system (Scheme 8-14). With this system, 1,3-cyclohexadiene is oxidized to *trans*-1,4-diacetoxy-2-cyclohexene at room temperature in 85–89 % yield (>91 % *trans*) [68]. With the use of 2-phenylsulfonyl-1,4-benzoquinone as quinone, the *trans*-selectivity of this process was >97 % [59].

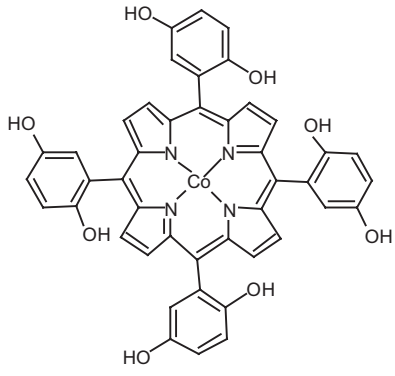
The success of this triple catalytic system relies on a highly selective kinetic control. From a thermodynamic point of view, there are ten possible redox reactions that could occur in this system. However, the energy barrier for six of these (O_2 + diene, O_2 + Pd(0), etc.) are too high, and only the kinetically favored redox reactions shown in Scheme 8-14 occur. A likely explanation for this kinetic control is that the barrier is significantly lowered by coordination. Thus, diene coordinates to Pd(II), BQ coordinates to Pd(0), HQ coordinates to $(ML_m)_{ox}$, and O_2 coordinates to ML_m. In a related system for aerobic oxidation, a heteropolyacid was employed in place of the metal macrocyclic complex (ML_m) as oxygen activator and electron transfer mediator [72]. Recent immobilization of the macrocylic complex in Zeolite-Y, led to efficient reoxidation of the hydroquinone in the palladium-catalyzed 1,4-diacetoxylation [73].



Scheme 8-14 Biomimetic aerobic oxidation of 1,3-dienes; ML_m = Co(TPP), Fe(phthalocyanine) or Co(salophene) [68a].

By building the quinone molecule into the macrocycle, a more efficient palladium-catalyzed aerobic 1,4-oxidation was developed [69]. Thus, with catalytic amounts of **48** and $Pd(OAc)_2$, 1,3-cyclohexadiene was oxidized to 1,4-diacetoxy-2-cyclohexene at more than twice the rate achieved with a system having quinone and porphyrin as separate molecules. The *trans* selectivity with quinone-porphyrin **48**, however, was moderate (*trans*/*cis* = 70/30).

The low *trans*-selectivity and increased propensity for 1,4-*cis*-addition is thought to arise from a direct interaction with the metal-porphyrin peroxo complex similar



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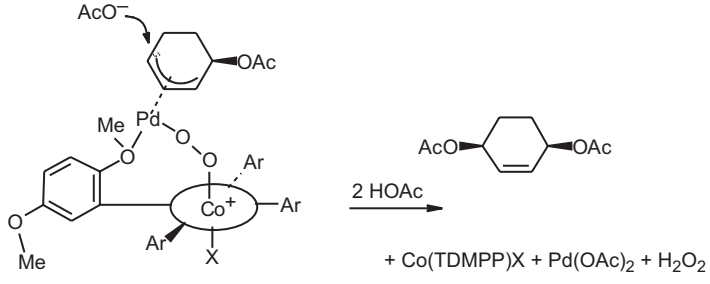


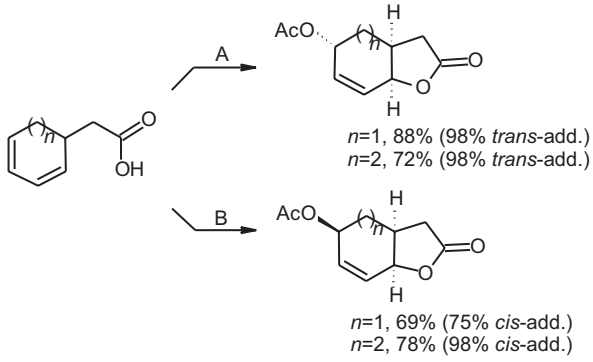
Scheme 8-15

to that suggested for the 2,5-dimethoxyphenyl derivatives shown below (Scheme 8-15). It was shown that the 2,5-dimethoxyphenyl derivative worked in the aerobic oxidation, even without *p*-benzoquinone being present [70]. Interestingly, in this case the 1,4-*cis*-addition product predominates. It was proposed that the π-allylpalladium complex is activated as shown in Scheme 8-15.

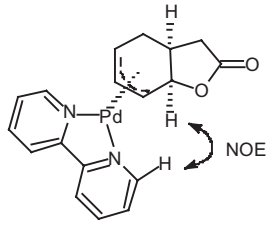
An asymmetric catalytic 1,4-diacetoxylation was achieved by the use of a chiral benzoquinone as a ligand [74].

Intramolecular 1,4-diacyloxylation

An intramolecular variant of the palladium-catalyzed 1,4-diacetoxylation was developed by utilizing dienes with a carboxyl group in the side chain (Scheme 8-16) [75, 76]. Also in this case the stereochemistry of the 1,4-addition can be controlled by variation of the ligand environment. Thus, in the absence of chloride a *trans*-acetoxylactonization takes place, whereas in the presence of a catalytic amount of chloride a *cis*-acetoxylactonization occurs. The catalytic intermediate was isolated and stereochemically assigned as its bipyridyl complex **49** [76]. In the stereochemical assignment, bipyridyl was utilized as a reporter ligand. An NOE between the bridgehead proton and the α-proton of the bipyridyl ligand confirmed the configuration assigned (i. e., palladium *trans* to oxygen).



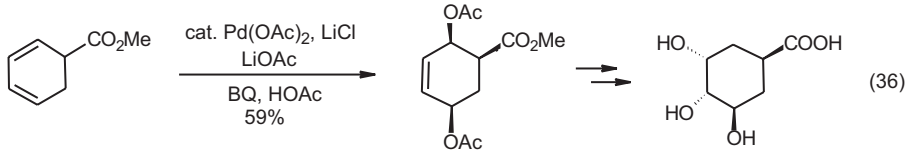
Scheme 8-16 Stereocontrolled oxylactonization. A: cat. $Pd(OAc)_2$, BQ, HOAc. B: cat. $Pd(OAc)_2$, BQ, LiOAc, cat. LiCl.



49

Synthetic applications

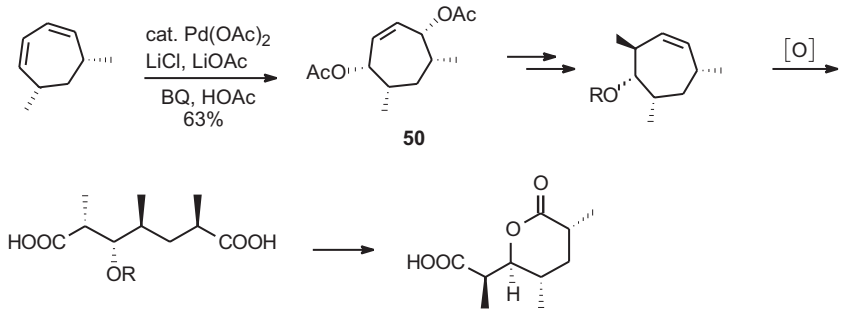
The stereocontrol associated with the palladium-catalyzed 1,4-diacetoxylation is useful in synthetic applications. An example is the *cis*-1,4-diacetoxylation of 5-carbomethxy-1,3-cyclohexadiene and subsequent transformation of the diacetate to shikimic acid (Eq. (36)) [57b].



Equation 8-36 Shikimik acid

In a synthesis of the Prelog-Djerassi lactone, a highly diastereoselective 1,4-diacetoxylation afforded intermediate **50** (Scheme 8-17) [77]. Subsequent transformations which include dimethylcuprate addition, oxidative cleavage of the double bond and lactonization afforded the target molecule.

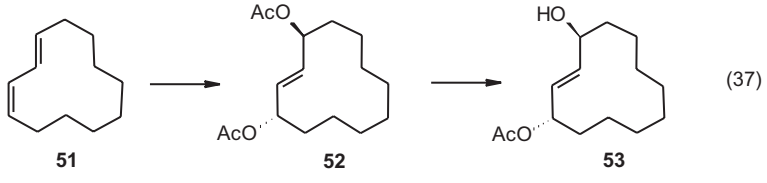
Palladium-catalyzed 1,4-diacetoxylation of diene **51** under chloride-free conditions stereoselectively afforded diacetate **52**, which was transformed into monoace-



Scheme 8-17 Prelog-Djerassi lactone

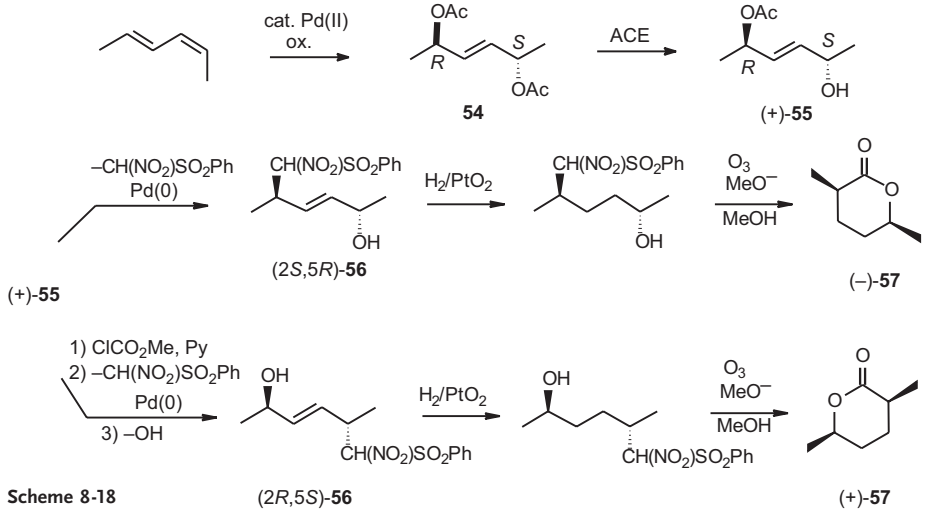
tate **53** (Eq. (37)) [78]. The latter compound was used in a ruthenium-catalyzed transformation.

Meso diacetates obtained from 1,4-diacetoxylation of conjugated dienes have been used for enzyme hydrolysis in enantioselective transformations [79–85]. In an application towards the carpenter bee pheromone (Scheme 8-18) [79], the *meso*-diacetate **54**, obtained from stereoselective 1,4-diacetoxylation of (*E,Z*)-2,4-hexadiene,

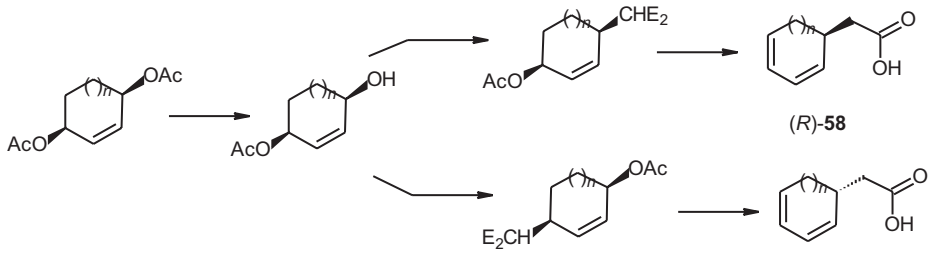


51 **52** **53** (37)

Equation 8-37



Scheme 8-18 (2*R*,5*S*)-**56** (+)-**57**



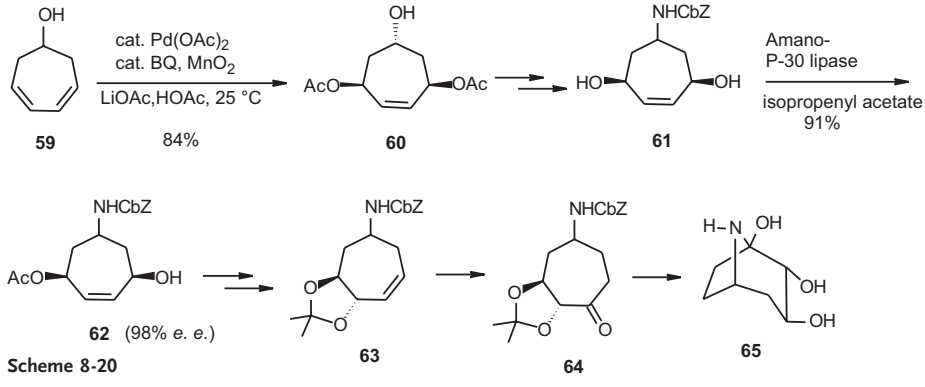
Scheme 8-19 E = CO_2Me.

was enzymatically hydrolyzed to hydroxyacetate **55** with 92 % *e. e.*. By taking advantage of the different reactivities of allylic leaving groups in Pd(0)-catalyzed allylic couplings, both enantiomers of *cis*-2-methylhexanolide (**57**) were obtained along an enantiodivergent route. The anion of (phenylsulfonyl)nitromethane was employed as nucleophile in the Pd(0)-catalyzed allylic substitution reactions, and served as a carboxy anion equivalent. Reaction of the hydroxyacetate (+)-**55** gave (2*S*,5*R*)-**56**, whereas reaction of the carbonate of the same hydroxyacetate and subsequent hydrolysis afforded (2*R*,5*S*)-**56**. The two enantiomers were subsequently transformed into lactones (–)-**57** and (+)-**57**, respectively.

In a similar manner the diacetates from cyclic dienes were enzymatically hydrolyzed and transformed to the enantiomers of cycloalkadienyl acetic acids (*R*)- and (*S*)-**58** (Scheme 8-19) [80]. The cycloheptadienylacetic acids from the cyclohexenyl diacetate were subsequently used in intramolecular *cis*- and *trans*-1,4-acetoxylactonization (*cf.* Scheme 8-16), leading to four different isomers of enantiomerically pure lactones.

The enantiomerically pure monoacetate ($n = 1$) of Scheme 8-19 was employed in combination with palladium-catalyzed reaction for enantiodivergent synthesis of *cis*- and *trans*-4-amino-2-cyclohexenol [81].

Synthesis of six-membered ring prostanoids via the diacetate ($n = 1$) and the enantiomerically pure monoacetate ($n = 1$) of Scheme 8-19 has been reported [82].

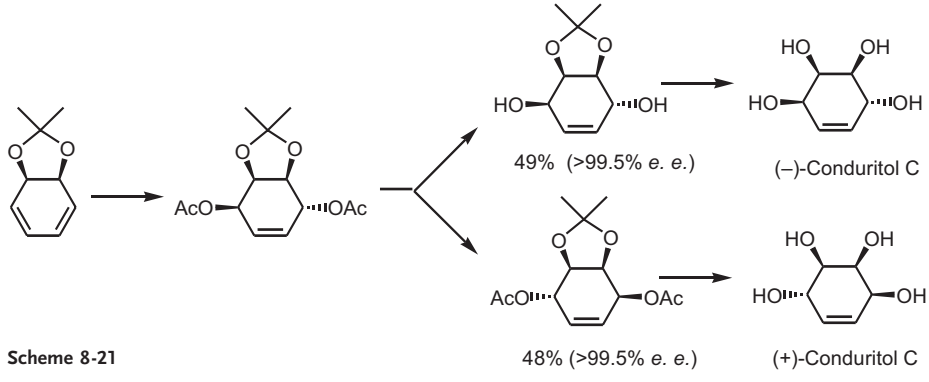


Scheme 8-20

In a synthesis of tropane alkaloids **65**, the strategy started with diastereoselective 1,4-diacetoxylation of diene **59** (Scheme 8-20) [83]. The diacetate **60** obtained was converted to diol **61** and subjected to an enzymatic transesterification to give hydroxyacetate **62** with 98 % *e. e.*. Hydroxyacetate **62** was transformed into acetal **63**, by a selenium-based [2, 3]-sigmatropic rearrangement. The acetal **63** was transformed into the target tropane alkaloid **65** via ketone **64**. By changing the reactivity of the allylic oxygen functions in the enantiomerically pure monoacetate **62**, the enantiomer of **65** was also obtained.

A short synthesis of Conduritol C was achieved utilizing the diacetoxylation reaction (Scheme 8-21). In this way, racemic Conduritol C was obtained, which was transformed via enzymatic kinetic resolution into enantiomerically pure (–)-Conduritol C (49 %, >99.5 % *e. e.*) and (+)-Conduritol C (48 %, >99.5 % *e. e.*) [86].

Additional examples on the use of the palladium-catalyzed 1,4-diacetoxylation including enzymatic transformations can be found in refs. [84, 85, 87, 88].



Scheme 8-21

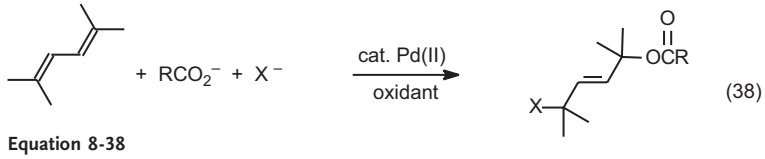
8.3.1.2 **1,4-Haloacyloxylation**

Palladium-catalyzed reactions of conjugated dienes in the presence of a halide anion can be controlled to selectively give 1-acyloxy-4-halo-2-alkene under appropriate reaction conditions. The catalyst for this system is a palladium(II) salt, usually $Pd(OAc)_2$ or Li_2PdCl_4. The reaction may be either intermolecular or intramolecular. In most cases, this transformation is stereoselective and provides a 1,4-*cis*-adduct of the diene. The products obtained from these reactions are useful synthetic intermediates since they have two allylic leaving groups with a large difference in reactivity (*vide infra* Section 8.3.1.2.3).

Intermolecular 1,4-haloacyloxylation

In intermolecular 1,4-haloacyloxylation, a carboxylate anion and a halide anion (X^-) are added to a conjugated diene in the presence of a palladium(II) catalyst and an oxidant (Eq. (38)).

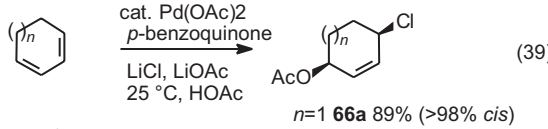
The reaction conditions are similar to those employed in the diacetoxylation reaction, the difference being that the halide concentration (usually Cl^-) has



(38)

Equation 8-38

been increased. Thus, palladium-catalyzed oxidation of 1,3-dienes with *p*-benzoquinone in the presence of lithium chloride and lithium acetate gives 1-acetoxy-4-chloro-2-alkenes [89]. For example, 1,3-cyclohexadiene and 1,3-cycloheptadiene afforded the corresponding chloroacetates **66a** and **66b** in good yields and with >98 % *cis*-selectivity (Eq. (39)). 1,3-Cyclooctadiene gave a 61 % yield of acetoxychlorination product (>98 % *cis*), but in this case a 3:1 mixture of 1,4- and 1,2-addition products was formed. A number of substituted cyclic conjugated dienes were found to work well, and in all cases tried the reaction proceeded with >97–98 % *cis*-addition [58, 89–92].

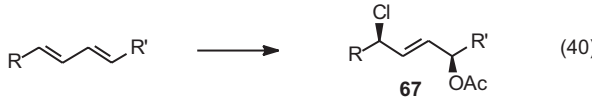


(39)

n=1 **66a** 89% (>98% *cis*)
n=2 **66b** 74% (>98% *cis*)

Equation 8-39

Acyclic dienes also afforded a regioselective 1,4-acetoxychlorination. For dialkyl-substituted dienes the reaction was stereoselective and gave exclusively the (*E*)-1,4-*syn*-addition product (Eq. (40)) [89, 93, 94]. Thus, (*E,E*)-2,4-hexadiene gave the (*R*,R**)-diastereoisomer, whereas (*E,Z*)-2,4-hexadiene afforded the (*R*,S**)-diastereoisomer [89, 91].



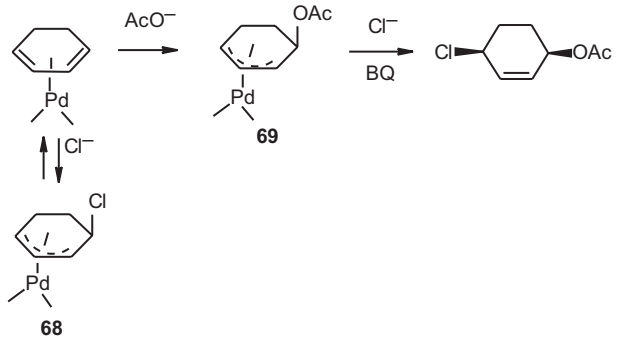
(40)

67

R and R' = alkyl groups >99% *E*, >95% *syn* adduct
R or R' = H 90–95% *E*

Equation 8-40

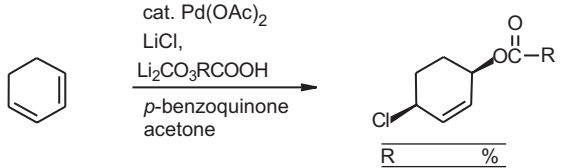
The chloroacetoxylation proceeds via the same type of intermediate as that involved in the palladium-catalyzed 1,4-diacetoxylation; that is, via a 4-acetoxy-1,2,3-π-allylpalladium intermediate (*cf.* Scheme 8-9). The high selectivity for unsymmetrical product (usually >98 %) is remarkable. Since chloride anion is the strongest nucleophile of the two present (Cl^- and AcO^-), 4-chloro-π-allyl-palladium intermediate **68** is initially formed (Scheme 8-22). However, the chloride in the



Scheme 8-22

4-position is rapidly exchanged for acetate to give a more stable π-allyl intermediate **69**, which leads to product. The presence of intermediate **68** was confirmed by its trapping by a faster oxidant (isoamyl nitrite) than *p*-benzoquinone (BQ), which furnished 1,4-dichloro-2-alkene [89, 95]. In the case of 1,3-cyclohexadiene this product was *cis*-1,4-dichloro-2-cyclohexene [95].

The haloacyloxylation of cyclic dienes can also be performed in acetone in the presence of 2 equiv. of LiCl and 5–10 equiv. of the appropriate carboxylic acid. In this way, a number of different chlorocarboxylates were obtained from 1,3-cyclohexadiene (Eq. (41)) with high regio- and stereoselectivities (>98 % *cis*, >98 % 1,4) [58].



R	%
Me	88
Me_2CH	87
Me_3C	87
Ph	70

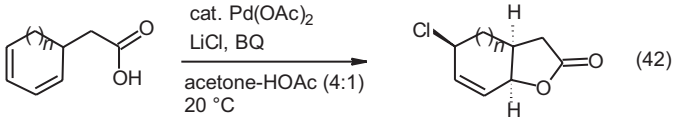
(41)

Equation 8-41

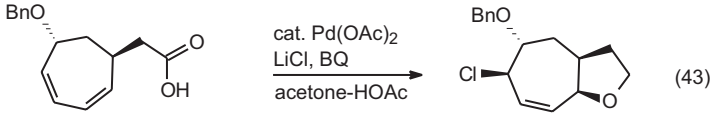
The use of LiBr in place of LiCl as the halide nucleophile in acetone resulted in a 1,4-bromoacetoxylation with poor stereoselectivity [58]. A change of the solvent to ethyl acetate improved the stereoselectivity, and gave a 65 % yield of the 1,4-bromoacetate with a *cis*:*trans* ratio of 89:11 and a selectivity for 1,4-addition of 92 %.

Intramolecular 1,4-haloacyloxylation

The use of dienylcarboxylic acids (*cf.* Subsection 8.3.1.1; intramolecular diacyloxylation) under the conditions for haloacyloxylation in acetone resulted in a highly stereoselective chlorolactonization (Eqs. (42) and (43)) [76]. The reaction proceeds



Equation 8-42 76–85% (>98% *cis*-add.)



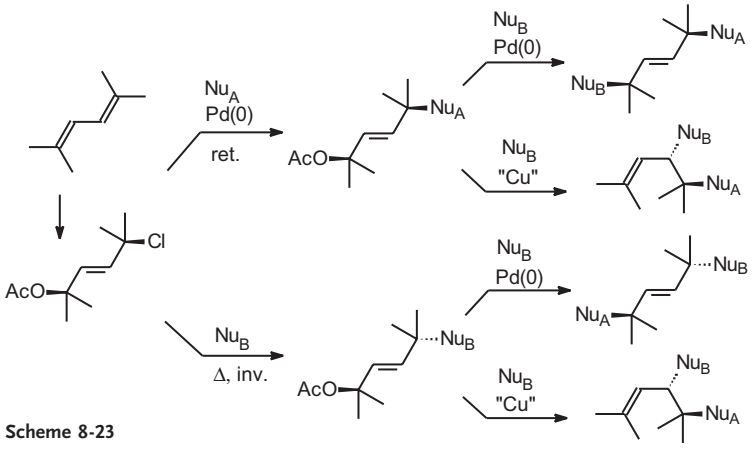
Equation 8-43 73% (>98% 1,4-*cis*-add.)

with >98% 1,4-*cis*-addition, and involves the same lactone π-allyl complex as was involved in the intramolecular diacyloxylation.

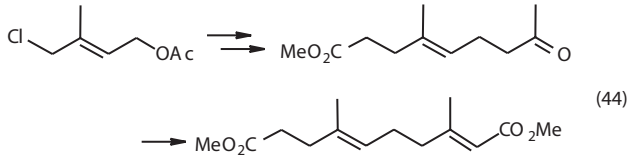
Synthetic applications of 1,4-haloacyloxylation

As mentioned above, the products from the palladium-catalyzed 1,4-haloacyloxylation are useful synthetic intermediates because of their two different allylic leaving groups. In particular, 1,4-chloroacetates have been used in a number of stereo- and regioselective transformations. The principle for their use as multi-coupling reagents is shown in Scheme 8-23. Sequential substitution of the chloro and acetoxy groups in a stereo- and regioselective manner leads to a useful functionalization of the original diene unit.

By the use of the chloroacetate from isoprene, two enolate nucleophiles were selectively coupled to the 1- and 4-positions via allylic substitution reactions, and



Scheme 8-23

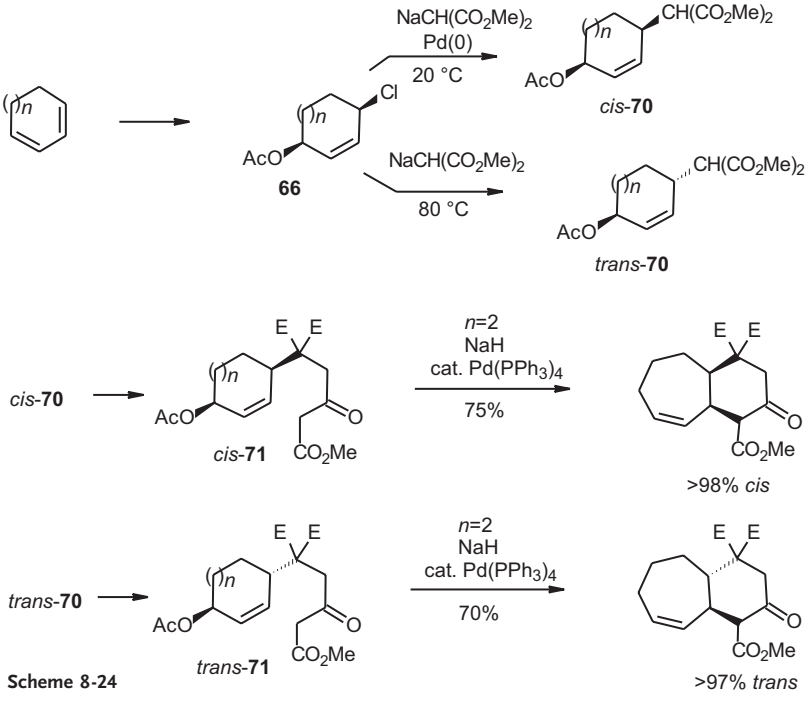


(44)

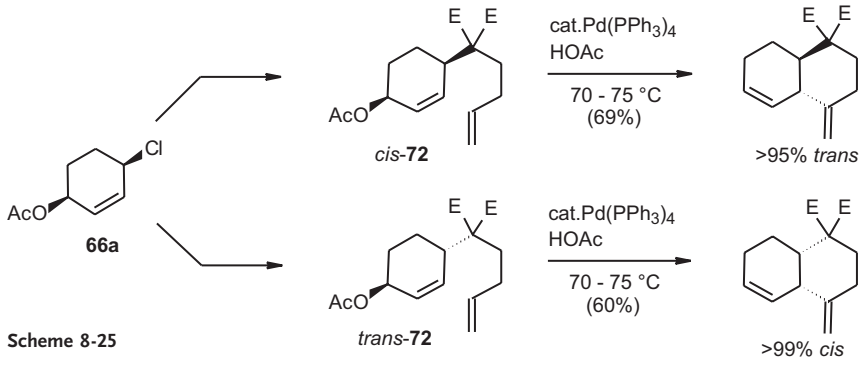
Equation 8-44 Monarch butterfly pheromone

the product was subsequently transformed to the Monarch butterfly pheromone (Eq. (44)) [96].

The allylic chloride offers a useful dual control of stereoselectivity in the allylic substitution since the chloride can be replaced with either retention (by a Pd(0)-catalyzed reaction) or inversion (by a normal S_N2 reaction or Cu(I)-catalyzed reaction). This was used in cyclic systems to achieve stereoselective *cis*- and *trans*-annulation reactions [97, 98]. The reaction starts with the transformation of 1,3-cycloalkadiene to *cis*- and *trans*-**70** via chloroacetate **66** (Scheme 8-24) [89, 99]. Subsequent transformation of *cis*- and *trans*-**70** to *cis*- and *trans*-**71**, respectively, followed by an intramolecular palladium-catalyzed allylic substitution (*syn*) afforded the *cis*- and *trans*-annelated products [97].



Scheme 8-24

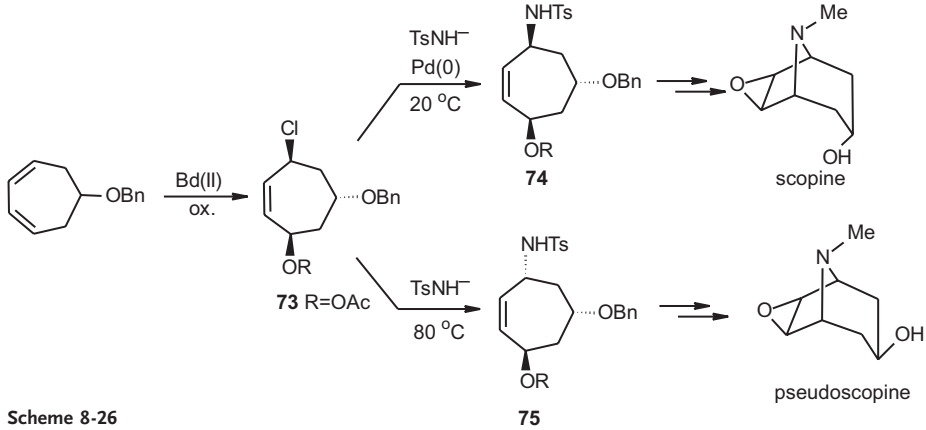


Scheme 8-25

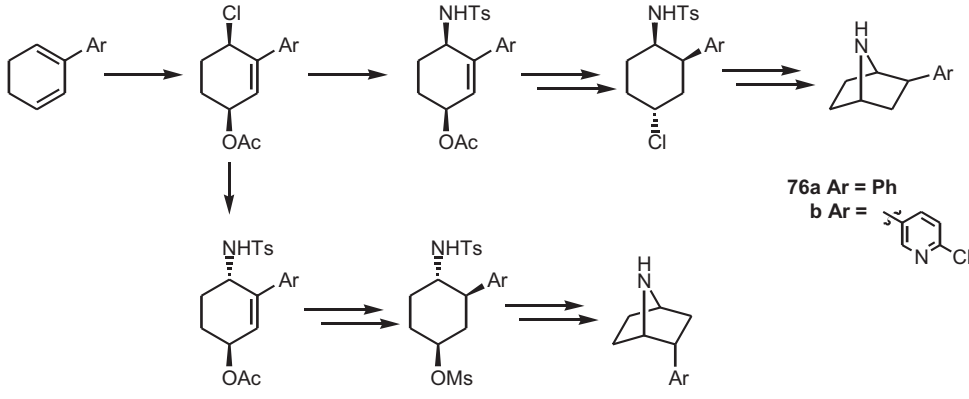
In another approach, the cyclization was carried out via a metalloene reaction (Scheme 8-25) [98]. In this case, the cyclization occurred with *anti* stereochemistry.

The chloroacetoxylation approach was also used for the stereoselective synthesis of tropine and pseudotropine employing a sulfonamide as the nucleophile [91]. Using the same approach, scopine and pseudoscopine were synthesized (Scheme 8-26) [92]. The chloroacetoxylation of 6-benzyloxy-1,3-cycloheptadiene was highly diastereoselective, and produced only the diastereoisomer **73** shown. Transformation of the chloroacetate **73** to **74** was realized by a Pd(0)-catalyzed substitution of the chloride by a sulfonamide, which occurred with retention of configuration. Reaction of the allylic chloride with the sulfonamide salt in DMSO-water at 80 °C afforded the inversion product **75**. Subsequent stereoselective epoxidation, cyclization, and deprotection afforded the target molecules scopine and pseudoscopine.

The synthesis of (±)-Epibatidine **76b** and analogues thereof was realized by regioselective chloroacetoxylation of 2-aryl-1,3-cyclohexadiene [100]. Subsequent stereoselective substitution of the chlorine atom by tosylamide with either retention or inversion provided both stereoisomers of the aminoalcohol derivative



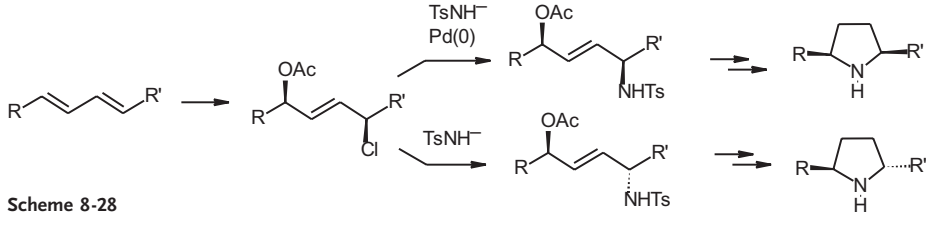
Scheme 8-26



Scheme 8-27 77

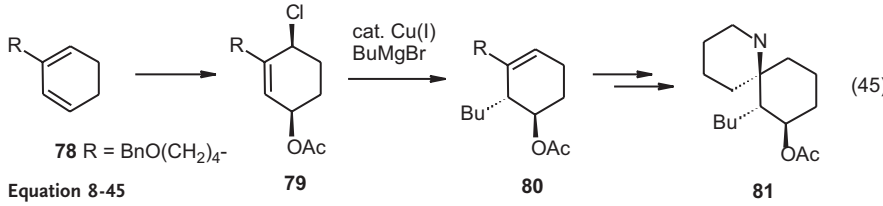
(Scheme 8-27). Highly stereoselective hydrogenation of the allylic amides gave the requisite stereoisomers for synthesis of the *exo*- and *endo*- isomers **76** and **77**, respectively.

Acylic *syn*-1,4-chloroacetates were used in a similar sulfonamide substitution-cyclization sequence for their transformation to stereodefined 2,5-disubstituted pyrrolidines (Scheme 8-28) [94]. Some of these 2,5-disubstituted pyrrolidines are ant venom pheromones, and are also found in the skin of frogs.



Scheme 8-28

A copper-catalyzed S_N2' nucleophilic substitution of the chloride in a cyclic chloroacetate by butylmagnesium bromide was employed in a synthesis towards perhydrohistrionicotoxin (Eq. (45)) [80]. Histrionicotoxins are found in South American "dart-poison" frogs of the Dendrobatid family. Palladium-catalyzed chlor-



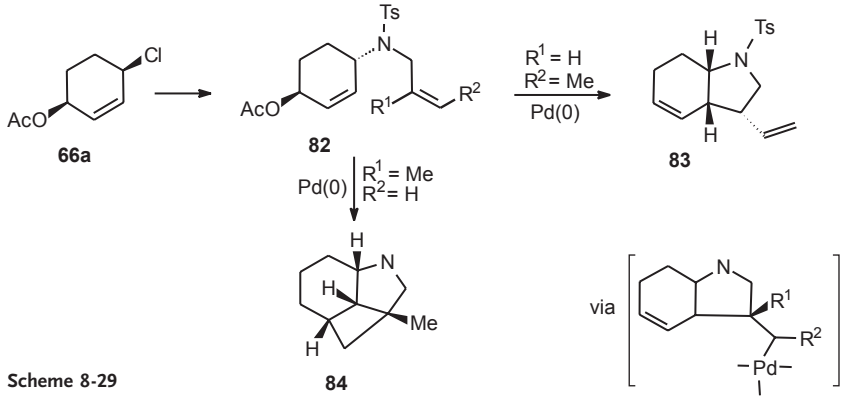
78 R = $BnO(CH_2)_4$- **79** **80** **81**

Equation 8-45

oacetoxylation of the 2-substituted diene **78** gave a highly regio- and stereoselective 1,4-addition product in which the chloride is ultimately located in the 1-position. Copper-catalyzed reaction of the chloroacetate **79** with butylmagnesium bromide afforded **80** in a completely selective SN2′-type substitution. Subsequent elaboration of the side chain followed by iodoamination and removal of iodine and protective groups afforded the target molecule, dependylperhydrohistrionicotoxin, **81**.

Transformation of the chloroacetate **66a** from 1,3-cyclohexadiene to amide **82** followed by a Pd(0)-catalyzed cyclization afforded products **83** [100] and **84** (Scheme 8-29) [101]. The product formation is dependent on the substitution pattern. Both reactions proceeded via a similar intermediate. When R^1 = Me and R^2 = H, β-elimination cannot occur and a cyclization takes place instead, by insertion of the double bond into the intermediate palladium-carbon bond.

An analogous reaction was performed via the carbon analogue of **82** (NTs is $CH(CO_2Me)_2$ to give the corresponding tricyclic system. In the latter case, the intermediate organopalladium species was trapped by tetraphenyl boranate or hydride (from HCOOH) [102–104].



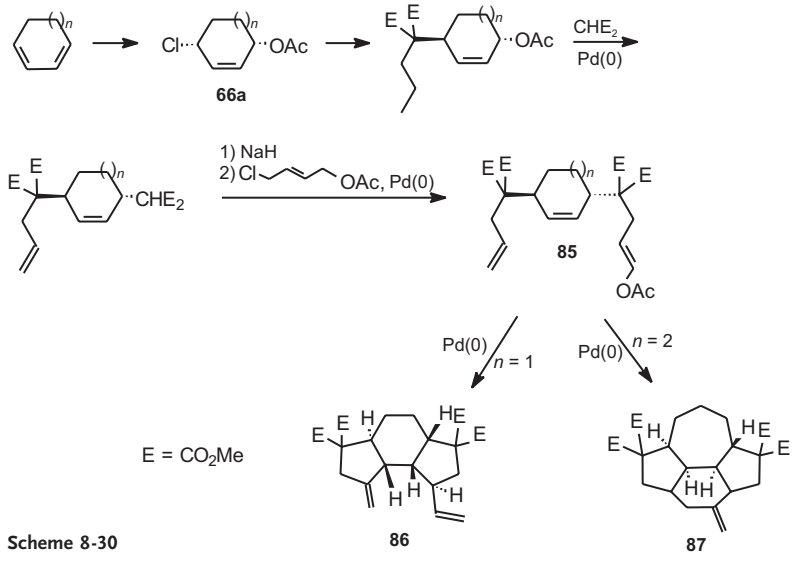
Scheme 8-29

The corresponding propargylamides prepared from the chloroacetate **66a** derived from 1,3-cyclohexadiene, were cyclized in an analogous manner [104, 105].

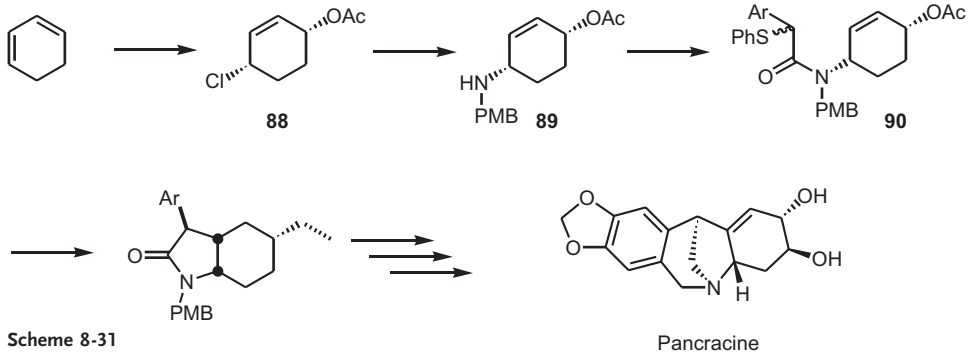
The metalloene reaction of the synthetic intermediates **72** in Scheme 8-25, when combined with a carbonylation reaction, afforded cyclized esters [106].

A stereocontrolled synthesis of polyfused ring systems utilizing the chloroacetoxylation approach is shown in Scheme 8-30 [107]. The use of sequential allylic substitution of the chloroacetates afforded key intermediate **85**. Subsequent palladium-catalyzed sequential metalloene-Heck insertion reactions afforded polyfused ring systems **86** and **87**.

The high regio- and stereocontrol of the chloroacetoxylation reaction makes it useful in organic synthesis. This was shown in a formal total synthesis of (±)-Pancracine, in which a chloroacetoxylation of 1,3-cyclohexadiene and subsequent



Scheme 8-30



Scheme 8-31

Pd(0)-catalyzed amination of the chloroacetate **88** with *p*-methoxybenzylamine (PMB-NH_2) to afford aminoacetate **89** were utilized (Scheme 8-31) [108]. The latter compound was converted to **90**, which was subsequently transformed to (±)-Pancracine by a stereoselective radical cyclization.

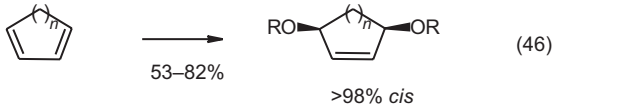
Additional examples in which chloroacetates from acyclic dienes have been used include synthesis of pentadienylamines [109], dienylsulfones [110], *α*-methylenecyclopentenones [111], marine natural products [112], and the carpenter bee pheromone [93]. Some additional synthetic applications of the chloroacetoxylation of cyclic dienes are given in refs. [113–117]. The chloroacetoxylation was also used to prepare a number of starting materials for the intramolecular reactions discussed in this chapter.

8.3.1.3 1,4-Addition of an Alkoxide and Another Oxygen Function or a Halide

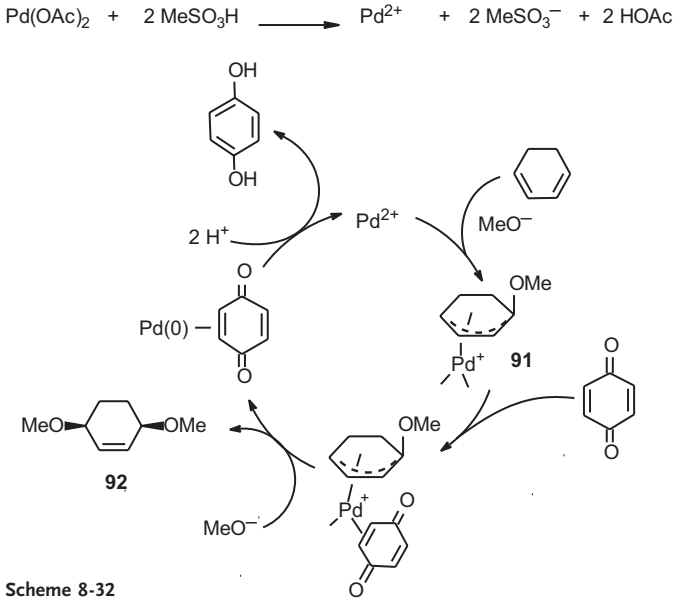
Palladium(II)-catalyzed 1,4-additions to conjugated dienes where at least one alkoxide function is added require the presence of an alcohol function. In all cases known so far, this involves an alkoxypalladation of the conjugated diene to give an intermediate 4-alkoxy-1,2,3-π-allylpalladium complex. Subsequent nucleophilic attack on the π-allyl intermediate by a second oxygen nucleophile or a halide gives the product. The second nucleophile may be an alcohol (alkoxide) and in this case a 1,4-dialkoxylation is obtained.

Intermolecular 1,4-addition

A palladium-catalyzed 1,4-dialkoxylation of conjugated dienes was achieved when the 1,4-oxidation was performed in an alcohol as the solvent [118]. In this case, it is necessary to run the reaction in the presence of a catalytic amount of a strong acid such as methanesulfonic acid or perchloric acid. Cyclic dienes underwent a highly stereoselective 1,4-*cis*-addition of the two alkoxy groups (Eq. (46)). The same type of reaction of acyclic conjugated dienes also proceeded in a 1,4-*syn*-addition. Thus, (*E,E*)-2,4-hexadiene gave the (*E*)-(2*R**,5*R**)-dimethoxy-3-hexene; the mechanism involved is depicted in Scheme 8-32.



Equation 8-46

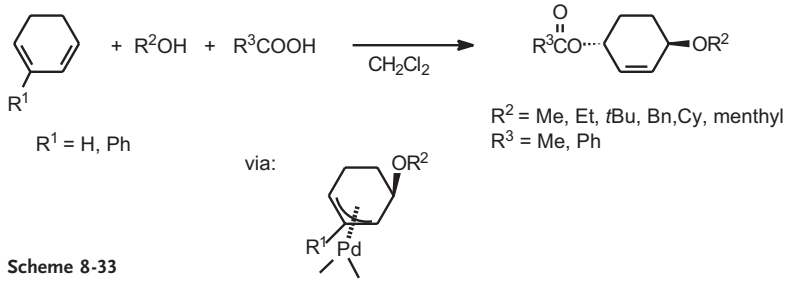


Scheme 8-32

The added acid most likely plays several roles. First, the acid is necessary for the redox transformation of Pd(0)-benzoquinone to Pd(II) + hydroquinone in the catalytic cycle [65]. Second, the acid will lead to the formation of a cationic π-allylpalladium intermediate which will facilitate coordination of benzoquinone. Third, the acid will protonate the oxygen of the coordinated benzoquinone, and in this way the quinone becomes more electron-withdrawing. It was found that the rate of the reaction increased with the amount of acid, and that there was a linear increase in the range of 0 to 30 mol % of acid; however, adding too much acid catalyzed the destruction of benzoquinone. The stereochemistry of the dialkoxylation is consistent with a *trans*-alkoxypalladation [119] of the diene to give π-allyl intermediate **91**, followed by external *trans*-attack of alcohol to give the *cis*-dialkoxy compound **92** (Scheme 8-32).

Palladium-catalyzed 1,4-alkoxy-trifluoroacetoxylation [60b] and other 1,4-alkoxy-acyloxylations were developed by the use of a carboxylic acid and an alcohol as nucleophiles. A 1,4-alkoxy-acyloxylation was achieved by the use of 5 mol % $Pd(OAc)_2$ and 2.5 mol % H_2SO_4, together with 2.6 equiv. of acid and 4 equiv. of alcohol (Scheme 8-33) [120].

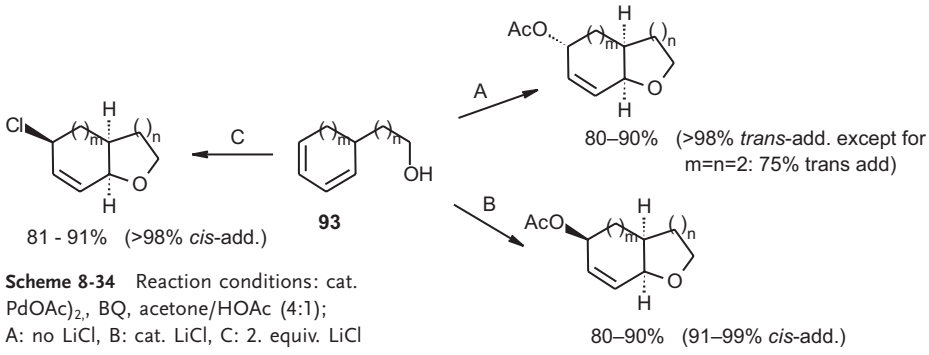
An asymmetric version of the 1,4-dialkoxylation was reported using chiral benzoquinone ligands [121]. An enantioselectivity of up to 54 % *e.e.* was obtained.



Scheme 8-33

Intramolecular 1,4-addition

Palladium-catalyzed reaction of dienylalcohol **93** in acetone in the presence of acetic acid and benzoquinone resulted in an intramolecular 1,4-oxyacetoxylation (Scheme 8-34) [122]. The stereochemistry of the reaction can be controlled by slight variation of the ligand environment. Thus, under chloride ion-free conditions a *trans*-oxyacetoxylation occurs. In most cases this reaction was highly stereoselective (>98 % *trans*-addition), except in one case for $m = n = 2$ in Scheme 8-34, in which the *trans*/*cis* ratio was 75/25. When the reaction was run in the presence of a catalytic amount of chloride, the stereochemistry was reversed, and a 1,4-*cis*-oxyacetoxylation took place. The effect by the chloride is the same as discussed above – that is, to block the coordination of acetate so that *cis*-migration by acetate cannot occur.

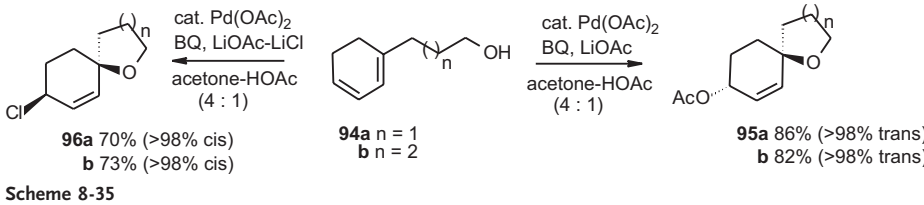


Scheme 8-34 Reaction conditions: cat. $PdOAc)_{2,}$ BQ, acetone/HOAc (4:1); A: no LiCl, B: cat. LiCl, C: 2. equiv. LiCl

With a stoichiometric amount of LiCl present the palladium-catalyzed reaction of dienylalcohol **93** underwent a highly regio- and stereoselective 1,4-*cis*-oxychlorination. In all cases the stereoselectivity was >98 %.

If the side chain with the nucleophile is located in the 1-position of the conjugated diene, a spirocyclization is achieved in a highly stereo- and regioselective 1,4-addition (Scheme 8-35) [123, 124]. Thus, palladium-catalyzed oxidation of dienylalcohols **94** in acetone-acetic acid without chloride ligands gave spiroethers **95** in good yields by a 1,4-*trans*-addition. In the presence of 1.8 equiv. LiCl, a highly stereoselective *cis*-1,4-oxychlorination took place to give spiroethers **96**, and the reactions were shown to proceed via a common oxaspirocyclic π-allyl intermediate.

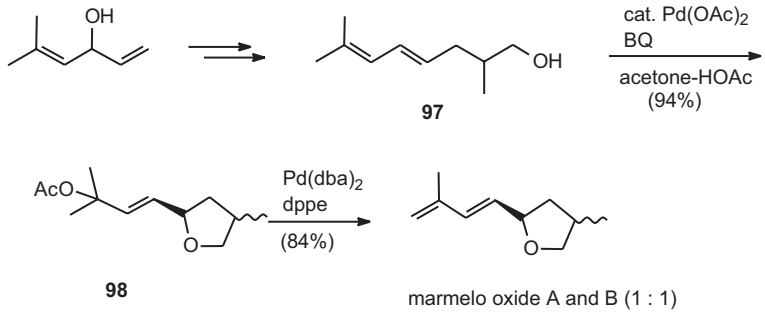
Intramolecular dialkoxylation of 1- and 2-substituted 1,3-cyclohexadienes has also been reported [125].



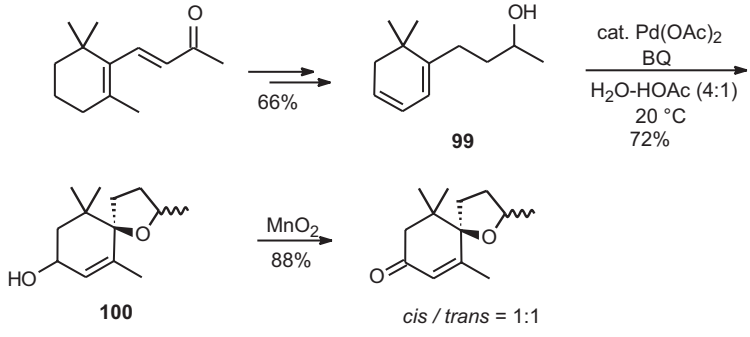
Scheme 8-35

Synthetic applications

In several syntheses towards naturally occurring furanoid terpenes, the intramolecular oxyacetoxylation was applied as a key step [126]. For example, in the synthesis of marmelo oxides A and B, 3,3-dimethylacroleine was transformed to dienol **97**, which was subjected to a palladium-catalyzed 1,4-oxidation (Scheme 8-36). This afforded the cyclized product **98** as a mixture of *cis*- and *trans*-isomers (1:1) The reaction was highly 1,4-regioselective (98 % 1,4-addition) and gave only the (*E*)-olefin (>98 % *E*). Subsequent regioselective palladium-catalyzed 1,2-elimination of



Scheme 8-36

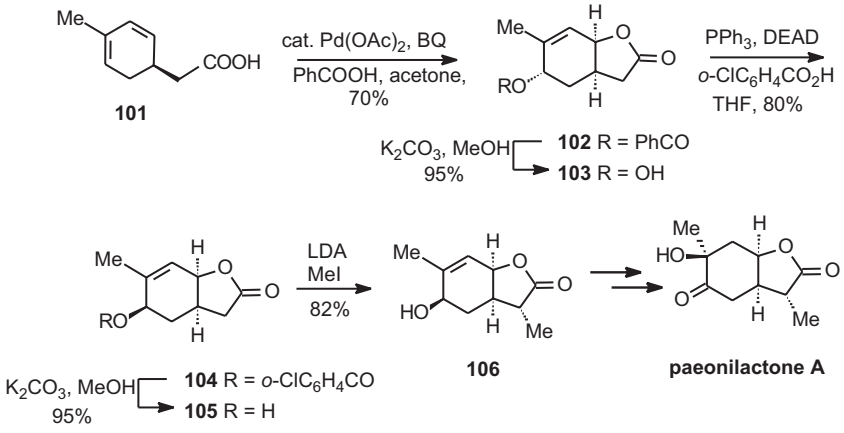


Scheme 8-37

acetic acid afforded marmelo oxide A (*cis*) and B (*trans*) as a 1:1 mixture in 84 % yield. Interestingly, this mixture is the one which occurs naturally.

In another application, theaspirone and vitispirane were synthesized utilizing a palladium-catalyzed oxaspirocyclization (Scheme 8-37) [127]. Readily available β-ionone was transformed to the dienylalcohol **99** in 66 % overall yield. Palladium-catalyzed oxaspirocyclization of **99** in water-acetic acid (4:1) afforded the allylic alcohol **100** as a mixture of isomers. Subsequent oxidation of **100** gave theaspirone as a 1:1 mixture of *cis*- and *trans*-isomers. Interestingly, when the cyclization step was performed with stoichiometric amounts of palladium(II), the product was a 93:7 mixture of the *trans*- and *cis*-isomers of theaspirone.

Palladium-catalyzed intramolecular lactonization was used as a key step in the enantioselective synthesis of paeonilactones A and B (Scheme 8-38) [128]. Intramolecular 1,4-diacyloxylation of the cyclohexadienylacetic acid **101** afforded **102**, which was hydrolyzed to **103**; this in turn was transformed to **104** in a Mitsunobu reaction. Hydrolysis of **104** to **105** and stereoselective alkylation afforded **106**, which was converted to paeonilactone A.



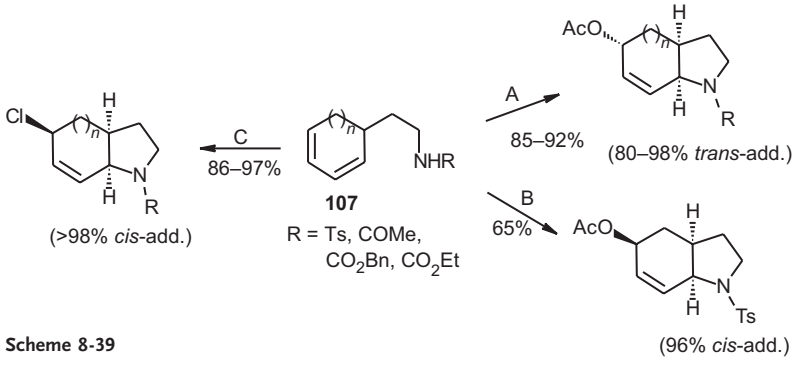
Scheme 8-38

8.3.1.4 1,4-Oxyamination and 1,4-Chloroamination

In these reactions, the nitrogen nucleophile is typically an amide, carbamate or a sulfonamide. Because of the low nucleophilicity of such nitrogen functions, no intermolecular 1,4-addition involving C-N bond formation is known. In all cases reported, the carbon-nitrogen coupling takes place in an intramolecular aminopalladation.

Intramolecular 1,4-oxyamination and 1,4-chloroamination

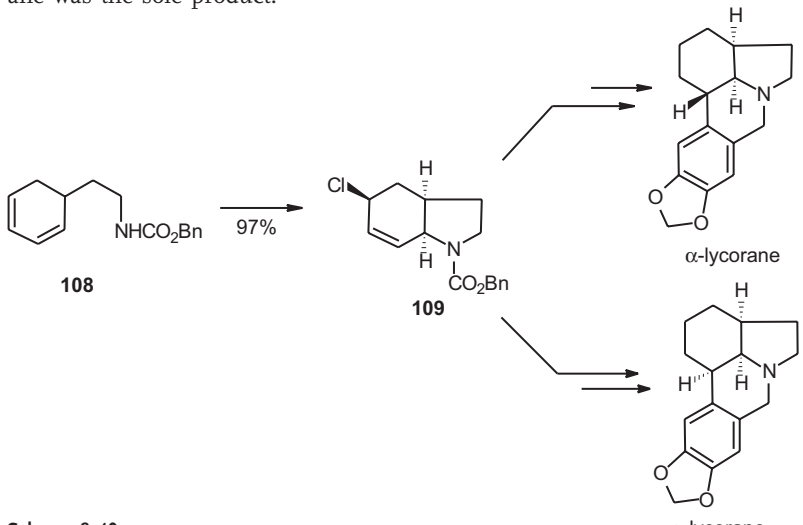
Palladium-catalyzed oxidation of dienylcarboxamides **107** in acetone in the presence of acetic acid gives oxyamination products in stereoselective reactions (Scheme 8-39) [129]. Depending on the reaction conditions, it was possible to achieve *trans*- or *cis*-1,4-oxyamination by choice. As with the other Pd(II)-catalyzed 1,4-additions, Cl^- (from LiCl) is used as a steering ligand to control the stereochemistry. When the chloride concentration is increased, a *cis*-1,4-chloroamination takes place.



Scheme 8-39

Synthetic applications

The intramolecular 1,4-chloroamination of **108** was applied to the synthesis of amaryllidaceae alkaloids α- and γ-lycorane (Scheme 8-40) [130]. The hexahydroindole **109** obtained was transformed to the target alkaloid α-lycorane by a copper-catalyzed reaction with 3,4-(methylenedioxy)phenylmagnesium bromide, followed by hydrogenation, Bischler-Napieralski cyclization, and $LiAlH_4$ reduction. When the Bischler-Napieralski cyclization was carried out before the hydrogenation, γ-lycorane was the sole product.



Scheme 8-40

8.3.1.5 Intramolecular 1,4-Additions with C-C Bond Formation

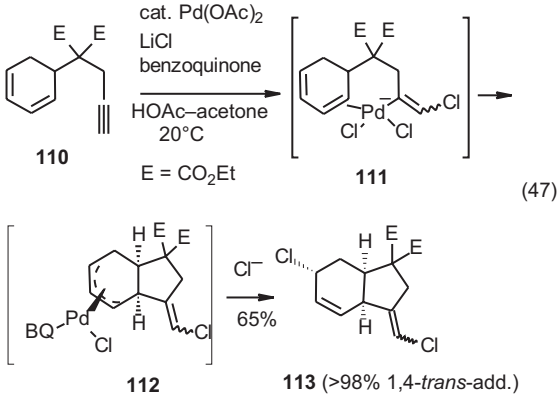
In the palladium-catalyzed 1,4-oxidation of conjugated dienes described so far, only heteroatom nucleophiles have been employed. There is an intrinsic problem in using free carbanions in an oxidation reaction, as the oxidant can readily remove an electron and oxidize the carbanion to a radical. Furthermore, in the procedure associated with the best selectivity – that is, the benzoquinone-based process – acid is required to reconvert the Pd(0)-(benzoquinone) complex to Pd(II) and hydroquinone.

The problem with free carbanions was circumvented by the use of masked carbon nucleophiles via vinyl palladation or the use of an allylsilane or allene (see the next three subsections). In another approach, the oxidation system was changed to comply with nonacidic conditions (see the fourth subsection below).

C-C bond formation via vinylpalladation

As described above in the Pd(0)-catalyzed reactions, carbon-carbon bonds can be created by the insertion of an olefin into a palladium-vinyl bond (vinylpalladation). This approach has been applied in palladium(II)-catalyzed exchange reactions of alkenes by generating the vinylpalladium species from chloropalladation of an acetylene [131, 132]. This technique to generate a vinylpalladium intermediate

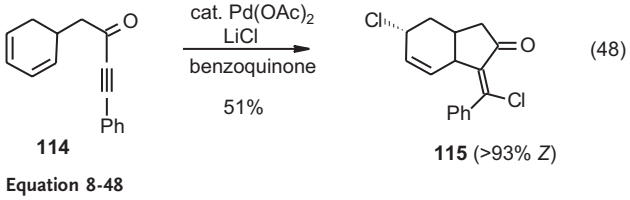
was later applied to the palladium-catalyzed 1,4-oxidation of conjugated dienes [133]. Thus, the use of substrate **110** in a palladium(II)-catalyzed oxidation in the presence of LiCl afforded **113** in 65 % yield (Eq. (47)). The reaction is an overall 1,4-*trans*-carbochlorination, and proceeds via chloropalladation of the acetylene to give the vinylpalladium intermediate **111**, which in turn reacts in a migratory insertion reaction to produce the π-allyl complex **112**. Subsequent chloride attack on **112** *anti* to palladium accounts for the product. The chlorodimer of the proposed π-allylpalladium intermediate was isolated and fully characterized. The chloromethylene function in **113** occurred as a mixture of (*E*)- and (*Z*)-isomers (*Z*:*E* = 1.5:1), indicating that chloropalladation of the acetylene is a nonstereoselective process [131, 134].



(47)

Equation 8-47

In another example, dienyne **114** was oxidized employing the same procedure to give **115** (Eq. (48)). Also in this case a 1,4-*trans*-addition took place and, interestingly, the chloropalladation was apparently more stereoselective with this substrate.

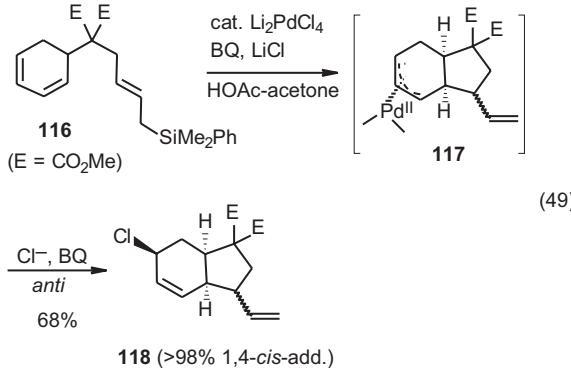


(48)

Equation 8-48

C-C bond formation with the use of an allylsilane

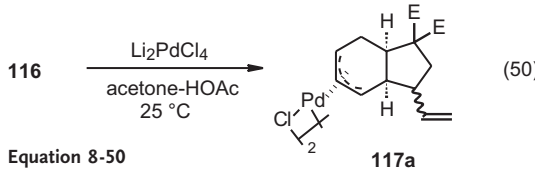
By using an allylsilane as a masked carbanion, it was possible to achieve C-C bond formation in intramolecular 1,4-oxidation of 1,3-dienes [135]. Reaction of the cyclohexadienyl-substituted allylsilane **116** under the usual reaction conditions for 1,4-oxidation, afforded the cyclized product **118** (Eq. (49)).



118 (>98% 1,4-*cis*-add.)

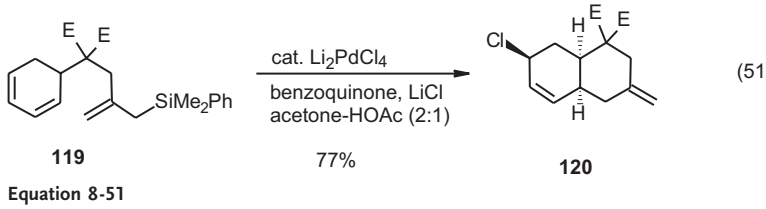
Equation 8-49

Interestingly, the 1,4-carbochlorination occurs *syn* in contrast to that via the vinylpalladation in Eq. (49), which occurs *anti*. An explanation for this difference is that the allylsilane attacks the palladium-diene complex *anti*, leading to a *trans*-carbopalladation of the double bond. This is the first example of nucleophilic attack by an allylsilane on an alkene coordinated to a metal. Direct evidence for a *trans*-carbopalladation was provided by the isolation of the proposed π-allyl intermediate of Eq. (51) as its chlorodimer **117a** from reaction of **116** with Li_2PdCl_4 in the absence of benzoquinone (Eq. (50)) [135b]. The *trans* relationship between palladium and the carbon that had attacked the diene was established by the repor-



Equation 8-50

117a

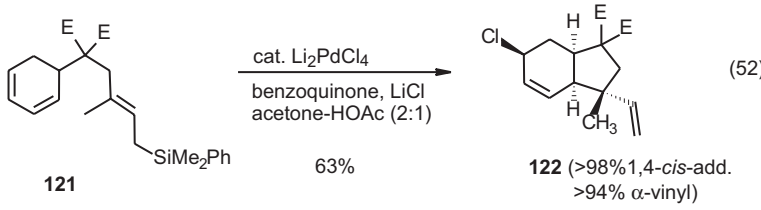


Equation 8-51

ter ligand technique used for **49** in Section 8.3.1.1, "Intramolecular 1,4-diacetoxylation".

In the reaction of (*E*)-allylsilane **116**, the product **118** was a 3:1 mixture of α-vinyl and β-vinyl isomers. When the corresponding (*Z*)-allylsilane isomer of **116** was cyclized under the same conditions, a reversed α-vinyl:β-vinyl ratio of 1:3 was obtained. In both cases the 1,4-addition was exclusively *syn*.

Two additional examples for the use of allylsilane-based 1,4-*cis*-carbochlorination are presented in Eqs. (51) and (52) [135b]. In each case, a highly stereoselective 1,4-*cis*-addition to the conjugated diene took place. 6-*endo*-*trig*-Cyclization of allylsilane **119** furnished product **120** (Eq. (51)). Interestingly, for the methyl-substituted allylsilane **121**, a stereoselective attack by the allylsilane occurred to give >94% of the α-vinyl product **122** (Eq. (52)). Thus, the relative configurations between four stereogenic centers are established in a single operational step.

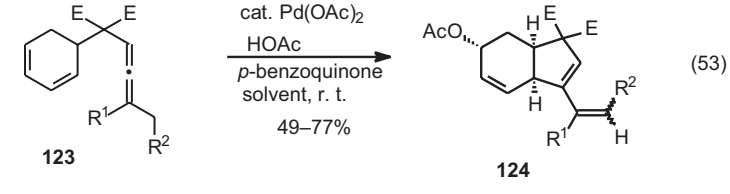


(52)

Equation 8-52

C-C bond formation via the use of an allene

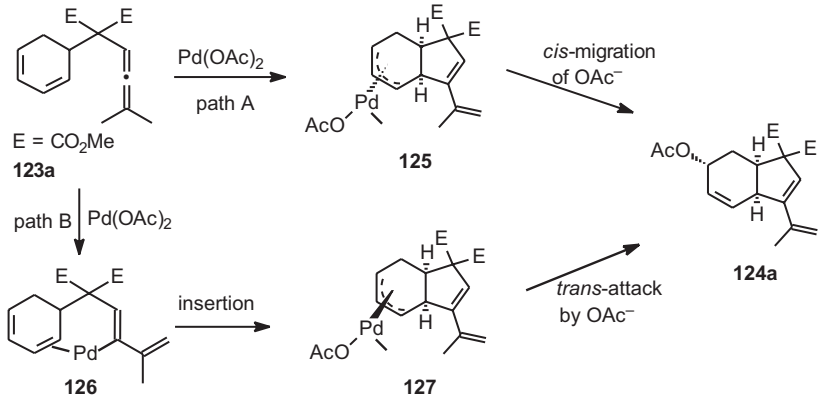
Palladium-catalyzed allenyl-substituted conjugated dienes **123** with the use of palladium acetate as the catalyst and benzoquinone as the oxidant afforded products **124** by a carbocylization (Eq. (53)) [136].



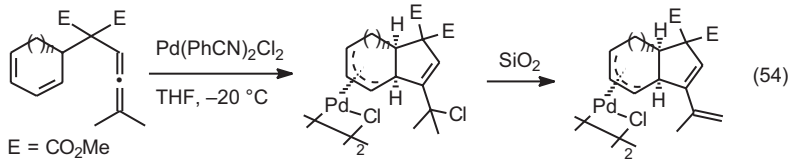
(53)

Equation 8-53

The reaction is highly regio- and stereoselective, and occurs with 1,4-*trans*-carboacyloxylation. The reaction was initially run in acetic acid as solvent [136a] and acetate as the nucleophile, but was later extended to the use of various carboxylic acids as nucleophiles in an organic solvent (e. g., acetone) [136b]. The reaction was run in differently substituted substrates, and generally good yields were obtained.



Scheme 8-41



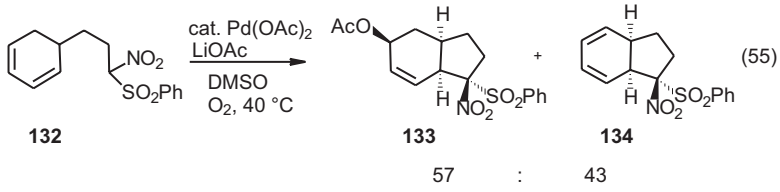
Equation 8-54

The transformation may start with an external attack by the allene to give the π-allylpalladium complex **125**, followed by *cis*-migration of acetate from palladium to carbon (path A, Scheme 8-41) or by the formation of a dienylpalladium complex **126** followed by insertion of the diene into the Pd-C bond to give π-allyl complex **127** and subsequent *trans* attack by acetate (path B, Scheme 8-41). Recently, the former pathway was demonstrated in a stoichiometric reaction in the presence of chloride ions in which **128** and **129** gave π-allyl complexes **130** and **131**, respectively (Eq. (54)) [137].

The configuration of the latter complexes was determined by the use of reporter ligands (*cf.* **49** in Section 8.3.1.1, "Intramolecular 1,4-diacetoxylation") and by transformation to allylic acetates. It is unclear whether the catalytic reaction in the absence of chloride proceeds via a *trans*-carbopalladation, as the seven-membered ring compound **129** gave the *trans*-fused bicyclo[5.3.0]octadienyl derivative in the catalytic reaction.

C-C bond formation via the use of stabilized carbanions

With a change of the oxidation system, it has been possible to obtain a 1,4-addition of a stabilized carbanion and an acetate anion in an intramolecular reaction [138]. The stabilized carbanions employed have a low pK_A so that LiOAc is sufficiently basic to generate the carbanion from the neutral compound. Reaction of



132 **133** **134**

57 : 43

Equation 8-55

conjugated diene **132** with molecular oxygen in DMSO in the presence of LiOAc produced a 57:43 mixture of **133** and **134** (Eq. (55)) in a moderate yield (50 %) [138, 139]. The configurations of the products **133** and **134** were unambiguously assigned by NMR spectroscopy using NOE measurements. Again, the relative configurations of four stereogenic centers are created in a single operational step.

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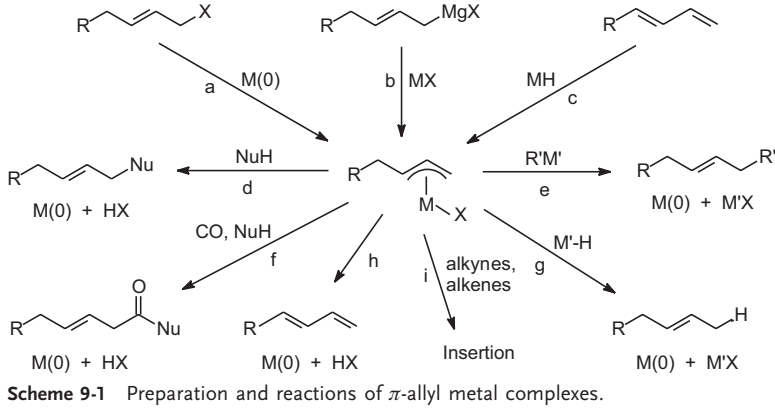
9
Cross-Coupling Reactions *via* π-Allyl Metal Intermediates

Uli Kazmaier and Matthias Pohlman

9.1
Introduction

π-Allyl metal complexes play an important role in modern organic synthesis. Among the different metals used, palladium takes a dominant role, but other metals – especially later transition metals such as Ni, Mo, Ir, and Rh – enlarge the synthetic potential of π-allyl-intermediates [1]. In modern organic synthesis, catalytic processes are becoming increasingly important, and therefore this review will focus on this topic.

π-Allyl metal complexes can be obtained by several different protocols (Scheme 9-1). The most popular are oxidative additions of allylic substrates to metal(0) complexes (protocol a), a process which can occur *via* a metal alkene complex or *via* a σ-allyl intermediate (σ-π-σ isomerization). Another approach starts from allyl Grignard and related reagents, which can be transmetallated with transition metal salts (protocol b). If conjugated dienes are used, then π-allyl complexes are formed either by hydrometallation (protocol c) or by nucleophilic attack on a metal diene complex [2].



Scheme 9-1 Preparation and reactions of π-allyl metal complexes.

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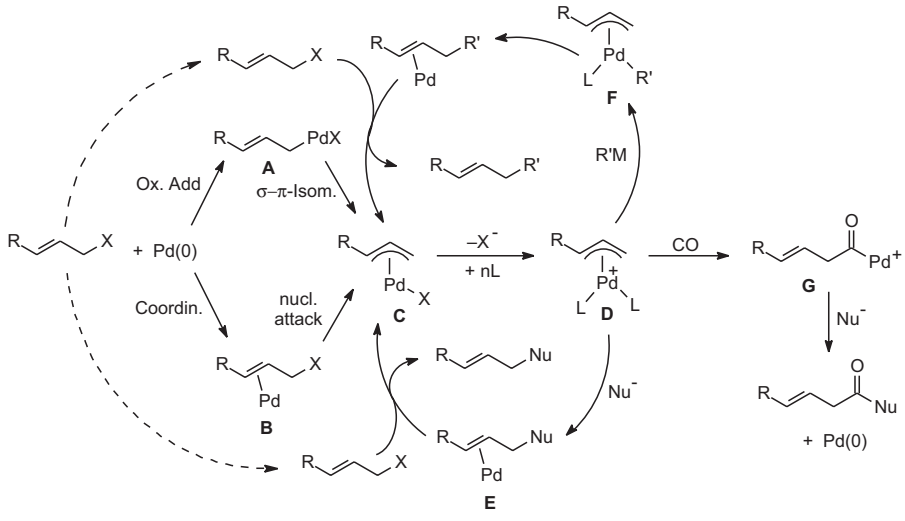
The π-allyl complexes can react with several types of nucleophiles, giving rise to the corresponding substitution product (protocol d). *O*- and *N*-nucleophiles, as well as soft carbon nucleophiles, attack the π-allyl complex directly at the allylic position, while hard *C*-nucleophiles react *via* transmetallations (protocol e) [3]. If the nucleophilic attack occurs under an atmosphere of CO, insertion of CO can occur, yielding carbonyl compounds (protocol f) [4]. Reaction with metal hydrides or other hydride sources results in a reduction of the π-allyl complex to an alkene (protocol g) [5]. If no nucleophile is present, or if the reaction is carried out in the presence of base, a proton can be cleaved off under formation of a diene (protocol h) [6]. Alkenes and alkynes can also insert into allyl metal bonds (protocol i), a scheme which is used preferentially for cyclizations [7]. Cyclizations can also occur, if the π-allyl metal complex contains an internal nucleophilic center. This chapter focuses on C-C-coupling reactions *via* these π-allyl intermediates.

9.2 Palladium-Catalyzed Allylic Alkylations

9.2.1 Mechanistic Aspects

9.2.1.1 Formation and Reactions of π-Allyl Complexes

The allylic position of an alkene is activated towards nucleophilic attack after conversion either of the alkene itself or a suitable precursor into a π-allylpalladium complex. These complexes can be generated in stoichiometric or catalytic amounts, preferentially from alkenes with an anionic leaving group in the allylic position [2]. Two different pathways are discussed for the formation of the π-allyl complexes (Scheme 9-2): a) Oxidative addition of the allylic C-X bond to Pd(0), giving rise to a σ-allylpalladium complex **A**. The corresponding π-allylpalladium complex **C** is then formed *via* σ-π isomerization [2c]; b) The same complex can also be created *via* coordination of the alkene to Pd(0) (**B**) and an internal S_N1-type nucleophilic attack of the electron-rich Pd at the allylic position [8]. The allyl complexes **C** are rather stable and can be isolated in many cases. As a consequence of their stability, these neutral complexes are relatively inert towards nucleophilic attack [9]. However, by replacing the anionic leaving group by neutral ligands, in general phosphanes, cationic complexes **D** can be formed which undergo reaction with various types of nucleophiles [10]. Heteronucleophiles and soft carbanions attack from the face opposite to the metal with clean inversion, resulting in net retention (two inversions) for the overall process. Pd(0) dissociates from the alkene complex **E** formed, under formation of the substitution product and coordination to another substrate molecule, starting the next catalytic cycle. If hard carbanions such as main group organometallics are used as nucleophiles, then transmetallation occurs. Reductive elimination of the π-allyl-σ-alkyl complex **F** results in the coupling product. In this case, the nucleophile is delivered from the same side as the metal. Retention of configuration is therefore observed for this step, leading to overall inversion.

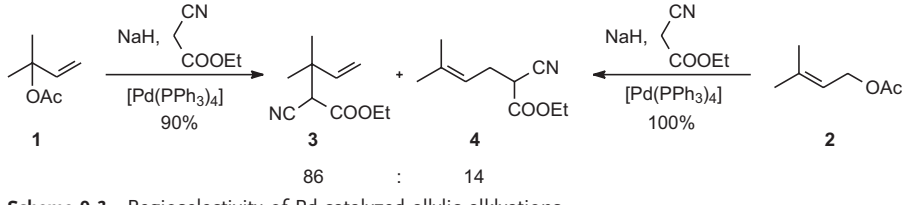


Scheme 9-2 Formation and reactions of π-allyl complexes from allylic substrates.

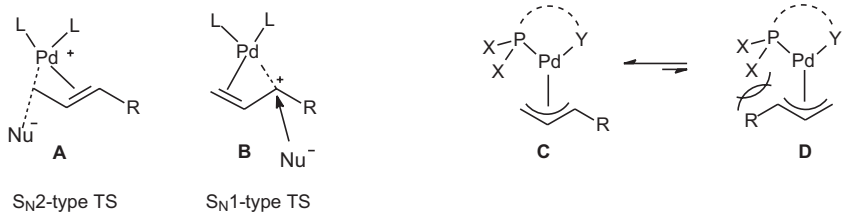
Finally, the π-allylpalladium complexes **D** can undergo CO insertion (in a CO atmosphere) under formation of an acylpalladium complex **G**, which then is attacked by the nucleophiles discussed.

9.2.1.2 **Regioselectivity**

With unsymmetrical π-allyl-Pd complexes, attack of the nucleophile usually occurs at the less substituted position, but the regioselectivity is strongly dependent on the structural features of the substrate and the reaction conditions [2]. Other metals, such as Ir [11], Ru [12], Rh [13], Mo [14] or W [15] show the opposite regioselectivity, which is especially interesting for asymmetrically catalyzed reactions. However, with Pd-catalysts reactions may also occur at the sterically more hindered position. For example, using the allylic acetates **1** and **2** (Scheme 9-3), the alkylation of stabilized *C*-nucleophiles preferentially gives rise to **3**, while the attack at the less hindered position (providing **4**) plays only a minor role [16]. The reactions most likely proceed *via* a S_N1-type transition state.

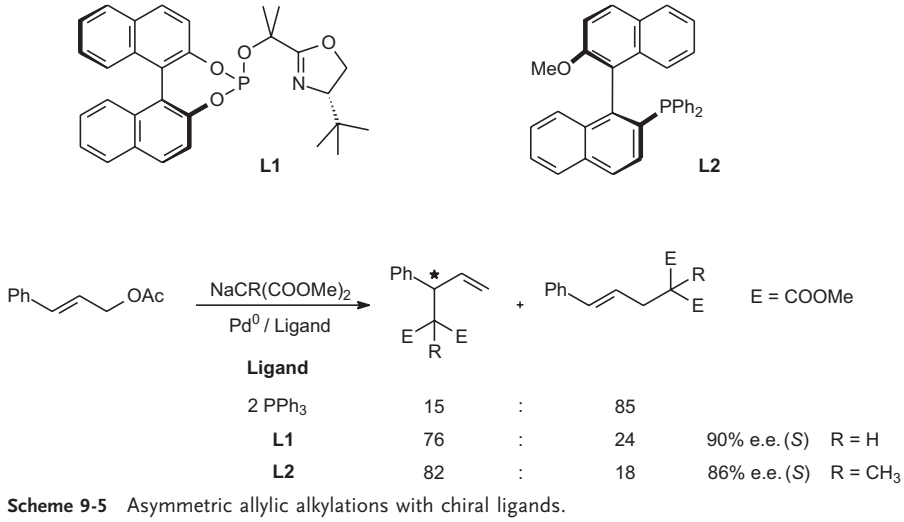


Scheme 9-3 Regioselectivity of Pd-catalyzed allylic alklyations.



Scheme 9-4 Transition states of allylic alkylations.

This indicates, that the regioselectivity can be influenced by "tuning the reaction mechanism" (Scheme 9-4) [17]. If the nucleophile attacks in a S_N2-type fashion, attack should occur at the sterically less hindered position (**A**). On the other hand, if the reaction proceeds *via* a cationic transition state (S_N1-type), the opposite regioselectivity can be expected (**B**). This transition state **B** can be favored by electron-withdrawing groups in the ligands; for example, phosphines can be replaced by phosphites [18]. Very good results are obtained with unsymmetrical ligands (Scheme 9-5), such as the phosphitoxazolines **L1** [17] or sterically demanding monophosphines **L2** [19]. The steric hindrance favors transition state **C** (Scheme 9-4), where the substituent on the allyl fragment is located *trans* to the bulky phosphorus ligand. Nucleophilic attack on the π-allyl system preferentially occurs *trans* to the P-atom [20], giving rise to the sterically more hindered product (Scheme 9-5). With chiral ligands, a good chirality transfer can be observed.

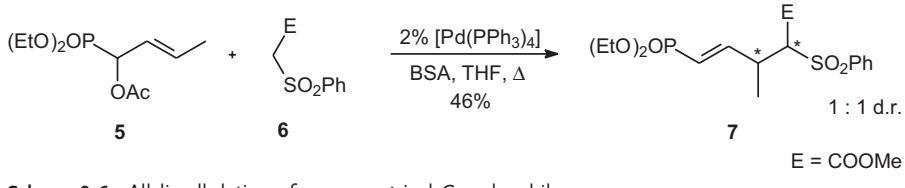


Scheme 9-5 Asymmetric allylic alkylations with chiral ligands.

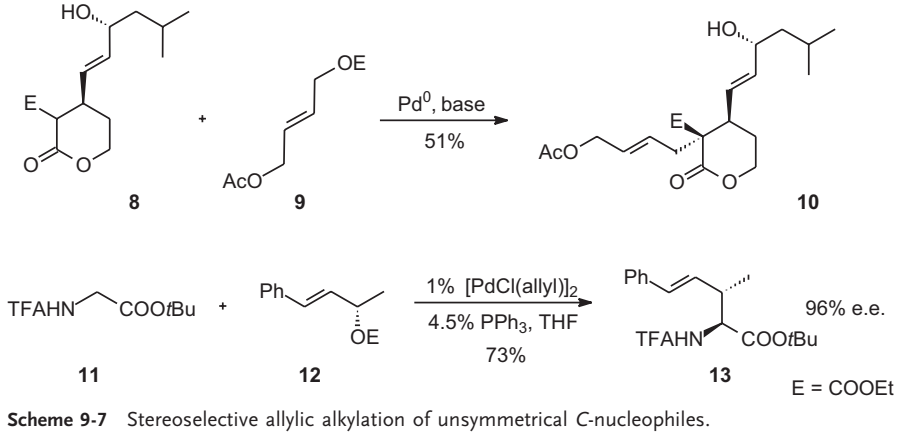
9.2.2
Stereochemical Aspects

The stereochemical course of the Pd-catalyzed allylic substitution has been studied extensively [21]. The first step – the attack of Pd(0) on a chiral allylic substrate – occurs from "the backside" under inversion of the configuration. The nucleophilic attack of *O*-, *N*-, and soft *C*-nucleophiles on the π-allyl complex again occurs from the *anti* face, and therefore overall retention of configuration is observed. In most cases, symmetrical nucleophiles such as malonates or disulfones are used to avoid a major problem of this reaction: the formation of a second stereogenic center in the "nucleophile moiety" of the product. Using unsymmetrical *C*-nucleophiles such as β-ketoesters [22] or imines of amino acid esters [23], mixtures of diastereomers are usually obtained. For example, reaction of the allylic acetate **5** with the unsymmetric nucleophile **6** gives the substitution products **7** in a 1:1 ratio [24] because of the configurational lability of the allylated nucleophile (Scheme 9-6).

Thus, considerably better results are obtained with alkylated derivatives [25], or with less acidic nucleophiles such as ester enolates (Scheme 9-7). For example, allylation of "cyclic malonate" **8** with **9** provides **10** as a single stereoisomer [26], while the attack of a chelated enolate obtained from **11** on allylic carbonate **12** gives rise to γ,δ-unsaturated amino acid derivative **13** (see Scheme 9-7) in a highly stereoselective fashion [27].



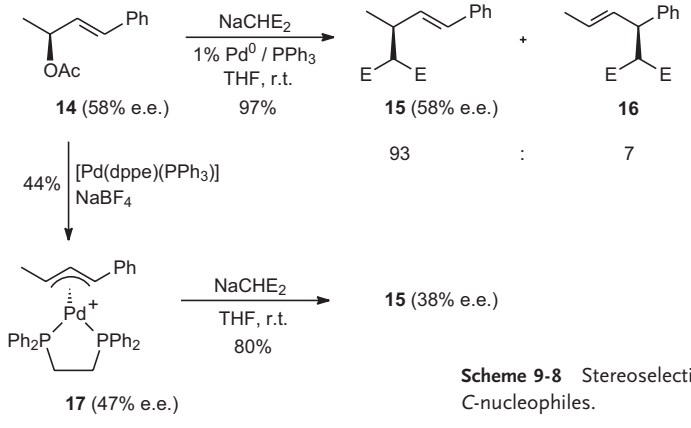
Scheme 9-6 Allylic alkylation of unsymmetrical *C*-nucleophiles.



Scheme 9-7 Stereoselective allylic alkylation of unsymmetrical *C*-nucleophiles.

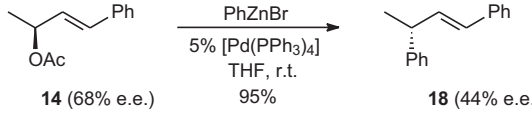
9.2.2.1 Substrate-Controlled Stereoselective Reactions

In general, the chiral information of the allylic substrate is completely transferred into the product (Scheme 9-8). Reaction of chiral allylic acetate **14** with sodium malonate in the presence of catalytic amounts of Pd(0) (1 mol %) provides the substitution product **15** preferentially and with the same enantiomeric excess [21e]. The minor product **16** is obtained by attack of the nucleophile at the other allylic position. Interestingly, if the reaction is carried out with stoichiometric amounts of palladium, the *e.e.* in the substitution product is significantly lower. This is also true, if the π-allylpalladium complex **17** is isolated and subsequently reacted with the nucleophile. Clearly, epimerization occurs under these conditions (see below).



Scheme 9-8 Stereoselective allylation of soft *C*-nucleophiles.

As already mentioned, hard *C*-nucleophiles such as main group organometallics react *via* transmetallation and transfer of the nucleophile from the side of the palladium onto the allyl fragment. In this case, overall inversion of configuration is observed [28], although some epimerization may occur (Scheme 9-9).



Scheme 9-9 Stereoselective allylation of hard *C*-nucleophiles.

9.2.2.2 Epimerization

Usually, epimerization can be suppressed in catalytic allylic alkylations, but if nucleophilic attack is not fast enough, then several processes for stereoscrambling become competitive.

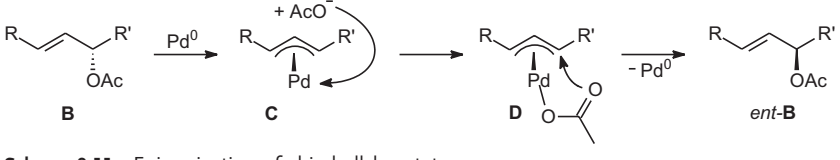
Epimerization *via* Pd-Pd-Exchange

This epimerization occurs preferentially if stoichiometric or high amounts of Pd-catalyst are used. The optically active π-allylpalladium complex (**A**) can be attacked by excess of Pd(0) catalyst (Scheme 9-10). In this case, the Pd(0) acts as a nucleophile and attacks the π-complex from the *anti* face giving rise to the enantiomeric π-allyl complex *ent*-**A** [29]. This mechanism might explain the fall in the optical purity described in Scheme 9-8 (**14** $\rightarrow$ **17** $\rightarrow$ **15**).

Scheme 9-10 Epimerization *via* Pd-Pd-exchange.

Epimerization *via* Acetate-Coordination

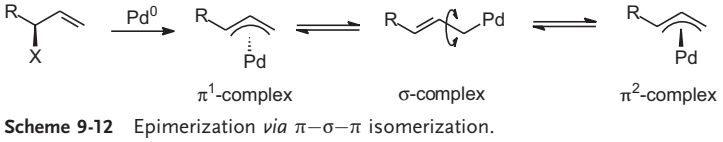
This epimerization occurs preferentially if chiral allyl acetates **B** are used as substrates (Scheme 9-11). After nucleophilic attack of Pd(0) on the acetate under inversion (**C**), the liberated acetate can coordinate to the palladium (**D**) and can be retransferred to the allyl fragment, this time not from the *anti* but from the *syn* face. This mechanism results in a racemization of the starting material, and might explain the fall in optical purity as observed in the conversion **14** $\rightarrow$ **18** (see Scheme 9-9).



Scheme 9-11 Epimerization of chiral allyl acetates.

π-σ-π isomerization

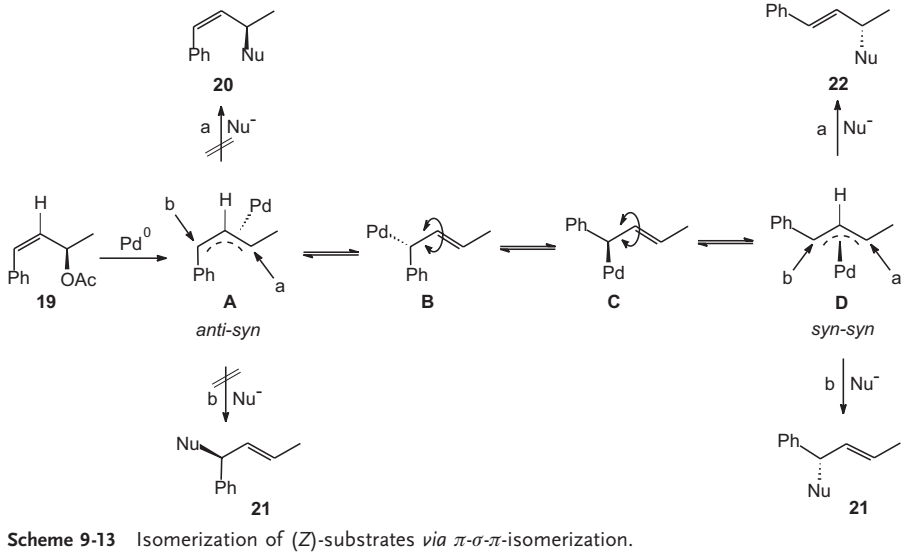
In addition, terminal alkenes can epimerize *via* π-σ-π isomerization (Scheme 9-12). This isomerization is an important mechanistic feature in π-allylpalladium chemistry and results in a rapid interconversion of π-allyl complexes into σ-complexes, and vice versa. On the stage of the σ-allyl complex, rotations around σ-bonds are possible, and therefore the thermodynamically most stable complexes are formed. If chiral allylic substrates are used with a terminal alkene moiety, this isomerization results in a loss of stereogenic information.



Scheme 9-12 Epimerization *via* $\pi-\sigma-\pi$ isomerization.

This is a general problem with this type of substrates, and chirality transfer is only observed for 1,3-disubstituted π-allyl complexes, which cannot racemize by this pathway. However, the isomerization might cause other consequences, depending on the substrate structure. No effect is observed with (*E*)-allylic substrates such as **14** (see Scheme 9-8), because the most stable *syn/syn*-complex is formed directly. The situation is quite different if (*Z*)-configured substrates such as **19** are used (Scheme 9-13). In this case, the *anti/syn*-complex **A** is formed. The *syn/anti* terminology is used to describe the orientation of the substituents at the allyl moiety relative to the H-atom at the central carbon atom. Reactions of **A** with nucleophiles would provide the (*Z*)-configured products **20** (attack a) or the (*E*)-configured product **21** (attack b) [30]. However, in general product **20** is not obtained. Instead, the π-σ-π isomerization causes a rapid interconversion of the π-complexes *via* rotation of the σ-complexes **B** and **C**, normally preferring the *syn/syn*-complex **D**, which gives rise to (*E*)-substitution products **22** and/or **21**.

Exceptions can only be observed if steric interactions either between the substituents in the allyl substrate [31] or between the allyl moiety and the ligands [32] destabilize the *syn/syn*-complex. However, selective palladium-catalyzed conversions of (*Z*)-allyl substrates with retention of the olefin geometry remain an unsolved problem [33]. A transfer of the (*Z*)-configuration from the allyl substrate to the product would only be possible if one could run the reaction at temperatures (below −60°C) where isomerization reactions do not yet take place. These can only be obtained with highly reactive nucleophiles such as chelated ester enolates, but not with the generally used stabilized soft *C*-nucleophiles [34].

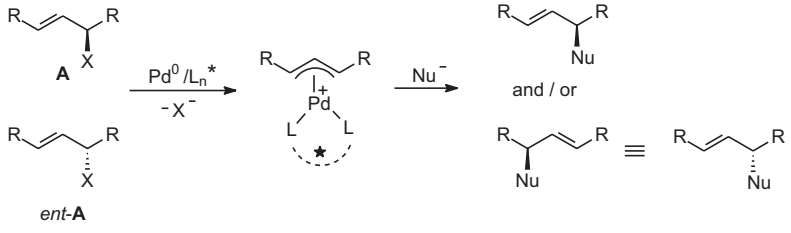


Scheme 9-13 Isomerization of (*Z*)-substrates *via* π-σ-π-isomerization.

9.2.2.3 Ligand-Controlled Stereoselective Allylation

Although the chirality transfer works very well in the case of unsymmetrical 1,3-disubstituted allylic substrates, problems arise if the substrates have two identical substituents either on both sides of the allyl fragment or on one side [35].

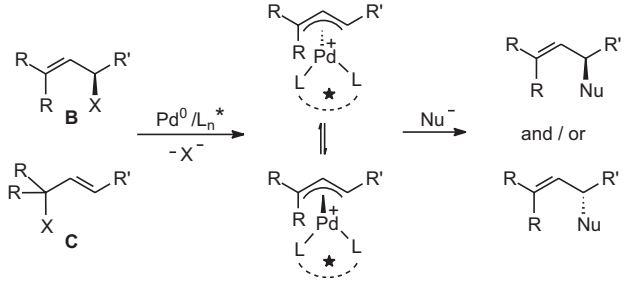
If 1,3-disubstituted substrates such as **A** or *ent*-**A** are used, symmetrical π-allylpalladium complexes (*meso*-complex) are formed which can react with nucleophiles at both allylic positions with the same probability (Scheme 9-14). Therefore, the chiral information of the substrates is lost, and the stereochemical outcome of the reaction can be controlled by chiral ligands (L*) on the palladium.



Scheme 9-14 Asymmetric allylic alkylations of symmetrical 1,3-disubstituted allylic substrates.

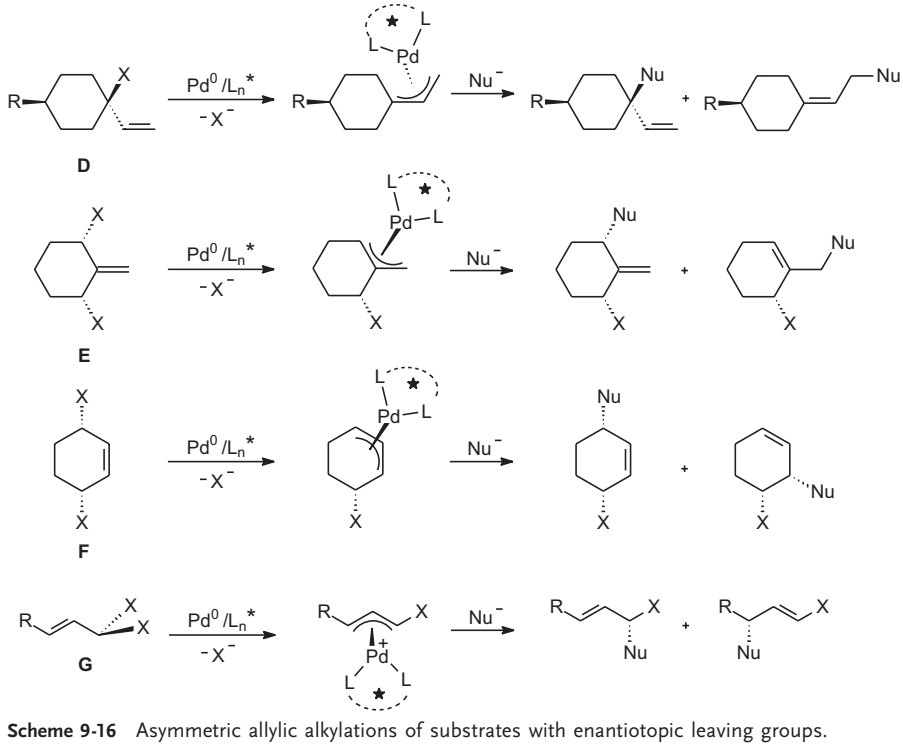
Enantiomeric substitution products can be obtained from enantiomeric ligands with the same rate of selectivity. In general, this is true in most cases, but sometimes different *e.e.*-values are observed, depending on the ligand or the leaving group used. This memory effect can only be explained if the substitution does not proceed *via* a fully symmetrical π-allyl complex, but a close ion pair mechanism [36].

Ionization of substrates **B** or **C**, both result in the formation of the 1,1-disubstituted π-allyl complexes, which can interconvert *via* π-σ-π-isomerization (Scheme 9-15). In this case, the reaction also can be controlled by chiral ligands. A high enantiomeric excess can be expected if the equilibrium is rapid, which is especially true if R = H, due to a low degree of steric congestion, and R = Ph because of π-benzyl participation. This is the reason, why chiral allylic substrates with terminal double bonds (**C**, R = H) in general lose their chiral information.



Scheme 9-15 Asymmetric allylic alkylations of symmetrical 1,1-disubstituted allylic substrates.

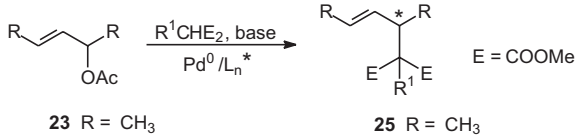
A third possibility is the use of *meso*-substrates with the leaving group in the mirror plane (**D**) or substrates bearing two enantiotopic leaving groups (**E–G**). In these cases, a chiral palladium-ligand complex must differentiate between the two enantiotopic faces of the alkene (**D**), or the two leaving groups, resulting in a chiral π-allylpalladium complex, which is then attacked by the nucleophile in a more or less regioselective fashion (Scheme 9-16). This overall process results in a desymmetrization of the allylic compound.



Scheme 9-16 Asymmetric allylic alkylations of substrates with enantiotopic leaving groups.

Reactions *via meso*-π-allylpalladium complexes

Enantioselective alkylation of a *meso*-π-allyl complex requires a regioselective attack of the carbanion at one of the diastereomeric π-allyl termini. Common substrates are 1,3-dialkylated or diarylated allylic acetates or carbonates such as **23** and **24** (Scheme 9-17). In general, the best results are obtained with the diphenyl substrate **24**, which gives the highest yields and stereoselectivities. Therefore, this substrate



23 R = CH_3
24 R = Ph

25 R = CH_3
26 R = Ph

Scheme 9-17 Allylic alkylations *via meso*-π-allylpalladium complexes.

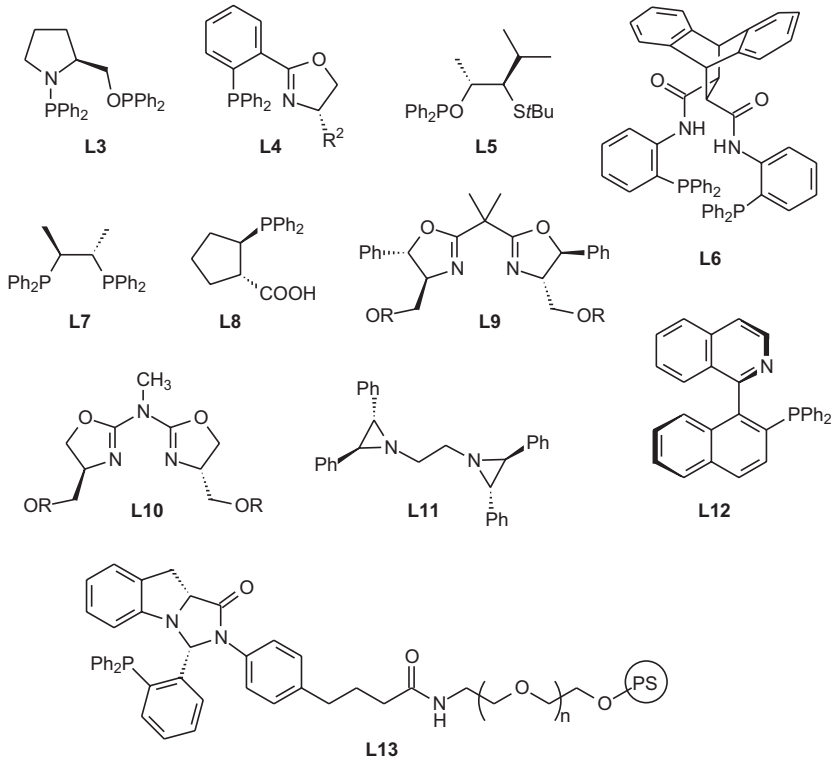


Figure 9-1 Selected ligands used in allylic alkylations of acyclic substrates.

is used for the development of new ligands. Their number is immense in the meanwhile. A few examples of commonly used types of ligands are shown in Figure 9-1, and further examples will be found in specialized reviews on this topic [35]. In by far the most cases, malonates or substituted malonates are used as nucleophiles, to avoid the problem of a second stereogenic center in the "nucleophile moiety". An overview over the results obtained is provided in Table 9-1.

The first investigations were carried out on dimethyl-substituted π-allylpalladium complexes in the presence of DIOP [40a] or Prolophos (**L3**) [41]. With these ligands the substitution product **25** was obtained with low optical purity ($\approx$ 20 % *e.e.*). A breakthrough was achieved by the introduction of the 2-(2-diphenylphosphinophenyl)-4,5-dihydrooxazoles (PHOX) **L4** as a new class of ligands [42, 43], and the C_2 symmetric diphosphine ligand **L6** [40b].

By far the most ligands are investigated with the diphenyl-substituted substrate **24**. The PHOX-ligands (**L4**) discussed are superior to most other ligands. Good results are also obtained with the *P,S*-ligand **L5** [38], Chiraphos (**L7**) [44] and the phosphinocarboxylic acid **L8** [45], but even higher enantioselectivities are obtained with the C_2-symmetric dihydroxyoxazol ligands **L9** [46b] and the *P,N*-ligand **L12** [46a]. The results of X-radiographic and NMR studies indicate that steric repulsion

Table 9-1 Allylic alkylations in the presence of chiral ligands

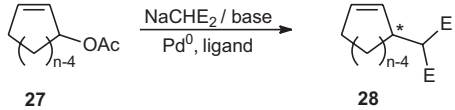
Substrate	*Ligand*	*R*	*R'*	*Base*	*e.e.* (%)	*Configuration*	*Ref.*
23	**L3**		H	NaH	20	(*S*)	[41]
	L4a,	Ph	H	BSA	50	(*S*)	[42a]
	L4b	*i*Pr	H	BSA	62	(*S*)	[37]
	L4c	*t*Bu	H	BSA	71	(*S*)	[42a]
	L5		H	BSA	65	(*S*)	[38]
	L6		H	NaH	74	(*S*)	[40b]
	L6		CH_3	NaH	87	(*S*)	[40b]
24	**L3**		H	NaH	30	(*R*)	[41]
	L4a	Ph	H	BSA	99	(*S*)	[42a]
	L4b	*i*Pr	H	BSA	98.5	(*S*)	[42a,b]
	L5		H	BSA	98	(*S*)	[38]
	L7		H	NaH	90	(*R*)	[44]
	L8		H	NaH	85	(*R*)	[50b]
	L9		H	BSA	97	(*S*)	[46b]
	L10		H	BSA	95	(*R*)	[46b]
	L11		H	BSA/NaH	99	(*S*)	[39]
	L12		H	NaH	98	(*R*)	[46a]
	L13		H	Li_2CO_3	91	(*S*)	[47]

between a phenyl group on the allyl moiety and the substituent in the chiral ligand enforces preferential attack at this more crowded terminus, since strain energy is relieved in the alkylation transition state.

With the recyclable polymer-bound ligand **L13** the allylic alkylation can be carried out also in aqueous solution, and surprisingly the catalyst is even more reactive in water than in organic solvents [47]. The corresponding palladium complex can be recovered by simple filtration, and can be reused without significant loss of activity.

In contrast especially to these diphenyl-substituted allylic substrates, the results obtained with cyclic substrates **27** were disappointing initially (Scheme 9-18). For example, if cyclohexenylacetate **27b** was reacted with dimethyl malonate in the presence of the PHOX-ligand **L4b**, no enantioselectivity was observed at all (Table 9-2) [43].

The results of NMR studies indicated that, in solution a mixture of *exo*- and *endo*-complex in a 1.8:1 ratio is formed. Obviously, the substituents in the ligand are not able to differentiate sufficiently between these two diastereomeric complexes. Based on these findings, a new type of PHOX-ligand **L14** was designed, bearing a 2-biphenyl (2-Bp) substituent on the phosphor atom (Figure 9-2) [48].



27
a n = 5, **b** n = 6, **c** n = 7

28

Scheme 9-18 Asymmetric allylic alkylations of cyclic substrates.

Table 9-2 Allylic alkylations with cyclic substrates 27

Ligand	*Substrate*	*Base*	*e.e.* (%)	*Configuration*	*Ref.*
L4b	**27b**	NaH	0	–	[24]
L8	**27b**	NaH	68	(*R*)	[45]
L14	**27b**	BuLi	51	(*R*)	[48]
L14	**27c**	BuLi	83	(*R*)	[48]
L15	**27b**	NaH	93	(*R*)	[49]
L15	**27c**	NaH	>99	(*R*)	[49]
L16	**27b**	BuLi	98	(*S*)	[51]
L16	**27c**	BuLi	98	(*S*)	[51]
L17	**27a**	NaH	98	(*S*)	[52]

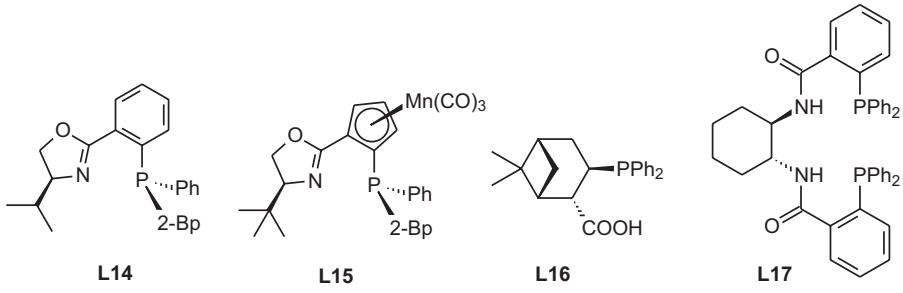


Figure 9-2 Ligands used for allylic alkylations of cyclic substrates.

The biphenyl group was chosen with the hope that this enlarged substituent might interact with the π-allyl fragment, resulting in a differentiation of the two possible diastereomeric complexes. And indeed, X-radiographic structure analysis of a corresponding cyclohexenyl-palladium complex confirmed, that in the crystal a conformer α is found in which the phenyl ring of the biphenyl group is located directly above the allylic moiety, as shown in Figure 9-3.

Nevertheless, results were still not satisfactory. Careful NMR investigations indicated that in solution several conformers exist, including the unfavorable conformer β with the crucial phenyl group rotated away from the allylic moiety. In order to destabilize conformers of this type, the cymantrene-based ligand **L15** was conceived [49], where this rotation is blocked by the manganese carbonyl complex, and indeed, high enantioselectivities were obtained (Table 9-2).

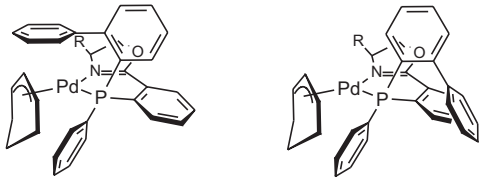
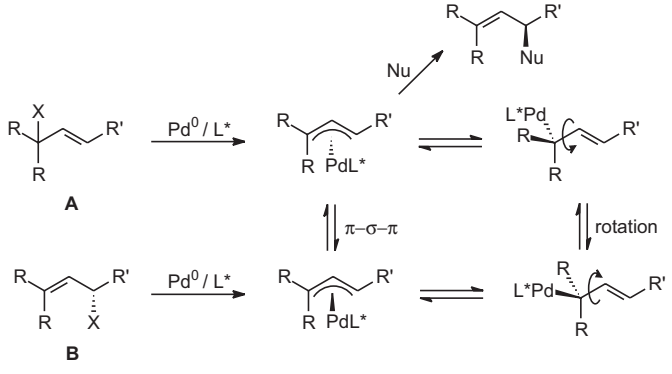


Figure 9-3 π-Allylpalladium complexes with ligand **L14** in solution.

The chiral phosphinocarboxylic acid ligand **L8** also exhibits good enantioselectivities [50]. Since the corresponding methyl ester only gives low enantiomeric excess, the free carboxylic acid is crucial for the success of the reaction. It is probable that a similar mode of action might explain the excellent selectivities obtained with ligand **L16** [51]. Both enantiomers can be obtained starting from (+)- and (–)-pinene. Excellent selectivities are also obtained with bis-2-diphenylphosphinobenzamide ligand **L17** [52].

Allylations *via* symmetrically 1,1-disubstituted π-allylpalladium complexes

Substrates with two identical substituents at one allyl terminus (a nonstereogenic center) are also interesting candidates for ligand-controlled allylations. For these reactions, either chiral or achiral substrates can be used. If achiral substrates such as **A** are investigated, the chiral catalyst can differentiate between the two enantiotopic faces of the alkene (Scheme 9-19). On the other hand, if substrates such as **B** are used as starting materials, the initially formed π-allyl complex must isomerize rapidly to ensure that the chiral information of the substrate is completely lost during the reaction and that the stereochemical outcome of the alkylation is only controlled by the chiral ligand.



Scheme 9-19 Isomerization of symmetrical 1,1-disubstituted allylic substrates.

Especially suitable in this respect are aryl-substituted substrates, because the aryl ring can participate in the "σ-complex", as shown for the triphenylated intermediate **C** (Figure 9-4). This complex isomerizes 1000-fold faster in comparison with the corresponding trimethylated complex.

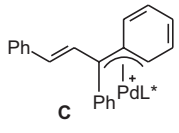
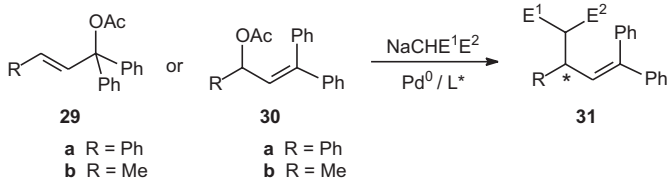


Figure 9-4 σ-Complex intermediate formed from triphenylated allylic substrates.



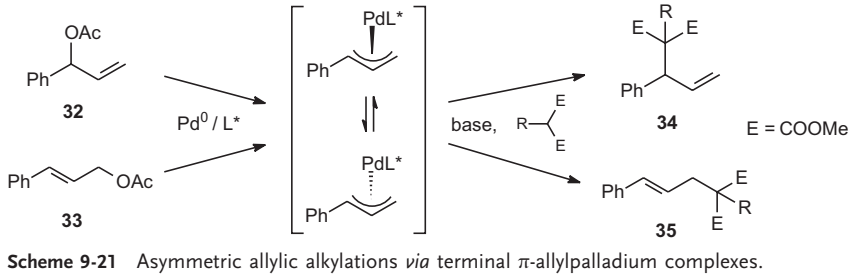
Scheme 9-20 Asymmetric allylic alkylations of 1,1-diphenylated allylic substrates.

Therefore, 1,1-diphenylated allylic compounds **29** and **30** are the most examined substrates of this class (Scheme 9-20), providing products **31**. Initial investigations conducted in the presence of Chiraphos **L7** gave high *e.e.* values which were independent of the substrate used [53]. In this case, the optical yield does not depend on the substrate used (**29** or **30**) (Table 9-3). The best results to date are obtained in the presence of the PHOX-ligands such as **L4b**.

Table 9-3 Allylic alkylations with 1,1-diphenylated allylic substrates

Substrate	*Nucleophile* E^1	E^2	*Ligand*	*e.e.* (%)	*Yield* (%)	*Configuration*	*Ref.*
29a	COOMe	COOMe	**L7**	84	100	(*R*)	[53]
30a	COOMe	COOMe	**L7**	84	100	(*R*)	[53]
30b	COOMe	COOMe	**L7**	65	96	(*R*)	[53]
29a	COOMe	COOMe	**L4b**	99	88	(*S*)	[54]
30a	COOMe	COOMe	**L4b**	99	88	(*S*)	[54]
30a	COOMe	CN	**L4b**	96	74	(*S*)	[55]
30b	COOMe	COOMe	**L4b**	95	95	(*S*)	[55]

From a synthetic viewpoint – for example, for natural product synthesis – terminal alkenes such as **32** (Scheme 9-21) are even more attractive, although the regioselectivity of the nucleophilic attack is the limiting factor, because attack at the less hindered position is preferred. However, as mentioned previously, the regioselectivity can be changed by switching to other metals or by using sterically demanding nucleophiles or phosphites [18] (see Section 9.2.1.2). Some currently



Scheme 9-21 Asymmetric allylic alkylations *via* terminal π-allylpalladium complexes.

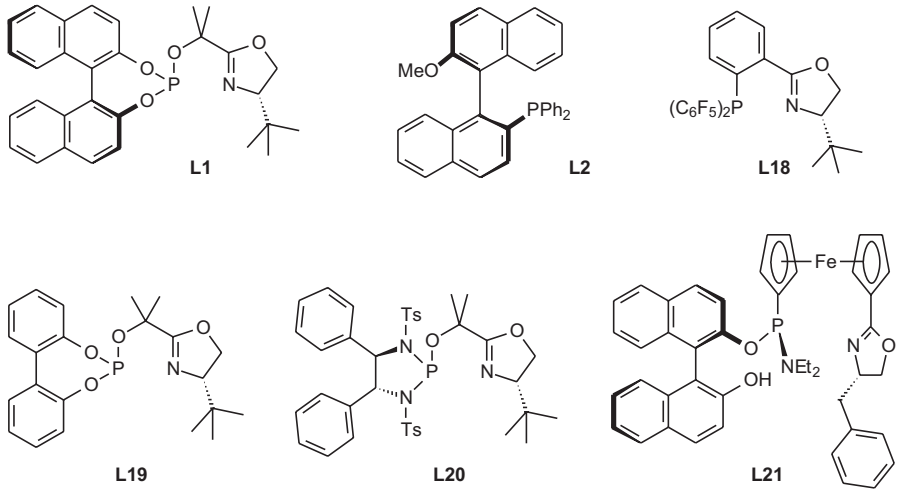


Figure 9-5 Chiral ligands for regioselective attack at the sterically more hindered position.

used ligands are shown in Figure 9-5, and the results obtained with these are summarized in Table 9-4.

The monodentate ligand (*R*)-MeO-MOP (**L2**) was investigated in several allylic substitutions [19]. It is noteworthy that the reaction catalyzed by palladium/PPh_3 requires 2 equiv. phosphane (to Pd) for the allylation to proceed smoothly, giving rise to linear product **35** preferentially. With 1 equiv. the reaction stopped at 60 % conversion. On the other hand, ligand **L2** gave the branched isomer **34** with good regioselectivity under the same conditions. In this case, the ratio phosphine/Pd affects neither the catalytic activity nor the regioselectivity.

Another class of ligands was developed starting from the phosphinoxazolines (PHOX) ligands (*vide infra*). The idea was to increase the S_N1-character of the reaction (see Section 9.2.1.2) by increasing the electrophilic nature of the Pd by using less electron-donating ligands such as **L18**. In addition, several phosphitoxazolines were investigated (up to 84 % *e. e.*). The stereochemical outcome of the reaction was

Table 9-4 Allylic alkylations of terminal π-allyl complexes

Substrate	*Ligand*	*R*	*Base*	*Ratio 34/35*	*e. e.* (%)	*Yield (%)*	*Configuration*	*Ref.*
32	**L2**	Me	NaH	79/21	68	99	(*S*)	[19]
33	**L18**	H	BSA/KOAc	47/53	84	87	(*S*)	[17]
33	**L19**	H	BSA/KOAc	63//37	81	75	(*S*)	[17]
33	**L1**	H	BSA/KOAc	76/24	90	86	(*S*)	[17]
32	**L1**	H	BSA/KOAc	66/34	88	82	(*S*)	[17]
33	**L20**	H	BSA/KOAc	84/16	94	95	(*S*)	[56]
33	**L21**	H	BSA/KOAc	95/5	95	98	n. r.	[57]

mainly controlled by the stereogenic center of the oxazoline ring (**L19**), but introduction of additional stereogenic centers in the ligand resulted in higher selectivities in the "*matched case*". The (*S*,*S*)-ligand **L1** gave the overall best results. The selectivities could even be improved by increasing the steric demand of the aryl substituent in the allyl substrate, while the position of the leaving group had no significant influence on the results obtained. Alkyl-substituted allylic substrates are less suitable. Further improvements were observed by introducing the bis(*N*-tosylamino)phosphine ligand **L20** [56] and especially the ferrocene P,N-ligand (**L21**), which is the best one for this purpose to date [57]. The problem of regioselectivity can be overcome if the allylic alkylation is performed not in an inter- but rather an intramolecular fashion. In this case, the formation of the "preferred ring size" can direct the nucleophilic attack to the sterically more hindered position [58, 59].

Allylic alkylations with *meso* substrates

If *meso* compounds are used as substrates, one can distinguish between three miscellaneous scenarios of enantiodifferentiation. In substrates of type **A** (Figure 9-6), the palladium atom will test out both faces of the olefin, and the enantiodifferentiating step is the formation of the alkene palladium complex. The situation is quite different if *meso*-diesters **B** are used. In this situation, the palladium atom coordinates to the alkene from the face opposite to both leaving groups, and the stereocontrolling step is the differentiation between these two enantiotopic leaving groups. Geminal diesters **C** involve both, enantioface complexation and ionization in the enantiodiscriminating step.

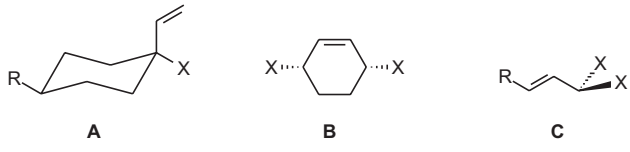
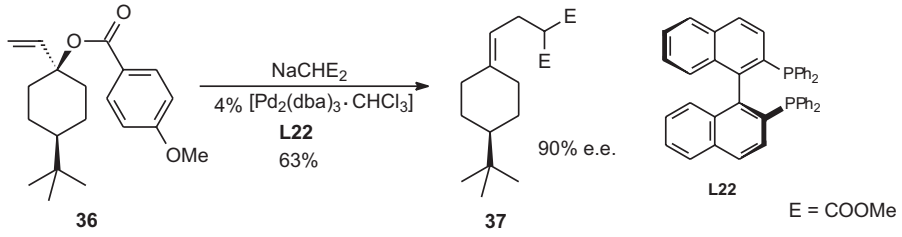


Figure 9-6 Allylic alkylations with *meso* substrates.

Enantioselective alkylation of *meso*-ester **36** occurs regioselectively at the sterically least hindered position, giving rise to axially chiral product **37** (Scheme 9-22). (*R*)-Binap (**L22**) has been found to yield the highest *e.e.* compared to a wide range of other ligands, while dioxane is the solvent of choice [60]. The most striking fact is that the *trans*- and *cis*-substrate diastereomers give rise to different *e.e.* values with the same chiral phosphine, indicating that isomerization of the π-allylpalladium complex is not fast compared to nucleophilic attack.

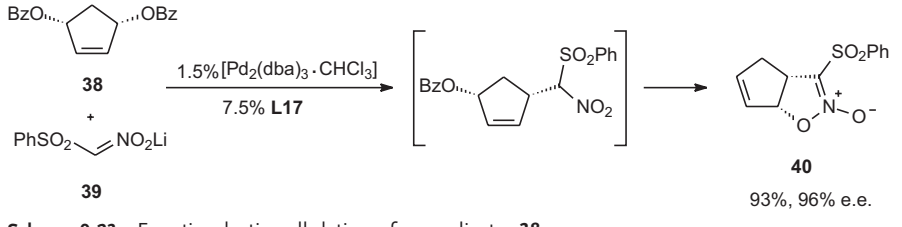
Ionization of the leaving group is the stereocontrolling step in the reaction of *meso*-diester **38** with several nucleophiles such as the lithium salts of nitromethylphenylsulfone **39** (Scheme 9-23). Substitution occurs on the chiral π-allyl complex with inversion of the configuration regioselectively at the allylic terminus distant to the electron-withdrawing ester group. Subsequent intramolecular *O*-alkylation yields the cyclization product **40**. The best results were obtained with C_2-symmetric ligands, while the previously described ligand **L17** (see Figure 9-1) proved superior



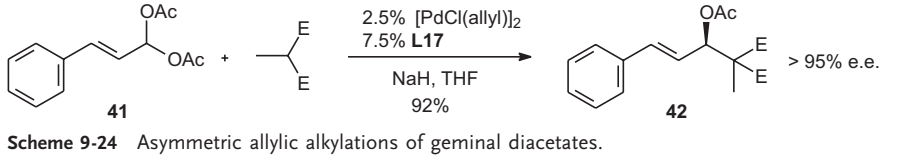
Scheme 9-22 Enantioselective alkylation of *meso*-ester **36**.

to all others [61]. Since the enantiodiscrimination occurs only in the ionization step, the results obtained are almost independent of the nucleophile used [62].

Geminal dicarboxylates convert the problem of asymmetric addition to the enantiotopic faces of an aldehyde into asymmetric ionization of enantiotopic leaving groups [63]. As in the other examples described, the ligand **L17** proved superior to other ligands, especially with regard to enantioselectivity. For example, if the diacetate **41** (Scheme 9-24), obtained from (*E*)-cinnamaldehyde, was reacted with dimethyl methylmalonate, the reaction gave the desired product **42** as a single regioisomer in high yield and enantiomeric excess. No double substitution was observed. The high *e. e.* values obtained with ligand **L17** or with the enantiomeric ligand *ent*-**L17** can be explained by a counterclockwise or clockwise rotation of the ligand with respect to the substrate [64]. With other alkyl-substituted substrates the regioselectivity was a little worse, but still >90 % for substitution at the oxygenated allyl terminus. This regioselectivity observed is primarily reflective of the strong electronic effect of an oxygen atom that stabilizes the α-cation through resonance, favoring nucleophilic attack at this carbon. The scope and limitation of this process was evaluated with a wide range of *C*- and heteronucleophiles. The *e. e.* values obtained for the first allylation step are about 90 % in most cases [65].



Scheme 9-23 Enantioselective alkylation of *meso*-diester **38**.



Scheme 9-24 Asymmetric allylic alkylations of geminal diacetates.

9.2.3
Substrates for Allylic Alkylations

π-Allyl complexes can be prepared stoichiometrically with palladium(II) starting from alkenes [66] and dienes [67] or – which is by far the most interesting method – catalytically with palladium(0) from allylic derivatives with a generally anionic leaving group. Suitable substrates are shown in Figure 9-7.

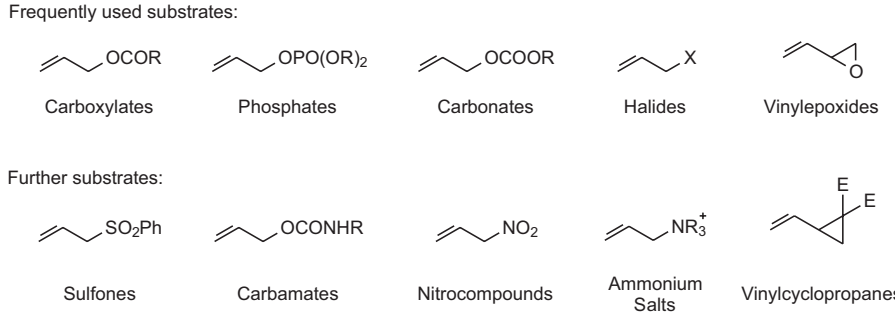


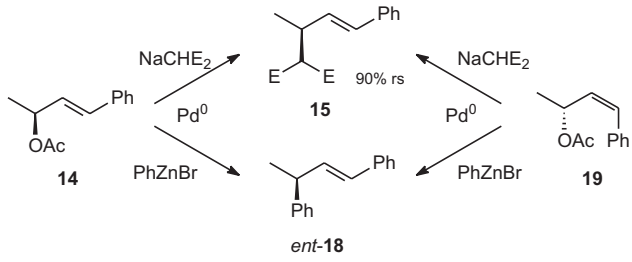
Figure 9-7 Common substrates for allylic alkylations [68–72].

9.2.3.1 Allylic Alkylations under Basic Conditions

Allyl esters

Allylic esters are used as main substrates for palladium-catalyzed allylic alkylations. Under these substrates, acetates play a dominant role, though other esters can also be used. In general, the reactivity of the allylic substrate correlates with the acidity of the carboxylic acid. For example, allylic trifluoroacetates are much more reactive than acetates. The great popularity of the carboxylates results from the fact, that these are notoriously bad leaving groups in comparison to, for example, either halides or tosylates. In general, allylic esters do not participate in substitution reactions, but they react very well *via* π-allyl-intermediates if transition metals are added.

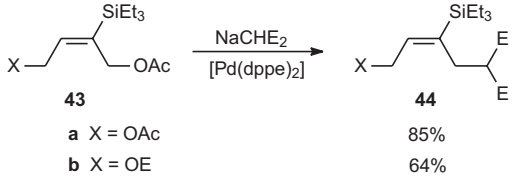
With allylic esters, the reactions are carried out under basic conditions. Tertiary amines or NaH are commonly used as bases, but basic alumina or KF on alumina are also quite attractive, because these can easily be removed by simple filtration [73]. With *N,O*-bis(trimethylsilyl)acetamide (BSA), the reactions can be carried out under near-neutral conditions, because the actual base is generated from the liberated carboxylate, and therefore only catalytic amounts of base are present in the reaction [74]. If optically active allylic carboxylates are used, the reaction proceeds with overall retention (double inversion) with stabilized, soft *C*-nucleophiles, while unstabilized carbanions react under inversion (Scheme 9-25). Substrates with (*Z*)-olefin geometry in general undergo π-σ-π isomerization, which is faster than substitution by the nucleophile [75]. Therefore, the (*S*)-configured (*E*)-sub-



Scheme 9-25 Allylic alkylations with allylic acetates (rs = ring structure).

strate **14** and the (*R*)-configured (*Z*)-acetate **19** both give rise to the same substitution products, independently of whether soft or hard nucleophiles are used [76]. The intramolecular allylation of soft *C*-nucleophiles with allylic acetates is a good protocol for the synthesis of ring structures of different size [77]. Several examples of this are outlined throughout this review.

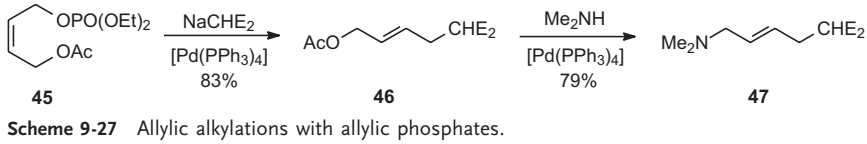
Interesting observations are made if silylated allylic acetates are used as substrates [78]. Comparative experiments indicated that *α*-silylated acetates are much more reactive in comparison to *β*-silylated acetates. Therefore, silylated substrates such as **43** undergo regioselective substitution at the acetate vicinal to the silyl substituent (Scheme 9-26) [79]. Since it is known that carbonates are better leaving groups than acetates, silylated substrate **43b** serves as an interesting example to investigate the influence of the silyl group. Under neutral conditions, no reaction was observed, yet surprisingly, in the presence of base, substitution occurred at the position of the acetate group, and not as expected at the carbonate position [21].



Scheme 9-26 Allylic alkylations with silylated allylic substrates.

Allyl phosphates

Allylic phosphates can also be used as substrates, while phosphates are in general more reactive in comparison with acetates [80]. The higher reactivity of the phosphates in comparison with acetates allows a stepwise substitution of allylic substrates such as **45** (Scheme 9-27). The phosphate group was replaced first under

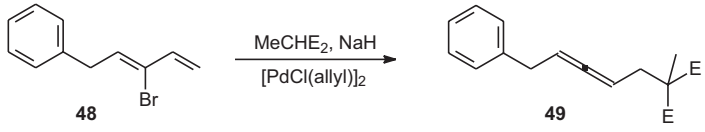


Scheme 9-27 Allylic alkylations with allylic phosphates.

double-bond isomerization, and the remaining acetate **46** can be subjected to a second allylation step, giving rise to the disubstituted product **47**.

Allyl halides

Allyl chlorides belong to the most reactive allylic substrates and, as such, should not be prone to epimerization on the stage of the π-allyl-Pd complexes. Therefore chemoselective substitutions are possible with allylic halides/acetates [81]. If halogenated dienes such as bromide **48** are used (Scheme 9-28), then the protocol gives access to substituted allenes **49** [82].



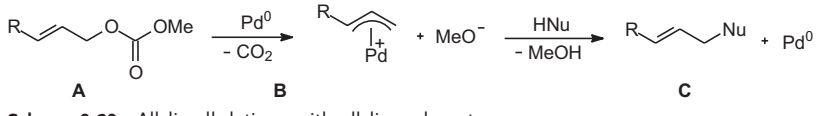
Scheme 9-28 Allylic alkylations with allyl chlorides.

9.2.3.2 Allylic Alkylations under Neutral Conditions

Reactions which proceed under neutral conditions are highly desirable, and several allylic substrates meet this requirement.

Allyl carbonates and carbamates

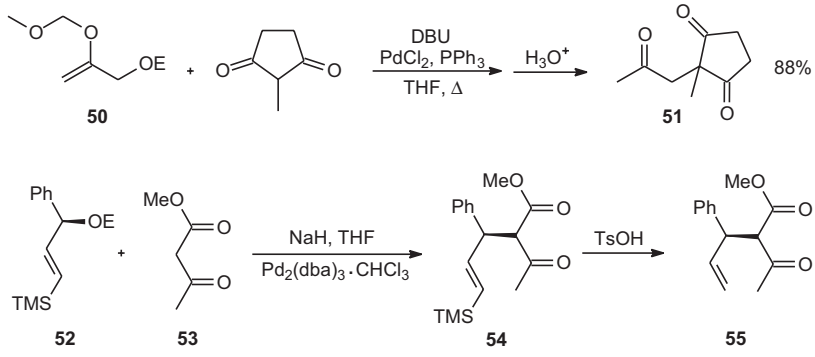
Allylic carbonates are the most reactive of these derivatives [83]. Oxidative addition of the allyl carbonate **A** is followed by decarboxylation to afford the positively charged π-allylpalladium complex **B** and alkoxide which acts as base for the deprotonation of the nucleophile (Scheme 9-29). The in-situ formation of the alkoxide, which is a poor nucleophile, is the reason why no additional base has to be used. In addition, the decarboxylation makes formation of the π-allyl complex an irreversible process, in contrast to the reactions of acetates.



Scheme 9-29 Allylic alkylations with allylic carbonates.

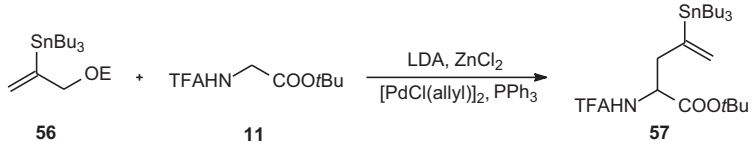
Allylic carbamates behave in a similar manner, and can also be used under neutral conditions [69]. Allylic carbonates are more reactive than acetates, and therefore, chemoselective reactions are possible [83]. Since allylation with allyl carbonates proceeds under relatively mild neutral conditions, this protocol finds wide applications for the allylation of labile compounds, and is sensitive towards acids and bases [84]. Allylic alkylation of *C*-nucleophiles with carbonates such as **50** (Scheme 9-30), followed by hydrolysis, is a good method for "acetonation" (**51**)

[85]. If silylated allylic carbonates such as **52** are used, then the nucleophilic attack of **53** occurs preferentially at the allyl terminus opposite to the silyl group [86]. The silyl group in **54** can subsequently be removed under acidic conditions, giving rise to **55**. Overall, substitution takes place at the sterically more hindered position.



Scheme 9-30 Reactions of functionalized allylic carbonates.

From a synthetic viewpoint, interesting substrates are stannylated carbonates such as **56** (Scheme 9-31), which can easily be obtained by molybdenum-catalyzed hydrostannation of propargyl esters in a highly regioselective fashion [87]. Reaction with highly reactive nucleophiles, such as chelated enolates of amino acid esters **11**, gives rise to stannylated amino acids **57** [88], which can be further modified by various palladium-catalyzed cross-coupling reactions [89].

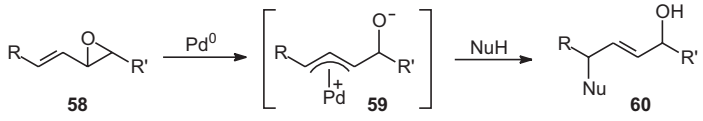


Scheme 9-31 Allylic alkylations with stannylated allylic carbonates.

Vinyl epoxides

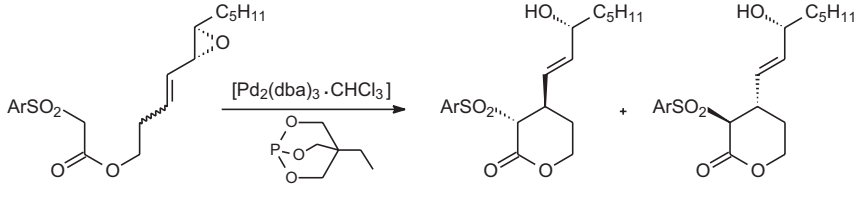
Vinyl epoxides (vinyl oxiranes) are highly efficient substrates which can also be reacted under neutral conditions (Scheme 9-32). The carbon-oxygen bond in **58** is easily cleaved with Pd(0) by oxidative addition under formation of the π-allylpalladium complex **59**. This cleavage generates an alkoxide, which in turn deprotonates the nucleophile. Nucleophilic attack occurs preferentially at the allylic position away from the remaining hydroxy group, giving rise to the 1,4-substituted product **60** [90]. The allylic alcohol thus formed is a good substrate (after acylation) for further palladium-catalyzed transformations.

Similar to allylic carbonates, vinyl epoxides are also more reactive in comparison with allylic acetates. In substrates containing both structural features, only the vinyloxirane moiety reacts chemoselectively under neutral conditions, and the



Scheme 9-32 Allylic alkylations with vinyl epoxides.

1,4-adduct is formed preferentially [91]. The stereochemical outcome of intramolecular reactions was investigated with substrates such as **61**. Palladium attacks the double bond from the face opposite to the oxirane ring (1. inversion). Nucleophilic attack occurs under inversion, and overall a *syn*-S_N2'-type reaction is observed. The relative configuration of the product (**62** or **63**) depends on both, the geometry of the epoxide and the geometry of the double bond (Scheme 9-33). Changing either of the geometries leads to the opposite diastereomer [92].



(*E*)-isomer	92	:	8
(Z)-isomer	5	:	95

Scheme 9-33 Stereoselective cyclizations with vinyl epoxides.

9.2.4 Nucleophiles used in Allylic Alkylations

9.2.4.1 Reaction with Stabilized, "Soft" Nucleophiles

π-Allylpalladium complexes can be regarded as "soft" electrophiles, and react most smoothly with "soft" nucleophiles. Representative examples (and their references) are shown in Figure 9-8. Typically, active methylene compounds activated by two electron-withdrawing groups are allylated by the palladium-catalyzed reaction. In general, carbonyl, sulfonyl, cyano, and nitro groups and combinations thereof are used for activation. Nitroalkanes alone are sufficiently acidic to be deprotonated and to function as a nucleophile. Other very suitable and popular nucleophiles include iminoesters and azlactones, because they provide amino acid derivatives. This group of nucleophiles will be discussed in further detail.

By far the most often used nucleophiles are malonates, which can be deprotonated by the alkoxide formed in the reaction of allyl carbonates, or by additional base such as NaH. This standard nucleophile was applied to all types of allylic alkylations, and many applications are reported in this chapter. The nucleophilic

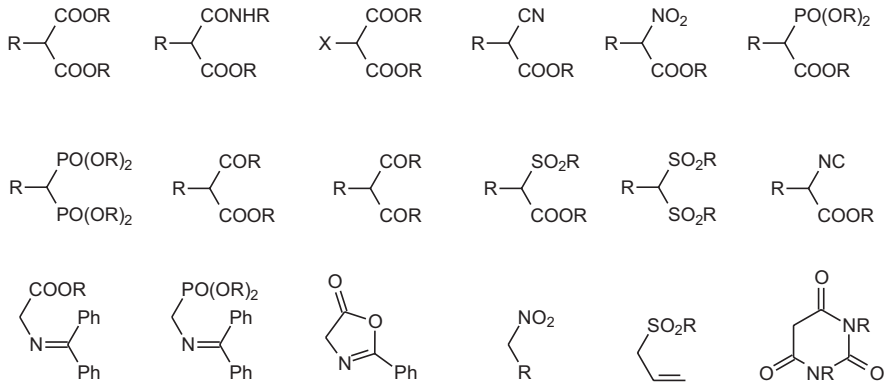


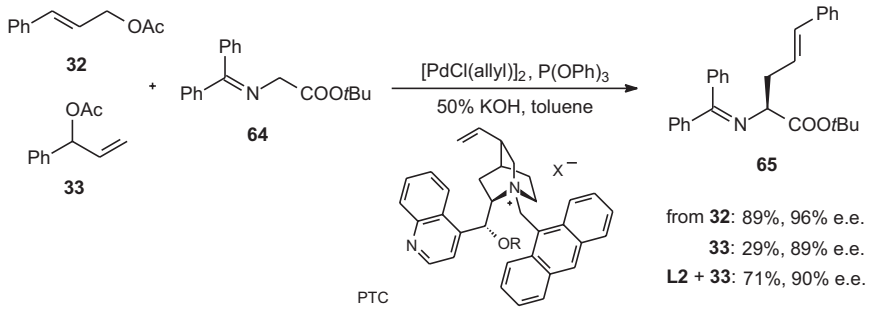
Figure 9-8 Common nucleophiles for Pd-catalyzed allylic alkylations [93–110].

species can also be generated by 1,4-addition (e. g., of alkoxides, generated from carbonates) onto alkylidene malonates in an inter- as well as an intramolecular fashion [111]. The substitution products can be subjected to a thermal decarboxylation, giving rise to carboxylic acids or esters [112]. Therefore, in combination with this decomposition, malonates can also be used as surrogates for ester enolates [113], which generally cannot be used as nucleophiles in allylic alkylations (see Section 9.2.4.2).

Reactions with β-keto esters in general are not as easy as those with malonates for several reasons. In contrast to the symmetrical malonates, reactions of β-keto esters, as well as all other unsymmetric nucleophiles, generate a stereogenic center which is configurationally labile (if α-CH is present), giving a mixture of stereoisomers. Also, one must consider the possibility of *C*- versus *O*-allylation, whilst products with different ring sizes may be obtained by intramolecular processes [114].

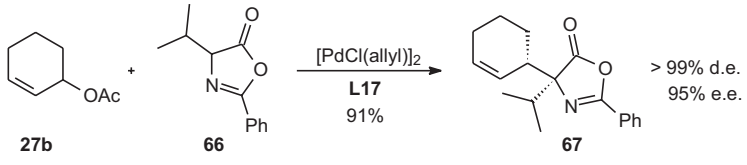
If nucleophiles activated by one or two sulfonyl groups are used, the sulfonyl residues can be removed afterwards under reductive conditions [115], or by elimination [116]. Nitrocompounds can easily be reduced to the corresponding amines [108], which is especially interesting for natural product synthesis.

From this viewpoint, the imines of amino acids **64** (Scheme 9-34) as well as azlactones **66** (Scheme 9-35) are interesting candidates, as they provide an easy access to γ,δ-unsaturated amino acids. Asymmetric versions with imines are possible to obtain, for example, by using chiral auxiliaries in the ester moiety [117], chiral ligands [118] or chiral phase transfer catalysts (PTC) [119]. Interestingly, the *e. e.* values obtained under PTC are better, with up to 96 % *e. e.* being obtained under optimized conditions in the allylation with cinnamyl acetate **32**, while the selectivity with the regioisomer **33** was little worse. Surprisingly, the yield was dramatically lower, because with the latter substrate the other regioisomer (attack at the phenyl-substituted terminus) was also formed [120]. The yield of **65** could be increased by using the chiral monodentate ligand (*R*)-MeO-MOP (**L2**), which surprisingly provided the linear product and not the branched one as expected (see Section 9.2.1.2).



Scheme 9-34 Asymmetric allylic alkylations under phase transfer conditions.

The major problem with stabilized nucleophiles with regard to stereoselectivity results from the configurational lability of the substitution product. Even if the allylation proceeds in a highly stereoselective fashion, subsequent epimerization of the newly generated stereogenic center wastes all efforts. This problem can be circumvented by using alkylated nucleophiles such as azlactone **66.** In the presence of chiral ligand **L17**, the substitution product **67** was obtained in excellent yield and selectivity. A wide range of substrates and azlactones was investigated, and the products were converted to several α-alkylated amino acids [121]. Besides allylic acetates and carbonates, *gem* diacetates can also be used for this purpose, as illustrated in an excellent synthesis of Sphingofungin F based on this approach [122].



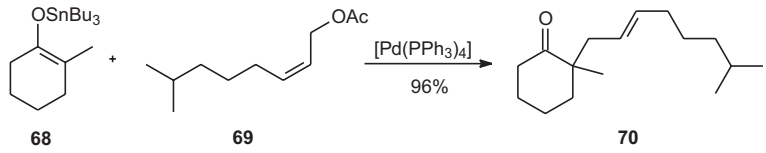
Scheme 9-35 Asymmetric allylic alkylations with azlactones as nucleophiles.

9.2.4.2 **Reaction with Enolates and Derivatives**

Nonstabilized enolates from ketones and esters often cause problems, and the developments and improvements made with these interesting nucleophiles are summarized in a little more detail [123].

Ketone enolates

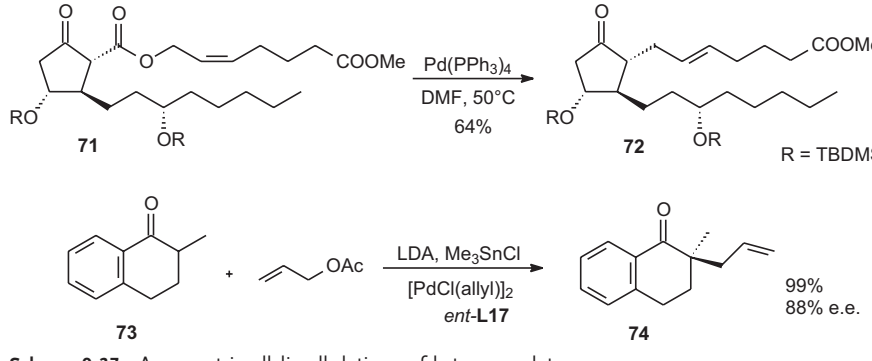
Allylic alkylation of simple enolates, such as that from acetophenone, with allyl acetate give the dialkylated product preferentially [124], whilst for sterically more demanding cyclic acetates monosubstitution is observed, though in moderate yield [125]. Similar results are obtained with the less-reactive silyl enol ethers, but herewith the reaction cannot be extended to substituted allyl acetates. A breakthrough brought a variation of the counterion of the enolate. Switching to tributyl-



Scheme 9-36 Allylic alkylations of tin enolates.

tin enolates such as **68** led to a remarkably rapid and clean monoalkylation with high regioselectivity (Scheme 9-36) [124]. Alkylation generally occurs at the sterically less hindered position of the allyl fragment, and the (*E*)-configured product **70** is obtained preferentially independently of the olefin geometry of the starting allylic acetate **69** [126].

The effect of the countercation was carefully investigated. Good results are also obtained with boron and zinc enolates, whilst a wide range of other counterions gave unsatisfying results or did not show any reaction at all [127]. The enolates can also be created in situ, for example by copper-catalyzed addition of alkylzinc reagents to *α,β*-unsaturated ketones [128], or from allyl *β*-ketocarboxylates such as **71** [129]. Subsequent decarboxylation gives rise to allylated ketone **72**. If optically active allylic substrates were used, the reactions proceeded with net retention, as with stabilized nucleophiles [130]. Chirality can also be induced by the use of chiral ligands such as **L17**, as shown for the allylation of ketone **73** to **74** (Scheme 9-37) [131]. Similar results are also obtained with ferrocene-based ligands [132].

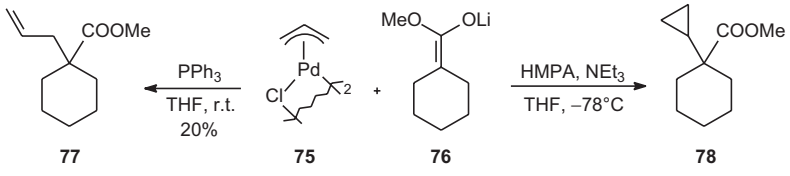


Scheme 9-37 Asymmetric allylic alkylations of ketone enolates.

Ester enolates

A quite different situation is that when ester enolates are used as nucleophiles. The yields obtained are generally low, and it is assumed that nonstabilized carbanions attack the metal in preference to the allyl group [133], resulting in reduction of the complex rather than alkylation. However, the addition of HMPA to this reaction completely suppresses reduction and permits the alkylation to proceed also with nonstabilized carbanions [134]. For example, treatment of *π*-allylpalladium chloride

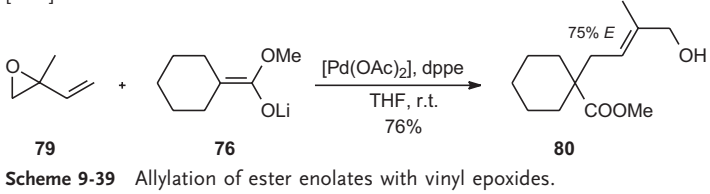
(**75**) with the enolate of methyl cyclohexanecarboxylate (**76**) (stoichiometric reaction) under standard conditions (PPh_3, THF) led to only a very low yield of the allylated product **77** (Scheme 9-38). Repeating the reaction in the presence of HMPA and triethylamine (replacing the PPh_3) gave rise not to the "expected" allylation product **77** but to the cyclopropane derivative **78** in good yield. Labeling studies indicated that the carbanion attacks the central carbon of the π-allyl complex. This is in sharp contrast to the attack of stabilized nucleophiles and the observations made with ketone enolates.



Scheme 9-38 Allylic alkylations of ester enolates.

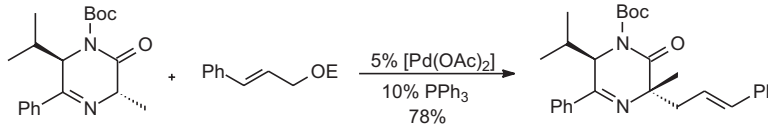
Interestingly, CO has a positive effect on the yield of the reaction, although it is not incorporated [135]. It is observed, that the combination TMEDA/CO is superior to HMPA/NEt_3 under the same reaction conditions. Under these conditions not only sterically hindered ester enolates can be reacted, but also deprotonated amides, lactams, ketones and sulfones, as well as Evans-enolates [136]. Tertiary anions give the best results.

In contrast, α-allylated products were obtained if ester enolates **76** were reacted with vinyl epoxides (**79**), though the yields varied depending on the vinyl epoxide used (Scheme 9-39) [137]. As usual, nucleophilic attack occurs at the sterically less hindered position, yielding a *E*/*Z*-isomeric mixture of **80**. Similar results are obtained with silyl ketene acetals in the presence of bidentate phosphine ligands [138].



Scheme 9-39 Allylation of ester enolates with vinyl epoxides.

The great importance of nonproteinogenic amino acids including α-substituted derivatives led to an investigation of modified amino acid ester enolates as nucleophiles in the palladium-catalyzed allylic alkylation (Scheme 9-40). Chiral pyrazinone derivative **81**, obtained from (*R*)-valine and (*S*)-alanine, was introduced as a new chiral auxiliary for the synthesis of γ,δ-unsaturated amino acids *via* palladium-catalyzed allylation [139]. Pyrazinone **81** underwent highly regio- and diastereoselective allylations (95–99 % d. s.) to **83** under neutral conditions if allylic carbo-



81 82 83

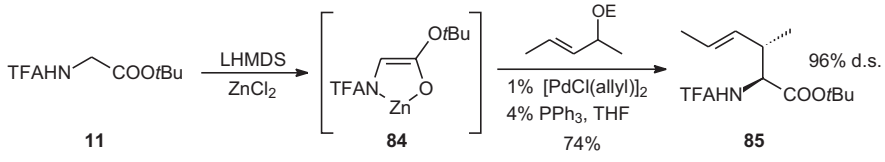
Scheme 9-40 Asymmetric allylic alkylation of pyrazinone **81**.

nates **82** were used as substrates. The alcoholate liberated is clearly sufficiently basic to deprotonate the auxiliary, indicating that **81** forms a (partly) stabilized anion. The free amino acid could be obtained under relatively drastic conditions (6 N HCl, 150 °C).

Similar amino acids, even without a α-methyl group can be synthesized if chelated amino acid ester enolates are used. These enolates were found to give especially good results in various types of standard enolate reactions including alkylations, aldol reactions, or Michael additions [140]. Chelation causes a marked enhancement of thermal stability without having any negative influence on the reactivity of these enolates, and due to the fixed enolate geometry, their conversions often proceed with a high degree of stereoselectivity. Stabilization of the enolate by chelation should also diminish the tendency of the enolate to coordinate to the palladium – perhaps a solution of the 'enolate problem'?

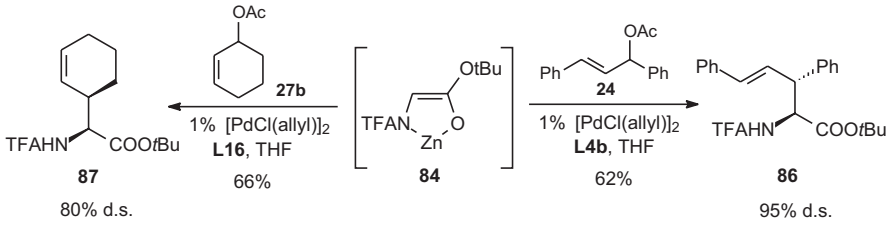
If amino acid esters such as **11** are deprotonated with excess LHMDS in the presence of zinc chloride, the resulting chelated ester enolate **84** can be trapped, for example, with dimethyl allyl carbonate in the presence of Pd(0) (Scheme 9-41). In general, the best results were obtained with allylpalladium chloride in the presence of triphenylphosphine. As a result of the high reactivity of the chelated enolates, the allylation already takes place under very mild conditions at –78 °C, giving rise to the desired monoallylated amino acid derivative **85** in a highly stereoselective fashion. The racemic, but diastereomerically pure *anti*-product **85** is accessible after a single crystallization step. Most common *N*-protecting groups can be used with comparable success, although the TFA-derivative in general gives the best selectivities [141].

In order to enlarge the potential of this approach, an asymmetric version is desirable. Depending on the allylic substrate used, two different strategies can be applied. Substrates such as **24** with two identical substituents at both allyl termini form symmetrical, achiral π-allylpalladium complexes, and therefore the stereochemical outcome of the reaction can be controlled *via* chiral ligands on the palladium. In order to assess the scope of ligand-directed asymmetric allyla-



11 84 85

Scheme 9-41 Allylic alkylation of chelated ester enolates.

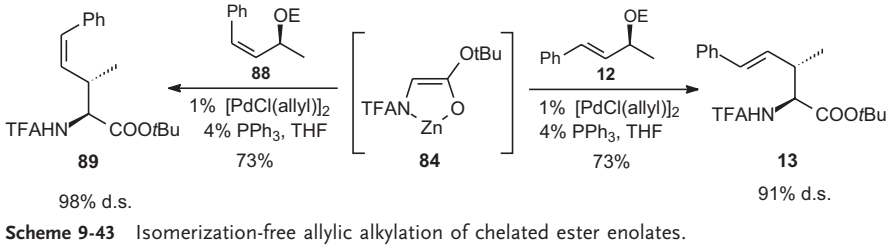


Scheme 9-42 Asymmetric allylic alkylation of chelated ester enolates.

tions with chelated enolates, a representative set of substrates was investigated (Scheme 9-42) [142]. High levels of selectivity were achieved with 1,3-diphenylallyl acetate (**24**) as substrate; especially with the PHOX ligand **L4b** (see Figure 9-1) a diastereoselectivity of up to 95:5 in favor of the *anti* isomer **86** and *e.e.*-values of up to 94 % could be obtained. Allylic alkylations of cyclic substrates such as cyclohexenyl acetate (**27b**) led to the cyclohexenyl-glycine derivative **87**. The chiral ligand **L15** gives an almost 1:1 diastereomeric mixture, while with **L16** the *syn* product is formed preferentially. *e.e.*-Values of up to 93 % can be obtained with these ligands, which is remarkable for such cyclic systems.

On the other hand, the allylic substitutions with chiral allyl substrates (such as **12**) proceeded cleanly and with good yields (Scheme 9-43). The only regioisomers obtained were those with the double bond in conjugation to the phenyl ring. The diastereoselectivities of the reaction were high, depending on the substitution pattern at the allyl moiety, and the diastereoselectivities obtained with the acetates were a little worse in comparison to those from the carbonates. The chirality could be transferred almost completely from allyl derivative **12** to product **13**.

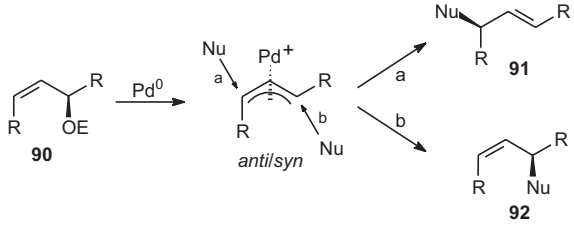
Since the palladium-catalyzed allylic substitution with chelated ester enolates already proceeds at –78 °C, these enolates provide a good chance to circumvent a nearly unsolved problem in palladium-catalyzed allylic alkylations: the π-σ-π-isomerization. Reactions of (*Z*)-substrates with the chelated enolate **84** gave interesting results. The reaction with the (*Z*)-carbonate **88** (97 % *e.e.*) almost exclusively yielded the desired (*Z*)-substitution product **89** (*Z*/*E*: > 99/1). The outstanding selectivities (98 % d.s., 97 % *e.e.*) observed even surpassed the very good results of the reaction with the (*E*)-carbonate **12**. In contrast, the reaction with the corresponding acetate furnished a (*E*/*Z*)-mixture in a very low yield. The selectivities were markedly worse than those obtained with the carbonate.



Scheme 9-43 Isomerization-free allylic alkylation of chelated ester enolates.

This difference in product formation may be explained by the higher reactivity of the allyl carbonates. Because these substrates already react at –78 °C, π-σ-π-isomerization clearly does not occur. In contrast, the reaction of the acetates takes place at a higher temperature during the warm-up. Simultaneously, the isomerization is setting in, and a partial conversion of the primarily formed *anti*/*syn*-complex into the more stable *syn*/*syn*-complex can be observed (see Scheme 9-13).

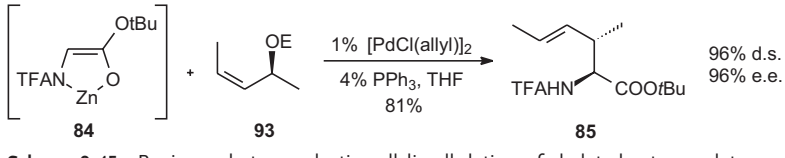
If the π-σ-π-isomerization can be suppressed as in this case, further interesting questions arise: What would happen to allylic substrates with (*Z*)-configuration and the same substituents at the allyl moiety (**90**)? In principle, there are two different reaction pathways, because the *anti*/*syn* π-allyl complex formed as an intermediate has two different allylic termini (Scheme 9-44). Nucleophilic attack (at **a**; *anti* position) would provide a product **91** with (*E*)-configuration of the double bond, whereas the attack (at **b**; *syn* position) would lead to a (*Z*)-double bond (**92**). Hence the question, which position is the more reactive – *syn* or *anti*?



Scheme 9-44 Reaction pathways of *syn*/*anti* π-allylpalladium complexes.

The clarification of this question is of major interest, because symmetrically substituted allyl derivatives are normally used in asymmetric catalyzed reactions. Irrespective of the configuration of the starting material, achiral *syn*/*syn* π-allylpalladium complexes are generally formed, and the nucleophilic attack on complexes of this type can be controlled, for example, by chiral ligands. Therefore, if enantiomerically pure allyl substrates are used, the chiral information is lost during the reaction. However, if it were possible to suppress the π-σ-π-isomerization during the reaction of (*Z*)-configured substrates, and if one of the two allylic positions is pronouncedly more reactive than the other one, then it should be possible also to generate optically active compounds with these substrates.

And indeed, the reaction with chiral allyl substrate **93** provided the chiral (*E*)-configured substitution product **85** exclusively in a very good yield (Scheme 9-45). Also in this case the selectivities, with which the *anti*-products were formed, were excellent. Moreover, the almost complete transfer of chirality shows that the reaction



Scheme 9-45 Regio- and stereoselective allylic alkylation of chelated ester enolates.

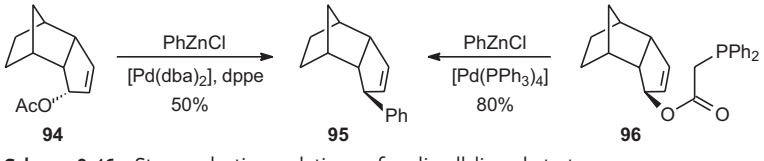
proceeds *via* the *anti*/*syn*-complex and not *via* the *syn*/*syn*-complex, which would inevitably lead to racemization.

9.2.4.3 Reaction with Hard Nucleophiles

In contrast to soft carbanions or enol derivatives, organometallic reagents generally attack the metal of a π-allyl complex. Since subsequent C-C bond formation occurs *via* reductive elimination, retention of configuration is observed for this last step of the reaction, giving overall inversion. Zn, B, Al, Sn, and Si compounds are the most widely used organometallics for these cross-coupling reactions [143]. In general, transmetallation is the rate-determining step, and sp^2 carbons are transferred more easily than sp^3 carbons. Therefore, arylations and vinylations are much more popular than alkylations.

Arylations

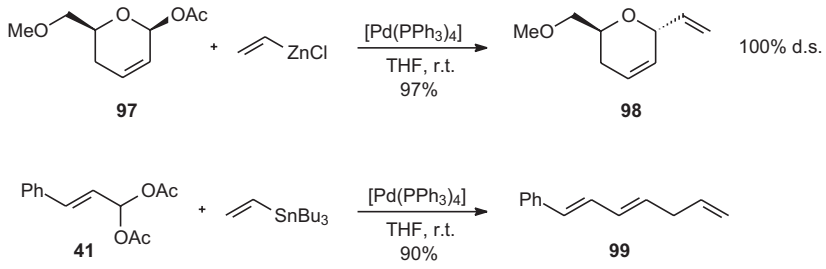
Arylations, and especially phenylations, can be carried out with a wide range of phenyl derivatives of zinc [144], tin [145], magnesium [146], or boron [147]. Typically, overall inversion is observed if chiral substrates such as **94** are used [148], but under special circumstances retention of configuration is also possible (Scheme 9-46). For example, if diphenylphosphinylacetates **96** are used as leaving groups, the phosphinyl moiety directs the palladium to the same face of the double bond where the leaving group is located, and the π-allyl complex is formed under retention [149].



Scheme 9-46 Stereoselective arylations of cyclic allylic substrates.

Vinylations

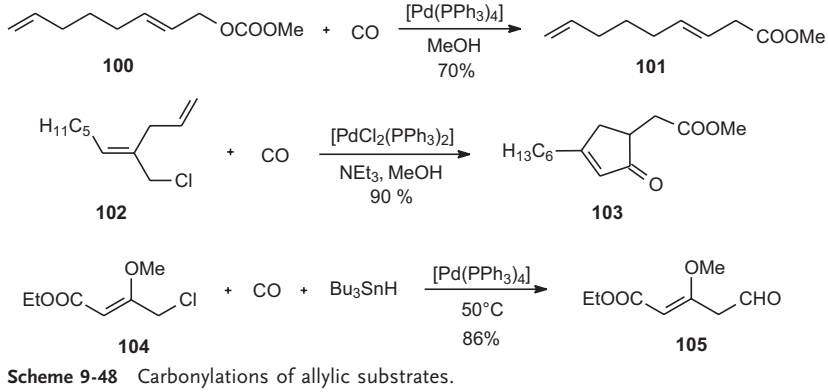
Hydrometallation of alkynes gives rise to vinyl metal compounds which can be coupled *via* palladium-catalyzed allylic alkylation. Therefore, vinyl zirconium [150] and tin reagents [145] play a dominant role, but other metals such as aluminum [151] or zinc [152] can also be used. For example, vinylzinc reacts with acetate **97** adjacent to the ring oxygen (Scheme 9-47) in a highly stereoselective fashion [144a]. If diacetates such as **41** are used as substrates, vinylation provides a terminal allylic acetate, which can undergo a second vinylation, and triene **99** is obtained in high yield. In contrast, with allylstannanes the reaction stops after the first cross-coupling step [153].



Scheme 9-47 Vinylations of allylic substrates.

9.2.4.4 **Carbonylations**

Carbonylation of various allylic compounds in alcohols gives *β,γ*-unsaturated esters, but in general allylic compounds are less reactive than aryl or vinyl halides. However, with the most reactive derivatives such as carbonate **100** the carbonylation proceeds under rather mild conditions, giving rise to **101** (Scheme 9-48) [154]. The same is true if allyl chlorides are used [155]. In the presence of an additional double bond (such as in **102**), the carbonylation is followed by an intramolecular insertion of the double bond into the Pd-acyl bond, affording the cyclopentenone derivative **103** [156]. In the presence of Bu_3SnH, the Pd-acyl intermediate obtained from **104** can be reduced to give the corresponding aldehydes (**105**) [157], while with other organometallics the corresponding ketones are formed [158]. If allylic phosphates are used, the best results are obtained under pressure and in the presence of amines [159]. In the presence of chiral ligands, asymmetric carbonylations are possible with high enantiomeric excess [160].



Scheme 9-48 Carbonylations of allylic substrates.

9.3
Allylic Alkylations with Other Transition Metals

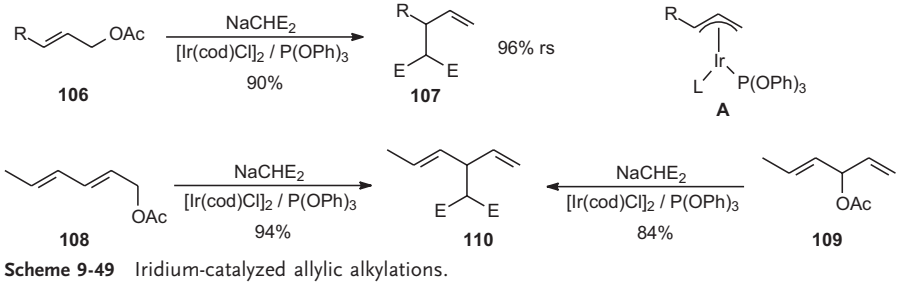
Although palladium is the most important transition metal for allylic alkylations, several others can be used, and these are discussed below in alphabetical order. From a mechanistical point of view, they react generally as discussed for the palladium complexes, although they show different reactivities and selectivities.

9.3.1
Iridium

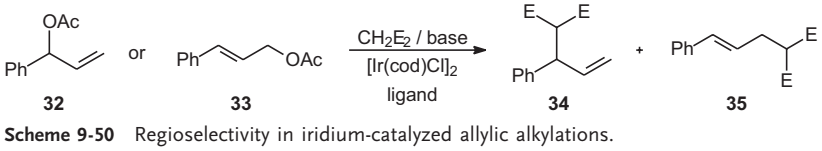
During the past few years, the chemistry of iridium has developed dramatically and the improvements made have been summarized in a recent review [161].

Mechanistically, iridium complexes behave similar to the corresponding palladium analogs, but show several specialties. For example, nucleophilic attack on a terminal π-allyliridium complex (**A**) formed from **106** (R = *n*Pr) or **108** occurs at the sterically more hindered position, giving rise to the branched products **107** and **110** preferentially [162a] (Scheme 9-49). The best results are obtained with $P(OPh)_3$, and NMR studies indicate that a monophosphite complex **A** is formed with the phosphite *trans* to the substituted allylic terminus. A S_N1-type transition state is favored by the electron-withdrawing properties of $P(OPh)_3$, as discussed in Section 9.2.1.2. The same is true if dienylacetates (**108** or **109**) are used, while the position of the leaving group has no influence on the regioselectivity [162b].

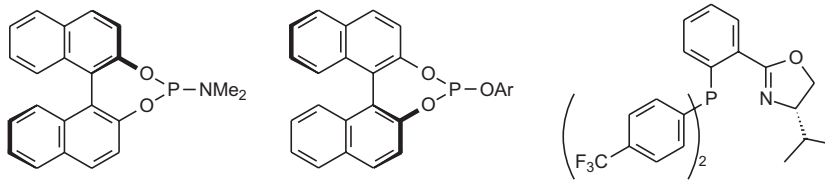
The regioselectivity is even higher if quaternary centers are formed, supporting the S_N1-type process. In this respect, iridium is superior to all other transition metals. The high preference for substitution at the sterically more hindered position predestines iridium for allylations in the presence of chiral ligands (Scheme 9-50).



Scheme 9-49 Iridium-catalyzed allylic alkylations.



Scheme 9-50 Regioselectivity in iridium-catalyzed allylic alkylations.



L23 **L24** **L25**

Figure 9-9 Ligands for iridium-catalyzed allylic alkylations.

The influence of mono- as well as bidentate ligands (Figure 9-9) was investigated, and provided rather interesting results (Table 9-5) [163, 164].

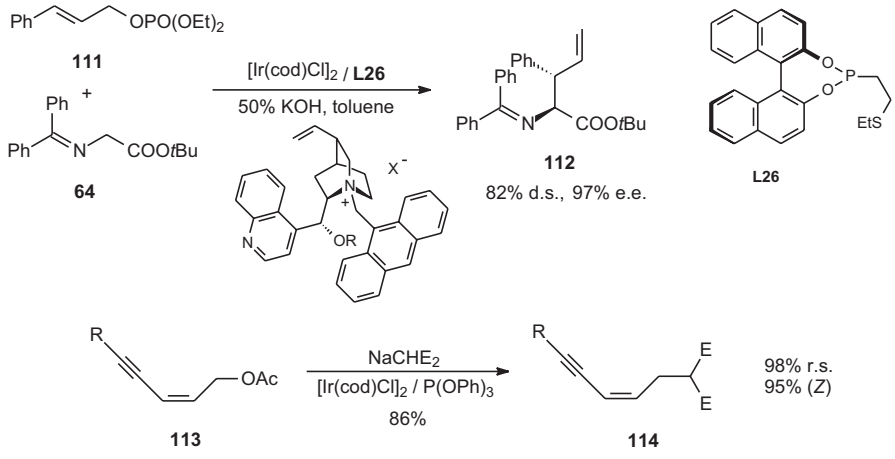
A significant memory effect was observed. Even in the presence of achiral $P(OPh)_3$ the chiral information could be partly preserved. Therefore, if *rac*-**32** was used as substrate the *e. e.* values obtained are significantly lower than in comparable experiments starting from achiral **33**. Clearly, π-σ-π-isomerization in the case of iridium complexes is significantly slower compared to the analog palladium complexes [163]. An interesting effect was also observed in the presence of ligand **L24**. While with $ZnEt_2$ the *e. e.* values obtained were only moderate, a dramatic increase was observed if BuLi was additionally used as base, illustrating the strong effect of the counterion [164].

Table 9-5 Asymmetric allylic alkylations with iridium complexes

Substrate	*Ligand*	*Base*	*Yield (%)*	*Ratio 34:35*	*e. e. (%)*	*Configuration*	*Ref.*
(*R*)-**32**	$P(OPh)_3$	NaH	98	95:5	56	(*S*)	[163b]
rac-**32**	**L23**	NaH	98	92:8	8	(*S*)	[163b]
33	**L23**	NaH	99	98:2	37	(*R*)	[163b]
33	**L24**	$ZnEt_2$	40	84:16	20	(*S*)	[164]
33	**L24**	$BuLi/ZnEt_2$	99	93:7	96	(*S*)	[164]
rac-**32**	**L25**	NaH	99	95:5	15	(*S*)	[163b]
33	**L25**	NaH	99	95:5	91	(*R*)	[163a]

A similar chiral phosphite ligand **L26** was used in combination with a chiral phase transfer catalyst for the allylic alkylation of iminoesters (Scheme 9-51). The branched isomers **112** are obtained exclusively with good stereoselectivity, while the best results are obtained with allylic phosphate **111** [165].

The suppressed π-σ-π-isomerization is another important feature of π-allyliridium complexes, because this allows the allylic alkylation of (*Z*)-substrates such as **113** under retention of the olefin geometry. Interestingly, (*Z*)-substrates also show a complete regioselectivity in comparison to (*E*)-configured allylic compounds because here the unbranched substitution product **114** is formed almost exclusively [166].

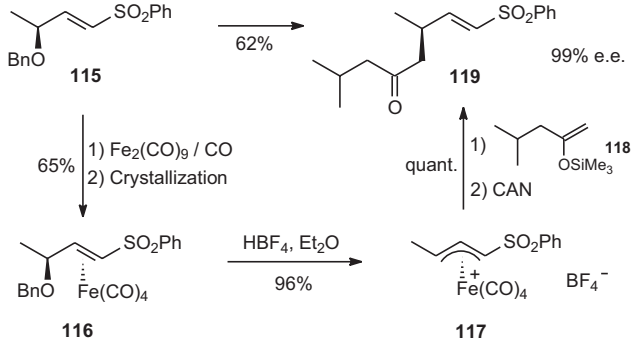


Scheme 9-51 Applications of iridium-catalyzed allylic alkylations.

9.3.2 Iron

Cationic [(allyl)$Fe(CO)_4$] complexes are found to be regio- and stereoselectively attacked by various types of nucleophiles, including stabilized enolates and organometallics [167]. In principle, the allylic alkylation can also be carried out with catalytic amounts of [$Fe_2(CO)_9$], but the reactions are relatively slow and show only moderate regioselectivity. However, if the reactions are carried out at room temperature the (*Z*)-olefin geometry can be preserved during substitution, illustrating that π-σ-π-isomerization is also slow in this case [168]. In general, allylic alkylations are carried out with stoichiometric iron complexes.

If acceptor-substituted allyl substrates such as **115** are used, nucleophilic substitution of the leaving group proceeds regioselectively and under net retention of the configuration (Scheme 9-52). A wide range of hetero- as well as *C*-nucleophiles can



Scheme 9-52 Iron-catalyzed allylic alkylations.

be used, providing good yields and selectivities [169]. With iron carbonyls, the alkene complex **116** can be isolated and purified by crystallization. Treatment of this neutral alkene complex with HBF_4 gives rise to the cationic π-allyliron complex **117**, which can be reacted with nucleophiles such as silylenolether **118** to give a substituted iron-alkene complex, which is cleaved oxidatively to **119**. Similar reactions are obtained with iron carbonylnitrosyl complexes [170].

9.3.3 Molybdenum

Molybdenum and tungsten complexes behave very similarly, in that both provide nucleophilic attack preferentially at the sterically more hindered position. However, the regioselectivity depends heavily on the remaining ligands on the metal. In principle, $Mo(CO)_6$ can be used as the catalyst, but better results are obtained with mixed isonitrile/CO complexes such as $[Mo(CNR)_4(CO)_2]$ [171]. These complexes show a higher reactivity as well as stability, because the isonitrile ligand dissociates more easily and stays in solution, regenerating the catalyst. In the presence of chiral ligands (Figure 9-10) high regio- and well as stereoselectivities can be obtained, even with critical substrates such as **120**. In principle, three different products can be obtained *via* π-complex equilibrium – an isomerization that clearly does not occur because **121** is formed with excellent regioselectivity (Scheme 9-53) [172].

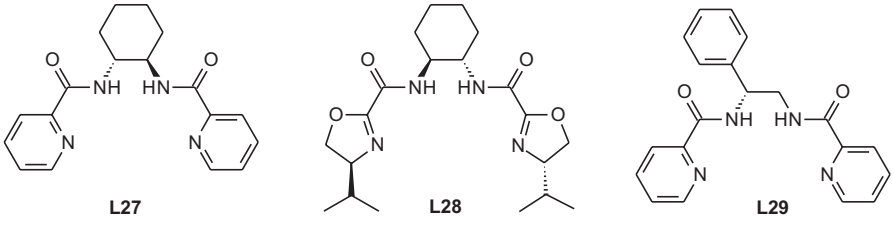
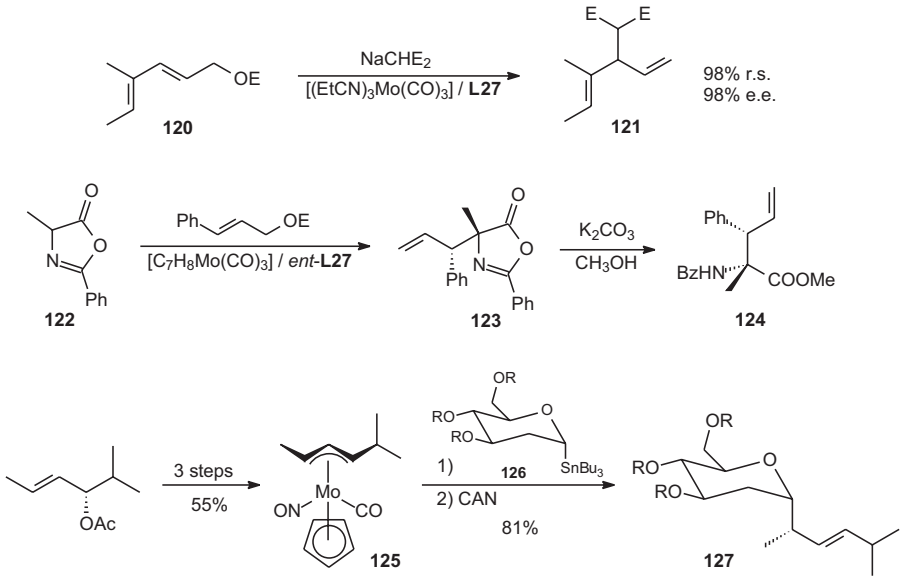


Figure 9-10 Ligands for molybdenum-catalyzed allylic alkylations [177–179].

Ligand *ent*-**L27** is also suitable for allylic alkylations of imines and azlactones such as **122**, giving rise to β-branched amino acid derivatives **123** and **124** [173]. Similar ligands can be used for microwave-accelerated allylations [174].

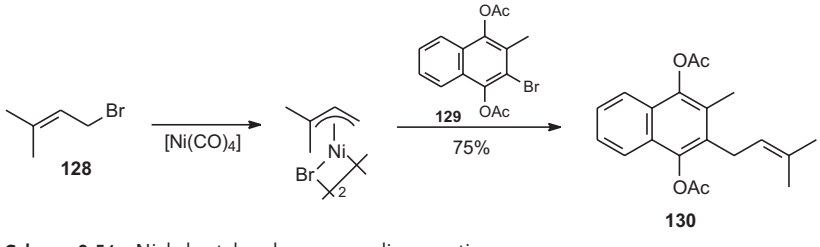
Stoichiometric allyl-nitrosyl molybdenum complexes **125** undergo nucleophilic substitution with a wide range of organometallics including metallated sugar derivatives **126** providing, for example, C-glycosides **127** (Scheme 9-53) [175]. On the other hand, similar complexes also react with aldehydes, giving rise to homoallylic alcohols [176].



Scheme 9-53 Molybdenum-catalyzed allylic alkylations [177–179].

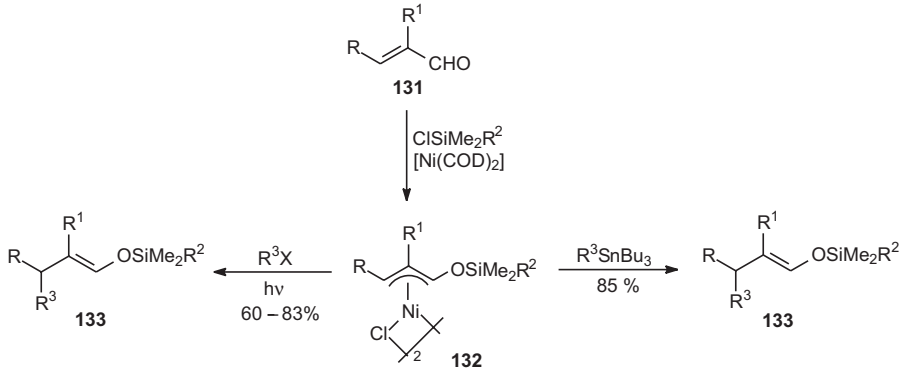
9.3.4 Nickel

π-Allylnickel complexes can be obtained from Ni(0) species such as $[Ni(CO)_4]$ or $[Ni(COD)_2]$, but they behave differently from palladium complexes. While palladium complexes are easily attacked by nucleophiles, the corresponding nickel complexes themselves can act as nucleophiles and react with a wide range of electrophiles. The most popular such reactions are the coupling of allyl halides (**128**) with alkyl and aryl halides (**129**), for example to **130**, whilst a wide range of functionalities are tolerated, making this protocol a synthetically valuable tool [180] (Scheme 9-54).



Scheme 9-54 Nickel-catalyzed cross-coupling reactions.

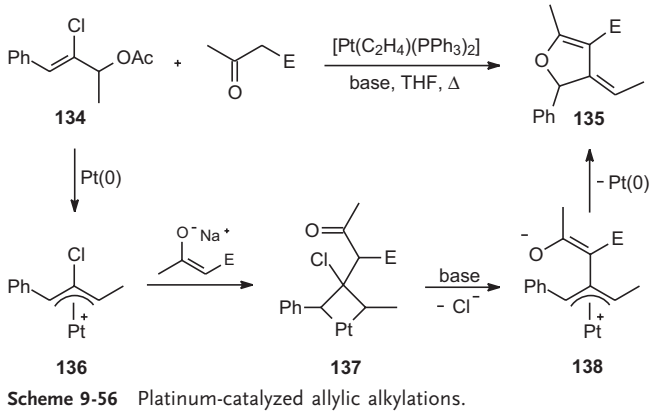
α,β-Unsaturated carbonyls such as **131** also react with Ni(0) in the presence of chlorosilanes, giving complexes **132** (Scheme 9-55) that can be coupled with both electrophiles [181] as well as nucleophiles to **133** [182]. Soft [183] as well as hard [184] nucleophiles also react in the presence of Ni in typical allylic alkylations with a wide range of allylic substrates.



Scheme 9-55 Reactions of π-allylnickel complexes.

9.3.5 Platinum

Few examples of platinum-catalyzed allylations have been reported to date, but interestingly, π-allylplatinum complexes show a high tendency for nucleophilic attack at the central position of the allyl fragment [185]. For example, if allylic acetate **134** is reacted with β-ketoesters or 1,3-diketones, furan derivative **135** is obtained in high yield, whereas with malonates the "normal" substitution product is obtained (Scheme 9-56). This unexpected product formation can be explained by a nucleo-

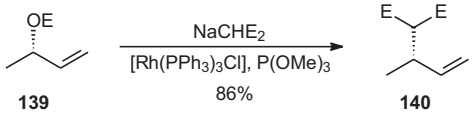


Scheme 9-56 Platinum-catalyzed allylic alkylations.

philic attack at the central position of the π-allylplatinum complex **136**, giving rise to platinacyclobutane **137**. The elimination of chloride, followed by deprotonation by the excess nucleophile, which serves as a base, affords the 2-alkylated π-allylplatinum complex **138**. A subsequent enolate *O*-cyclization provides furan derivative **135**.

9.3.6 Rhodium

Wilkinson's catalyst can be modified *in situ* to furnish a catalytically active species that facilitates the allylic alkylation of a wide range of allylic substrates, favoring the more substituted product [186]. Interestingly, rhodium shows a strong memory effect, and nucleophilic attack occurs preferentially at the position where the leaving group was located. If chiral substrates such as **139** are used, almost complete chirality transfer is observed (**140**) (Scheme 9-57). Clearly, π-σ-π-isomerization does not play a significant role, and most likely σ-allylrhodium complexes are responsible for this interesting reaction behavior [187]. α-Allylated ketones and esters can be obtained from silylenolethers and silylketenacetals [188], or from allyl β-keto carboxylates *via* decarboxylation [189].

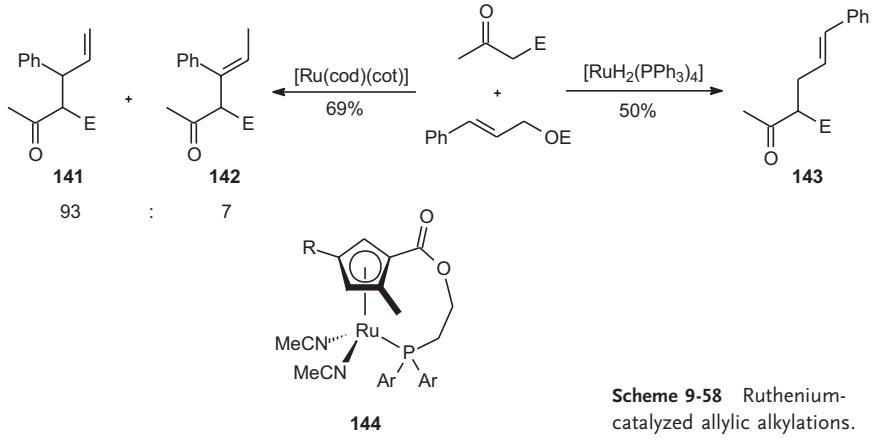


139 97% e.e. **140** 95% e.e.

Scheme 9-57 Rhodium-catalyzed allylic alkylations.

9.3.7 Ruthenium

Comparable with nickel complexes, π-allylruthenium complexes also can act as electrophiles and as nucleophiles [190]. Ru(0) complexes show different reactivity and selectivity compared with palladium complexes, while the ligands have a strong influence (Scheme 9-58). For example, the (η^4-1,5-cyclooctadiene)(η^6-1,3,5-cyclooctatriene) complex [Ru(cod)(cot)] is highly reactive, providing the branched products **141** and **142**, whilst with the less-reactive [$RuH_2(PPh_3)_2$] nucleophilic attack occurs at the less sterically hindered position (**143**) [191]. With the planar chiral ruthenium complexes **144**, high *e.e.*-values and yields are obtained [192].

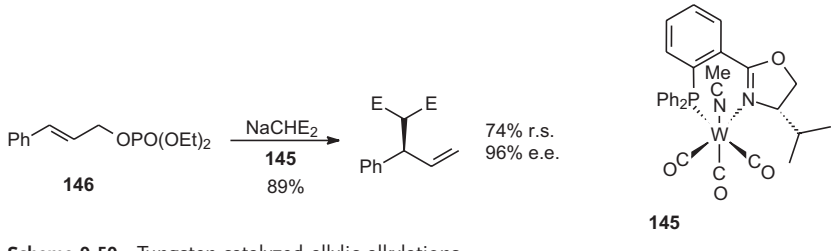


Scheme 9-58 Ruthenium-catalyzed allylic alkylations.

9.3.8 Tungsten

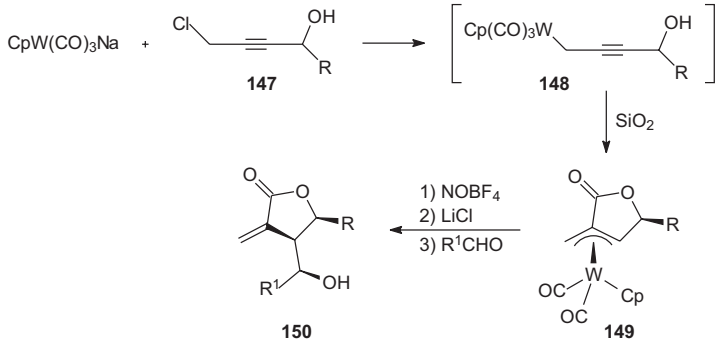
π-Allyltungsten complexes behave very similarly to the related molybdenum species, and nucleophilic attack occurs preferentially at the sterically more hindered position. The reactivity and selectivity strongly depend on the ligands on the metal [193], while with chiral ligands such as the Phox-ligand **L4** high *e.e.*-values can be obtained. The corresponding chiral complex **145** is obtained easily by ligand exchange from $[W(CO)_3(MeCN)_3]$, and provides *e.e.*-values of up to 96 % in the alkylation of cinnamylphosphates **146** (Scheme 9-59) [194].

Comparable with Mo complexes, tungsten complexes can also act as nucleophiles in reactions with aldehydes.



Scheme 9-59 Tungsten-catalyzed allylic alkylations.

An interesting synthetic application of π-allyltungsten complexes is shown in Scheme 9-60. Treatment of propargylic halide **147** with $CpW(CO_3)Na$ yields a highly reactive η^1-propargyl complex **148**. Elution of this species through a column of silica gel introduces intramolecular alkoxycarbonylation, giving rise to *syn*-π-allyl complex **149**. Subsequent treatment of **149** with $NOBF_4$ and LiCl generates an allyl anion equivalent which can be trapped by aldehydes, yielding α-methylenebutyrolactones **150** [195].



Scheme 9-60 Tungsten-catalyzed reactions of propargylic halides.

9.4
Experimental Procedures

9.4.1
(2*S*,3*S*) *tert*-Butyl (*E*)-3-methyl-5-phenyl-2-(trifluoroacetyl)amino-4-pentenoate (13) (Scheme 9-7)

A solution of LHMDS, obtained from HMDS (111 mg, 0.69 mmol) and 1.6 *M* BuLi (0.39 mL, 0.625 mmol) in THF (1 mL) was prepared at –20 °C. This solution was cooled to –78 °C before being added to a solution of the protected amino acid ester **11** (57 mg, 0.25 mmol) in THF (1 mL). After 20 min at –78 °C, a solution of $ZnCl_2$ (38 mg, 0.275 mmol) in THF (1 mL) was added under vigorous stirring. After 30 min, a solution of $[allylPdCl]_2$ (1 mg, 2.5 μmol, 1 mol %), PPh_3 (3 mg, 11.3 μmol, 4.5 mol %), and the allylic carbonate **12** (0.5 mmol) in THF (3 mL) was added. The solution was stirred and warmed up to room temperature in the cooling bath overnight. The solution was diluted with diethyl ether and hydrolyzed with 1 N $KHSO_4$ solution. After drying of the organic layer and evaporation of the solvent, the crude product was purified by silica gel column chromatography (hexanes/ethyl acetate, 9/1) giving rise to **13** as a colorless solid in 73 % yield. Ratio *anti*/*syn* 91:9. Recrystallization from diethyl ether/hexanes provided a diastereomerically pure white powder.

9.4.2
2-Acetonyl-2-methyl-1,3-cyclopentanedione (51) (Scheme 9-30)

A mixture of 2-methyl-1,3-cyclopentadienone (1.0 g, 8.9 mmol), allyl carbonate **50** (1.8 g, 13.0 mmol), triphenylphosphine (2.3 g, 8.9 mmol), DBU (2.0 g, 13.0 mmol), and $PdCl_2$ (80 mg, 0.45 mmol) in THF (100 mL) was heated under reflux for 18 h. After removal of the solid material by filtration and evaporation of the solvent, 1 % aq. H_2SO_4 (2 mL) and dioxane (2 mL) were added to the residue, and the solution

was stirred at 60 °C for 2 h. The product was extracted with CH_2Cl_2 and dried ($MgSO_4$). The acetonylated product **51** was isolated in 88 % yield as a colorless oil by Kugelrohr distillation ($bp_{0.1}$: 110 °C).

9.4.3

(2*S*) *tert*-Butyl (*E*)-2-[(diphenylmethylene)amino]-5-phenyl-4-pentenoate (65) (Scheme 9-34)

To a suspension of phase-transfer catalyst (50.0 mg, 0.169 mmol), **64** (10.6 mg, 0.169 mmol), $[PdCl(C_3H_5)]_2$ (5.4 mg, 0.015 mmol), and triphenylphosphite (21.0 mg, 0.677 mmol) in toluene (0.28 mL) were successively added a solution of cinnamyl acetate (30 mg, 0.169 mmol) in toluene (0.56 mL) and an aqueous 50 % KOH solution (66.4 mg, 0.591 mmol) at 0 °C under an argon atomsphere. After being stirred vigorously at 0 °C for 7 h, the mixture was diluted with diethyl ether (15 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (3 × 5 mL) and saturated aqueous NaCl (5 mL). The extract was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (hexanes/ethyl acetate, 300/1) to give **65** in 89 % yield.

9.4.4

(5*E*)-PGE_2 Methyl ester (72) (Scheme 9-37)

Tetrakis(triphenylphosphine)palladium(0) (13 mg, 0.0112 mmol) was added to a solution of the TBDMS-protected ester **71** (143 mg, 0.224 mmol) in *N,N*-dimethylformamide (1 mL) under an argon atmosphere, and the reaction mixture was stirred at 50 °C for 30 min. Saturated aqueous NaCl (30 mL) was added, and the resulting mixture extracted with ethyl acetate (4 × 50 mL). The separated organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Purification of the crude product (136 mg) by silica gel column chromatography (hexanes/ethyl acetate, 19/1 up to 4/1) gave the bis-silyl ether of (5*E*)-PGE_2 **72** in 64 % yield.

A stirred solution of the bis-silyl ether (51 mg, 0.086 mmol) in acetonitrile (3 mL) was treated with hydrogen fluoride-pyridine (0.1 mL) at room temperature for 3 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate (4 × 50 mL). The combined extracts were washed with saturated aqueous NaCl, and dried over $MgSO_4$. Removal of the solvents *in vacuo* left a crude product, which was purified by silica gel column chromatography (hexanes/ethyl acetate, 1/1 up to 1/4) to give (5*E*)-PGE_2 methyl ester (R = H) **72** in 85 % yield.

9.4.5

Methyl (2*R*,3*S*)-2-Benzoylamino-2-methyl-3-phenyl-4-pentenoate (124) (Scheme 9-53)

The catalyst is very sensitive to oxygen, and thus thorough degassing must be carried out. Freshly distilled THF was further degassed with argon before use. The test tube containing $[Mo(CO)_3C_7H_8]$ (2.8 mg, 0.01 mmol) and (*S*,*S*)-ligand *ent*-**L27** (4.9 mg, 0.015 mmol) was evacuated and flushed with argon three times, at which point 0.3 mL THF was added. The resulting mixture was heated with stirring at 60 °C for 5–10 min under argon until the purple-black color of active catalyst was seen. A second test tube containing azlactone **122** (37 mg, 0.21 mmol) was evacuated and flushed with argon three times, at which point 0.5 mL THF was added, followed by dropwise addition of LiHMDS (1 *M* in THF) (0.2 ml, 0.2 mmol) with stirring at room temperature. The resulting nucleophile was stirred for 5 min and added as such to the active catalyst, followed by addition of allyl carbonate (19.2 mg, 0.1 mmol). Additions were made *via* a syringe at 60 °C, and the resulting mixture was heated at THF reflux (oil bath temperature 75 °C) for 3 h (TLC showed that all the carbonate had been consumed).

The reaction mixture was opened to the air and 1–2 equiv. K_2CO_3 in anhydrous MeOH was added. The mixture was stirred at room temperature until TLC showed no more azlactone adduct **123**. The mixture was then taken up with 10 mL CH_2Cl_2, after which water (5 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL), dried over $MgSO_4$, and the solvent removed *in vacuo*. Flash chromatography (hexanes/ethyl acetate, 9/1) gave 29.8 mg (92 %) of the branched product **124**.

9.4.6

4-Ethoxycarbonyl-5-methyl-3-methylene-2-phenyl-2,3-dihydrofuran (135) (Scheme 9-56)

Ethyl acetoacetate (260 mg, 2.0 mmol) was added to a suspension of NaH (60 wt. % in mineral oil, 80 mg, 2.0 mmol) in THF (10 mL) at 0 °C. The mixture was stirred at room temperature for 30 min, at which time $[Pt(C_2H_4)(PPh_3)_2]$ (74.7 mg, 0.1 mmol) was added. 2-Chloroallyl acetate **134** (134.5 mg, 1.0 mmol) was added, and the flask then immersed in an oil bath at 80 °C. The reaction was monitored by analytical GC, and after 2 h the substrate had been completely consumed. The reaction mixture was then cooled to room temperature, and water (10 mL) was added. The resulting solution was extracted with diethyl ether, and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. The residue was subjected to silica gel column chromatography (hexanes/ethyl acetate, 10/1) to give **135** as a white solid in 76 % yield; m. p. 56–58 °C.

Abbreviations

Ac	acetyl
bp	biphenyl
BSA	*N,O*-bis(trimethylsilyl)acetamide
Bz	benzoyl
CAN	cerium ammonium nitrate
Chiraphos	2,3-bis(diphenylphosphino)butane
cod	1,5-cyclooctadiene
cot	1,3,5-cyclooctatriene
Cp	cylopentadienyl
dba	dibenzalacetone
DIOP	2,2-dimethyl-4,5-bis[(diphenylphosphino)methyl]dioxolane
dppe	bis(diphenylphosphino)ethane
d. r.	diastereomeric ratio
d. s.	diastereoselectivity
E	methoxycarbonyl
e. e.	enantiomeric excess
Et	ethyl
HMPA	hexamethyl phosphoric acid triamide
*i*Pr	isopropyl
L	ligand
LDA	lithiumdiisopropylamide
LHMDS	lithium hexamethyldisilazide
Me	methyl
MOP	2-diphenylphosphino-1,1′-binaphthyl
Nu	nucleophile
Ph	phenyl
Phox	2-(2-diphenylphosphinophenyl)-4,5-dihydrooxazoles
Prolophos	1-diphenylphosphanyl-2-[(diphenylphosphanyl)-methyl]-pyrrolidine
PTC	phase transfer catalyst
TBDMS	*tert*-butyldimethylsilyl
*t*Bu	*tert*-butyl
TFA	trifluoroacetyl
TMEDA	tetramethyl ethylenediamine
Ts	tosyl

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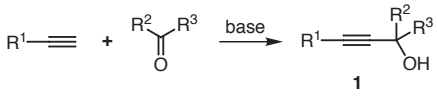
10
Palladium-Catalyzed Coupling Reactions of Propargyl Compounds

Jiro Tsuji and Tadakatsu Mandai

10.1
Introduction

Although propargyl compounds are 2-alkynyl derivatives, Pd-catalyzed reactions of propargyl compounds – particularly their alcohols, esters, and halides – are mechanistically different from those of simple alkynes, except for a few cases. Therefore, the Pd-catalyzed reactions of propargyl compounds should be treated independently from those of simple alkynes. Propargyl compounds undergo several types of Pd-catalyzed transformations [1]. In many cases, allene derivatives (1,2-dienes) are formed from propargyl compounds, and these highly unsaturated products are susceptible to palladium catalysis, undergoing further – sometimes complex – transformations. Thus, careful selection of reaction conditions and isolation methods in the reactions of propargyl compounds are required. Since propargyl alcohols **1** are easily prepared by the reaction of terminal alkynes with carbonyl compounds (Scheme 10-1), the Pd-catalyzed transformations of various propargyl compounds derived from propargyl alcohols have high synthetic value.



1 **Scheme 10-1**

10.2
Classification of Pd-Catalyzed Coupling Reactions of Propargyl Compounds

Complex formation by stoichiometric reactions of propargyl chlorides **2** and **4** with $Pd(PPh_3)_4$ have been studied, and σ-allenylpalladium complex **3** as well as propargylpalladium complex (or σ-prop-2-ynylpalladium complex) **5** have been isolated as yellow powders (Scheme 10-2) [2]. The complex **3** is formed by S_N2' type displacement of chlorine with Pd(0). The latter **5** is generated by direct oxidative addition, and formed when a bulky group such as trimethylsilyl or *t*-butyl is attached to the

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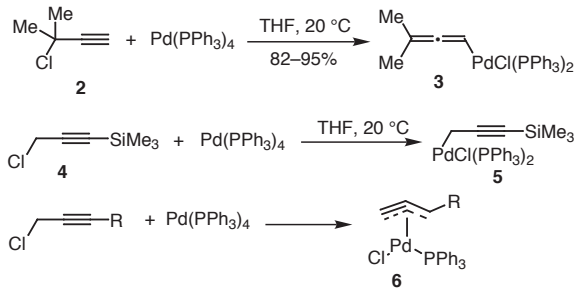
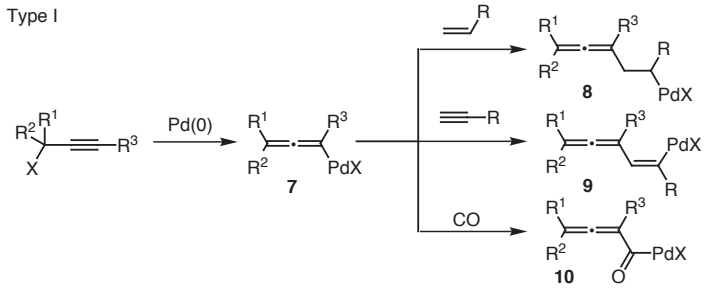


Scheme 10-2

alkyne terminal. It is reasonably expected that Pd(0)-catalyzed reactions of various propargyl compounds should proceed by the formation of either **3** or **5** as intermediates. Recently, Kurosawa proposed the formation of η^3-propargyl complexes **6** from propargyl chlorides [3].

Pd(0)-catalyzed coupling reactions of propargyl compounds so far discovered can be classified, from a mechanistic viewpoint, into three types, **I**, **II**, and **III**. Allenylpalladium complex **7** undergoes three types of transformation depending on the reactants. The type **I** reactions proceed by insertion of unsaturated bonds of alkenes, alkynes, and CO to the σ-bond between Pd and an sp^2 carbon atom in **7** (Scheme 10-3). Heck-type couplings, carbonylations and other reactions are expected to occur via intermediates **8**, **9**, and **10**. Allene derivatives are formed by these reactions.

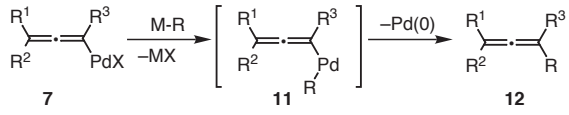


Scheme 10-3

The type **II** reactions occur by transmetallation of **7**. Hard carbon nucleophiles MR (M = main group metals) such as Grignard reagents and metal hydrides MH undergo the transmetallation with **7** to generate **11** (Scheme 10-4). Subsequent reductive elimination gives allenes **12** as a final product.

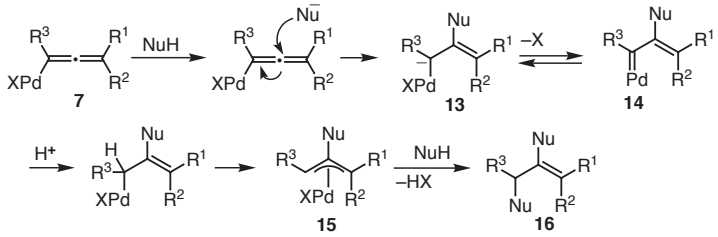
The type **III** reactions take place by the attack of a nucleophile at the sp-carbon of **7**. Reactions of soft carbon nucleophiles such as β-keto esters and malonates, as well as oxygen nucleophiles, belong to this type. The attack of a nucleophile generates **13**, which is regarded as a Pd-carbene complex **14**. The intermediate **13** picks up a proton from an active methylene compound, and the π-allylpalladium complex **15** is formed, which further reacts with another nucleophile; hence, two nucleophiles are introduced to provide alkenes **16** (Scheme 10-5).

Type II



M = Mg, Zn, B, Si, Cu R = aryl, alkenyl, alkynyl **Scheme 10-4**

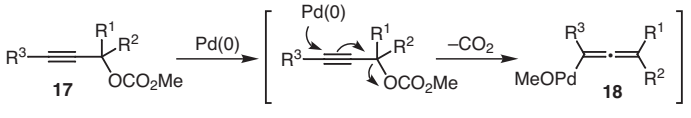
Type III



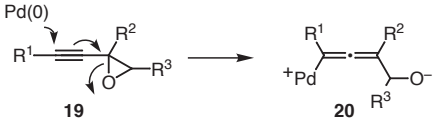
Scheme 10-5

Most of the Pd(0)-catalyzed reactions of propargyl compounds can be understood by the formation of **7**, and belong to reaction types **I**, **II**, and **III**.

Several propargyl derivatives such as acetates, phosphates, mesylates, and carbonates can be used for Pd-catalyzed reactions, but these have different reactivities. Propargyl carbonates **17** are the most reactive, and undergo various Pd-catalyzed reactions smoothly, especially under neutral conditions. The high reactivity of allylic carbonates is well known [4]. The reaction of **17** with Pd(0) provides allenylpalladium complex **18**, the methoxide group of which serves as a base (Scheme 10-6). Therefore, most extensive studies on propargyl compounds have been carried out with propargyl carbonates as convenient substrates. 2-(1-Alkynyl)oxiranes **19** also undergo facile reactions with Pd(0) catalysts under neutral conditions by forming palladium complexes **20** as intermediates (Scheme 10-7). These reactions proceed under neutral conditions. Halides, acetates, and mesylates are used mainly in type **II** reactions in the presence of bases.



Scheme 10-6

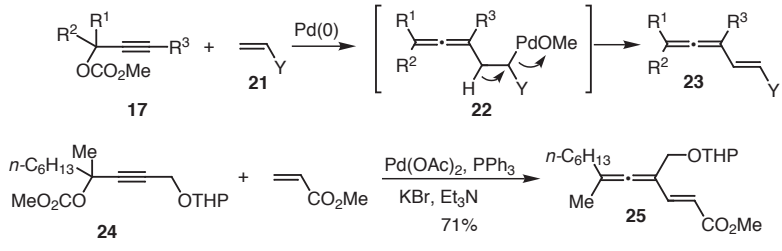


Scheme 10-7

10.3
Reactions with Insertion into the sp^2 Carbon Bond of Allenylpalladium Intermediates (Type I)

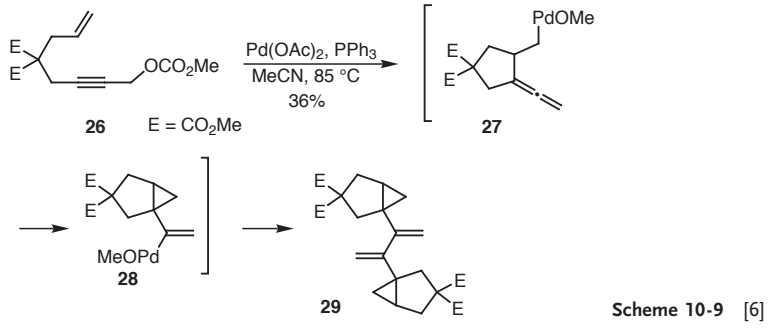
10.3.1
Reactions of Alkenes: Formation of 1,2,4-Alkatrienes

Reaction of **17** with alkenes **21** offers a novel synthetic method for 1,2,4-alkatrienes **23**. Smooth insertion of the alkene **21** into the allenylpalladium bond generates **22**, and subsequent elimination of a β-hydride affords **23** [5]. The reaction proceeds smoothly in DMF at 70 °C with $Pd(OAc)_2$ and PPh_3 as the catalyst. Addition of KBr and Et_3N is important. The reaction of methyl acrylate with **24** affords **25** in good yield (Scheme 10-8).



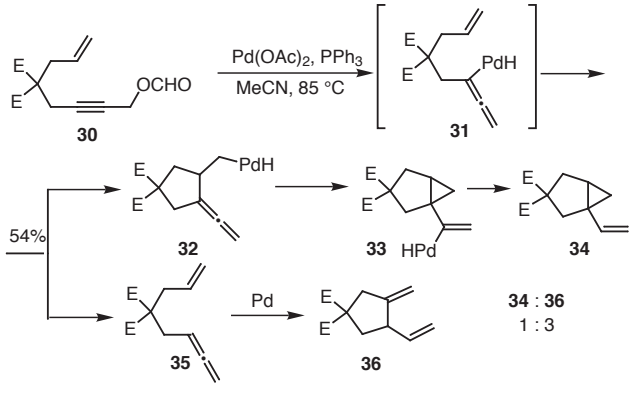
Scheme 10-8 [5]

Intramolecular reactions proceed smoothly. The propargyl carbonate **26** provides the unique dimeric product **29** via generation of **27** and its 3-*exo-trig*-cyclization product **28** (Scheme 10-9) [6].



Scheme 10-9 [6]

The palladium-catalyzed reaction of the propargyl formate **30** generates the allenylpalladium hydride complex **31**, the reaction of which affords two types of products **34** and **36**. Bicyclo[3.1.0]hexane **34** is provided through intramolecular 3-*exo-trig*-carbopalladation, followed by reductive elimination. Cyclopentane **36** is formed

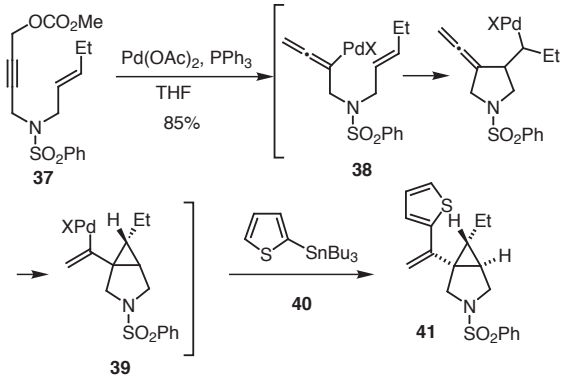


30 **31** **32** **33** **34** **35** **36**

Scheme 10-10 [6]

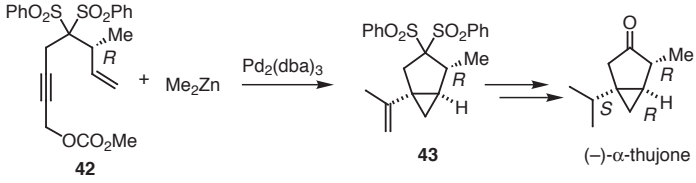
by reductive elimination of **31** producing enallene **35**, which subsequently undergoes palladium-catalyzed cyclization to **36** [6].

The azabicyclo[3.1.0]hexane **41** is provided by a Pd-catalyzed transformation of **37**. The reaction initially generates the allenylpalladium complex **38**, which undergoes 5-*exo-trig*- and 3-*exo-trig* cyclizations to afford **39**. Transmetallation of **39** with tributylthiophenylstannane **40** followed by reductive elimination affords **41** diastereoselectively (Scheme 10-11) [7,8]. The synthesis of (–)-α-thujone has been achieved by employing a diastereoselective domino cyclization of the chiral carbonate **42**, followed by trapping with dimethylzinc to give **43** as a key reaction (Scheme 10-12) [9].



37 **38** **39** **40** **41**

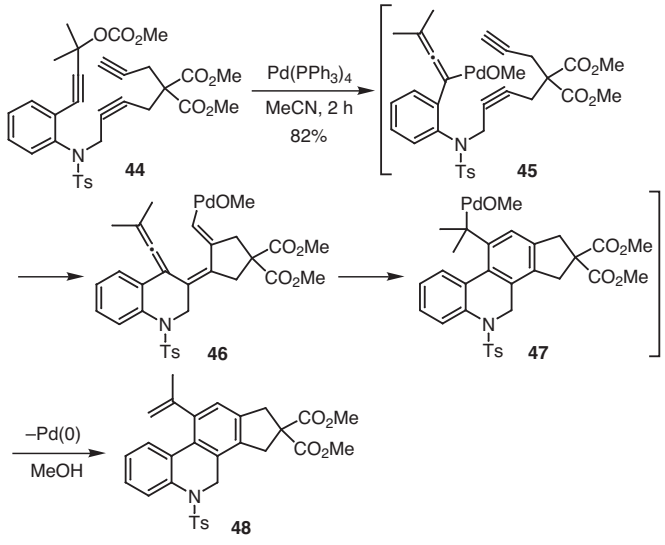
Scheme 10-11 [7, 8]



42 **43**

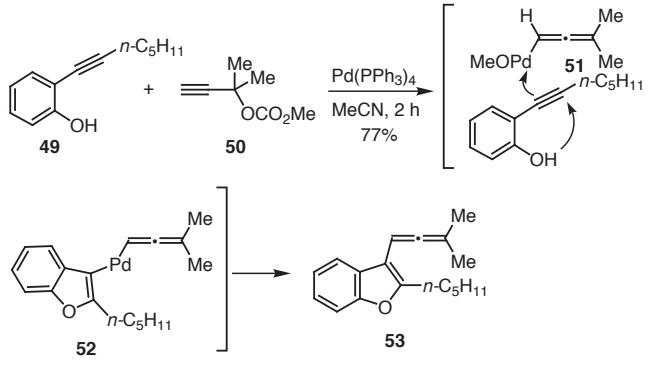
Scheme 10-12 [9]

The domino cyclization of propargyl carbonate **44** with two triple bonds proceeds smoothly to yield **48** in surprisingly high yield (82 %) (Scheme 10-13). The reaction pathway involves the successive 6-*exo-dig*- and 5-*exo-dig*-cyclizations of **45** leading to **46** followed by 6-*exo-trig*-cyclization affording **47**. Finally, **48** is released from **47** with regeneration of the Pd(0) species [10].



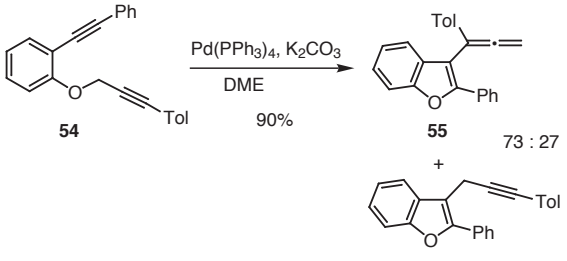
Scheme 10-13 [10]

Internal alkynes react with propargyl carbonates smoothly. The Pd-catalyzed reaction of *o*-alkynylphenol **49** with **50** provides benzo[*b*]furan **53** under neutral conditions (Scheme 10-14). Attack of a phenoxide anion on the triple bond from the opposite side of the allenylpalladium species **51** generates the allenylpalladium intermediate **52**, from which the final product **53** is produced via reductive elimination [11].



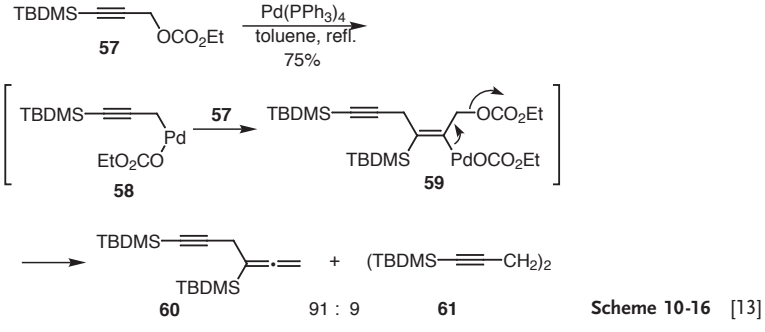
Scheme 10-14 [11]

The allenyl-substituted benzo[*b*]furan **55** has been prepared by a Pd-catalyzed transformation of **54** (Scheme 10-15). The isomer **56** was obtained as a minor product [12]. This reaction may proceed intramolecularly via the formation of a phenoxyallenyl- and/or a phenoxypropargylpalladium species.



Scheme 10-15 [12]

The propargyl carbonate **57** undergoes an interesting reductive coupling via the propargylpalladium complex **58** to give allene **60** as the major product and 1,5-diyne **61** as the minor one. The reaction is rationalized by insertion of the triple bond of **57** to **58** to furnish the vinylpalladium complex **59**, followed by *β*-carbonate elimination to afford **60** (Scheme 10-16) [13].



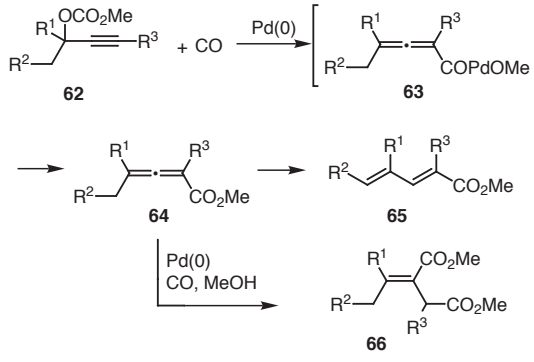
Scheme 10-16 [13]

10.3.2 Carbonylations

10.3.2.1 Introduction

Propargyl compounds undergo facile Pd-catalyzed mono- and dicarbonylations depending on the reaction conditions [14]. Carbonylation of propargyl alcohols has been carried out under somewhat harsh conditions to afford mainly dicarbonylation products [15]. More recently, it has been found that facile monocarbonylation of propargyl carbonates proceeds under milder conditions [16]. The mono- and dicarbonylations of propargyl carbonate **62** in an alcohol can be understood by the following mechanism. First, CO insertion into the allenylpalladium inter-

mediate generates acylpalladium complex **63** which reacts with the alcohol to give 2,3-alkadienoate **64**. Under certain conditions, isomerization of **64** to 2,4-dienoate **65** takes place (Scheme 10-17). Carbonylation of **62** under mild conditions stops at this stage. Under high pressure of CO, or in the presence of an activating group on the substrate (for example, $R^3 = CO_2Me$), further attack of CO at the *sp*-carbon of **64** occurs to give diester **66** (Scheme 10-17).

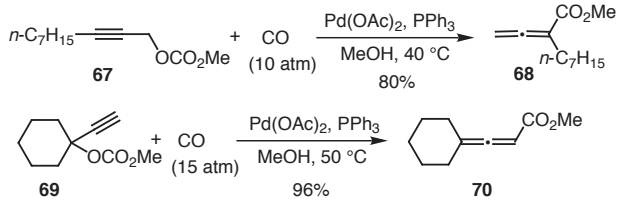


Scheme 10-17 [16]

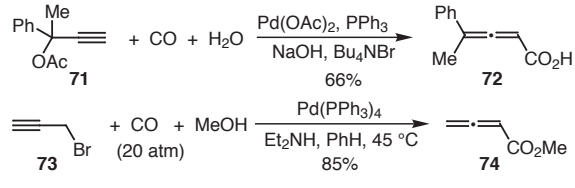
10.3.2.2 Preparation of 2,3-Alkadienoates and Their Derivatives by Monocarbonylation

The terminal allenic ester **68** is obtained in good yield from **67**. The tertiary propargyl carbonate **69** with a terminal acetylenic bond is most reactive and gives the ester **70** in high yield (Scheme 10-18) [16].

Carbonylation of propargyl acetate **71** gives 2,3-alkadienoic acid **72**, which is carried out under mild conditions (1 atm, 55 °C) in a two-phase system of aqueous NaOH and 4-methyl-2-pentanone in the presence or absence of Bu_4NBr [17]. Carbonylation of **73** in MeOH in the presence of Et_3N or Et_2NH under pressure (20 atm) at 45 °C affords methyl 2,3-butadienoate (**74**) in 85 % yield (Scheme 10-19) [18].

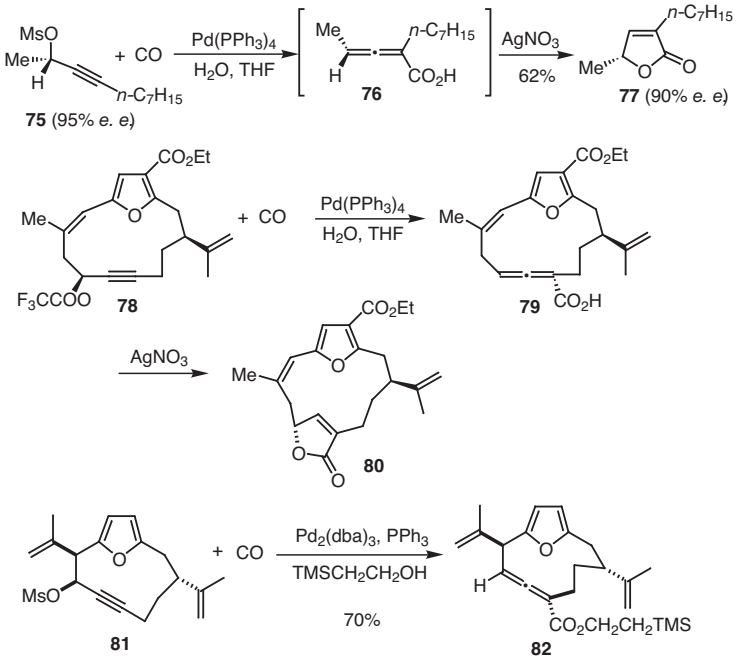


Scheme 10-18 [16]



Scheme 10-19 [18]

The intermediate allenic acid **76**, generated by carbonylation of the chiral propargyl mesylate **75**, is converted stereoselectively to butenolide **77** by the treatment with $AgNO_3$ as a catalyst. Racemization occurs by carbonylation of the corresponding propargyl carbonate [19]. Carbonylation of the trifluoroacetate **78** affords the allenic acid **79**, which is similarly converted to the butenolide **80** (Scheme 10-20) [20]. Carbonylation of the mesylate **81** to give the ester **82** proceeds with net inversion of configuration (Scheme 10-20) [21].

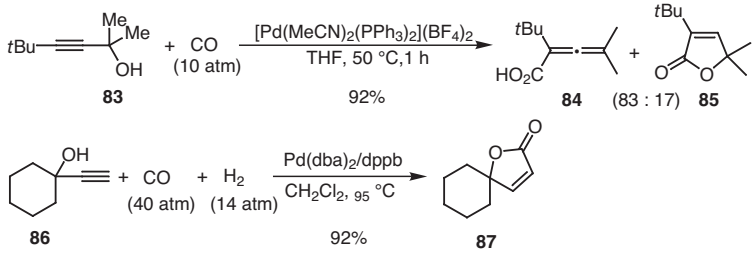


75 (95% *e. e*) **76** **77** (90% *e. e*) **78** **79** **80** **81** **82**

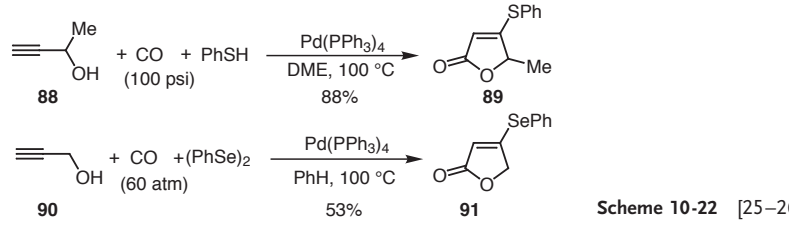
Scheme 10-20 [19–21]

Propargyl alcohols are less reactive than their esters, and their carbonylation has been carried out under somewhat harsh conditions. Carbonylation of propargyl alcohol **83**, catalyzed by a cationic Pd complex in THF, gives the 2,3-alkadienoic acid **84** and 2(5*H*)-furanone **85** in high yields in a ratio of 83:17 within 1 h. The compound **84** is readily converted into furanone **85** by treatment with *p*-toluenesulfonic acid [22,23]. Similarly, the carbonylation of propargyl alcohol **86** at 95 °C under pressure of CO (40 atm) and H_2 (14 atm) in dichloromethane under neutral conditions with the use of dppb as a ligand affords 2(5*H*)-furanone **87** (Scheme 10-21). It has been claimed that H_2 is required for this reaction [24].

Carbonylation of **88** in the presence of thiophenol gives rise to 3-phenylthiobutenolide **89** in high yield [25]. Similarly, 3-phenyselenobutenolide **91** is obtained from **90** in the presence of diphenyl diselenide (Scheme 10-22) [26].



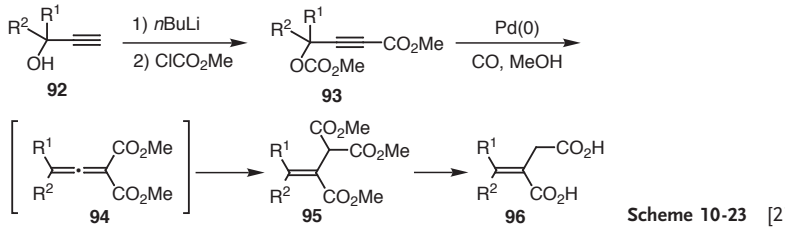
Scheme 10-21 [22–24]



Scheme 10-22 [25–26]

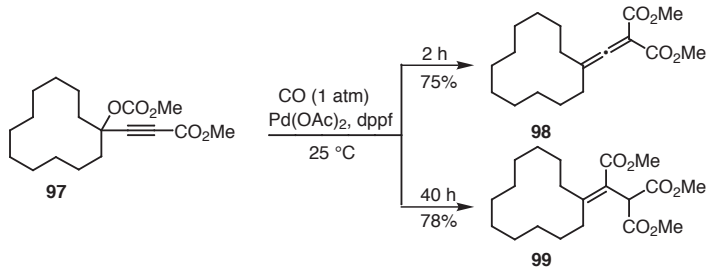
10.3.2.3 Preparation of Triesters by Dicarbonylation

By introduction of an ester group at the acetylenic terminus of propargyl carbonates, facile dicarbonylation becomes a main pathway. That is, vicinal dicarbonylation to afford triesters **95**, rather than the monocarbonylation, occurs by the carbonylation of **93**, demonstrating that the ester group has a strong activating effect [27a]. Propargyl carbonates **93** are readily available from **92**. The dicarbonylation of **93** proceeds very smoothly under 1 atm of CO at room temperature to give triesters **95**. The isolation of **94** is impossible in most cases since they are extremely susceptible to the carbonylation conditions (Scheme 10-23). Hydrolysis of **95** affords the dicarboxylic acid **96**.



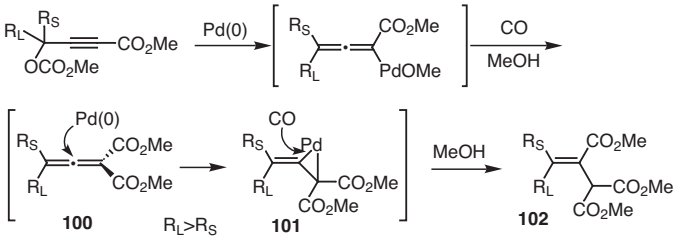
Scheme 10-23 [27]

Exceptionally, the monocarbonylation product **98** from the cyclododecyl derivative **97** can be isolated when the reaction is stopped after 2 h. Further carbonylation of **98** gives **99** (Scheme 10-24). Bidentate ligands such as dppp and dppf are the most effective ones for the dicarbonylation [27b].



Scheme 10-24 [27b]

These transformations can be rationalized by the following mechanism (Scheme 10-25). The geminal allene diester **100** may be susceptible to Michael-type addition of a Pd(0) species to the *sp*-carbon, resulting in the formation of palladacyclopropane **101**. Insertion of CO into **101** and methanolysis affords the triester **102**. The alkene configuration of **102** is exclusively *E*. The high stereoselectivity can be rationalized by assuming that a nucleophilic attack of the Pd(0) species on the *sp*-carbon in **101** takes place from the less hindered side of the smaller alkyl substituent (R_S).

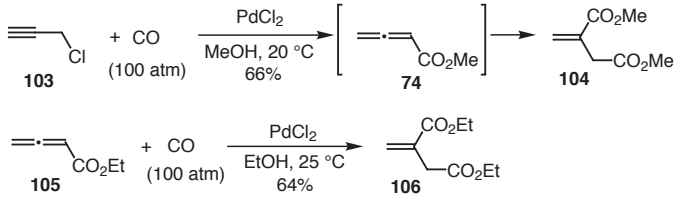


Scheme 10-25 [27]

10.3.2.4 **Dicarbonylation of Propargyl Chlorides and Alcohols**

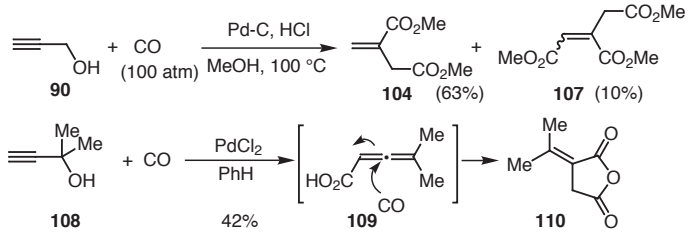
Dicarbonylation products are obtained by the carbonylation of propargyl halides and alcohols under high pressure of CO. Dimethyl itaconate (**104**) is provided by $PdCl_2$ or Pd on charcoal-catalyzed carbonylation of propargyl chloride (**103**) in MeOH at room temperature under 100 atm of CO. The primary product appears to be **74**, which is carbonylated further [15]. As a supporting evidence, formation of diethyl itaconate (**106**) in 64 % yield by the carbonylation of **105** in EtOH at room temperature under high pressure has been confirmed (Scheme 10-26).

Propargyl alcohols are less reactive than their esters, and their carbonylation has been carried out under somewhat harsh conditions (100 °C, 100 atm) [15]. Carbonylation of **90** in MeOH without a phosphine ligand proceeds in the presence of HCl to afford diester **104** as the main product and trimethyl aconitate (**107**) as the minor



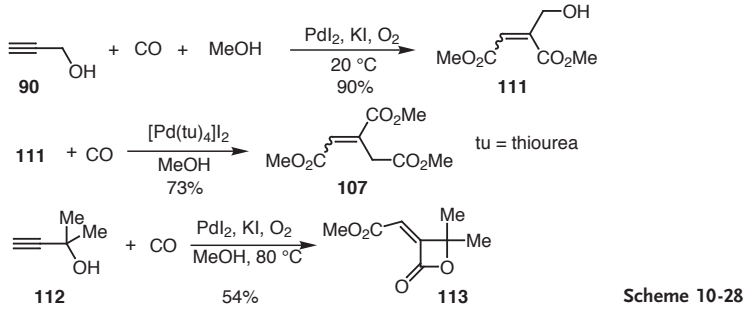
Scheme 10-26 [15]

product (Scheme 10-27). $PdCl_2$ or Pd/C are active catalysts [15]. Dicarbonylation in aprotic solvents yields acid anhydrides. Teraconic anhydride (**110**) is obtained by the dicarbonylation of **108**, which may proceed via the allene carboxylic acid **109**.



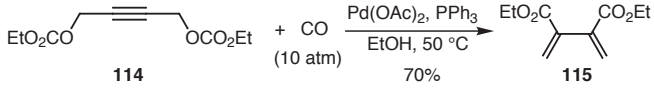
Scheme 10-27 [15]

Under these reaction conditions, **90** may be converted to the propargyl chloride **103**. Thus, Pd-catalyzed carbonylation of **90** proceeds via **74** as a primary product to give **104** as the dicarbonylation product. Formation of **107** is rationalized as occurring by the oxidative dicarbonylation of a triple bond with a Pd(II) species, followed by the Pd(0)-catalyzed allylic carbonylation. As a supporting evidence, **107** is obtained selectively in 65 % overall yield by the Pd-catalyzed two-step carbonylation of **90**. The first step is the oxidative dicarbonylation of the triple bond using PdI_2 under oxygen atmosphere to give hydroxymethylfumarate (**111**), and its allylic alcohol moiety is carbonylated further to give **107**. The *β*-lactone **113** is obtained when **112** undergoes dicarbonylation under similar oxidative conditions (Scheme 10-28) [28]. It is known that fumarate and maleate are obtained by the oxidative dicarbonylation of acetylene with $PdCl_2$ [29].



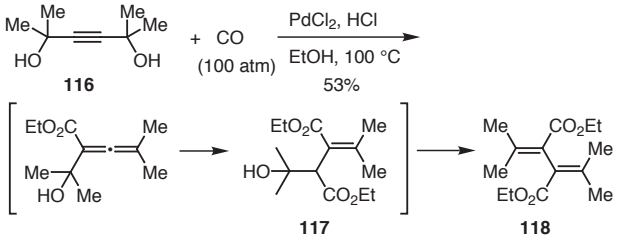
Scheme 10-28 [28]

Carbonylation of dicarbonate **114** at 50 °C offers a simple method for the preparation of diethyl buta-1,3-diene-2,3-dicarboxylate **115**. (Scheme 10-29) [30]. Carbonylation of diol **116** in EtOH containing HCl (5 %) affords **118**. The transformation is explained by the Pd(0)-catalyzed dicarbonylation to give **117** and subsequent elimination of water to give **118** (Scheme 10-30) [15].



114 **115**

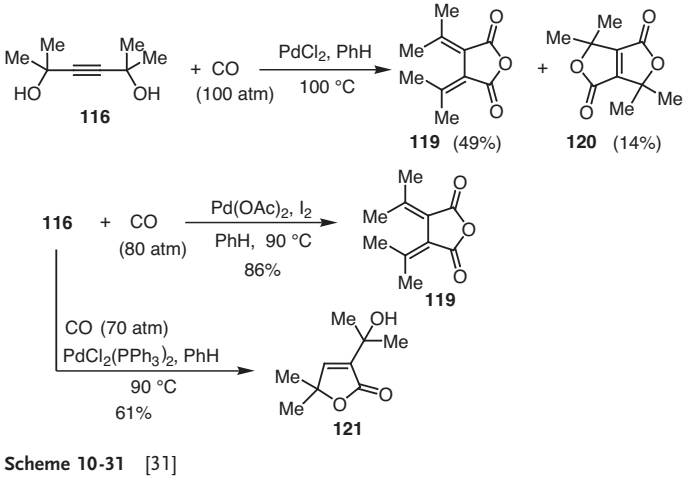
Scheme 10-29 [30]



116 **117** **118**

Scheme 10-30 [15]

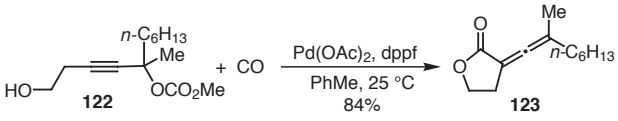
The sequential Pd(0)-catalyzed carbonylation and Pd(II)-catalyzed oxidative carbonylation in aprotic solvents yields acid anhydrides and, in some cases, lactones. Fulgide **119** was obtained in 49 % yield by palladium-catalyzed dicarbonylation of **116** in benzene. In addition, dilactone **120** was obtained as the byproduct (14 %). This dilactone is the product of the oxidative dicarbonylation and bislactonization [15]. The fulgide-forming reaction has been improved by the use of $Pd(OAc)_2$ as a catalyst in the presence of iodine ($Pd:I_2 = 1:1$) instead of HCl. When $PdCl_2(PPh_3)_2$ was used as the catalyst, furanone **121** was obtained in 61 % yield by monocarbonylation (Scheme 10-31) [31].



Scheme 10-31 [31]

10.3.2.5 Preparation of α-Alkenylidene-γ-lactones

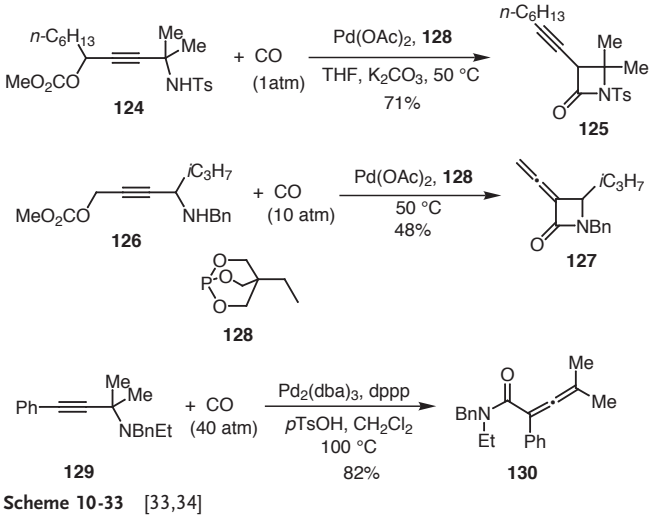
α-Alkenylidene-γ-lactone **123** was prepared by carbonylation of the propargyl carbonate **122** at room temperature under 1–10 atm of CO in good yields (Scheme 10-32) [32]. Bidentate ligands, particularly dppp and dppf, were found to be the best ligands in this respect.



Scheme 10-32 [32]

10.3.2.6 Preparation of α-Alkenylidene-β-lactams

α-Alkenylidene-β-lactams were prepared by the carbonylation of 4-protected amino-2-alkynyl methyl carbonates [33]. For example, α-alkynyl-β-lactam **125** was obtained as the sole product by the carbonylation of *p*-tosylamide **124** in the presence of a base. Formation of an α-vinylidene isomer was not observed. On the other hand, the carbonylation of benzylamine **126** afforded α-vinylidene-β-lactam **127** (Scheme 10-33). The carbonylation was carried out in THF or MeCN as solvents at 50 °C under 1–10 atm of CO. The cyclic phosphite **128** was the ligand of choice. Carbonylation of propargylamine **129** takes place under the harsh conditions to give 2,3-alkadienamide **130** (Scheme 10-33) [34].

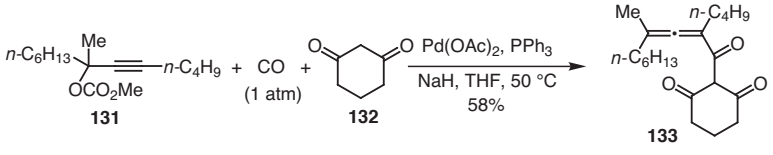


Scheme 10-33 [33,34]

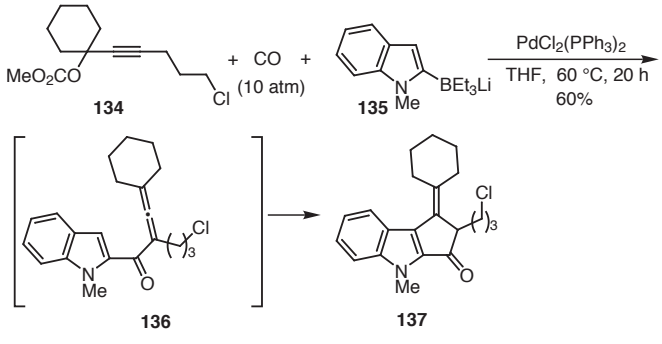
10.3.2.7 Carbonylations in the Presence of Active Methylene and Methyne Compounds

The acylpalladium complex as an intermediate of the carbonylation can be trapped by active methylene compounds to give allenyl ketones without forming a methyl ester. The results show that these carbanions are more reactive toward an acylpalladium intermediate than a methoxide anion [35]. The triketone **133** was obtained by the carbonylation in the presence of cyclohexane-1,3-dione (**132**) (Scheme 10-34). The carbonylation proceeds under CO (1 atm) at 50 °C.

Carbonylation of the propargyl carbonate **134** in the presence of indolylboranate **135** gave the allenyl ketone **136**, which, without isolation, underwent 1,4-addition to the allenyl ketone to afford cyclopenta[*b*]indole **137** (Scheme 10-35) [36].



Scheme 10-34 [35]

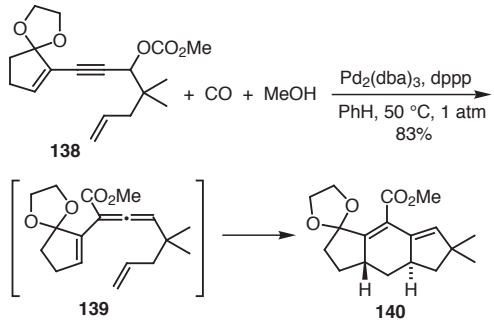


Scheme 10-35 [36]

10.3.2.8 Domino Carbonylations, Diels-Alder and Ene Reactions

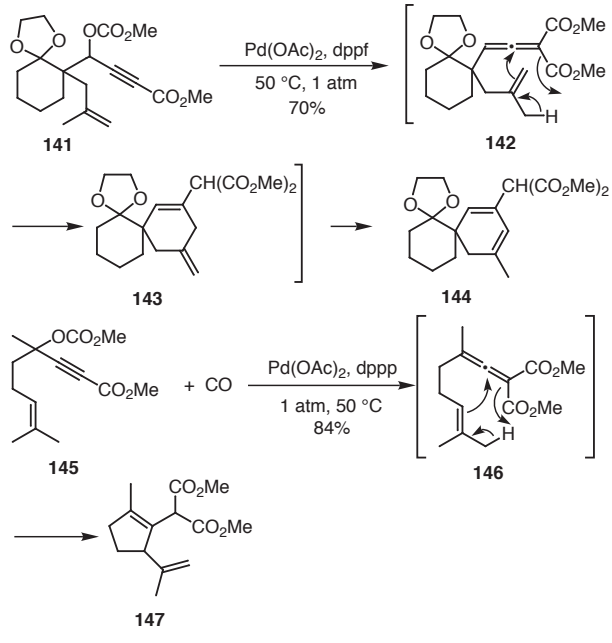
2-Vinyl-2,3-dienoates formed by the carbonylation of propargyl carbonates are highly reactive, and undergo further reactions with an internal double bond. As an example, the carbonylation of **138** gave the allenyldiene ester **139** which underwent an intramolecular Diels-Alder reaction to give the tricyclic compound **140** (Scheme 11-36) [37]. As a ligand, dppp was most effective. The intramolecular Diels-Alder reaction proceeds under surprisingly mild conditions, showing that the trisubstituted allene system is unexpectedly reactive towards the [4+2] cycloaddition.

Palladium-catalyzed carbonylation of the 1,6-enyne **141** bearing a terminal isopropenyl group gave rise to the spiroannelated cyclohexadiene **144** instead of a triester as shown in Scheme 10-23. Allenyl diester **142** initially formed underwent an ene reaction with the proximal 2-propenyl unit to yield an unisolable 4-methyl-



Scheme 10-36 [37]

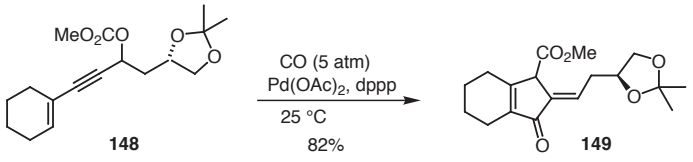
enecyclohexene derivative **143**, which isomerized to the 1,3-cyclohexadiene **144** in 70% yield (Scheme 10-37) [38]. In sharp contrast, the carbonylation of the 1,6-enyne **145** yielded the five-membered ring **147** having an isopropenyl substituent, via the intermediate **146**.



Scheme 10-37 [38]

10.3.2.9 **Preparation of 4-Oxocyclopent-2-enecarboxylates**

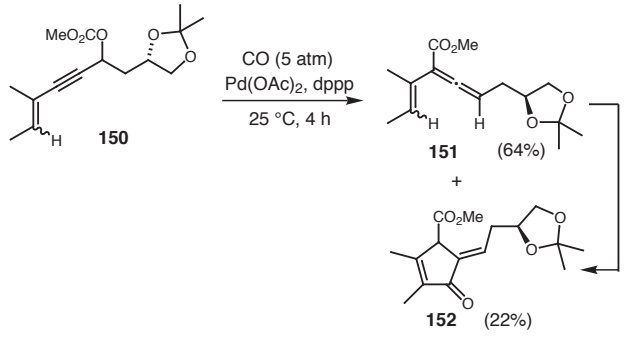
An attempted intermolecular Diels-Alder reaction of the in-situ-formed carbonylation product of **148** in the presence of various alkenes as dienophiles under 5 atm of CO at room temperature did not take place, but provided entirely different products. The 4-oxocyclopent-2-enecarboxylate **149** was formed unexpectedly by the incorporation of two molecules of CO in 82% yield at 50 °C under 1 atm of CO (Scheme 10-38) [39].



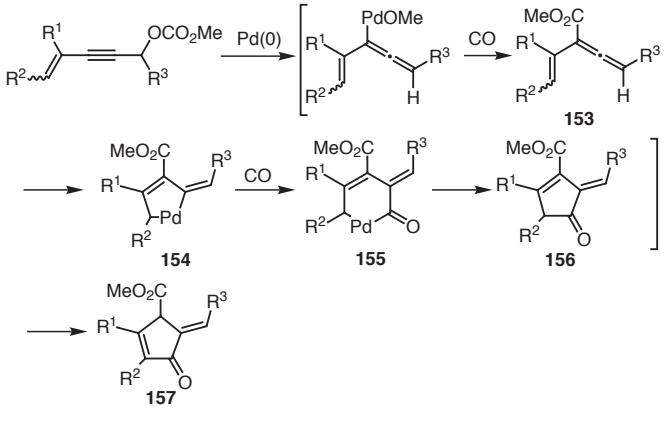
Scheme 10-38 [39]

Additional experimental evidence provided some important clues concerning the mechanism of this transformation. In one case, the most likely intermediate, the 2-vinyl-2,3-dienoate **151** was isolated (64 %) along with the oxocyclopentenecarboxylate **152** (22 %) after 4 h of exposure of **150** to the carbonylation conditions. Upon extended exposure of **151** to the same conditions, it was converted to **152**, thus indicating that **151** is indeed the precursor to **152** (Scheme 10-39).

The proposed reaction mechanism is as follows. The initially formed 2-vinyl-2,3-dienoate **153** may be susceptible to a Michael-type addition of a Pd(0) species to the *sp*-carbon to give a palladacyclopentene **154**. This then undergoes CO insertion to furnish an acylpalladium **155** which, upon reductive elimination, affords the oxocyclopentenecarboxylate **156**. Finally, the latter isomerizes to the thermodynamically more stable isomer **157** (Scheme 10-40).



Scheme 10-39 [39]

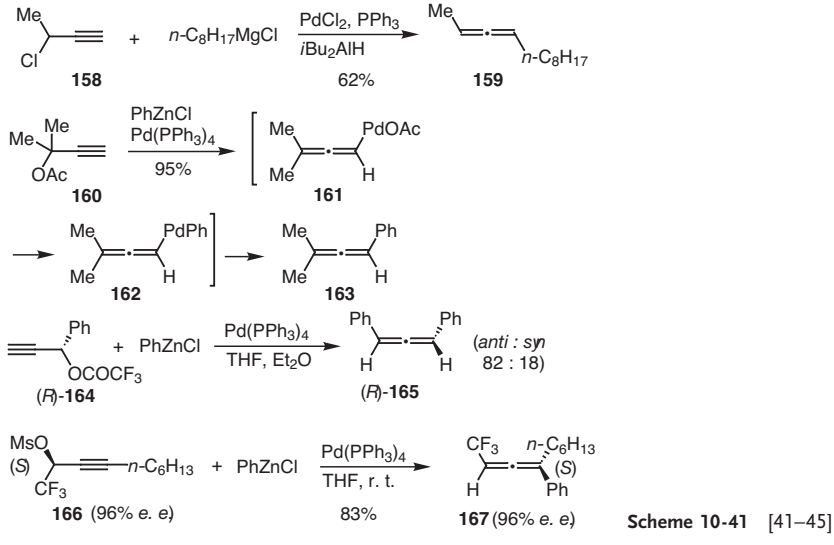


Scheme 10-40 [39]

10.4
Transformations via Transmetallation of Allenylpalladium Intermediates and Related Reactions (Type II)

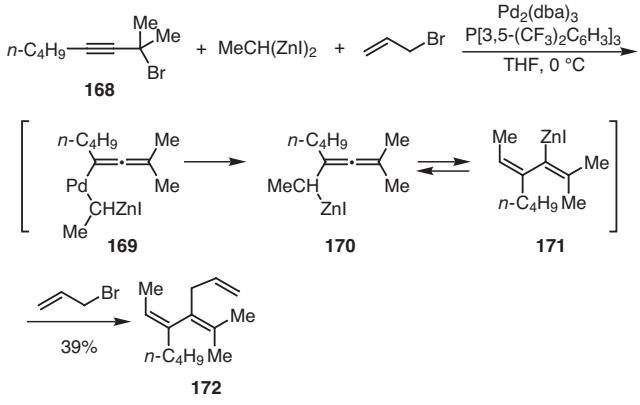
10.4.1
Reactions with Hard Carbon Nucleophiles

Reactions of propargyl halides, acetates and phosphates with hard carbon nucleophiles MR (M = main group metals such as Mg, Zn, B, Si) under palladium catalysis give allenyl derivatives [40]. Octylmagnesium chloride reacts with 3-chloro-1-butyne (**158**) to give 2,3-dodecadiene (**159**) (Scheme 10-41) [41]. Reaction of PhZnCl with propargyl acetate **160** gives 1,2-diene **163** in high yield [42–44]. The transformation can be rationalized with a transmetallation of the allenylpalladium intermediate **161** with PhZnCl to generate allenyl(phenyl)palladium intermediate **162** which undergoes a reductive elimination to afford **163**. *anti*-Stereoselectivity was observed in the reaction of (*R*)-(–)-1-phenyl-1-trifluoroacetoxy-2-propyne (**164**) with PhZnCl to produce levorotatory allene (*R*)-**165**. The ratio of *anti*- to *syn*-1,3-substitution was 82:18. The observed *anti*-stereoselectivity is rationalized by assuming that an allenylpalladium species is formed with inversion of configuration, while the transmetallation and the ensuing reductive elimination proceed with retention of configuration [44]. Similarly, the reaction of the chiral propargyl mesylate **166** with PhZnCl proceeded with complete retention of configuration to give **167** (Scheme 10-41) [45].



Scheme 10-41 [41–45]

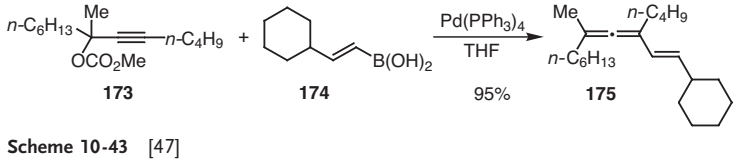
Reaction of propargyl bromide **168** with *gem*-(diiodozinc)ethane in the presence of allyl bromide generates organozinc intermediates **170** and **171** via **169**. Then **171** is trapped by allyl bromide to afford the triene **172** (Scheme 10-42) [46].



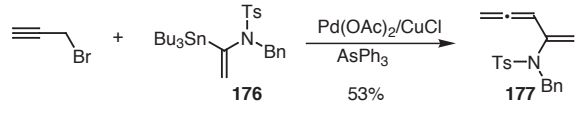
Scheme 10-42 [46]

Organoboranes also react with propargyl carbonates. Usually, the addition of a base is indispensable for the Pd-catalyzed reactions of organoboranes with aryl, alkenyl, and allyl halides. But the reaction of organoboranes with methyl propargyl carbonates proceeds without addition of a base, because a methoxide as a base is generated *in situ* from the carbonate. For example, 1,2,4-alkatriene **175** is obtained by the reaction of alkenylborane **174** with propargyl carbonate **173** under neutral conditions (Scheme 10-43) [47].

The α-allenylenamine **177** can be prepared by the coupling of *α*-stannylenamide **176** with propargyl bromide. $AsPh_3$ as a ligand and CuCl as an additive were used (Scheme 10-44) [48].

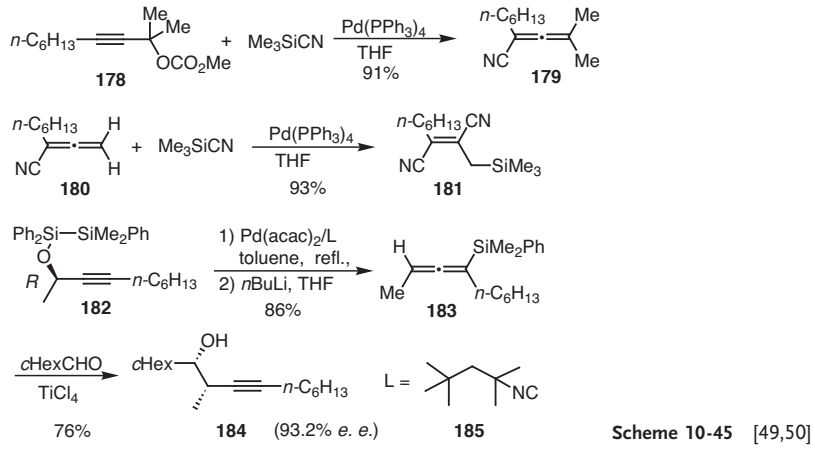


Scheme 10-43 [47]



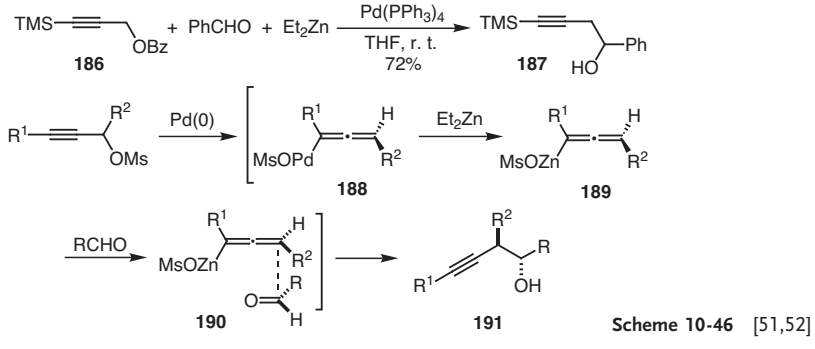
Scheme 10-44 [48]

The cyanoallene **179** was prepared by the reaction of carbonate **178** with trimethylsilyl cyanide. In the presence of an excess of trimethylsilyl cyanide, the dicyanated product **181** was obtained in high yield (Scheme 10-45) [49]. Treatment of the enantiomerically pure (*R*)-disilanyl ether **182** with a Pd catalyst coordinated by the sterically demanding isonitrile **185**, generated allenylsilane **183**, which could be trapped with cyclohexanecarbaldehyde to give the *syn*-homopropargyl alcohol **184** with 93.3 % *e.e.* and high diastereoselectivity (Scheme 10-45) [50].



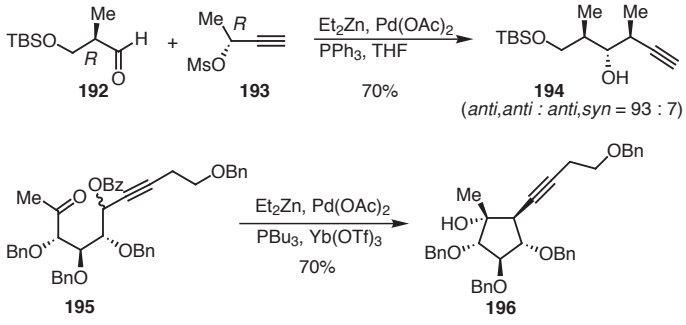
Scheme 10-45 [49,50]

The Pd-catalyzed reaction of propargyl benzoate **186** in the presence of Et_2Zn affords homopropargyl alcohol **187** in good yield (Scheme 10-46) [51]. Further studies on the reaction of chiral propargyl mesylates with Et_2Zn have been carried out [52]. The intermediate allenylpalladiums **188** react with Et_2Zn to yield nucleophilic allenylzinc reagents **189**, which attack carbonyl groups to give homopropargyl alcohols **191**. The high diastereoselectivities observed in this transformation can be explained with the coordination of an aldehyde to zinc from the less-hindered side, as shown in transition structure **190** (Scheme 10-46).



Scheme 10-46 [51,52]

Under carefully controlled conditions, the reaction proceeds with excellent diastereoselectivity. Addition of the allenylzinc reagent derived from the (*R*)-mesylate **193** to (*R*)-aldehyde **192** proceeds at –20 °C to give the *anti,anti*-configurated product with a stereo triad **194** in 70 % yield with a small percentage of the *anti,syn*-isomer [53]. In an intramolecular version of this transformation, the propargyl benzoate **195**, in the presence of Et_2Zn and a Lewis acid, attacks a proximal carbonyl

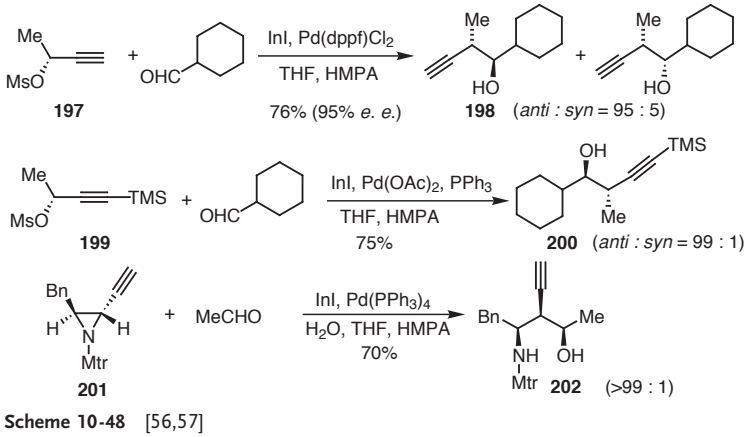


Scheme 10-47 [53,54]

group to afford cyclopentanol **196** with high diastereoselectivity (Scheme 10-47). The most effective Lewis acid was found to be $[Yb(Otf)_3]$, and a very effective catalyst was $Pd(OAc)_2/PBu_3$ [54].

Allenylindium derivatives, prepared by transmetallation of allenylpalladium intermediates with indium iodide, are used for the addition to aldehydes to afford homopropargyl alcohols. Addition of the transient allenylindium reagent from chiral propargyl mesylate **197** to cyclohexanecarbaldehyde produced the *anti*-stereoisomer **198** with high selectivity upon use of $Pd(dppf)Cl_2$ as a catalyst [55], but $Pd(OAc)_2/PPh_3$ was found to be a superior catalyst to $Pd(dppf)Cl_2$ in the reaction of propargyl mesylate **199** with cyclohexanecarbaldehyde to give the *anti*-isomer **200** with higher selectivity [56].

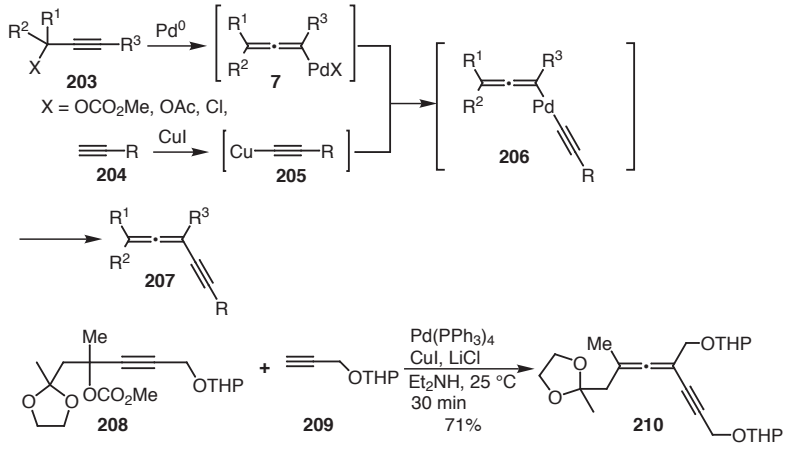
An allenylindium reagent bearing a protected amino group was obtained from the aziridine **201**, and diastereoselective addition of the allenylindium species to acetaldehyde afforded the 1,3-amino alcohol **202** bearing three stereogenic centers in good yield (Scheme 10-48) [57].



Scheme 10-48 [56,57]

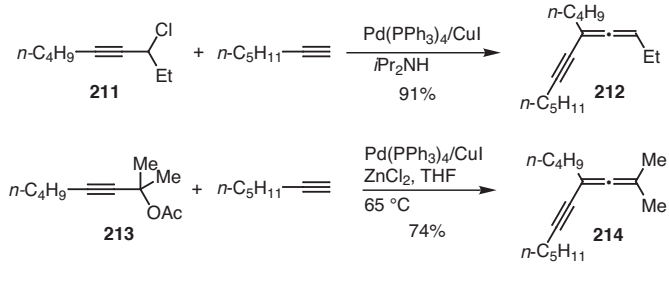
10.4.2
Reactions of Terminal Alkynes: Formation of 1,2-Alkadien-4-ynes

1,2-Dien-4-ynes **207** can be prepared in good yields by Pd-catalyzed coupling of propargyl derivatives **203** such as carbonates, acetates, and halides with terminal alkynes **204** in the presence of a catalytic amount of CuI as a co-catalyst. Addition of CuI is not necessary when metal acetylides are used. The reaction proceeds rapidly at room temperature within 30 min [58]. The reaction path is as follows. Reaction of CuI with **204** affords the copper acetylide **205**, which undergoes transmetallation with the allenylpalladium **7** to form allenyl(alkynyl)palladium species **206**. Reductive elimination of **206** gives the allenylalkyne **207**. Coupling of **208** with the protected propargyl alcohol **209** gave rise to 1,2-dien-4-yne **210** at room temperature in 85 % yield (Scheme 10-49).



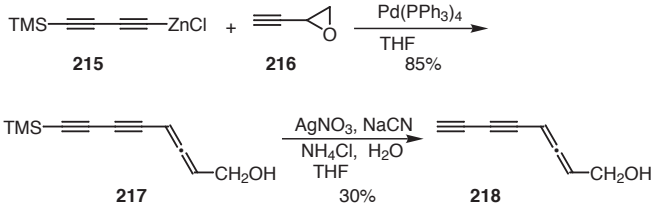
Scheme 10-49 [58]

In addition to propargyl carbonates, propargyl chlorides, acetates and tosylates react with terminal alkynes in the presence of Et_3N or iPr_2NH. The 1,2-alkadiene-4-yne **212** was obtained in 91 % yield by the reaction of **211** with 1-heptyne in iPr_2NH. The coupling of propargyl acetate **213** with 1-heptyne was possible in the presence of 3 equiv. of $ZnCl_2$, with or without the use of CuI, to give **214** (Scheme 10-50) [59].



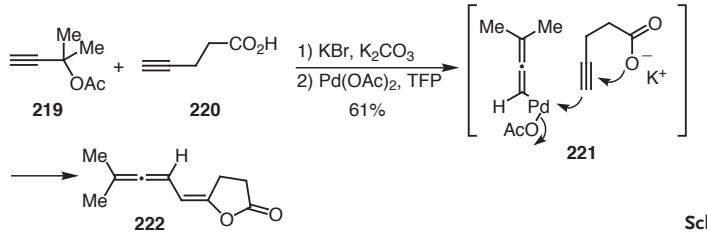
Scheme 10-50 [59]

Various metal acetylides were used for smooth coupling with propargyl halides, acetates and 2-(1-alkynyl)oxiranes to give 2,3-alkadien-5-yn-1-ols [43, 60]. To demonstrate the synthetic applicability, unstable 2,3-octadiene-5,7-diyn-1-ol (**218**), a fungal metabolite, has been synthesized by coupling of the alkynylzinc reagent **215** with **216**, leading to alcohol **217**, followed by desilylation (Scheme 10-51) [60].



Scheme 10-51 [60]

The 4-(allenylmethylene)-γ-butyrolactone **222** was obtained by coupling the dimethylpropargyl acetate **219** with 4-pentynoic acid (**220**) in the presence of KBr using tri(2-furyl)phosphine (TFP) as a ligand. Oxypalladation of the triple bond of **220** with an allenylpalladium species and the carboxylate as shown in **221** must have been the first step, and the subsequent reductive elimination afforded lactone **222** (Scheme 10-52). The (*E*)-configurated double bond was formed because the oxypalladation is a *trans*-addition [61].



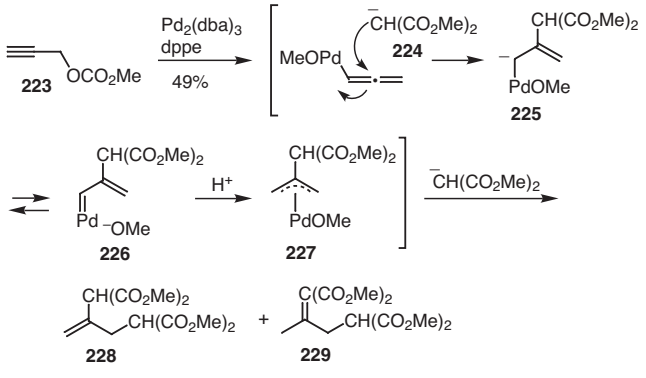
Scheme 10-52 [61]

10.5
Reactions with Attack of Soft Carbon and Oxo Nucleophiles on the *sp*-Carbon of Allenylpalladium Intermediates (Type III)

10.5.1
Reactions with Soft Carbon Nucleophiles

Reactions which proceed by an attack of a nucleophile at the *sp*-carbon of an allenylpalladium complex have been classified as type III. In contrast to the facile Pd(0)-catalyzed reactions of allylic esters with soft carbon nucleophiles via π-allylpalladium intermediates, propargyl esters – under palladium catalysis – are less reactive towards soft carbon nucleophiles. No reaction of soft carbon nucleophiles occurs with propargyl acetates. However, soft carbon nucleophiles such as β-keto esters and malonates react under neutral conditions with propargyl carbonates using dppe as a ligand for the palladium catalyst [62].

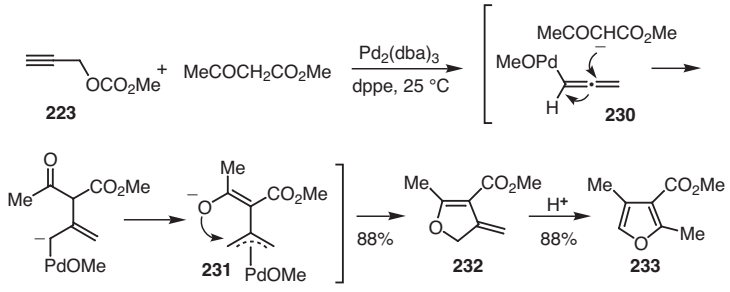
Methyl 2-propynyl carbonate (**223**) reacts with 2 equiv. of malonate to give 2,3-disubstituted propenes **228** and **229** under neutral conditions in boiling THF. The carbanion **224** attacks the *sp*-carbon of the allenylpalladium intermediate to furnish **225**, which picks up a proton from dimethyl malonate to form the π-allylpalladium intermediate **227**. Intermediate **225** can also be described as a palladiumcarbene complex **226**. Then, **224** attacks **227** to give **228** which isomerizes to **229** (Scheme 10-53) [62, 63]. Thus, **223** has two reaction sites for the attack of nucleophiles.



Scheme 10-53 [62, 63]

Methyl acetoacetate reacts with propargyl carbonate **223** in a 1:1 ratio in THF at room temperature, giving an entirely different product. At first, *C*-alkylation in **230** takes place to generate the π-allylpalladium intermediate **231**, which is then attacked intramolecularly by the oxygen nucleophile of the enolate to give the methylenedihydrofuran **232** in 88 % yield under neutral conditions. This product

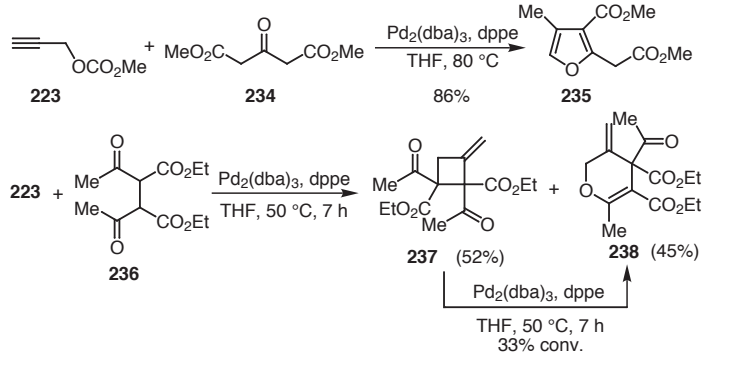
232 was found to be unstable, and isomerized to the stable furan derivative **233** under slightly acidic conditions (Scheme 10-54) [62, 63].



Scheme 10-54 [62, 63]

Similarly, the reaction of 3-oxoglutarate **234** with **223** afforded the furan **235** in good yield. The formation of a substituted furan has been applied to the synthesis of a phenylthiomethyl-substituted furan and used for syntheses of natural products such as Neoliacine [64].

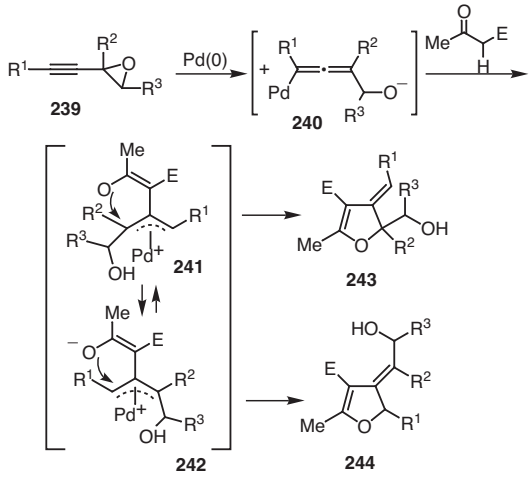
The reaction of **223** with the β-keto ester **236** afforded the cyclobutane **237** by double *C*-alkylation and 3-methylenedihydropyran derivative **238** by a sequence of *C*- and *O*-alkylations in 52 and 45 % yield, respectively. The compound **237** is a product of a reversible reaction, and 33 % of **237** is converted to **238** by treatment with the same catalyst (Scheme 10-55) [65].



Scheme 10-55 [65]

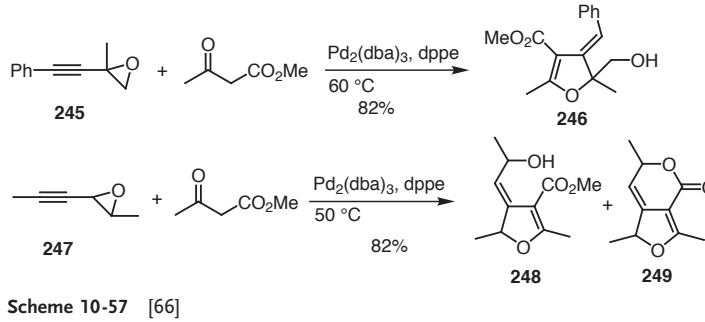
The Pd-catalyzed reactions of 2-alkenyloxiranes **239** with soft carbon nucleophiles can proceed along two cyclization pathways to give either **243** or **244**, depending on the substituents [63, 66]. At first, the allenylpalladium **240** is generated, and this is then converted to two kinds of π-allylpalladium complexes, **241** and **242**,

respectively. When R^2 is not H, the enolate oxygen attacks the more substituted end to give the furan **243**. When R^2 is H, furan **244** is obtained (Scheme 10-56).



Scheme 10-56 [63,66]

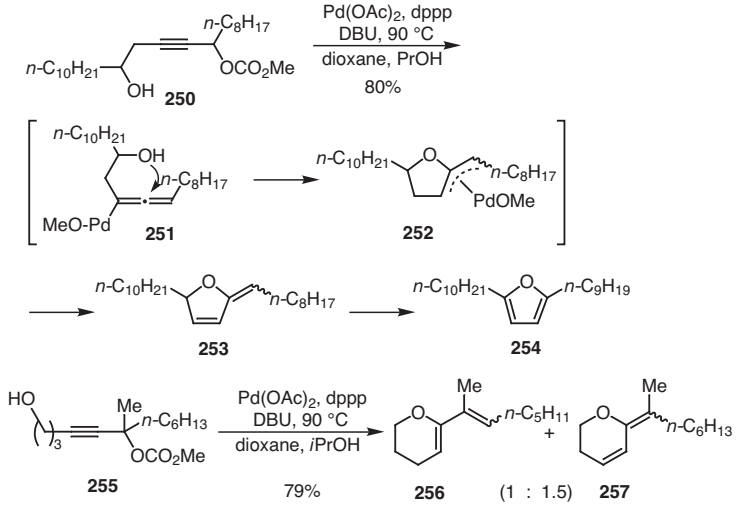
The 2-alkynyloxirane **245** reacted with methyl acetoacetate in the presence of $Pd_2(dba)_3$ and dppe in anhydrous THF at 60 °C to give the hydroxylmethyldihydrofurancarboxylate **246** in 82 % yield. The double bond had (*E*)-configuration as the reaction proceeded via the π-allylpalladium intermediate **241**, in which R^1 = Ph prefers to adopt the *syn*-orientation for steric reasons. In addition, the observation that the furan **248** formed from **247** cyclizes to give dihydrofurolactone **249** supports the (*E*)-configuration of the *exo*-double bond in **248** (Scheme 10-57).



Scheme 10-57 [66]

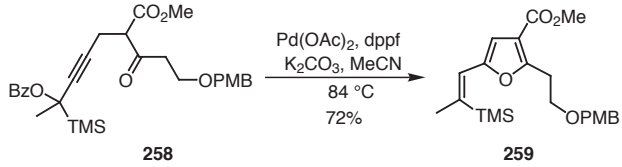
10.5.2
Reaction with Oxo Nucleophiles

The propargyl carbonate **250** bearing a hydroxyl group at C-5 undergoes cyclization by attack of the hydroxyl group on the *sp*-carbon of the allenyl system **251**. The intermediate π-allylpalladium complex **252** undergoes β-elimination to give the diene **253**, which is converted to the more stable furan **254** as a final product in 80 % yield [68]. DBU was found to be the base of choice. Similarly, dihydropyrans **256** and **257** were formed from 6-hydroxy-substituted propargyl carbonates **255** (Scheme 10-58) [68,69].



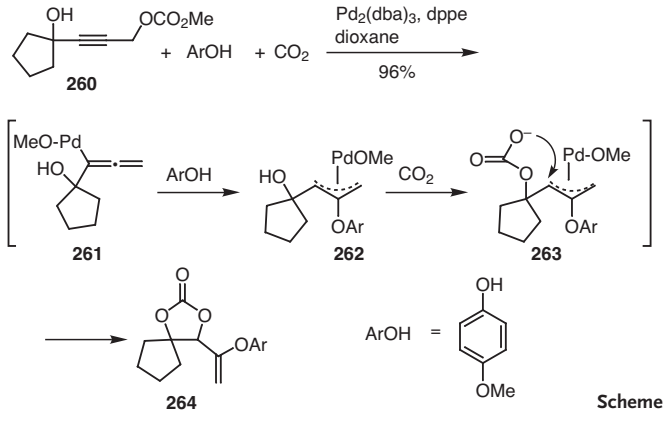
Scheme 10-58 [68,69]

The furan **259** was obtained by an intramolecular reaction of the propargyl benzoate **258** with the enolate anion of the β-keto ester moiety in **258** in the presence of $Pd(OAc)_2$ and dppf as a ligand (Scheme 10-59). This transformation was applied to the synthesis of the C(1)-C(18) segment of lophotoxin [70]. Reaction of the carbonate **260** with *p*-methoxyphenol under CO_2 atmosphere afforded the cyclic carbonate **264**. The allenylpalladium intermediate **261** initially formed appears to be converted to the π-allylpalladium intermediate **262** by attack of



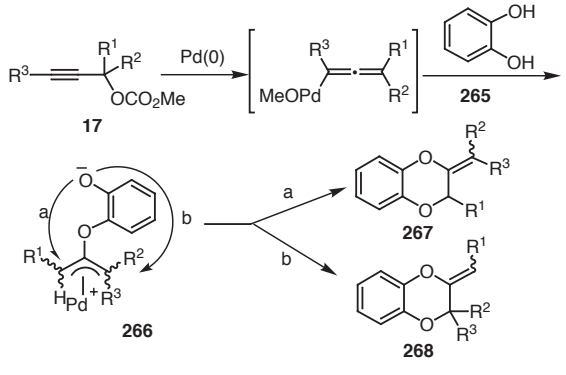
Scheme 10-59 [70]

p-methoxyphenol on the *sp*-carbon of **261**. Then, the reaction of carbon dioxide with **262** generates **263**, which attacks the π-allylpalladium terminal to form the cyclic carbonate **264** (Scheme 10-60) [71].



Scheme 10-60 [71]

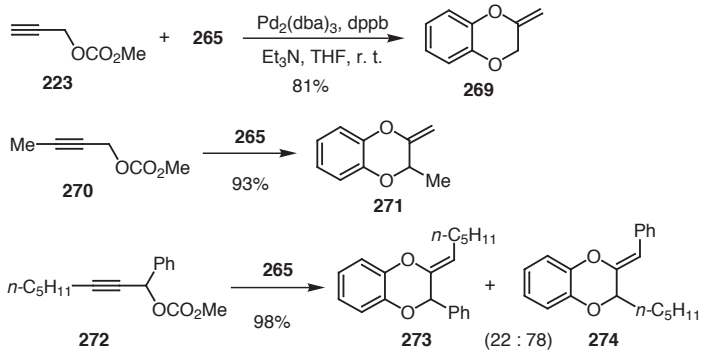
1,4-Benzodioxines **267** and **268** were prepared by the reaction of propargyl carbonates **17** with catechol (**265**), which attacks either side of the π-allylpalladium intermediate **266** (Scheme 10-61).



Scheme 10-61 [72]

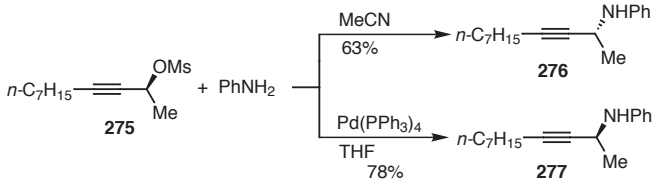
Reaction of the propargyl carbonate **223** with catechol (**265**) gave methylenebenzodioxin **269**. The propargyl carbonate **270** afforded benzodioxin **271**, and a mixture of **273** and **274** in a ratio of 22:78 was obtained from **272** (Scheme 10-62). In these reactions, the use of dppb as a ligand provided the highest yields [72].

Reaction of the propargyl mesylate **275** with aniline proceeded without a catalyst to afford the propargylamine **276** with inversion of configuration. On the other



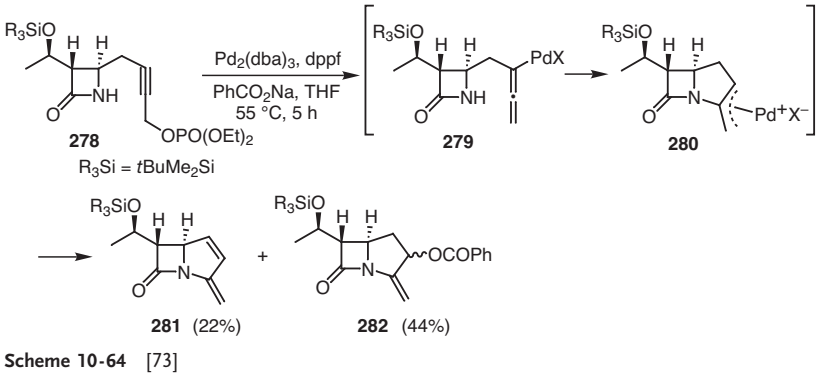
Scheme 10-62 [72]

hand, the Pd-catalyzed reaction of **275** gave **277** with retention of configuration (Scheme 10-63) [73].



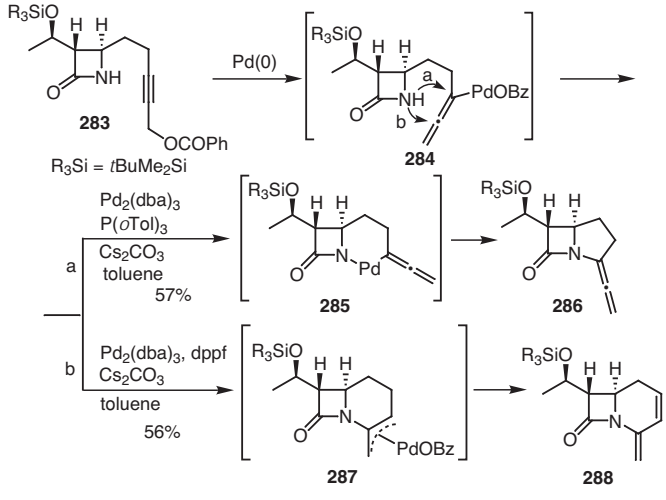
Scheme 10-63 [73]

In intramolecular amination reactions, an amino group attacks either an sp^2 or the sp carbon of an allenylpalladium intermediate, depending on the ligands used. Carbapenam skeletons were prepared by intramolecular attack of amines (Scheme 10-64). Treatment of the propargyl phosphate **278** with $Pd_2(dba)_3$ and dppf afforded carbapenam skeletons **281** and **282** in high yields. In this transformation, the lactam nitrogen attacks the *sp* carbon of the σ-allenylpalladium complex **279** to generate the π-allylpalladium intermediate **280**.

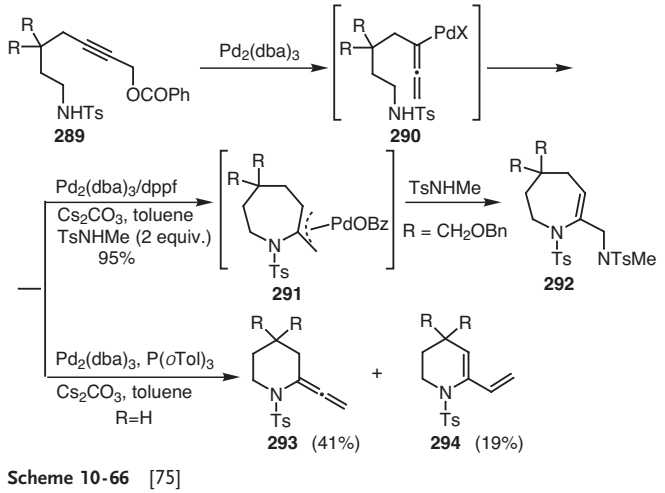


Scheme 10-64 [73]

The Pd-catalyzed reaction of the propargyl benzoate **283** provides the allenylpalladium species **284**. The β-lactam nitrogen then attacks the allenyl moiety of **284** in either of two ways, depending on the phosphine ligands used. When $P(o\text{Tol})_3$ is applied as a ligand, the carbapenam **286** is formed via ligand exchange on palladium with the lactam nitrogen, followed by reductive elimination from **285**. The use of dppf as a ligand dramatically changes the reaction pathway, and the nitrogen attacks the *sp* carbon of **284** to produce the π-allylpalladium species **287** leading to the carbacepham skeleton **288** (Scheme 10-65).



Scheme 10-65 [73]



Scheme 10-66 [75]

Upon treatment of the propargyl benzoate **289** with $Pd_2(dba)_3$ and dppf in the presence of *N*-methyltosylamide, the allenylpalladium species **290** is generated. The proximal amino group then attacks the *sp* carbon to furnish the π-allylpalladium intermediate **291**. Finally, *N*-methyltosylamide attacks **291** to give the azepine **292** in 95 % yield (Scheme 10-66). The six-membered heterocycles **293** and **294** were obtained from **289** when $P(o\text{Tol})_3$ was used [75].

10.6
Experimental Procedures

10.6.1
Reaction of Carbonate with Alkenes (Scheme 10-8) [5]

A mixture of the propargyl carbonate **24** (0.5 mmol), methyl acrylate (1.5 mmol), Et_3N (1.0 mmol), KBr (1 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), and water (0.1 mL) in DMF (3 mL) was stirred at 70 °C for 1 h. After the usual work-up, the 1,2,4-triene **25** was isolated by column chromatography (71 %).

10.6.2
Domino Carbonylation-Diels Alder Reaction (Scheme 10-36) [35]

A mixture of $Pd_2(dba)_3$ (5 mol %) and dppp (20 mol %) was dissolved in benzene (1 mL), and the solution was stirred under argon at room temperature for a few minutes. A solution of the propargyl carbonate **138** (0.5 mmol) in benzene/MeOH (1 mL each) was added and a rubber balloon, filled with CO, was attached. After heating at 50–60 °C for 6 h, the reaction mixture was passed through Florisil, eluting with diethyl ether, and the combined solution was concentrated. The residual oil was purified by chromatography (silical gel, *n*-hexane:ethyl acetate, 15:1) to give the tricyclic compound **140** as an oil in 83 % yield.

10.6.3
Reaction of a Propargyl Carbonate with an Alkyne (Scheme 10-49) [54]

A solution of the propargyl carbonate **208** (365 mg, 1.06 mmol) and the protected propargyl alcohol **209** (148.4 mg, 1.06 mmol) in THF (2 mL) was added to a dispersion of CuI (20.2 mg, 0.106 mmol), LiCl (89.9 mg, 2.12 mmol), Et_2NH (2.19 mL, 21.2 mmol), and $Pd(PPh_3)_4$ (62 mg, 0.053 mmol) in THF (3 mL) at 25 °C. The mixture was stirred for 30 min and then diluted with hexane (30 mL). After the usual work-up, the 1,2-alkadien-4-yne **210** was isolated by column chromatography as a pale yellow oil (306 mg, 71 %) as an inseparable mixture of four diastereomers.

10.6.4

Furan Formation by the Reaction of a Propargyl Carbonate with Methyl Acetoacetate (Scheme 10-54) [62]

$Pd_2(dba)_3 \cdot CHCl_3$ (52 mg, 0.1 mmol) and dppe (80 mg, 0.2 mmol) were placed in a 30-mL, two-necked flask which was flushed with argon. THF (2 mL) was added to dissolve the catalyst. Then, a solution of the propargyl carbonate **223** (228 mg, 2 mmol) and methyl acetoacetate (232 mg, 2 mmol) in THF (3 mL) was added, and the mixture stirred at room temperature for 4 h. The reaction mixture was filtered through Florisil. The furan **233** (272 mg, 88 %) was isolated by column chromatography on alumina.

Abbreviations

dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1′-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
Naph	naphthyl
TFP	tris(2-furyl)phosphine
TMS	trimethylsilyl
Tol	*p*-tolyl
Ts	*p*-toluenesulfonyl

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11
Carbon-Carbon Bond-Forming Reactions Mediated by Organozinc Reagents

Paul Knochel, M. Isabel Calaza, and Eike Hupe

11.1
Introduction

The chemo-, regio-, and stereoselective formation of new carbon-carbon bonds is one of the major goals of organic chemistry. Organometallic reagents (R^1M) are particularly well suited for such reactions since the polarity of the carbon-metal bond of these reagents confers a nucleophilic character to the carbon atom bound to the metal and allows reactions with a variety of carbon-centered electrophiles (R^2X) furnishing products of the type R^1-R^2. Some of the first organometallic species used by organic chemists for performing this task were organozinc compounds (R_2Zn or RZnX) [1]. However, these were soon replaced by the more reactive organomagnesium and organolithium reagents. The increased reactivity of these latter two classes of organometallics were very beneficial to organic synthesis, and led to an explosive development. However, it soon became clear that this increased reactivity had some drawbacks, such as a low chemoselectivity. Also, it only allowed introduction of R^1 groups bearing relatively few functionalities. The high reactivity of carbon-magnesium or carbon-lithium bonds precludes the presence of many organic functionalities in these organometallics.

The first solutions to these problems were found between 1970 and 1980, by performing transmetallation reactions of organomagnesiums and organolithiums with copper [2] or titanium [3] salts, leading to highly chemoselective reagents. Unfortunately, since these transition-metal organometallics were prepared from lithium or magnesium reagents, still no "highly" functionalized titanium or copper organometallics could be prepared. However, it was soon noticed that organozincs – although very unreactive towards most organic electrophiles – smoothly undergo transmetallations [4,5] with a variety of transition-metal salts or complexes leading to new transition-metal compounds which then react with a range of organic electrophiles due to the presence of *d*-orbitals on the metals which allow new reaction pathways that are not available to main-group organometallics (Scheme 11-1) [6,7].

A major part of this chapter will show the synthetic applications of these transmetallation reactions for the performance of cross-coupling reactions. After a short

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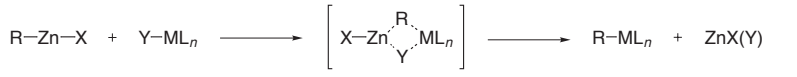


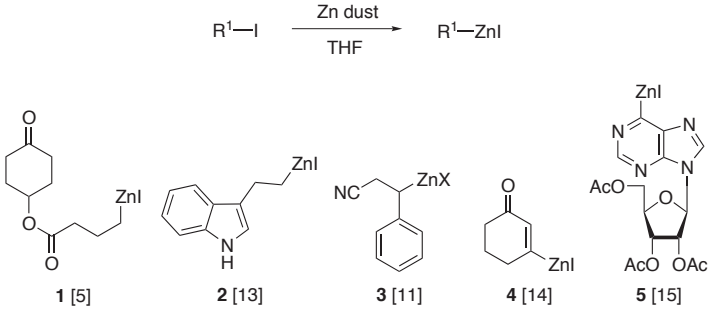
Scheme 11-1 [6,7]

description of the preparation of organozinc halides (RZnX) and diorganozincs (R_2Zn), the utility of these reagents for forming new carbon-carbon bonds will be presented. Emphasis will be placed on reactions having a good generality and high synthetic potential. Experimental procedures will be given for some of the most significant reactions.

11.2
Methods of Preparation of Zinc Organometallics

Polyfunctional organozinc halides are best prepared by the direct insertion of zinc (applied as zinc dust) into the carbon-iodine bond of alkyl iodides. This method allows one to prepare organozinc iodides bearing almost all possible organic functionalities, with the exception of nitro, azido, and hydroxy groups. With primary alkyl iodides, the insertion reaction is usually performed by adding a concentrated solution (3 *M*) of the alkyl iodide in THF to a suspension of zinc dust (around 325 mesh, ca. 3 equiv.) in THF at 40 °C. The zinc dust is treated with 1,2-dibromoethane and chlorotrimethylsilane (TMSCl) prior to the halide addition [5,8,9]. Secondary alkyl iodides react with zinc dust even at 25 °C [5,9,10], whereas benzylic bromides undergo an optimal insertion reaction at 0 °C [11]. The insertion of zinc into C_{sp^2}-I bonds is usually less straightforward, and may require longer reaction times, higher temperatures, or the use of a polar solvent [12]. The polyfunctional zinc reagents **1–5** have been prepared in high yields using these procedures (Scheme 11-2).

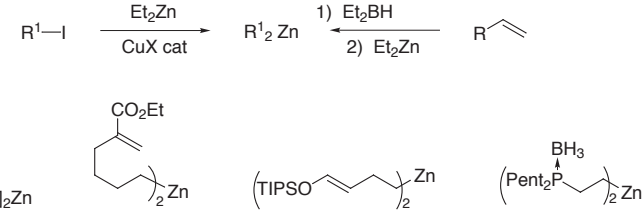
Alternatively, more reactive zinc powder prepared by the reduction of zinc halides (Rieke zinc) can be used when starting with the less reactive aryl iodides or bromides, but also with secondary and tertiary alkyl bromides [16–18].



1 [5] **2** [13] **3** [11] **4** [14] **5** [15]

Scheme 11-2

Diorganozincs ($R^1{}_2Zn$) are more reactive than organozinc halides [7,19] and undergo transmetallation reactions more readily. They are important for the performance of catalytic asymmetric additions to various aldehydes, making possible the general preparation of polyfunctional secondary alcohols with high enantioselectivity [20,21]. Two general methods have been developed in our laboratory for the preparation of these zinc reagents (Scheme 11-3). The first involves an iodine-zinc exchange reaction [22], and this is suitable for primary or secondary alkyl iodides. It requires a catalytic amount of CuX and Et_2Zn or iPr_2Zn as starting materials. The second method involves a boron-zinc exchange, and starts with functionalized olefins which are hydroborated with Et_2BH [23] and treated in a second step with Et_2Zn or iPr_2Zn [23,24].

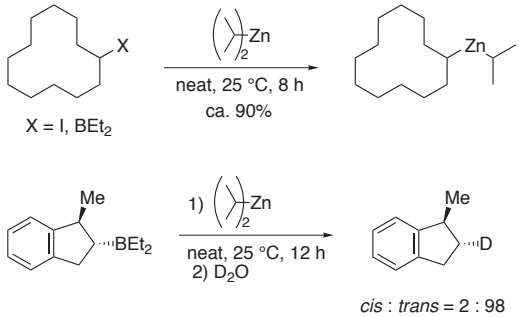


6 [22a] **7** [24] **8** [25] **9** [26]

Scheme 11-3

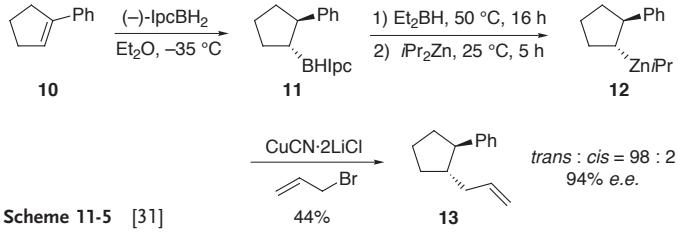
Under these conditions, a broad range of new polyfunctional dialkylzincs such as **6**–**9** have been prepared. The boron-zinc exchange proceeds under significantly milder conditions (0 °C instead of 50 °C) for primary alkyl derivatives and requires only a few minutes compared with the several hours which are necessary in the case of the iodine-zinc exchange [27].

Remarkably, it was found that the use of diisopropylzinc (iPr_2Zn) considerably facilitates the boron-zinc and iodine-zinc exchange with primary and secondary substrates allowing the preparation of secondary dialkylzincs. When the reaction is performed at low temperature (–10 °C), the boron-zinc exchange occurs with several systems with retention of the configuration [28], allowing for the first time a diastereoselective synthesis of nonstabilized secondary alkyl organometallics (Scheme 11-4) [29].



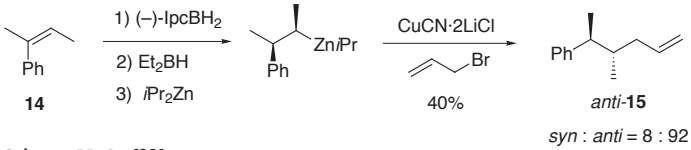
cis : *trans* = 2 : 98 **Scheme 11-4** [29]

These secondary organozinc reagents can also be prepared in enantiomerically enriched form. Thus, the hydroboration of phenylcyclopentene **10** with monoisopinocampheylborane [(–)-IpcBH$_2$; 99 % *e. e.*] [30] provides, after recrystallization, the chiral borane **11** with 94 % *e. e.* Treatment of **11** with diethylborane to remove the Ipc group (50 °C, 16 h) followed by the addition of *i*Pr$_2$Zn provides the configurationally stable mixed diorganozinc reagent **12** which, in the presence of CuCN · 2LiCl and allyl bromide, furnishes the alkylated product **13** (Scheme 11-5) [31].



Scheme 11-5 [31]

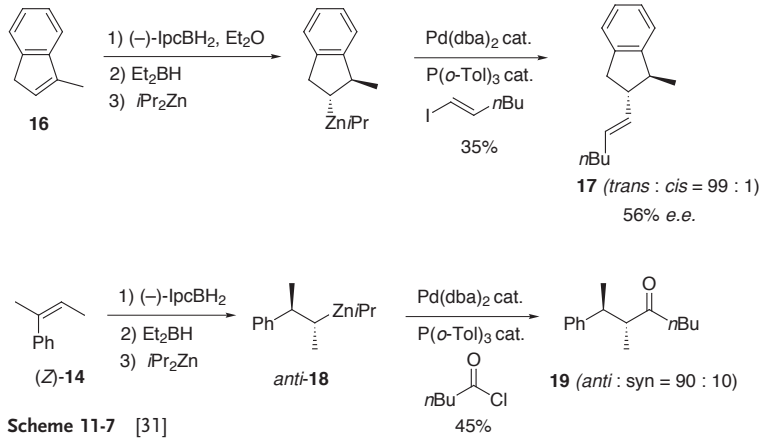
Interestingly, this reaction sequence can be extended to open-chain alkenes. The (*Z*)-styrene (*Z*)-**14** furnishes the *anti* product (*anti*-**15**) with high diastereoselectivity (*syn*:*anti* = 8:92) under these conditions. The asymmetric hydroboration enantioselectivity of these open-chain organoboranes lies between 46 and 47 % *e. e.* (Scheme 11-6) [31]. Several other electrophiles react with the intermediate zinc-copper reagents with retention of configuration [31a].



Scheme 11-6 [31]

It is also possible to perform stereoselective palladium(0)-catalyzed cross-coupling reactions. Thus, the palladium(0)-catalyzed alkenylation of 1-methylindene (**16**) by the hydroboration/boron-zinc exchange sequence provides *trans*-indane derivative **17** with 99:1 *trans*:*cis* selectivity. Similarly, the palladium(0)-catalyzed acylation of styrene (*Z*)-**14** furnishes the *anti*-ketone **19** (*anti*:*syn* ratio = 90:10; 88 % *e. e.*) *via* the zinc reagent *anti*-**18** (Scheme 11-7).

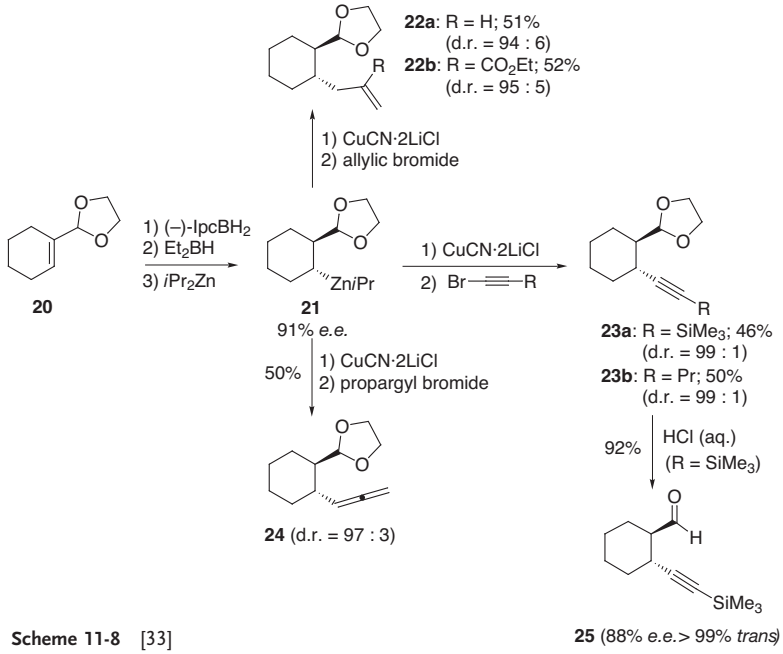
The hydroboration/boron-zinc exchange sequence allows one to perform conjugate additions with an umpolung [32] of reactivity. Whereas *α*,*β*-unsaturated carbonyl compounds react with a nucleophile, the reaction of a protected Michael acceptor with an electrophile can be envisioned [33]. Thus, the unsaturated acetal **20** is hydroborated with (–)-IpcBH$_2$ and converted by the addition of *i*Pr$_2$Zn into the optically active diorganozinc reagent **21** (91 % *e. e.*). Its reaction, after transmetallation to the corresponding copper reagent, with a variety of different electro-



Scheme 11-7 [31]

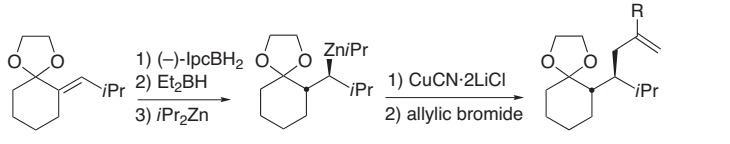
philes affords the desired products **22–24** with excellent selectivities and in 46–52 % overall yields (Scheme 11-8) [33].

The zinc reagent **21** shows a high configurational stability after transmetallation and reaction with various alkynyl bromides. Reaction with allyl bromides or propargyl bromide leads to small amounts (3–6 %) of the undesired *cis* product, but the alkynylated products **23a-b** were obtained with selectivities of ≥99:1 and in acceptable overall yields (see Section 11.7.1; Scheme 11-8). To demonstrate the validity of



Scheme 11-8 [33]

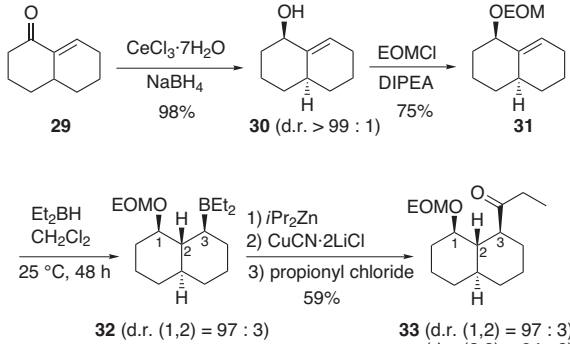
the umpolung procedure, the functionalized alkyne **23a** was deprotected by treatment with dilute aqueous HCl furnishing the free *trans*-aldehyde **25** as one diastereoisomer with 88 % *e.e.* and in 93 % yield (42 % overall yield starting from the unsaturated acetal **20**) (Scheme 11-8). An extension to open chain systems is also possible. Thus, the protected *exo*-alkylidene enone **26** was hydroborated with (–)-$IpcBH_2$ affording, after further treatment with Et_2BH and iPr_2Zn, the optically active secondary alkylzinc reagent **27** with 76 % *e.e.*. After transmetallation with Cu(I) and allylation, the desired products **28a-b** were obtained with excellent diastereoselectivities (≥94:6) (Scheme 11-9) [33].



26 **27** (76% *e.e.*) **28a**: R = H; 51% (d.r. = 96 : 4; 76% *e.e.*) **28b**: R = Me; 63% (d.r. = 94 : 6; 76% *e.e.*)

Scheme 11-9 [33]

Substrate-controlled hydroboration is a useful reaction for performing diastereoselective syntheses [34]. One major drawback of these reactions is that the resulting chiral organoboranes are usually not reactive enough to participate in new carbon-carbon bond formations. The boron-zinc exchange allows one to convert usually unreactive organoboranes to more reactive organozinc reagents which, in the presence of appropriate catalysts, are efficiently used for the formation of new carbon-carbon bonds. Thus, the trisubstituted alkene **31**, obtained after diastereoselective reduction according to Luche [35] and protection of **29** [36], is diastereoselectively hydroborated (d. r. (1,2) = 97:3) by using CH_2Cl_2 as a co-solvent. Further conversion to the corresponding diorganozinc reagent and Cu(I)-mediated reaction with propionyl chloride (d. r. (2,3) = 94:6) leads to the desired product **33** which is obtained in 59 % overall yield. It is possible to generate a chiral diorganozinc reagent with the control of four stereogenic centers (see Section 11.7.2; Scheme 11-10) [37].

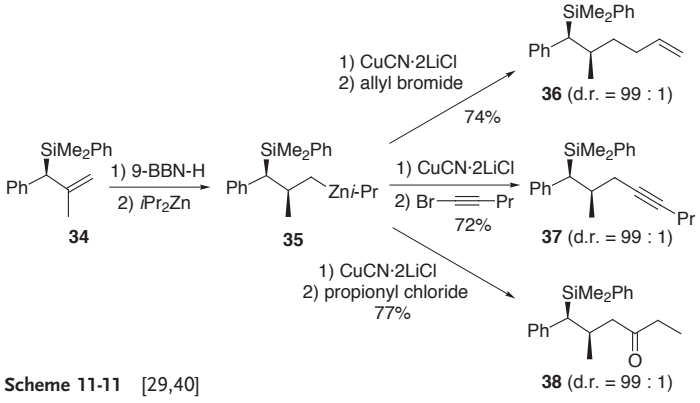


29 **30** (d.r. > 99 : 1) **31**

32 (d.r. (1,2) = 97 : 3) **33** (d.r. (1,2) = 97 : 3) (d.r. (2,3) = 94 : 6)

Scheme 11-10 [37]

Most published procedures for substrate-controlled diastereoselective hydroborations use sterically encumbered hydroborating reagents. Fleming and Lawrence have reported excellent diastereoselectivities for the hydroboration of the chiral allyl silane **34** using 9-BBN-H [38]. The hydroboration of **34** under Fleming's conditions followed by a boron-zinc exchange affords the corresponding zinc reagent **35**, which readily reacts with a variety of different electrophiles. The desired products **36**–**38** are obtained in good yields and with excellent diastereoselectivities (Scheme 11-11) [39,40].

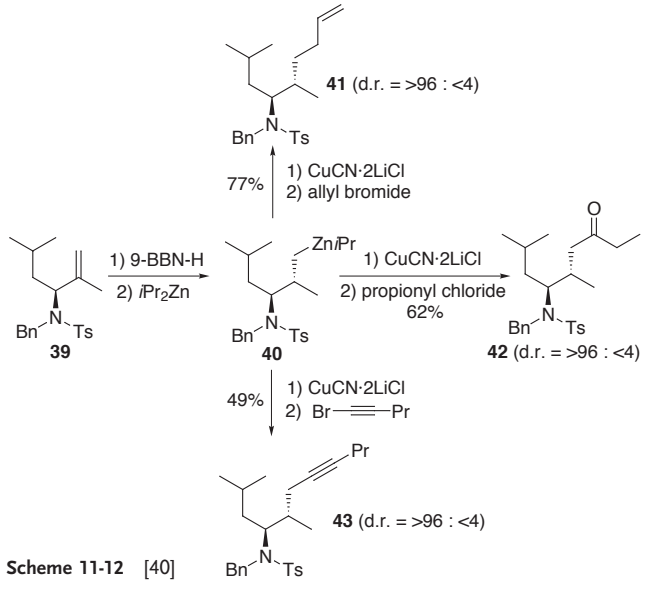


Scheme 11-11 [29,40]

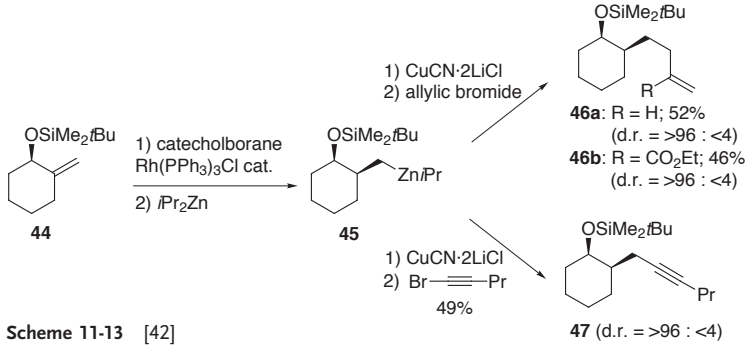
Similarly, Burgess and Ohlmeyer have shown that protected chiral allylic amines such as **39** can be hydroborated with 9-BBN-H yielding, after oxidative work-up, the corresponding amino alcohol with a selectivity of >96:<4 [41]. Hydroboration of **39** under Burgess's conditions leads to a triorganoborane that is then converted to the corresponding zinc organometallic **40**, which by the reaction with different electrophiles provides the desired functionalized amines **41**–**43** in good overall yields and with excellent diastereoselectivities (see Section 11.7.3; Scheme 11-12) [40].

A boron-zinc exchange reaction is also possible after rhodium-catalyzed hydroborations with catecholborane [39, 40]. The silyl-protected 2-methylenecyclohexanol **44** is hydroborated with catecholborane under catalysis of $Rh(PPh_3)_3Cl$ according to a procedure described by Evans [42]. Treatment with iPr_2Zn leads to the diorganozinc compound **45**, which can then be allylated yielding **46a**-**b** in 52 and 46 % overall yield (see Section 11.7.4; Scheme 11-13) or trapped with 1-bromopentyne yielding the alkyne **47** in 49 % overall yield (Scheme 11-13). The diastereoselectivities obtained for the products **46a**-**b** and **47** are the same as described by Evans for the corresponding alcohol obtained after oxidative work-up of the intermediate boronic ester [42].

This example demonstrates that the scope of substrate-controlled diastereoselective hydroborations can be considerably enhanced by performing a B-Zn exchange sequence.



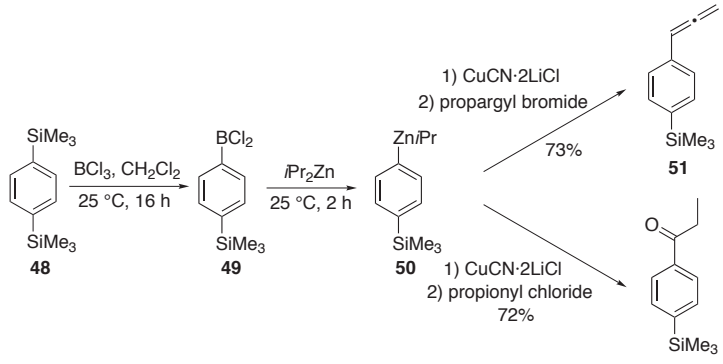
Scheme 11-12 [40]



Scheme 11-13 [42]

Silicon-boron exchanges can also be performed. Arylboranes of type $ArBCl_2$ are easily available by a silicon-boron exchange of arylsilanes with BCl_3 [43]. Thus, starting from the aromatic 1,4-disilane **48**, the arylborane **49** is obtained by adding BCl_3. Transmetallation of **49** to the corresponding zinc reagent **50** with iPr_2Zn is quantitative after 2 h at 25 °C. Further transmetallation of **50** with Cu(I) and subsequent reaction with propargyl bromide or propionyl chloride leads to the desired aromatic products **51** and **52** in 73 and 72 % yield by a one-pot procedure (see Section 11.7.5; Scheme 11-14) [44].

It is possible to treat the disilane **48** with BCl_3 yielding the mixed B-Si-aryl derivative **49**. Its treatment in a one-pot procedure with ICl allows the regio- and chemoselective exchange of the second Si-functionality to iodine furnishing the iodo-



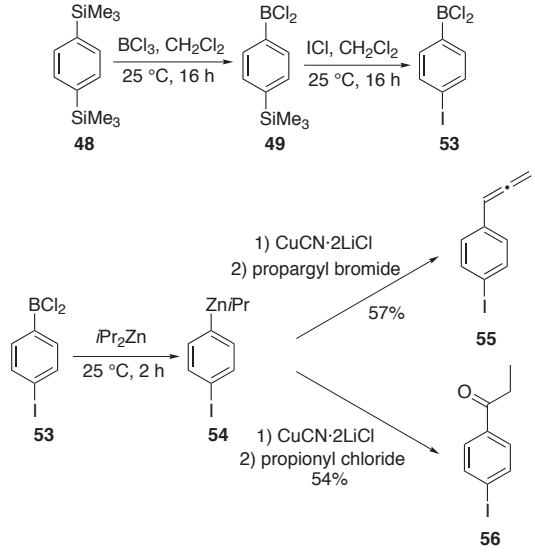
48 49 50 51 52

Scheme 11-14 [44]

arylboron derivative **53**, which is then transmetallated, via a chemoselective boron-zinc exchange to the zinc reagent **54.** The arylzinc reagent **54** can be trapped, after transmetallation to Cu(I), with a variety of different electrophiles providing the desired products **55–56** in acceptable overall yields (Scheme 11-15) [44].

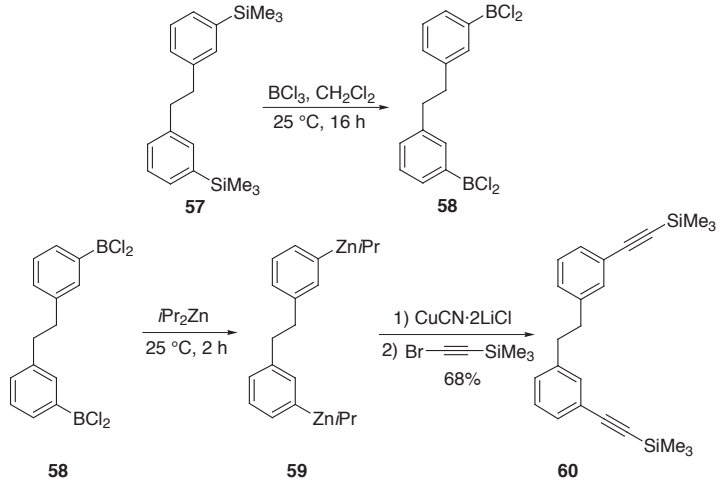
The aromatic disilane **57** can be similarly functionalized twice by a double Si-B exchange yielding the aromatic diborane **58**, which is then easily converted into the corresponding *bis*-diorganozinc reagent **59** by addition of $i\text{Pr}_2\text{Zn}$. After Cu(I)-mediated reaction with 1-bromo-2-trimethylsilylacetylene, the desired product **60** is obtained in good overall yield (68 %, one-pot procedure) (Scheme 11-16) [44].

A few less-general methods are available for the preparation of zinc organometallics. Thus, organozinc halides can also be obtained from the alkyl mesylates in



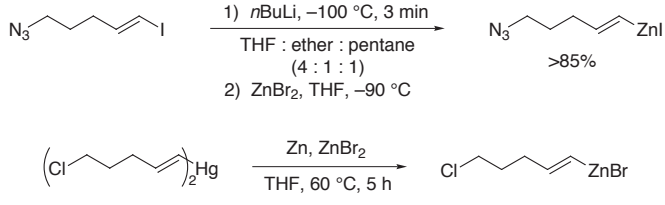
48 49 53 54 55 56

Scheme 11-15 [44]



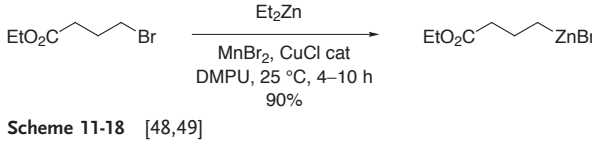
Scheme 11-16 [44]

the presence of sodium bromide and iodide in *N,N*-dimethylpropyleneurea (DMPU) [45] using zinc dust [46] or by an iodine-lithium exchange performed on functionalized alkenyl or aryl iodides followed by a transmetallation with zinc bromide [47] (Scheme 11-17). A less general preparation of organozinc halides involves the treatment of diorganomercurials with zinc dust in the presence of zinc bromide [48] (Scheme 11-17).

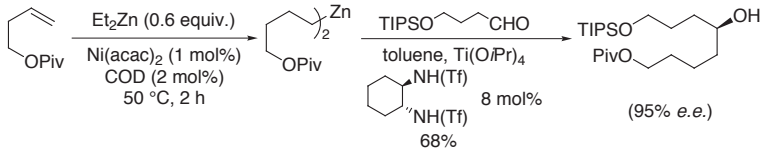


Scheme 11-17 [47,48]

Finally, some transition-metal (Ni, Mn)-catalyzed iodine- or bromine-zinc exchange reactions using Et_2Zn constitute a convenient approach to organozinc halides under mild reaction conditions [48,49] (Scheme 11-18).



Scheme 11-18 [48,49]



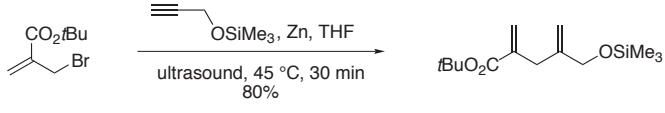
Scheme 11-19 [49,50]

Diorganozincs can be obtained by the hydrozincation of alkenes using diethylzinc and a catalytic amount of $Ni(acac)_2$. The resulting diorganozincs are well suited for applications in asymmetric synthesis [49,50] (Scheme 11-19).

The presence of a heteroatom in the alkene at an allylic or homoallylic position considerably stabilizes the zinc organometallic compound obtained after the hydrozincation of the alkene. Thus, allylic alcohols and amines are especially well suited as substrates for this hydrozincation procedure.

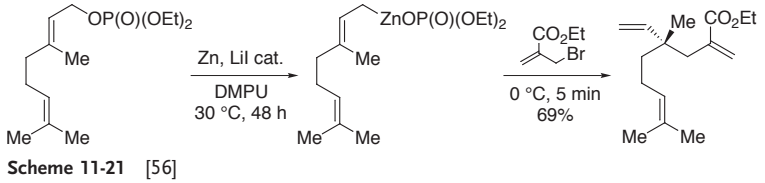
11.3 Uncatalyzed Cross-Coupling Reactions

Many organometallic zinc species are too unreactive to undergo cross-coupling reactions with carbon nucleophiles. This general statement is not valid for allylic organometallic reagents which smoothly react with several electrophiles, such as carbonyl compounds [51,52], nitriles [53,54], or triple bonds [55] (Scheme 11-20).



Scheme 11-20 [55]

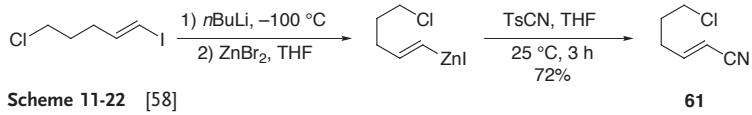
Allylic zinc reagents undergo cross-coupling reactions with reactive halides, leading to 1,5-dienes. Usually, the new carbon-carbon bond is formed from the more substituted end of the allylic system (Scheme 11-21) [56]. A very reactive and selective carbon electrophile such as tosyl cyanide (TsCN) [57] reacts with various organozinc halides affording polyfunctional nitriles in good yields (see Section 11.7.6;



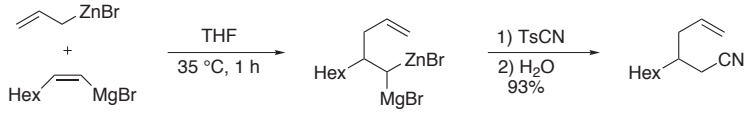
Scheme 11-21 [56]

Scheme 11-22) [58]. The reaction can be used to convert 1,1-bismetallic reagents of zinc and magnesium, such as **62**, to unsaturated nitriles, such as **63** (Scheme 11-23) [58]. The regioselectivity of the reaction of benzylzinc bromide with TsCN affords *o*-methylbenzonitrile (**64**), whereas the reaction of the corresponding zinc-copper derivatives provides the benzyl cyanide **65** (Scheme 11-24).

The reactivity of diorganozincs can be increased by performing the reaction in a polar solvent. Thus, it was found that NMP is especially well suited and allows the performance of Michael addition reactions with a variety of double bonds bearing electron-withdrawing groups such as enones, alkylidenemalonates, or nitroalkenes (Scheme 11-25) [59]. One equivalent of NMP is sufficient to promote the addition

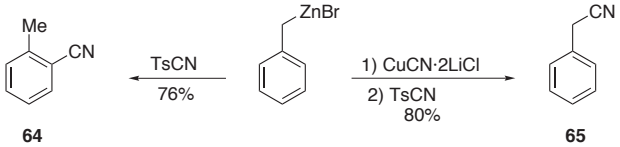


Scheme 11-22 [58] **61**



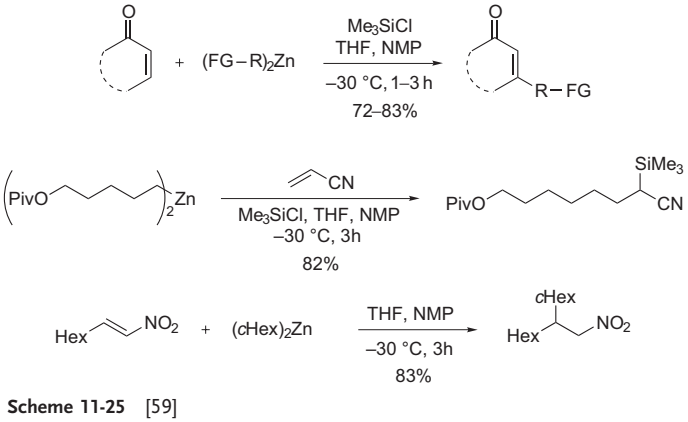
62 **63**

Scheme 11-23 [58]

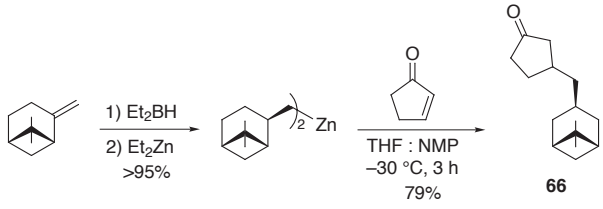


64 **65**

Scheme 11-24 [58]



Scheme 11-25 [59]



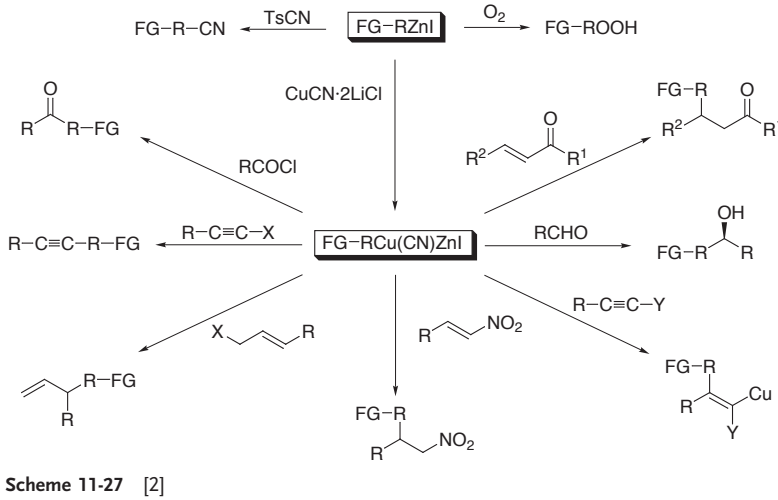
Scheme 11-26 [59]

reaction but the presence of Me_3SiCl is mandatory. With regard to the addition to enones, a range of β-monosubstituted enones can be used, but β-disubstituted enones undergo the Michael addition only reluctantly (see Section 11.7.7; Scheme 11-26).

11.4
Copper-Catalyzed Cross-Coupling Reactions

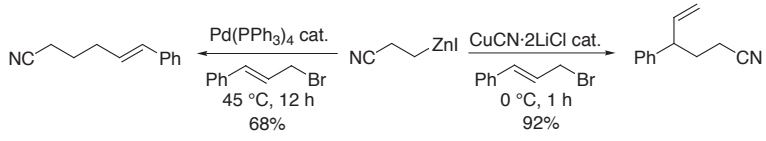
11.4.1
Cross-Coupling Reactions with Allylic and Related Reactive Halides

Whereas the direct cross-coupling reactions of zinc organometallics with organic electrophiles is of limited utility, the scope of these reagents after transmetallation with the THF-soluble copper salt $CuCN \cdot 2LiCl$ [5] is greatly enhanced [7,19]. A broad range of electrophiles reacts with zinc-copper species RCu(CN)ZnX in good to excellent yields. The same reactions as with lithium- or magnesium-derived copper compounds [2] are possible, with a few exceptions like the opening of epoxides (Scheme 11-27).



Scheme 11-27 [2]

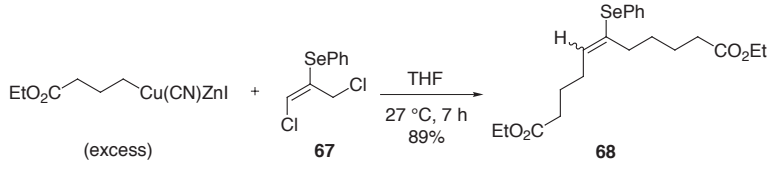
Cross-coupling reactions with allylic halides are especially high yielding reactions. They occur with high S_N2' selectivity, in contrast to the corresponding Pd(II)- or Ni(II)-catalyzed reactions which give the S_N2 product (Scheme 11-28) [60–62].



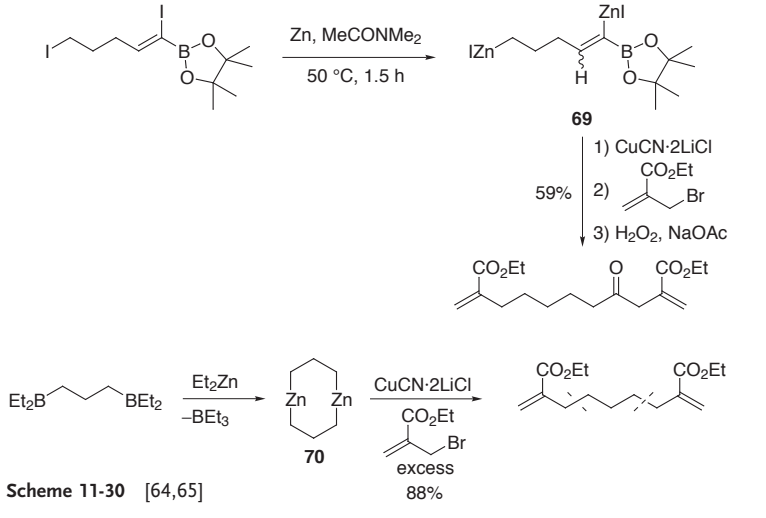
Scheme 11-28 [60–62]

The high S_N2' selectivity makes it possible to perform multiple allylic substitution reactions with excellent results. Thus, the reaction of various 2-substituted 1,3-dichloropropenes such as **67** with organozinc-copper compounds provides only products such as **68** obtained after two successive S_N2' reactions (Scheme 11-29) [63].

Bimetallic reagents such as **69** and **70** can be smoothly allylated under mild conditions, leading to polyfunctional products (Scheme 11-30) [64,65].



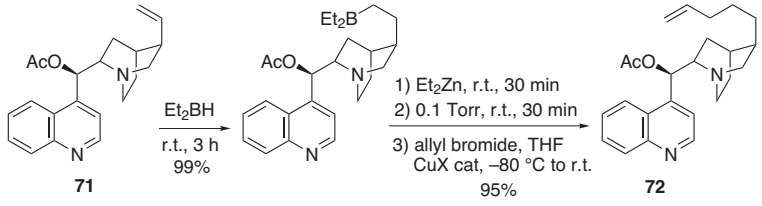
Scheme 11-29 [63]



Scheme 11-30 [64,65]

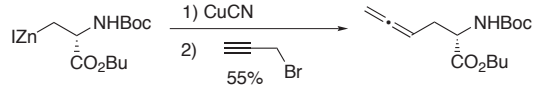
A quinidine alkaloid derivative containing a vinyl group, such as **71**, has been readily allylated in a sequence of a hydroboration, boron-zinc exchange, and copper(I)-catalyzed allylation, leading to the alkaloid derivative **72** (see Section 11.7.8; Scheme 11-31) [66].

Besides allylic halides, propargylic halides or sulfonates show a similarly high reactivity, providing allenes (Scheme 11-32) [62,66,67].



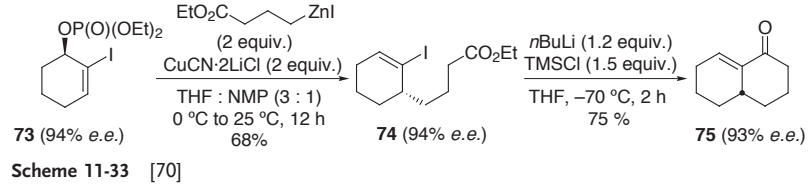
71 **72**

Scheme 11-31 [66]



Scheme 11-32 [66]

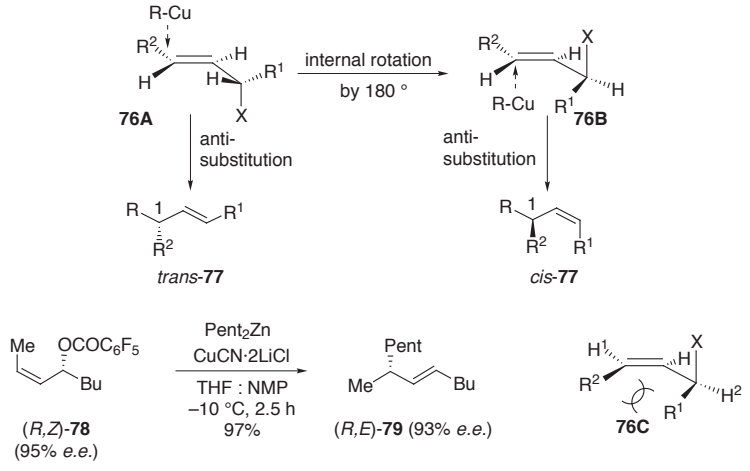
Copper-catalyzed reactions of functionalized diorganozincs with chiral allylic reagents proceed with high *anti*-stereoselectivity [68] and very high regioselectivity, especially if a polar co-solvent such as *N*-methylpyrrolidinone (NMP) is added. Thus, the reaction of the chiral allylic phosphate **73** [69] with a functionalized alkylzinc reagent such as $EtO_2C(CH_2)_3ZnI$ in the presence of CuCN · 2LiCl in a 3:1 THF:NMP mixture provides the S_N2'-substitution product **74** in 68 % yield with 94 % *e.e.*, showing a perfect transfer of the chiral information. The vinylic iodide **74** reacts with *n*-butyllithium (1.2 equiv.) at –70 °C in the presence of TMSCl furnishing the bicyclic enone **75** in 75 % yield and with 93 % *e.e.* (see Section 11.7.9; Scheme 11-33) [70].



73 (94% *e.e.*) **74** (94% *e.e.*) **75** (93% *e.e.*)

Scheme 11-33 [70]

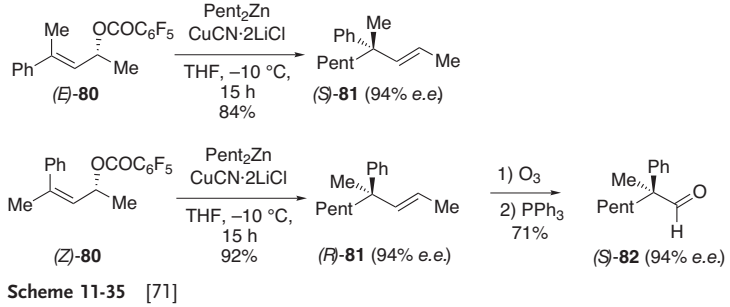
This reaction can also be extended to open-chain systems. In this case, chiral allylic alcohols have been converted into pentafluorobenzoates which proved to be perfect leaving groups. Whereas both (*E*)- and (*Z*)-allylic pentafluorobenzoates undergo the S_N2'-substitution, in the case of (*E*)-substrates of type **76**, two confor-



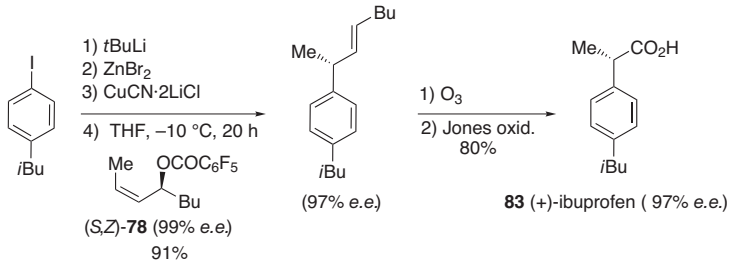
Scheme 11-34 [71]

mations **76A** and **76B** are available for an *anti*-substitution providing, besides the major *trans*-product (*trans*-**77**), also ca. 10 % of the minor product *cis*-**77** (Scheme 11-34). By using the (*Z*)-allylic pentafluorobenzoates, only *trans*-substitution products are produced since the conformation **76C** leading to a *cis*-product is strongly disfavored due to allylic 1,3-strain [34b]. Thus, the *cis*-allylic pentafluorobenzoates (*R,Z*)-**78** reacts with $Pent_2Zn$, furnishing only the *trans*-S_N2'-substitution product (*R,E*)-**79** in 97 % yield and with 93 % *e. e.* [71] (see Section 11.7.10; Scheme 11-34).

Interestingly, this substitution reaction can be applied to the stereoselective assembly of chiral quaternary centers. The reaction of the trisubstituted allylic pentafluorobenzoates (*E*)- and (*Z*)-**80** undergo readily a substitution reaction at –10 °C with $Pent_2Zn$, furnishing the enantiomeric products (*S*)- and (*R*)-**81** in 94 % *e. e.*. The ozonolysis of (*R*)-**81** gives, after reductive work-up, the chiral aldehyde (*S*)-**82** in 71 % yield and with 94 % *e. e.* (Scheme 11-35). The *anti*-selectivity is observed with a wide range of diorganozincs such as primary and secondary dialkylzincs, as well as diaryl- and dibenzylzinc reagents [71]. This approach has been applied to an enantioselective synthesis of (+)-ibuprofen **83** (Scheme 11-36).

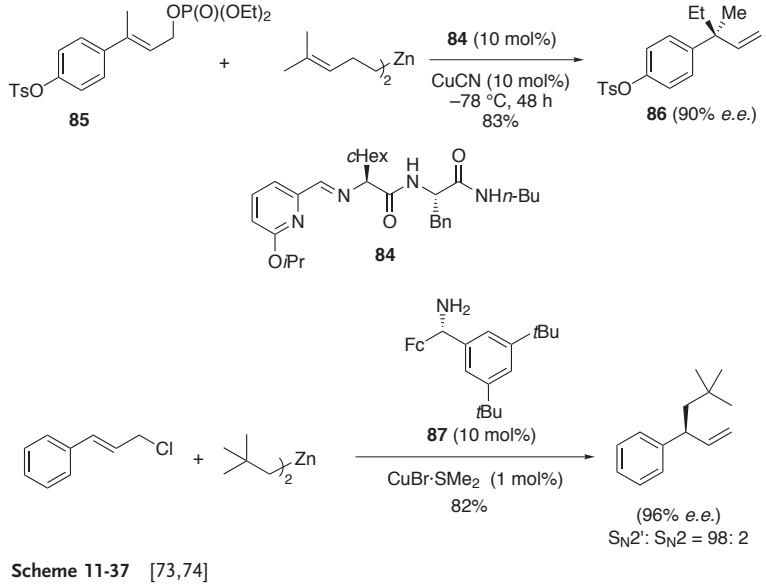


Scheme 11-35 [71]



Scheme 11-36 [71]

Allylic substitutions using organozinc reagents can also be performed using a chiral catalyst [72]. The use of a modular catalyst is an especially versatile strategy, and has been applied to the stereoselective preparation of quaternary centers [73]. In the presence of 10 mol % of the modular ligand **84**, highly enantioselective substitutions of allylic phosphates like **85**, leading to the fish deterrent sporochnol (**86**: 83 % yield, 90 % *e. e.*), have been performed. Sterically highly congested diorganozincs such as dineopentylzinc react enantioselectively with allylic chlorides in the presence of the chiral ferrocenylamine **87**, with up to 98 % *e. e.* [74] (see Section 11.7.11; Scheme 11-37).

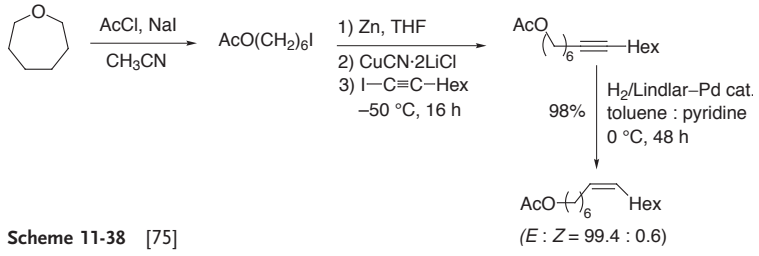


Scheme 11-37 [73,74]

11.4.2

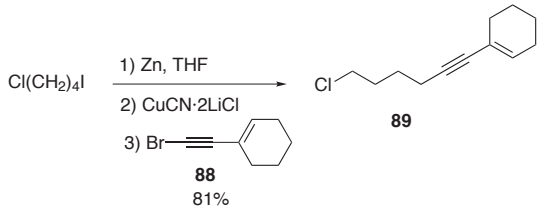
Cross-Coupling Reactions with Alkynyl, Alkenyl, and Aryl Halides

Polyfunctional zinc-copper reagents react efficiently with 1-bromo- or 1-iodoalkynes to furnish functionalized alkynes in good yields. The reaction proceeds at low temperature (–65 to –55 °C), and has been applied in the preparation of pheromones (Scheme 11-38) [75] and polyfunctional acetylenic ethers [76].



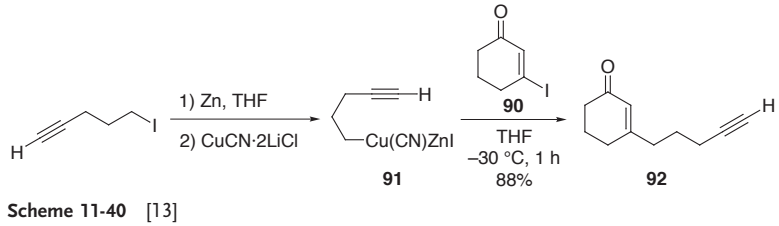
Scheme 11-38 [75]

The procedure has been successfully applied to conjugated systems such as bromoenyne **88**, leading to substrates such as **89** which are susceptible to undergoing cyclization reactions (Scheme 11-39; see Section 11.7.12) [75].



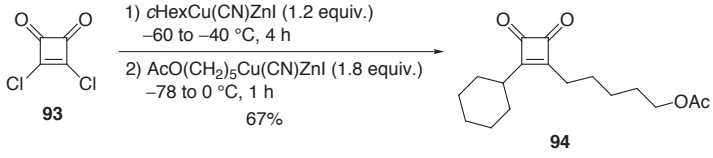
Scheme 11-39 [75]

The extension of this cross-coupling to iodoalkenes is also possible. If the iodo-, bromo-, or chloroalkene is further conjugated with an electron-withdrawing group, a facile substitution according to an addition-elimination mechanism is observed. Typically, 3-iodo-2-cyclohexen-1-one **90** [77] reacts with a zinc-copper reagent such as **91** to furnish the expected cross-coupling product **92** (see Section 11.7.13; Scheme 11-40) [13].



Scheme 11-40 [13]

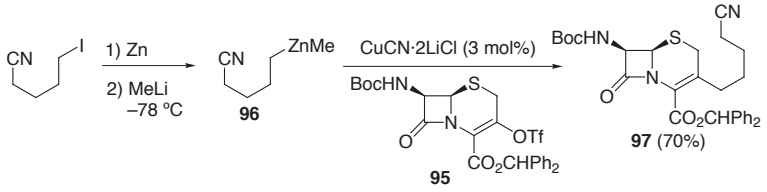
This addition-elimination reaction can be applied to the preparation of squaric acid derivatives. Thus, the treatment of 3,4-dichlorocyclobutene-1,2-dione **93** with two different zinc-copper reagents furnishes polyfunctional squaric acid derivatives like **94**, provided that the first zinc-copper reagent bears a secondary or tertiary alkyl group (Scheme 11-41) [78].



93 **94**

Scheme 11-41 [78]

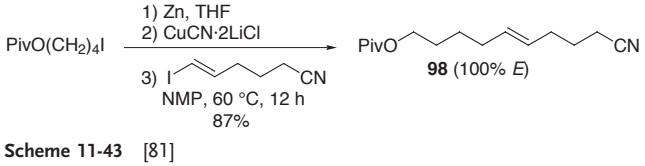
By using mixed diorganozinc reagents of the type FG-RZnMe [79], a catalytic addition-elimination can be performed with a wide range of β-keto-alkenyl triflates. Thus, the penicillin derivative **95** reacts with the mixed copper reagent **96** to provide the desired product **97** in excellent yield (Scheme 11-42) [80].



96 **95**

Scheme 11-42 [80]

The cross-coupling reaction with nonactivated iodoalkenes proceeds well only by using a polar solvent such as NMP or DMPU [45] and elevated reaction temperatures (60 °C, 12 h). The compatibility of the zinc-copper reagents with these harsh conditions shows the remarkable thermal stability of zinc-copper organometallics. The cross-coupling reaction occurs with complete retention of the configuration of the double bond, and allows the stereospecific synthesis of highly functionalized alkenes such as **98** (see Section 11.7.14; Scheme 11-43) [81].

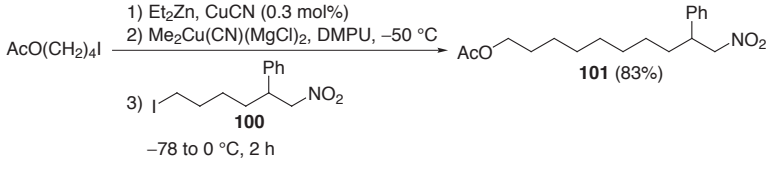


Scheme 11-43 [81]

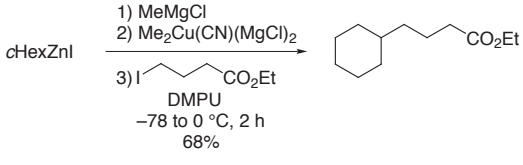
11.4.3
Cross-Coupling Reactions with Alkyl Halides

Alkyl halides are unreactive towards zinc-copper reagents under standard reaction conditions. However, by using a polar solvent such as DMPU [45] and a new copper species of type **99** ($R_2Cu(CN)(MgX)_2 \cdot Me_2Zn$), a smooth coupling reaction is observed at 0 °C [82]. This method tolerates the presence of many functional groups, and can be extended to coupling reactions with benzylic bromides [82]. It displays a high chemoselectivity that makes it possible to couple substrates bearing a primary nitro group. For example, the alkyl iodide **100** leads to the polyfunctional nitroalkene **101** without the formation of appreciable amounts of zinc nitronate (resulting from a deprotonation of **100** by the organozinc-copper reagent; see Section 11.7.15; Scheme 11-44) [82].

Remarkably, the methyl group is not transferred in these cross-coupling reactions. Interestingly, the reaction can be extended to secondary alkylzinc derivatives (Scheme 11-45) [82].



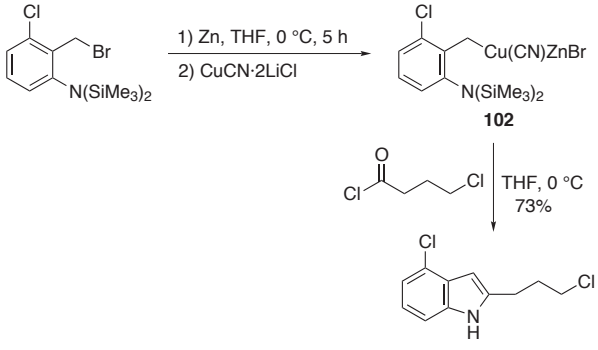
Scheme 11-44 [82]



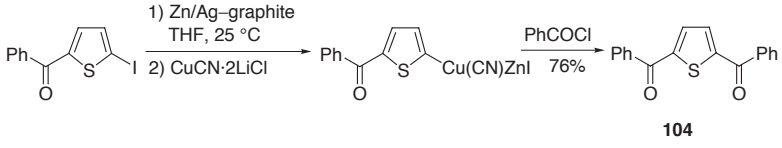
Scheme 11-45 [82]

11.4.4
Acylation Reactions

The reaction of zinc-copper reagents with acid chlorides has a remarkable generality [7, 19], and has found many applications in synthesis (Scheme 11-46) [16,83–88]. The treatment of silyl-protected *o*-aminated benzylic zinc-copper derivatives such as **102** with an acid chloride leads to a 2-substituted indole **103** [87]. Aromatic and heterocyclic zinc compounds provide polyfunctional aromatic or heterocyclic ketones like **104** (see Section 11.7.16; Scheme 11-47) [84].



Scheme 11-46 [87]



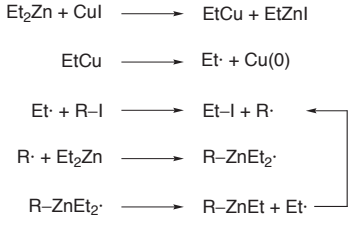
Scheme 11-47 [84]

11.5
Transition Metal-Catalyzed Cross-Coupling Reactions

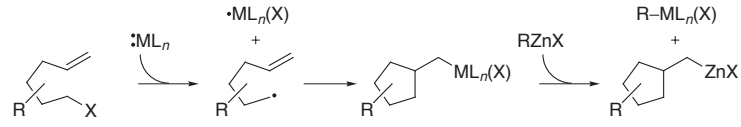
11.5.1
Palladium- and Nickel-Catalyzed C-C Bond-Forming Reactions

11.5.1.1 Additions to Unactivated Double Bonds

The iodine-zinc exchange of an alkyl iodide with Et_2Zn is promoted by the addition of small amounts of copper(I) salts such as CuCN or CuI. Although the exact reason for this copper catalysis is not known, it has been speculated that the presence of copper(I) salts promotes a radical chain-reaction resulting in the formation of a dialkylzinc species (Scheme 11-48) [22b]. Similarly, the addition of other transition metals such as nickel and palladium salts promotes radical reactions.



Scheme 11-48 [22b]

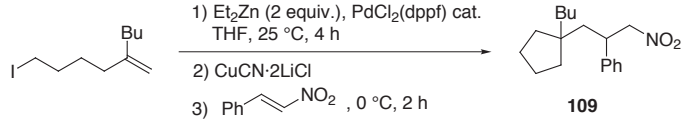


105 X = Br, I **106** **107** M = Ni, Pd **108**

Scheme 11-49 [95]

These reactions were found to be preparatively very useful as they allow the performance of radical cyclization reactions but lead to an organozinc halide as the final product (Scheme 11-49) [89–94]. The treatment of an unsaturated alkyl halide **105** (X = Br, I) with a palladium(0) or nickel(0) complex produces, by a one-electron transfer [95], a paramagnetic nickel(I) or palladium(I) salt $ML_n(X)$ (M = Ni, Pd) and a radical **106** which undergoes a smooth cyclization reaction and produces, after recombination with the transition-metal moiety, the nickel(II) or palladium(II) species **107**. After transmetallation with a zinc(II) salt, a stable organozinc cyclopentylmethyl derivative of type **108** is produced.

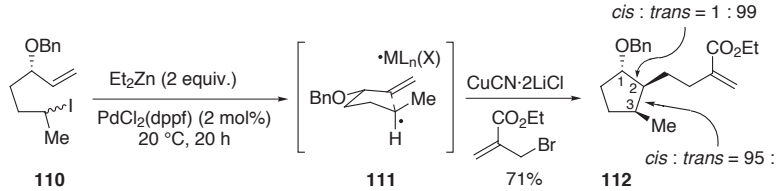
The overall reaction makes it possible to perform intramolecular carbozincations [89–94,96] via a radical cyclization. This useful preparation of cyclopentylmethylzinc derivatives proceeds with excellent stereoselectivity, and allows the assembly of quaternary centers. After cyclization, the zinc organometallic can be transmetallated with CuCN · 2LiCl, and it subsequently reacts with a broad range of electrophiles such as acid chlorides, allylic and alkynyl halides, ethyl propiolate, 3-iodo-2-cyclohexen-1-one, and nitroalkenes such as nitrostyrene, leading to products of type **109** (see Section 11.7.17; Scheme 11-50) [89,94].



81% **109**

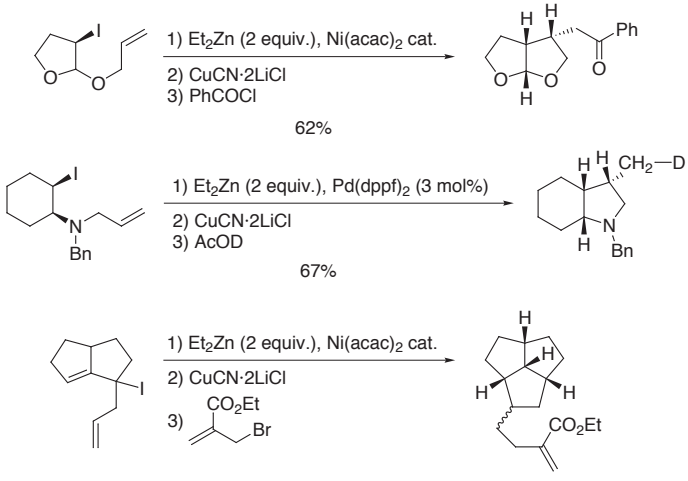
Scheme 11-50 [89, 94]

The cyclization is highly stereoselective according to Beckwith's radical cyclization rules [97]. Thus, the allylic benzyl ether **110** (a 1:1 mixture of diastereoisomers) undergoes a smooth stereoconvergent cyclization in the presence of Et_2Zn (2 equiv.) and $PdCl_2$(dppf) (2 mol %) through a radical intermediate **111** which adopts a conformation such that all substituents are in pseudo-equatorial positions. After allylation with ethyl 2-(bromomethyl)acrylate, the cyclopentane derivative **112** is obtained with >99:1 *trans*-selectivity for substituents at positions 1 and 2 and 95:5 *cis*-selectivity for the substituents at positions 2 and 3 (Scheme 11-51).



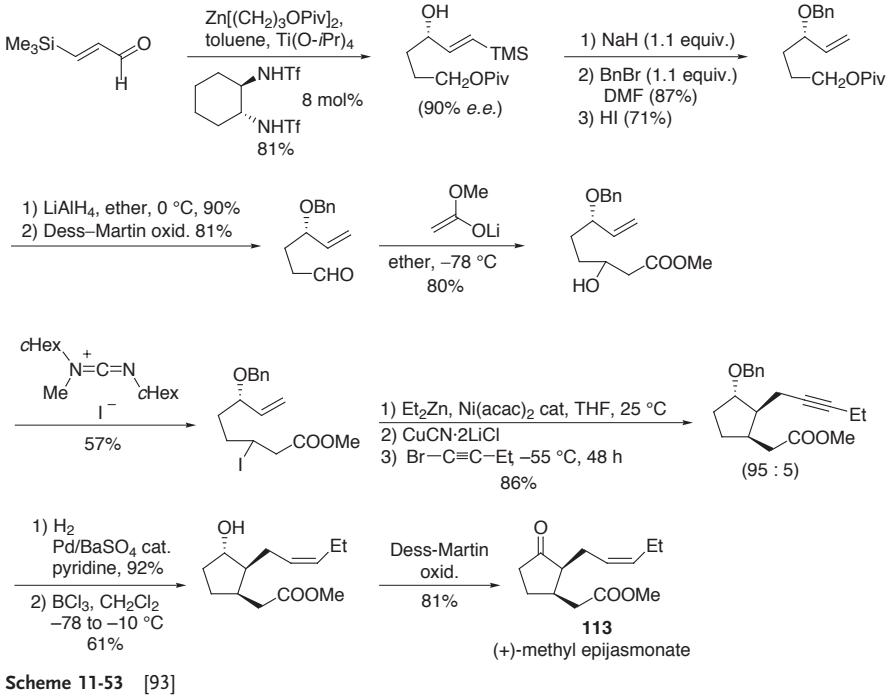
110 **111** 71% **112**

Scheme 11-51

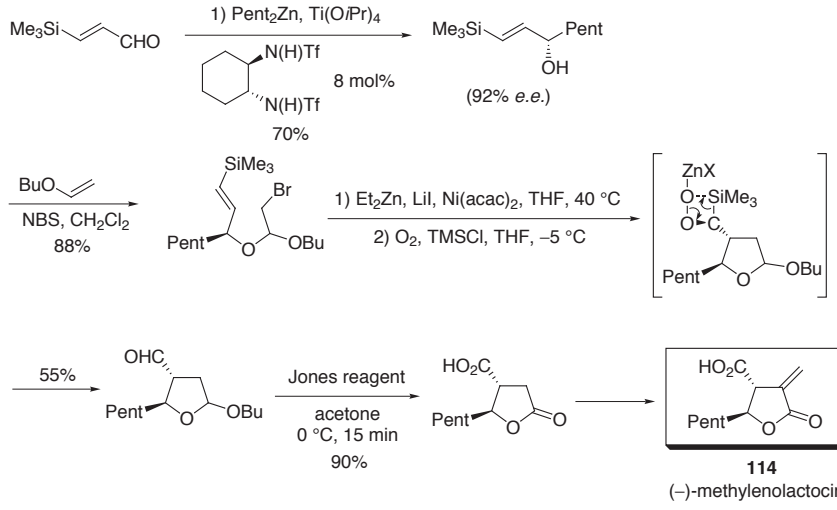


Scheme 11-52 [89–94]

Multiple cyclization reactions are possible, as well as preparation of heterocycles (Scheme 11-52) [89–94]. Several natural products, such as (+)-methyl epijasmonate (**113**) (Scheme 11-53) [93] and the antitumor antibiotic (–)-methylenolactocin **114** [92, 98] (Scheme 11-54) have been prepared using this method.



Scheme 11-53 [93]

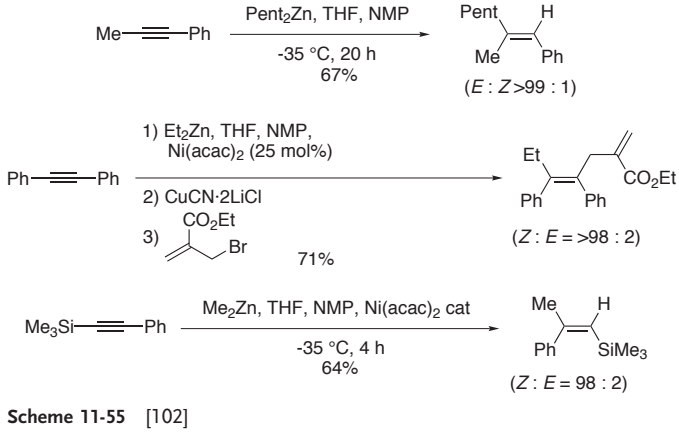


Scheme 11-54 [98]

11.5.1.2 **Addition to Unactivated Triple Bonds: Nickel-Catalyzed Carbozincation**

The addition of organometallics to internal alkynes is rare [99–101], and proceeds with moderate stereoselectivity [100]. In the presence of a nickel catalyst such as $Ni(acac)_2$, it is possible to add diorganozincs to substituted phenylacetylenes. This recently reported reaction proceeds with high stereoselectivity (>99 % *syn*-addition) and is often highly regioselective. The resulting alkenylzinc organometallics can be quenched with several types of electrophiles (Scheme 11-55) [102].

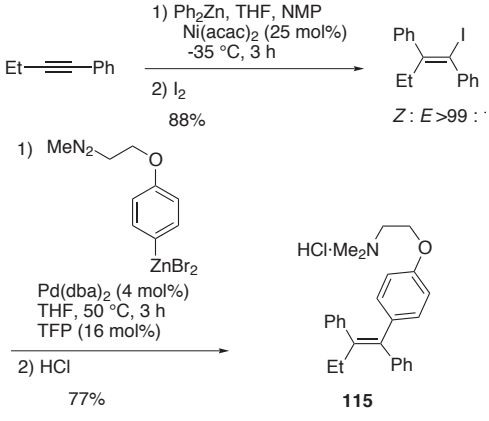
Remarkably, this carbozincation procedure works well at low temperature, and even allows an efficient addition of the relatively unreactive Me_2Zn. It was soon found that diarylzincs undergo the addition even more readily, and this reaction



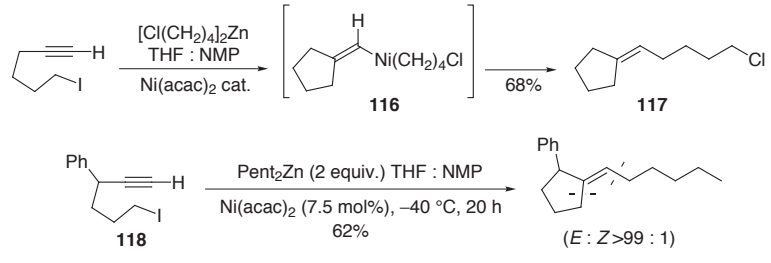
Scheme 11-55 [102]

has been used to prepare (*Z*)-tamoxifen **115**, a commercial antitumor drug (Scheme 11-56) [102].

The carbometallation can be performed intramolecularly, leading in this case to an unsaturated diorganonickel species of type **116**, which undergoes a rapid reductive elimination to furnish oligofunctional alkylidenecyclopentane derivatives of type **117** (Scheme 11-57). The *syn*-addition is proven by using a phenyl-substituted acetylenic iodide such as **118** [102].



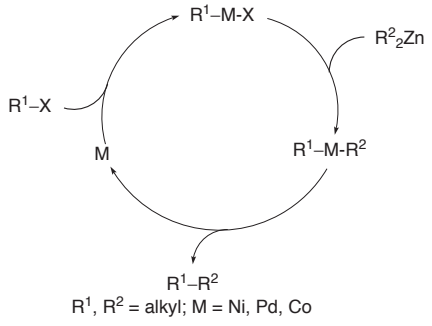
Scheme 11-56 [102]

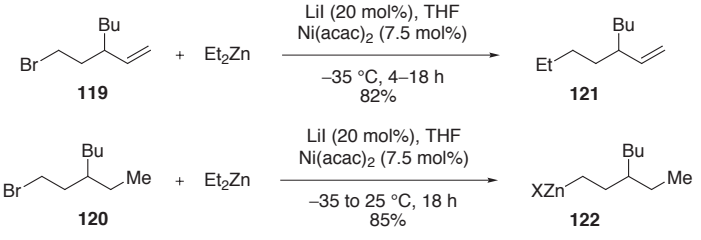


Scheme 11-57 [102]

11.5.1.3 Catalytic Csp^3-Csp^3 Cross-Coupling Reactions and Related Ni-Catalyzed Cross-Coupling Reactions

The performance of Csp^3-Csp^3 cross-coupling reactions using catalytic amounts of a transition metal remains a major problem in organic synthesis. Whereas the use of organocuprates makes it possible to perform these cross-couplings with stoichiometric amounts of copper(I) organometallics [2], the use of catalytic amounts of transition metal salt remains a challenge. The difficulty in performing such a reaction lies in the reductive coupling, which is slow with unsaturated diorganometallic intermediates such as R^1-M-R^2 (Scheme 11-58).

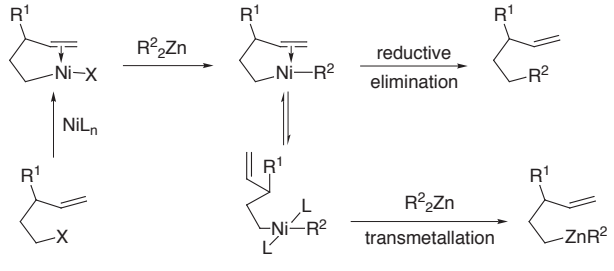




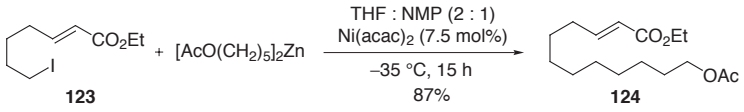
Scheme 11-58 [106]

By removing electron density from the metal center, such reductive eliminations should be made easier [103–105]. Thus, it was observed that, whereas the unsaturated alkyl bromide **119** undergoes a smooth cross-coupling reaction with Et_2Zn in the presence of $Ni(acac)_2$ leading to **121**, the corresponding saturated alkyl bromide **120** does not undergo the cross-coupling reaction, but instead produces the bromide-zinc exchange product **122** (Scheme 11-58) [106].

This behavior can be rationalized by assuming that the remote double bond coordinates to the nickel center. Although a double bond coordinated to a metal center acts as a σ-donor, it is also a π-acceptor and therefore removes electron density from the metal center and facilitates the reductive coupling reaction. The reductive elimination does not occur if the coordination to the double bond is too weak, or if it is prohibited due to steric hindrance. Instead, a ligand exchange reaction occurs, leading to the transmetallation product (Scheme 11-59) [106].



Scheme 11-59 [106]



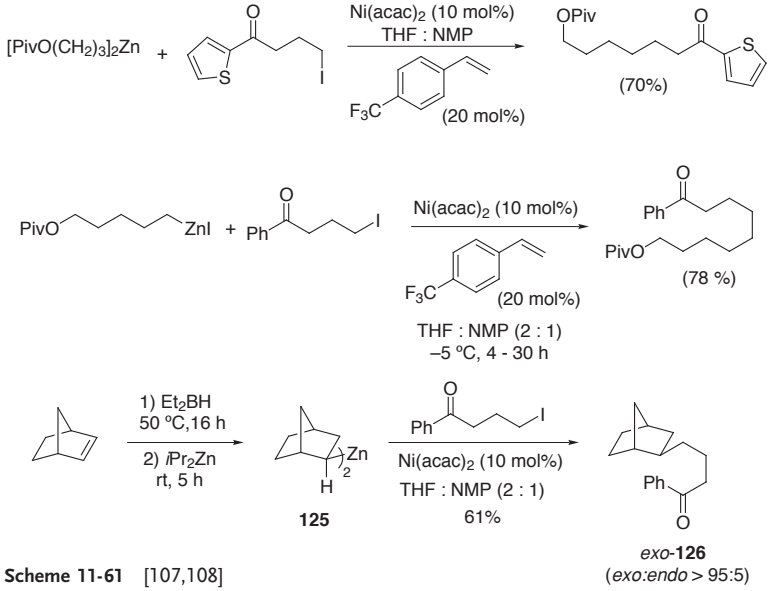
123 **124**

Scheme 11-60 [106]

The synthetic applications can be greatly extended by using the polar co-solvent NMP, which makes it possible to couple a variety of polyfunctional zinc organometallics with alkyl iodides such as **123** bearing a remote double bond, leading to cross-coupling products such as **124** (see Section 11.7.18; Scheme 11-60) [106].

The addition of a ligand such as *m*- or *p*-trifluoromethylstyrene or 4-fluorostyrene in a catalytic amount allows the performance of cross-coupling reactions between Csp^3-Csp^3 centers with an excellent generality. Thus, functionalized diorganozincs [107] and organozinc halides [108] undergo smooth cross-coupling reactions under mild conditions. If organozinc iodides are used, the cross-coupling reaction has to be performed in the presence of Bu_4NI (3 equiv.). Under these conditions, a complete conversion occurs within 30 h at –5 °C to 0 °C.

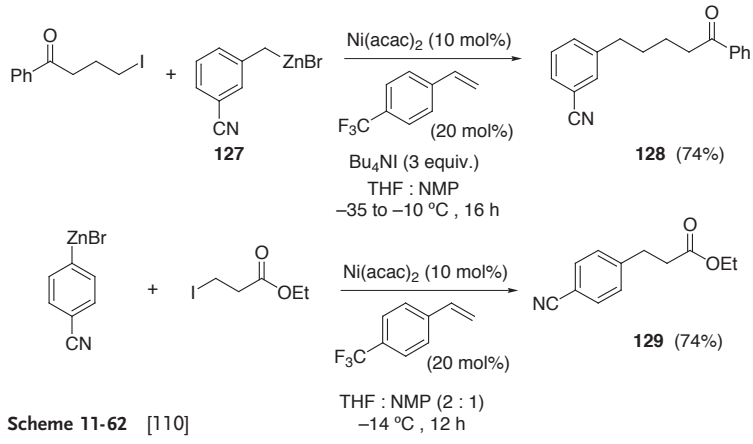
Secondary organozincs like **125** obtained by the hydroboration of norbornene followed by a B/Zn exchange reaction with retention of configuration leads to *exo*-**126** in 61 % yield [108] (Scheme 11-61). Besides being applicable for alkylzinc reagents, this reaction can be extended to benzylic organozinc reagents [109]. The presence of Bu_4NI in large excess (3 equiv.) dramatically accelerates the cross-coupling reaction. Thus, the functionalized benzylic zinc reagent **127** reacts with 3-iodopropyl phenyl ketone in THF:NMP at –35 °C to –10 °C to furnish the functionalized ketone **128** in 74 % yield (Scheme 11-62). Arylzinc reagents obtained by transme-



125

exo-**126**
(*exo*:*endo* > 95:5)

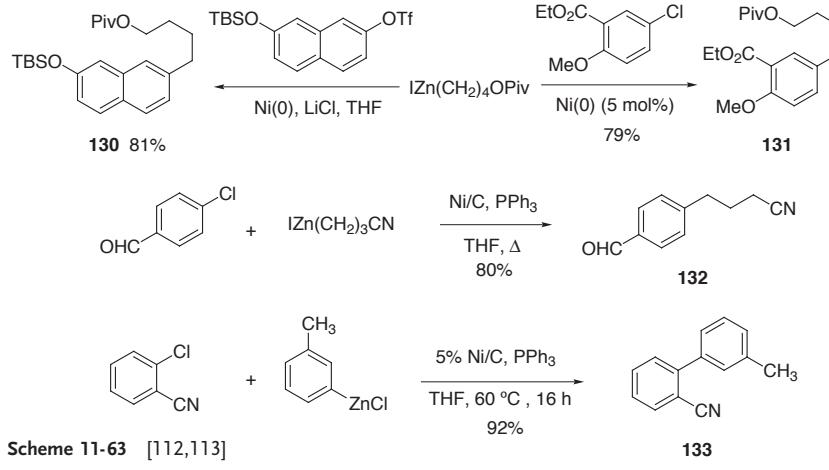
Scheme 11-61 [107,108]



Scheme 11-62 [110]

tallation reactions either from aryllithiums or arylmagnesium halides also undergo – under standard conditions in the presence of 4-fluorostyrene (20 mol %) or 4-trifluoromethylstyrene (20 mol %) – the expected cross-coupling reaction, leading to polyfunctionalized aromatic products of type **129** in satisfactory yield (see Section 11.7.19; Scheme 11-62) [110]. Applications of these Ni-catalyzed cross-couplings on the solid phase have been performed [111].

In the presence of the appropriate Ni-catalyst, a range of functionalized organozinc reagents undergo cross-coupling reactions. The preparation of the nickel catalyst is especially important, and the treatment of $(Ph_3P)_2NiCl_2$ with PPh_3 (2 equiv.) and *n*BuLi (2 equiv.) produces *in situ* a very reactive catalyst which allows one to perform the cross-coupling between various functionalized alkylzinc reagents with aryl chlorides and aryl triflates leading to products of type **130** or **131** in good yields (Scheme 11-63) [112].



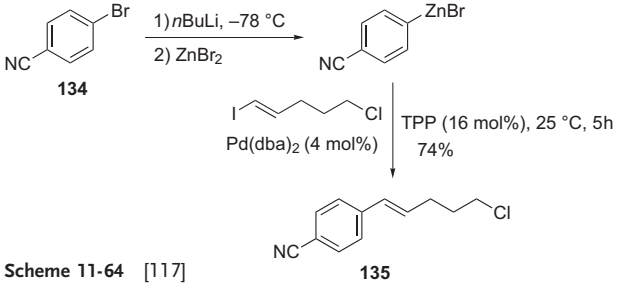
Scheme 11-63 [112,113]

The use of nickel(0) on charcoal ("Ni/C") is an efficient heterogeneous catalyst for the cross-coupling of chloroarenes and functionalized organozinc compounds. The reaction shows an excellent chemoselectivity, and the reaction of 4-chlorobenzaldehyde with 3-cyanopropylzinc iodide provides the desired product **132** in 80 % yield. Arylzinc halides similarly undergo cross-coupling reactions with 2-chlorobenzonitrile in THF at 60 °C, leading to the expected biaryl **133** in 92 % yield (see Section 11.7.20; Scheme 11-63) [113].

11.5.1.4 Palladium-Catalyzed Cross-Coupling between Polyfunctional Unsaturated Substrates

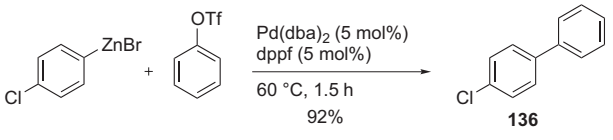
The presence of an unsaturation close to the transition-metal center considerably facilitates the reductive elimination step. Alkenyl or aryl iodides readily react with a variety of zinc organometallics (Negishi reaction) [4, 114]. When polyfunctional aryl or alkenyl zinc reagents are used, optimal reaction conditions are obtained by using bis(dibenzylidene-acetone)palladium(0) ($Pd(dba)_2$) [115] (4 mol %) and tris(*o*-furyl)phosphine (TFP) [116] or triphenylphosphine (TPP) as a ligand. Under these conditions, the reaction is complete within a few hours at ambient temperature. Thus, the aryl bromide **134** undergoes a cross-coupling reaction with a functionalized alkenyl iodide, furnishing the polyfunctional styrene **135** (see Section 11.7.21; Scheme 11-64) [117].

Attempts to apply these reaction conditions to the cross-coupling between alkenyl or arylzinc derivatives with aryl triflates were disappointing. However, in the presence of 1,1-(diphenylphosphino)ferrocene (dppf) [118], the cross-coupling reaction occurred at 60 °C with satisfactory yields, leading to biphenyls such as **136** (see Section 11.7.22; Scheme 11-65) [117].



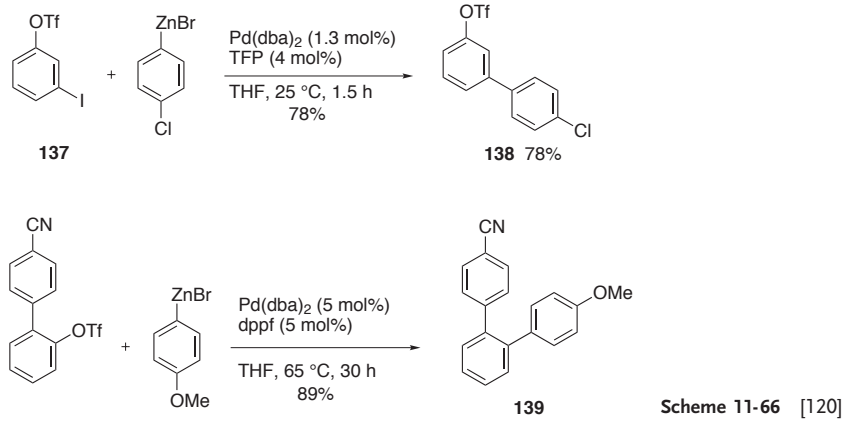
134 **135**

Scheme 11-64 [117]



136

Scheme 11-65 [117]

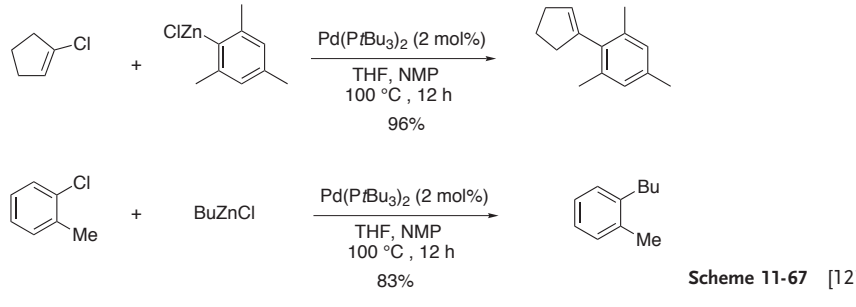


Scheme 11-66 [120]

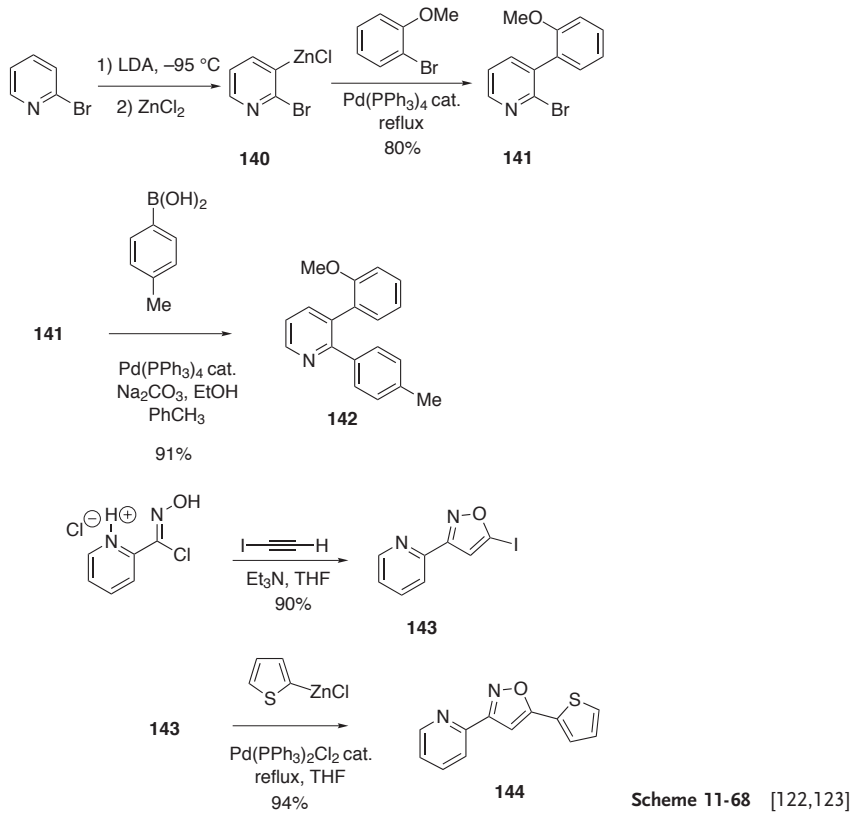
Selective palladium(0)-catalyzed arylation can be performed with aryl iodides bearing a triflate function using an appropriate palladium catalyst. Under these conditions, aromatic iodotriflates such as **137** can play the role of multi-coupling reagents [119]. Thus, the reaction of **137** with a functional arylzinc bromide provides the functionalized biphenyl triflate **138** (see Section 11.7.23; Scheme 11-66) [120].

By using dppf as a ligand, these biphenyl triflates can be selectively converted to a terphenyl such as **139** (see Section 11.7.24; Scheme 11-66) [120]. The Negishi cross-coupling reaction has found considerable applications in recent years, and has proved to be one of the most versatile method for performing transition metal-catalyzed cross-coupling reactions. By using very basic and sterically encumbered phosphines such as tBu$_3$P, a range of aryl and alkenyl chlorides undergo the cross-coupling reaction under very mild reaction conditions (Scheme 11-67) [121].

The Negishi cross-coupling reaction is perfectly well suited for performing cross-coupling reactions with heterocycles. Thus, the readily available pyridylzinc reagent **140** undergoes a cross-coupling reaction with a range of halides, leading to bromopyridines of type **141**. These heterocycles can be used for a second reaction with a different organometallic reagent to afford 2,3-diarylated pyridines of type **142**



Scheme 11-67 [121]

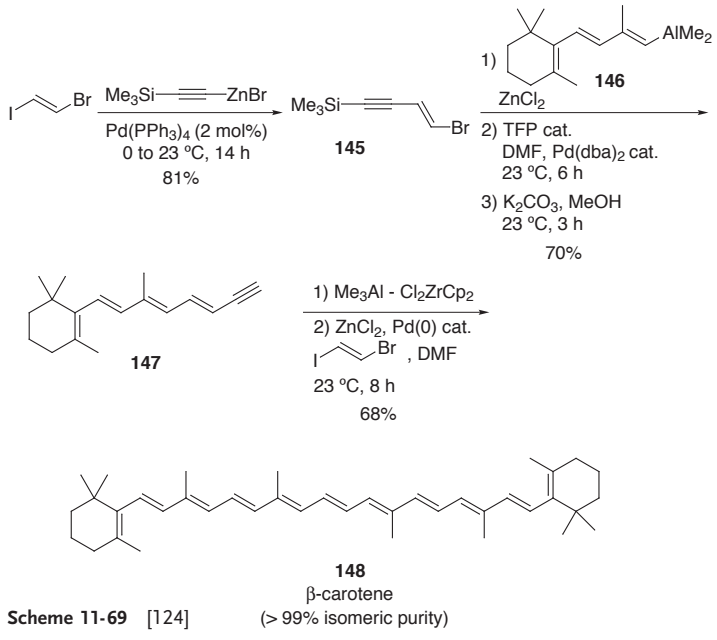


Scheme 11-68 [122,123]

(Scheme 11-68) [122]. Complex iodo-substituted heterocycles can be prepared according to numerous methods. The [3+2]-dipolar cycloaddition of iodoacetylene with 2-pyridyl oxime chloride in the presence of Et_3N provides the iodoisoxazole **143** in 90 % yield. The Pd-catalyzed cross-coupling of this compound with 2-thienylzinc chloride furnishes the heterocyclic system **144** in 94 % yield (Scheme 11-68) [123].

Especially interesting is the application of the Negishi cross-coupling reaction for the preparation of carotenoids. The cross-coupling of 1-bromo-2-iodoethylene with an alkynylzinc bromide provides the alkenyl bromide **145** in 81 % yield. Its cross-coupling with the (*E*)-alkenylaluminum reagent **146** obtained by a Zr-mediated methylalumination reaction affords the alkyne **147**, in 70 % yield (Scheme 11.69) [124].

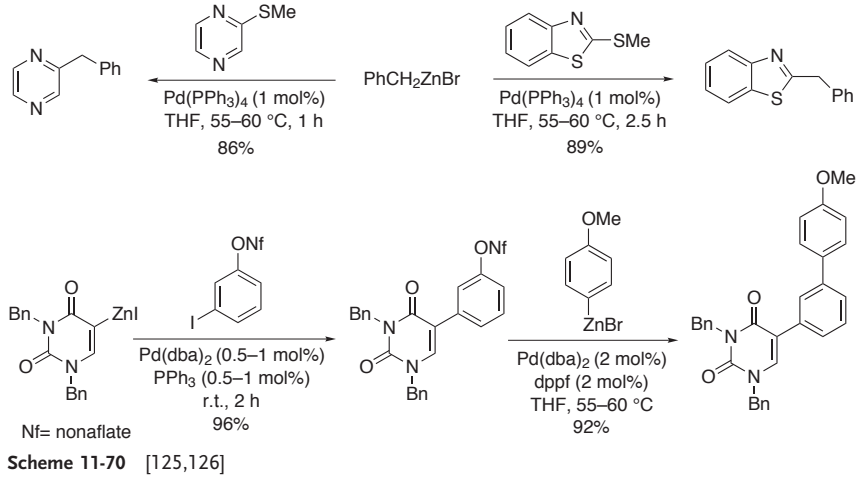
The methylalumination of **147** with Me_3Al and Cl_2ZrCp_2 followed by a transmetallation of the intermediate aluminum reagent to the corresponding organozinc species allows one to perform a double cross-coupling reaction with (*E*)-1-bromo-2-iodoethylene leading to *β*-carotene **148** in 68 % yield (>99 % isomeric purity) (see Section 11.7.25; Scheme 11-69) [124]. Significant extensions of the Negishi



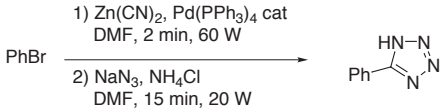
Scheme 11-69 [124]

cross-coupling procedure have been reported. It was found that thiomethyl-substituted heterocycles react readily with benzylic zinc reagents in the presence of catalytic amounts of $Pd(PPh_3)_4$ (1 mol %) [125].

Although Negishi-type cross-coupling reactions with aryl triflates proceed very well, the preparation of aryl triflates – and especially their purification – is often difficult. The aryl triflates can be replaced by aryl nonaflates ($ArOSO_2(CF_2)_3CF_3$=ArONf), which have an excellent stability on silica gel and



Scheme 11-70 [125,126]



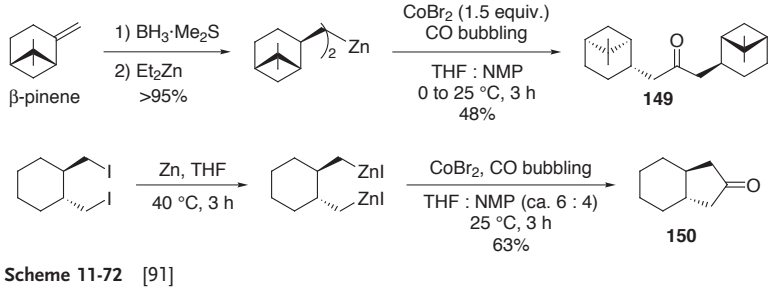
Scheme 11-71 [127]

can be readily prepared and purified using chromatography. They undergo Negishi cross-coupling reactions under mild conditions (Scheme 11-70) [126]. Aryl and alkenyl nitriles can be prepared in high yields from the corresponding organic bromides and $Zn(CN)_2$ using palladium-catalyzed reactions under microwave irradiation. The resulting nitriles can be converted to phenyltetrazoles by treatment with sodium azide in DMF. A one-pot procedure combining the two reactions is possible (see Section 11.7.26; Scheme 11-71) [127].

11.5.2
Cobalt-, Manganese- and Iron-Catalyzed Cross-Coupling Reactions

11.5.2.1 Carbonylations and Acylations

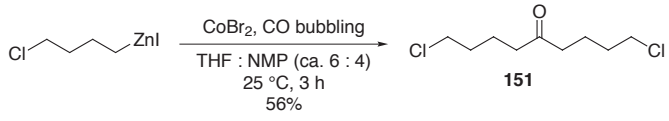
The reaction of cobalt(II) salts with organo-lithiums or -magnesiums leads to a rapid decomposition, even at low temperature, to provide homocoupling products. These transmetallations have therefore found limited applications in organic synthesis [128]. It was recently reported that the reaction of organozinc compounds with cobalt(II) bromide in mixtures of ether and NMP produces blue solutions of organocobalt intermediates which have a half-life of ca. 40 min at –10 °C. Similarly, the reaction of iron(III) chloride with diorganozincs furnishes a gray solution of an organometallic species having an even longer half-life (2.5 h at –10 °C). These new transition-metal organometallics have interesting synthetic properties, and organocobalt species prepared in this way undergo a smooth carbonylation at 25 °C, furnishing symmetrical ketones in moderate to good yields [129]. Thus, starting from *β*-pinene, the C_2-symmetrical ketone **149** is obtained in 48 % overall yield (Scheme 11-72) [91]. Chiral bicylic ketones such as **150** can be prepared in similar manner.



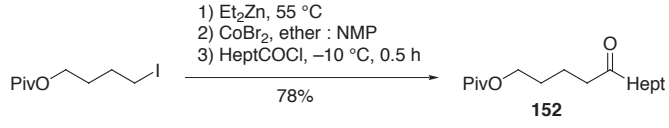
Scheme 11-72 [91]

Finally, this mild carbonylation method is well-suited for the preparation of polyfunctional symmetrical ketones such as **151** (see Section 11.7.27; Scheme 11-73) [129].

Not only are stoichiometric reactions, mediated by $CoBr_2$, possible, but catalytic reactions can also be performed. Catalytic acylation of diorganozincs with acid chlorides in the presence of $CoBr_2$ (10 mol %) is a very rapid reaction in NMP/ether mixtures, furnishing unsymmetrical ketones such as **152** (see Section 11.7.28; Scheme 11-74) [130].



Scheme 11-73 [129]

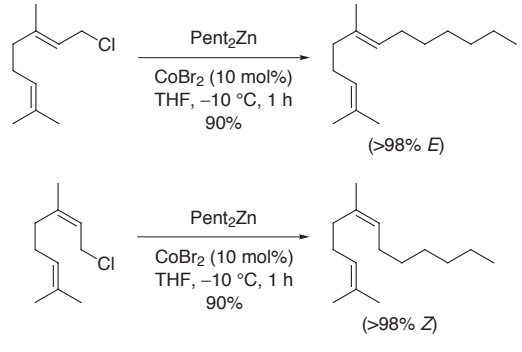


Scheme 11-74 [130]

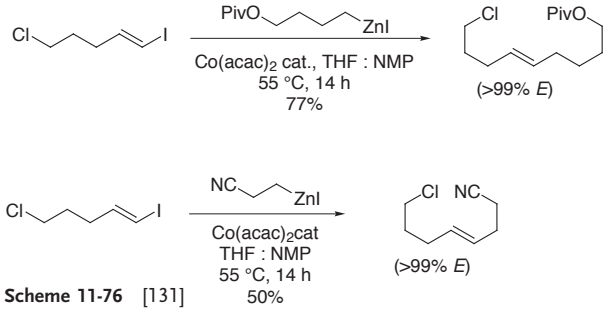
11.5.2.2 **Cobalt-Catalyzed Cross-Coupling Reactions**

Allylic chlorides react with organozinc halides or diorganozincs in the presence of catalytic amounts of $CoBr_2$ [130]. These reactions lead to the S_N2 cross-coupling product with retention of the double bond configuration. The reaction proceeds equally well with allylic phosphates (Scheme 11-75) [130].

Finally, cross-coupling reactions of alkenyl iodides with diorganozincs in the presence of cobalt salts furnish the expected cross-coupling products (Scheme 11-76) [131].



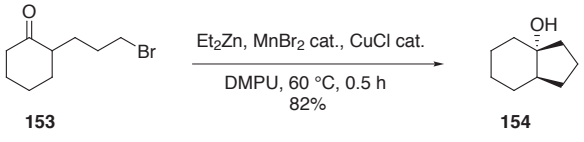
Scheme 11-75 [130]



Scheme 11-76 [131]

11.5.2.3 **Manganese- and Copper-Catalyzed Radical Cyclizations**

Transmetallation of zinc organometallics with manganese(II) salts does not occur, and cannot be used to produce functionalized organomanganese compounds. The reaction of unsaturated alkyl bromides furnishes, in the presence of a mixed metal-salt system composed of copper(I) chloride and manganese(II) bromide [48], cyclization products in satisfactory yields (see Section 11.7.29, Scheme 11-77) [132].



153 **154** **Scheme 11-77** [132]

11.6 Conclusions

The cross-coupling reactions between various polyfunctional organozinc derivatives and a range of electrophiles provide expeditious access to numerous polyfunctional molecules. The functional group compatibility allows an unusual amount of diversity for the organometallic reagent. After transmetallation by the addition of catalytic quantities of transition metal salts [Cu(I), Pd(II), Ni(II), Co(II), Co(III), Fe(III), Mn(II)], smooth cross-coupling reactions can be performed, with high yields. The applications of organozinc compounds range from asymmetric synthesis to the preparation of biologically relevant molecules, and of new materials as well as to combinatorial chemistry. It can be predicted that broader applications will be developed in the future.

11.7 Experimental Procedures

11.7.1 {[(1*R**,2*S**)-2-(1,3-Dioxolan-2-yl)cyclohexyl]ethynyl}(trimethyl)silane (23a) (Scheme 11-8)

A flame-dried 25-mL flask equipped with a magnetic stirring bar, an argon inlet and a septum was cooled to –25 °C and charged with freshly prepared (–)-IpcBH$_2$ (1.1 mL, 1.1 mmol, 1.1 equiv., 1 *M* solution in THF). The protected alkene **20** (154 mg, 1.0 mmol, 1.0 equiv., 1 *M* in THF) was added dropwise over a period of 1 h. Stirring at this temperature was continued for 48 h. After pumping off the volatiles (0.1 mmHg, 25 °C, 2 h), Et$_2$BH (0.69 mL, 5.0 mmol, 5 equiv., 7.3 *M* in Me$_2$S) was added, and the resulting mixture was stirred for 16 h at 50 °C. After pumping off the volatiles (0.1 mmHg, 25 °C, 2 h), *i*Pr$_2$Zn (1.0 mL, 5.0 mmol, 5 equiv., 5.0 *M* in Et$_2$O,) was added and the mixture was stirred 5 h at 25 °C. The volatiles were pumped off (0.1 mmHg, 25 °C, 0.5 h), the gray-black residue was diluted with THF (3 mL) and cooled to –78 °C. A freshly prepared solution of CuCN · 2LiCl (1.5 mL, 1.5 mmol, 1.5 equiv., 1 M in THF) was slowly added over 40 min via a syringe pump, and the mixture was stirred for 30 min at –78 °C. Then, a solution of 1-bromo-2-trimethylsilylacetylene (885 mg, 5 mmol, 5 equiv.) in THF (1 mL) was slowly added (40 min) via syringe pump. After stirring for 30 min at –78 °C, the mixture was allowed to warm to –40 °C and stirred at this temperature for 16 h. The reaction mixture was then poured into a saturated aqueous NH$_4$Cl solution (150 mL) containing NH$_{3\ (aq.)}$ (2 mL, 30 % in H$_2$O). After extraction with Et$_2$O (3 × 100 mL) the combined organic phases were dried over MgSO$_4$. The solvent was removed and the crude product purified by column chromatography (SiO$_2$, hexanes/Et$_2$O, 19:1) affording **23a** as a colorless oil (116 mg, 46 %).

11.7.2 1-[(1*S**, 4a*S**, 8*S**, 8a*S**)-8-(ethoxymethoxy)decahydro-1-naphthalenyl]-1-propanone (33) (Scheme 11-10)

A flame-dried 25-mL flask equipped with a magnetic stirring bar, an argon inlet and a septum was charged with 1-(ethoxymethoxy)-1,2,3,4,4a,5,6,7-octahydronaphthalene **31** (0.210 g, 1 mmol) in CH$_2$Cl$_2$ (2 mL). Et$_2$BH (0.4 mL, 7.3 *M* in Me$_2$S, 3 equiv.) was slowly added and the resulting mixture was stirred for 48 h at 25 °C. After pumping off the excess volatiles (0.1 mmHg, 25 °C, 2 h), *i*Pr$_2$Zn (0.6 mL, 5 *M* in Et$_2$O, 3 equiv.) was added and the mixture stirred for 5 h at 25 °C. The boron-zinc exchange was ca. 80 % complete as monitored by GC analysis of oxidized aliquots (aqueous 3 M NaOH/aqueous 30 % H$_2$O$_2$). The excess volatiles were pumped off (0.1 mmHg, 25 °C, 0.5 h), and the gray-black residue was diluted with THF (2.5 mL) and cooled to –78 °C. A freshly prepared solution of CuCN · 2LiCl (0.7 mL, 1 *M* in THF, 0.7 equiv) was added over 1 h. The mixture

was stirred for 30 min at –78 °C. Then, allyl bromide (0.363 g, 3 mmol, 3 equiv.) in anhydrous THF (1 mL) was slowly added (40 min). After stirring for 1 h at –78 °C, the mixture was allowed to warm to room temperature overnight. It was then poured into a saturated aqueous NH_4Cl solution (150 mL) containing $NH_{3\ (aq.)}$ (2 mL, 30 % in H_2O). After extraction with Et_2O (3 × 100 mL), the combined organic phases were dried over $MgSO_4$. The solvent was removed and the crude product purified by column chromatography (SiO_2, pentane:Et_2O = 98:2) affording **33** as a colorless oil (0.164 g, 0.65 mmol, 65 %) and as a diastereomeric mixture: d. r. (1,2) = 97:3 and d. r. (2,3) >98:2 (GC-MS analysis).

11.7.3

_N_-Benzyl-_N_-(1-isobutyl-2-methyl-5-hexenyl)-4-methylbenzene-sulfonamide (41) (Scheme 11-12)

A flame-dried 25-mL flask equipped with a magnetic stirring bar, an argon inlet and a septum was cooled to 0 °C and charged with the alkene **39** (0.186 g, 0.5 mmol, 1.0 equiv.) in THF (1.9 mL) at –78 °C; 9-BBN-H (3 mL, 1.5 mmol, 3 equiv., 0.5 *M* solution in THF) was added dropwise over a period of 1 h. The reaction mixture was allowed to warm up to 25 °C overnight. After pumping off the volatiles (0.1 mmHg, 25 °C, 2 h), iPr_2Zn (0.5 mL, 2.5 mmol, 5 equiv., 5.0 *M* in Et_2O) was added and the mixture stirred for 5 h at 25 °C. The volatiles were pumped off (0.1 mmHg, 25 °C, 0.5 h), and the gray-black residue was diluted with THF (2 mL) and cooled to –78 °C. A freshly prepared solution of CuCN · 2LiCl (0.75 mL, 0.75 mmol, 1.5 equiv., 1 *M* in THF) was slowly added over 40 min via a syringe pump, and the mixture was stirred for 30 min at –78 °C. Then, a solution of allyl bromide (0.212 g, 1.75 mmol, 3.5 equiv.) in THF (1 mL) was slowly added over 40 min via a syringe pump. The reaction mixture was allowed to warm up to 25 °C overnight. It was then poured into a saturated aqueous NH_4Cl solution (150 mL) containing $NH_{3\ (aq.)}$ (2 mL, 30 % in H_2O). After extraction with Et_2O (3 × 100 mL), the combined organic phases were dried over $MgSO_4$. The solvent was removed and the crude product purified by column chromatography (SiO_2) affording **41** as a colorless oil and a diastereomeric mixture of >96:4 (quant. ^{13}C-NMR), (0.159 g, 77 %).

11.7.4

{[2-(3-Butenyl)cyclohexyl]oxy}(*tert*-butyl)dimethylsilane (46a) (Scheme 11-13)

A flame-dried 25-mL flask equipped with a magnetic stirring bar, an argon inlet and a septum was charged with $RhCl(PPh_3)_3$ (14 mg, 0.03 equiv., 0.015 mmol). THF (2 mL) was added and the mixture stirred for 10 min at rt. The alkene **44** (0.113 g, 0.5 mmol, 1.0 equiv.) was added and the mixture cooled to 0 °C. Catecholborane (0.180 g, 1.5 mmol, 3 equiv.) was added and the solution was allowed to warm up to r. t. and stirred for 6 h. After pumping off the volatiles (0.1 mmHg, 25 °C, 3 h), iPr_2Zn (1.6 mL, 8.0 mmol, 16 equiv., 5.0 *M* in Et_2O) was added in two portions and the mixture was stirred for 36 h at 25 °C. The volatiles were

pumped off (0.1 mmHg, 25 °C, 0.5 h, co-evaporation with 2 × 1 mL THF), and the gray-black residue was diluted with THF (2 mL) and cooled to –78 °C. A freshly prepared solution of CuCN · 2LiCl (0.75 mL, 0.75 mmol, 1.5 equiv., 1 *M* in THF) was slowly added over 40 min via a syringe pump, and the mixture was stirred for 30 min at –78 °C. Then, allyl bromide (0.303 g, 2.5 mmol, 5.0 equiv.) in THF (1 mL) was slowly added (40 min) via a syringe pump. The reaction mixture was allowed to warm up to 25 °C overnight, and then poured into a saturated aqueous NH_4Cl solution (150 mL) containing $NH_{3\ (aq.)}$ (2 mL, 30 % in H_2O). After extraction with Et_2O (3 × 100 mL), the combined organic phases were dried over $MgSO_4$. The solvent was removed and the crude product purified by column chromatography (pentane). The desired product **46a** was obtained as a diastereomeric mixture with a ratio of >94:6 (GC-MS) (70 mg, 52 %).

11.7.5
1-(4-Iodophenyl)-1-propanone (56) (Scheme 11-15)

To 1,4-bis(trimethylsilyl)benzene (1.0 mmol, 222 mg) in CH_2Cl_2 (1.5 mL) at 0 °C was added BCl_3 (3.0 equiv., 3.0 mmol, 3 mL, 1 *M* in CH_2Cl_2). The reaction mixture was stirred at r. t. for 10 h. After pumping off the volatiles (0.1 mmHg, 25 °C, 30 min), CH_2Cl_2 (2 mL) was added and the reaction mixture was cooled to 0 °C. After addition of ICl (1.0 equiv., 1.0 mmol, 162 mg) the reaction mixture was stirred for 16 h at 25 °C. After pumping off the volatiles (0.1 mmHg, 25 °C, 30 min), iPr_2Zn (3.0 equiv., 3.0 mmol, 0.5 mL, 6.0 *M* in Et_2O) was added carefully and the mixture was stirred for 2 h at 25 °C. The volatiles were pumped off (0.1 mmHg, 25 °C, 0.5 h), the residue was diluted with THF (2 mL) and cooled to –30 °C. A freshly prepared solution of CuCN · 2LiCl (1.0 equiv., 1.0 mmol, 1.0 mL, 1 *M* in THF) was slowly added over 10 min and the mixture was stirred for 10 min at –30 °C. Propionyl chloride (3.0 equiv., 3.0 mmol, 278 mg) in THF (1 mL) was added slowly (10 min). The mixture was allowed to warm up to r. t. and stirred at this temperature for 3 h. The reaction mixture was then poured into a saturated aqueous NH_4Cl solution (150 mL) containing $NH_{3(aq)}$ (2 mL, 30 % in H_2O). After extraction with Et_2O (3 × 100 mL), the combined organic phases were dried over $MgSO_4$. The solvent was removed and the crude product purified by column chromatography (SiO_2) affording **56** as a colorless oil (140 mg, 54 %).

11.7.6
(*E*)-6-Chloro-2-hexenenitrile (61) (Scheme 11-21)

A three-necked flask was charged with 5-chloro-1-iodo-1-pentene (1.8 g, 6.0 mmol) in THF (5 mL), cooled to –100 °C (liquid N_2/ether bath), and *n*BuLi (6.3 mmol, 1.6 *M* in hexane) was added over 4 min. The resulting colorless solution was stirred at 0 °C for 2 min and cooled back to –78 °C. *p*-Toluenesulfonyl cyanide (0.90 g, 5.0 mmol) in THF (5 mL) was added and the reaction mixture was warmed to r. t. and stirred for 3 h. After the usual work-up and evaporation of the solvents, the crude residue obtained was purified by flash chromatography (hexane/ether,

10:1) yielding the unsaturated nitrile **61** (466 mg, 72 %) as a clear oil (100 % (*E*) according to GLC analysis and ^{13}C-NMR spectrum).

11.7.7
(3-Myrtanyl)cyclopentanone (66) (Scheme 11-26)

A 25-mL two-necked flask was charged with *β*-pinene (1.36 g, 10 mmol), and diethylborane (2.0 g, 10 mmol) in ether was added at 0 °C. The resulting solution was stirred for 15 min, allowed to warm to 25 °C, and further stirred for an additional 1-h period. It was then cooled to 0 °C, and the solvents were removed by applying high vacuum (0.1 mmHg) for 15 min at 0 °C, and for 30 min at r. t.. The reaction mixture was cooled to 0 °C and Et_2Zn (2 mL, 20 mmol) was added. The reaction mixture was stirred for 10 min at 0 °C, and for 20 min at r. t.. It was again cooled to 0 °C, and the solvents were removed as described above. The resulting zinc reagent was diluted with THF (3 mL) and was ready to use. A 50-mL, three-necked flask was charged with THF (2 mL) and NMP (3 mL) and cooled to –30 °C. 2-Cyclopenten-1-one (410 mg, 5 mmol) and chlorotrimethylsilane (500 mg, 5 mmol) were added, followed by bis(myrtanyl)zinc (3 mL of the above prepared solution, 5 mmol). The resulting reaction mixture was stirred for 3 h at –30 °C and then poured into an aqueous 10 % HCl solution (20 mL) in THF (20 mL), stirred for 15 min, and was worked-up as usual after evaporation of the solvents. The crude residue was purified by flash chromatography (hexane/ether, 95:5) providing (3-myrtanyl)cyclopentanone **66** (869 mg, 79 %) as a colorless oil.

11.7.8
Quinidine Derivative (72) (Scheme 11-31)

Diethylborane (4 mmol) prepared by mixing borane dimethyl sulfide complex (101 mg, 1.33 mmol, 1.1 equiv.) and triethylborane (261 mg, 2.66 mmol, 2 equiv.) at 25 °C was added at 0 °C to a solution of the alkaloid **71** (1.35 g, 4 mmol) in ether (8 mL), and the mixture was stirred at 40 °C for 12 h to produce a white suspension. All the solvents were pumped off at 40 °C (0.2 mmHg) during 6 h, yielding the diethylborane adduct as a white powder (1.63 g, 4 mmol). Et_2Zn (8.0 mmol, ca. 0.8 mL, 2 equiv.) was added at 25 °C to a suspension of the intermediate diethylborane derivative (1.63 g, 4 mmol, 1 equiv.) in CH_2Cl_2 (5 mL). After 10 min of stirring, the white suspension turned into a clear orange solution. The solvent, the excess diethylzinc, and the triethylborane formed were removed under vacuum at 25 °C (0.2 mmHg, 2 h). The entire procedure [CH_2Cl_2 (5 mL), Et_2Zn (1 mL), then pumping off solvent] was repeated to ensure complete conversion to the diorganozinc compound. Traces of remaining Et_2Zn were removed by evaporating twice the added toluene (5 mL) and finally with CH_2Cl_2 (5 mL) at 40 °C (0.2 mmHg, 6 h), giving an orange foam of the intermediate zinc reagent. A suspension of copper(I) cyanide (36 mg, 0.4 mmol, 0.1 equiv.), lithium chloride (34 mg, 0.8 mmol, 0.2 equiv.), allyl bromide (4.84 g, 40 mmol, 10 equiv.) and THF (1 mL) was

added at –80 °C to a solution of the diorganozinc compound (2 mmol, 0.5 equiv.), in THF (8 mL). The cooling bath was removed and the reaction mixture allowed to warm slowly to r. t.. After the usual work-up, the solvents were evaporated and the remaining volatile compounds removed at 50 °C (0.2 mmHg, 3 h). The crude product was purified by flash chromatography (ether/THF, 4:1) yielding the desired product **72** as a yellow foam (1.44 g, 95 %).

11.7.9
(*S*)-4-(2-Iodo-2-cyclohexen-1-yl) ethylbutanoate (74) (Scheme 11-33)

3-Ethoxycarbonylpropylzinc iodide was freshly prepared by treatment of 3-ethoxycarbonylpropyl iodide (0.726 g, 3.0 mmol, 1.0 equiv.) with activated Zn foil (0.6 g, 9.0 mmol, 3.0 equiv.) in THF (2 mL) at 48 °C for 4.5 h. After insertion of Zn was complete (monitored by GC analysis of hydrolyzed aliquots), the resulting solution was titrated with sodium thiosulfate. A flame-dried 25-mL flask equipped with a magnetic stirring bar, an argon inlet, and a septum was charged with a solution of CuCN · 2LiCl (1 *M* solution in THF; 1.0 mL, 1.0 mmol, 2.0 equiv.) and cooled to –30 °C. The freshly prepared alkylzinc halide reagent (1.5 *M* solution in THF, 0.66 mL, 1.0 mmol, 2.0 equiv.) was added dropwise and the resulting mixture was stirred for 0.5 h at –30 °C. Then, (*R*)-2-iodo-2-cyclohexen-1-yl diethylphosphate **73** (94 % *e. e.*; 0.180 g, 0.5 mmol, 1.0 equiv.) was added dropwise as a solution in NMP (sufficient to give an overall ratio of THF:NMP = 3:1) and the reaction mixture was allowed to stir for 12 h while warming up to 25 °C. Saturated aqueous NH_4Cl solution (20 mL) was added, followed by 25 % aqueous ammonia solution (1 mL); the reaction mixture was then stirred at 25 °C until the copper salts had dissolved. The mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were washed with brine and dried over Na_2SO_4. Evaporation of the solvents and purification by column chromatography (SiO_2, pentane/Et_2O, 20:1) afforded **74** as a colorless oil (94 % *e. e.*, 0.110 g, 68 %).

11.7.10
(5*E*, 7*R*)-7-methyl-5-dodecene ((*R*,*E*)-79) (Scheme 11-34)

A flame-dried 25-mL flask equipped with a magnetic stirring bar, an argon inlet, and a septum was charged with a solution of CuCN · 2LiCl (1 *M* solution in THF; 0.6 mL, 0.6 mmol) and cooled to –30 °C under an argon atmosphere. NMP was added as a co-solvent (overall ratio of THF:NMP = 2:1). $Pent_2Zn$ (5.1 *M* solution in THF, 0.24 mL, 1.2 mmol) was added dropwise, and the resulting mixture was stirred for 0.5 h at –30 °C. The pentafluorobenzoate ester (*R*,*Z*)-**4** (160 mg, 0.5 mmol, 95 % *e. e.*) was then added dropwise as a solution in THF (0.8 mL) and the reaction mixture was allowed to warm to –10 °C and stirred for 2.5 h. Water (20 mL) was added, followed by 25 % aqueous ammonia solution (2 mL); the reaction mixture was then stirred at 25 °C until the copper salts had dissolved. The mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were washed with brine and dried over $MgSO_4$. Evaporation of the solvents

and purification by column chromatography (SiO_2, pentane) afforded the desired alkene (*R*,*E*)-**79** as a colorless liquid (88 mg, 97 %, 93 % *e.e.*).

11.7.11
[(1-*R*)-1-neopentyl-2-propenyl]benzene (Scheme 11-37)

To a cooled (–30 °C) solution of CuBr · SMe_2 (4.11 mg, 0.02 mmol) and the ligand **87** (68.2 mg, 0.20 mmol) in THF (5 mL) was added dineopentylzinc (2.40 mmol) in THF and cinnamyl chloride (0.31 g, 2.00 mmol) simultaneously over a period of 3 h. After the usual work-up, the crude residue was purified by column chromatography (SiO_2, pentane). Evaporation of the solvents furnished the desired product as a colorless oil (309 mg, 82 % yield, 96 % *e.e.*).

11.7.12
6-Chloro-1-cyclohexenyl-1-hexyne (89) (Scheme 11-39)

A THF solution of 4-chlorobutylzinc iodide (7 mmol, 1.4 equiv.) prepared in over 90 % yield from 4-chloro-1-iodobutane [40 °C, 2 h, then 23 °C, 10 h] was added at –10 °C to a solution of CuCN · 2LiCl (7 mmol) in THF (7 mL). After 5 min at 0 °C, the yellow-green solution was cooled to–78 °C and the 1-bromoalkyne **88** (925 mg, 5 mmol) in THF was slowly added. The reaction mixture was stirred for 18 h at –65 °C. After the usual work-up and purification by flash chromatography (SiO_2, hexane), the pure enyne **89** was obtained (800 mg, 81 %).

11.7.13
3-(4-Pentynyl)-2-cyclohexen-1-one (92) (Scheme 11-40)

A dry, three-necked 100-mL flask was charged with zinc dust (3.27 g, 50 mmol) and flushed with argon. After zinc activation with 1,2-dibromoethane and chlorotrimethylsilane as reported previously, a THF solution of 4-pentenyl iodide (4.46 g, 23 mmol) in THF (8 mL) was added slowly. The temperature was maintained below 40 °C during the addition. After 0.5–1 h of stirring at 25 °C, the reaction was complete, as indicated by GLC analysis. After the addition of 10 mL anhydrous THF, the excess of zinc was allowed to settle for 1 h. One half of this solution (ca. 10 mmol) was transferred via a syringe to a solution of CuCN (0.90 g, 10 mmol) and LiCl (0.84 g, 20 mmol), dried for 1 h under vacuum at 140 °C) in THF (10 mL) at –20 °C. A dark-red solution of the zinc-copper reagent **91** was immediately formed. The reaction mixture was cooled to –60 °C after 5 min of stirring and 3-iodo-2-cyclohexen-1-one (1.55 g, 7 mmol, 0.7 equiv.) was added. The reaction mixture was stirred for 1 h at –30 °C and then slowly warmed to 0 °C (1–2 h) and worked-up as usual. The resulting crude oil was purified by flash chromatography (CH_2Cl_2/ether/hexane, 1:1:5), and afforded analytically pure cyclohexenone derivative **92** (1.0 g, 88 %).

11.7.14
(*E*)-10-Pivaloylxy-5-decenenitrile (98) (Scheme 11-43)

To a suspension of zinc dust (1.3 g, 20 mmol, -325 mesh; Aldrich) previously activated with 1,2-dibromoethane (3 mol %) and chlorotrimethylsilane (1 mol %) in THF (3 mL) was added 4-iodobutyl pivalate (2.84 g, 10 mmol) in THF (1 mL). The reaction mixture was stirred for 4 h at 25–35 °C. THF (3 mL) was added and the excess of zinc powder allowed to settle. The solution of the alkylzinc iodide (ca. 8 mmol) was transferred via a syringe to an NMP solution (10 mL) of CuCN (0.89 g, 10 mmol) and LiCl (0.85 g, 20 mmol) at 0 °C. After 5 min, 6-iodo-5-hexenenitrile (1.1 g, 5 mmol) was added and the reaction mixture was stirred at 60 °C overnight. GLC analysis of a hydrolyzed reaction aliquot showed that no alkenyl iodide was left. The reaction mixture was cooled to 25 °C and poured into a mixture of ether (100 mL) and a saturated aqueous NH_4Cl solution (25 mL). The aqueous phase was extracted with ether (2 × 30 mL), and the combined organic phase was washed with brine (2 × 30 mL), dried over $MgSO_4$ and concentrated. The crude residue was purified by chromatography (hexanes/ether, 3:1) affording the pure product **98** (1.09 g, 87 %); 100 % (*E*) by GC and by ^{1}H- and ^{13}C-NMR analyses.

11.7.15
10-Nitro-9-phenyldecyl acetate (101) (Scheme 11-44)

A three-necked flask equipped with a stirring bar, a rubber septum, and an argon inlet was charged with CuCN (5 mg) and 4-iodobutyl acetate (2.42 g, 10 mmol), Et_2Zn (2.0 mL, 20 mmol) was added, and the reaction mixture was stirred for 5 h at 50 °C. The excess Et_2Zn and the EtI formed were removed under vacuum (0.1 mmHg, 50 °C, 1.5 h), and anhydrous THF (5 mL) was added with stirring. The suspension was allowed to settle, and the supernatant liquid was transferred to a THF solution of $Me_2Cu(CN)(MgCl)_2$ (5 mmol, 1 *M* solution) at –50 °C. The resulting solution was warmed to 0 °C and then cooled to –78 °C, and DMPU (5 mL) was added, followed by 6-iodo-1-nitro-2-phenylhexane (**100**; 1.00 g, 3.0 mmol). The reaction mixture was allowed to warm slowly to 0 °C and stirred for 2 h. After work-up, drying over $MgSO_4$, and evaporation of the solvents, the residual oil was purified by flash column chromatography (hexane/ether, 4:1), yielding the functionalized nitroalkene **101** (0.80 g, 83 %) as a clear oil.

11.7.16
2,5-Dibenzoylthiophene (104) (Scheme 11-47)

A 100-mL three-necked flask equipped with an argon inlet, a glass stopper and a septum cap was charged with graphite (1.65 g, 137 mmol) and heated to 160 °C. Potassium (0.67 g, 17.1 mmol) was added in small pieces under a steady stream of argon with vigorous stirring, resulting in the formation of bronze-colored C_8K within 15 min, as a fine powder. A second three-necked flask was charged with zinc chloride (1.17 g, 8.6 mmol) which had been dried at 140 °C for 2 h under

vacuum. After cooling to 25 °C, THF (10 mL) was added, affording a solution to which AgOAc (140 mg, 0.85 mmol) was added. The resulting heterogeneous slurry was transferred at 25 °C with a syringe to the previously prepared C_8K with vigorous stirring (alternatively, a mixture of $ZnCl_2$ and AgOAc can be added as a solid to a suspension of C_8K in THF). A slightly exothermic reaction occurred. After 1 h of stirring, 5-benzoyl-2-iodothiophene (900 mg, 2.9 mmol) was added as a solid. GC analysis of an iodolyzed and hydrolyzed reaction aliquot indicated that a complete insertion had occurred after a reaction time of 15 min. The excess zinc/silver-graphite was allowed to settle for 1–2 h, and the supernatant solution of the zinc reagent was then transferred to a THF (2 mL) solution of CuCN (0.26 g, 3.0 mmol) and LiCl (0.24 g, 5.7 mmol) at –60 °C. The solution was allowed to warm to –10 °C and then stirred for 0.5 h before cooling back to –60 °C. Benzoyl chloride (0.30 g, 2.14 mmol, 0.75 equiv.) was added and the reaction mixture was warmed to –10 °C, stirred for ca. 14 h at –10 °C, and worked-up in the usual way. The crude light-brown residue was purified by flash chromatography (hexane/ether, 10:1, then hexane/chloroform, 5:1) affording 470 mg (76 %) of analytically pure 2,5-dibenzoylthiophene (**104**).

11.7.17

1-Butyl-1-(3-nitro-2-phenylpropyl)cyclopentane (109) (Scheme 11-50)

A three-necked flask equipped with a magnetic stirring bar, a thermometer and a gas inlet was charged with $PdCl_2$(dppf) (0.07 g, 2 mol %) in THF (5 mL) and cooled to –78 °C. 2-Butyl-6-iodohexene (1.33 g, 5 mmol) and Et_2Zn (1 mL, 1.23 g, 10 mmol) were added. The mixture was warmed to 25 °C and stirred for 4 h. The solvent and excess of Et_2Zn were removed under vacuum (0.1 mmHg, 25 °C, 1 h). After addition of THF (5 mL) and cooling of the mixture to –40 °C, CuCN · 2LiCl (5 mmol) in THF (5 mL) was added and the reaction mixture warmed to 0 °C (5 min) and cooled to –78 °C. Nitrostyrene (1.12 g, 7.5 mmol) in THF (3 mL) was added, and the reaction mixture was slowly warmed to 0 °C and stirred for 2 h. After the usual work-up, the residual oil was purified by flash column chromatography (hexane/ether, 9:1), to yield **109** as a clear oil (1.16 g, 81 %).

11.7.18

Ethyl 12-Acetoxy-2-decanoate (124) (Scheme 11-60)

A 50-mL two-necked flask equipped with an argon inlet and a rubber septum was charged with $Ni(acac)_2$ (116 mg, 0.045 mmol, 7.5 mol %). The flask was cooled to −40 °C, and THF (2.5 mL), NMP (1.5 mL), and the alkyl iodide **123** (1.69 g, 6 mmol, 1.0 equiv.) were successively added by syringe. The reaction mixture was cooled to –78 °C, and a solution of di(5-acetoxypentyl)zinc (3.38 mg, 12 mmol, 2 equiv.) in THF (2 mL), prepared from 5-iodopentyl acetate (6.14 g, 24 mmol) and Et_2Zn by an iodine-zinc exchange reaction, was slowly added. The reaction mixture was allowed to warm to –35 °C and stirred for 15 h at this temperature. Excess Et_2Zn

was quenched with saturated aqueous NH_4Cl solution. After the usual work-up, the resulting crude oil obtained after evaporation of the solvents was purified by column chromatography (hexane/ether, 20:1 to 5:1), affording the functionalized acrylate **124** (1.33 g, 78 %) as a colorless oil.

11.7.19

Ethyl 3-(4-cyanophenyl)propionate (129) (Scheme 11-62)

A dry 100-mL three-necked flask, equipped with an argon inlet and a stirring bar, was charged with $Ni(acac)_2$ (520 mg, 2 mmol) and evacuated for 10 min before being flushed with argon. THF (6.7 mL), NMP (3.3 mL), 4-fluorostyrene (496 mg, 4 mmol) and ethyl 3-iodopropionate (4.56 g, 20 mmol) were successively added; the flask was then equipped with an internal thermometer. The reaction mixture was cooled to –60 °C before slowly adding the zinc reagent with a syringe through a large-diameter cannula. After complete addition, the reaction mixture was allowed to warm to –14 °C in a cryostat. The conversion was complete within 12–15 h. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (15 mL) and allowed to warm to r. t.. The resulting reaction mixture was extracted with diethyl ether (7 × 150 mL), after which the ethereal extracts were combined, dried over magnesium sulfate, and evaporated to dryness by rotary evaporation at 40 °C under atmospheric pressure. The resulting yellow oil was purified by column chromatography, and afforded ethyl 3-(4-cyanophenyl)propionate **129** as a pale yellow oil (3.01 g, 74 %).

11.7.20

3′-Methylbiphenyl-2-carbonitrile (133) (Scheme 11-63)

To a flame-dried, 25-mL round-bottomed flask equipped with an argon inlet and a stirring bar was added Ni(II)/C (171 mg, 0.369 mmol/g, 0.063 mmol) and triphenylphosphine (66 mg, 0.252 mmol) under argon at r. t.. Anhydrous THF (1.8 mL) was added, and the slurry was stirred for 20 min. *n*BuLi (48 µL, 2.6 *M* in hexane, 0.126 mmol) was added dropwise with swirling. After 5 min, 2-chlorobenzonitrile (143 mg, 1.25 mmol) was added. After the mixture had been cooled to –78 °C, the zinc reagent (prepared from *m*-tolylmagnesium chloride (2.0 mL, 1.0 *M*, 2.0 mmol) and zinc chloride (anhydrous; 273 mg, 2.0 mmol) at r. t. for 20 min) containing lithium chloride (85 mg, 2.0 mmol) was then added slowly via a cannula. The mixture was warmed to r. t. over a 30-min period and then finally heated under reflux for 16 h. The crude reaction mixture was then filtered through a pad of Celite, and the filter cake further washed with THF (30 mL). The solvent was removed on a rotary evaporator, and the resulting oily residue was purified by chromatography on silica gel (hexane/ethyl acetate, 20:1) affording **133** as a pale yellow oil in 92 % yield.

11.7.21
(*E*)-4-(5-Chloro-1-pentenyl)benzonitrile (135) (Scheme 11-64)

A three-necked flask equipped with a thermometer, a gas inlet, and an addition funnel was charged with 4-bromobenzonitrile (1.09 g, 6.0 mmol) and *n*BuLi (3.91 mL, 6.2 mmol, 1.6 *M* in hexane) was added over a period of 4 min. A precipitate formed immediately, and the reaction mixture was stirred for 30 min at this temperature. A THF solution (3 mL) of $ZnBr_2$ (1.35 g, 6 mmol) was slowly added and the mixture was warmed up to 0 °C for 5 min. After cooling back to –20 °C, bis(dibenzylideneacetone)palladium(0) (0.13 g, 0.24 mmol, 4 mol %), TPP (0.25 g, 0.96 mmol, 16 mol %), and (*E*)-5-chloro-1-iodopentene (1.15 g, 5 mmol) in THF (5 mL) were added. The reaction mixture was stirred for 5 h at 25 °C and diluted with ether (10 mL). The organic phase was worked-up, leading to a crude product which was purified by flash chromatography, thus affording the benzonitrile derivative **135** (0.76 g, 74 %) as a clear oil.

11.7.22
4-Chlorobiphenyl (136) (Scheme 11-65)

To a solution of $Pd(dba)_2$ (163 mg, 0.3 mmol, 5 mol %) in THF (4 mL) was added dppf (125 mg, 0.3 mmol, 5 mol %) at 0 °C. After a few minutes, phenyl triflate (0.91 g, 4 mmol) was added, followed by a solution of 4-chlorophenylzinc bromide (6 mmol) in THF/hexane prepared as described for 4-cyanophenylzinc bromide above. The reaction mixture was heated to 60 °C for 1.5 h; then, after cooling to r. t., it was worked-up as usual and the crude residue obtained after evaporation of the solvents was purified by flash chromatography (hexane) affording the biphenyl **136** (695 mg, 92 %) as a clear oil.

11.7.23
(4′-Chloro-3-trifluoromethanesulfonyloxy)biphenyl (138) (Scheme 11-66)

In a dry, three-necked round-bottomed flask equipped with an argon inlet, rubber septum, and thermometer, $Pd(dba)_2$ (35 mg, 0.06 mmol, 1.3 mol %) and tri(*o*-furyl)phosphine (28 mg, 0.12 mmol, 2.6 mol %) were dissolved in THF (2 mL). After the wine-red color had disappeared (4 min at r. t.), the solution was cooled to 0 °C, and 3-iodophenyl triflate (1.41 g, 4 mmol) was added followed by 4-chlorophenylzinc bromide (12 mL, 0.5 *M* solution in 2:1 THF/hexane, 1.5 equiv.). The reaction mixture was allowed to warm to 25 °C and then stirred for 1.5 h. After aqueous work-up with saturated NH_4Cl solution and brine and extraction with ethyl acetate, the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography (hexane/ether, 98:2), yielding the desired biphenyl **138** (1.06 g, 78 %) as a colorless oil.

11.7.24
4″-Cyano-4-methoxy-1,1′,2′,1″-terphenyl (139) (Scheme 11-66)

To a solution of $Pd(dba)_2$ (72 mg, 0.12 mmol, 5 mol %) and dppf (68 mg, 0.12 mmol, 5 mol %) in THF (2 mL) was added 4-cyano-(trifluoromethanesulfonyloxy)biphenyl (0.67 g, 4 mmol) at 0 °C, followed by a solution of 4-methoxyphenylzinc bromide (1.2 mL, 0.5 *M* in 2:1 THF/hexane, 3.0 equiv.). The reaction mixture was heated at 65 °C for 30 h. After the usual work-up as described above (Section 11.7.13) and purification by flash chromatography (hexane/ethyl acetate, 98:2), the desired terphenyl **139** (0.53 g, 89 %) was obtained as a white solid (m. p. 95–96 °C).

11.7.25
***β*-Carotene** (Scheme 11-69)

To a slurry of Cp_2ZrCl_2 (207 mg, 0.71 mmol) in 4 mL of 1,2-dichloroethane was added Me_3Al (0.13 mL, 1.42 mmol) at r. t.. To the lemon-yellow solution thus obtained was added dropwise 1-(*E,E,E*)-3-methyl-1,3,5-octatrien-7-ynyl)-2,6,6-trimethyl-1-cyclohexene (170 mg, 0.71 mmol) in 1,2 dichloroethane (2 mL) at 0 °C. After the mixture had been stirred for 20 h at r. t., volatile compounds were evaporated at reduced pressure (maximum 50 °C, 0.3 mmHg), and anhydrous THF (2 mL) was added. In another flask, $Pd_2(dba)_3$ (16 mg, 0.018 mmol) was dissolved in DMF (3 mL) to which TFP (16 mg, 0.071 mmol) was added at 0 °C. After 10 min, the clear pale-green solution thus obtained was treated with (*E*)-1-bromo-2-iodoethylene (84 mg, 0.36 mmol). After an additional 5-min period, the alkenylalane obtained above was transferred via a cannula to this solution at 0 °C, and this was followed by addition of $ZnCl_2$ (96 mg, 0.71 mmol) in THF (0.5 mL). After stirring at r. t. for 5 h, the reaction mixture was quenched with water, and the resultant mixture extracted with ether, washed with brine, dried over $MgSO_4$, and concentrated. Purification by column chromatography (neutral alumina, pentane) afforded *β*-carotene (129 mg, 68 %, >99 % isomerically pure by ^{13}C- NMR spectroscopy) as a red solid.

11.7.26
5-Phenyltetrazole (Scheme 11-71)

A dried, heavy-walled Pyrex tube was charged with bromobenzene (10.5 µL, 0.1 mmol), $Zn(CN)_2$ (11.7 mg, 0.1 mmol), and $Pd(PPh_3)_4$ (11.6 mg, 10 µmol) in DMF (1 mL). The reaction mixture was flushed with nitrogen and the screw-cap tightened thoroughly before mixing with a Whirlimixer. The reaction mixture was exposed to microwave irradiation (60 W) for 2 min. The reaction tube was allowed to reach r. t.. Thereafter, the tube was charged with NaN_3 (78 mg, 1.2 mmol) and NH_4Cl (64 mg, 1.2 mmol). The reaction mixture was flushed with nitrogen and the screw-cap tightened thoroughly before mixing with a Whirlimixer. The reaction mixture was once again exposed to microwave irradiation (20 W) for 15 min.

The reaction tube was allowed to reach r. t. before the reaction mixture was diluted with saturated $NaHCO_3$ (60 mL) and washed with EtOAc. The water phase was acidified to pH <1 with concentrated HCl and extracted with $CHCl_3$. The combined organic phase was dried, and the solvent removed under reduced pressure to give pure 5-phenyltetrazole (14 mg, 96 %).

11.7.27
Di(4-chlorobutyl) ketone (151) (Scheme 11-73)

A THF (25 mL) solution of 4-chlorobutylzinc iodide (25 mmol) prepared from 1-iodo-4-chlorobutane (5.59 g, 25 mmol) and zinc dust (3.25 g, 50 mmol) was added dropwise to $CoBr_2$ (4.10 g, 18.8 mmol) in NMP (15 mL) at 0 °C while CO was bubbled through the reaction mixture. After completion of the addition, the reaction mixture was stirred for 3 h at 25 °C with continuous bubbling of CO and an additional 2 h without CO bubbling. The reaction mixture was poured into hexane (200 mL) and stirred for 2 h in order to decompose any cobalt carbonyl complexes formed as intermediates. The hexane layer was separated and the residue treated with brine (30 mL) and extracted with ether (2 × 50 mL). The combined organic layers were washed with brine (2 × 30 mL) and dried over $MgSO_4$. After evaporation of the solvents, the crude residue was purified by flash chromatography (hexane/ether, 95:5) providing di(4-chlorobutyl) ketone **151** (1.48 g, 56 %) as a clear oil.

11.7.28
5-Oxododecyl Pivalate (152) (Scheme 11-74)

Stage 1: A 50-mL three-necked flask was charged with 4-iodobutyl pivalate (8.52 g, 30 mmol), CuI (60 mg, 0.3 mol %), and Et_2Zn (4.5 mL, 40 mmol, 1.3 equiv.). The reaction mixture was warmed to 55 °C (oil-bath temperature) and stirred for 14 h. The volatiles were removed under vacuum (55 °C, 0.1 mmHg, 2 h). Decane (10 mL) was added and then distilled off under vacuum (1 h) in order to remove traces of Et_2Zn. This last operation was performed twice. The resulting zinc reagent was diluted in ether (10 mL) and was ready to be used.

Stage 2: A 50-mL three-necked flask was charged with $CoBr_2$ (218 mg, 1 mmol) in NMP (4 mL) and ether (2 mL). The reaction mixture was cooled to –10 °C and *n*-octanyl chloride (1.62 g, 10 mmol) was added, followed by bis(4-pivaloxybutyl)-zinc (4 mL of the solution prepared in Stage 1, 10 mmol). The resulting deep-blue solution was stirred for 0.5 h at –10 °C and worked-up as usual. After evaporation of the solvents, the crude residue was purified by flash chromatography (hexane/ether, 95:5), thus providing the ketone **152** (2.2 g, 78 %) as a colorless oil.

11.7.29
***cis*-Bicyclo[4.3.0]nonan-1-ol (154)** (Scheme 11-77)

A 20-mL three-necked flask was charged with $MnBr_2$ (53 mg, 0.25 mmol), CuCl (15 mg, 0.15 mol %), and DMPU (4.5 mL). Diethylzinc (1.0 mL, 10 mmol) was added at 25 °C, resulting in the formation of a black solution. The bromoketone **153** (1.1 g, 5 mmol) was added, and the reaction mixture was heated at 60 °C for 0.5 h. The reaction mixture was cooled back to 25 °C and worked-up as usual, affording after purification by flash chromatography (hexane/AcOEt, 9:1) the desired bicyclic alcohol **154** (575 mg, 82 %) as a clear oil.

Abbreviations

Ac	acetyl
acac	acetylacetonate
Bn	benzyl
Boc	*tert*-butyloxylcarbonyl
COD	1,4-cyclooctadiene
dba	dibenzylideneacetone
DMF	dimethylformamide
DMPU	*N*,*N*-dimethylpropyleneurea
dppf	1,1′-bis(diphenylphosphino)ferrocene
Et	ethyl
Fc	ferrocenyl
FG	functional group
Hept	heptyl
Hex	hexyl
Me	methyl
NMP	*N*-methylpyrrolidinone
Pent	pentyl
Piv	pivaloyl
r. t.	room temperature
TBDMS	*tert*-butyldimethylsilyl
Tf	trifluoromethansulfonyl (triflyl)
TFP	tris(*o*-furyl)phosphine
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMSCl	trimethylsilyl chloride
Ts	tosyl (*p*-toluenesulfonyl)
TPP	triphenylphosphine

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12
Carbon-Carbon Bond-Forming Reactions Mediated by Organomagnesium Reagents

Paul Knochel, Ioannis Sapountzis, and Nina Gommermann

12.1
Introduction

Organomagnesium derivatives are key organometallic reagents for organic synthesis. Since their first synthesis disclosed by Grignard [1], numerous applications for the elaboration of complex organic molecules have been reported. Although organomagnesium reagents undergo substitution reactions only sluggishly, it was soon recognized that transition-metal catalysts allow the performance of a wide range of substitutions. The pioneering studies of Kharasch and Fuchs [2] have opened new synthetic avenues for Grignard reagents. Kumada and colleagues [3] and Corriu and Masse [4] have demonstrated the synthetic utility of nickel cross-coupling reactions [5–7]. Most cross-coupling reactions have been performed with unfunctionalized Grignard reagents, since no general method for preparing polyfunctional organomagnesium reagents was available. At the end of the 1990s, it became clear that the carbon-magnesium bond is compatible with a number of sensitive electrophilic functional groups [8]. The halogen-magnesium exchange reaction was found to be a general method for preparing a range of functionalized organomagnesium compounds [9]. In this chapter, we propose to describe the scope and limitations of the preparation of polyfunctional organomagnesium species and show their use for forming new C-C and C-N bonds.

12.2
Preparation of Polyfunctionalized Organomagnesium Reagents via a Halogen-Magnesium Exchange

Although first discovered during the early 1930, the halogen-magnesium exchange has recently experienced a renaissance. This reaction had allowed, for the first time, a general approach to magnesium carbenoids [10]. Villiéras et al. found that the reaction of *i*PrMgCl with $CHBr_3$ at –78 °C furnishes the corresponding magnesium carbenoid **1** which could be trapped with various electrophiles, leading

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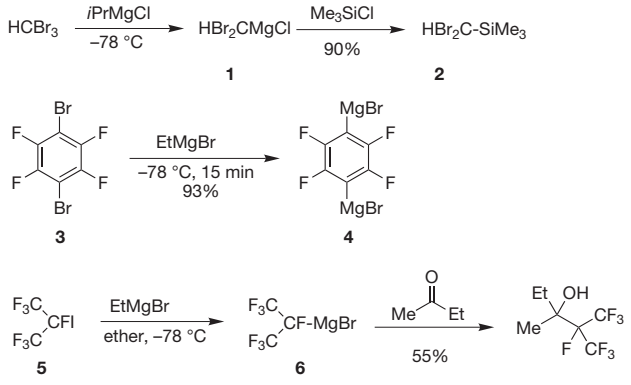


Scheme 12-1 Bromine-magnesium exchange of polyhalogenated compounds [10–14].

to products of type **2** (Scheme 12-1). These pioneering studies opened the way to the systematic study of magnesium carbenoids [11]. It was found that 1,4-dibromo-2,3,5,6-tetrafluorobenzene (**3**) is readily converted to the corresponding 1,4-dimagnesium species **4** with EtMgBr (Scheme 12-1) [12]. Similarly, Furukawa et al. have shown that 2-iodopyridine leads to the corresponding Grignard reagent within 0.5 h upon reaction with EtMgBr at 25 °C [13].

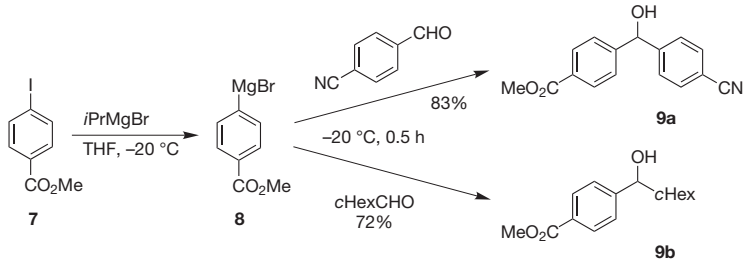
Interestingly, perfluoroalkyl iodides like **5** undergo an iodine-magnesium exchange at –78 °C leading to the perfluorinated Grignard reagent **6** which reacts well with carbonyl compounds (Scheme 12-1) [14].

These early results indicated the synthetic potential of the halogen-magnesium exchange reaction [15]. The reactivity of carbon-magnesium bonds are strongly dependent on the reaction temperature, with only reactive electrophiles like aldehydes and most ketones reacting rapidly at temperatures below 0 °C. Performing the halogen-magnesium exchange at temperatures below 0 °C has the potential for the preparation of magnesium organometallics bearing reactive functional groups.

12.2.1 Preparation of Functionalized Arylmagnesium Reagents

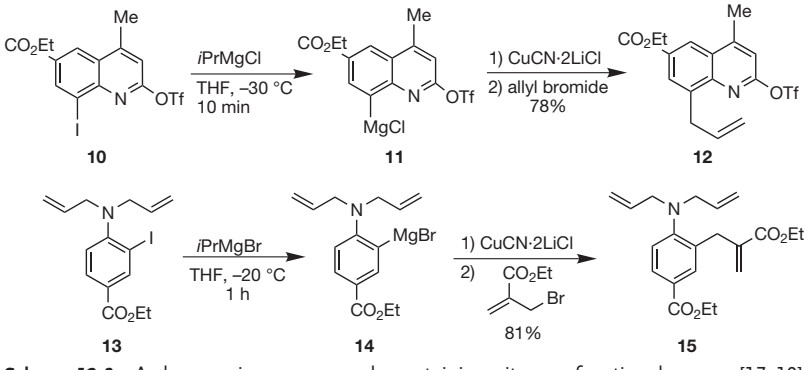
Functionalized aryl iodides react readily with *i*PrMgBr in THF below 0 °C, leading to a range of functionalized arylmagnesium iodides [16]. Sensitive carbonyl groups and analogues like nitriles, esters or amides are well tolerated. Typically, the treatment of methyl 4-iodobenzoate (**7**) with *i*PrMgBr in THF at –20 °C for 1 h produces the functionalized Grignard reagent **8** which is stable for several hours below –10 °C, but reacts smoothly with aldehydes at –20 °C, leading to the expected alcohols **9a-b** in 72–83 % yield (Scheme 12-2) [17].

A wide range of basic nitrogen functionalities are compatible with the iodine-magnesium exchange. Thus, the functionalized iodoquinoline **10** is converted at –30 °C in 10 min to the corresponding magnesium reagent **11**. Transmetallation



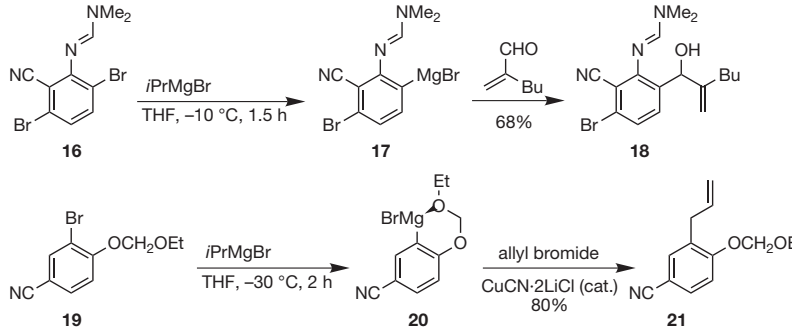
Scheme 12-2 The reaction of ester group-containing arylmagnesium reagents with aldehydes [17].

with CuCN · 2LiCl [18] and reaction with allyl bromide furnishes the allylated quinoline **12** in 78 % yield (Scheme 12-3) [19]. Similarly, the diallylaniline **13** is allylated via the intermediate Grignard reagent **14**, leading to the functionalized aniline derivative **15** in 81 % yield (Scheme 12-3).



Scheme 12-3 Arylmagnesium compounds containing nitrogen functional groups [17–19].

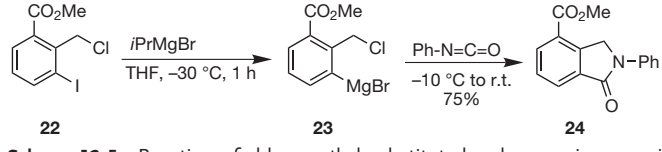
The Br/Mg exchange reaction, although slower than the I/Mg exchange, is sufficiently fast below 0 °C for the preparation of Grignard reagents bearing sensitive functional groups. The exchange rate depends strongly on the electron-density of the aromatic ring. Thus, whereas bromopentafluorobenzene undergoes a complete Br/Mg exchange at –78 °C within 0.5 h, 1-bromo-2,4,5-trifluorobenzene requires 1 h at –10 °C for full conversion to the corresponding magnesium reagent [20]. Polyfunctional aromatic bromides such as **16** [21] and **19** [20] (Scheme 12-4) bearing at the *ortho*-position a chelating group, rapidly undergo the Br/Mg exchange. The chelating group complexes *i*PrMgBr prior to the Br/Mg exchange, and this facilitates the exchange by making it an intramolecular reaction. Thus, the dibromide **16** undergoes a chemoselective Br/Mg exchange leading only to the reagent **17** magnesiated *ortho* to the amidine functionality. After the addition to 2-butylacrolein, the allylic alcohol **18** is formed in 68 % yield [21]. A chelating oxygen func-



Scheme 12-4 Br/Mg exchange of functionalized aromatic bromides [20,21].

tional group, such as an ethoxymethoxy group at an *ortho* position, as in the bromide **19**, enhances the Br/Mg exchange rate and allows the preparation of the magnesium derivative **20** at –30 °C within 2 h. In the presence of a catalytic amount of CuCN · 2LiCl (10 mol %), the arylmagnesium reagent **20** can be allylated, leading to the aromatic nitrile **21** in 80 % yield (Scheme 12-4) [21].

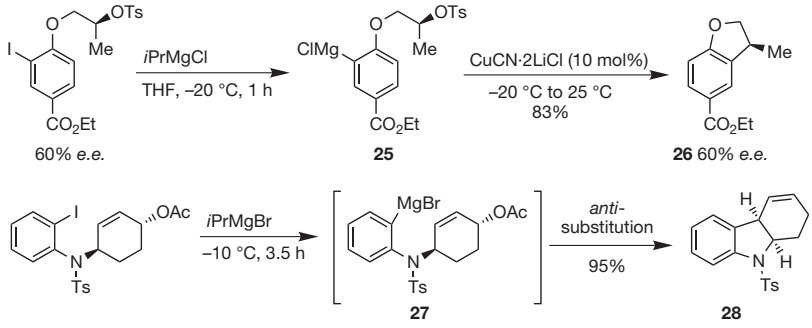
Incorporating electrophilic functional groups in the *ortho*-position to the carbon-magnesium bond allows two sequential bond formations leading to ring closure (Scheme 12-5). Reacting the benzylic chloride **22** with *i*PrMgBr in THF (–30 °C, 1 h) furnishes the corresponding Grignard reagent **23** which reacts at –10 °C with phenyl isocyanate leading to the functionalized *N*-arylphthalimide derivative **24** in 75 % yield (Scheme 12-5) [22].



Scheme 12-5 Reaction of chloromethyl-substituted arylmagnesium species [22].

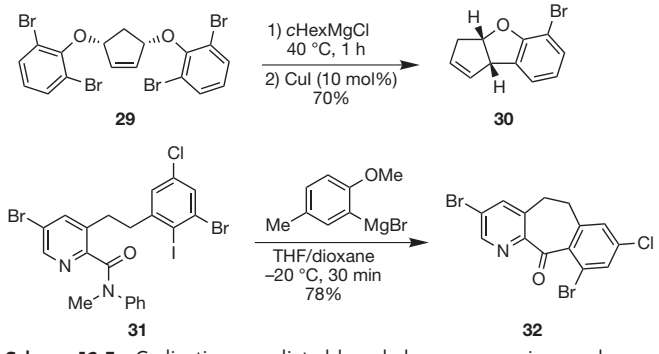
Cyclizations can be achieved with functionalized arylmagnesium reagents such as **25** or **27** bearing a more remote leaving group like a tosylate or an allylic acetate. In both cases, a stereoselective substitution reaction is observed (Scheme 12-6) [23]. The S_N2 ring closure of **25** is catalyzed by CuCN · 2LiCl [18], and proceeds with complete inversion of configuration leading to **26** without eroding the original enantiomeric excess of 60 % *e. e.*. An *anti*-S_N2' substitution is observed with **27**, providing the *cis*-tetrahydrocarbazole **28** in quantitative yield. In this case, the Grignard reagent undergoes the ring closure in the absence of a catalyst [23].

*i*PrMgCl is the magnesium reagent of choice for performing a halogen-magnesium exchange. However, in some cases, the use of more or of less reactive organomagnesium compounds is advantageous. Thus, cyclohexylmagnesium chloride



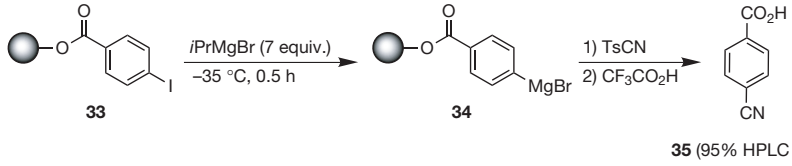
Scheme 12-6 Stereoselective ring closure of arylmagnesium intermediates [23].

performs a Br/Mg exchange at 40 °C on the bis-(2,5-dibromophenyl) 3,5-cyclopent-1-enyl diether **29** with a subsequent copper-catalyzed *syn*-S_N2'-substitution reaction furnishing the benzofuran derivative **30** in 70 % yield [15d]. In the search for a potent farnesyl protein transferase inhibitor synthesis, the polyfunctional amide **31** needed to be converted into the tricyclic product 32. This was achieved via an iodine-magnesium exchange reaction using 5-methyl-2-methoxyphenylmagnesium bromide in a THF:dioxane mixture. The reaction was complete within 30 min at –20 °C, leading to the cyclized product **32** in 78 % yield (Scheme 12-7) [24].



Scheme 12-7 Cyclizations mediated by a halogen-magnesium exchange [24].

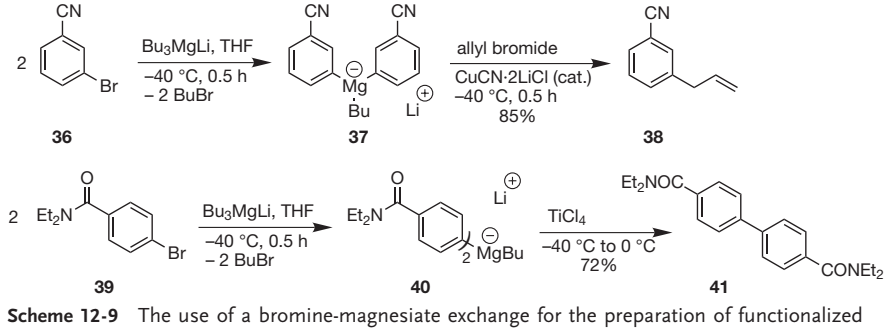
The generation of polyfunctional organomagnesium reagents on a resin can be readily achieved by using an iodine- or bromine-magnesium exchange [8]. Various functionalized iodobenzoic acids have been attached to Wang resins through a carbonyl group. The immobilized ester of type **33**, when treated with an excess of *i*PrMgBr at –30 °C for 15–30 min, generates the corresponding arylmagnesium compound **34**, which can be quenched successfully with a range of electrophiles, in high yields. The resulting adducts are released from the resin by reaction with trifluoroacetic acid, leading for example to the acid **35** (Scheme 12-8). This method has an excellent generality, and the yields and HPLC-purities of products



Scheme 12-8 Immobilized functionalized arylmagnesium reagents for combinatorial synthesis [25,26].

obtained via immobilized organomagnesium reagents prepared by a halogen-magnesium exchange are usually excellent, and allows their application in combinatorial chemistry [25,26].

Oshima et al. have shown that, besides alkylmagnesium halides, lithium trialkylmagnesiates (R_3MgLi) readily undergo iodine- or bromine-magnesium exchange reactions [27,28]. Lithium trialkylmagnesiates are prepared by the reaction of an organolithium (RLi; 2 equiv.) with an alkylmagnesium halide (RMgX; 1 equiv.) in THF at 0 °C. Either 1 equiv. or 0.5 equiv. of the lithium magnesiate (Bu_3MgLi), relative to the aromatic halide (X = I or Br), can be used, showing that two of the three butyl groups undergo the exchange reaction. Thus, the reaction of 3-bromobenzonitrile **36** provides the lithium diarylbutylmagnesiate **37**, which is allylated in the presence of CuCN · 2LiCl [18] leading to the nitrile **38** in 85% yield (Scheme 12-9).



Scheme 12-9 The use of a bromine-magnesiate exchange for the preparation of functionalized arylmagnesium reagents [27–29].

Compared to the halogen-magnesium exchange performed with *i*PrMgBr, lithium trialkylmagnesiates undergo the exchange reaction more readily and are less sensitive to the electron density on the aromatic ring. Importantly, trialkylmagnesiates react more rapidly with aryl bromides than does *i*PrMgCl. However, the resulting lithium triorganomagnesiates of type **37** are more sensitive to the presence of electrophilic functional groups displaying a reactivity, which is intermediate between that of organolithium and organomagnesium species. This higher reactivity limits the number of functional groups usually tolerated with these reagents.

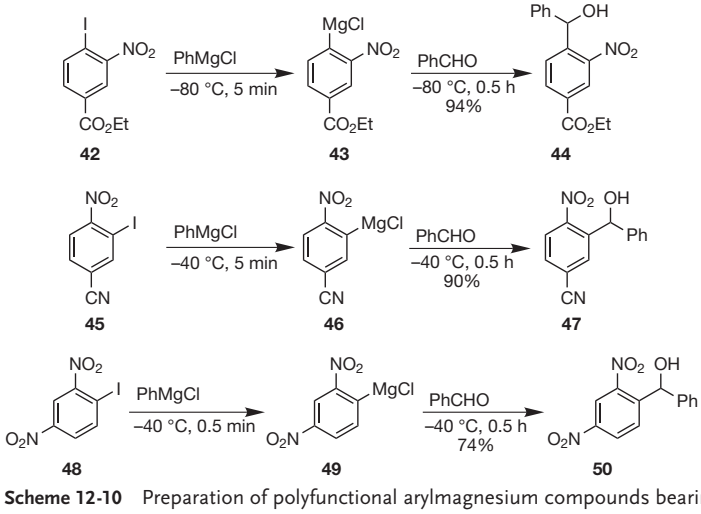
The presence of an extra butyl group in **37** may also compete in reacting with electrophiles. However, Bu_3MgLi is an excellent reagent for preparing functionalized biaryls of type **41**. Thus, lithium tributylmagnesiate induced bromine-magnesium exchange of the amide **39** provides the magnesiate species **40** which undergoes a smooth titanium-mediated homo-coupling reaction leading to the biphenyl derivative **41** in 72 % yield (Scheme 12-9) [29].

12.2.2

Reactions of Nitroarene Derivatives with Organomagnesium Reagents. A Procedure for the N-Arylation of Aryl and Heteroaryl Magnesium Reagents

The reaction of nitroarenes with Grignard reagents was first investigated in pioneering studies conducted by Wieland et al. in 1903 [30]. Several reactions between nitroaromatics and organometallics have also been carefully investigated by Bartoli et al. [31]. Due to the high electrophilicity of the nitro functionality, organometallics can trigger either nucleophilic attacks or electron-transfer reactions. However, it has been shown that *ortho*-lithiated nitrobenzene is stable at very low temperature [32]. Interestingly, the corresponding zinc and copper species obtained by transmetallation with zinc or copper(I) salts, exhibit excellent stability and show, under appropriate reaction conditions, no tendency to undergo electron-transfer reactions [33].

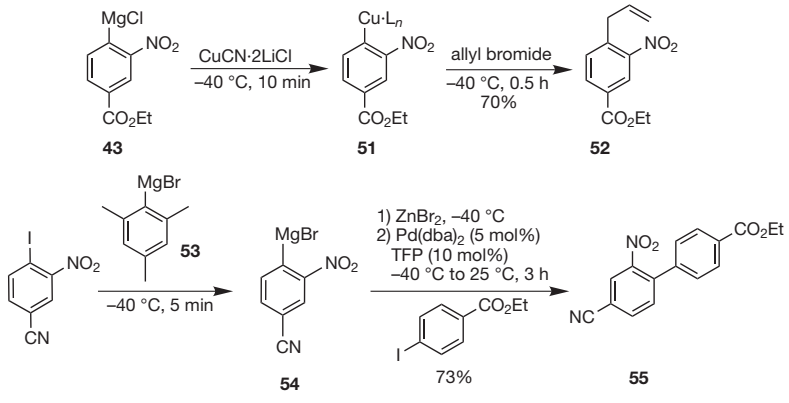
A broad range of functionalized arylmagnesium compounds bearing a nitro function in the *ortho*-position can be prepared by an iodine-magnesium exchange [34]. Thus, the nitro-substituted aryl iodides **42** and **45** undergo a smooth I/Mg exchange with phenylmagnesium chloride within a few minutes at –80 °C or –40 °C, leading to the expected Grignard reagents **43** and **46**. After the addition of benzaldehyde, the benzylic alcohols **44** and **47** are obtained respectively in 94 and 90 %



Scheme 12-10 Preparation of polyfunctional arylmagnesium compounds bearing a nitro function [34].

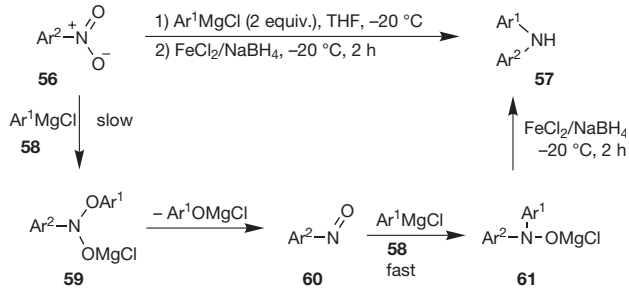
yield [34]. A dinitrophenyl iodide such as **48** can also be smoothly converted to the corresponding magnesium reagent, without the occurrence of electron-transfer reactions.

Transmetallation of the Grignard reagent **43** with CuCN · 2LiCl [18] furnishes the correspondding copper reagent **51** which can be trapped by various electrophiles such as acyl halides or allylic halides, thereby affording products of type **52** (Scheme 12-11) [34]. These results indicate that, contrary to general belief, a one-electron transfer reaction between nitro groups and organometallics (especially organomagnesium compounds) is less favorable than the halogen-magnesium exchange reaction. Palladium(0)-catalyzed Negishi-cross-coupling [35] can be performed by converting the magnesium reagent to the corresponding zinc reagents. The nitro-substituted arylmagnesium species **54** is best prepared using the sterically encumbered mesitylmagnesium bromide **53**. Thus, the reaction of the zinc derivative of **54** with ethyl *p*-iodobenzoate (THF, −40 °C to r.t., 3 h) using [$Pd(dba)_2$] (5 mol %; dba = dibenzylideneacetone) and tri-*o*-furylphosphine (tfp) (10 mol %) [36] provides the biaryl **55** in 73 % yield (Scheme 12-11) [34]. The *ortho*-relationship between the carbon-magnesium bond and the nitro function is essential for a clean and fast exchange reaction. *Meta*- and *para*-substituted iodonitroarenes lead to unselective reactions with addition of the organometallic species to the nitro group. The *o*-nitro-substitution pattern facilitates the I/Mg exchange by precomplexation of the Grignard reagent to the nitro function prior to I/Mg exchange.



Scheme 12-11 Transmetallation of nitro-substituted arylmagnesium compounds [34].

In the absence of sterically encumbered substituents, phenylmagnesium chloride reacts with nitroarenes [30,31]. This reaction proceeds according to the mechanism originally proposed by Köbrich et al. (Scheme 12-12) [32a]. The arylmagnesium reagent (**58**) adds first to the oxygen of the nitroarene (**56**) furnishing the adduct (**59**) which eliminates one equivalent of a magnesium phenolate (Ar^1OMgCl) providing the arylnitroso derivative **60**. The addition of a second equi-

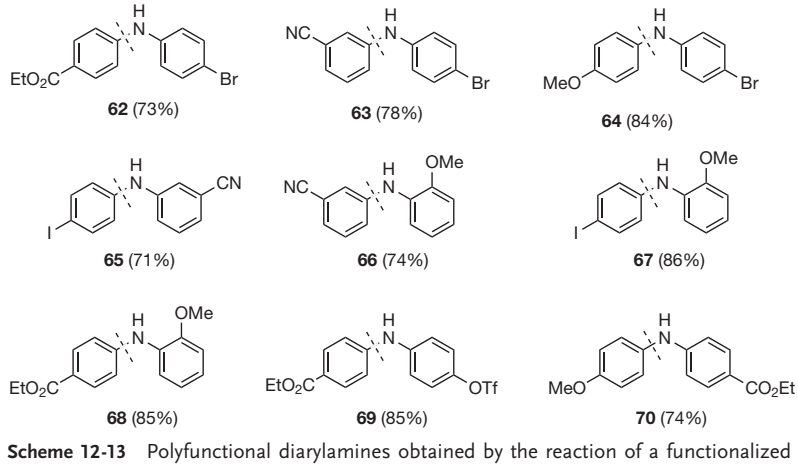


Scheme 12-12 Mechanism of the reaction of arylmagnesium compounds with nitroarenes leading to diarylamines [30–32].

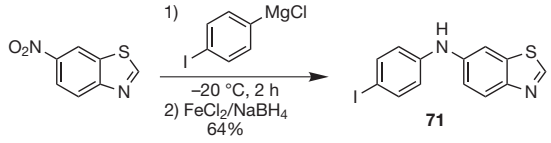
valent of Ar^1MgCl to **60** furnishes the magnesium salt of a diarylhydroxylamine (**61**). Diarylhydroxylamines are air-sensitive and difficult to isolate in pure form.

To make this reaction preparatively interesting, a subsequent reduction with $FeCl_2/NaBH_4$ is required to provide the diarylamine **57** (Scheme 12-12) [37]. The method allows arylation of nitrobenzene derivatives, and therefore is ideal for preparing a range of functionalized diarylamines such as **62–70** (Scheme 12-13) [38]. This reaction complements recently developed palladium(0)-catalyzed amination reactions [39] and related procedures applying copper(I) [40] or nickel(0)catalysis [41]. As indicated above, the mild reaction conditions are compatible with a range of functional groups.

The Grignard reagent can bear electron-withdrawing groups, as for example in **62**, **63**, **66**, **68** and **69**, or electron-donating groups as in **64** and **70**. The same feature is true for the nitroarene. Interestingly, sensitive functions like an iodine, bromine or triflate [38] group can be present in either reaction partner, which is a difficult requirement for transition metal-catalyzed amination procedures



Scheme 12-13 Polyfunctional diarylamines obtained by the reaction of a functionalized arylmagnesium compound with a nitroarene. The dotted lines indicate the new C-N bond formed [38].

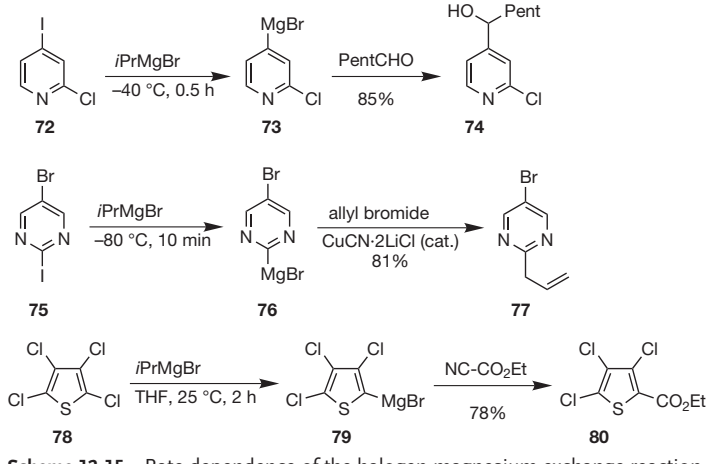


Scheme 12-14 The reaction of arylmagnesium reagents with nitro- and nitrosoarenes [38].

[39–41]. As shown in the mechanistic pathway described in Scheme 12-12, 2 equiv. of the arylmagnesium compound are required to produce amines of type **61**. The reaction of heterocyclic nitroarenes provides functionalized heterocycles such as **71** in 64 % yield (Scheme 12-14) [38].

12.2.3
Preparation of Functionalized Heteroarylmagnesium Reagents

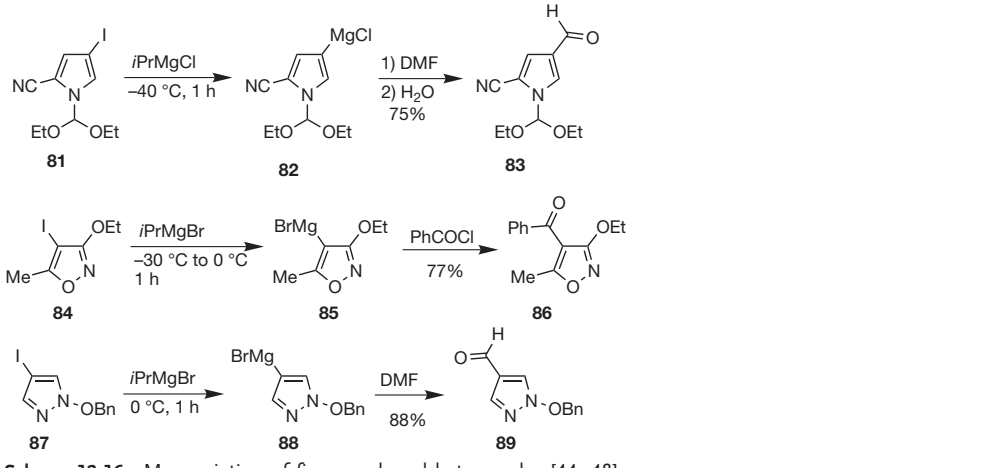
A variety of functionalized heterocyclic Grignard reagents can be prepared using an iodine- or bromine-magnesium exchange reaction [20,42]. The electronic nature of the heterocycle influences the halogen-magnesium exchange rate, and electron-poor heterocycles react faster in the halogen-magnesium exchange reaction. Also, electron-withdrawing substituents strongly accelerate the exchange. 2-Chloro-4-iodopyridine **72** reacts with *i*PrMgBr at –40 °C within 0.5 h [20,43], furnishing selectively the magnesium species **73** which adds to hexanal leading to the alcohol **74** in 85 % yield. If, instead of a pyridine, a pyrimidine derivative such as **75** is used, a selective iodine-magnesium exchange occurs at –80 °C within 10 min, providing the organomagnesium compound **76**. Subsequent reaction of **76** with allyl bromide in the presence of CuCN · 2LiCl [18] gives the 2-allylpyrimidine **77** in 81 % yield [20]. Although a chlorine-magnesium exchange is a very slow reaction, the presence of four chlorine atoms in tetrachlorothiophene



Scheme 12-15 Rate dependence of the halogen-magnesium exchange reaction on the heterocycle nature [20,42,43].

78 accelerates this exchange (25 °C, 2 h), leading to the magnesiated heterocycle **79** that reacts with ethyl cyanoformate to give the thienyl ester **80** in 78 % yield (Scheme 12-15) [20b]. A range of functionalized iodinated heterocycles have been magnesiated using an iodine-magnesium exchange, thereby allowing a rapid synthesis of polyfunctionalized heterocycles [44,45]. Thus, the protected iodopyrrole **81** undergoes an iodine-magnesium exchange at –40 °C within 1 h, leading to the magnesiated pyrrole **82** that reacts with DMF to furnish the formyl derivative **83** in 75 % yield [46]. 4-Iodo-3-ethoxy-5-methylisoxazole (**84**) is converted to the corresponding Grignard reagent **85**, which reacts directly with PhCOCl giving the ketone **86** in 77 % yield [47].

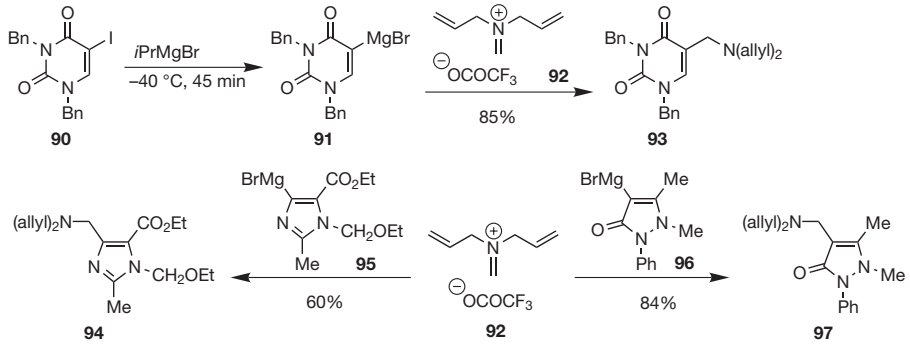
4-Iodopyrazoles such as **87** are also converted at 0 °C into the intermediate organomagnesium reagents like **88**. Subsequent reaction of **88** with DMF furnished the formylated derivative **89** in 88 % yield (Scheme 12-16) [48].



Scheme 12-16 Magnesiation of five-membered heterocycles [44–48].

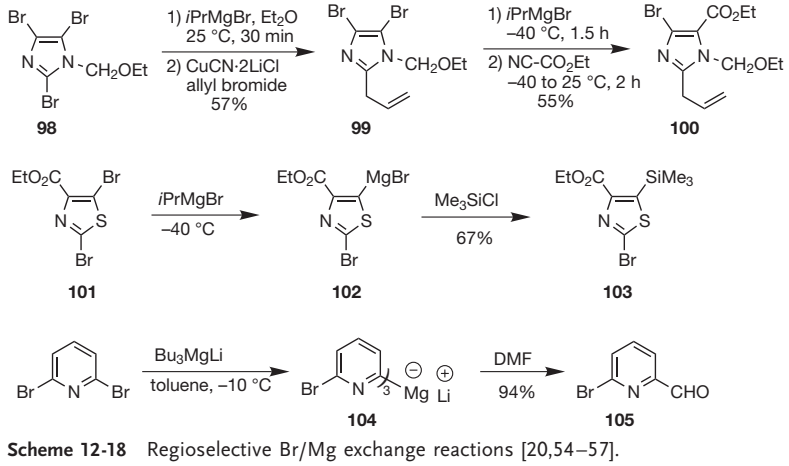
The preparation of functionalized uracils is of interest due mainly to the potential biological activities of this important class of heterocycles [49]. Starting from various protected 5-iodouracils such as **90**, treatment with *i*PrMgBr (–40 °C, 45 min) leads to the formation of the corresponding magnesium compound **91** which can be trapped by various electrophiles such as aldehydes, ketones and acid chlorides, and in the case of the imminium salt **92** [50,51] this trapping leads to the addition product in 85 % yield (Scheme 12-17) [52]. Various magnesiated imidazoles such as **95** or antipyrines such as **96** react with the imminium reagent **92**, thereby affording the aminomethylated products **94** and **97** in satisfactory yield [53].

Polyhalogenated substrates usually undergo a selective, single halogen-magnesium exchange (Scheme 12-18). After a first magnesiation, the electron density of the heterocycle increases to such an extent that a subsequent second exchange



Scheme 12-17 Aminomethylation of heterocyclic magnesium reagents [52,53].

is very slow. This behavior is very general, with a high chemoselectivity for the Br/Mg exchange being observed. Starting from the tribromoimidazole **98** [54], the first exchange reaction occurs at position 2 leading, after a copper-catalyzed allylation, to the 4,5-dibromoimidazole **99**. Treatment of **99** with a second equivalent of *i*PrMgBr occurs now only in position 5, since the intermediate Grignard reagent is stabilized by chelation. After quenching with ethyl cyanoformate (–40 to 25 °C, 2 h) the corresponding 4-bromo-5-carbethoxyimidazole **100** was obtained in 55 % yield (Scheme 12-18) [20]. The presence of chelating groups strongly influences the regioselectivity of the Br/Mg exchange. Thus, the dibromothiazole **101** undergoes a selective exchange at position 3 due to the chelating effect of the carbethoxy group, leaving the bromide in position 2 unaffected. The reaction of the intermediate Grignard reagent **102** with Me_3SiCl provides the expected product **103** in 67 % yield (Scheme 12-18) [20b].

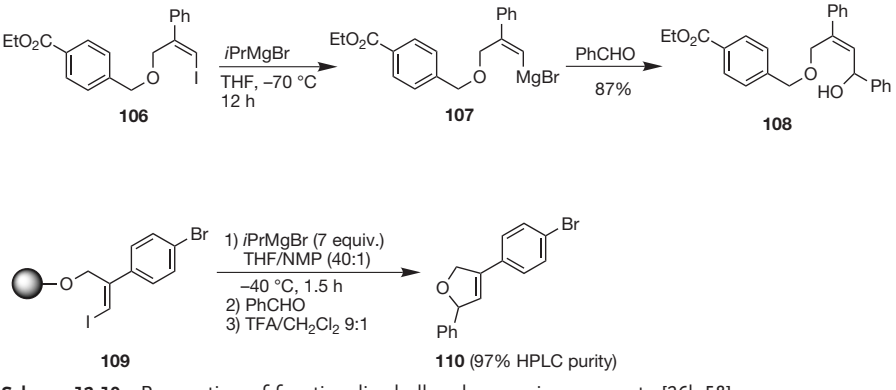


Scheme 12-18 Regioselective Br/Mg exchange reactions [20,54–57].

This selectivity has been used to convert 4,5-diiodoimidazoles to the corresponding 4-iodoimidazole using an I/Mg exchange followed by a protonation [55]. Similarly, 2,5-dibromopyridine has been selectively exchanged with *i*PrMgX to generate the mono-magnesium species [20,56]. The use of the magnesiate species Bu_3MgLi proves to be advantageous for performing this exchange reaction as it leads to the ate complex **104** which reacts rapidly with DMF, furnishing the aldehyde **105** in 94 % yield [57]. The use of magnesiate reagents for preparing various pyridylmagnesium species generally requires 1 equiv. of $BuMe_2MgLi$ [28].

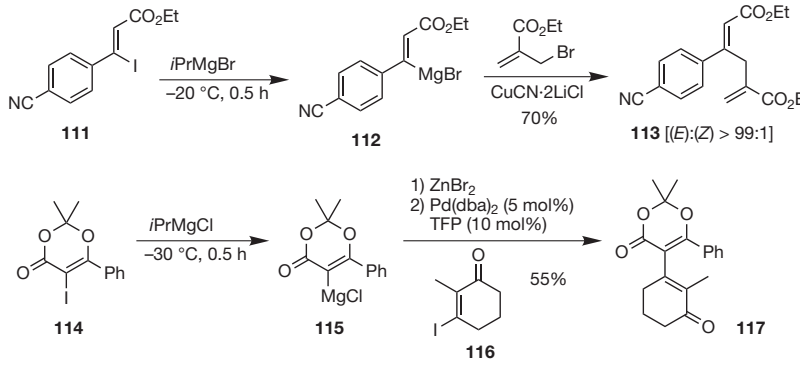
12.2.4
Preparation of Functionalized Alkenylmagnesium Reagents

Alkenyl iodides react with *i*PrMgBr or $i Pr_2Mg$ leading to an I/Mg exchange. However, this exchange reaction is slower than that with aryl iodides. Thus, (*E*)-iodooctene only undergoes the exchange reaction at 25 °C, and the reaction requires 18 h, thereby precluding the presence of functionality at a remote position in iodoalkenes [58]. However, the presence of a chelating heteroatom or of an electron-withdrawing functionality directly linked to the double bond greatly enhances its propensity for undergoing the iodine-magnesium exchange. Thus, the functionalized (*Z*)-allylic ether **106** reacts at –78 °C with *i*PrMgBr, providing the corresponding alkenylmagnesium reagent **107**. Allylation of **107** with PhCHO gives the (*Z*)-alcohol **108** in 87 % yield (Scheme 12-19) [58]. Similarly, the resin-attached allylic ether **109** reacts smoothly with *i*PrMgBr in THF:NMP (40:1) within 1.5 h at –40 °C, leading to the desired Grignard reagent. In the absence of NMP, the exchange reaction occurs considerably more slowly. Quenching with benzaldehyde, and cleavage from the resin with TFA in CH_2Cl_2, provides the dihydrofuran **110** in 97 % purity [26b,58].



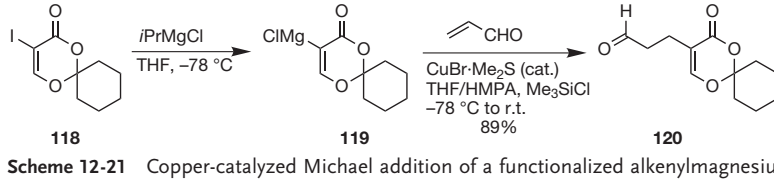
Scheme 12-19 Preparation of functionalized alkenylmagnesium reagents [26b,58].

The presence of an electron-withdrawing group attached to the double bond considerably facilitates the iodine-magnesium exchange reaction. A range of *β*-iodoenoates such as **111** are converted to the corresponding Grignard reagent **112**



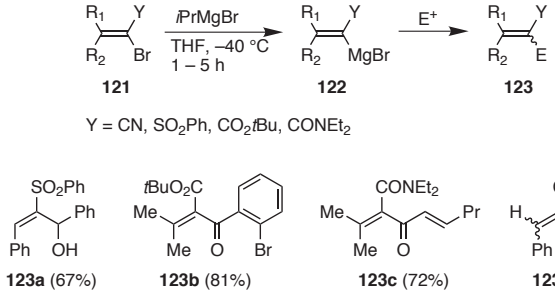
Scheme 12-20 Preparation of carbonyl-containing alkenylmagnesium compounds [59–62].

(–20 °C, 0.5 h) leading, after the reaction with an allylic bromide in the presence of CuCN · 2LiCl, to the (*E*)-enoate **113** and demonstrating a high configurational stability of the intermediate alkenylmagnesium species **112** [59]. Whereas alkenylmagnesium compounds bearing a *β*-leaving group such as a halide, alkoxide are elusive reagents [60], the incorporation of the leaving group into a ring system leads to more robust reagents. The reaction of 5-iodo-1,3-dioxin-4-one (**114**) with *i*PrMgCl at –30 °C furnished the desired Grignard reagent **115**, which proved to have a half-life of ca. 2 h at –30 °C. After transmetallation with $ZnBr_2$, **115** undergoes a smooth Negishi cross-coupling with 2-methyl-3-iodo-1-cyclohexenone (**116**), leading to the enone **117** in 55 % yield (Scheme 12-20) [61, 62]. The preparation of related carbonyl-containing alkenylmagnesium reagents has been reported by Hiemstra in the course of synthetic studies toward the synthesis of Solanoeclepin A [63, 64]. The treatment of the cyclic alkenyl iodide **118** with *i*PrMgCl in THF at –78 °C furnished the desired Grignard reagent **119**, which reacted with acrolein in the presence of catalytic CuBr · Me_2S in THF:HMPA in the presence of TMSCl to furnish the Michael adduct **120** in 89 % yield (Scheme 12-21) [64].



Scheme 12-21 Copper-catalyzed Michael addition of a functionalized alkenylmagnesium reagent [64].

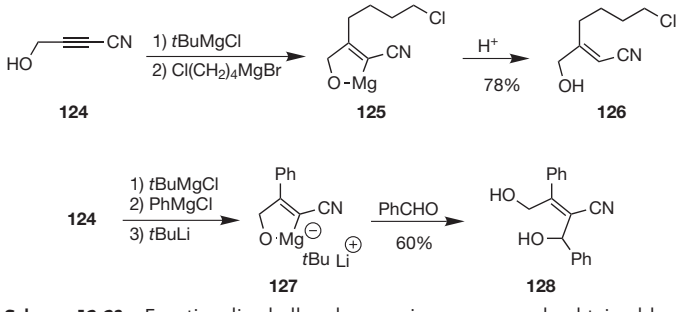
If the sp^2 carbon atom bears an electron-withdrawing group and a bromine atom, a very rapid Br/Mg exchange reaction is usually observed (–40 °C, 15 min to 1 h). This behavior is very general for alkenyl bromides of type **121** (Y = CN, SO_2Ph, CO_2tBu and $CONEt_2$) that react readily with *i*PrMgBr to afford Grignard reagents of type **122**. Reaction of **122** with electrophiles is not always stereoselective [65], producing a mixture of diastereoisomers of type **123**, although



Scheme 12-22 Functionalized alkenylmagnesium compounds bearing an electron-withdrawing group in α-position [65–67].

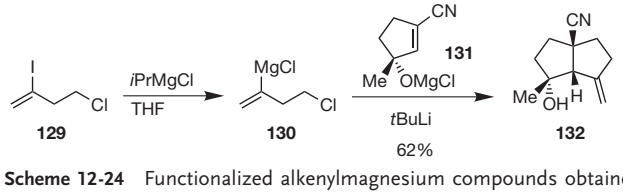
this method provides **123a-d** an efficient synthesis of tri- and tetrasubstituted alkenes (Scheme 12-22) [66,67].

Remarkably, the conjugate addition of various Grignard reagents to the alkynyl cyanide **124** generates the stabilized and unreactive cyclic magnesium chelate **125** which, after protonation, furnishes the polyfunctionalized nitrile **126**. Fleming has shown that a more reactive cyclic organomagnesium reagent of type **125** is obtained by generating an intermediate magnesiate species **127**. This magnesiate species now reacts with PhCHO, leading to the allylic diol **128**, with complete retention of the double bond configuration in 60 % yield (Scheme 12-23) [68].



Scheme 12-23 Functionalized alkenylmagnesium compounds obtained by carbomagnesiation [68].

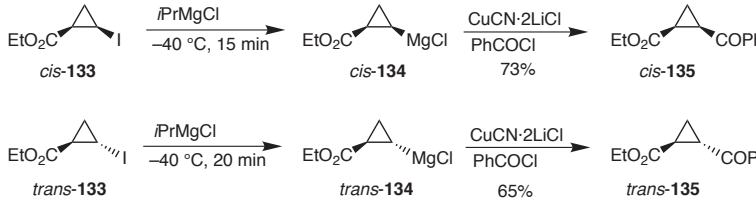
The I/Mg exchange on 2-iodo-4-chloro-1-butene **129** provides a functionalized alkenylmagnesium species **130** which reacts with high diastereoselectivity with the magnesiated unsaturated nitrile **131**, providing the interesting bicyclic product **132** in 62 % yield (Scheme 12-24) [68].



Scheme 12-24 Functionalized alkenylmagnesium compounds obtained by I/Mg exchange [68].

12.2.5
Preparation of Functionalized Alkylmagnesium Reagents

Although the preparation of polyfunctional alkylmagnesium reagents may be envisioned, only a few examples have been reported [69]. The difficulties arise from the higher reactivity of the resulting alkylmagnesium compounds compared to alkenyl-, aryl- or heteroarylmagnesium species. The rate of the iodine-magnesium exchange also appears to be slower. However, a range of polyfunctional cyclopropylmagnesium compounds can be prepared using the iodine-magnesium exchange [70]. Thus, ethyl *cis*-2-iodocyclopropane carboxylate (*cis*-**133**) and the corresponding *trans*-isomer (*trans*-**133**) are readily converted to the corresponding Grignard reagents (*cis*-**134** and *trans*-**134**). The formation of the magnesium organometallics **134** is stereoselective, and their reaction with benzoyl chloride furnishes, after a transmetallation with CuCN · 2LiCl [18], the expected *cis*- and *trans*-1,2-ketoester **135** with retention of configuration [71,72] in 73 and 65 % yield, respectively (Scheme 12-25) [70].

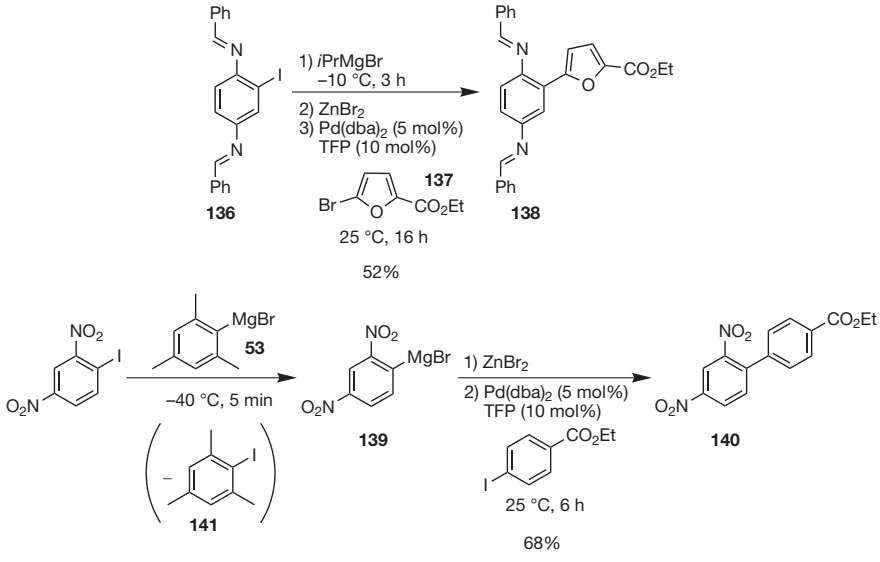


Scheme 12-25 Stereoselective preparation of functionalized cyclopropylmagnesium compounds [70].

12.2.6
Application of Functionalized Magnesium Reagents in Cross-Coupling Reactions

The availability of functionalized Grignard reagents considerably enhances the scope of these reagents for performing cross-coupling reactions. Especially interesting are arylmagnesium reagents bearing amino groups [17,73]. A range of 2-arylated-1,4-phenylenediamines of type **137** can be prepared starting from the bisimine **136**, with the I/Mg exchange being complete within 3 h at –10 °C. After transmetallation to the zinc reagent with $ZnBr_2$, bis(dibenzylideneacetone)palladium ($[Pd(dba)_2]$; 5 mol %), tri-*o*-furylphosphane (TFP; 10 mol %) and 5-bromo-2-carbethoxyfuran (**137**) are added. The cross-coupling reaction is usually complete after 16 h at 25 °C, leading to the 1,4-phenylenediamine **138** in 52 % yield (Scheme 12-26) [73].

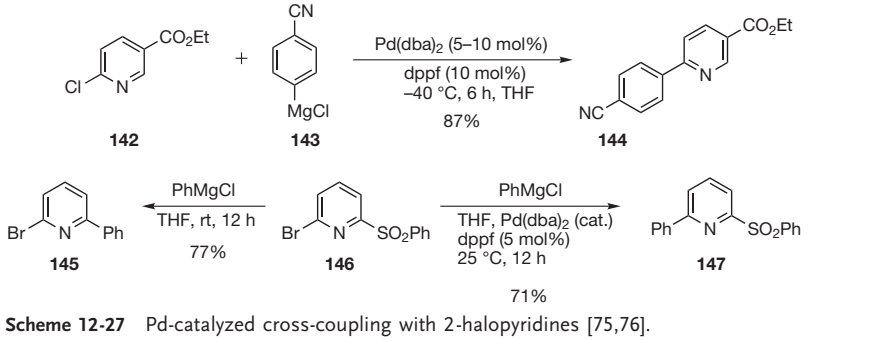
Nitro-group-containing Grignard reagents such as **139** prepared by an iodine-magnesium [34] exchange in THF with mesitylmagnesium bromide **54**, smoothly undergo Negishi cross-coupling reactions leading to polyfunctionalized nitroarenes like **140**. The mesityl iodide **141** generated in the iodine-magnesium exchange re-



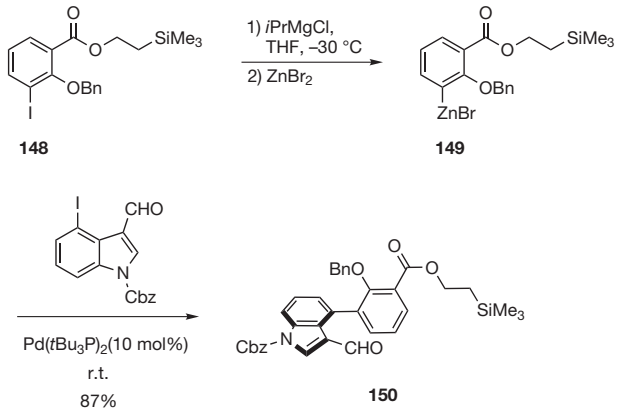
Scheme 12-26 Cross-coupling with nitrogen-functionalized Grignard reagents [73,74].

action is unreactive under the conditions used in these cross-couplings (Scheme 12-26) [74]. Functionalized Grignard reagents such as **143** directly undergo cross-coupling reactions with various 2-halopyridines of type **142** in the presence of Pd(0) catalysts. These remarkably rapid cross-coupling reactions require the presence of a Pd(0) complex, and therefore are not direct addition-elimination reactions of the Grignard reagent. In the absence of Pd(0), no reaction is observed. The corresponding arylzinc reagents also react more slowly. These reactions may proceed via the formation of an organopalladate [75] of the type $ArPdL_2^{(-)}\ MgX^{(+)}$, which would undergo a fast addition-elimination reaction with the 2-chloropyridine derivative **142**, leading to the functionalized pyridine **144** in 87 % yield (Scheme 12-27) [76]. This reaction can be extended to several haloquinolines [77].

Quéguiner et al. found an interesting selectivity [76] in the cross-coupling of bromosulfone **146**. Thus, PhMgCl reacts with the disubstituted pyridine **146** by direct



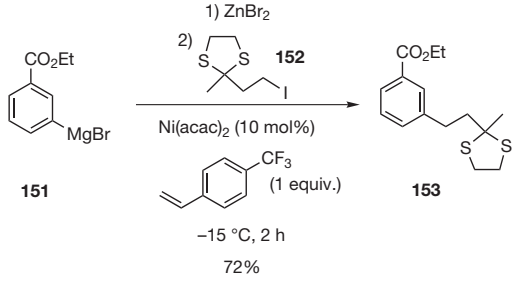
Scheme 12-27 Pd-catalyzed cross-coupling with 2-halopyridines [75,76].



Scheme 12-28 Pd-catalyzed cross-coupling of a highly functionalized arylzinc reagent [78].

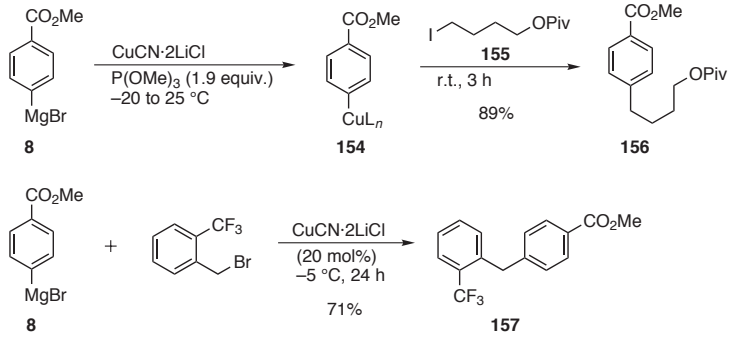
substitution of the phenylsulfonyl group, leading to the bromopyridine **145** in 77 % yield (Scheme 12-27). However, under palladium catalysis the preparation of highly functionalized biaryls of type **147** and **150** is possible [78]. Thus, the polyfunctional zinc reagent **149**, obtained from the iodide **148** by a I/Mg exchange and subsequent transmetallation, reacts readily in the presence of the palladium catalyst [Pd(tBu$_3$P)$_2$] [79] under mild conditions furnishing the biaryl **150** in 87 % yield (Scheme 12-28).

The cross-coupling of functionalized arylzinc compounds, obtained by transmetallation of the corresponding magnesium reagents, can be accomplished by using Ni(acac)$_2$ (10 mol %) as the catalyst in the presence of 4-trifluoromethylstyrene or 4-fluorostyrene as promoter of the reductive elimination step. Under these conditions, the Grignard reagent **151** reacts with the iodothioacetal **152**, providing the desired cross-coupling product **153** in 72 % yield (Scheme 12-29) [80].



Scheme 12-29 Ni-catalyzed cross-coupling between functionalized Grignard reagents and functionalized alkyl iodides [80].

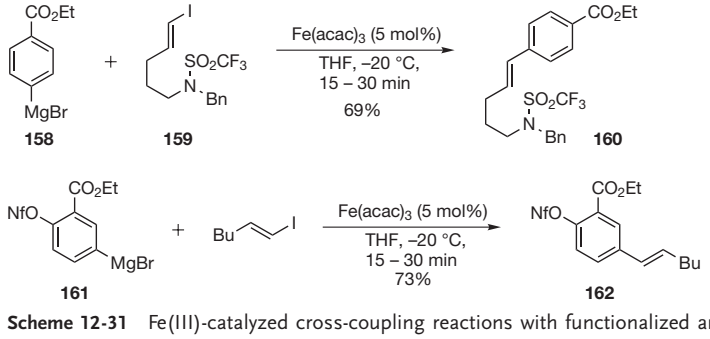
An alternative to this Ni-catalyzed reaction is the corresponding copper-mediated reaction. In this case, the functionalized arylmagnesium species is transmetallated to the corresponding arylcopper reagent with CuCN · 2LiCl [18] and trimethylphosphite (1.9 equiv.) (Scheme 12-30). This last additive confers an excellent stability



Scheme 12-30 Cu-mediated cross-coupling reactions of functionalized arylmagnesium compounds [80,81].

to the copper reagent, which can be handled at room temperature under these conditions. Thus, the reaction of the magnesium species **8** with CuCN · 2LiCl [18] and $P(OMe)_3$ furnishes the stable arylcopper **154**, which undergoes a smooth cross-coupling reaction with functionalized alkyl iodides such as the iodopivalate **155** leading to the substitution product **156** in 89 % yield [80].

Interestingly, reactive benzyl halides undergo the cross-coupling reaction in the presence of a catalytic amount of CuCN · 2LiCl [18] leading to diphenylmethane derivatives such as **157** (Scheme 12-30) [81]. Due to the low cost and low toxicity of iron(III) salts, these complexes have been used with success in several cross-coupling procedures [82–84]. Functionalized arylmagnesium species undergo efficient cross-coupling reactions with polyfunctionalized alkenyl iodides such as **159** in the presence of $Fe(acac)_3$ (5 mol %), leading to the styrene derivatives of type **160** in 69 % yield. Remarkably, the cross-coupling reaction is complete at –20 °C within 15–30 min (Scheme 12-31) [85]. The arylmagnesium compound can bear various electrophilic functions like a nonaflate [86] (see Grignard reagent **161**). The iron(III)-catalyzed cross-coupling reaction still proceeds with a good yield, leading to the highly functionalized nonaflate **162** in 73 % yield (Scheme 12-31) [85].



Scheme 12-31 Fe(III)-catalyzed cross-coupling reactions with functionalized arylmagnesium species [85].

12.3 Conclusions

The halogen-magnesium exchange reaction has opened new perspectives in organic synthesis. Many more functional groups than previously thought, are compatible with magnesium organometallics. The mild conditions required for performing a halogen-magnesium exchange were the key for assuring a high functional group tolerance. This again places Grignard reagents in a central position for organic synthesis, and opens fascinating new perspectives [87]. Cross-coupling reactions with functionalized organomagnesium reagents make possible the preparation of a range of new polyfunctional organic molecules.

12.4 Experimental Procedures

12.4.1 Ethyl 8-allyl-4-methyl-2-{[(trifluoromethyl)sulfonyl]oxy}-6-quinolinecarboxylate (12) (Scheme 12-3)

To a mixture of the iodoquinoline derivative **10** (3.42 g, 7.0 mmol) and tetradecane (3 drops, internal standard) in THF (7 mL) at −30 °C, *i*PrMgCl (0.94 *M*, 8.2 mL, 7.7 mmol) was added within 10 min at −30 °C. Following the addition of CuCN · 2LiCl (1.0 *M*, 7.7 mL, 7.7 mmol), allyl bromide (2.54 g, 21.0 mmol) was added. The cooling bath was removed and the reaction mixture was stirred at r. t.. The reaction was complete after 1 h, and was quenched with aqueous saturated NH_4Cl solution (5 mL). The mixture was poured into half-saturated NH_4Cl solution and extracted with EtOAc (3 × 100 mL), the combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), and purified by flash chromatography (pentane/ethyl acetate = 93:7) yielded **12** (2.16 g, 77 %) as an orange solid.

12.4.2 Ethyl 4′-cyano-2′-nitro[1,1′-biphenyl]-4-carboxylate (55) (Scheme 12-11)

A dry and argon-flushed 25-mL flask, equipped with a magnetic stirring bar and a septum, was charged with 4-iodo-3-nitrobenzonitrile (411 mg, 1.5 mmol). Anhydrous THF (6 mL) was added, and the mixture cooled to −40 °C. Mesitylmagnesium bromide **53** (1.3 mL, 1.7 mmol, 0.7 *M* in THF) was added dropwise. The I/Mg exchange was complete after 10 min (checked by GC analysis of reaction aliquots), and $ZnBr_2$ (1.7 mL, 1.7 mmol, 1 *M* in THF) was added to the magnesiated benzonitrile **54**. Another dry, two-necked flask equipped with a magnetic stirring bar and a septum was charged with bis(dibenzylideneacetone)palladium(0) ([$Pd(dba)_2$]) (43.5 mg, 5 mol %) and tri-*o*-furylphosphine (TFP) (37.0 mg, 10 mol %), followed by THF (2 mL). The initial red color disappeared after 2 min, leading to a yellow solution, and ethyl-4-iodobenzoate (621 mg, 1.5 mmol)

was added. This solution was added via a cannula after 10 min of stirring the reaction mixture at –40 °C, and the cooling bath was removed. The reaction mixture was stirred for 3 h at room temperature, treated with ethanol (2 mL) and poured into water (25 mL). The aqueous phase was extracted with ethyl acetate (3 × 40 mL), the collected organic phases were washed with brine (30 mL), dried (Na_2SO_4), and vacuum-concentrated. Purification by flash chromatography (pentane/ethyl acetate = 6:1) yielded ethyl 4′-cyano-2′-nitro[1,1′-biphenyl]-4-carboxylate (**55**) as a pale yellow solid (325 mg, 73 %).

12.4.3

Preparation of *N*-(4-iodophenyl)-1,3-benzothiazol-5-amine (71) (Scheme 12-14)

In a dry and argon-flushed 25-mL flask, equipped with a magnetic stirring bar and a septum, 1,4-diiodobenzene (1.14 g, 3.45 mmol) was dissolved in anhydrous THF (8 mL), cooled to –20 °C and *i*PrMgCl (4.2 mL, 3.6 mmol, 0.85 *M* in THF) was added dropwise. The I/Mg-exchange was complete after 30 min (indicated by GC analysis of reaction aliquots) and 6-nitro-benzothiazole (270 mg, 1.5 mmol) was added. After 2 h of stirring at –20 °C, the reaction was quenched with ethanol (1 mL), and $FeCl_2$ (378 mg, 3 mmol) and $NaBH_4$ (57 mg, 1.5 mmol) were added. After 2 h stirring at r. t., the reaction mixture was poured into water (25 mL). The aqueous phase was extracted with diethyl ether (3 × 40 mL). The organic fractions were washed with 2 *M* NaOH, brine (30 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography (pentane/ethyl acetate = 2:1) yielded the amine **71** as a yellow solid (337 mg, 64 %).

12.4.4

6-Bromo-2-formylpyridine (102) (Scheme 12-18)

Anhydrous toluene (45.3 kg) and *n*BuLi (1.63 *M* in hexane, 1.23 kg, 2.97 mol) were charged to a 800-L reactor and cooled to –10 °C. *n*BuMgCl (1.95 *M* in THF, 26.9 kg, 54.6 mol) was added over 30 min, while maintaining the temperature at –10 to 0 °C, and the mixture was stirred at –10 °C for 30 min. A solution of 2,6-dibromopyridine (34.92 kg, 144.8 mol) in toluene (30.2 kg), was added dropwise over a period of 1 h while keeping the temperature of the mixture below –5 °C. The resulting suspension was stirred at –10 °C for 2.5 h. The mixture was transferred via a cannula to a cooled solution (–10 °C) of DMF (14.0 kg, 188.9 mol) in toluene (43.2 kg) while maintaining the temperature below 10 °C. The solution was allowed to stand at –5 to –10 °C for 30 min and then transferred via a Teflon cannula to an aqueous citric acid solution (56.6 kg in 105 L water) while maintaining the temperature of the mixture below 20 °C. After stirring the mixture below 20 °C for 10 min, the organic layer was separated and washed with water (105 L). The organic layer was concentrated to ca. 130 L, *in vacuo*, and then used in the next step. HPLC analysis showed that the desired product **102** was obtained in 91 % assay yield (25.0 kg).

12.4.5

2,2-Dimethyl-5-(2-methyl-3-oxo-cyclohex-1-enyl)-6-phenyl-[1, 3]dioxin-4-one (116) (Scheme 12-20)

A solution of *i*PrMgCl (0.37 mmol) in THF (1.62 *M*, 0.23 mL) was added dropwise over 5 min to a solution of **114** (113 mg, 0.34 mmol) in THF (3 mL) at –30 °C under argon. The resulting solution was then stirred for 30 min, and $ZnBr_2$ (0.41 mmol) in THF (1.2 *M*, 0.34 mL) was added. The reaction mixture was allowed to warm to r. t.. Another dry, three-necked flask equipped with an argon inlet, septum and thermometer was charged with $[Pd(dba)_2]$ (8.1 mg, 5 mol %) and TFP (6.6 mg, 10 mol %), followed by THF (1 mL). The initial red color disappeared after 2 min, leading to a yellow solution. **117** (66.1 mg, 0.28 mmol) was added, followed by the organozinc compound. The reaction mixture was heated under reflux for 12 h, worked-up by pouring it into aqueous saturated NaCl solution (10 mL), and then extracted with ether. The crude residue was purified by column chromatography on silica (pentane/ether = 3:1) to give **116** (48 mg, 55 %).

12.4.6

5-[2,5-bis[[(*E*)-phenylmethylidene]amino]phenyl]-2-furanecarboxylic acid Ethyl Ester (138) (Scheme 12-26)

A dry and argon-flushed 10-mL flask, equipped with a magnetic stirring bar, was charged with **136** (410 mg, 1 mmol) in anhydrous THF (1 mL) and cooled to –10 °C. *i*PrMgBr (3.3 mL, 0.6 *M* in THF, 2 mmol) was added slowly. After 1 h, the exchange was complete (checked by TLC analysis) and $ZnBr_2$ (0.8 mL, 1.5 *M* in THF, 1.1 mmol) was added. The reaction mixture was allowed to warm to r. t.. Another dry and argon-flushed 10-mL Schlenk flask, equipped with a magnetic stirring bar, was charged with $[Pd(dba)_2]$ (29 mg, 0.05 mmol) and TFP (23 mg, 0.10 mmol) in anhydrous THF (1 mL). After formation of the active catalyst, ethyl 5-iodo-2-furoate **137** (153 mg, 0.7 mmol) was added, followed by the zinc reagent. The reaction mixture was stirred at r. t. for 16 h, then quenched with aqueous saturated NH_4Cl solution (2 mL), poured into water (50 mL), and extracted with ether (3 × 40 mL). The combined organic fractions were washed with brine (70 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (pentane/ether/TEA = 20:1:2) to yield **138** as a yellow oil (153 mg, 52 %).

12.4.7

Ethyl-6-(4-cyanophenyl)nicotinate (144) (Scheme 12-27)

*i*PrMgCl (0.6 mL, 2 *M* in ether, 1.2 mmol) was added to a solution of 4-iodobenzonitrile (275 mg, 1.2 mmol) in THF (4 mL) at –40 °C under argon, and the mixture was stirred for 40 min, leading to the functionalized arylmagnesium chloride **143**. The resulting mixture was transferred into a solution of **142** (186 mg, 1 mmol), bis(dibenzylideneacetone)palladium(0) ($[Pd(dba)_2]$) (29 mg, 0.05 mmol, 5 mol %),

and 1,1′-bis(diphenylphosphino)ferrocene (dppf) (28 mg, 0.05 mmol, 5 mol %) in THF (2 mL) at –40 °C. Stirring was continued at this temperature for 6 h, followed by quenching using aqueous saturated NH_4Cl solution (5 mL). Extraction with diethyl ether, drying over $MgSO_4$ and solvent removal afforded a crude solid, which was purified by flash chromatography on silica (elution with CH_2Cl_2) affording the pure product **144** as a colorless solid (219 mg, 87 %).

12.4.8
Phenyl 6-phenylpyridine-2-sulfone (147) (Scheme 12-27)

Bis(dibenzylideneacetone)palladium(0) ($[Pd(dba)_2]$) (29 mg, 0.05 mmol), 1,1′-bis(diphenylphosphino)ferrocene (dppf) (27 mg, 0.050 mmol) and, 10 min later, the bromo-compound **146** (298 mg, 1.0 mmol) were added to anhydrous THF (3 mL). After stirring for 30 min at r. t., a solution of PhMgCl (1.2 mmol) in THF (0.60 mL) was added dropwise at –40 °C. After stirring for 12 h at r. t., the reaction was quenched with an aqueous saturated NH_4Cl solution (5 mL). Extraction with diethyl ether, drying over $MgSO_4$, and solvent removal afforded the crude product which was purified by column chromatography (CH_2Cl_2/Et_2O = 90:10) affording **147** as a solid (209 mg, 71 %).

12.4.9
Ethyl 3-[(2-methyl-1,3-dithiolan-2-yl)ethyl]benzoate (153) (Scheme 12-29)

A three-necked flask equipped with a thermometer, a gas inlet and an addition funnel was charged with ethyl 3-iodobenzoate (3.45 g, 12.5 mmol) in anhydrous THF (20 mL). The reaction mixture was cooled to –40 °C and *i*PrMgBr (1 *M* in THF, 12.9 mL) was added within 10 min. After 0.5 h, the formation of the arylmagnesium reagent was complete (as checked by iodolysis and hydrolysis of reaction aliquots). The reaction mixture was cooled to –78 °C, a THF solution of $ZnBr_2$ (2.81 g, 6.25 mL, 12.5 mmol) was added, and the reaction mixture was allowed to warm to r. t.. The milky suspension was treated with 1,4-dioxane and stirred for 2 h, leading to a heavy precipitate which was filtered under argon. The filtrate was concentrated to give a 1.2 *M* solution. A second two-necked flask equipped with an argon inlet and a septum was charged with $Ni(acac)_2$ (128 mg, 0.5 mmol, 10 mol %), 4-(trifluoromethyl)styrene (5 mmol, 0.75 mL) and **152** (1.37 g, 5 mmol) and cooled to –78 °C. The solution of the arylzinc reagent was added, and the reaction mixture was warmed to –15 °C and stirred for 5 h. The reaction mixture was worked-up as usual and afforded, after flash-chromatographical purification (hexane/ether), the desired product **153** (1.067 g, 72 %).

12.4.10
Methyl 4-(4-pivaloyloxybutyl)benzoate (156) (Scheme 12-30)

Methyl 4-iodobenzoate (655 mg, 2.5 mmol) was dissolved in anhydrous THF (2.5 mL) under argon, cooled to –25 °C, and *i*PrMgBr (5.1 mL, 0.54 *M* in THF, 2.75 mmol) was added slowly over 5 min, keeping the temperature below –20 °C. The reaction mixture was stirred for 30 min at –20 °C until exchange was complete (as indicated by TLC or GC). A solution of CuCN · 2LiCl (2.75 mL, 1 *M* in THF, 2.75 mmol) was then added, again keeping the temperature below −20 °C, and on completion of the addition the reaction mixture was warmed up to r. t. within 30 min. Trimethyl phosphite (596 mg, 4.8 mmol) was added, and the clear solution was stirred for an additional 5 min. The iodide **155** was then added (568 mg, 2 mmol, 0.8 equiv.) using a syringe, and the reaction mixture stirred at this temperature until all the alkyl iodide was consumed (as indicated by TLC or GC). The reaction was quenched with aqueous saturated NH_4Cl solution (2 mL) and poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (3 × 50 mL), and the combined organic phases were washed with water (50 mL) and dried over $MgSO_4$. After removal of the solvents *in vacuo*, the residue was purified by flash column chromatography (CH_2Cl_2/pentane = 2:1). Product **156** was obtained as a pale yellow oil (520 mg, 89 %).

12.4.11
4-[(1*E*)-5-[(phenylmethyl)[(trifluoromethyl)sulfonyl]amino]-1-pentenyl] benzoic acid ethyl ester (160) (Scheme 12-31)

Ethyl 4-iodobenzoate (384 mg, 1.4 mmol) was placed in a dry argon-flushed 50-mL flask equipped with a rubber septum and magnetic stirring bar. Anhydrous THF (3.0 mL) was added, and the solution was cooled to –20 °C. *i*PrMgBr (6.0 mL, 0.55 *M* in THF, 3.3 mmol) was then added slowly and the reaction mixture was stirred at this temperature until the exchange reaction was complete (checked by TLC). The resulting suspension was then transferred dropwise via a cannula into another dry argon-flushed Schlenk flask containing a solution of iron(III) acetylacetonate (18 mg, 5.1 μmol) and iodosulfonamide **159** (433 mg, 1.0 mmol) in anhydrous THF (2.0 mL) with stirring at –20 °C. After the reaction was complete (checked by TLC and GC), methanol (3 mL) and water (30 mL) were added and the reaction mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (pentane/ethyl acetate = 98:2) providing product **160** (314 mg, 0.69 mmol; 69 %) as a colorless oil.

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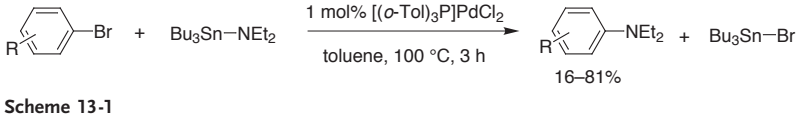
13
Palladium-Catalyzed Aromatic Carbon-Nitrogen Bond Formation

Lei Jiang and Stephen L. Buchwald

13.1
Introduction

Aromatic amines are important in a variety of fields both for their function [1], and also to serve as intermediates for the preparation of other important molecules, particularly heterocycles [2]. Many useful techniques exist for the preparation of aniline derivatives. A partial list includes electrophilic methods such as nitration followed by reduction [3], nucleophilic aromatic substitution [4], benzyne processes [5], and Ullmann-type methods [6]. The importance of these processes cannot be overestimated. Nonetheless, it was desirable to have a general method that could be employed to convert a single substrate directly into a range of aromatic amines under mild conditions. The advent of palladium (Pd)-catalyzed cross-coupling reactions for the formation of C-C bonds pioneered by Kumada [7], Corriu [8], Stille [9], Negishi [10], Sonogashira [11], Miyaura [12] and Suzuki [13] stimulated the search for analogous cross-coupling methods for the formation of aromatic C-N bonds.

The early development of Pd-catalyzed C-N bond-forming processes has been documented previously [14], and thus will be described only briefly. The first protocol for Pd-catalyzed C-N bond formation was reported by Migita and Kosugi in 1983 (Scheme 13-1) [15]. The method required the use of a stoichiometric quantity of a tin amide, and this – together with the hydrolytic sensitivity of such reagents – limited the application of their protocol. A year later, while working on the total synthesis of lavendamycin [16], Boger and Panek reported on intramolecular aromatic C-N bond-forming processes mediated by a stoichiometric quantity of a Pd complex. In 1994, Buchwald and Guram modified Migita's procedure to allow for a relatively general means for the in-situ generation of aminostannanes [17] which,



Scheme 13-1

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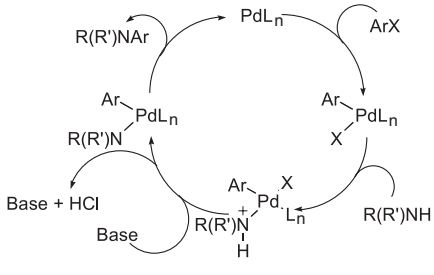
nonetheless, still required a stoichiometric quantity of diethylamino tributyltin. Based on these preliminary results and further mechanistic studies, Buchwald [18] and Hartwig [19] independently disclosed tin-free methods for the Pd-catalyzed formation of aromatic C-N bonds. This technique has now evolved into one of the most important modern cross-coupling processes [14]. Recently, improved versions of the Cu-catalyzed Goldberg-type and Ullmann-type processes have been disclosed [20] which are complementary to their Pd counterpart. When combined, these C-N bond-forming protocols have become routinely practiced by chemists both in industrial and academic laboratories. Due to space limitations, this chapter will cover only Pd-catalyzed C-N bond-forming processes. Methodologies that employ catalysts based on other metals (particularly copper [6, 20] and nickel [21]) that are capable of effecting aromatic C-N bond formations will not be included.

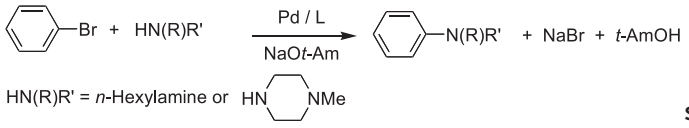
This chapter consists of three main sections. The first section describes the current mechanistic viewpoint of this transformation. By discussing the reaction mechanism, it is hoped that the reader will be provided with a conceptual framework for both ligand design and selection of reaction conditions. In the second section some general features of this transformation will be presented. Subsequently, selected examples based on the nature of the nitrogen nucleophiles employed will be detailed. Within the description of the chemistry of each nucleophile, the effect of electronic and steric properties of the aryl or heteroaryl halides or sulfonates will be considered. An attempt will also be made to point out the functional group limitations in various protocols.

13.2
Mechanistic Studies

During the past decade, several kinetic and mechanistic studies have been reported that have attempted to rationalize the effects of different ligands and additives on the Pd-catalyzed aryl amination reactions [22]. A catalytic cycle consisting of four basic steps including: oxidative addition of the aryl halide; association of amine; dehydrohalogenation; and reductive elimination of product is generally accepted (Scheme 13-2). The order of these steps, however, may vary. For example, while the most conventional mechanism involves initial oxidative addition of the aryl



Scheme 13-2



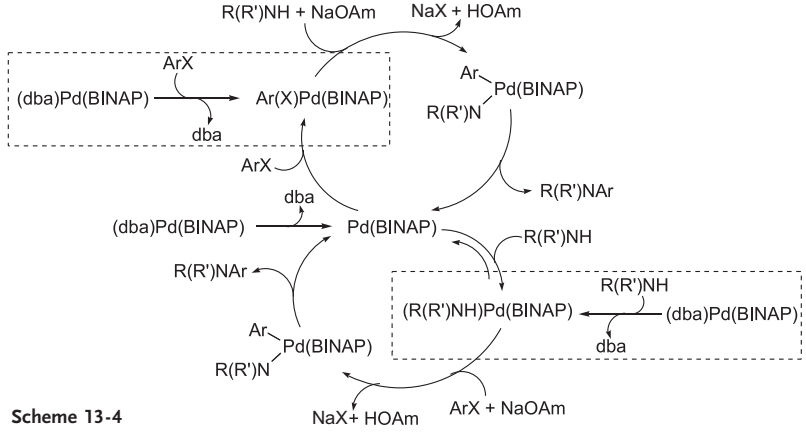
Scheme 13-3

halide to a LPd or L_2Pd complex, an alternative pathway that involves the binding of a nucleophile to the Pd(0) species prior to oxidative addition (Schemes 13-4 and 13-6) has also been proposed. Two representative studies will be discussed in detail; various precatalysts and reaction conditions have been used to conduct these kinetic experiments, and different catalytic cycles have been proposed.

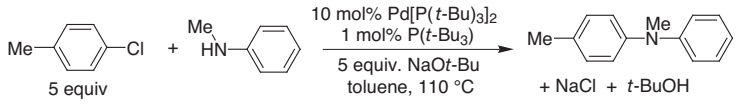
Recently, Buchwald and Blackmond reported a mechanistic study of the Pd(BINAP)-catalyzed arylation of primary and secondary amines (Scheme 13-3) [23]. By monitoring the reaction with reaction calorimetry, the kinetics of the reaction could be examined under synthetically relevant conditions.

A number of precatalysts including $Pd_2(dba)_3$/BINAP, (dba)Pd(BINAP), (*p*-tolyl)(Br)Pd(BINAP), and $Pd(BINAP)_2$ were examined for the reaction of *N*-methylpiperazine and bromobenzene. Using $Pd_2(dba)_3$/BINAP, a significant induction period was observed. This induction period can be attributed to the slow conversion of the catalyst precursor into the active form. The presence of the induction period can mask the true kinetics of the reaction, and lead to a false interpretation of kinetic data. According to the kinetic data, the reaction rate exhibited a positive-order dependence on both aryl bromide and secondary amine and a zero-order dependence on the base (NaO*t*-Am) concentration. It was also determined that $Pd(BINAP)_2$ was not, as had been previously suggested [22], involved in the catalytic cycle. Blackmond had previously cast doubt on the intermediacy of this species [24].

Besides the route involving the oxidative addition of the aryl halide to a Pd(BINAP) species (Scheme 13-4), an additional pathway consisting of amine association to the Pd(BINAP) species prior to oxidative addition was suggested.



Scheme 13-4

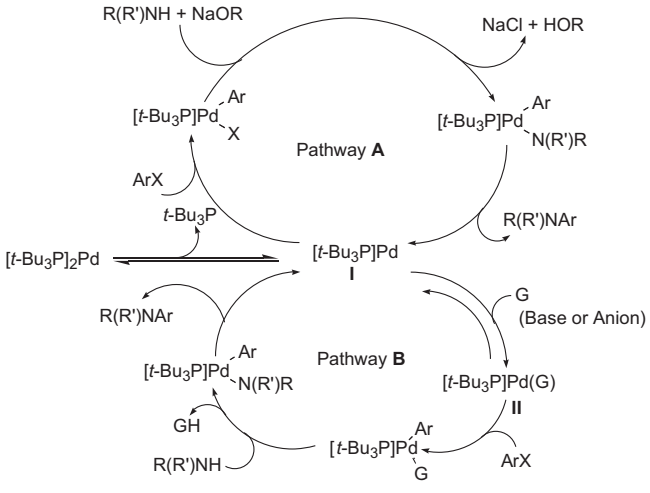


Scheme 13-5

This was supported by a positive-order dependence of the reaction rate on the amine concentration and the higher reaction rate obtained by longer premixing times with amine, base, and precatalyst. Accordingly, a mechanistic scenario for Pd-catalyzed C-N bond formation was proposed to account for these observations as shown in Scheme 13-4. The competition between amine and aryl bromide for the Pd(BINAP) species permits these two separate catalytic cycles with relative ratio of amine to aryl bromide dictating the contribution of each cycle.

Hartwig carried out a mechanistic study of the Pd/*t*Bu$_3$P-catalyzed amination of *p*-chlorotoluene with *N*-methylaniline (Scheme 13-5) [25]. The kinetic measurements were made from reactions that were monitored in a NMR tube using a large excess of *p*-chlorotoluene and NaOCEt$_3$. These authors suggested that oxidative addition was rate-limiting, as the reaction showed a first-order dependence of reaction rate on aryl chloride. Further deconvolution of the kinetic data suggested two catalytic cycles. Pathway **A** is comprised of the oxidative addition of the aryl halide to [*t*-*B*u$_3$P]Pd (**I**) followed by the amine association, deprotonation (with loss of NaCl), and reductive elimination to afford the product and regenerate **I**. This pathway predicts a zero-order dependence of the reaction rate on the concentration of base, which was observed when NaOCEt$_3$ was used. The competing reaction cycle, anionic pathway **B**, consists of the association of a base or an anion to [*t*Bu$_3$P]Pd to form intermediate **II** preceding the oxidative addition of aryl halide. Subsequent amine-base (or amine-anion) exchange is followed by reductive elimination to complete the catalytic cycle. With this anionic pathway, a first-order dependence on base (or anion) should be obtained; a positive-order dependence on NaO*t*Bu or NaO(2,4,6-*t*Bu)$_3$C$_6$H$_5$ suggested the presence of pathway **B**. The relative contribution of the two pathways depends on the binding ability of the anion present. Further support for the proposed mechanism was provided by examining the effect of the addition of different halides on the reaction rates. The inclusion of tetraoctylammonium chloride had no measurable effect on the reaction rates, while in the presence of the corresponding ammonium bromide, a rate acceleration even more pronounced than that observed in the presence of added alkoxides was seen. The different behavior manifested in the presence of Br^- compared to that seen with Cl^- was attributed to the different binding abilities of the halides to **I**.

It is important to point out that, in each of these investigations, a pathway in which a nucleophile binds to a Pd(0) species prior to oxidative addition was proposed. Both mechanistic studies described above also suggested that the initial dissociation of a ligand from a L$_2$Pd species to generate a catalytically active L$_1$Pd intermediate was occurring, the possibility of this was first suggested by Hartwig



Scheme 13-6

several years ago [26]. Therefore, it is important to point out that the L/Pd ratio can be critical to the success of this reaction, and that the addition of excess ligand may retard the reaction rate. However, if an insufficient quantity of ligand is present, catalyst deactivation may occur.

13.3 General Features

It is important to realize that Pd-catalyzed C-N bond-forming reactions are different from the better-studied C-C cross-coupling processes. The diversity in the nature of nitrogen nucleophiles employed is much greater than, for example, that between different boronic acids. This can be readily appreciated if one compares primary alkylamines, cyclic and acyclic secondary amines, anilines, diarylamines, amides and nitrogen heterocycles. Moreover, an amine is more likely than an arylboronic acid or a trialkyltin reagent to bind (sometimes more than one at a time) to the Pd center of an intermediate complex. Since the original reports of tin-free procedures, myriad protocols using a wide array of ligands, metal precatalysts, bases, and solvents have been reported. This has, in many instances, left the synthetic chemist feeling overwhelmed. Therefore, we feel it is important to discuss the general aspects of the precatalysts, ligands, and bases as well as solvents used for this transformation.

13.3.1 Precatalyst

Two types of precatalysts are primarily used for Pd-catalyzed C-N bond-forming processes, namely $Pd(OAc)_2$ and $Pd_2(dba)_3$ (or $Pd(dba)_2$). In $Pd(OAc)_2$, the Pd is in the +2 oxidation state, and therefore it needs to be reduced to Pd(0) prior to the initiation of the catalytic cycle. In general, the reducing agent is the amine substrate; amines possessing a β-hydrogen are efficient in this regard. In other cases, for example, with aniline or amide substrates lacking a β-hydrogen, the process may be slow. A catalytic quantity of phenylboronic acid [27], or a more reducing amine (e. g., Et_3N, iPr_2NH) can be added if necessary, to facilitate reduction. The use of $Pd_2(dba)_3$, which is a source of Pd(0), does not require prereduction to take place. In some cases, however, the presence of the dba ligand can inhibit or facilitate the desired transformation [23, 28].

13.3.2 Ligand

The nature of the ligand plays a key role in Pd-catalyzed C-N bond-forming processes. Electron-rich ligands will increase the electron density around a Pd center, thereby facilitating the oxidative addition step. Bulky ligands will shift the equilibrium between LPd and L_2Pd in favor of LPd, which is believed to be the active species in the catalytic cycle. Moreover, sterically encumbered ligands will also accelerate the rate of reductive elimination step. However, simply increasing the steric bulk may lead to a situation where the binding of the ligand to Pd is ineffective and precipitation of Pd black occurs.

The evolution of ligands used for Pd-catalyzed C-N bond formation has experienced four stages (Figure 13-1). In the first stage, *o*-Tol_3P – the ligand that was used by Migita and Kosugi in their pioneering studies on the coupling of an aminostannane with aryl bromides – was employed in the initial work of Buchwald and Hartwig. Subsequently, it was found that by utilizing chelating ligands, such as BINAP [29] (initially enantiomerically pure, subsequently in racemic form) or DPPF [30], the substrate scope and efficiency of the transformation could be significantly improved. Additionally, two ligands developed by Van Leeuwen [31], Xantphos (**4**) [32] and DPEPhos (**5**) [33], produced catalysts that have exhibited excellent activity for certain type of substrates. The discovery of 2′-dimethylamino-2-dicyclohexylphosphinobiphenyl (**12b**) [34] provided the first example of a new class of ligands that allowed the use of unactivated aryl chlorides and aryl bromides under mild conditions, even at room temperature. Subsequently, structurally simpler ligands 2-dicyclohexyl- (**19a**) and 2-di-*t*-butylphosphino biphenyl (**21a**) and their derivatives were prepared [35]. This class of biphenyl ligands could handle a wide array of substrates for C-N bond formation [36]. Moreover, a practical and efficient one-step protocol was developed to prepare the more highly substituted biaryl ligands that allowed flexible manipulation of the substituents in the non-phosphine-containing benzene ring (Scheme 13-7) and for their preparation on

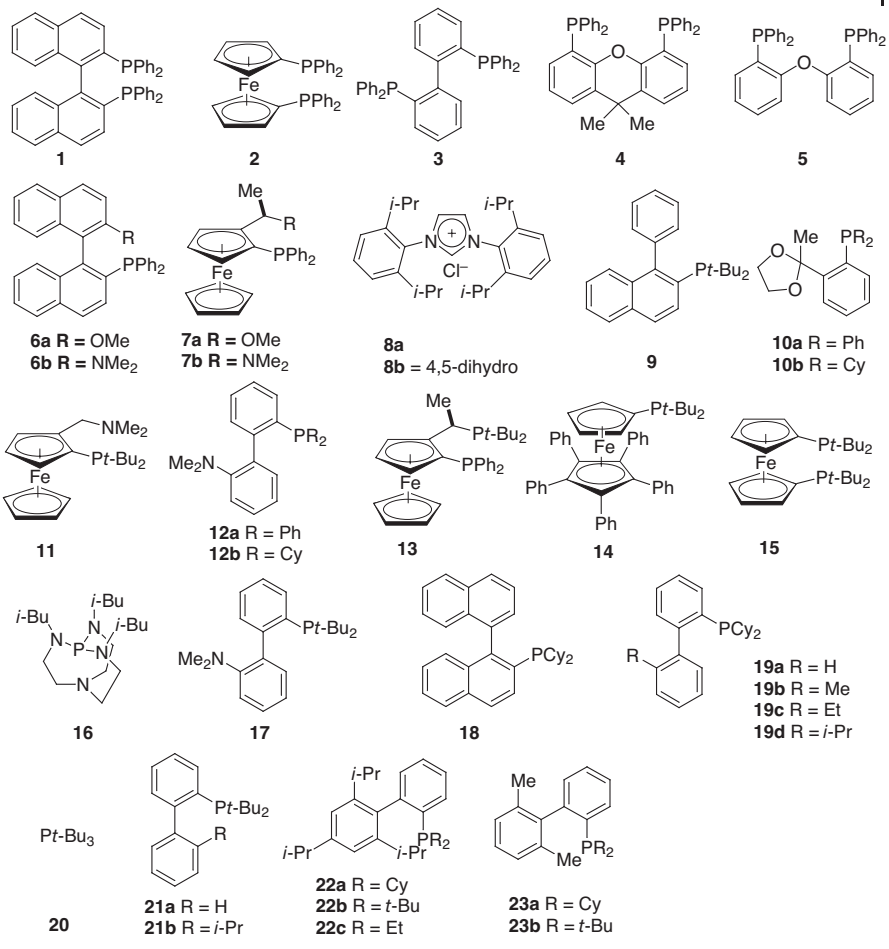
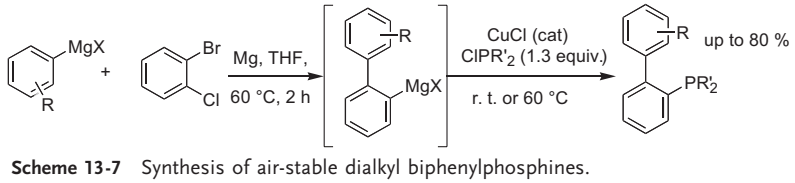


Figure 13-1 Ligands used in Pd-catalyzed amination reactions.



Scheme 13-7 Synthesis of air-stable dialkyl biphenylphosphines.

multi-kilogram scale [37]. Significantly, all biaryl ligands synthesized to date are air- and moisture-stable.

The use of the biarylphosphine ligands for the C-N coupling process has been demonstrated on a 70-kg scale by workers at Rhodia Pharmaceutical Solutions [38]. This, combined with the recent preparation of nearly 100 kg of the ligands, augurs well for their use in commercial ventures [38].

Koie et al. at Tosoh were the first to study *t*Bu$_3$P (**20**) as a supporting ligand for the amination reaction [39], and showed that it could be used to effect the coupling of unactivated aryl chlorides and enjoyed a general substrate scope. Hartwig subsequently modified the Tosoh method. In particular, he demonstrated that by adjusting the **20**/Pd ratio [40], the amination reaction could be conducted under milder conditions. Heterocyclic carbene ligands such as **8a** and **8b** have also been used in C-N bond forming processes [41], but they are less general than **12a**, **19a**, **20**, and **21a**. One reason for this is their need to employ a strong base, which limits the functional group tolerance of the catalytic system.

The third-generation ligands (**8**–**21**) were the standard bearers until the recent preparation and study of 2′,4′,6′-triisopropyl-2-dicyclohexylphosphinobiphenyl, XPhos, **22a**. The kinetics of the amination of an aryl chloride using **22a** showed that this bulky electron-rich ligand is the most active and the most stable of the biphenyl ligands studied to date [42]. As shown in Figure 13-2, with *p*-chlorotoluene and morpholine as prototypical substrates, the amination reaction catalyzed by **22a**/Pd was much faster than those with catalysts derived from **19b-d**. Due to its recent discovery, a detailed study of the scope of application of **22a** has not yet been undertaken. However, for the limited cases that have been studied so far, no example has been seen where **22a** is less effective than any of the third-gen-

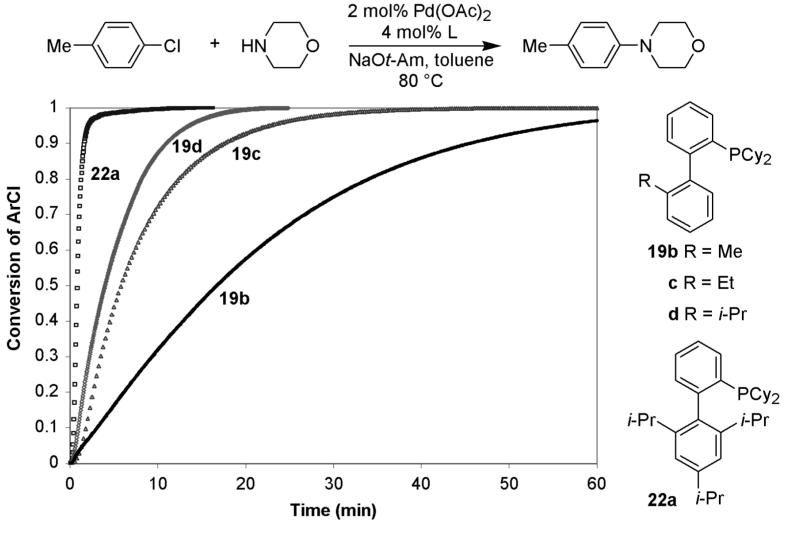


Figure 13-2 Conversion versus time with biaryl ligands.

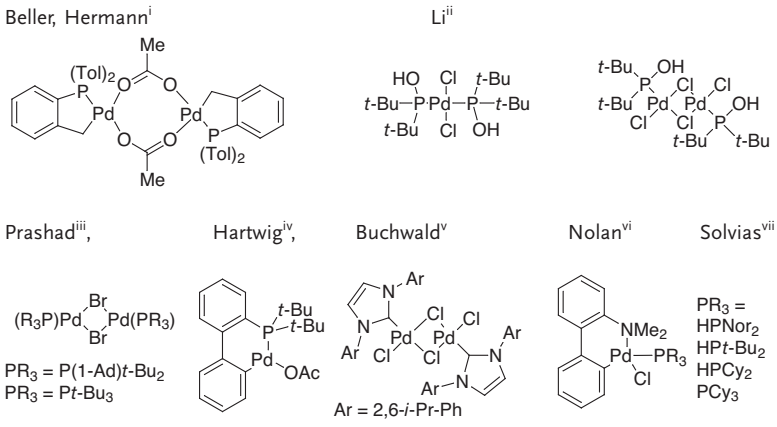


Figure 13-3 One-component catalysts for Pd-catalyzed amination.

[i] Beller, M., Riermeier, T. H., Reisinger, C. P., Herrmann, W. A., *Tetrahedron Lett.* **1997**, *38*, 2073.
[ii] Li, G. Y., Zheng, G., Noonan, A. F., *J. Org. Chem.* **2001**, *66*, 8677.
[iii] Prashad, M., Mak, X. Y., Liu, Y., Repic, O., *J. Org. Chem.* **2003**, *68*, 1163.
[iv] Stambuli, J. P., Kuwano, R., Hartwig, J. F., *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 4746.
[v] Zim, D., Buchwald, S. L., *Org. Lett.* **2003**, *5*, 2413.
[vi] Viciu, M. S., Kissling, R. M., Stevens, E. D., Nolan, S. P., *Org. Lett.* **2002**, *4*, 2229.
[vii] Schnyder, A., Indolese, A. F., Studer, M., Blaser, H. U., *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 3668.

eration ligands, including **19a** and **21a**. Thus, for the cases described below utilizing **19a** and **21a**, the reader should consider **22a** as the first choice to investigate.

A variety of "single-component" precatalysts have also been employed, as shown in Figure 13-3. These have the advantage that a predetermined ratio of L:Pd is already attained. Their use is also of convenience for derivatizing via a high-throughput screening approach.

13.3.3
Nature of the Base

The selection of the correct base is crucial for the success of C-N coupling processes. This is particularly true with respect to functional group tolerance and reaction rate. Reactions that utilize relatively strong bases such as NaO*t*Bu are invariably faster than those that utilize milder bases. This is presumably due to the fact that deprotonation of the Pd-bound amine becomes rate-limiting when weaker bases are employed. The use of NaO*t*Bu (or other strong bases) is currently required for processes that are carried out at room temperature and those carried out with low quantities of catalyst (much below 0.5 %). An economical alternative to NaO*t*Bu is the use of KOH (or NaOH) either as an aqueous solution or in solid form in other solvents such as toluene and *t*BuOH. The first reported use of hydroxide bases in amination reactions came from Boche [50]. Subsequently, Nolan [51], Hartwig [52], and Buchwald [27, 47] have extended these findings.

Buchwald's introduction of Cs_2CO_3 as an alternative base [53] was significant in terms of increased functional group compatibility. This base is particularly effective when chelating ligands such as BINAP, Xantphos or DPEphos are used. Later, Buchwald found that K_3PO_4 was an excellent base [34] for use with the biaryl ligands, and it was subsequently used with tBu_3P [40] but not, for the most part, with chelating ligands. Recently, Buchwald has found that in some cases the use of K_2CO_3 in *t*BuOH is effective. It is important to note that when one considers functional group compatibility, it is the *combination of the base and the nitrogen nucleophile* that is responsible for side reactions. For example, while the reactions of many functionalized substrates work well with an aniline employing NaO*t*Bu as base, this does not mean that the reaction will work with an *N*-alkyl amine in combination with the same base.

13.3.4 Solvent

Pd-catalyzed carbon-nitrogen coupling reactions are air-sensitive and need to be carried out in deoxygenated solvents. Toluene, the most popular solvent for this transformation, has been dried through the use of dry-stills. Other solvents or co-solvents, such as *t*BuOH, DME, dioxane, DMF, and NMP can often be used directly from commercially available SureSeal® bottles from Aldrich without further degassing; toluene of this quality should also be fine. The degree of scrupulousness that is necessary depends on the rate of a specific reaction. A relatively slow reaction (e. g., 24 h) would be expected to be more sensitive than a faster one and therefore require greater care. Similarly, the lower the quantity of catalyst that is employed, the more sensitive the reaction will be to solvent impurity.

13.3.5 Reaction Temperatures

In general, amination reactions have been carried out at temperatures between room temperature and 120 °C, although in a few instances the use of reaction temperatures as high as 150 °C have been reported. A combination of thermal sensitivity of the substrates and/or products, the reaction's efficiency toward product formation, and the convenience of running the reaction (minimization of reaction time *vs.* ease of setup for high throughput screening applications) leads the chemist to use a particular set of reaction temperatures and conditions.

13.3.6 Use of a Glovebox

In the present authors' studies, a conscious decision was made not to employ a glovebox to either set up or run reactions. However, bulk quantities of hygroscopic bases (NaO*t*Bu, Cs_2CO_3) are stored in a glovebox, with small quantities (2–3 g) being removed and used for a two- to three-week period and stored in a desiccator.

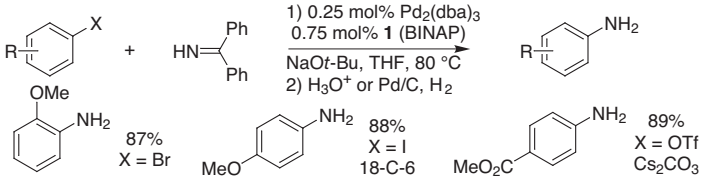
The chemist is warned to read very carefully the experimental procedures (usually in the supporting information) to identify whether the reaction has been set up or conducted in a glovebox. Attempts to utilize the described reaction condition without employing a glovebox may affect the efficiency of the procedure. This is expected to be particularly true for difficult substrate combinations, or when small quantities of catalyst are employed.

13.4
Palladium-Catalyzed C-N Bond Formation

13.4.1
Arylation with Amines

13.4.1.1 Ammonia Equivalents

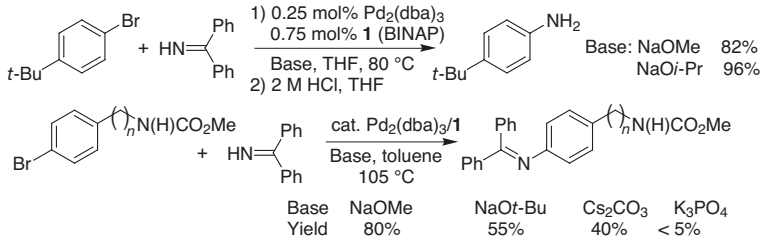
The use of ammonia as the nucleophilic component in Pd-catalyzed amination reactions has not been reported. Fortunately, alternate means to meet the needs of the synthetic chemists have been developed. Buchwald first reported the use of benzophenone imine as an ammonia surrogate in Pd-catalyzed C-N bond formations (Scheme 13-8) [54], and showed that it could be successfully coupled with a variety of aryl bromides, iodides, and triflates; the resulting imine coupling products were conveniently cleaved to the corresponding primary anilines in good yields. With NaO*t*Bu as a base, BINAP, **1**, was an efficient ligand for this transformation. Substrates which are prone to base hydrolysis, such as 4-carbomethoxyphenyl triflate, were also effectively coupled to benzophenone imine using Cs_2CO_3 as base.



Scheme 13-8

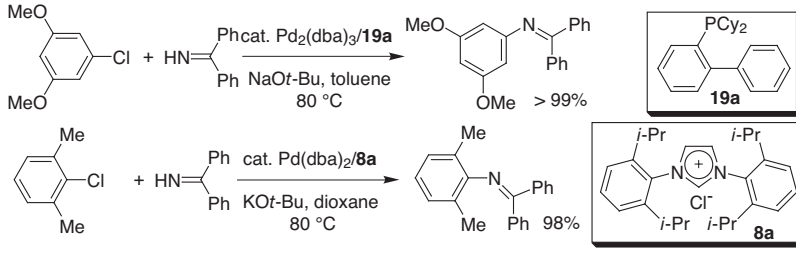
Prashad found that other alkoxides were also effective bases in the coupling of benzophenone imine [55]. For example, treatment of 4-*t*-butylbromobenzene with benzophenone imine in the presence of NaO*i*Pr at 80 °C followed by acid hydrolysis afforded 4-*t*-butylaniline in 96 % yield (Scheme 13-9). Replacing NaO*i*Pr with NaOMe gave the desired product in only slightly diminished yield. As shown in Scheme 13-9, in one example where the use of mild bases was inefficient, switching to NaOMe gave the product in good yield.

A catalyst derived from Arduengo's heterocyclic carbene [56] (**8a**) was shown to effect the amination of aryl chlorides with benzophenone imine at 80 °C with



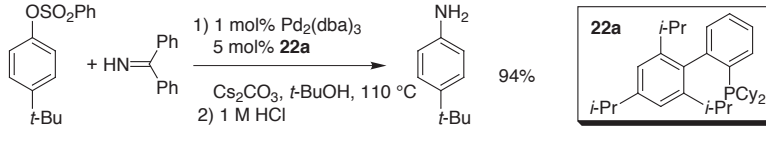
Scheme 13-9

KO*t*Bu as base [51]. Primary anilines were obtained in high yield upon hydrolysis. However, the need to use a strong base in these procedures limited the functional group compatibility of this protocol. Commercially available **19a** also proved to be an excellent ligand for the amination of aryl chloride (Scheme 13-10).



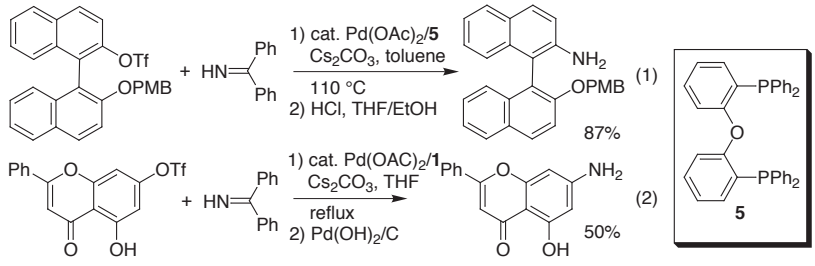
Scheme 13-10

With the discovery of XPhos, **22a**, the efficient coupling between benzophenone imine and aryl benzenesulfonates was realized for the first time (Scheme 13-11) [27]. A catalyst derived from this ligand was demonstrated to have a broad substrate scope for the amination of aryl sulfonates.



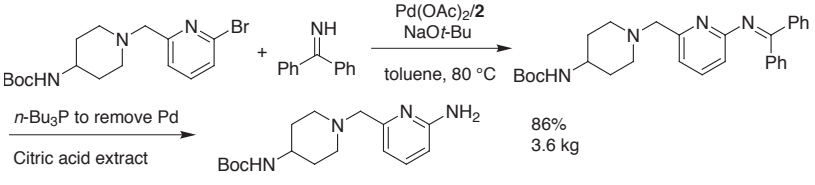
Scheme 13-11

Several applications of the use of benzophenone imine as an ammonia equivalent have appeared. For example, Singer and Buchwald synthesized the amino-BINOL precursor using a catalyst derived from DPEphos (**5**) [Scheme 13-12, Eqn. (1)] [57]. Lemiére prepared the aminoflavone in 50 % yield (two steps) employing the Pd/BINAP protocol [Scheme 13-12, Eqn. (2)] [58]. This example is notable in that the presence of a free phenol in the triflate substrate was well tolerated.



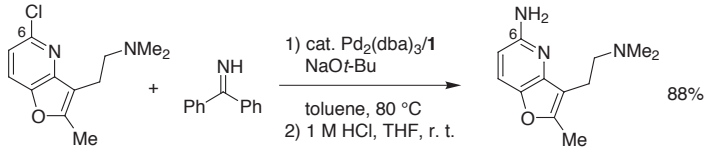
Scheme 13-12

The benzophenone imine protocol has proved to be reliable; Merck chemists utilized it on moderate scale (Scheme 13-13) [59]; in this case, 3.6 kg of product was isolated in 86 % yield with DPPF as the supporting ligand.



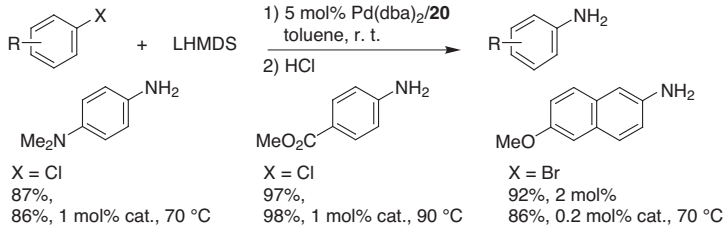
Scheme 13-13

In the preparation of a selective 5-HT_{1F} receptor agonist, Filla and Mathes [60] installed the 6-amino group at the end of their synthetic sequence. Employing the original BINAP protocol, the desired product was isolated in 88 % yield over two steps (Scheme 13-14).



Scheme 13-14

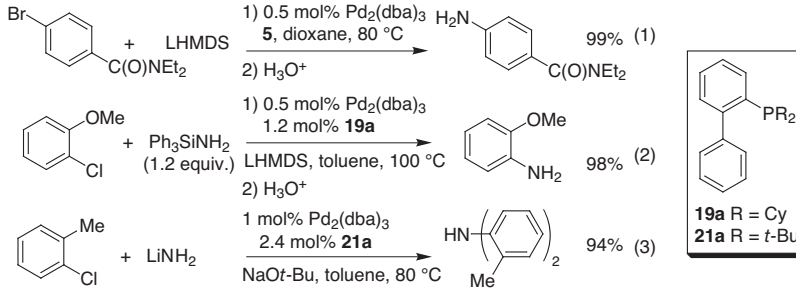
Hartwig [61] reported the use of LHMDS as the ammonia equivalent for the coupling of *m*- or *p*-substituted aryl halides (Br and Cl). Screening various ligands using a 1:1 ratio of L:Pd revealed that tBu_3P, **20**, was effective (Scheme 13-15). In the presence of 2–5 mol % $Pd(dba)_2$/**20**, aryl bromides and chlorides bearing sensitive functional groups were coupled with LHMDS at room temperature. The reaction also proceeded at low catalyst loading (0.2–1 mol %) at 70–90 °C. One limitation of this protocol is that aryl halides bearing *ortho*-substituents were not viable substrates.



Scheme 13-15

Using a L:Pd ratio of 2:1, Buchwald demonstrated that other ligands such as **5**, **19a**, and **21a** were efficient for the coupling of LHMDS [62]. For example, with **5** as supporting ligand, *N,N*-diethyl-4-aminobenzamide was prepared from the corresponding bromide in near-quantitative yield. In order to expand the method to *o*-substituted aryl halides, triphenylsilylamine was used as the ammonium surrogate (Scheme 13-16). It was also found that $LiNH_2$ could be used to obtain di- or tri-arylamine products in a one-pot protocol, with **21a** serving as the most efficient ligand.

Other reagents have also been reported as ammonia equivalents in Pd-catalyzed C-N bond-forming reactions. For example, the use of allylamine [63] and a Ti N_2-fixation complex [64] have also been described.



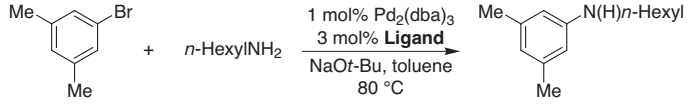
Scheme 13-16

13.4.1.2 **Primary Aliphatic Amines**

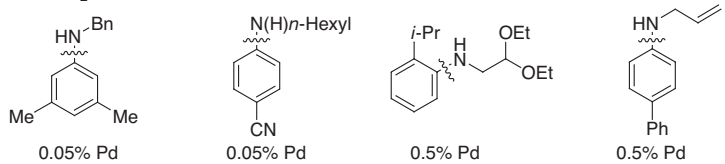
Early examples of the coupling of primary alkylamines with electron-neutral aryl bromides and *m*- or *p*-substituted aryl iodides employing *o*-Tol_3P as a ligand often yielded a significant quantity of the reduced arene product [65]. Racemization was observed when the coupling of enantiomerically pure *α*-methylbenzylamine was used [66]. Both results can be attributed to competing *β*-hydride elimination processes, although the reasons for arene formation are more complex. The other major side product in the arylation of primary amines was the bis-arylation product. This undesired process could be mitigated by employing an excess (up to 2 equiv.) of the primary amine. In order to circumvent the *β*-hydride elimination pathway, Buchwald examined the effect of other ligands and found that use of

BINAP, **1**, could significantly alleviate the amount of arene formation, thereby improving the yield of the desired products [29]; a comparison of the yield of product formed with various ligands is shown in Table 13-1. It is important to note that the efficiency of BINAP is not solely due to the fact that it is a chelating bisphosphine. As shown below, various *N*-alkylanilines were prepared from the corresponding aryl bromides and primary alkylamines in good yield using a low catalyst loading.

Table 13-1



Ligand	Conversion(time)	Product/reduced SM ratio	Product/double arylation ratio	Yield (%)
1 (BINAP)	100% (2 h)	40/1	39/1	88
P(*o*-Tol)$_3$	88% (22 h)	1.5/1	7.6/1	35
DPPE	7% (6 h)	1/5.4	–	–
DPPP	> 2% (6 h)	–	–	–
DPPB	18% (3 h)	1/1.6	–	–
2 (DPPF)	100% (3 h)	13.2/1	2.2/1	54
	22% (12 h)	2.5/1	10/1	–



0.05% Pd
79% yield

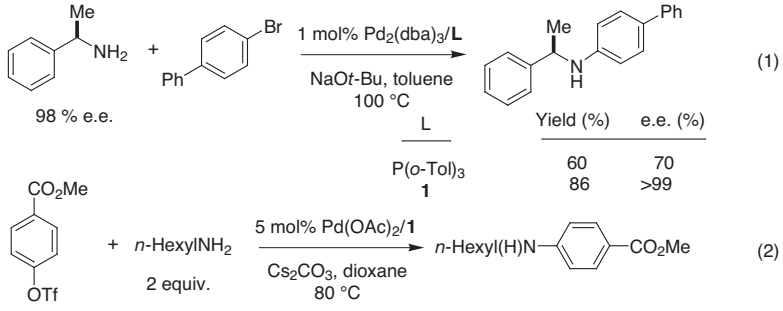
0.05% Pd
97% yield

0.5% Pd
90% yield

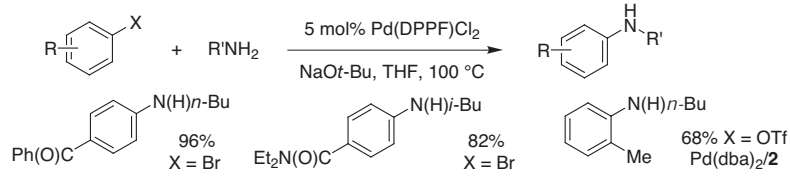
0.5% Pd
83% yield

In addition, with **1** as a supporting ligand, (*R*)-*α*-methyl benzylamine and 4-bromobiphenyl were coupled to give the desired product in 86 % yield without erosion of optical activity (>99 % *e. e.*) [66]. Typically, NaO*t*Bu was the base of choice, although the use of other strong bases has also been reported. However, certain functional groups, particularly aryl triflates, were not compatible with the use of strong bases. Buchwald and Åhman [67] discovered that the use of Cs_2CO_3, a weaker base, would allow for the coupling of substrates containing these sensitive groups.

Catalysts derived from DPPF [30] have also provided better results than that from the *o*-Tol$_3$P on the arylation of primary alkylamines in certain situations. As shown below, *N*-alkylanilines were synthesized from primary alkylamines and electron-deficient or *ortho*-substituted aryl bromides, as well as aryl triflates [68].

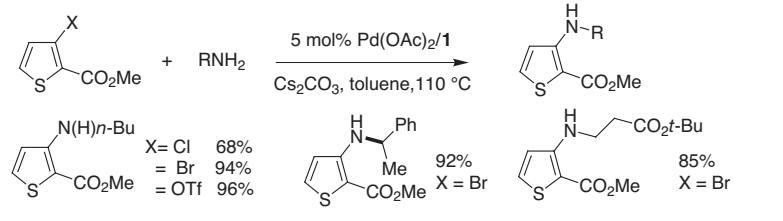


Scheme 13-17



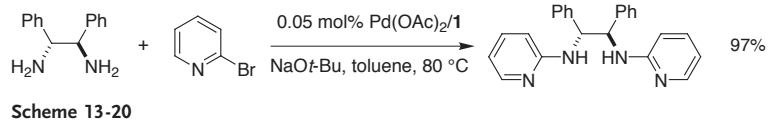
Scheme 13-18

Procedures employing BINAP as a ligand have been shown to be more efficient than those with DPPF and DPPP for the amination of halothiophenes with primary alkylamines. Luker [69] demonstrated that with Cs_2CO_3 as a base, various primary alkylamines could be coupled with 3-halothiophene-2-carboxylic acid methyl esters in good yield.



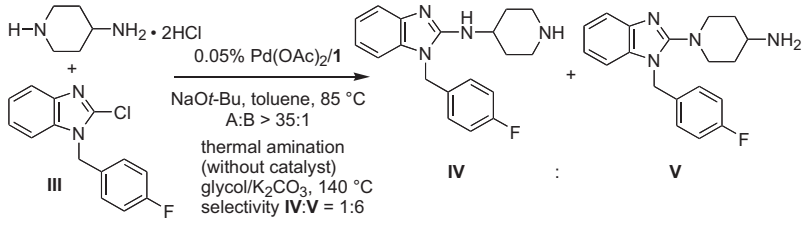
Scheme 13-19

Mangeney prepared a new set of nitrogen-containing ligands using a Pd/**1**-catalyzed amination protocol [70]. *N,N′*-diaryl-1,2-diphenyl-1,2-diaminoethanes were synthesized in excellent yield. No *meso*-products were detected by ^{1}H-NMR, indicating that no epimerization had occurred.



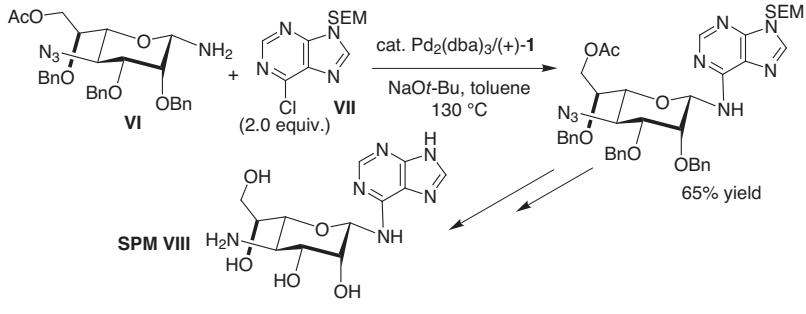
Scheme 13-20

In the synthesis of the nonsedating antihistaminic norastemizole (Scheme 13-21), Senanayake reported the observation of a high level of chemoselectivity between a primary amino and a secondary amino group in the coupling of chlorobenzimidazole (**III**) [71] employing the original Pd/**1** reaction conditions. In contrast, under thermolytic conditions, the selectivity was reversed and the more nucleophilic secondary amine was arylated, with good selectivity.



Scheme 13-21

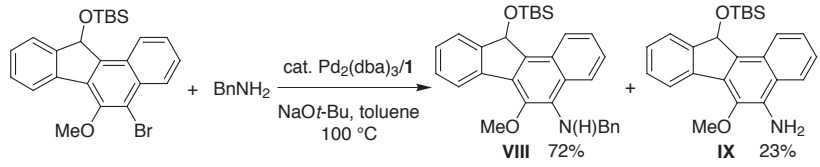
Chida reported the construction of a *N*-glycosidic linkage via the Pd/**1**-catalyzed reaction between *O*-benzyl-β-D-mannopyranosylamine (**VI**) and chloropurine (**VII**) [72]. Anomerization (thermal) of the glycoside occurred under the reaction conditions to give the thermodynamically more stable β-anomer. This efficient coupling paved the way for the first total synthesis of nucleoside antibiotic spicamycin congeners-SPM VIII.



Scheme 13-22

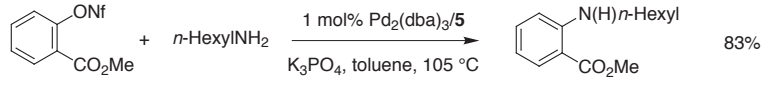
In order to study the molecular mechanism of the antitumor activity of kinamycins [73], Dmitrienko synthesized a structurally simplified analogue of kinamycin involving a Pd-catalyzed C-N bond-forming process. Utilizing the Pd/**1** catalyst system, benzylamine was coupled with an aryl bromide to give the secondary amine **VIII** and debenzylated product **IX** in a combined 95 % yield. **VIII** was subsequently debenzylated to afford **IX**.

Owing to their higher stability, aryl nonaflates are attractive alternates to aryl triflates. The first general study of the Pd-catalyzed amination of nonaflates has



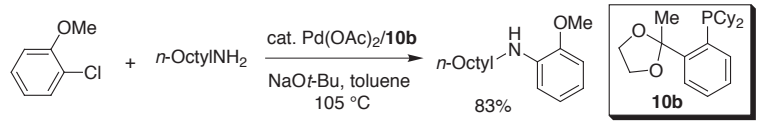
Scheme 13-23

recently been carried out [74]. With DPEPhos, **5**, as the supporting ligand, the amination of methyl 2-[(nonafluorobutanesulfonyl)oxy]benzoate with hexylamine was realized (Scheme 13-24). This coupling of a primary alkylamine with an *o*-halo- (or sulfonato-) benzenecarboxylate ester has, to our knowledge, never been accomplished [75].



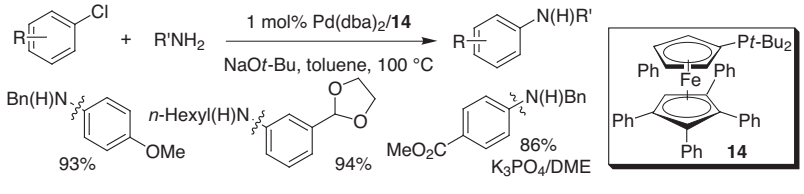
Scheme 13-24

A series of P,O and P,N ligands were synthesized by Guram and examined for their utility in Pd-catalyzed aminations [76]. Among these ligands, **10b** proved to be especially useful since, when combined with $Pd(OAc)_2$, it efficiently catalyzed the amination of aryl chlorides, bromides, and iodides. As shown below, 2-chloroanisole – an electron-rich *ortho*-substituted aryl chloride – was coupled with octylamine to furnish the product in good yield.



Scheme 13-25

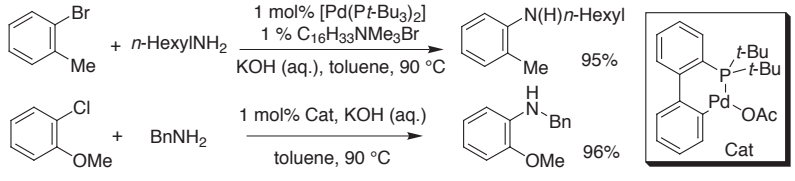
Recently, the use of the sterically encumbered, electron-rich ligand Q-Phos **14** [77] was shown to be efficient for the coupling of primary alkylamines with aryl chlorides (Scheme 13-26). For base-sensitive substrates, weaker bases such as



Scheme 13-26

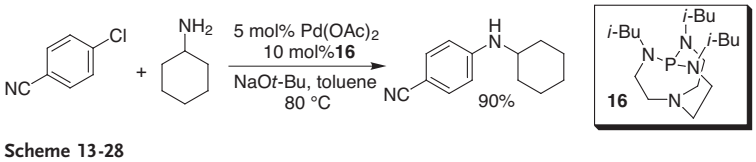
K_3PO_4, could be used. Catalyst systems derived from imidazolium salt **8a** and **8b** could also be employed to effect the amination of aryl chlorides with NaO*t*-Am as a base to give the desired *N*-alkylanilines in good yields [41, 51]. 4-Chlorotoluene, however, was the only aryl halide described in this study. Attempts to substitute weaker bases for NaO*t*-Am were not successful; decomposition of the catalyst was observed.

The use of aqueous hydroxide in amination processes was first reported by Boche [50], who also studied the reaction under two-phase conditions. Nolan reported the use of a hydroxide base in reactions that utilize a carbene ligand [51]. Hartwig subsequently reported a protocol where solid or aqueous alkaline hydroxides were used as bases [52]. In latter study, cetyltrimethylammonium bromide was used as a phase-transfer agent, and $Pd[PtBu_3]_2$ as a catalyst (Scheme 13-27). Good yields were realized in a number of instances; however, the combination of aqueous potassium hydroxide and a primary alkylamine was not compatible with methyl or ethyl esters. With an air-stable, one-component palladacycle catalyst derived from **21a** [47], Buchwald found that the use of a phase-transfer reagent was unnecessary. As shown below, the reaction of 2-chloroanisole and benzylamine occurred at 90 °C to give the *N*-benzyl-2-methoxyaniline in excellent yield.



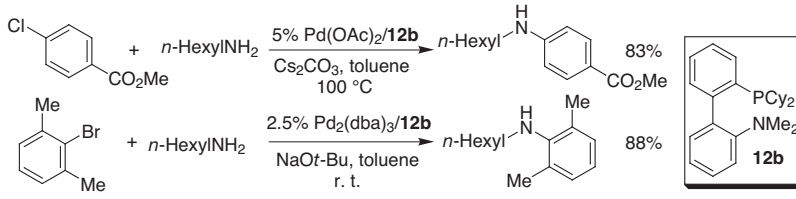
Scheme 13-27

Recently, Verkade reported the use of bicyclic triaminophosphine (**16**) as a new class of ligand for Pd-catalyzed amination reactions [78]. The catalyst based on this interesting ligand has demonstrated the ability to conduct the reaction between primary alkylamines and aryl chlorides.



Scheme 13-28

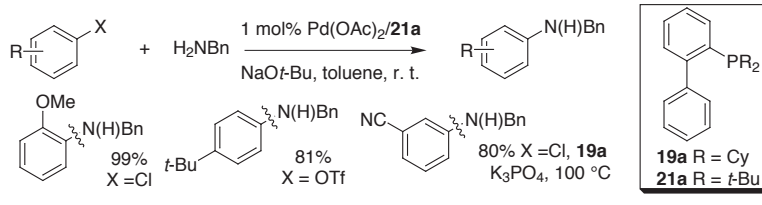
The discovery and commercial availability of **12b** led to the development of procedures with greatly expanded substrate scope for the arylation of primary alkylamines [34, 79]. The highly active catalyst derived from this ligand could effect the reaction of primary alkylamines with aryl bromides at room temperature,



Scheme 13-29

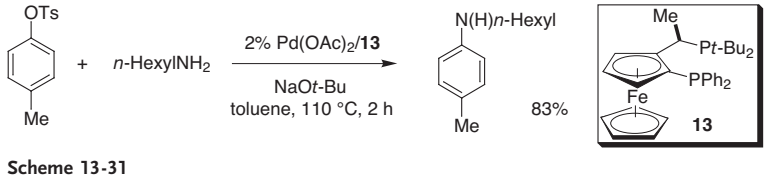
and of aryl chlorides at 100 °C. Employing weaker bases, ester groups, *meta* or *para* (not *ortho*) to the leaving group are compatible with the reaction conditions.

The catalyst derived from the simple biaryl ligand **21a** showed higher activity for the arylation of primary alkylamines relative to **12b** (Scheme 13-30) [36]. For example, reactions between aryl chlorides and primary alkylamines occurred at room temperature. As for functionalized substrates, **19a** provided better results and, using a combination of the weak base K_3PO_4 and primary alkylamine, functionalized aryl chlorides were successfully coupled at 100 °C.

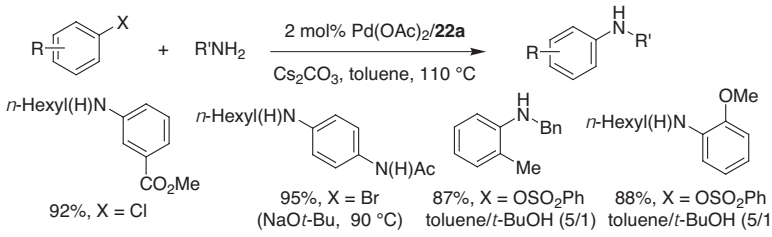


Scheme 13-30

The amination of aryl tosylates is more challenging than that of aryl triflates because aryl tosylates undergo oxidative addition significantly more slowly than the corresponding aryl triflates. Before the introduction of XPhos, **22a**, only one example of the amination of a tosylate with an aliphatic primary amine was reported [80]. Using Solvias' ligand **13** [81], hexylamine was combined with *p*-tolyl tosylate to give the desired product in 83 % yield (Scheme 13-31). This catalyst system could also be used for the coupling of primary alkylamines and aryl chlorides at 110 °C.



Scheme 13-31

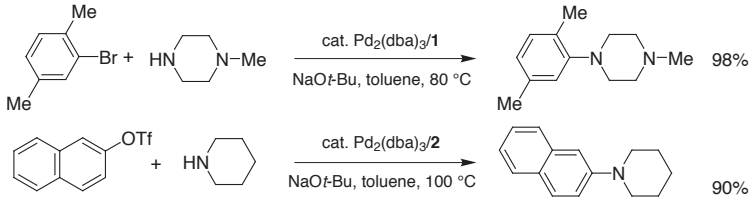


Scheme 13-32

Catalysts derived from the biaryl ligand XPhos, **22a**, have been shown to possess an excellent level of stability and selectivity in the reaction of primary alkylamines with aryl chlorides or bromides bearing sensitive functional groups (Scheme 13-32) [27]. Moreover, using **22a** it was possible, with good generality, to effect the amination of aryl benzenesulfonates with primary aliphatic amines.

13.4.1.3 Cyclic Secondary Alkylamines

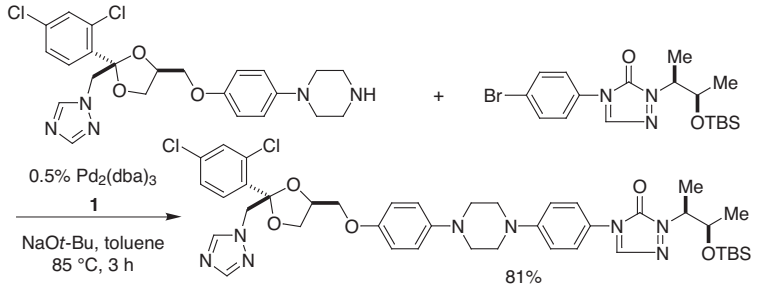
Cyclic secondary alkylamines are among the easiest substrates for amination reactions, most likely due to the fact that they are less prone to β-H elimination and less bulky compared to their acyclic counterparts. Most catalysts reported to date that are effective in the C-N bond-forming processes allow the coupling of aryl halides with cyclic secondary amines to occur, including those derived from the first- and second-generation ligands (o-Tol$_3$P [18], BINAP **1** [29c], and DPPF **2** [30]). The use of ligand **1** was generally more effective than o-Tol$_3$P, as lower levels of arene formation were observed. Catalysts derived from **2** have been reported to be effective for the amination of aryl triflates (Scheme 13-33) [69].



Scheme 13-33

While NaO*t*Bu was generally employed as the base for the reactions, other strong bases such as NaOMe and NaO*i*Pr have also been employed [55] in combination with Pd/**1** to give, in some instances, comparable yields of the desired products. When base-sensitive functional groups were present, weaker bases were generally employed.

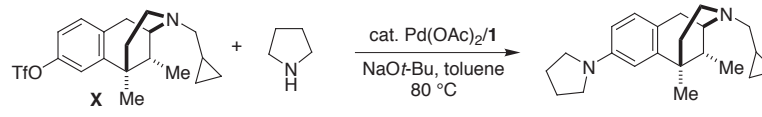
An application that demonstrated the utility of Pd-catalyzed amination is found in Tanoury's highly convergent synthesis of the antifungal, hydroxyitraconazole



Scheme 13-34

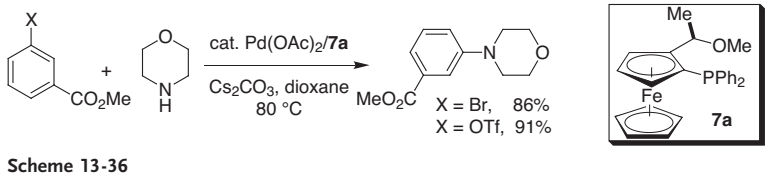
(Scheme 13-34) [82]. The construction of two key C-N bonds between aromatic units and piperidine was realized with the Pd/**1** system. In particular, in the last step, two highly functionalized heterocyclic pieces were coupled to give the desired product in 81 % yield [83]. Removal of the silyl group with TBAF furnished enantiomerically pure hydroxyitraconazole in 91 % yield which had an *e.e.* >99 %.

In the synthesis of the analgesic cyclozine [84], Wentland found that the pyrrolidine unit could be concatenated to the aromatic ring via Pd-catalyzed C-N bond formation from the corresponding aryl triflate **X**.



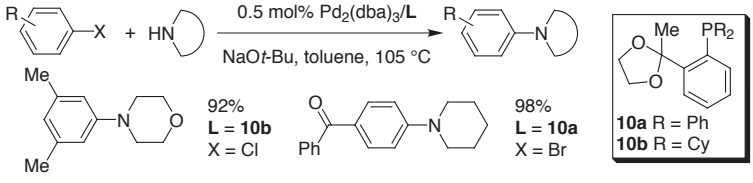
Scheme 13-35

Ferrocene-based monophosphine **7a**, was also a useful ligand for the arylation of cyclic amines, as well for that of the acyclic secondary amines [53]. It was during the course of the study of this ligand that Cs_2CO_3 was found to be a suitable base for aryl bromides and triflates bearing base-sensitive groups such as cyano, alkoxycarbonyl and nitro, as well as enolizable ketones. The discovery of the use of weaker bases (compared to metal alkoxides) dramatically impacted on the substrate scope for Pd-catalyzed C-N bond-forming processes, and their use has been embraced by other workers in this field [85].



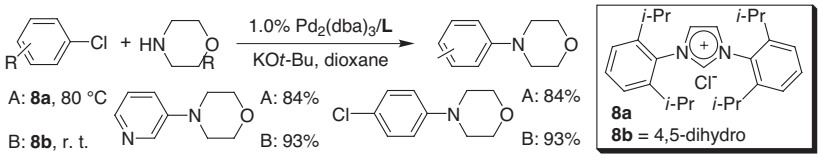
Scheme 13-36

Guram also reported the use of the tri-aryl P,O ligand **10a** for the arylation of cyclic amines [76]. With as little as 1 mol % catalyst (Pd/**10a**), 4-bromobenzophenone was allowed to react with piperidine to give the amination product in good yield (Scheme 13-27). Replacing the diphenylphosphine group (**10a**) with the more electron-donating dicyclohexylphosphino moiety (**10b**) allowed the coupling of aryl chlorides with morpholine to proceed at 105 °C.



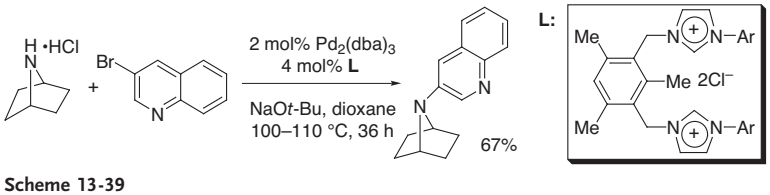
Scheme 13-37

Nolan reported that the unsaturated heterocyclic carbene **8a**/Pd system could successfully catalyze the reaction between aryl bromides (as well as aryl chlorides) and cyclic secondary amines at 80 °C (Scheme 13-38) [41a]. Hartwig found that the same reaction could be conducted at room temperature in the presence of the more active catalyst derived from the saturated carbene **8b** [41b].



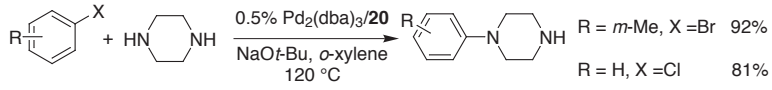
Scheme 13-38

Trudell reported the arylation of 7-azabicyclo[2,2,1]heptane with heteroaryl halides in the presence of a Pd bis-imidazol-2-ylidene complex [86].



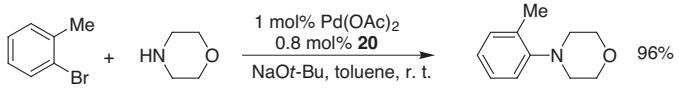
Scheme 13-39

The chemoselective amination of piperazine was achieved by the Tosoh group using *t*Bu$_3$P, **20**, as a ligand (Scheme 13-40) [39]. In order to obtain high yields of the monoarylation product, a six-fold excess of piperazine was employed.



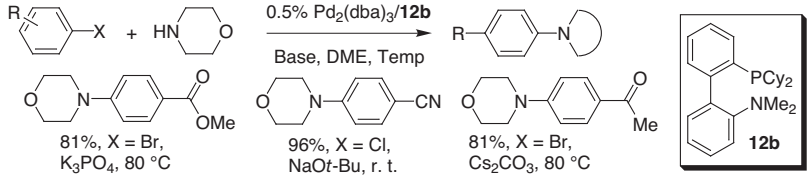
Scheme 13-40

Hartwig carried out a more detailed study [40] on the Tosoh system, and found that the efficient coupling of cyclic secondary amines and aryl bromides could be performed at room temperature when a Pd:**20** ratio of 1:0.8 was used (Scheme 13-41). The amination of aryl chlorides proceeded at 70 °C with this system. Substrates bearing a variety of functional groups were tolerated with this catalytic system when weak bases were employed.



Scheme 13-41

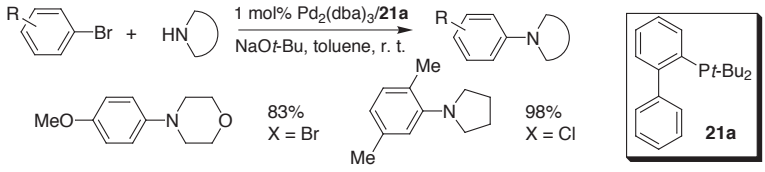
The catalyst derived from **12b** demonstrated a broader substrate scope than that from **1** [34]. Aryl chlorides as well as bromides could be used with this supporting ligand (Scheme 13-42). $Pd_2(dba)_3$/**12b** can effect the cross-coupling of morpholine and methyl 4-bromobenzoate in the presence of K_3PO_4. When stronger bases were used, a substantial amount of byproduct produced by ester cleavage was observed. Substrates bearing enolizable carbonyl groups (e. g., 4-bromoacetophenone) could also be coupled with morpholine using Cs_2CO_3 as base, without undesired side reactions such as aldol processes.



Scheme 13-42

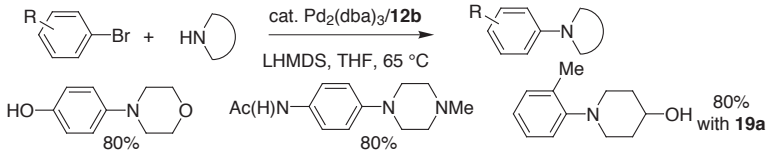
Catalysts derived from the bulky, electron-rich ligands **19a** and **21a** have demonstrated even higher catalytic activities (but not better catalyst longevity or scope) for amination reactions [36]. These ligands can be used to effect the amination of a variety of aryl bromides as well as aryl chlorides at room temperature. For example, in the presence of NaO*t*Bu, electron-rich 4-bromoanisole coupled with morpholine at room temperature to afford the desired product in 83 % yield (Scheme 13-43).

Substrates containing unprotected hydroxyl, phenol, or primary and secondary amide functional groups are problematic under most amination conditions. This is presumably due, in some instances, to the strong binding affinity of the depro-



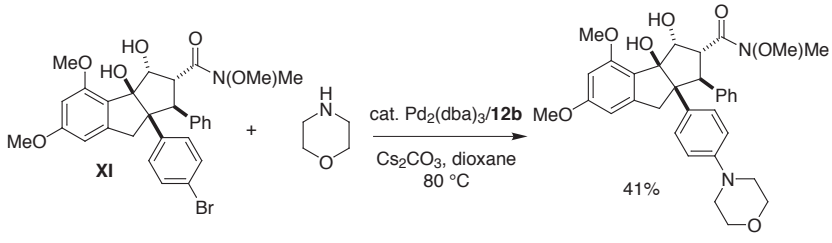
Scheme 13-43

tonated species towards Pd(II). A recently reported protocol [87] employing a combination of LHMDS and **12b** (or **19a**) demonstrated expanded functional group tolerance (Scheme 13-44). In particular, free hydroxyl, secondary amide and enolizable ketones are tolerated under these reaction conditions.



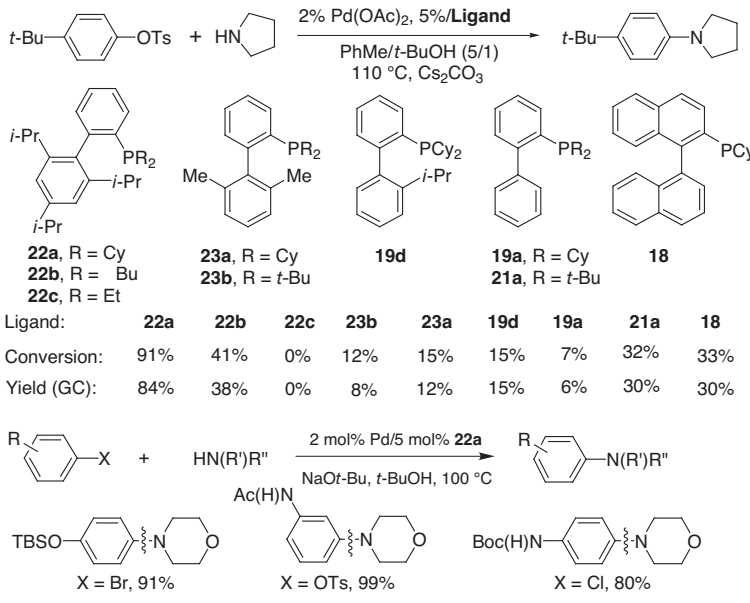
Scheme 13-44

Dobler [88] employed the Pd-catalyzed amination protocol as a key step in the total synthesis of rocaglamide analogues (Scheme 13-45). Several ligands were examined, and only the Pd/**12b** catalyst system allowed the coupling of the highly functionalized aryl bromide **XI** with morpholine to give the product in even moderate yield.



Scheme 13-45

Using pyrrolidine and 4-*t*-butylphenyl tosylate as a prototypical substrate combination, Buchwald carried out a comparative study of various ligands that demonstrated the high efficiency that ligand **22a** possesses (Scheme 13-46) [27]. The size of the dialkylphosphino group and the substituents at the 2- and 6-positions of the bottom ring were key. For example, substituting the two isopropyl groups in **22a** with methyl groups as in **23a** provided a ligand that was inefficient for this transformation. With the bottom ring as 2,4,6-triisopropylphenyl held constant,



Ligand:	22a	22b	22c	23b	23a	19d	19a	21a	18
Conversion:	91%	41%	0%	12%	15%	15%	7%	32%	33%
Yield (GC):	84%	38%	0%	8%	12%	15%	6%	30%	30%

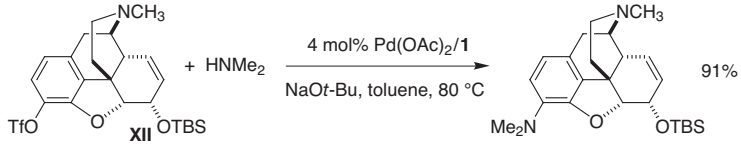
Scheme 13-46

the effect of varying the size of the PR_2 moiety was examined. Neither the ligand with the smallest group (Et_2P, **22c**) nor the largest group (tBu_2P, **22b**) was as efficient as **22a**. Now commercially available **22a** [89] has proven to be the most general ligand for the amination of arenesulfonates. Interestingly, it was discovered that reactions of benzenesulfonates, in many instances, provided higher yields and/or proceeded with shorter reaction times than the corresponding tosylates.

13.4.1.4 Acyclic Aliphatic Secondary Amines

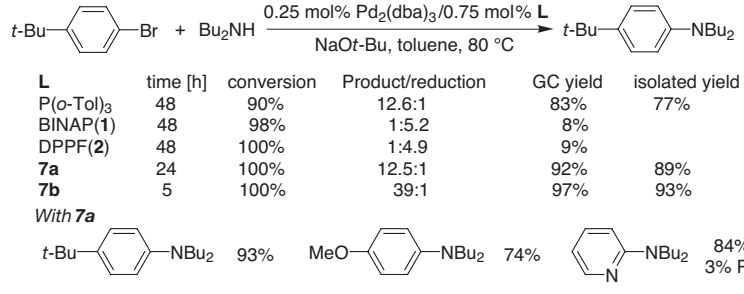
Acyclic aliphatic secondary amines are more challenging substrates for aromatic amination processes as they are sterically more demanding and more prone to β-H elimination than cyclic dialkylamines. The level of steric encumbrance of the substrates can be extremely important to the success of a particular outcome. For example, the coupling of *ortho*-substituted aryl halides with dialkylamines remains a challenge to date. In most cases, *N*-methylaniline is an excellent substrate, whereas the arylation of other alkyl arylamines or dialkylamines could be problematic. Success with this particular amine does not necessarily presage success with any other amine nucleophiles. Therefore, protocols that only show results using *N*-methylaniline will not be discussed at this point.

The initial catalytic system based on *o*-Tol_3P was somewhat effective for the arylations of dialkylamines [18], whereas catalysts based on chelating ligands were much poorer [29c]. An exception was the amination of the aryl triflate **XII** with the smallest amine in this class, dimethylamine, using Pd/**1** to provide the morphine derivatives in 91 % yield [90].



Scheme 13-47

A study of the efficiency of different ligands revealed that **7a** and **7b** [91] were superior to either **1** or **2** for the arylation of acyclic secondary amines, with both rate enhancements and higher yields being observed (Scheme 13-48). Using Pd/**7a**, even electron-rich aryl bromides could be coupled with acyclic dialkylamines in good yield.

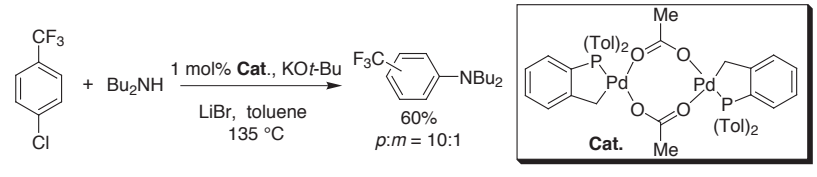


L	time [h]	conversion	Product/reduction	GC yield	isolated yield
P(*o*-Tol)$_3$	48	90%	12.6:1	83%	77%
BINAP(**1**)	48	98%	1:5.2	8%	
DPPF(**2**)	48	100%	1:4.9	9%	
7a	24	100%	12.5:1	92%	89%
7b	5	100%	39:1	97%	93%

With ***7a***

Scheme 13-48

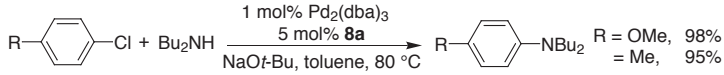
The first amination of an aryl chloride was reported by Beller, who discovered that palladacycle derived from *o*-Tol$_3$P was able to catalyze the arylation of acyclic secondary amines with activated chlorides in the presence of added LiBr (Scheme 13-49) [43]. The formation, in some cases, of substantial amounts of regioisomeric products indicated the presence of a competing benzyne pathway.



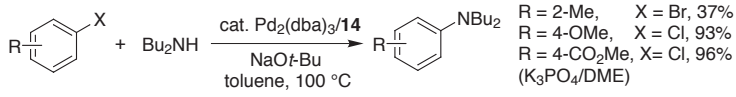
Scheme 13-49

The carbene ligand derived from the imidazolium salt **8a** provided a catalyst that was active enough to effect the Pd-catalyzed coupling of dibutylamine and aryl chlorides at 80 °C (Scheme 13-50) [41a].

Recently, Hartwig reported that the arylation of acyclic dialkylamines could be efficiently carried out using Q-Phos, **14** (Scheme 13-51) [77]. While the reaction of *para*-substituted aryl halides with dialkylamines afforded products in good



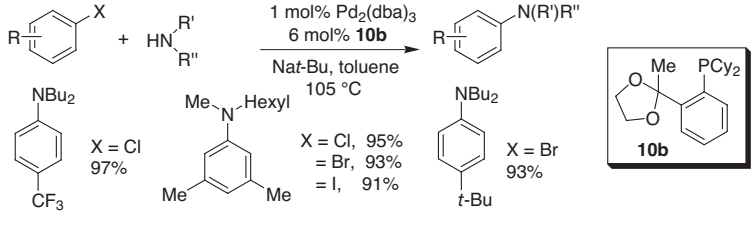
Scheme 13-50



Scheme 13-51

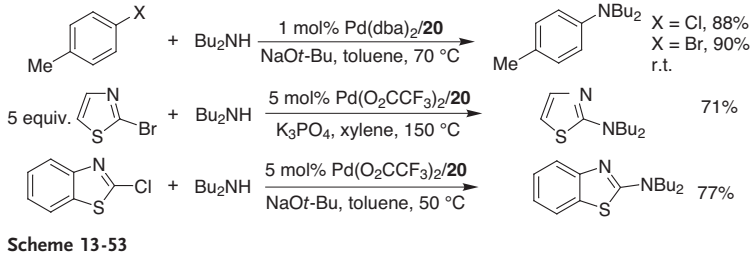
yield, the amination of the *ortho*-substituted aryl halides was troublesome, and large amounts of arene product were observed. It should be noted that, at present, no system is available for the efficient catalysis of this type of substrate combination.

The P,O ligand, **10b**, developed by Guram was equally effective for the coupling of aryl halides and dialkylamines (Scheme 13-52) [76]. Unfortunately, only the reactions of simple aryl halides were reported, although the amination of electron-neutral aryl chlorides proceeded with good yield.



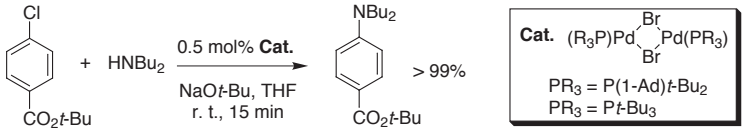
Scheme 13-52

Hartwig has shown that the Pd/**20** system could effectively catalyze the amination of simple aryl chlorides, as well as aryl bromides, with acyclic secondary alkylamines, even at room temperature (Scheme 13-53) [40]. Moreover, the reactions between hetero-aromatic aryl halides and acyclic dialkylamines were realized at a temperature between 50–150 °C, although the use of $Pd(O_2CCF_3)_2$ was necessary [92]. In some instances, up to a five-fold excess of the heteroaryl halide was used.



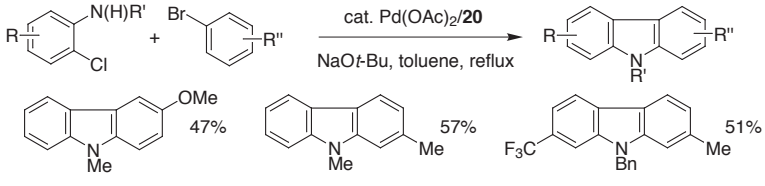
Scheme 13-53

Recently, the Yale group also reported that Mingos-type Pd(I) dimer complexes [93], $[(PdBrL)_2]$, were active catalysts for the reaction of various aryl chlorides and dialkylamines at room temperature in minutes (Scheme 13-54) [46]. However, the scope of this catalytic system was narrower than those previously described that employed biphenylphosphines (**12b**, **19a**, **21a**) and t*Bu*$_3$P, **20**, as primary amines and diarylamines gave no reaction at room temperature.



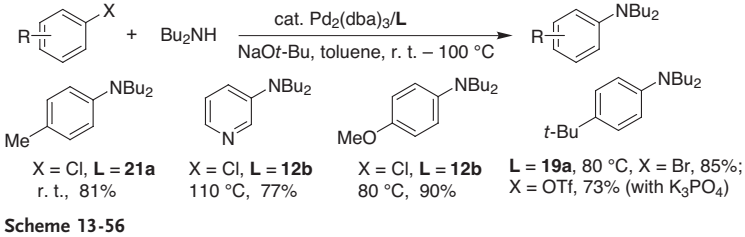
Scheme 13-54

In light of the recent focus on the aromatic C-H functionalization processes, Bedford devised an ingenious one-pot amination/C-H functionalization sequence for the synthesis of carbazoles from aryl halides and *N*-alkyl-2-chloroanilines (Scheme 13-55) [94]. The optimized reaction conditions included the use of $Pd(OAc)_2$/**20** as catalyst and NaOt*Bu* as base. It is important to note that the key C-H functionalization step was precedented by the investigations of Sakamoto [95].



Scheme 13-55

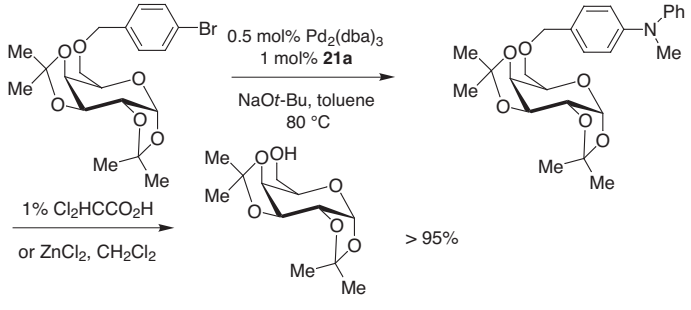
The aminophosphine **12b** proved to be an excellent supporting ligand for the coupling of acyclic secondary alkylamines. The catalyst system derived from this ligand is active enough to allow the arylation of acyclic dialkylamines with aryl halides (including iodides, bromides, and chlorides) to proceed at room temperature (Scheme 13-56) [36]. Due to the mild reaction conditions, a broad range of substrates including electron-rich, electron-neutral, and electron-poor aryl bromides



Scheme 13-56

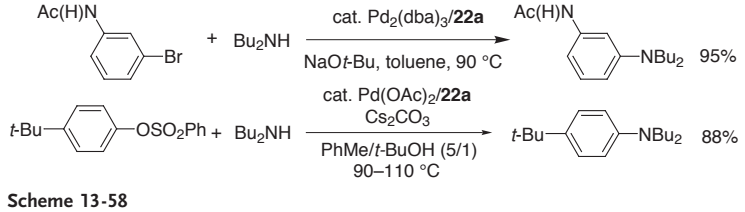
could be successfully coupled in good yield. For example, as shown in Scheme 13-56, the reaction of 4-chloroanisole with dibutylamine occurred at 80 °C in excellent yield. The simple biphenyldialkylphosphines (**19a** and **21a**) were also able to effect the amination of various aryl halides at room temperature. The use of ligand **19a** was more effective than ligand **21a** for the arylation of acyclic secondary amines. The reactions of aryl chlorides as substrates often gave better yields than those of aryl bromides.

An unusual application of Pd-catalyzed C-N bond formation employing this particular catalytic system was reported by Seeberger and Buchwald, where C-N bond formation was used as an integral component of protecting group cleavage [96]. As shown in Scheme 13-57, Pd-catalyzed coupling of *N*-methylaniline with the 4-bromobenzyl ether afforded an electron-rich benzyl ether that can be easily cleaved by acid treatment. This strategy also offered the possibility of selective removal of protecting groups by taking advantage of the different reactivity of 4-chloro-, 4-bromo-, and 4-iodobenzyl groups in the Pd-catalyzed C-N bond-forming step.



Scheme 13-57

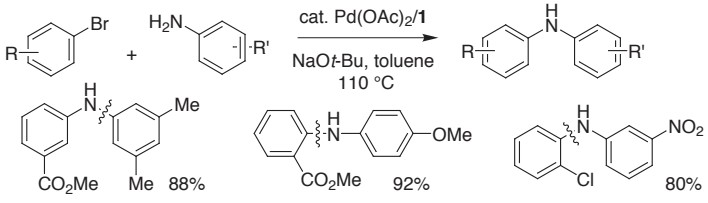
XPhos, **22a**, despite its relative youth, has shown high reactivity and generality in Pd-catalyzed C-N bond-forming processes [27]. With different bases and solvent combinations (Scheme 13-58), various acyclic dialkylamines were coupled with aryl bromides, aryl chlorides, and aryl tosylates, including those that possessed potentially problematic functional groups.



Scheme 13-58

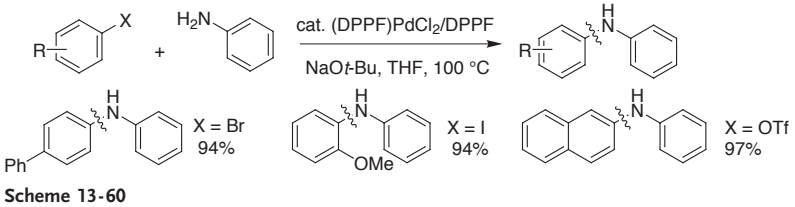
13.4.1.5 **Primary Anilines**

Primary anilines are among the most easily coupled substrates, and their reactions enjoy a high level of functional group compatibility. However, similar to what is observed for primary alkylamines, double arylation can be a competing pathway. A slight excess of amine relative to aryl halide is generally employed in order to mitigate this side reaction. The initial *o*-Tol_3P/Pd catalyst was moderately effective for the arylation of primary anilines [18], while that derived from **1** was more reliable and enjoyed a broad substrate scope (Scheme 13-59) [29c].



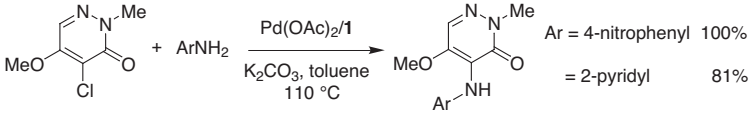
Scheme 13-59

Catalysts derived from other chelating phosphines, particularly DPPF, could also efficiently catalyze the arylation of anilines. Employing this catalyst system in combination with NaO*t*Bu, aryl bromides, iodides [30], and triflates [68] were seen to be viable substrates for amination reactions.



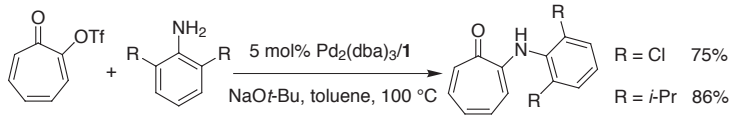
Scheme 13-60

The amination of 4-chloro-3(2*H*)-pyridazinones with anilines was realized using $Pd(OAc)_2$/**1** along with the weak base Cs_2CO_3 (Scheme 13-61) [97]. The selection of base is extremely important, as the use of NaO*t*Bu failed to give the desired products. Moreover, an excess of base was necessary in order to conduct the reaction with low catalyst loading.



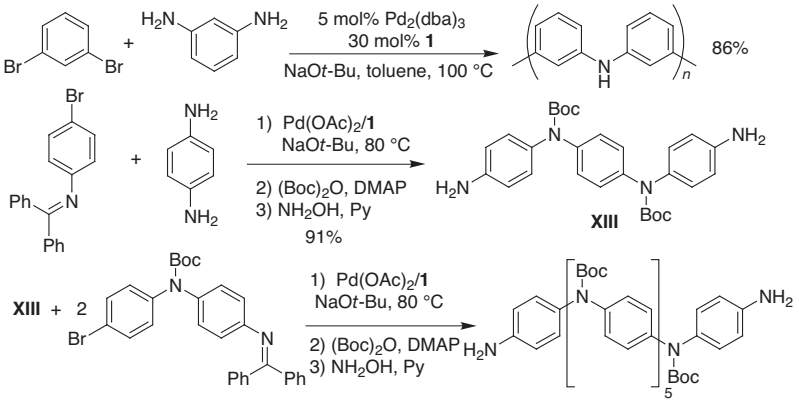
Scheme 13-61

Employing Pd/**1**, Brookhart and Hicks [98] reported the amination of the homoaromatic 2-triflatotropone with a wide variety of anilines including electron-deficient as well as sterically congested ones (Scheme 13-62). Attempts to effect thermal nucleophilic substitution yielded only a trace amount of product.



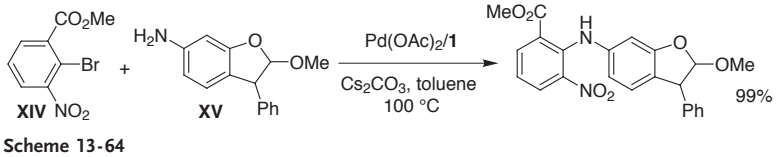
Scheme 13-62

The Pd/**1** system has also found wide application in the area of polymer synthesis. Using 1,3-dibromobenzene and 1,3-diaminobenzene as monomers, Kanbara prepared poly(imino-1,3-phenylene) in excellent yield with $Pd_2(dba)_3$/**1** as catalyst (Scheme 13-63) [99]. By employing the same catalyst combination, Buchwald was also able to synthesize well-defined, end-functionalized oligoanilines [100].



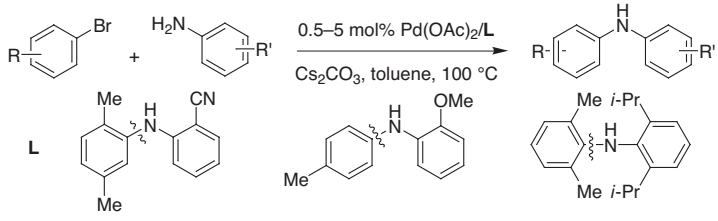
Scheme 13-63

The Pd/**1**-catalyzed combination of aryl bromide **XIV** and aniline **XV** was the key step in Kamikawa's synthesis of phenazine derivatives (Scheme 13-64) [101], and the coupling occurred smoothly to provide the amination product in near-quantitative yield.



Scheme 13-64

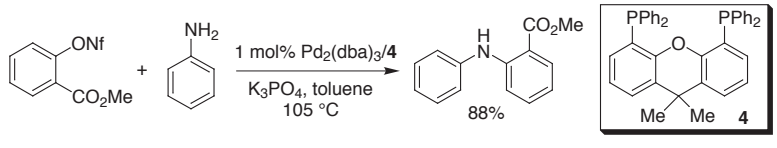
Buchwald reported that the $Pd(OAc)_2$/DPEphos (**5**) system could efficiently accomplish the arylation of anilines with aryl bromides (Scheme 13-65) [33]. This system was at least as active as $Pd(OAc)_2$/**1**, and is more active than the $Pd(OAc)_2$/**2** system for this transformation. It was particularly effective for sterically encumbered substrate combinations.



BINAP	82%	87%	94% (GC)
DPPF	20%	88%	44% (GC)
DPEphos	87%	90%	94%

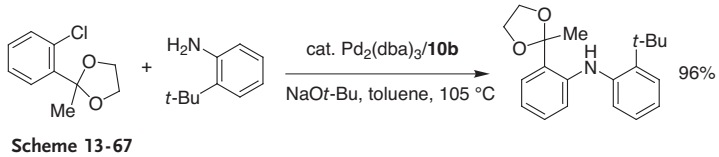
Scheme 13-65

For the amination of nonaflates, Buchwald found that a catalyst derived from **4** gave excellent results [74]. As shown in Scheme 13-66, the cross-coupling of 2-methoxycarbonyl-phenyl nonaflate with aniline afforded the desired product in 88 % yield at 105 °C.



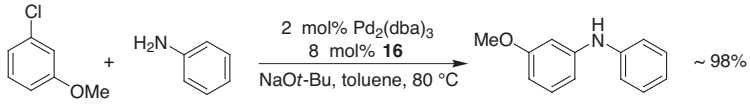
Scheme 13-66

Guram reported that **10b** was an effective ligand for the amination of aryl bromides as well as aryl chlorides (Scheme 13-67) [76]. This highly active catalyst also allowed coupling between sterically hindered anilines and sterically hindered aryl chlorides.



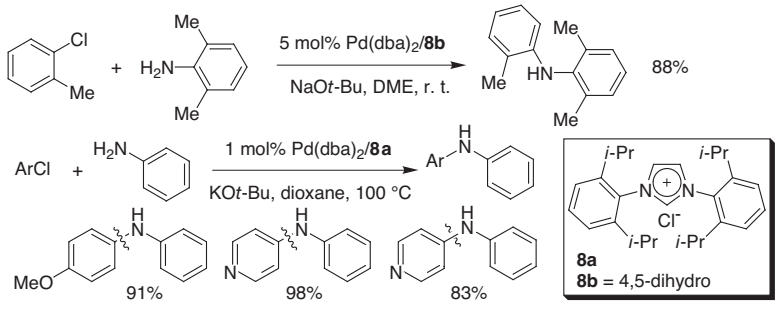
Scheme 13-67

Verkade demonstrated that the bicyclic triaminophosphine P[N(*i*Bu)CH_2CH_2]$_3$N (**16**) could be used as a supporting ligand for the amination of aryl chlorides with anilines (Scheme 13-68) [78].



Scheme 13-68

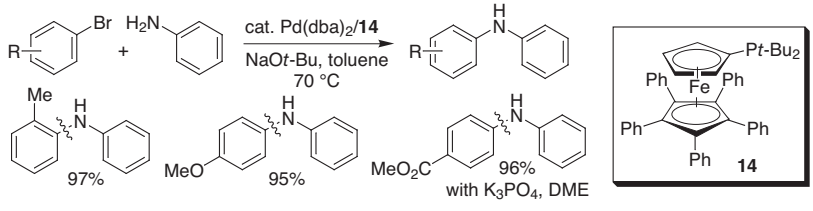
With saturated (**8b**) [41b] and unsaturated carbenes **8a** [41a] as ligands, the amination of aryl chlorides could also be carried out at room temperature or with heating, respectively (Scheme 13-69). Nolan reported the synthesis of an air-stable complex [Pd(**8a**)Cl_2]$_2$, and found that this complex was able to catalyze the arylation of anilines [48].



Scheme 13-69

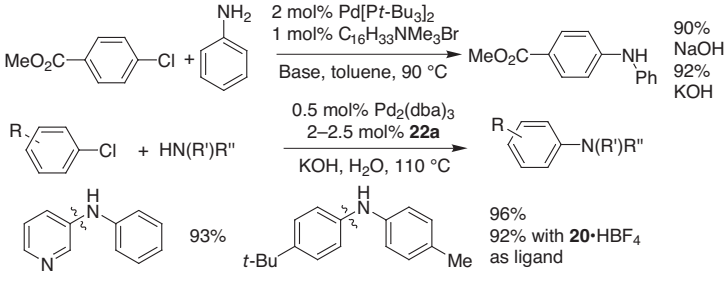
The combination of Pd(dba)$_2$ and Q-Phos, **14**, was also a successful catalyst for the arylation of anilines [77]. As shown below, the amination of aryl bromides was carried out at 70 °C in high yield using 2 mol % of a Pd catalyst.

Employing NaO*t*Bu as base, the coupling of aryl chlorides and anilines could be achieved at room temperature using Pd/**20** [40]. In addition, Hartwig reported that



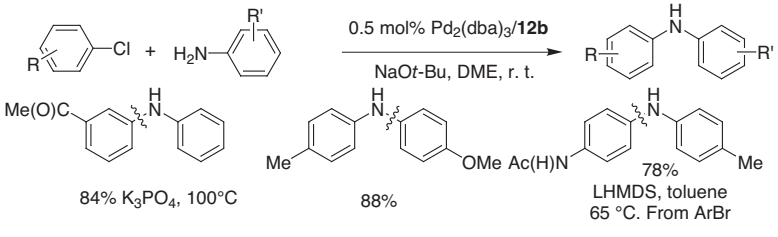
Scheme 13-70

using this catalytic system, amination reactions could be carried out under biphasic conditions with aqueous alkaline hydroxides as bases and cetyltrimethylammonium bromide as a phase-transfer catalyst (Scheme 13-71) [52]. Sodium and potassium hydroxide gave similar results. For the arylation of anilines, a variety of functional groups could survive under these biphasic conditions with the combination of anilines and hydroxide bases. Interestingly, with **22a** as a ligand [27], Buchwald found that the amination reaction could be carried out with KOH in H_2O in the absence of a phase-transfer catalyst.



Scheme 13-71

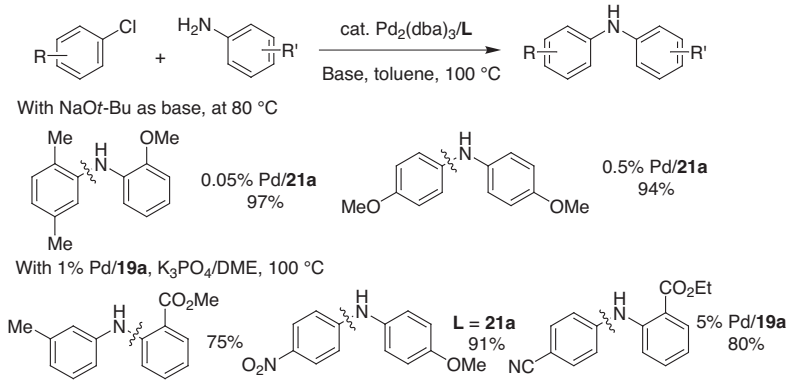
With the introduction of ligand **12b**, the amination of functionalized aryl chlorides was realized using the weaker base, K_3PO_4 [34, 36]. Moreover, with stronger bases, the reaction of aryl chlorides as well as aryl bromides with anilines could be conducted at room temperature with 1 mol % catalyst loading (Scheme 13-72). It was also discovered that the use of LHMDS extended the functional group compatibility of this system [87].



Scheme 13-72

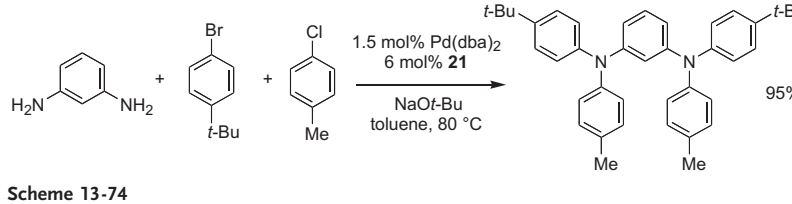
The catalysts formed from biphenyl ligands **19a** and **21a** and $Pd_2(dba)_3$ were highly effective and enjoyed a broad substrate scope, as electron-rich, electron-neutral, and electron-poor aryl chlorides were efficiently coupled with anilines with high turnover numbers [36].

An application of this highly active catalytic system was reported by Harris and Buchwald in the synthesis of triarylamines [102]; these authors exploited the differ-



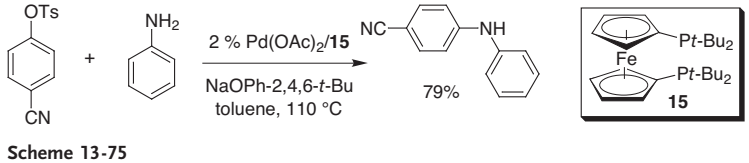
Scheme 13-73

ence in reactivity of aryl chlorides and aryl bromides in devising a one-pot synthesis of triarylamines. Simply heating the mixture of an aryl chloride, an aryl bromide and an aniline in the presence of Pd/**21**-catalyst and NaO*t*Bu afforded the desired triarylamine in excellent yield. For example (Scheme 13-74), heating a mixture of 3-aminoaniline, 4-bromo-*t*-butylbenzene (2 equiv.), 4-chlorotoluene (2 equiv.), base and the catalyst resulted in the formation of four C-N bonds to provide the desired triarylamine in 95 % yield.



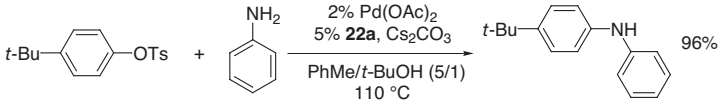
Scheme 13-74

Hartwig disclosed the first example of the coupling of an aryl tosylate with an aniline using a catalyst derived from **15** (Scheme 13-75) [78]. Only one example of the amination of 4-cyanophenyl tosylate with aniline was reported. The use of sterically hindered sodium 2,4,6-tri-*t*-butylphenoxide as the base was critical to the success of this reaction.



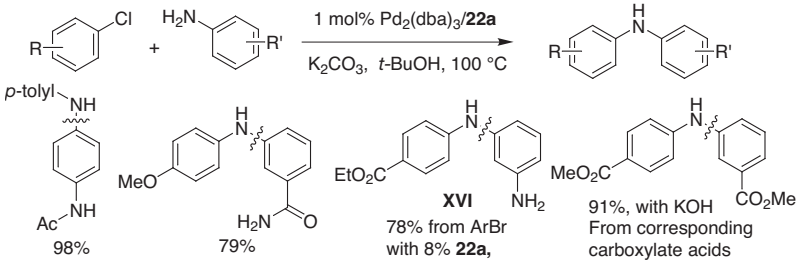
Scheme 13-75

Buchwald recently discovered that the Pd/**22a** system was a more general catalyst for the arylation of tosylates [27]. Excellent yields were obtained in the coupling of a variety of nitrogen nucleophiles and aryl benzenesulfonates or aryl tosylates using this catalyst system.



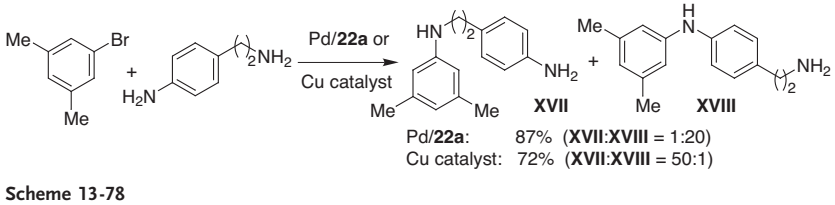
Scheme 13-76

Besides the aryl tosylates, Pd/**22a** was very efficient for the amination of functionalized aryl halides [27]. Particularly noteworthy was that the amination reaction could be carried out with substrates containing free amino, free amido, and even free carboxylate. An example carried out in aqueous KOH was also reported. Note that in the case of **XVI** the aniline group with more acidic proton was selectively coupled.



Scheme 13-77

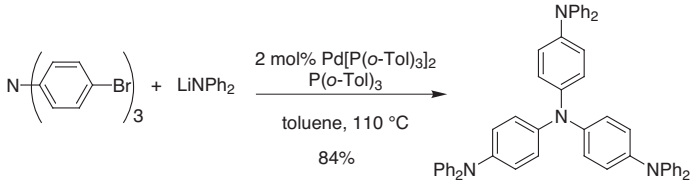
The complementary results seen for Pd-catalyzed and Cu-catalyzed C-N bond-forming processes were exemplified in the highly chemoselective arylation of a compound that contained a primary alkylamine and a primary arylamine [27]. As shown below, with Pd/**22a**, C-N bond formation occurred almost exclusively at the aniline nitrogen, whereas, the selectivity was reversed when CuI/*N,N′*-dimethyl-1,2-cyclohexyldiamine was used as the catalyst.



Scheme 13-78

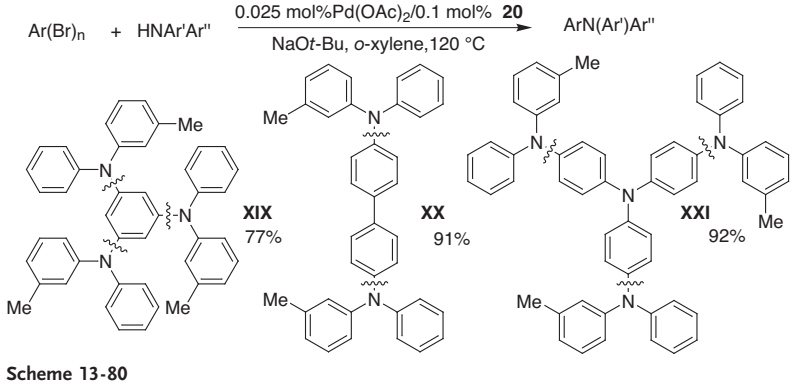
13.4.1.6 **Diarylamines**

Due to their lower nucleophilicity, the arylation of diarylamines is generally slower than that of primary arylamines. As such, the selective monoarylation of anilines can be achieved. Aimed at generating new materials, considerable effort has been devoted to the preparation of triarylamines. By employing *o*-Tol_3P or DPPF as the ligand (Scheme 13-79), Hartwig reported the synthesis of dendrimeric triarylamines [103].



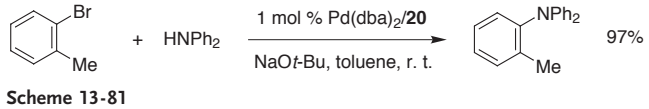
Scheme 13-79

Nishiyama and Koie disclosed the efficient coupling of aryl bromides with diarylamines using $tBu_3P/Pd(OAc)_2$ (Scheme 13-80) [104]. The efficiency of this protocol was exemplified by the synthesis of hole-transport materials **XIX-XXI** from polybrominated aromatic compounds and diarylamines with only 0.025 mol % $Pd(OAc)_2$ used.



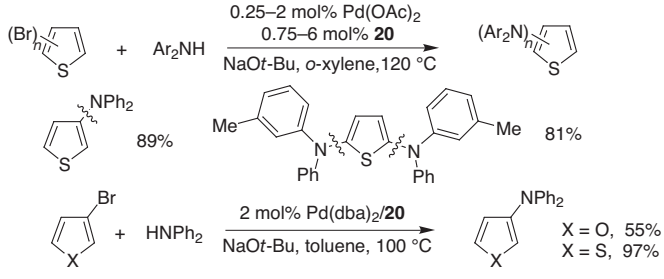
Scheme 13-80

By lowering the ratio of L:Pd to 1:1, Hartwig found that enhanced reaction rates could be achieved with **20**. With this system, the amination of aryl chlorides with diarylamines proceeded at room temperature [40, 105].



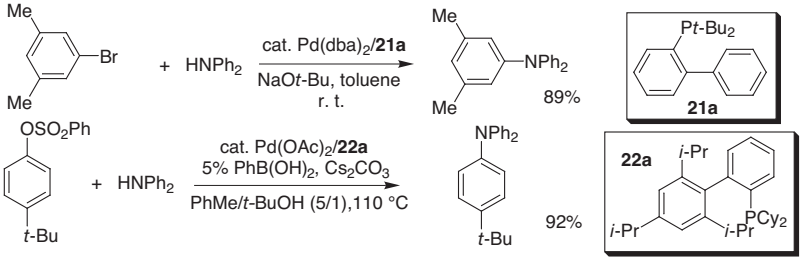
Scheme 13-81

The arylation of diarylamines with heteroaromatic halides was first reported by Watanabe [106] using the Pd/**20** catalytic system (Scheme 13-82). In this way, a variety of thiophene-containing triarylamines were synthesized, and high turnover numbers were realized in many of these examples. Later, using the same catalytic system, Hartwig found that this protocol could also be used for the cross-coupling between bromofurans and diarylamines to give the triarylamines in moderate to good yields [92].



Scheme 13-82

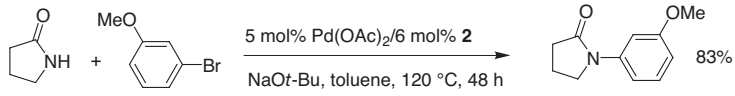
Buchwald also reported that the Pd/**21** system was capable of performing the arylation of diarylamines with aryl bromides and chlorides at room temperature [36]. The catalyst derived from the sterically more congested XPhos, **22a**, allowed the first amination of aryl benzenesulfonates with diarylamines [27].



Scheme 13-83

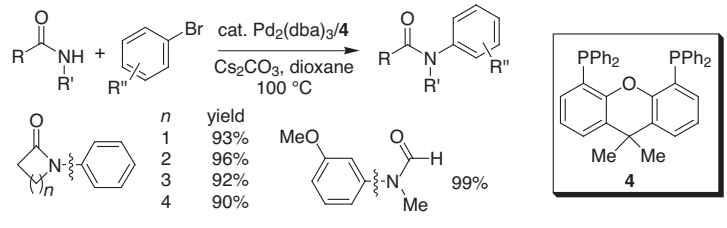
13.4.2
Arylation with Amides

The reactivity of amides in Pd-catalyzed coupling processes is quite different from that of amines, presumably due to the differences in their pK_a values. Shakespeare first reported the intermolecular arylation of amides in 1999 [107]. Using the Pd/DPPF system, the arylation of lactams were realized as shown in Scheme 13-84. With the exception of 2-pyrrolidinone, other lactams could only be coupled with electron-poor aryl bromides.



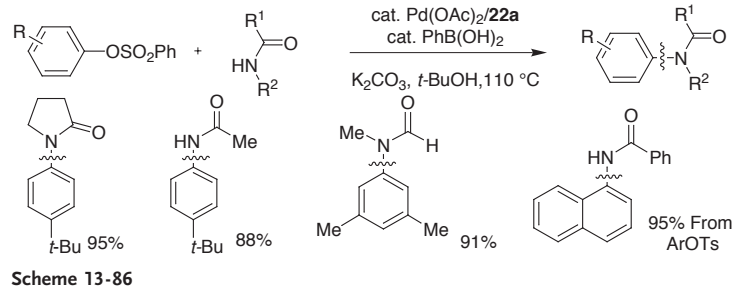
Scheme 13-84

A more efficient and general system based on Xantphos, **4**, for Pd-catalyzed amidation was reported by Yin and Buchwald (Scheme 13-85) [32]. The optimal conditions required the use of dioxane as solvent and Cs_2CO_3 as base. Ester, nitro, and cyano groups were compatible with the reaction conditions. Enolizable ketones were problematic substrates for C-N bond formation of this sort, as products derived from the α-arylation of ketones were generally isolated as the major product. Primary amides, acyclic secondary amides, lactams of various ring size and formamides could be successfully arylated with electron-poor and electron-neutral aryl bromides (Scheme 13-85). For electron-rich aryl halides, byproducts arising from the exchange of the phenyl group of **4** with the aryl group of the product were observed [108]. The catalyst loading and the concentration of the reaction mixture were crucial to the success of the reaction as more phenyl exchange side product arising from **4** was seen with increased quantities of catalyst.



Scheme 13-85

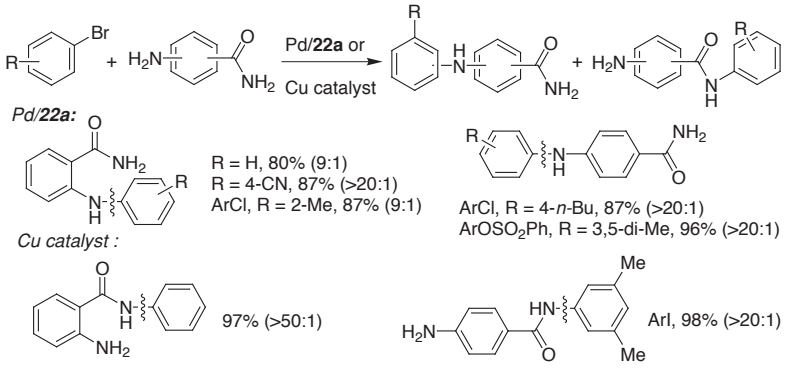
XPhos **22a** allowed the coupling of simple amides with aryl arenesulfonates for the first time [27]. The arylation of lactams, primary amides, and *N*-methylformamide proceeded smoothly with K_2CO_3 as a base in *t*BuOH (Scheme 13-86), though other solvents such as toluene or dioxane provided less satisfactory results. The



Scheme 13-86

addition of a catalytic quantity of phenylboronic acid in these reactions was important to ensure complete reduction of the Pd(II) precatalyst to Pd(0). The application of other ligands including **13**, **15**, and **20** that were able to effect the amination of tosylates, was not efficient for this transformation, and none of these provided more than a 4% yield of the desired product.

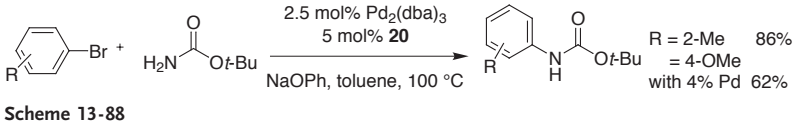
An interesting interplay between Pd and Cu catalysts was observed when aminobenzamides were used as nucleophiles [27]. With CuI/*N,N′*-dimethylethylenediamine as catalyst, the arylation reactions occurred exclusively at the amido moiety. In contrast, when the combination Pd/**22a** was employed, the amino nitrogen was selectively arylated.



Scheme 13-87

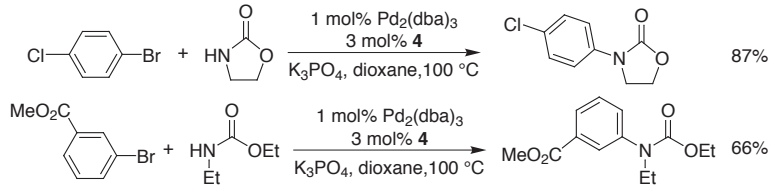
13.4.3 Arylation with Carbamates

Hartwig first reported the Pd-catalyzed arylation of carbamates using tBu_3P, **20**, as ligand (Scheme 13-88) [40]. The optimal reaction conditions involved a 2:1 ratio of L:Pd, and this worked well for electron-deficient and electron-neutral aryl bromides. However, for electron-rich aryl bromides the yield of product was lower. The use of sodium phenoxide as the base was crucial to the success of this reaction.



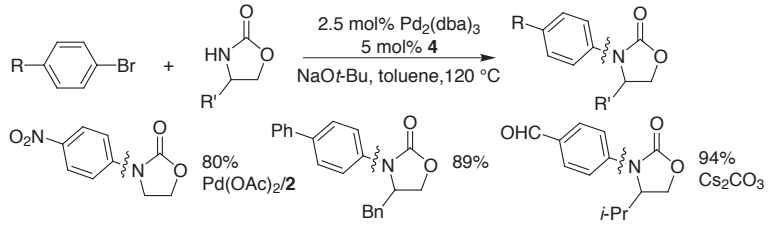
Scheme 13-88

The Pd/Xantphos, **4**, system that was effective for the arylation of amides was also effective for the arylation of carbamates [32]. As shown in Scheme 13-89, both cyclic and acyclic carbamates were efficiently arylated with functionalized aryl bromides.



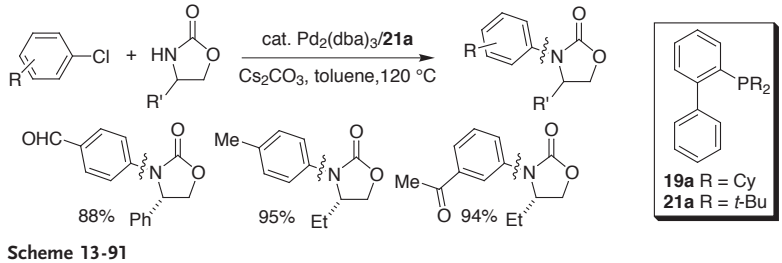
Scheme 13-89

Recently, Cacchi et al. reported the arylation of oxazolidinones through Pd-catalyzed C-N bond formations using **4** as the supporting ligand [109]. These authors determined that the choice of ligand and base was dependent on the electronic nature of the aryl bromides, as shown in Scheme 13-90. For aryl bromides bearing enolizable ketones, products derived from ketone arylation processes were isolated.



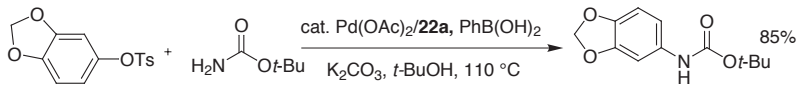
Scheme 13-90

Ghosh et al. examined the effects of various ligands on the arylation of oxazolidinones using aryl chlorides [110]. It was found that in most cases, catalysts derived from the chelating ligand BINAP, **1**, DPPF, **2**, Xantphos, **4**, and DPEphos, **5**, were markedly less efficient than those from **12b**, **19a**, and **21a**. Particularly noteworthy was the finding that aryl chlorides bearing enolizable ketones were successfully used as substrates.



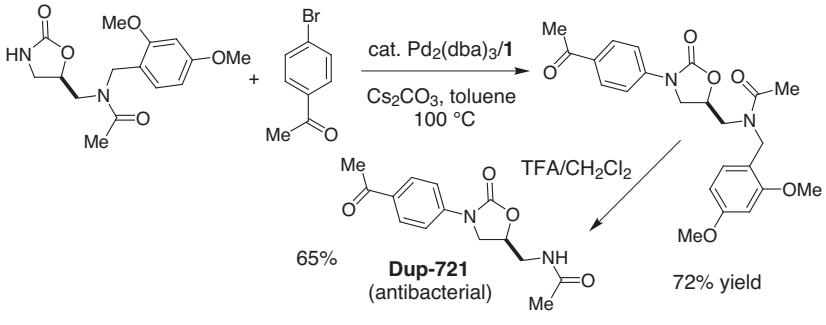
Scheme 13-91

The general utility of XPhos, **22a**, has been demonstrated here again [27], as Buchwald and Huang reported the first coupling between an aryl tosylate and a carbamate with Pd/**22a** (Scheme 13-92).



Scheme 13-92

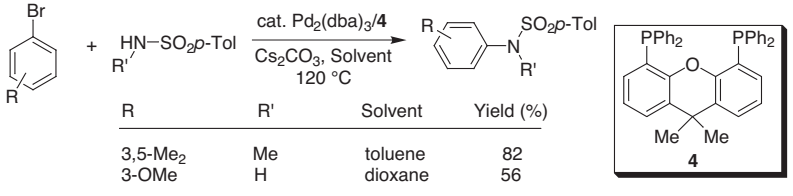
An interesting example of Pd-catalyzed arylation of a carbamate with an aryl bromide was reported by Madar et al. [111]. In their study towards the synthesis of antibacterial agents, these authors found that BINAP, **1**, was an efficient ligand for the arylation of oxazolidinones. This protocol was applied to the total synthesis of a known antibacterial Dup-721, as shown below.



Scheme 13-93

13.4.4
Arylation with Sulfonamides and Sulfoximines

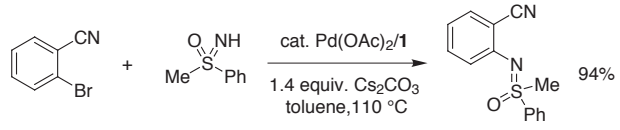
In addition to amides and carbamates, sulfonamides were effectively coupled with aryl bromides using Xantphos, **4**, as the ligand [32]. Both primary and secondary sulfonamides were successfully arylated at 120 °C and with Cs_2CO_3 as base.



R	R'	Solvent	Yield (%)
3,5-Me_2	Me	toluene	82
3-OMe	H	dioxane	56

Scheme 13-94

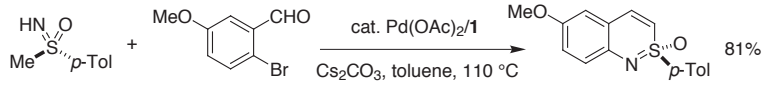
Bolm et al. reported the Pd catalyzed *N*-arylation of sulfoximines with electron-neutral and electron-deficient aryl bromides and aryl iodides with chelating ligands [112], namely BINAP, **1**, *tol*-BINAP, and DPEphos, **5** (Scheme 13-95). Although



Scheme 13-95

aryl bromides were effectively coupled, aryl iodides required the addition of lithium and silver salts.

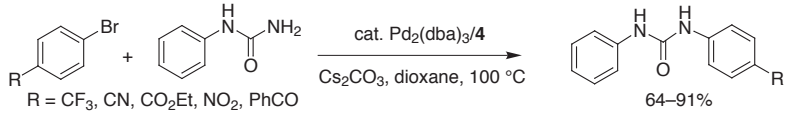
Based on Bolm's result, Harmata reported a clever one-pot transformation involving C-N bond formation followed by an intramolecular condensation to yield benzothiazines, as shown in Scheme 13-96 [113].



Scheme 13-96

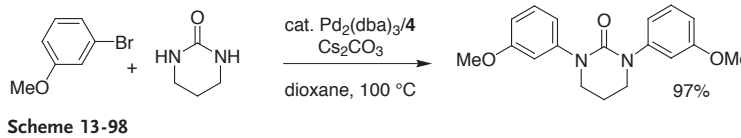
13.4.5
Arylation with Ureas

Beletskaya found that coupling reactions between electron-deficient aryl halides and ureas could be accomplished with XantPhos, **4**, as the supporting ligand with $Pd_2(dba)_3$ [114]. When *N*-phenylurea was used as a substrate, *N*-aryl-*N*′-phenylureas were isolated as the major products.



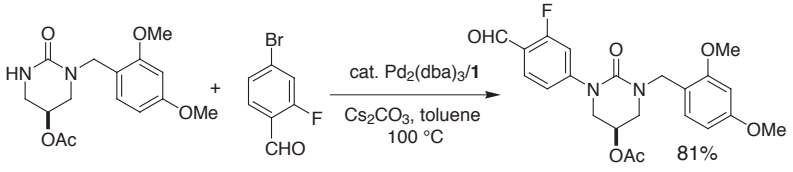
Scheme 13-97

Employing the same catalytic system, Buchwald reported the arylation of cyclic ureas with electron-neutral aryl bromides to give the symmetrical products in excellent yield [32].



Scheme 13-98

In their study on the arylation of oxazolidinones [111], Madar discovered that the $Pd_2(dba)_3$/**1** system could be used to catalyze the coupling between ureas and electron-deficient aryl bromides, as shown below. Noteworthy is the selective substitution of the bromide in the presence of the fluoride at the 2-position.



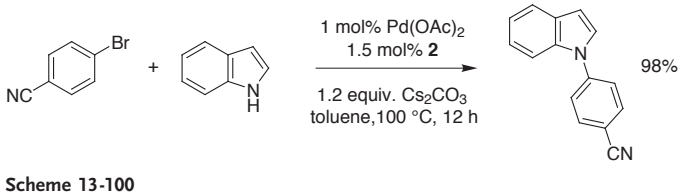
Scheme 13-99

13.4.6
Arylation with Heterocycles

The scope of Pd-catalyzed C-N bond formation between heterocycles and aryl halides has so far been limited. In most instances, only simple examples have been employed as substrates. With the resurgence of interest in the Ullmann-type coupling reactions over the past ten years [20], use of the traditional Ullmann reaction has been greatly expanded. Milder reaction conditions have been discovered, mainly due to the emergence of new ligands for such processes. Consequently, the reader is encouraged to consult references related to this chemistry [115].

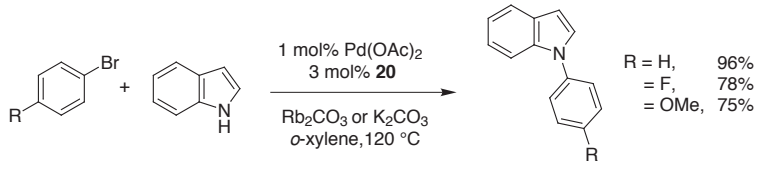
13.4.6.1 Indoles

One major challenge encountered in the arylation of indoles is the control of regioselectivity between *N*-arylation and *C*-arylation. Hartwig first reported the arylation of indoles using Pd/**1** and Pd/**2** [116]. With these, only aryl bromides bearing a *para*-electron-withdrawing group could be efficiently coupled with indole.



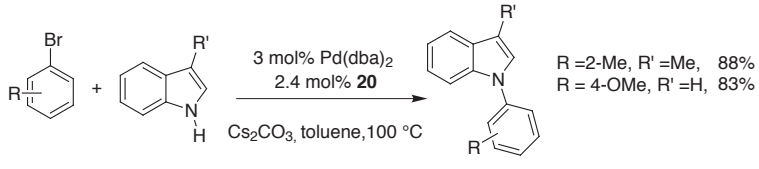
Scheme 13-100

Subsequently, milder reaction conditions for the arylation of indole were discovered by employing the $Pd(OAc)_2$ and *t*-Bu_3P, **20**, system (Scheme 13-101). With this catalyst system, Watanabe disclosed that the arylation of indole could proceed with electron-rich, electron-neutral, and electron-deficient aryl bromides [117].



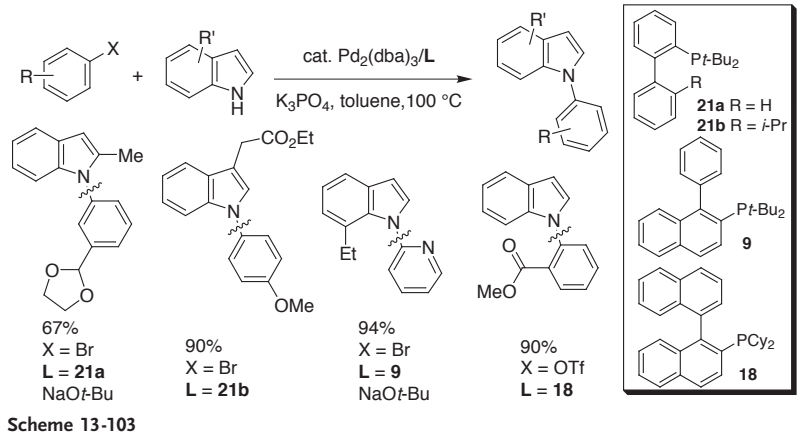
Scheme 13-101

Using the same catalytic system, but with a Pd:**20** ratio of 1:0.8 (Scheme 13-102), Hartwig found that aryl chlorides as well as aryl bromides could be coupled with indoles in a shorter reaction time than with the original system [40]. When most *ortho*-substituted aryl bromides were used, a mixture of *N*-arylated, *C*-arylated, and diarylated products were formed.

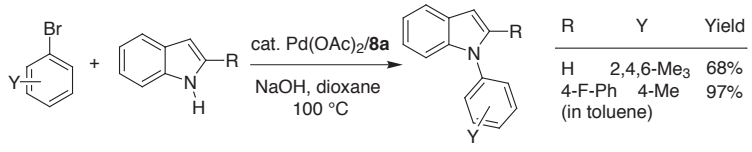


Scheme 13-102

Buchwald found that the coupling of aryl halides and triflates with indoles exhibited a strong ligand-dependence [118]. For example, a catalyst derived from either the binaphthyl ligand **18** or the biphenyl ligand **12b** worked well for the coupling of aryl triflates with indoles lacking substituents at the 2- and/or 7-positions (Scheme 13-103). In addition, Pd/**18** was also effective for the coupling with *o*-substituted aryl halides. For the arylation of 2- and/or 7-substituted indoles, either **9** or **21a** was used in combination with $Pd_2(dba)_3$.



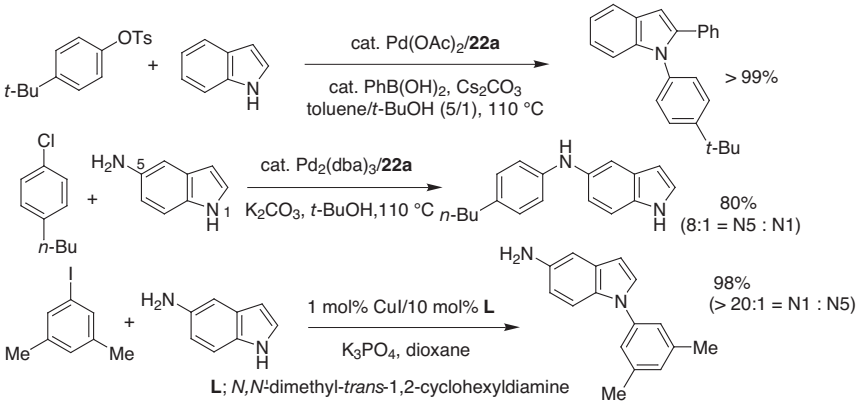
Scheme 13-103



R	Y	Yield
H	2,4,6-Me_3	68%
4-F-Ph	4-Me	97%
(in toluene)		

Scheme 13-104

Using the unsaturated carbene **8a** as the supporting ligand and NaOH as base [51], Nolan reported the *N*-arylation of indoles with aryl bromides (Scheme 13-104). Other bases such as KO*t*Bu, K_3PO_4 were not effective. Noteworthy was the efficiency for the coupling with the hindered substrates, as shown in Scheme 13-104.

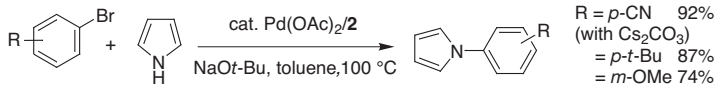


Scheme 13-105

XPhos, **22a**, was used in the first demonstration of the coupling of a nitrogen heterocycle [27], in this case indole, with an aryl tosylate. Another interesting result with **22a** was seen when 5-aminoindole was used as the nucleophile, and selective arylation either at the amino or the indole nitrogen was accomplished simply by switching between a Cu catalyst and a Pd catalyst, as shown in Scheme 13-105.

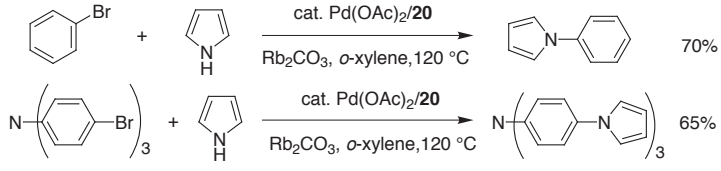
13.4.6.2 **Pyrroles**

Very few studies have been conducted on the *N*-arylation of pyrroles, and only studies with pyrrole have been described. There appear to be no reports on the coupling of *o*-substituted aryl halides with simple pyrrole, but in those which do exist the pyrrole exhibited similar reactivity to indole. Hartwig reported the arylation of pyrrole with electron-deficient aryl bromides using DPPF, **2**, as supporting ligand and Cs_2CO_3 as base (Scheme 13-106) [116]. For electron-neutral or electron-rich aryl bromides, the use of the stronger base, NaO*t*Bu, was required.



Scheme 13-106

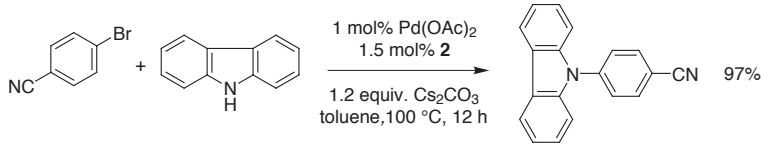
Watanabe, by using **20**, was able to effect the coupling between pyrrole and electron-neutral aryl bromides with Rb_2CO_3 as base [117], and applied this protocol to the synthesis of triazole derivatives. As shown in Scheme 13-107, 4,4′,4″-tris(*N*-pyrrolyl) triphenylamine was prepared from pyrroles and tris(4-bromophenyl) amine in 65 % yield.



Scheme 13-107

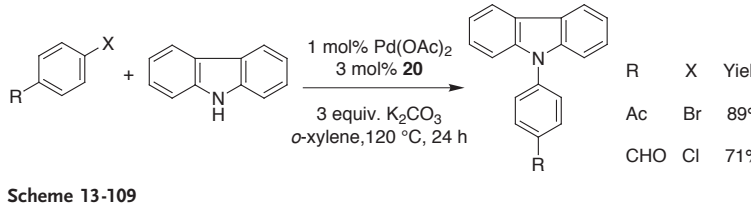
13.4.6.3 **Other Heterocycles**

The protocol described for the arylation of pyrroles using Pd/**2** was also applied to the arylation of carbazole (Scheme 13-108) [116]. Electron-deficient aryl bromides reacted with carbazole to give the desired products in 97 % yield.



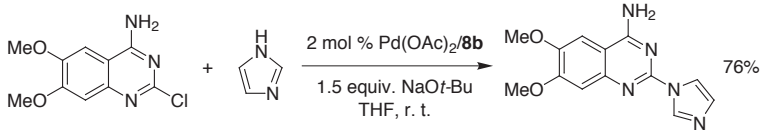
Scheme 13-108

Using the Pd/**20** catalyst system, Watanabe found that the arylation of carbazoles enjoys a broader substrate scope than that of pyrrole [117]; consequently, electron-poor and electron-neutral aryl bromides, as well as activated aryl chlorides, were successfully coupled.



Scheme 13-109

Recently, in a study related to multi-drug resistance and P-glycoprotein binding, Andrus et al. [119] reported an alternate route to the known antihypertension agent iodoazidoaryl prazosin (IAAP) that involved a Pd-catalyzed amination reaction. These authors also reported the coupling of imidazole with 4-amino-2-chloroquinazoline in the presence of the Pd/**8b** system.

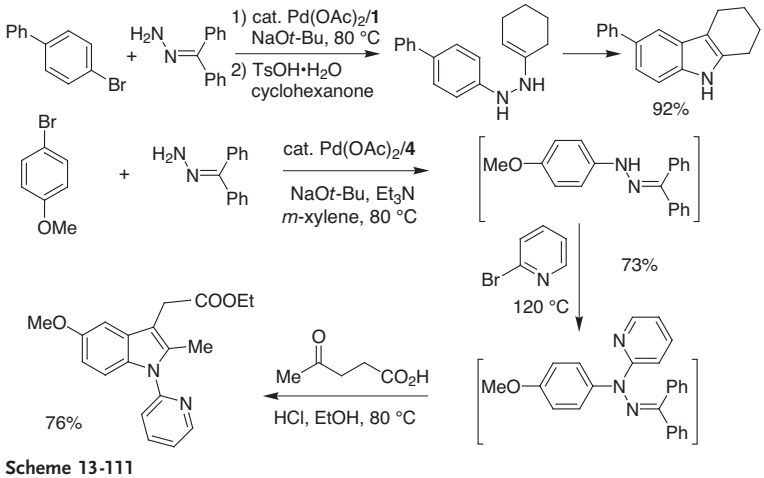


Scheme 13-110

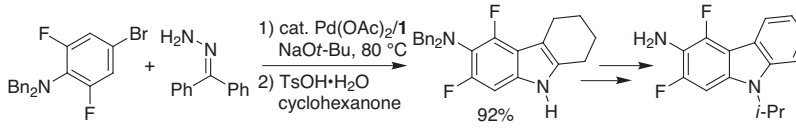
13.4.7
Amination with Other Nitrogen Sources

Since the discovery of the Pd-catalyzed C-N bond-forming processes, a plethora of nitrogen nucleophiles has been employed. Buchwald first reported the cross-coupling reactions of aryl halides or triflates with benzophenone hydrazone and applied this reaction to a one-pot, modified Fisher indole synthesis (Scheme 13-111) [120]. Both BINAP, **1**, and Xantphos, **4**, were used as ligands for this transformation; **4** gave slightly better results. A sequential Pd-catalyzed arylation of benzophenone hydrazone to give *N*-arylhydrazone, followed by treatment with various ketones under acidic conditions, afforded various 2-substituted indoles in good yield. A modification of this protocol was used to access *N*-aryl- or *N*-alkylindoles.

In search of active neuropeptide Y5 antagonists for the treatment of obesity, Block et al. [121] applied this indole synthesis to the preparation of carbazoles. Using **1** as a ligand, the desired indole was isolated and further subjected to



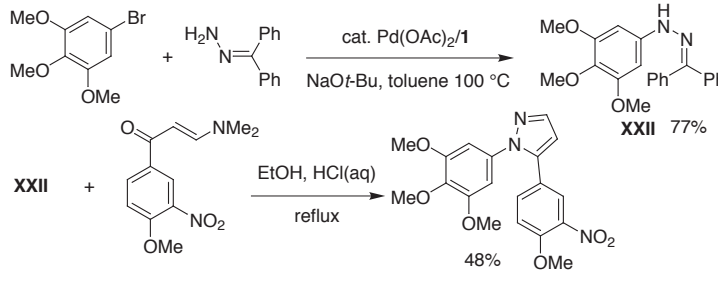
Scheme 13-111



Scheme 13-112

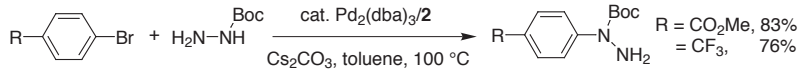
alkylation and aromatization to provide the desired substituted carbazole in good yield.

The Pd-catalyzed arylation of benzophenone hydrazones has also been applied to the synthesis of pyrrazoles. With **1** as a ligand, Wang et al. [122] disclosed a two-step synthesis of *N*-arylpyrrazoles from an aryl bromide, benzophenone hydrazone, and a β-amino-α,β-unsaturated ketone.



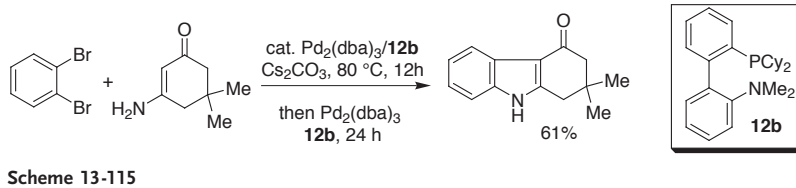
Scheme 13-113

The arylation of *t*-butylcarbazate with aryl bromides has also been demonstrated [123]. With DPPF, **2**, as the ligand, C-N bond formation occurred mostly at the less substituted nitrogen atom [124]. *N,N′*-Bisarylation products were also observed as a minor byproduct. However, only electron-deficient aryl bromides were used successfully as substrates.



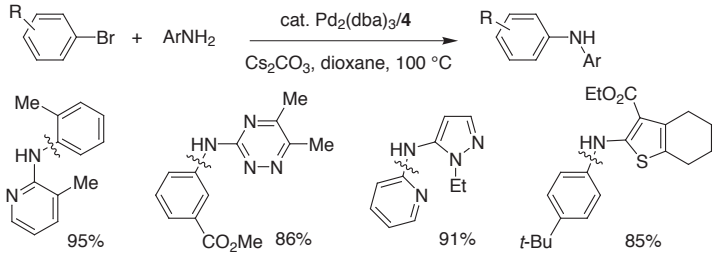
Scheme 13-114

In the presence of **12b**, vinylogous amides have also been used as nucleophiles in Pd-catalyzed cross-coupling reactions [125]. This process is applicable to a wide variety of aryl bromides or chlorides, including heterocyclic halides. In addition, this methodology was extended to a one-pot synthesis of polycyclic heterocycles.



Scheme 13-115

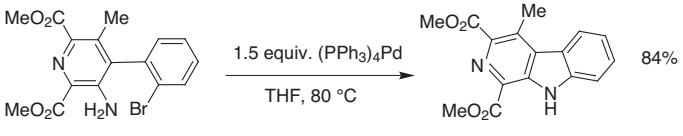
Yin et al. reported the arylation of a series of heteroaryl amines using Xantphos, **4**, as a supporting ligand and NaO*t*Bu as base [126]. In cases where functional group compatibility was an issue, Cs_2CO_3 was used. For example, the reaction between 3-methyl-2-aminopyridine and 2-bromotoluene occurred to give the desired product in 95 % yield.



Scheme 13-116

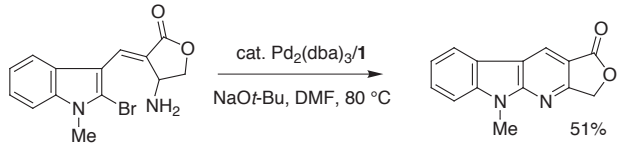
13.4.8
Intramolecular Processes

Intramolecular Pd-catalyzed C-N bond-forming processes have been widely employed in organic synthesis, particularly in the synthesis of nitrogen-containing heterocycles. Owing to the space limitation, only a few selected examples will be described herein. The first tin-free Pd-mediated C-N bond formation was reported by Boger [16] as part of the total synthesis of lavendamycin. As shown in Scheme 13-117, the intramolecular amination mediated by stoichiometric Pd proceeded in 84 % yield. Attempts to render this transformation catalytic were unsuccessful.



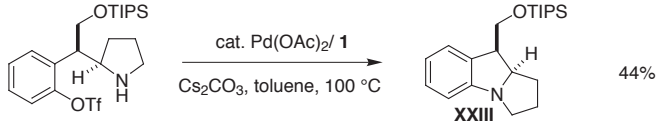
Scheme 13-117

Abouabdellah and Dodd [127] reported the preparation of a series of pharmaceutically interesting α-carbolines employing Pd-catalyzed intramolecular amination as a key step (Scheme 13-118). Their initial attempts to effect direct Michael-additions failed to provide any product, prompting them to examine the Pd-catalyzed coupling reaction. By employing $Pd_2(dba)_3$/**1** as the catalyst, the desired α-carboline was isolated in 51 % yield.



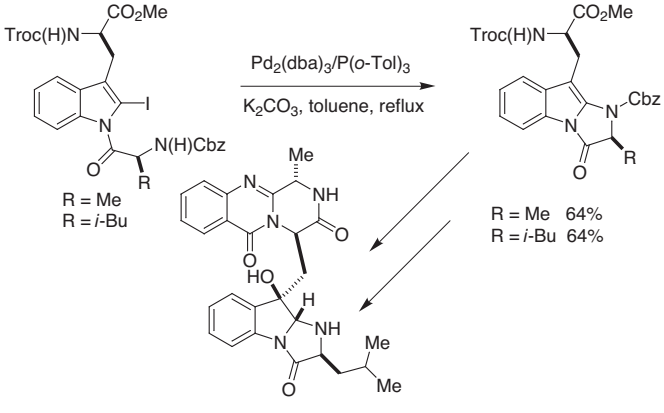
Scheme 13-118

Another application of an intramolecular amination process was Coleman's approach to the synthesis of the mitomycin core ring system (Scheme 13-119) [128]. Utilizing **1** as the ligand in combination with a weak base, the tricyclic ring system **XXIII** was formed in 44 % yield, with the low yield being attributed to the air-sensitivity of the dihydroindole product.



Scheme 13-119

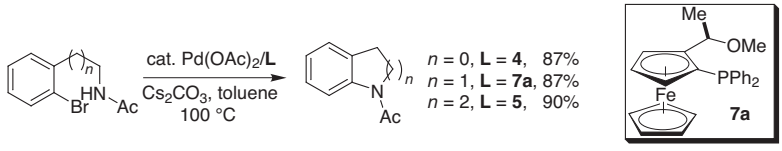
In Snider's total synthesis of fumiquinazolines A, B, and I [129], the imidazoindolone unit was formed via a Pd-catalyzed cyclization of an iodoindole carbamate. The key cyclization step yielded the desired product in 64 % yield.



Scheme 13-120

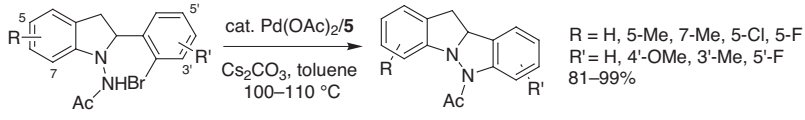
A detailed study of Pd-catalyzed intramolecular amidation was reported by Yang and Buchwald [130]. Using a combination of **4**, **5**, as well as **7a**, five-, six-, and seven-membered rings were efficiently formed from secondary amides or second-

ary carbamates. Particularly noteworthy was the formation of the seven-membered rings which proved problematic in earlier reports with the Pd/BINAP system [131].



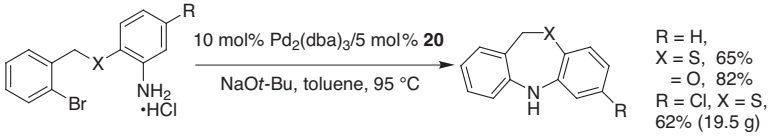
Scheme 13-121

The intramolecular cyclization between a hydrazide and an aryl bromide was achieved using ligand **5** [132] to access a variety of indolo[1,2-*b*]indazoles in good yield.



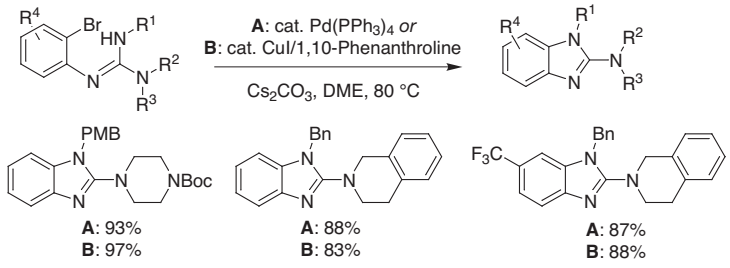
Scheme 13-122

Rogers [133] reported an improved route for the construction of the heterobenzazepine ring system which involved a Pd-catalyzed intramolecular cyclization reaction. Both oxazepine and thiazepine were prepared using ligand **20**, as shown in Scheme 13-123. To demonstrate the scalability of this transformation, the reaction was performed with 127 mmol of the thioether substrate to afford 19.5 g of thiazepine.



Scheme 13-123

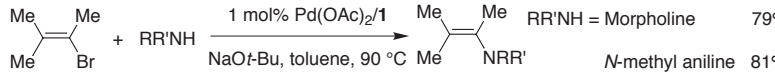
The use of guanidines as nucleophiles in intramolecular coupling processes was achieved by Evindar and Batey [134]. The cyclization between guanidines and aryl bromides was conducted with either a Pd or a Cu catalyst. In most cases reported, both catalysts gave comparable yields (Scheme 13-124). However, when $R^3 = H$, the Cu catalyst was superior to the Pd catalyst in terms of both reaction rate and yield.



Scheme 13-124

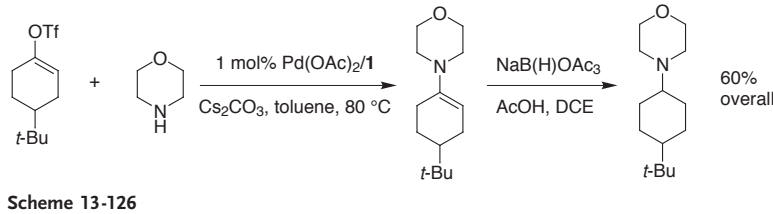
13.5 Vinylation

The formation of enamines by an analogous route to that used for aromatic C-N bond formation was first reported by Barluenga [135]. In his report, cyclic and acyclic secondary amines were effectively coupled with di-substituted as well as tetra-substituted alkenyl bromides to give the desired enamines in good yield.



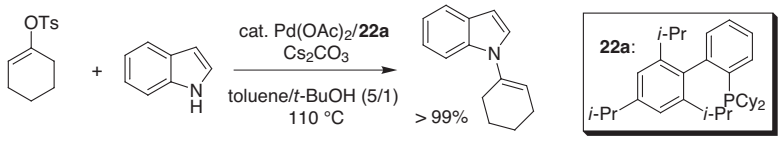
Scheme 13-125

Willis and Brace reported the amination of vinyl triflates in the presence of $Pd(OAc)_2$ and **1** [136], with both Cs_2CO_3 and KO*t*Bu serving as effective bases. Only cyclic secondary amines were reported as substrates. Owing to the difficulties that these authors encountered in isolating the unstable enamines, an in-situ reduction was performed to provide the corresponding tertiary amine products.



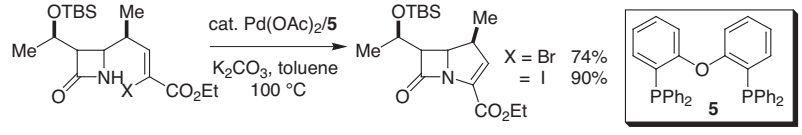
Scheme 13-126

The vinylation of indole using XPhos (**22a**) as ligand with cyclohexenyl tosylate was recently accomplished in near-quantitative yield [27].



Scheme 13-127

In the synthesis of carbapenems [137], Kozawa and Mori reported a Pd-catalyzed intramolecular cyclization of a lactam and a vinyl bromide (Scheme 13-128). These authors found that employing DPEphos, **5**, as a ligand provided better results than when BINAP, **1**, was used. The corresponding vinyl iodide was also successfully coupled.

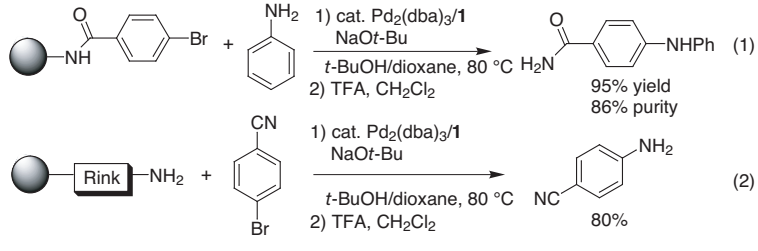


Scheme 13-128

13.6
Amination On Solid Support

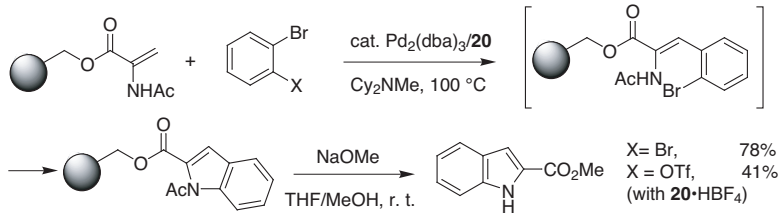
Combinatorial chemistry has shown promising potential for drug discovery and/or lead optimization, and therefore it is important to apply Pd-catalyzed amination processes on solid supports [138]. Willoughby and Chapman were able to effect the amination of resin-bonded aryl bromide with aniline substrates (Scheme 13-129, Eqn. 1) [139]. Weigand and Pelka [140] reported that Pd-catalyzed C-N bond formation between aryl bromides and anilines that were immobilized on a Rink resin (Scheme 13-129, Eqn. 2). While the reaction with electron-poor aryl bromides proceeded smoothly, electron-rich aryl halides failed to react. The use of a solvent mixture (dioxane:*t*BuOH = 1:1) helped to enhance selectivity favoring monoarylation.

Ligand **20** has also found application in solid-phase synthesis [141]. A one-pot indole synthesis was realized by Kondo on REM resin with methyldicyclohexyla-



Scheme 13-129

mine as a base. This intermolecular Heck/intramolecular amidation cascade proceeded smoothly at 100 °C to afford the desired product in good yield. However, only a moderate yield was obtained when the corresponding aryl triflate was used.



Scheme 13-130

13.7 Conclusion

Pd-catalyzed C-N bond-forming reactions are powerful tools for use in synthetic organic chemistry. Tremendous progress has been realized in recent years to allow these processes to be part of the everyday repertoire of synthetic chemists. Nevertheless, the chemistry is still in its infancy, and future studies should be directed at developing more general ligands that can be used to carry out the transformation under mild reaction conditions. In particular, the concept of a coupling reaction being run with a simple substrate combination (e. g., morpholine with *p*-chloroanisole) and small quantities of catalyst being viewed as significant is no longer applicable. Rather, the development of catalysts which are able to tolerate substrates containing multiple heteroatoms, or where both substrates are sterically encumbered, are among the future goals for this facet of chemical synthesis.

13.8 Representative Experimental Procedures

13.8.1 Amination Employing BINAP, 1, as a Ligand: Preparation of *N*-methyl-*N*-(2,5-xylyl)piperazine (Scheme 13-33) [29c]

A Schlenk flask was charged with 2,5-dimethylbromobenzene (1.0 mmol), *N*-methylpiperazine (1.2 mmol), sodium *tert*-butoxide (1.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.0050 mmol), BINAP (0.01 mmol), and toluene (2 mL) under argon. The flask was immersed in an oil bath and heated at 80 °C with stirring until the starting material had been completely consumed as judged by GC analysis. The mixture was allowed to cool to r. t., taken up in ether (15 mL), filtered, and concentrated. The crude product was then purified further by flash chromatography on silica gel to give 199 mg (98 %) of the title compound as a colorless oil.

13.8.2

Amination of a Functionalized Aryl Halide with a Weak Base Employing 21a as a Ligand: Preparation of 4-Methoxy-4′-nitrodiphenylamine (Scheme 13-73) [36]

An oven-dried, resealable Schlenk flask was evacuated and back-filled with argon. The flask was charged with $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol, 1 mol % Pd), **21a** (7.0 mg, 0.02 mmol, 2 mol %), and K_3PO_4 (297 mg, 1.4 mmol). The flask was evacuated, back-filled with argon, and capped with a rubber septum. DME (2 mL), 4-chloronitrobenzene (1.0 mmol), and 4-aminoanisole (1.2 mmol) were added through the septum. The septum was removed, and the flask sealed with a Teflon screw-cap. The mixture was heated at 100 °C with stirring until the starting aryl halide had been completely consumed, as judged by GC analysis. The mixture was cooled to r. t., diluted with ether or 1/1 ether/ethyl acetate (40 mL), filtered through Celite, and concentrated in vacuo. The product was purified by recrystallization from toluene/ethanol rather than chromatography to give 222 mg (91 %) of the title compound as an orange solid.

13.8.3

Amination Reaction Employing 20 as a Ligand: Preparation of *N*-(2-Tolyl)diphenylamine (Scheme 13-81) [40]

In a drybox, 2-bromotoluene (188 mg, 1.10 mmol), diphenylamine (169 mg, 1.00 mmol), $Pd(dba)_2$ (0.01 mmol), **20** (1.6 mg, 0.008 mmol, 0.8 equiv./Pd), and sodium *tert*-butoxide (144 mg, 1.50 mmol) were weighed directly into a screw-cap vial. A stirring bar was added, followed by 1.5 mL toluene to give a purple mixture. The vial was removed from the drybox, and the mixture stirred at r. t.. After 4 h, the reaction mixture was adsorbed onto silica gel and chromatographed with 2.5 % ethyl acetate/hexane to give 247 mg (95 %) of *N*-(2-tolyl)diphenylamine as a colorless oil that crystallized to a white solid.

13.8.4

Amination Reaction Employing Imidazolium Salt 8a as a Ligand: Preparation of 4-Methoxylphenylaniline (Scheme 13-69) [51].

Under an atmosphere of argon, 1,4-dioxane (3 mL), KO*t*Bu (168 mg, 1.5 mmol), 4-chloroanisole (1.0 mmol), and aniline (1.2 mmol) were added in turn to a Schlenk tube charged with $Pd_2(dba)_3$ (10 mg, 0.01 mmol), **8a** (17 mg, 0.04 mmol or 8 mg, 0.02 mmol), and a magnetic stirring bar. The Schlenk tube was placed in a 100 °C oil bath and the contents stirred for 3–30 h. The mixture was then allowed to cool to r. t.. The mixture was diluted with water, and then extracted with diethyl ether. The extracts were combined, washed with saturated saline solution, and then dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by flash chromatography (hexane/ethyl acetate, 10:1) to give the desired product in 91 % yield.

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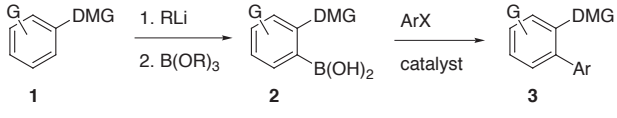
14
The Directed *ortho*-Metallation Cross-Coupling Nexus. Synthetic Methodology for the Formation of Aryl-Aryl and Aryl-Heteroatom-Aryl Bonds

Eric J.-G. Anctil and Victor Snieckus

14.1
Introduction

Although transmetallation is an established and common practice in synthetic chemistry, connecting this transformation to the directed *ortho* metallation (DoM) reaction for Li-B exchange (**1** → **2**, Scheme 14-1) in 1985 provided the first opportunity to take advantage of the then recently disclosed Suzuki-Miyaura reaction [1], → **3** for the construction of biaryls with assured regiochemistry [2]. In the context of the dramatically different face of synthetic chemistry today –



DMG = Directed Metallation Group

Scheme 14-1 The DoM-Suzuki-Miyaura synthetic link.

Table 14-1 Prominent transition metal-catalyzed cross-coupling reactions for the aryl-aryl bond

$Ar^1Met + Ar^2LG \xrightarrow{NiL_n \text{ or } PdL_n} Ar^1\text{-}Ar^2$

Met	LG	Investigator	Yr	Ref.
MgX	Br, I	Corriu	1972	[4]
		Kumada	1972	[5]
ZnX	Br, I	Negishi	1977	[6]
$B(OH)_2$	Br, I	Suzuki	1981	[1]
SnR_3	OTf	Migita, Stille	1977-78	[7,8]
SnR_3, (Ln = solv)	I	Beletskaya	1981 (1983)	[9]
$SiRF_2$	I	Hiyama	1989	[10]

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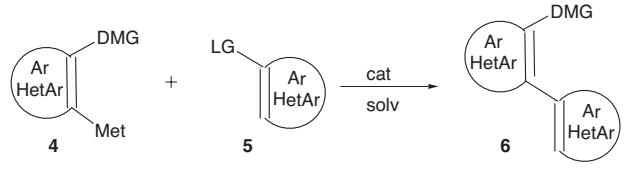
which in the large part is due to discoveries in transition metal-catalyzed cross-coupling reactions made during in the past 30 years [3] – this simple concept was readily extended to the related, and now widely recognized, Kumada-Corriu-Tamao, Negishi, and Migita-Stille reactions (Table 14-1). Subsequently, these reactions have opened new doors for aryl-aryl bond formation, and hence have led to the development of general regioselective synthetic methods for polysubstituted biaryls and heterobiaryls (**4** → **5** → **6**; Scheme 14-2) [11].



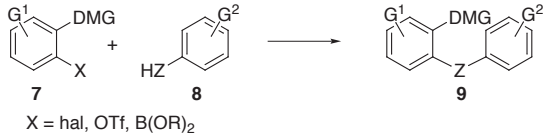
Met	LG	cat	cross-coupling
$B(OR)_2$	I, Br, OTf	Pd	Suzuki-Miyaura
MgX	hal, OTf	Ni	Kumada-Corriu-Tamao
MgX	$OCONEt_2$, $SCONEt_2$, SO_2NEt_2	Ni	Snieckus
ZnX	hal, OTf	Ni	Negishi
SnR_3	hal, OTf	Pd	Stille-Migita

DMG = $CONEt_2$, $OCONEt_2$, OMOM, NHBoc, SO_2tBu

Scheme 14-2 The DoM-cross-coupling nexus.

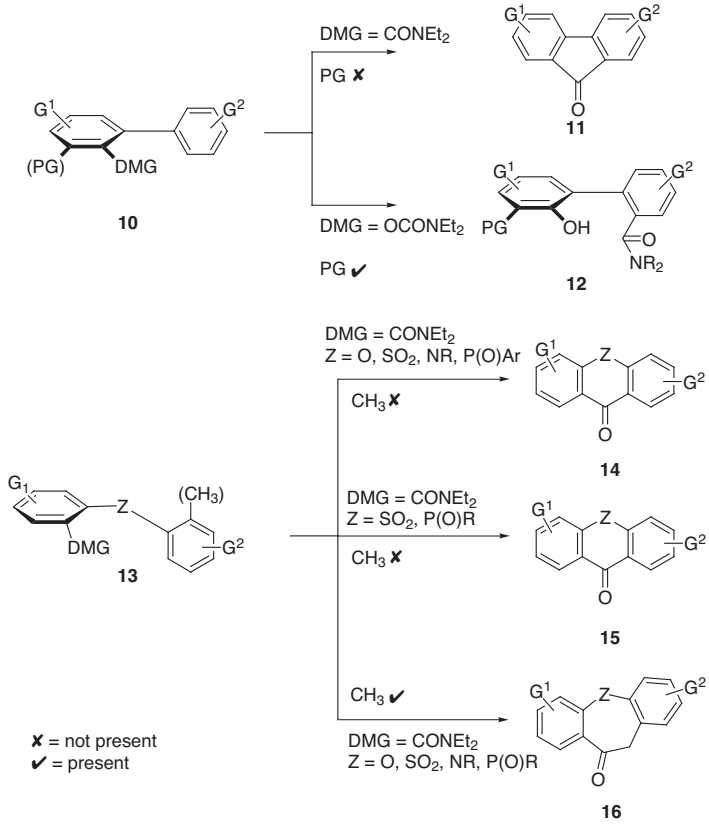
The regioselective halogen and triflate introduction by DoM allows extension of the Ar-Ar′ (Scheme 14-2) to Ar-O and Ar-N (Scheme 14-3) bond-forming reactions. Thus **7**, X = hal, OTf undergo regioselective cross-coupling with **8**, Z = O [12], S [12], NR [12, 13] partners and hence establishes routes to ArZAr′ (**9**) derivatives by the traditional Ullmann protocol which has been rendered synthetic chemist user-friendly by the investigations of Hartwig [14] and Buchwald [15].

To further advance the ArZAr′ construct, the recent findings [16] that organoborons cross-couple with phenols and anilines invites further experimentation. The initial report on the Directed remote Metallation (DreM) reaction which, like DoM, is of the late 1980s vintage [17], provided an adjunct, synthetically useful



X = hal, OTf, $B(OR)_2$
Z = O, S, NR

Scheme 14-3 Ullmann-Buchwald-Hartwig links to DoM.



Scheme 14-4 DreM connections to DoM-cross-coupling.

link (Scheme 14-4). Thus, in the Ar-Ar′ context (**10**), fluorenones (**11**) and polysubstituted biaryls (**12**) may be targeted and, in the ArZAr′ motif (**13**), a rich harvest of heterocycles (**14–16**) may be obtained [11b, 18].

The rational C-C bond-forming DoM-cross-coupling, and the ancillary C-O and C-N cross-coupling and DreM links, allow starting points in various carbon- and heteroatom-based DMGs (Scheme 14-2), of yet unrecognized limitation, possibility of functional group incorporation in pre- or post-cross-coupling events, and circumvention of harsh, non-regioselective classical methods for the construction of Ar-Ar and Ar-Z-Ar′ (Z = O, N, S, P) motifs [19]. In a broader context, extensions to unrelated, and as yet minimally explored, transition metal-catalyzed reactions (e. g., Heck, Sonogashira, Ullmann, Hartwig-Buchwald, Grubbs) are readily envisaged. Perhaps most significantly, the utility of the combined DoM-cross-coupling protocol in process research and development is being increasingly demonstrated [20].

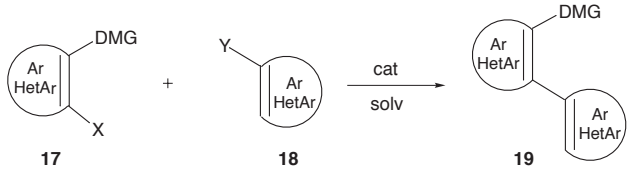
14.2
The Aim of this Chapter

The aim of this chapter is to provide cogent illustrations of the concepts enunciated in Schemes 14-2 to 14-4, as extracted from the current synthetic literature. In this increasing world of over-specialization, it is possible that to focus on studies from the present authors' laboratories may be absolved; nevertheless, the choice of examples to be discussed will target objectivity in terms of their synthetic value.

14.3
Synthetic Methodology derived from the DoM-Cross-Coupling Nexus

14.3.1
DoM-C-C Cross-coupling Methodology for Biaryls and Heterobiaryls

In all cross-coupling strategies, two modes of partnerships of the ArMet and ArLG substrates may be established. For Ar-Ar cross-coupling protocols, this translates into the overall reaction, **17** + **18** → **19** (Scheme 14-5), in which the X and Y groups may be inverted. The choice will be dictated by the availability of starting materials and/or intermediates, the relative rates of the cross-coupling process as a function of substituents, steric effects, and competitive side reactions such as protodemetallation of ArMet, hydrogenolysis of ArLG, homocoupling of either or both partners, and other side reactions.



Scheme 14-5 Cross-coupling partnerships for biaryl synthesis.

14.3.1.1 **Li → Boron Transmetallation: the Suzuki-Miyaura Cross-Coupling** [21]

Mechanistic knowledge of the Suzuki-Miyaura reaction is far from complete [21c, 22]. Although base is obligatory, and phenylboronic acids are known to form borates at high pH, evidence is not available for the $RB(OH)_3^-$ intermediate. Especially intriguing, compared with other cross-coupling processes, is the transmetallation step.

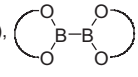
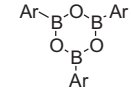
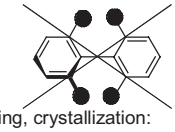
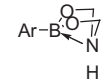
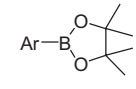
Although heteroaromatic DoM-Suzuki-Miyaura cross-coupling reactions may be problematic due to instability or to the uncharacterizability of boronic acid coupling partners, promising solutions have been accumulating in the recent litera-

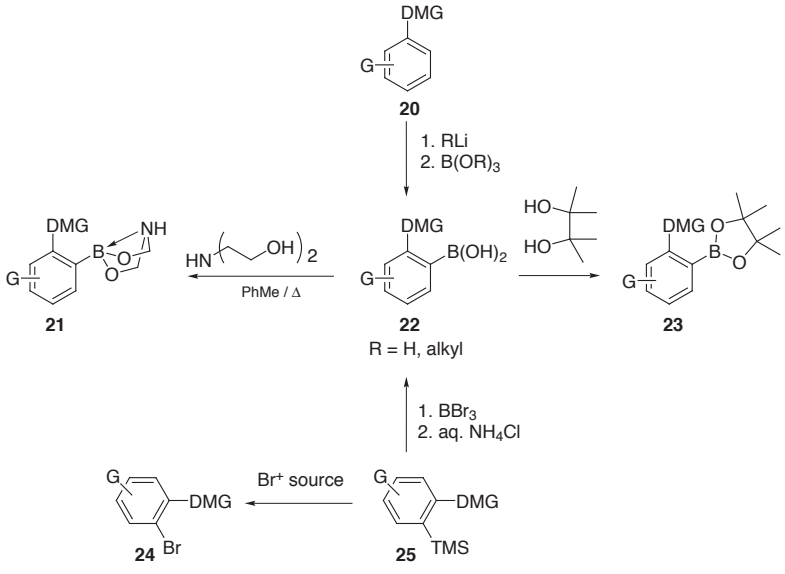
ture. Division according to π-excessive and π-deficient heteroaromatics is followed, and discussion is limited to systems in which true DoM chemistry is used to generate ArMet and/or ArLG systems, thus excluding cases of using the inherent C-2 acidity of π-excessive heteroaromatics for the generation of these species. Examination of the tabular data confirms that the strategy for both π-excessive and π-deficient systems is still at the early stages of development, both for simple and benzocondensed systems.

Practical advantages and disadvantages of the Suzuki-Miyaura protocol over other Ar-Ar cross-coupling methods to be discussed are generally appreciated by synthetic chemists (Table 14-2). Nevertheless, this cross-coupling reaction – as others – may still be relegated partially to an art, requiring empirical observation, preferably by parallel synthesizer technology, of catalyst, ligand, base, temperature and solvent variation to establish optimum conditions. The purity of the arylboronic acid **22** derived from **20** in the Li → B transmetallation, often uncertain either as prepared or purchased, may be ascertained by formation of the usually crystalline and stable diethanolamine adduct **21** (Scheme 14-6) [2] or, with less certainty of these properties, pinacolates **23** [23] and undoubtedly other boronates yet to be tested [24]. Current practice, however, is to use hastily the crude **22** in the cross-coupling reaction. An alternative route [25] to **22** by *ipso*-borodesilylation of arylsilanes of **25** deserves broader exploration. Of additional synthetic value may be the *ipso*-bromodesilylation of **25**, which provides **24** poised for modification by unre-

Table 14-2 The Suzuki-Miyaura Ar-Ar cross-coupling reaction

ArLG + $Ar'B(OH)_2$ $\xrightarrow{Pd^o}$ Ar-Ar'

Advantages	Disadvantages
• $ArB(OH)_2$ prep ⇓ ArLi, $ArMgX$, $ArSiMe_3$ (*ipso*),  / Pd^o	• Structural intergrity, purity? $ArB(OR)_2$, $ArB(OH)OR$, Ar_2BOH, 
• $ArB(OH)_2$, $ArBF_3^-X^+$ air-stable, low toxicity (ecofriendly), storage OK	• Steric 
• Anhydrous conditions unnecessary	• Handling, crystallization:
• LG diversity I > OTf > Br >>Cl, OMs, OTs	 
• Base flexibility Na_2CO_3, K_2CO_3, Cs_2CCO_3, $Ba(OH)_2$	diethanol amine adduct No XCoupl pinacolate XCoupl OK
• FG compatibility, e.g. CO_2R, CN, CHO, NH_2, NO_2	• Protodeboronation → ArH
	• FG incompatibility, e.g. CO_2H, OH

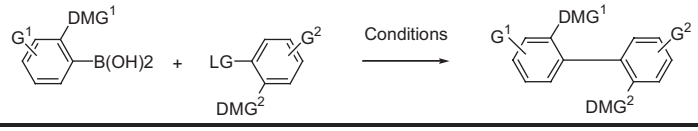


Scheme 14-6 Diethanolamine adducts and pinacolates of DoM-derived boronic acids. Borodesilylation route to arylboronic acids.

lated chemistry before the regeneration of the *ortho*-lithiated species, by diffusion controlled rate metal-halogen exchange processes, for other electrophile quenching experiments. This concept of **24** serving as an *ortho*-lithio surrogate has also not been adequately generalized [26].

Selected examples of the DoM-Suzuki-Miyaura cross-coupling sequence (Tables 14-3 and 14-4) provide some appreciation of its scope for biaryl synthesis. Thus, for carbon-based DMGs (Table 14-3): (1) benzamide *ortho*-boronic acids (entries 7–16) have received by far the most attention with additional cases from benzoates (entries 5–6) and benzonitriles (entries 2–4); (2) the scope of substitution patterns on the DMG^1-containing arylboronic acid partner has been inadequately explored (e. g., entries 10–14); (3) variation of substituents on the DMG^2-containing arylLG partner has been more widely tested with OR, NO_2, F, Cl, and OMOM being compatible with the cross-coupling conditions (entries 4, 6–9, 11–14, 16); (4) benzoate *ortho*-boronic acids, resulting from milder *ortho*-metallation using LiTMP [28], provide somewhat lower yields of cross-coupling products (entries 5–6) while benzonitrile *ortho*-boronic acids provide diverse functionality and substitution patters (entries 2, 3, and 4); (5) more variation in substituents on the DMG^2 arylLG partner compared to the corresponding DMG^1 arylboronic acid system has been explored. For heteroatom-based DMGs (Table 14-4): (1) likely due to synthetic advantage for C-C bond formation to *ortho* to amino and alkoxy groups, exploration of DMG^1 = NHBoc and OMe arylboronic acids has been significantly tested (entries 1–4 and 5–6); (2) surprisingly, the synthetic more valuable corresponding DMG^1 = $OCONEt_2$ and OMOM cases have received less attention (entries 11–12 and

Table 14-3 Selected DoM-Suzuki-Miyaura cross-coupling forming Ar-Ar. Carbon-based DMGs



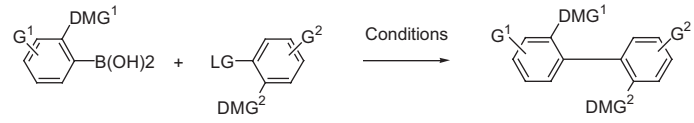
Entry	DMG^1	G^1	LG	DMG^2	G^2	Conditions	Yield (%)	Ref.
1	H	H	Br	CO_2H	H	$Pd(OAc)_2$ Na_2CO_3/H_2O	60	[27]
2	CN	H	I	H	H	$[Pd(PPh_3)_4]$ K_2CO_3 aq./PhMe/EtOH	53	[28]
3	CN	H	Br	CHO	H	$[Pd(PPh_3)_4]$ K_2CO_3 aq./PhMe/EtOH	91	[28]
4	CN	H	I	H	3-NO_2	$[Pd(PPh_3)_4]$ K_2CO_3 aq./PhMe/EtOH	84	[28]
5	CO_2Et	H	I	F	H	$[Pd(PPh_3)_4]$ dioxane/$K_3PO_4 \cdot H_2O$	72	[28]
6	CO_2Et	H	Br	H	4-NO_2	$[Pd(PPh_3)_4]$ dioxane/$K_3PO_4 \cdot H_2O$	72	[28]
7	$CONEt_2$	H	Br	H	2-NO_2	$[Pd(PPh_3)_4]$ Na_2CO_3 aq./DME	79	[25b]
8	$CONEt_2$	H	Br	H	2-Me 4-Cl	$[Pd(PPh_3)_4]$ Na_2CO_3 aq./DME	85	[25a]
9	$CONEt_2$	H	Br	OMe	2-Me 4,5-diOMe	$[Pd(PPh_3)_4]$ Na_2CO_3 aq./DME	70	[29]
10	$CONEt_2$	3-Ph	Br	H	H	$[Pd(PPh_3)_4]$ Na_2CO_3 aq./DME	86	[25b]
11	$CONEt_2$	3-OMe	Br	OMOM	4-OMe	$[Pd(PPh_3)_4]$ Na_2CO_3 aq./DME	85	[30]
12	$CONEt_2$	3-O*i*Pr	I	OMe	3-OMe 4-O*i*Pr	$PdCl_2(dppf)$ K_3PO_4/DMF	50	[30b]
13	$CONEt_2$	5-OMe	I	OMe	2-Me	$[Pd(PPh_3)_4]$ Na_2CO_3 aq./DME	78	[25b]
14	$CONEt_2$	6-OMe	I	H	2-Me	$[Pd(PPh_3)_4]$ Na_2CO_3 aq./DME	78	[25a]
15	$CONiPr_2$	H	Br	H	H	$[Pd(PPh_3)_4]$ Na_2CO_3/PhH	95	[2,31]
16	$CONiPr_2$	H	Br	OMe	4-OMe	$[Pd(PPh_3)_4]$ Na_2CO_3 aq./DME	85	[2]

8–10); and (3) with one exception (entry 20) a relative large number of DMG^2 = $P(O)R_2$ arylLG derivatives provide evidence of useful cross-coupling chemistry with, however, the negative aspect that further P-substituent modification is difficult (entries 17–20 and 21–23).

The DoM-cross-coupling sequence represents a significant entry into chiral BINOL and BIPOL ligands (Table 14-5). Thus, in representative examples, 3,3′-dihalobinaphthols and biphenyls, which are readily available by dianionic DoM chemistry, provide corresponding diaryl and diheteroaryl systems which may have potential utility for testing new ligand-metal combinations for asymmetric synthesis.

An examination of Table 14-6 leads to the clear conclusion that considerably less data are available on the synthesis of Ar-HetAr derivatives based on the DoM-cross-

Table 14-4 Selected DoM-Suzuki-Miyaura cross-coupling forming Ar-Ar. Heteroatom-based DMGs



Entry	DMG^1	G^1	LG	DMG^2	G^2	Conditions	Yield (%)	Ref.
1	NHBoc	H	Br	CHO	4-NO_2	$[Pd(PPh_3)_4]$ Na_2CO_3 aq./DME	89[a]	[32]
2	NHBoc	3-Ph	Br	H	H	$[Pd(PPh_3)_4]$ Na_2CO_3 aq./DME	44	[32]
3	NHBoc	5-OMe	Br	CHO	R	$[Pd(PPh_3)_4]$ Na_2CO_3 aq./DME	69[a]	[32]
4	NHBoc	5-OMe	Br	$CONMe_2$	4-NO_2	$[Pd(PPh_3)_4]$ Na_2CO_3 aq./DME	67[a]	[32]
5	OMe	H	I	NHAc	H	$[Pd(PPh_3)_4]$ K_3PO_4/DMF	90[b]	[33]
6	OMe	H	I	P(O)*t*-Bu_2	H	$[Pd(PPh_3)_4]$ K_3PO_4/dioxane	95	[34]
7	OMe	3-OMe	I	H	2-Cl	$[Pd(PPh_3)_4]$ Na_2CO_3 aq./DME	40[c]	[35]
8	OMOM	H	Br	H	H	$[Pd(PPh_3)_4]$ Na_2CO_3 aq./PhMe	90	[31]
9	OMOM	3-Ph	Br	$OCONEt_2$	H	$[Pd(PPh_3)_4]$ K_3PO_4/DMF	87	[31]
10	OMOM	3-OMe 6-Cl	Br	H	H	$[Pd(PPh_3)_4]$ Na_2CO_3 aq./PhMe	45[d]	[35]
11	$OCONEt_2$	H	Br	H	H	$[Pd(PPh_3)_4]$ Na_2CO_3 aq./DME	52	[31]
12	$OCONEt_2$	H	I	SO_2NEt_2	3-Me	$[Pd(PPh_3)_4]$ K_3PO_4/DMF	87	[33]
13	F	H	Br	CN	3-NO_2	$[Pd(PPh_3)_4]$ K_2CO_3/PhMe/EtOH	86	[28]
14	Cl	H	Br	H	H	$[Pd(PPh_3)_4]$ K_2CO_3/PhMe/EtOH	94	[28]
15	SO_2tBu	H	Br	H	H	$[Pd(PPh_3)_4]$ Na_2CO_3 aq./DME	78	[36]
16	SO_2tBu	H	Br	H	3-NO_2	$[Pd(PPh_3)_4]$ Na_2CO_3 aq./DME	52	[36]
17	H	H	I	P(O)*t*-Bu_2	H	$[Pd(PPh_3)_4]$ K_3PO_4/dioxane	90	[37]
18	H	5-OMe	I	P(O)*t*-Bu_2	H	$[Pd(PPh_3)_4]$ K_3PO_4/dioxane	81	[37]
19	H	H	I	P(O)*t*-Bu_2	H	$[Pd(PPh_3)_4]$ K_3PO_4/dioxane	67	[37]
20	1-naphthylboronic acid			P(O)*t*-Bu_2	H	$[Pd(PPh_3)_4]$ K_3PO_4/dioxane	0	[37]
21	H	H	I	$P(O)Ph_2$	H	$[Pd(PPh_3)_4]$ K_3PO_4/dioxane	83	[37]
22	H	H	I	$P(O)Ph_2$	H	$[Pd(PPh_3)_4]$ K_3PO_4/dioxane	75	[37]
23	1-naphthylboronic acid			$P(O)Ph_2$	H	$[Pd(PPh_3)_4]$ K_3PO_4/dioxane	71	[37]

[a] Isolated yields of the condensation products, phenanthridine. [b] From dioxaborolane instead of boronic acid. [c] Yields of the pure coupled and bis-demethylated products. [d] Overall yields for the pure DoM - Boron quench - Cross coupling sequence products. R = 4,5-catechol

Table 14-5 DoM-Suzuki-Miyaura cross-coupling sequence for construction of BINOLs and BIPOLs

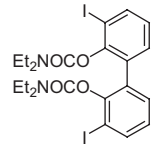
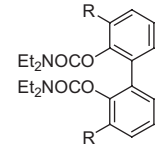
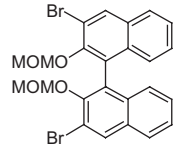
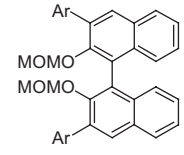
Entry	$RB(OH)_2$	R'X	Conditions	Product	Yield (%)	Ref.
1	R-$B(OH)_2$		$[Pd(PPh_3)_4]$ aq. Na_2CO_3 DME		R = Ph 82 R = 2-pyridyl 76	[38]
2	Ar-$B(OH)_2$		$[Pd(PPh_3)_4]$ aq. Na_2CO_3 DME		R = Ph 82 R = 2-naphthyl 76	[39]

Table 14-6 Selected DoM-Suzuki-Miyaura cross-coupling forming Ar-5-HetAr systems

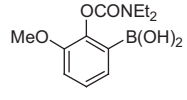
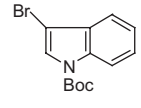
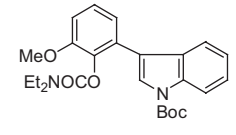
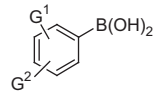
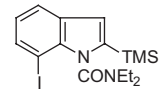
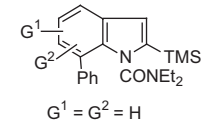
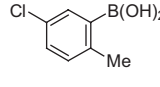
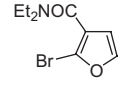
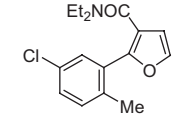
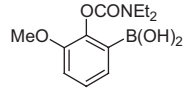
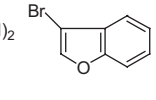
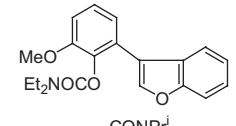
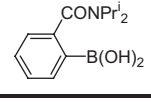
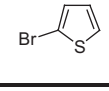
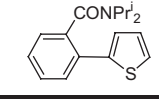
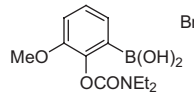
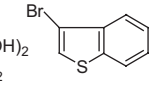
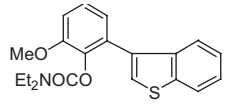
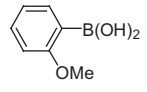
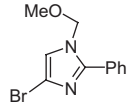
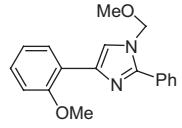
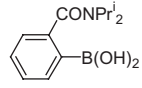
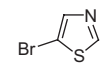
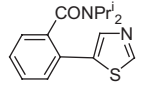
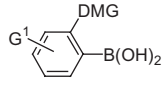
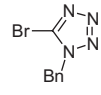
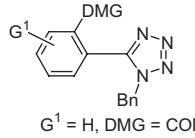
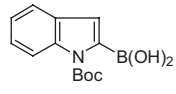
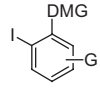
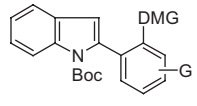
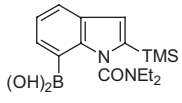
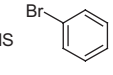
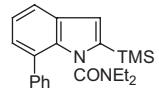
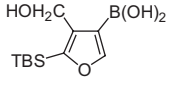
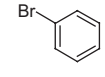
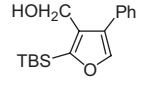
Entry	$RB(OH)_2$	R'X	Conditions	Product	Yield (%)	Ref.
	$ArB(OH)_2$ - HetArLG					
1			$[Pd(PPh_3)_4]$ aq. Na_2CO_3 PhMe		60	[42]
2			$[Pd(PPh_3)_4]$ K_3PO_4 DMF		$G^1 = G^2 = H$ 90 G^1 = 2-OMe, $G^2 = H$ 70 G^1 = 2-F, $G^2 = H$ 82 G^1 = 3-OMe, G^2 = 4-OMe 99	[23b]
3			$[Pd(PPh_3)_4]$ aq. Na_2CO_3 DME		88	[43]
4			$[Pd(PPh_3)_4]$ aq. Na_2CO_3 PhMe		34	[42]
5			$[Pd(PPh_3)_4]$ aq. Na_2CO_3 PhMe		92	[2]

Table 14-6 (Contd.)

Entry	$RB(OH)_2$	R'X	Conditions	Product	Yield (%)	Ref.
6			$[Pd(PPh_3)_4]$ aq. Na_2CO_3 PhMe		86	[42]
7			$[Pd(PPh_3)_4]$ Na_2CO_3 $EtOH/H_2O$		91	[44]
8			$[Pd(PPh_3)_4]$ aq. Na_2CO_3 PhMe		87	[2]
9			$[Pd(PPh_3)_4]$ Na_2CO_3/PhMe $EtOH/H_2O$			[45]
				G^1 = H, DMG = CON^iPr_2	88	
				G^1 = H, DMG = OMe	96	
HetArB(OH)$_2$ - ArLG						
10			$[Pd(PPh_3)_4]$ aq. Na_2CO_3 PhMe			[42]
				DMG = H, G = H	34	
				DMG = OMe, G = H	87	
				DMG = $OCONEt_2$, G = 3-OMe	54	
11			$[Pd(PPh_3)_4]$ aq. Na_2CO_3 PhMe		94	[23b]
12			$[Pd(PPh_3)_4]$ aq. Na_2CO_3 DME		68	[46]

coupling nexus. Thus, in the $ArB(OH)_2$-5-ring HetArLG cross-coupling series (entries 1–9), indoles, furans, and thiophene systems have been tested but only a sparse number of less-conventional heterocycles have received attention. The picture here may be incomplete in view of the significant amount of this type of chemistry that is being pursued in the pharmaceutical industry. In the inverted $HetArB(OH)_2$-ArLG series (entries 10–11), recent studies on indoles have highlighted the potential of the DoM-cross-coupling methodology in this under explored area. Turning attention to the $ArB(OH)_2$-6-ring HetArLG group (Table 14-7) shows the not surprising dominance of pyridines (entries 1–8), some of which bear dihalogen substitution patterns that provide cross-coupling selectivity and hence interesting azabiaryls for further manipulation (entries 3, 7). The few

Table 14-7 Selected DoM-Suzuki-Miyaura cross-coupling forming Ar-6-HetAr systems

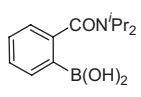
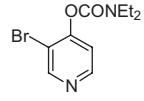
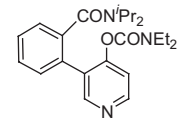
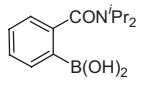
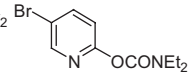
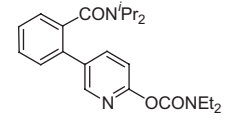
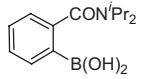
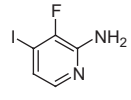
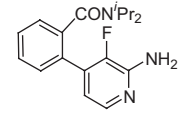
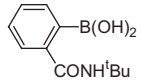
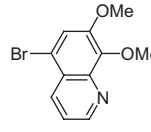
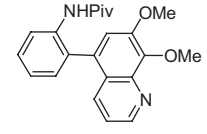
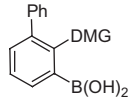
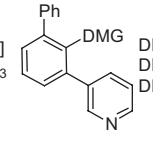
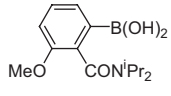
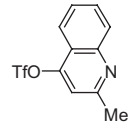
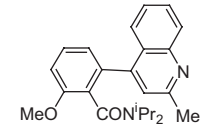
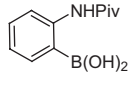
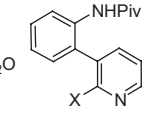
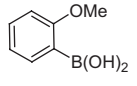
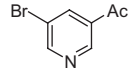
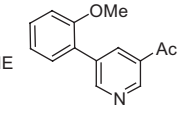
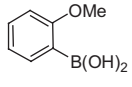
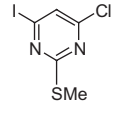
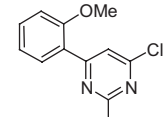
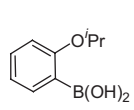
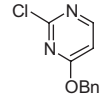
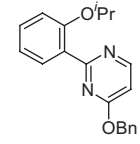
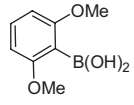
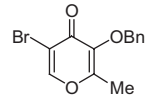
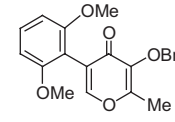
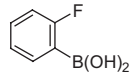
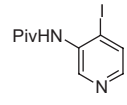
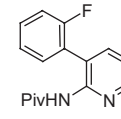
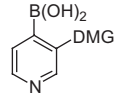
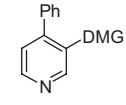
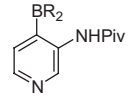
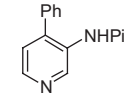
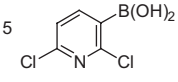
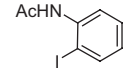
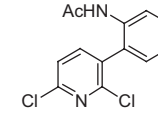
Entry	$RB(OH)_2$	R'X	Conditions	Product	Yield (%)	Ref.
$Ar(BOH)_2$ - HetArLG						
1			$[Pd(PPh_3)_4]$ aq. Na_2CO_3 DME		80	[2]
2			$[Pd(PPh_3)_4]$ aq. Na_2CO_3 DME		80	[2]
3			$[Pd(PPh_3)_4]$ K_2CO_3/PhMe EtOH		99	[47]
4			$[Pd(PPh_3)_4]$ Na_2CO_3 aq. EtOH/PhME		94	[48]
5			$[Pd(PPh_3)_4]$ aq. Na_2CO_3 DME		DMG = $CONEt_2$ 80 DMG = OMOM 73 DMG = $OCONEt_2$ 87	[25b,31]
6			$[Pd(PPh_3)_4]$ aq. Na_2CO_3 PhMe		87	[49]
7			$[Pd(PPh_3)_4]$ K_2CO_3/PhMe/H_2O		X = Cl or F, 99	[47]
8			$[Pd(PPh_3)_4]$ Na_2CO_3 aq./DME		70	[49]
9			$[Pd(PPh_3)_4]$ THF		75	[50]

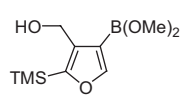
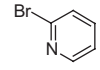
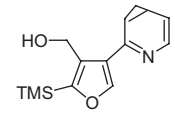
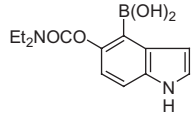
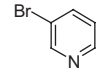
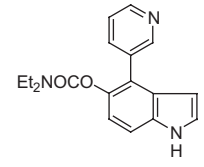
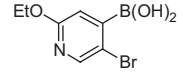
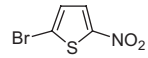
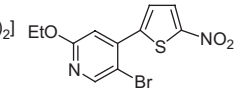
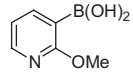
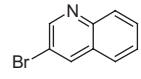
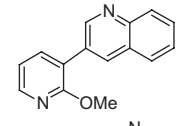
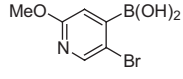
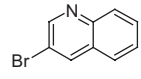
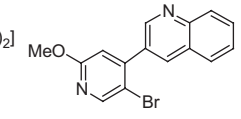
Table 14-7 (Contd.)

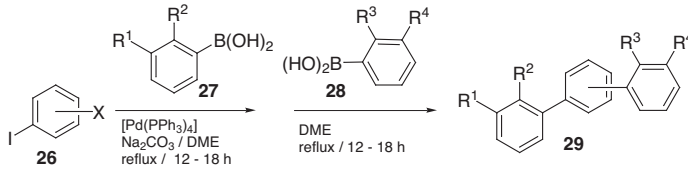
Entry	$RB(OH)_2$	R'X	Conditions	Product	Yield (%)	Ref.
10			$PdCl_2(dppb)$ $NaHCO_3/PhMe/H_2O$		66	[51]
11			$[Pd(PPh_3)_4]$ Na_2CO_3 aq./DME		21	[52]
12			$[Pd(PPh_3)_4]$ aq. Na_2CO_3/EtOH PhMe		96	[47]
HetAr$(BOH)_2$ - ArLG						
13			$[Pd(PPh_3)_4]$ aq. Na_2CO_3 PhMe		DMG = $CONEt_2$ 73 DMG = F 30 DMG = Cl 63	[53]
14			$[Pd(PPh_3)_4]$ aq. Na_2CO_3/EtOH PhMe		99	[47]
15			$Pd(OAc)_2$ $P(o\text{-}Tol)_3/Et_3N$ DMF		83	[54]

entries of heterocycles such as quinolines (entry 4), pyrimidines (entries 9–10), and pyrones (entry 11) are perhaps harbingers of generalizations. The brevity of the inverted HetArB$(OH)_2$-ArLG list (entries 13–15) is undoubtedly due to the difficulties in instability and handling of the pyridine boronic acid derivatives [53a,56]. The HetArB$(OH)_2$-HetArLG series (Table 14-8), undoubtedly for similar reasons, is short and perhaps underscores our lack of appreciation of heterocyclic organoboron compounds.

Extension of the DoM-Suzuki-Miyaura protocol to teraryls and higher-order polyaryls also affords molecules that, due to the regioselectivity dictated by DoM, are of interesting architecture and not available by conventional routes [57]. Thus, taking advantage of the I > Br LG reactivity difference, sequential coupling of **26** (Scheme 14-7) with arylboronic acids **27** and **28**, even without additional catalyst in the second step, leads to modest to good yields of teraryls **29** which may clearly be further subjected to DoM chemistry.

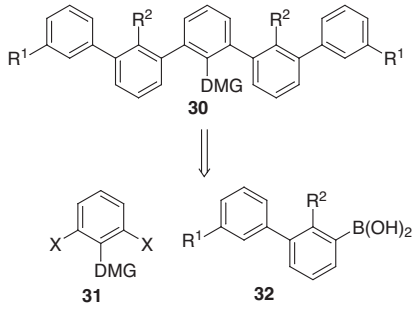
Table 14-8 Selected DoM-Suzuki-Miyaura cross-coupling forming HetAr-HetAr systems

Entry	$RB(OH)_2$	R'X	Conditions	Product	Yield (%)	Ref.
1			$[Pd(PPh_3)_4]$ DME		71	[46b]
2			$[Pd(PPh_3)_4]$ THF		19	[55]
3			$[PdCl_2(PPh_3)_2]$ $CsCO_3$ dioxane		44	[56]
4			$[PdCl_2(PPh_3)_2]$ $CsCO_3$ dioxane		77	[56]
5			$[PdCl_2(PPh_3)_2]$ $CsCO_3$ dioxane		50	[56]



X	R^1	R^2	R^3	R^4	Yield. (%)
p-Br	H	Me	H	H	79
m-Br	H	Me	H	H	77
p-Br	H	CON^iPr_2	CON^iPr_2	TMS	43
p-Br	TMS	CON^iPr_2	CON^iPr_2	H	47
p-Br	H	CON^iPr_2	H	CH_2OMe	63
m-Br	H	CON^iPr_2	H	CH_2OMe	61

Scheme 14-7 DoM-Suzuki-Miyaura cross-coupling sequence for construction of teraryls.



DMG	X	R^1	R^2	Yield. (%)
$CONEt_2$	Br	H	H	44
$CONEt_2$	I	H	H	69
NH_2	Br	H	H	67
CN	I	CH_2OMe	H	85
OMOM	Br	H	OMOM	86

Scheme 14-8 DoM-Suzuki-Miyaura cross-coupling sequence for construction of quiniquearyls.

In an alternative 2:1 cross-coupling motif, *meta*-related quinquearyls **30** (Scheme 14-8) may be readily prepared from the combination of 2,6-disubstituted DMG substrates **31** with biarylboronic acids **32** [58].

Solid-support Suzuki-Miyaura cross-coupling in conjunction with solution-phase DoM chemistry has been achieved [23c].

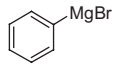
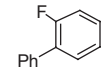
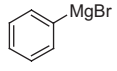
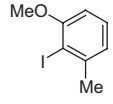
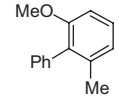
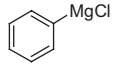
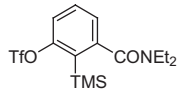
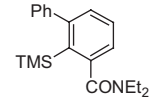
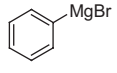
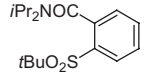
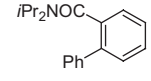
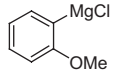
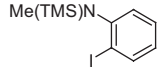
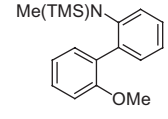
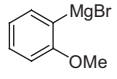
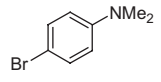
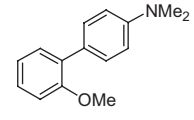
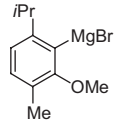
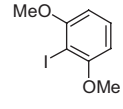
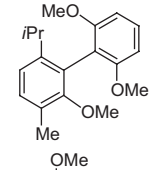
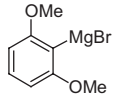
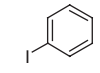
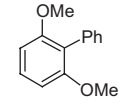
14.3.1.2 Li → Magnesium Transmetallation: Kumada-Corriu-Tamao Cross-Coupling

This venerable reaction, which led to the deluge of cross-coupling methods [3a] enjoys reasonable utility, detracted mainly by a chemoselectivity handicap – that is, the incompatibility of Grignard reagents with a number of functional groups (e. g., CHO, COR, CO_2R, CN, NO_2) and, although not noted widely, a propensity for homocoupling competition. The recent advances in the technology for generation of Grignard reagents [59] and deeper mechanistic insight [60] may overcome this deficiency. Although, of all the ArMet coupling partners, Grignards are the most readily available commercially, they also constitute the most moisture-sensitive reagents.

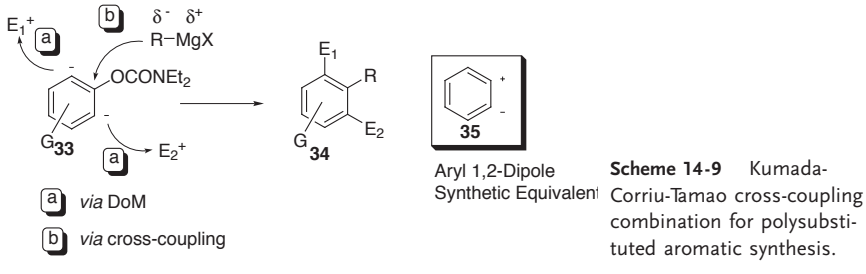
Tables 14-9 and 14-10 present a potpourri of DoM-Kumada-Corriu-Tamao-derived biaryl and heterobiaryl syntheses which demonstrate the scope of DMGs and the prevalence of Ni(0) catalysis. In the Ar-Ar bond-forming series (Table 14-9), the lack of functional group complexity in either ArMgX and ArLG coupling partner and the impact of steric effects (entry 7) is noted; equally uninformative is the current short list of HetArMgX-HetArLG cross-coupling reactions (Table 14-10). The attempt to generate and use the *ortho*-NHBoc phenyl Grignard reagent for simple cross-coupling reactions [68a] underscores the potential great stability of such complexes due to coordination effects.

Although discovered and assessed in scope and limitation over a decade ago [63, 68], the aryl *O*-carbamate cross-coupling partner for the Kumada-Corriu-Tamao reaction has not seen wide-scale application, although its preparation from phenols

Table 14-9 Selected DoM-Kumada-Corriu-Tamao cross-coupling forming Ar-Ar systems

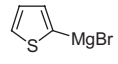
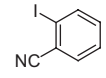
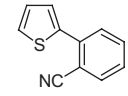
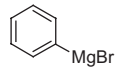
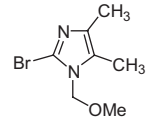
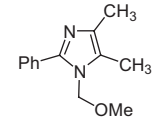
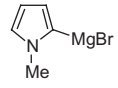
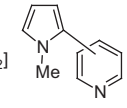
Entry	RMgX	R'X	Conditions	Product	Yield (%)	Ref.
1			$[Pd(Ph)I(PPh_3)_2]$ THF		34	[61]
2			$[NiCl_2(dppp)]$ THF		93	[62]
3			$[NiCl_2(dppp)]$ THF		70	[63]
4			$[NiCl_2(dppp)]$ THF		92	[64]
5			$[Pd(PPh_3)_4]$ THF		66	[65]
6			$[Pd(PPh_3)_4]$ THF		62	[65]
7			$[NiCl_2(dppp)]$ THF		10	[62]
8			$[NiCl_2(dppp)]$ THF		88	[62]

(which are more readily available than the corresponding aryl halides) and the position of the *O*-carbamate as the most powerful in the hierarchy of DMGs [69] bodes well for synthetic application. The conceptual 1,2-dipole synthetic equivalent, **33** → **34** ≡ **35** (Scheme 14-9) has been reasonably tested using simple,

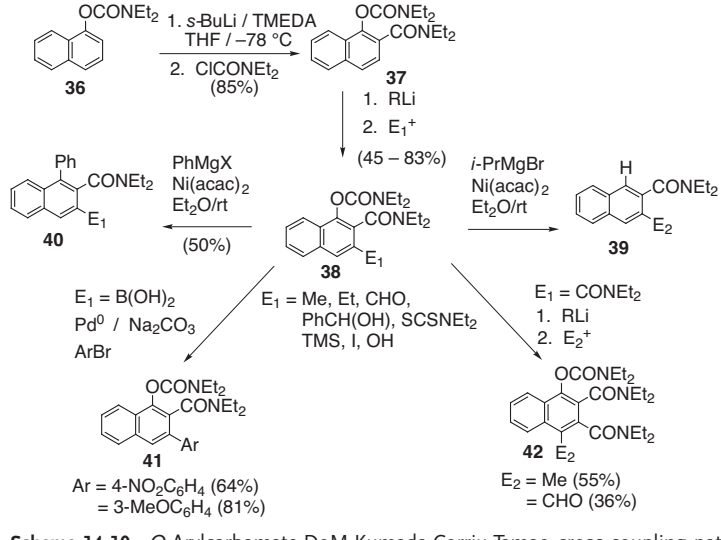


Scheme 14-9 Kumada-Corriu-Tamao cross-coupling combination for polysubstituted aromatic synthesis.

Table 14-10 Selected DoM-Kumada-Corriu-Tamao cross-coupling forming Ar-HetAr and HetAr-HetAr systems

Entry	RMgX	R'X	Conditions	Product	Yield (%)	Ref.
1			$[Pd(PPh_3)_4]$ THF		73	[66]
2			$[Pd(PPh_3)_4]$ Et_2O		15	[44]
3			$[PdCl_2(dppb)_2]$ THF		2-Br = 71 3-Br = 66	[67]

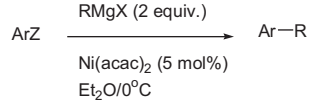
though not necessarily always aromatic, Grignard reagents, and these have been compared with the corresponding OTf-Grignard cross-coupling processes (Table 14-11) [70]. Latitude has also been taken to include examples which, although not derived from the DoM process, embody such potential (entries 6 and 7). Aspects to be gleaned are the steric effect of $OCONEt_2$ over $OCONMe_2$ groups (entry 1), more efficient cross-coupling for OTf over $OCONEt_2$ in sterically encumbering situations (entry 3), successful coupling of an ArOTf with a Grignard containing β-hydrogens (entry 4), a reaction not achievable with the corresponding



Scheme 14-10 *O*-Arylcarbamate-DoM-Kumada-Corriu-Tamao cross-coupling pathways for polysubstituted naphthalenes.

$OCONEt_2$ derivative, and, perhaps most significantly, the survival of heterocyclic rings to nucleophilic attack by Grignards (entries 7–9). The corresponding $SCONEt_2$-Grignard cross-coupling process (entries 10–12) requires definition of scope and limitations. Taking advantage of the observation that longer-chain alkyl Grignards promote β-hydride-induced reductive cleavage (entry 4), and extension of this cross-coupling reaction to naphthalenes allows formulation of regioselective routes to polysubstituted naphthalenes. Thus, the *O*-carbamate **36** (Scheme 14-10), upon metallation and treatment with $ClCONEt_2$, affords **37** which upon a second DoM reaction and electrophile quench leads to **38**. Compound **38** may be taken in cross-coupling directions with selected Grignard reagents to give the 1,2,3-trisubstituted naphthalene **40** and, by β-hydride elimination

Table 14-11 Grignard with *O*-Carbamates, triflates and *S*-carbamates cross-coupling reactions



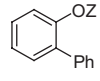
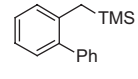
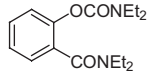
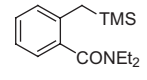
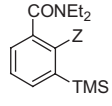
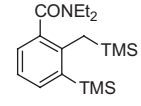
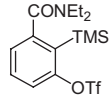
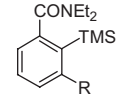
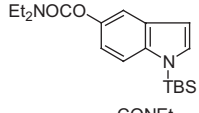
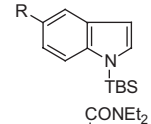
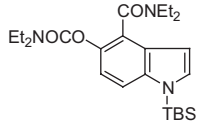
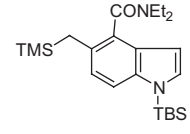
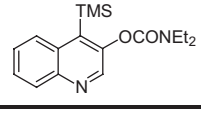
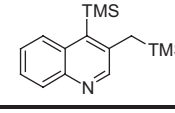
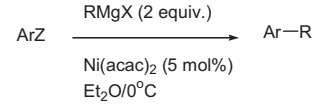
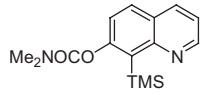
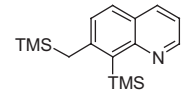
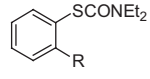
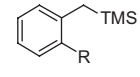
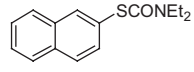
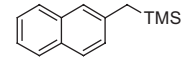
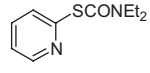
Entry	ArZ	RMgX	Product	Yield (%)	Ref.
1		$ClMgCH_2TMS$		Z = $CONEt_2$ 40 Z = $CONMe_2$ 81 Z = Tf 12	[63]
2		$ClMgCH_2TMS$		55	[63]
3		$ClMgCH_2TMS$		Z = $OCONEt_2$ 44 Z = OTf 73	[63]
4		RMgX		R = Ph 70[a] R = *n*-Bu 65[a]	[63]
5		RMgX		R = CH_2TMS 89 R = Ph 59	[70b]
6		$TMSCH_2MgCl$		59	[70a]
7		PhMgCl		Z = 2-$OCONEt_2$ 30-80 Z = 3-$OCONEt_2$ 72 Z = 3-OTf 65 Z = 4-$OCONEt_2$ 81	[63]
8		$ClMgCH_2TMS$		72	[63]

Table 14-11 (Contd.)



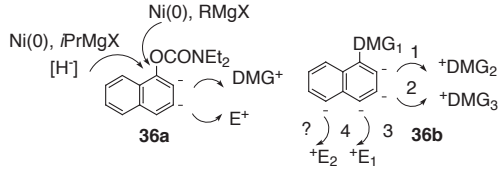
Entry	ArZ	RMgX	Product	Yield (%)	Ref.
9		$ClMgCH_2TMS$		76	[63]
10		$TMSCH_2MgCl$		R = Me 88 R = Ph 79 R = OMe 62 R = F 45 R = TMS 70	[71]
11		$TMSCH_2MgCl$		87[b]	[72]
12		PhMgCl		55	[72]

[a] $NiCl_2(PPPh_3)_2$ was used as catalyst
[b] $NiCl_2(PEt_3)_2$ was used as catalyst

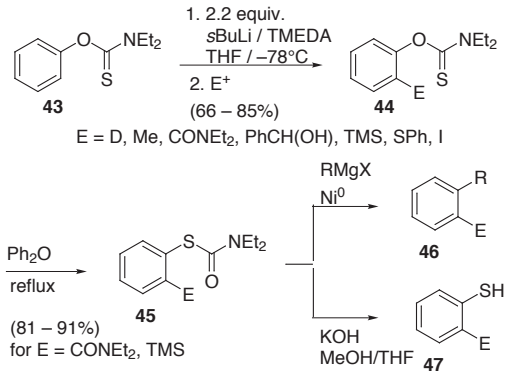
using *i*PrMgX, the 2,3-disubstituted derivative **39** with the *proviso*, in both cases, that the introduced E_1 electrophile is compatible with the Grignard reagent or is appropriately protected.

A different contiguous trisubstituted pattern resulting from boron introduction in the second metallation step from **38**, X = $B(OH)_2$ leads to mixed aryl-naphthyl systems **41**, while a further DoM reaction-electrophile quench sequence on **38**, E = $CONEt_2$ affords 1,2,3,4-tetrasubstituted naphthalene (albeit in low yield) for the two derivatives **42** investigated to date [71]. The conceptual elements **36a** and **36b** (Scheme 14-11) inherent in the above transformations are considered for profitable exploitation perhaps not only in the Kumada-Corriu-Tamao cross-coupling connection.

The salient work of Wenkert and Julia [36, 64, 73] on aryl sulfide, sulfoxide, and sulfone derivative-Grignard cross-coupling may be advanced to *S*-aryl carbamates (Table 14-11, entries 10–12) for which more vigorous conditions than those used for the *O*-aryl carbamates are required [72]. Thus, the *S*-arylcarbamate **45** (Scheme



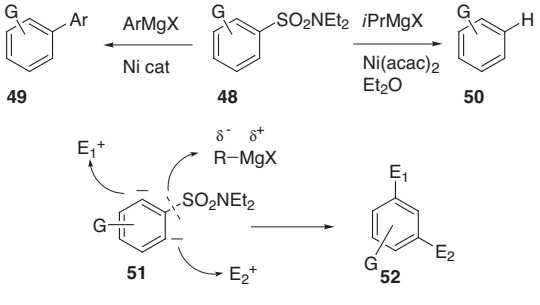
Scheme 14-11 Conceptual *O*-aryl-carbamate-DoM-Kumada-Corriu-Tamao cross-coupling pathways.



Scheme 14-12 Newman-Kwart *O*-arylthiocarbamate rearrangement to *S*-arylthiocarbamate.

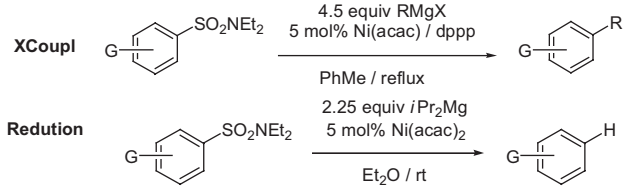
14-12) constitutes, *via* the DoM-cross-coupling synthetic link, another 1,3-dipole equivalent, although it does not enjoy the DMG property of the *O*-arylcarbamate **33** (Scheme 14-9). A direct DoM route to *ortho*-substituted *S*-arylcarbamates **45** has not yet been achieved, thus requiring the sequence **43** → **44** → **45.** The latter may then participate in Grignard cross-coupling to give **46**, or it may undergo hydrolysis under much milder conditions than those needed for the *O*-carbamate counterpart, to give *ortho*-substituted thiophenols **47** [74]. Oxidative complications in direct electrophilic aromatic substitution reaction to obtain **47** render the present route of potential synthetic value for polysubstituted thiophenols.

Consideration of qualitatively similar cross-coupling reactivity allows extension of the Kumada-Corriu-Tamao reaction to sulfonamide leaving groups and provides yet another 1,2-dipole synthetic equivalent (Scheme 14-13; Table 14-12). Successful only on tertiary and not secondary sulfonamides, the reaction **48** → **49** not only constitutes a viable synthetic route to biaryls but also, by virtue of the *i*PrMgX-induced hydrodesulfamoylation reaction **48** → **50**, provides a potentially general route to *meta*-substituted aromatics, conceptualized by **51** and **52**, which are not available by direct electrophilic substitution [75]. Substituent effects are evident in comparisons of entries 1 and 5 and entries 16 and 17.



Scheme 14-13 Arylsulfonamide-Grignard cross-coupling to biaryls and hydrodesulfamoylation to *meta*-substituted aromatics.

Table 14-12 Selected arylGrignard sulfonamides cross-coupling and reduction reactions



XCoupl				Reduction		
Entry	G	RMgX	Yield (%)[a]	Entry	G	Yield (%)[a]
1	2-OMe	Me	91	10	H	(74)
2	2-OMe	Ph	(87)	11	2-Me	(74)
3	4-OMe	Ph	(80)	12	2-$CONEt_2$	60(64)
4	2-(*p*-MeO-C_6H_4)	Ph	77	13	2-N(Me)Ph	53
5	4-(*p*-MeO-C_6H_4)	Ph	10	14	4-N(Me)Ph	18
6	2-Me	Ph	63	15	2-OMe	(97)
7	4-Me	Ph	89	16	2-OBn	68
8	2-TMS	Ph	(54)	17	2-O*i*Pr	(18)
9	4-TMS	Ph	53 (60)	18	2-TMS	(48)
				19	2-(*p*-MeO-C_6H_4)	90

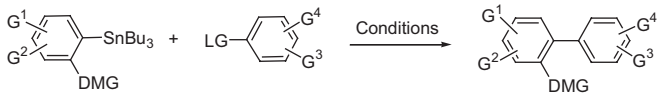
[a] parenthesis indicates yields by GC analysis.

14.3.1.3 **Li → Sn Transmetallation: Migita-Stille Cross-Coupling** [3b,21b]

Owing to the careful and comprehensive work of Stille and, more recently, by Amadore and Jutand [76], the Migita-Stille cross-coupling enjoys the position of the most mechanistically understood of the named cross-coupling processes [22a]. Nevertheless, there is no ideal catalytic system, and the fact that each reaction requires individual optimization is the didactic statement. Furthermore, additives such as copper and other metal salts have a considerable impact on the synthetic viability [77]. The high toxicity of organotins notwithstanding, the use of the Migita-Stille reaction in heteroaryl synthesis surpasses all other named cross-coupling processes, perhaps owing to ease of purification, stability to oxygen and moisture, and long shelf-life of stannylated heterocycles compared to the corresponding boronated systems.

Table 14-13 delineates the Migita-Stille cross-coupling processes which are linked to the DoM tactic. Yields are good to excellent, with the exception of cases which bear multiple oxygen substitutions in both cross-coupling partners (entries 7 and 8). Although systematic investigation is not evident, dependable cross-coupling has also been achieved in diverse classes of 5- and 6-ring heterocycles (Table 14-14). The higher stability of heterocyclic stannanes, combined with the potential for their isolation and purification, have provided greater dependence on the Migita-Stille reaction compared to the Suzuki-Miyaura, Kumada-Corriu-Tamao, and Negishi protocols for the construction of unusual heterobiaryl derivatives.

Table 14-13 Selected DoM-Migita-Stille Ar-Ar cross-coupling reactions



Entry	DMG	G^1	G^2	LG	G^3	G^4	Conditions	Yield (%)	Ref.
1	H	H	H	OTf	2-OMe	6-CH_2OMe	$[PdCl_2(PPh_3)_2]$ PPh_3/LiCl/DMF	79	[78]
2	H	H	H	OTf	2-OMe	6-CO_2Me	$[PdCl_2(PPh_3)_2]$ PPh_3/LiCl/DMF	87	[79]
3	H	H	H	OTf	2-OMe	6-OMe	$[PdCl_2(PPh_3)_2]$ PPh_3/LiCl/DMF	74	[78]
4	NHBoc	H	H	Br	2-Cl	H	$[PdCl_2(PPh_3)_2]$ PhMe	74	[80]
5	OMe	H	H	OTf	2-Me	5-Me	$[PdCl_2(PPh_3)_2]$ LiCl/CuBr	94	[81]
6	OMe	4-OMe	6-Me	OTf	2-OMe	6-OMe	$[PdCl_2(PPh_3)_2]$ P(*o*-Tol)$_3$/LiCl/CuBr	25	[81]
7	OMe	3-OMe	4-OMe	I	2-Me	4-NO_2	$[Pd(PPh_3)_4]$ CuI/NMP	51	[82]
8	OMe	3-OMe	4-OMe	I	2-Me	4-OMs	$[Pd(PPh_3)_4]$ CuI/NMP	33	[82]
9	OMe	3-OMe	4-OMe	OTf	2-Et	4-NO_2	$[Pd(PPh_3)_4]$ CuI/LiCl/NMP	77	[82]

Table 14-14 Selected DoM-Migita-Stille Ar-HetAr and HetAr-HetAr cross-coupling reactions

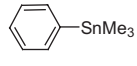
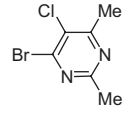
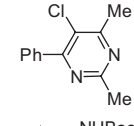
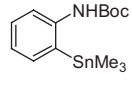
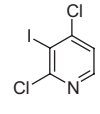
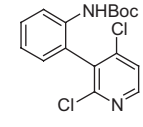
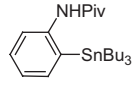
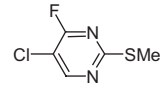
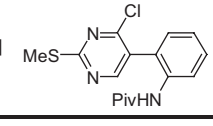
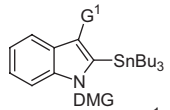
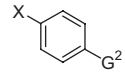
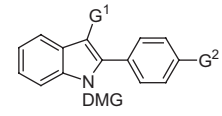
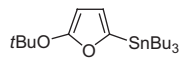
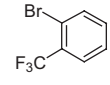
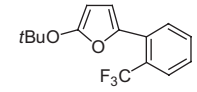
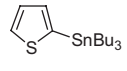
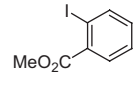
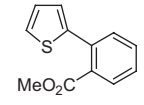
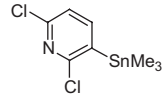
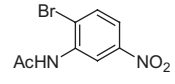
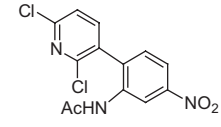
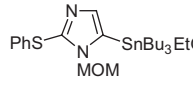
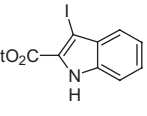
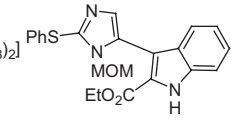
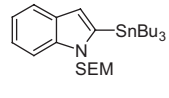
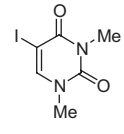
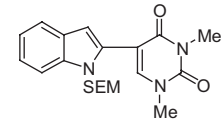
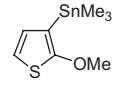
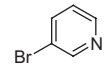
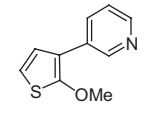
Entry	$RnSnR'_3$	R"X	Conditions	Products	Yield (%)	Ref.
1			$[PdCl_2(PPh_3)_2]$ Et_4NCl/K_2CO_3 DMF		73	[83]
2			$[Pd(PPh_3)_4]$ CuI/dioxane		81	[54]
3			$[PdCl_2(CH_3CN)_2]$ LiCl/dioxane		82	[84]

Table 14-14 (Contd.)

Entry	RnSnR'$_3$	R"X	Conditions	Products	Yield (%)	Ref.
4						

DMG	G^1	X	G^2			
H	CH_2CO_2Me	Br	Ac	$[Pd(PPh_3)_4]/Et_3N/MeCN$	81	[85]
COO^-	H	I	H	$[PdCl_2(PPh_3)_2]/EtOH$	80	[86]
SEM	H	I	H	$[Pd(PPh_3)_4]/DMF$	98	[87]
SEM	H	OTf	Me	$[PdCl_2(PPh_3)_2]/THF$	66	[88]
SEM	H	Br	CN	$[PdCl_2(PPh_3)_2]/THF$	96	[87]
Boc	H	Br	CN	$[PdCl_2(PPh_3)_2]/THF$	66	[87]
SEM	$(CH_2)_2NH_2$	I	NO_2	$[Pd(PPh_3)_4]/DMF$	86	[87]

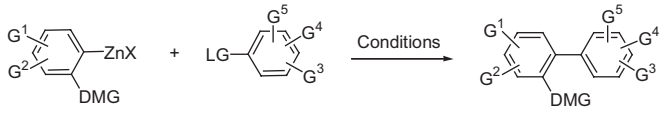
Entry			Conditions	Products	Yield (%)	Ref.
5			$[Pd(Bn)Cl(PPh_3)_2]$ DMF		90	[89]
6			$[PdCl_2(PPh_3)_2]$ THF		81	[90]
7			$[Pd(PPh_3)_4]$ CuI/dioxane		81	[54]
8			$[PdCl_2(PPh_3)_2]$ DMF		70	[91]
9			$[Pd(PPh_3)_4]$ DMF		92	[87]
10			$[Pd(PPh_3)_4]$ DMF		67	[92]

14.3.1.4 Li → Zn Transmetallation: Negishi Cross-Coupling

As for Grignard reagents, the nontolerance by organozincs of moisture is by far compensated by compatibility, owing to their weak basicity and nucleophilicity, to a variety of functional groups: CHO, COR, CO_2R, $CONR_2$, CN, NO_2. Also parallel to Grignards, the zinc reagents may be generated by transmetallation of Li with commercially available ZnX_2 or by activated Zn insertion, although the former process is mostly applied in DoM-connected procedures. Although the Suzuki-Miyaura reaction is still the most widely used, the Negishi cross-coupling protocol has increased in use during recent years.

Functional group compatibility in DoM-Negishi cross-coupling sequences is clearly evident in Table 14-15, entries 1, 2 and 8 for a variety of DMGs and both bromide and triflate ArLG partners. A less-investigated aspect is the heteroaryl construct (Table 14-16), although non-DoM-related Negishi cross-coupling procedures have been reasonably established, for example, for pyridines (entries 2, 4, and 7) [100] and indoles (entry 7) [101].

Table 14-15 Selected DoM-Ar-Ar Negishi cross-coupling reactions



Entry	DMG	G^1	G^2	LG	G^3	G^4	G^5	Conditions	Yield (%)	Ref.
1	$CONMe_2$	H	H	OTf	3-CO_2Me	H	H	$[Pd(PPh_3)_4]$ THF	81	[93]
2	$CONEt_2$	4-OMe	H	OTf	3-NO_2	H	H	$[Pd(PPh_3)_4]$ THF	85	[93]
3	Ox	H	H	I	2-Me	H	H	$[Pd(PPh_3)_4]$ THF	66	[93]
4	Ox	H	H	I	3-NO_2	H	H	$[Pd(PPh_3)_4]$ THF	54	[93]
5	Ox	H	H	OTf	4-CF_3	H	H	$[Pd(PPh_3)_4]$ THF	78	[93]
6	OMe	H	H	Br	2-CN	H	H	$[PdCl_2(PPh_3)_2]$ DMF	65	[94]
7	OMOM	H	H	OTf	3-$OCONEt_2$	H	H	$Ni(acac)_2$ *i*PrMgBr/THF	57	[95]
8	$OCONEt_2$	6-OMe	H	OTf	3-$OCONEt_2$	H	H	$Ni(acac)_2/PPh_3$ DIBAL/THF	65	[95]

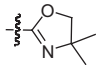
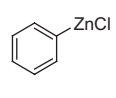
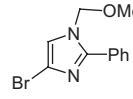
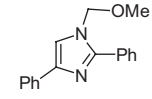
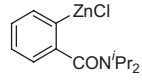
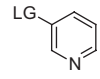
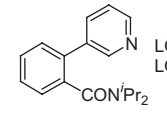
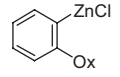
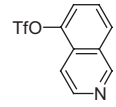
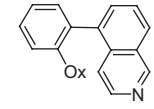
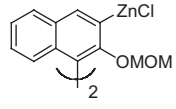
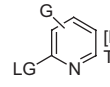
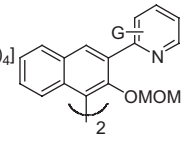
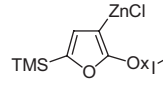
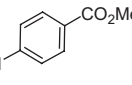
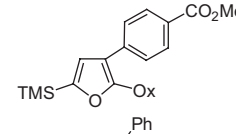
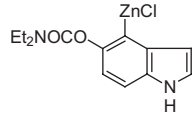
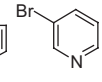
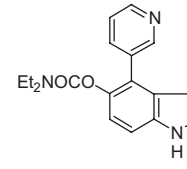
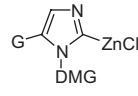
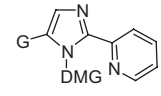
Ox = 

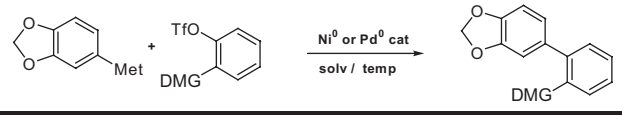
Table 14-16 Selected DoM-Ar-HetAr and HetAr-HetAr Negishi cross-coupling reactions

Entry	R-ZnX	R'-X	Conditions	Product	Yield (%)	Ref.
1			$[Pd(PPh_3)_4]$ THF		45	[44]
2			$Ni(acac)_2$ $PPh_3/MeMgBr$ THF		LG = Br LG = OTf	94 89	[95]
3			$[Pd(PPh_3)_4]$ THF		54	[93]
4			$[Pd(PPh_3)_4]$ THF		LG = Br, G = H LG = Br, G = 3-Me LG = I, G = 3-OC_6H_{13}	68 41 42	[96]
5			$[Pd(PPh_3)_4]$ THF		86	[97]
6			$[Pd(PPh_3)_4]$ THF		81	[97]
7			$[Pd(PPh_3)_4]$ THF		90	[98]
8			$[Pd(PPh_3)_4]$ THF		DMG = MOM, G = H DMG = SO_2NEt_2, G = H DMG = MOM, G = SPh	93 60 58	[99]

14.3.2
Comparison of Named C-C Cross-Coupling Reactions in the DoM Context

With some exceptions [102], systematic studies into comparisons of efficacy for the Suzuki-Miyaura, Migita-Stille, Negishi, and Kumada-Corriu-Tamao technologies for Ar-Ar bond formation are not available. With regard to DoM, a single comprehensive study (Table 14-17) [68a,103] detailed the synthetic advantage of the Suzuki-Miyaura and Negishi protocols. Thus, coupling of aryl triflates bearing ester (entry 1), NHBoc (entry 7) groups with ArMgX partners failed and provided only modest yields with fluoro (entry 13) and *O*-carbamate (entry 10) -containing aromatics. In contrast, ArZnX and $ArB(OH)_2$ provided good to excellent yields of biaryls, with the exception of the triflate from an *N*-Boc aniline (entry 8), which failed – perhaps owing to the presence of the acidic N-H.

Table 14-17 Qualitative comparison among combined DoM-Suzuki-Miyaura, Corriu-Kumada-Tamao, and Negishi cross-coupling processes

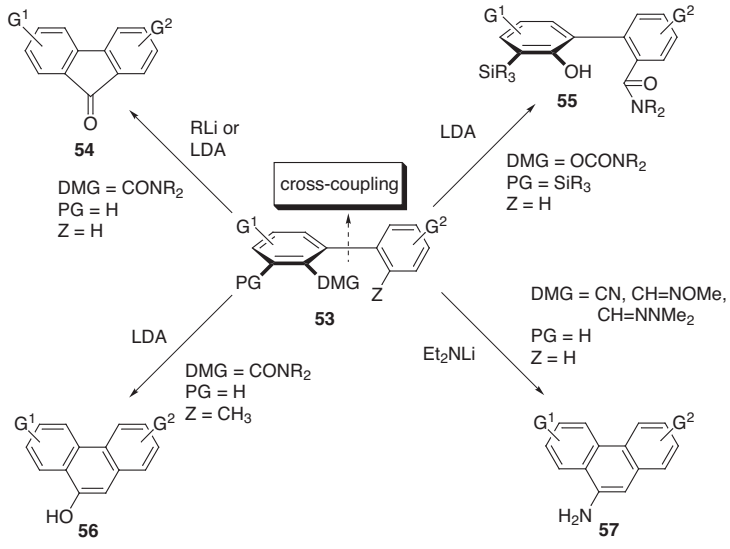


Entry	Met	DMG	Cat	Yield (%)	Entry	Met	DMG	Cat	Yield (%)
1	MgBr	CO_2R	-	-	9	$B(OH)_2$	NHBoc	D	79
2	ZnCl	CO_2R	A	96	10	MgBr	$OCONEt_2$	B	23
3	$B(OH)_2$	CO_2R	E	40	11	ZnCl	$OCONEt_2$	A	92
4	MgBr	$CONEt_2$	C	78	12	$B(OH)_2$	$OCONEt_2$	D	97
5	ZnCl	$CONEt_2$	A	85	13	MgBr	F	C	48
6	$B(OH)_2$	$CONEt_2$	D	66	14	ZnCl	F	A	95
7	MgBr	NHBoc	-	-	15	$B(OH)_2$	F	D	86
8	ZnCl	NHBoc	-	-					

Cat: A = $Ni(acac)_2$ / PPh_3 / MeMgBr / THF; B = [$NiCl_2$(dppe)] / THF; C = $Ni(acac)_2$ / THF; D = [$Pd(PPh_3)_4$] / DME / EtOH / 2M Na_2CO_3; E = [$Pd(PPh_3)_4$] / DME / 2M Cs_2CO_3

14.3.2.1 Directed Remote Metallation (DreM) Connections

Over 15 years ago, the complex-induced proximity effect (CIPE) heuristic suggested [104] that strong coordination effects of organometallic donor reagents be rationalized in enhancement of acidity at remote, nonthermodynamic sites, and this has been translated into DreM strategies for the synthesis of condensed aromatics and heteroaromatics which originate from the readily constructed DoM-cross-coupling-derived intermediates **53** (Scheme 14-14). Thus **53**, which originates predominantly from the Suzuki-Miyaura cross-coupling tactic, is at the hub of the Ferris wheel to fluorenones **54**, polysubstituted biaryls **55**, 9-phenanthrols **56**, and 9-aminophenanthrenes **57**, including a variety of heteroaromatic analogues. Synthetic utility towards bioactive molecules and natural products and extension to tandem DreM processes are feasible, and further development and generalization is anticipated in this respect [105].

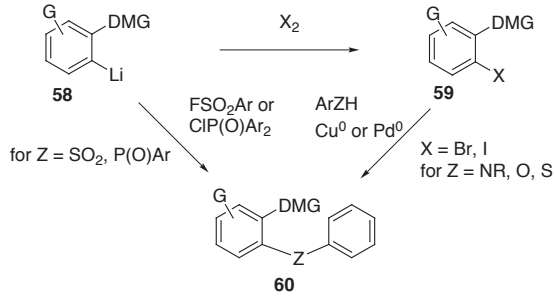


Scheme 14-14 Directed remote Metallation (DreM) strategies to condensed aromatics and heteroaromatics.

14.3.3
DoM C-N, C-O and C-S Cross-Coupling: Methodology for Ar-Z-Ar Systems

Synthetic routes to Ar-Z-Ar systems, which traditionally were derived from classical Ullmann, Ullmann-Gomberg, and related reactions [19], have been considerably advanced by the development of new conditions for the traditional processes, new coupling partners, and, most significantly, Pd and Ni rather than Cu catalytic procedures [14,15]. The future significance of the C-N, C-O and C-S cross-coupling methodologies is anticipated, based on evolving mechanistic knowledge [106].

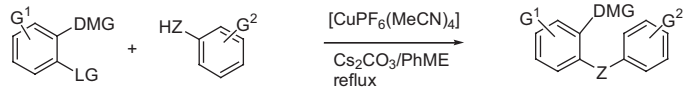
The DoM connection in the context of the synthesis of Ar-Z-Ar systems (Scheme 14-15) assumes both direct substitution, **58** → **60** (for Z = SO_2 [107], P(O)Ar [108]) and Cu- or Pd-mediated cross-coupling, **58** → **59** → **60** (for Z = O, NR) modes. While the routes to **60**, Z = SO_2, P(O)Ar have not been tested in metal-catalyzed reactions, classical [109] and modern [110] Ullmann-type conditions applied to



Scheme 14-15 DoM-C-N, C-O and C-S bond-forming sequences to substituted Ar-Z-Ar′ systems. Z = SO_2, P(O)Ar, O, NR.

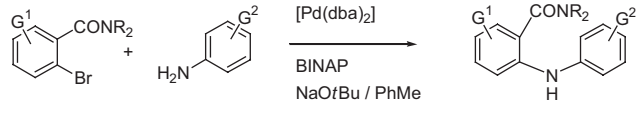
the cross-coupling of phenols with *ortho*-halo DMG systems provides a series of diaryl ethers in reasonable yields (Table 14-18), while the Buchwald-Hartwig technology affords diarylamines in overall smooth and high-yielding reactions (Table 14-19) [111]. In the former series (Table 14-18), even arylthiols undergo Ullmann-cross-coupling (entry 12) – a somewhat rare observation in the Ullmann literature. In view of the ready availability of *ortho*-DMG arylboronic acids, the new *N*-thioimide-ArB(OH)$_2$ cross-coupling reaction may advance this area [112]. For the same reason, a further influence on synthesis may result from the recent findings that ArBF$_3^-$K$^+$ derivatives undergo Cu-catalyzed cross-coupling with phenols [113], and that ArB(OH)$_2$ undergoes cross-coupling with both phenols and anilines [16].

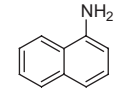
Table 14-18 DoM-Ullmann synthesis of aryl ethers



Entry	DMG	G^1	LG	Z	G^2	Yield (%)
1	CONHEt	H	I	NH	3-Me	37
2	CONHEt	H	Cl	O	3-Me	58
3	CONHEt	H	Br	O	3-Me	92
4	CONHEt	H	I	O	H	97
5	CONEt$_2$	H	I	S	2-Me	74
6	CONEt$_2$	H	I	O	4-F	77
7	CONEt$_2$	H	I	O	4-OMe	77
8	COOH	H	Br	O	3-Me	43
9	NHBoc	H	Br	O	3-Me	25
10	OMOM	H	I	O	3-Me	30
11	SO$_2$NHEt	H	I	O	3-Me	75
12	SO$_2$NHEt	4-Me	I	S	2-CO$_2$H	65
13	SO$_2$NEt$_2$	4-Me	I	O	H	76

Table 14-19 DoM Buchwald-Hartwig synthesis of *N,N*-dialkylanilinobenzamides

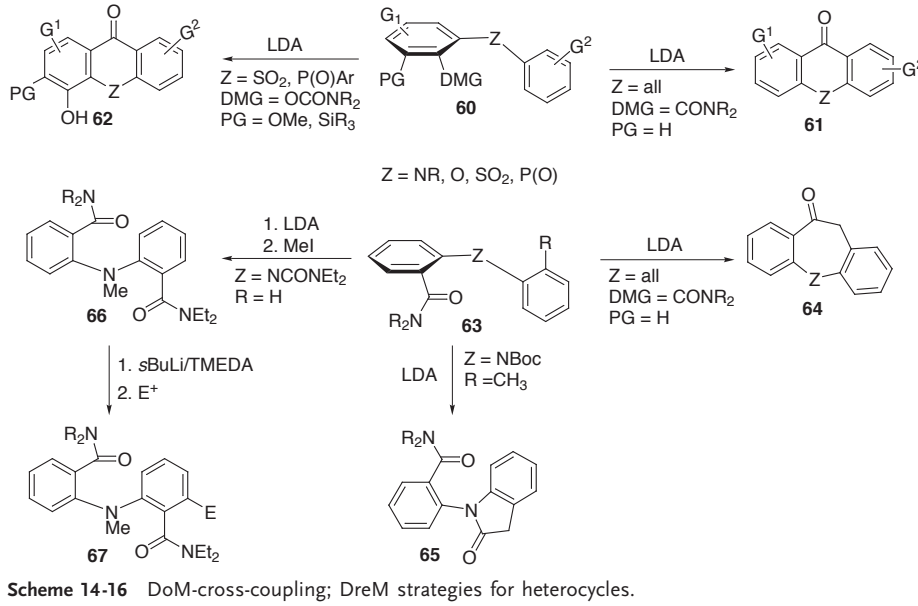


Entry	R	G^1	G^2	Yield (%)	Entry	R	G^1	G^2	Yield (%)
1	Me	H	3-OMe	68	6	Et	6-OMe	4-OMe	60
2	Et	H	3-OMe	60	7	Et	4,5-diOMe	2-OMe	53
3	*i*-Pr	H	3-OMe	83	8	Et	H		81
4	Et	H	H	81					
5	Et	H	3,5-diOMe	93					

14.3.3.1 DreM Connection

As with the DreM link to the DoM-cross-coupling discussed in Ar-Ar bond formation context (see Section 14.3.1.1), the corresponding connections for Ar-Z-Ar systems open new avenues for anionic aromatic chemistry (Scheme 14-16). Thus [105], from all of the heteroatom-bridged biaryls, **60**, DMG = $CONR_2$, derived either by direct electrophile quench or by cross-coupling sequences (Scheme 14-15), LDA-mediated reactions lead to acridones, xanthones, thioxanthones, and dibenzophosphorinones **61**, while from the corresponding *O*-carbamates, **60**, DMG = $OCONR_2$ but only in the Z = SO_2 and P(O)Ar series, and in the PG = OMe and SiR_3 derivatives, a sequential ring-to-ring carbamoyl migration-anionic cyclization leads to substituted thioxanthones and dibenzophosphorinones (**62**). The tolyl derivatives **63**, R = Me in all of the heteroatom-bridged series undergo a different DreM process to furnish dibenzazepinones, dibenzoxepinones, dibenzothioxepinones, and dibenzphosphorinones (**64**), reactions which still remain unoptimized and ungeneralized.

Other potentially useful reactions which are similarly unexplored involve the lateral metallation cyclization to oxindoles, **63** → **65**, the *N*-to-*ortho C* carbamoyl migration to anthranilamides, **63** → **66**, and the thereby facilitated further DoM chemistry to produce **67** – all substances which may be further used in cross-coupling reactions, for example E = hal, $B(OR)_2$ [114].This anionic aromatic chemistry has complementarity to Friedel-Crafts reactions (for **62** and **67**) and also synthetic consequences for a variety of heterocyclic frameworks represented in the structures of Scheme 14-16.



Scheme 14-16 DoM-cross-coupling; DreM strategies for heterocycles.

14.4
Applications of DoM in Synthesis

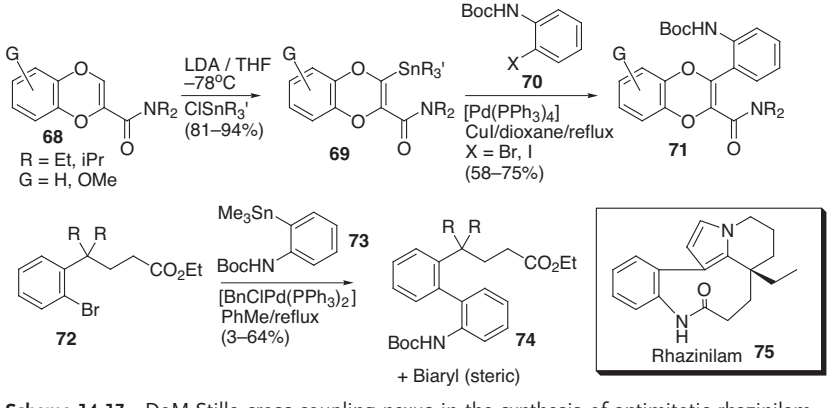
While the individual application of DoM and all of the named cross-coupling strategies for the construction of bioactive molecules and natural products is ascertained by even a cursory perusal of the current literature, their use in combination could enjoy increased and broader attention. The dictum "larger than the sum of individual parts" may be adapted in such work in terms of the opportunities that are presented owing to: (1) DoM regioselectivity; (2) pre- and post-DoM modification to achieve specific substitution patterns in aromatics; (3) DoM-derived regioselective cross-coupling, post-cross-coupling modification by DoM; (4) interconnection at all stages, but especially post- DoM-cross-coupling with other useful synthetic reactions; and finally (5), which is not discussed here [105], DreM links.

To illustrate the DoM-cross-coupling nexus in service of targeted synthesis, a hopefully cogent selection of bioactive molecule, natural product, and organic material syntheses are presented in this section.

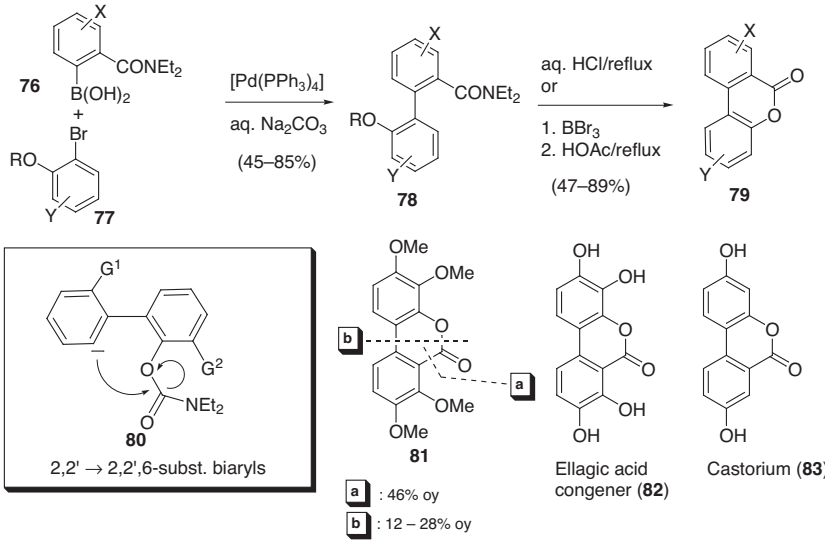
14.4.1
Synthesis of Bioactive Molecules

14.4.1.1 DoM-Cross-Coupling Tactics involving Ar-Ar Bond Formation

In the search for mimics of the antimitotic alkaloid, Rhazinilam (**75**, Scheme 14-17), a DoM-Stille cross-coupling tactic was pursued [115]. Thus, metallation of the benzodioxene **68** followed by stannylation affords **69** which, upon Stille cross-coupling with the 2-halo-*N*-Boc aniline **70** gives derivatives **71** in modest to good yields. In an alternate series, cross-coupling of the 2-stannylated aniline **73** with the simple bromobenzene **72** leads to the biaryls **74** in low to modest yields, complicated by the formation also of the dimer from aniline **73** by homocoupling, presumably due to steric effects. These sequences demonstrate the use of inverted ArMet



Scheme 14-17 DoM-Stille cross-coupling nexus in the synthesis of antimitotic rhazinilam (**75**) mimics.

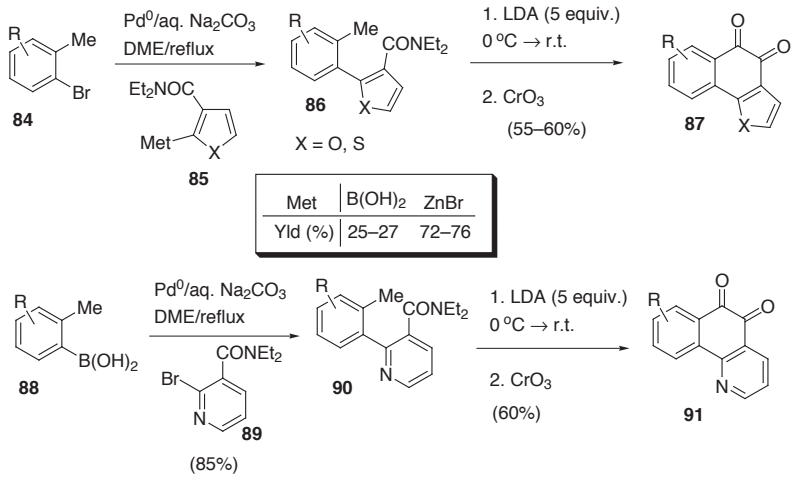


Scheme 14-18 General route for dibenzo[*b,d*]pyran-6-ones *via* direct Suzuki-Miyaura or DreM *O*-carbamate pathways.

and ArLG partners **70** and **73**, both of which are derivable by DoM and amenable to structural generalization.

A DoM-Suzuki-Miyaura cross-coupling combination was established [116] for the construction of dibenzopyranones **79** (Scheme 14-18), a condensed heterocyclic class represented in bioactive as well as naturally occurring molecule domains. Thus, cross-coupling of the DoM-derived benzamide boronic acid **76** with bromobenzenes **77**, which may also be prepared by DoM chemistry, furnishes biaryls **78** which, under either HCl or BBr_3/HOAc conditions, produce the methyl ether or free phenol dibenzopyranones **79**, respectively. The establishment of regiochemistry by DoM in the thereby derived biaryls **80** and hence, unusually substituted dibenzopyrans **81**, is a valuable aspect of this route which leads to antimutagenic ellagic acid congeners, its metabolite, **82**, "castorium" a component of the scent gland of the Canadian beaver, **83**, as well as an assortment of heterocyclic analogues. The remote anionic Fries approach **80** (see Section 14.3.1.1) to the same systems shows advantages (in **81**, compare **a:** anionic Fries versus **b:** direct cross-coupling) in overall yields (oy), presumably due to a less sterically encumbered cross-coupling event, has also been demonstrated [116, 117].

The benefit of testing at least two of the named cross-coupling methodologies in order to achieve optimum results has been clearly illustrated in the synthesis of heterocyclic annelated *ortho*-naphthoquinones **87** (Scheme 14-19). Thus, a comparison of Suzuki-Miyaura and Negishi cross-coupling reactions of the furan and thiophene amides **85** with simple bromotoluenes **84** shows advantages of the latter, presumably due to protodeboronation of heterocyclic boronic acid partner. A DreM (see Section 14.3.1.1) reaction followed by oxidation affords the target mole-

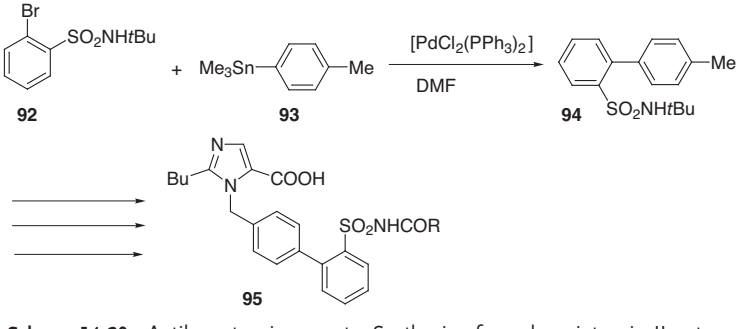


Scheme 14-19 Route to heteroring-anneleted *ortho*-naphthoquinones.

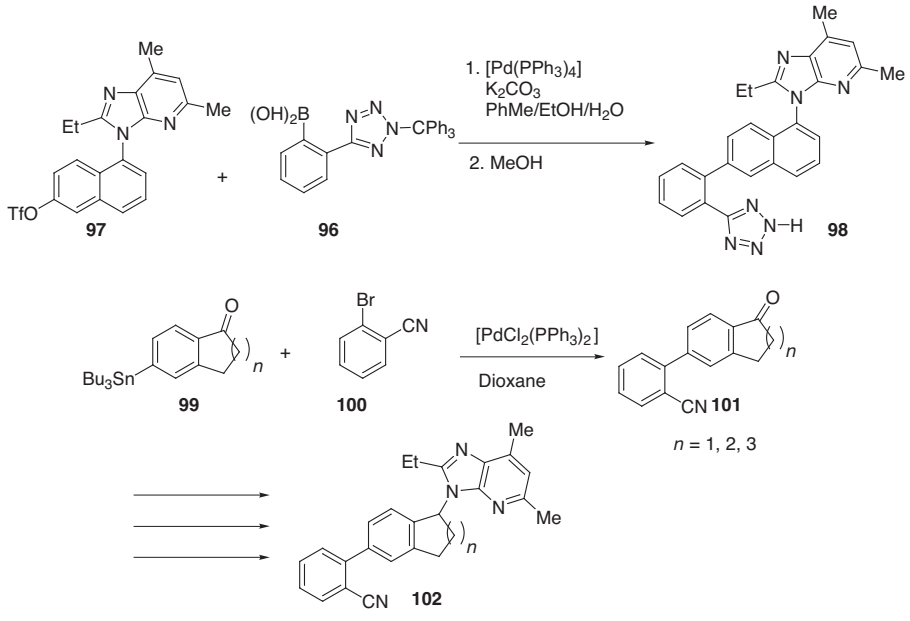
cules **87**, some of which show antimalarial/antitumor properties. Pyrido-fused *ortho*-naphthoquinones (**91**) were also prepared by this methodology [43].

Potentially derivable by DoM chemistry [118], the *ortho*-bromoarylsulfonamide **92** (Scheme 14-20) has been shown to undergo smooth Stille cross-coupling with the *para*-tolylstannane **93** to give the biaryl **94** which, upon further modification, leads to **95**, an angiotensin AII antagonist of potential use as an antihypertensive agent [119]. The sulfonamide is envisaged as a tetrazole surrogate in this class of drug indication.

The aryltetrazole has become a recognizable moiety in new drug candidates as a result of its presence in the commercial antihypertensive drug, Losartan® [120]. As in the commercial metric-ton synthesis, the preparation of the analogue **98** relies on the DoM reaction to give the boronic acid **96** (Scheme 14-21) which, upon



Scheme 14-20 Antihypertensive agents. Synthesis of novel angiotensin II antagonists.

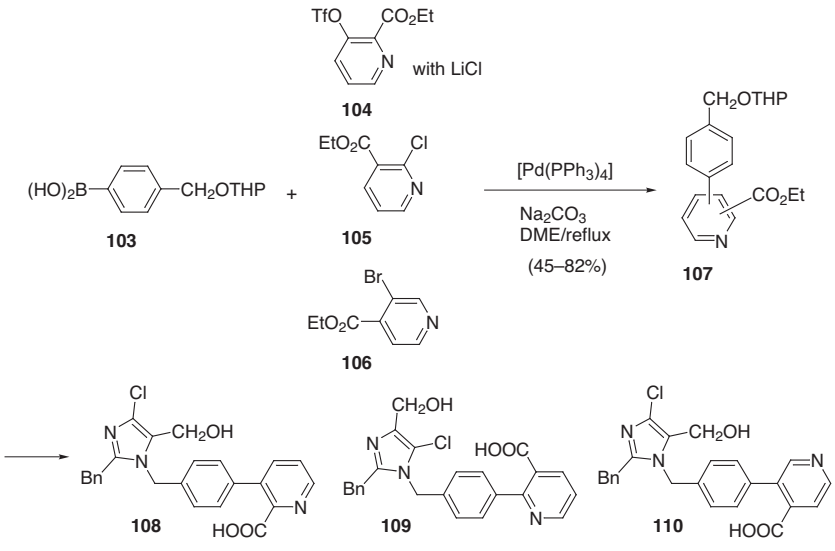


Scheme 14-21 Antihypertensive agents. Synthesis of angiotensin II antagonists.

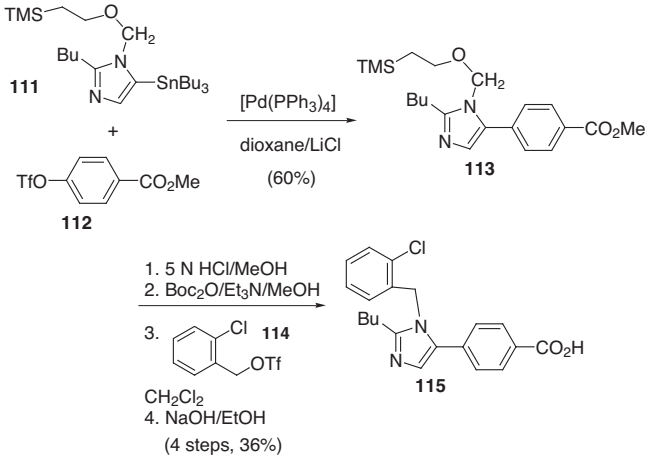
Suzuki-Miyaura cross-coupling with **97**, followed by detrytilation, affords **98**. The *ortho*-substituted biaryl motif in **98** is also noted in **101** which is obtained by a Stille cross-coupling of the stannane **99** with *ortho*-bromobenzonitrile (**100**). Benzonitriles are converted into aryl tetrazoles, hence the connection between **98** and **102** [121]. Higher substituted derivatives of the prototype compound **98** may be available by using an *in situ* DoM silylation-*ipso*-halodesililyation method [26].

DoM-Suzuki-Miyaura cross-coupling strategies also dominate the synthesis of the potential angiotensin II antagonists **108**, **109**, and **110** (Scheme 14-22). The simple but key pyridine esters **105** and **106** – but not **104** – are prepared by using the rich metallation chemistry of halopyridines [122]; their cross-coupling with the simple arylboronic acid **103** affords the isomeric heterobiaryls **107** which, by obvious modification are transformed into the potential drug candidates [123]. The fact that LiCl is required for the Suzuki-Miyaura cross-coupling of the triflate **104** is unusual feature which is a common practice in the Stille cross-coupling reaction.

A DoM-Stille connection was established for the synthesis of **115**, and also undertaken for potential demonstration of angiotensin II antagonist activity (Scheme 14-23). Thus, the stannylated imidazole **111**, derived by virtue of the OSEM DMG, undergoes cross-coupling with the aryl triflate **112** under standard Stille conditions to afford **113** which is further converted by conventional reactions into **115** [124]. Inversion of the cross-coupling partners in **111** and **112**, tested in related systems, was shown to proceed in higher yields.



Scheme 14-22 Antihypertensive agents. Synthesis of angiotensin II antagonists.



Scheme 14-23 Antihypertensive agents. Synthesis of angiotensin II antagonists.

14.4.1.2 **DoM-Cross-Coupling Tactics involving Ar-Z-Ar Bond Formation**

Comprehensive studies of DoM- cross-coupling methods for the construction of Ar-Z-Ar (Z = heteroatom) systems are not obvious in the current literature, although ongoing and concealed activities by medicinal and process chemists will undoubtedly change this situation in the future. Advantage may be taken of classical and modern Ullmann and Buchwald-Hartwig methods to prepare diarylamines, diarylsulfones, diarylphosphine oxides and diarylethers which, using DreM tactics, may be converted into acridones, thioxanthones, dibenzophosphorinones,

and xanthones respectively, structural types of which are known to exhibit a variety of biological activities [11b]. In the context of diarylamines, the DreM method has been applied to the synthesis of the dibenzazepinone, oxcarbazepine (Trileptal®) [125].

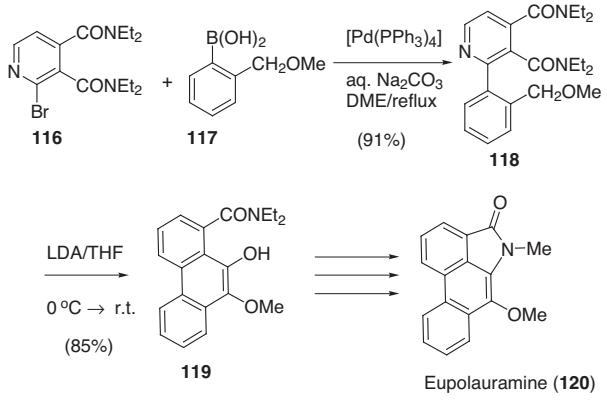
14.4.2 Synthesis of Natural Products

14.4.2.1 Suzuki-Miyaura Cross-Coupling

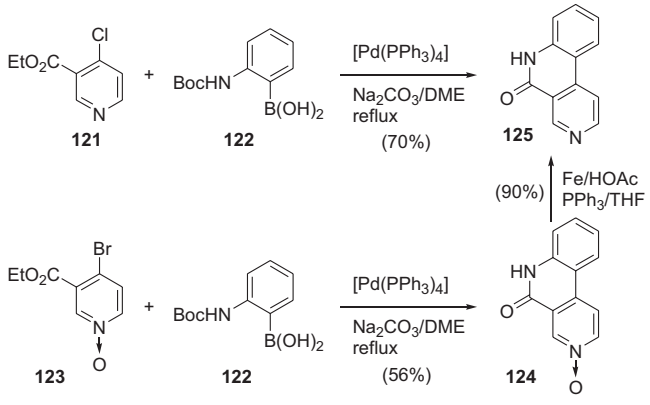
The compact structure of eupolauramine (**120**, Scheme 14-24), a biogenetically unusual azaphenthrene alkaloid isolated from *Eupomalia laurina*, serves as a typical application of combined DoM-Suzuki-Miyaura cross-coupling and DreM concepts [126]. Thus, the pyridinediamide **116**, obtained by C-3 metallation-carbamoylation of the respective, readily available nicotinamide, undergoes cross-coupling with the simple arylboronic acid **117** to give azabiaryl **118** in high yield. Remote tolyl methyl deprotonation-cyclization (DreM) affords the azaphenanthrene **119** which, by further manipulation, including a Weinreb amide synthesis step, efficiently leads to eupolauramine (**120**) [127].

The marine alkaloids constitute a rich arena for innovative DoM-cross-coupling approaches, and an opportunity which has as yet been rarely taken [128]. In these systems, a predominant motif, the benzo[*c*][2,7]naphthyridinone has been approached by both ArMet + Ar′LG and Ar′Met and ArLG approaches (Schemes 14-25 and 14-26). Thus, 4-chloronicotinate **121** (Scheme 14-25) and the *ortho*-boronic acid *N*-Boc aniline **122**, both derived by DoM chemistry, undergo smooth cross-coupling with concomitant lactamization to afford **125** in good yield. Alternatively, cross-coupling of the bromonicotinate *N*-oxide **123** with the same boronic acid **122** provides the analogous tricyclic **124** which, upon deoxygenation, leads to the same benzonaphthyridinone **125** [129].

The hydrolytic instability of the bromonicotinate corresponding to **121** to the standard Suzuki-Miyaura conditions necessitated the use of the *N*-oxide. Inversion of the cross-coupling partners was used for the construction of the alkaloid amphi-



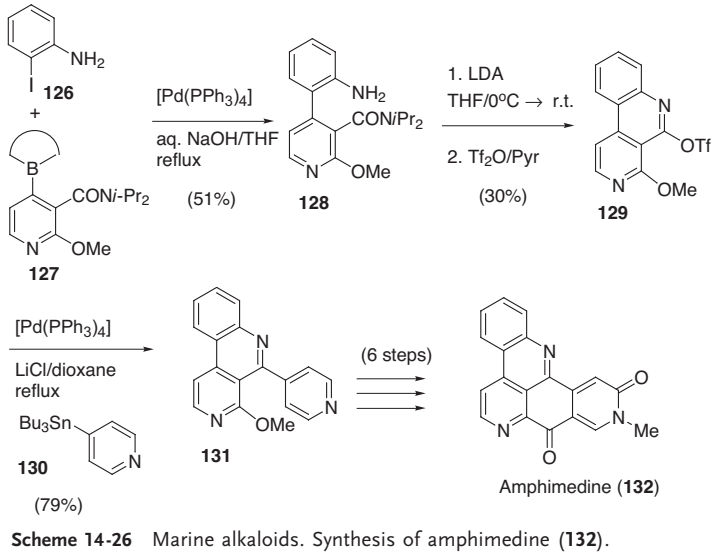
Scheme 14-24 Terrestrial alkaloids. Synthesis of eupolauramine (**120**).



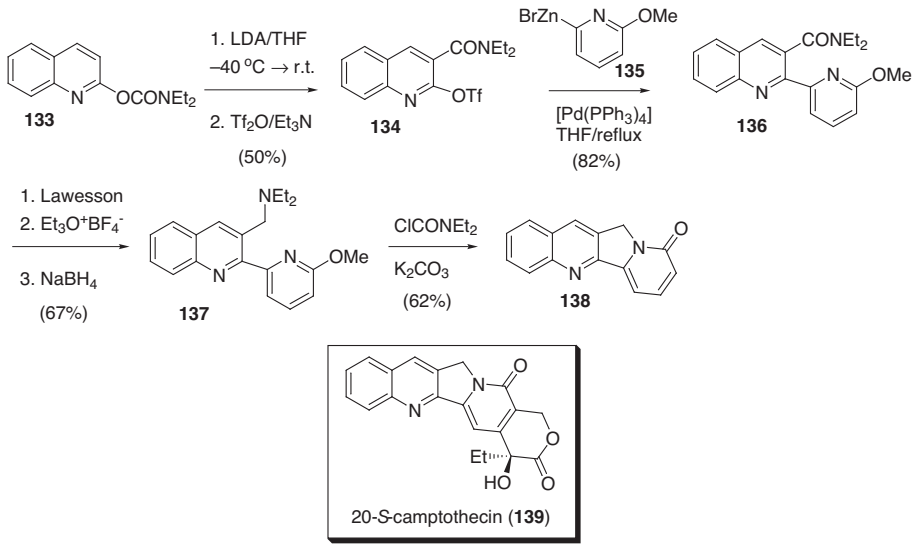
Scheme 14-25 Marine alkaloids. Methodology for key benzo[c][2,7]-naphthyridinone moiety (**125**).

medine (**132**, Scheme 14-26). Cross-coupling of *ortho*-iodoaniline (**126**) with the 4-(9-BBN)-nicotinamide **127**, obtained by an appropriate DoM procedure, afforded the azabiaryl **128** in modest yield. Unsuccessful acid-catalyzed cyclization of **128** necessitated change to basic conditions which leads, after triflation, to **129**. A Stille cross-coupling with the 4-stannylated pyridine **130** affords **131**, the conversion of which into amphimedine **132** has been previously established [130].

The synthesis of the tetracyclic fragment **138** of the important antitumor alkaloid, 20-*S*-camptothecin (**139**) (Scheme 14-27) is initiated by an anionic ortho-Fries rearrangement of the quinoline-*O*-carbamate **133** which leads, after triflation, to **134**. Negishi cross-coupling with the readily prepared pyridyl zinc **135** proceeds in high yield to afford the heterobiaryl **136**. Further conventional manipulation pro-



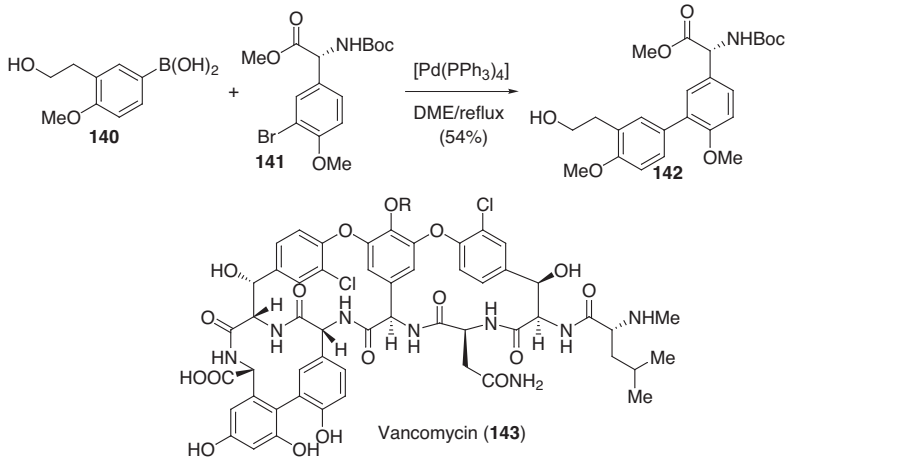
Scheme 14-26 Marine alkaloids. Synthesis of amphimedine (**132**).



Scheme 14-27 Terrestrial alkaloids. Synthesis of the A/B/C/D fragment of 20-*S*-camptothecin.

ceeding *via* **137** leads to the A/B/C/D ring fragment **138** of 20-*S*-camptothecin (**139**) [131,142].

The structure of vancomycin **143** (Scheme 14-28), the complexity of which is due, among other aspects, to multiple atropisomeric chirality, has attracted intense synthetic interest [132]. An early, simple but useful example involves the cross-coupling of **140** with a brominated aromatic dipeptide **141** to give the polyfunctionalized biaryl **142** [133].



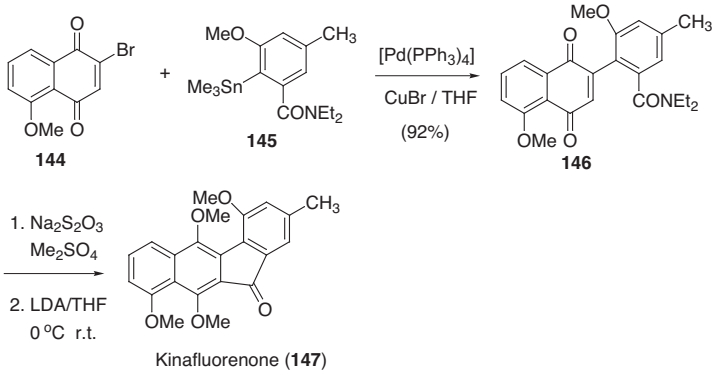
Scheme 14-28 Fungal metabolites. Synthesis of vancomycin (**143**) fragments.

14.4.2.2 **Stille Cross-Coupling**

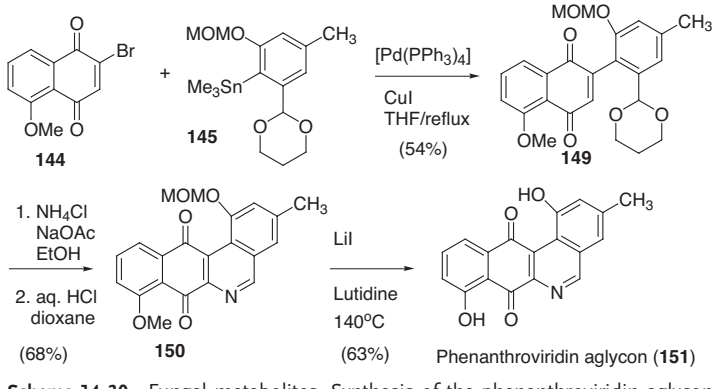
Stille cross-coupling plays a prominent role in the construction of kinafluorenone **147**, a precursor of kinamycins isolated from *Streptomyces murayamaensis* (Scheme 14-29) and phenanthroviridin aglycone **151** (Scheme 14-30). Thus, the bromojuglone derivative **144** (Scheme 14-29) undergoes cross-coupling with the highly hindered stannylated benzamide **145**, obtained by a DoM procedure, affording **146** in excellent yield. Reductive methylation followed by an LDA-induced cyclization according to the DreM concept affords kinafluorenone **147** [134].

Starting with the same juglone derivative **144** (Scheme 14-30) and a similar stannylated benzamide (**148**), the product **149** is obtained by cross-coupling and, upon oxidative ammonolysis followed by two deprotection steps, furnishes product **151** in low yields [135]. Both **147** and **151** exhibit antibiotic activity, while **151** is an anticarcinogen that has the distinction of being first reported in the patent literature.

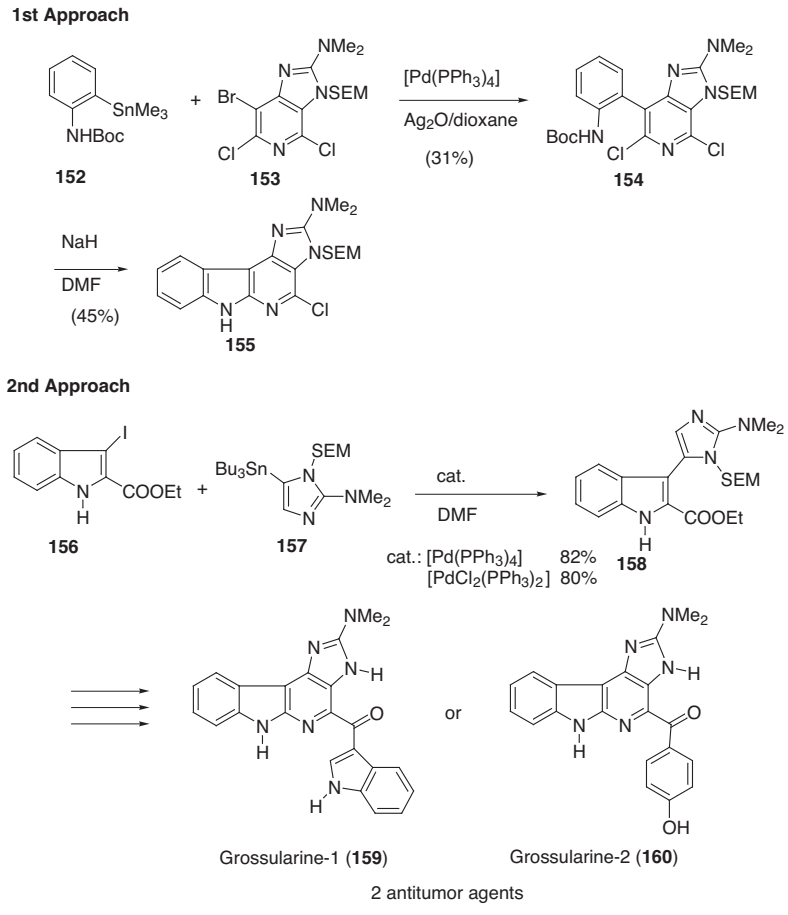
A study of the synthesis of grossularines I (**159**) and II (**160**) (Scheme 14-31), constituting antitumor marine alkaloids isolated from the tunicate *Dendrodoa grossularia*, is instructive in terms of different modes of heterocyclic ring assemblage



Scheme 14-29 Fluorenones. Synthesis of kinafluorenone **147**.



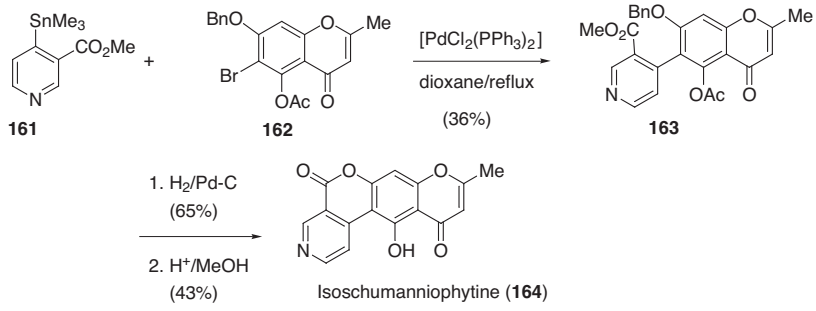
Scheme 14-30 Fungal metabolites. Synthesis of the phenanthroviridin aglycon **151**.



Scheme 14-31 Marine alkaloids. Synthesis of grossularines I (**159**) and II (**160**).

and the finer elements of cross-coupling. Thus, the cross-coupling of *ortho*-stannylated *N*-Boc aniline **152** with the imidazolopyridine **153** proceeds, as expected on the basis of halo reactivity, to give product **154** albeit under special Ag_2O conditions and in low yield. Taking advantage of nucleophilic heteroaromatic substitution (see also Scheme 14-35, **181**), NaH treatment leads to the indoloannelated product **155** [54]. In an alternate approach, in which the α-carbazole ring construction is a key step, the simple iodoindole **156** is subjected to cross-coupling with the stannylated imidazole **157**, obtained by SEM-mediated DoM chemistry, to give product **158** in high yields under two catalytic conditions. Further manipulation including an interesting carbonylative coupling in the final steps leads in high yield to the marine natural products **159** and **160** [136].

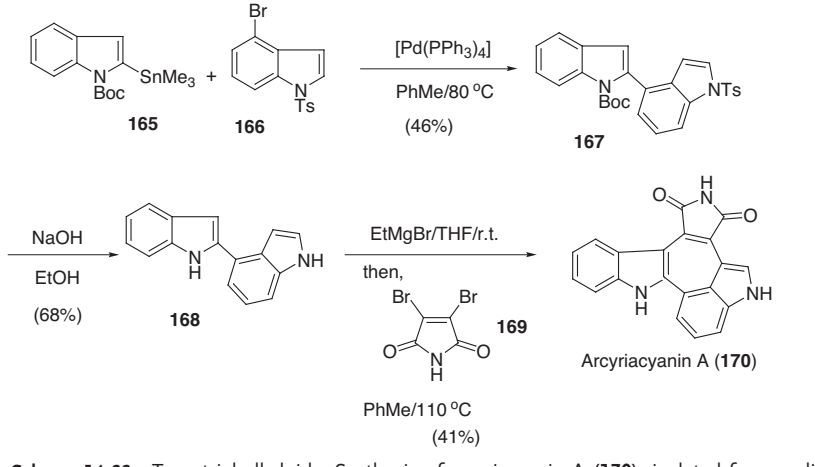
The fundamental Stille cross-coupling tactic received a test of considerable steric hindrance in the synthesis of isoschumanniophytine **164** (Scheme 14-32), one of



Scheme 14-32 Dibenzopyranones. Synthesis of isoschumanniophytine **164**.

two unique compounds isolated from the bark of *Schummaniophyton problematicum*. Thus, the conventionally constructed benzopyrone **162** undergoes coupling with the stannylated nicotinate **161** to give product **163** in low yield. Catalytic debenzylation followed by hydrolysis-cyclization leads, in modest yield, to isoschumanniophytine **164**, used in the prophylaxis and treatment of infections by HIV and herpes simplex virus [137].

The construction of the indolocarbazole **170** (Scheme 14-33) originating from a mushroom source, begins by taking advantage of a widely used indole C-2 DoM reaction to give the starting stannylated derivative **165** which, upon cross-coupling with the 4-bromoindole **166** affords the bis-indole **167** in modest yield. Deprotection with base leads to **168** which is subjected to a Grignard-induced double addition-elimination sequence with dibromomaleimide (**169**) to give the natural product **170** [138].

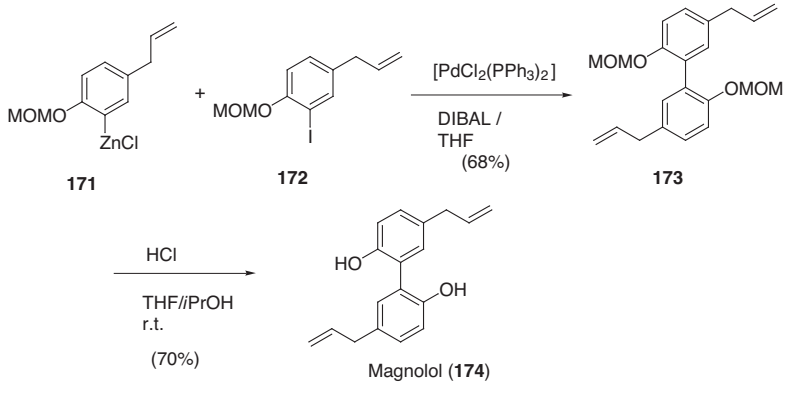


Scheme 14-33 Terrestrial alkaloids. Synthesis of arcyriacyanin A (**170**), isolated from a slime mold, *Arcyria denudata*.

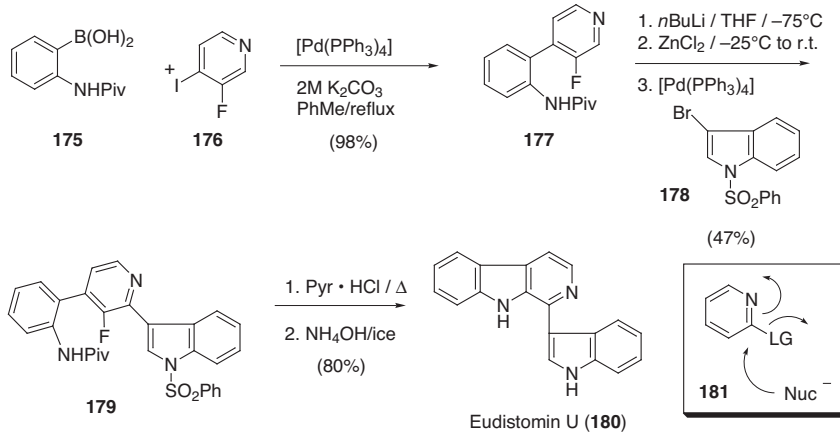
14.4.2.3 Negishi Cross-Coupling

Magnolol **174** (Scheme 14-34), a simple antiviral biaryl biphenol isolated from the bark of *Magnolia officinalis*, is readily constructed by the Negishi cross-coupling of **171** with its corresponding iodide **172**, both readily obtained by DoM and transmetallation or iodination reactions to yield **173** which, upon simple hydrolysis, affords the natural product **174** [139].

The construction of the indolocarboline alkaloid, eudistomin U **180**, is instructive not only from the DoM-Negishi cross-coupling strategy perspective but also from the point of view of an additional synthetic link to nucleophilic aromatic substitution (Scheme 14-35) [140]. The DoM regimen is showcased in the construction of the azabiaryl **177**, which is derived from a Suzuki-Miyaura cross-coupling of **175**



Scheme 14-34 Biaryl natural products. Synthesis of magnolol (**174**), component of magnoliaceae.



Scheme 14-35 Terrestrial alkaloids. Synthesis of eudistomin U, an antibacterial marine alkaloid isolated from *Lissoclium fragile*.

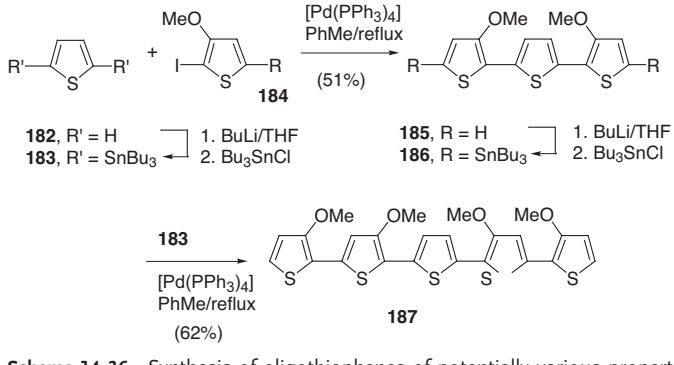
with the dihalopyridine **176**, with both partners also originating from DoM chemistry. Taking advantage of the higher pyridine ring C-H acidity compared to that of benzene, metallation followed by Zn transmetallation and cross-coupling with the bromoindole **178**, *not* derived by DoM, affords the interesting azateraryl **179**. In spite of the C-3 orientation of the fluoro substituent in the pyridine ring, an intramolecular nucleophilic substitution reaction is achieved, together with desulfonylation, under vicious conditions, to afford the natural product **180** [141].

14.4.3
Synthesis of Organic Materials

While metallation-cross-coupling strategies dominate in the construction of materials for the investigation of conduction, liquid crystal, transistor, fluorescence, electroluminescence, ion receptor, cluster catalysis, among other properties, the application of the DoM connection has not been widely tested. As is evident from the discussion relating to the synthesis of bioactive molecules and natural products (*vide supra*), DoM-cross-coupling synthetic design may lead to the provision of new molecules with unusual – and perhaps also useful physical and chemical – properties due to derived electronic and steric factors.

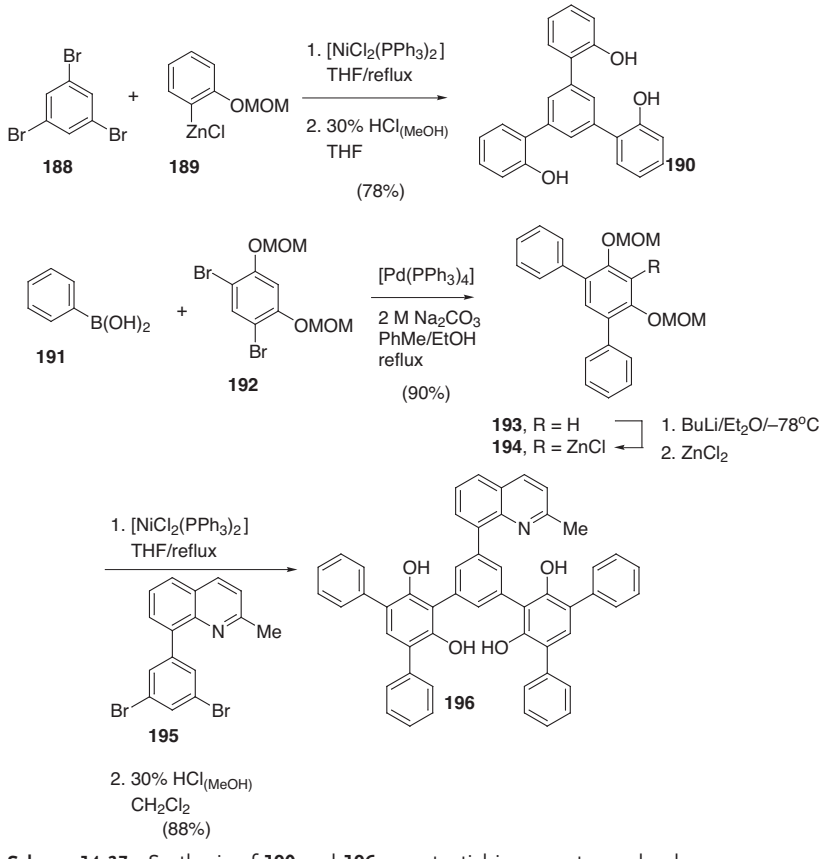
Oligothiophenes constitute a very large and diverse class of materials which have been studied largely for their properties shown in electrically conducting materials, electrooptical and electronic devices, and highly organized molecular assemblies. The DoM-Stille cross-coupling strategy has been demonstrated in the synthesis of **187** (Scheme 14-36). Thus, cross-coupling of the iodothiophene, derived by DoM chemistry, with the stannylated counterpart leads to **185**. Further metallation by taking advantage of the inherent high C-2 acidity of thiophene and stannylation leads to **186**. The latter then undergoes 2:1 cross-coupling to give the pentathiophene **187** [143].

In several synthetic endeavors to produce ion receptor molecules, the simple tetra-aryl triphenol **190**, the more complex quinoline-containing derivative **196**, and the related **200** have been prepared by DoM-Negishi cross-coupling strategies

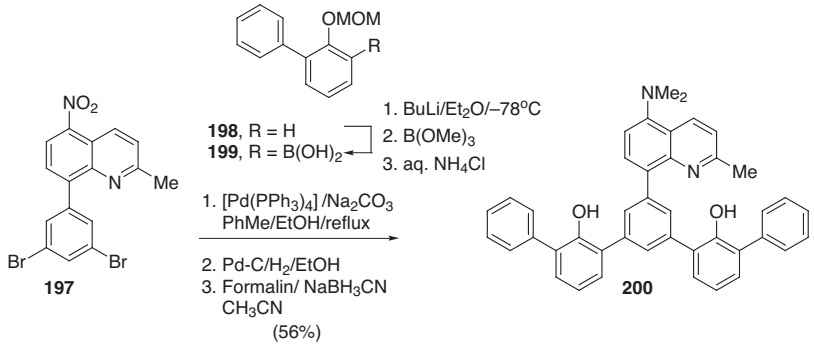


Scheme 14-36 Synthesis of oligothiophenes of potentially various properties.

(Schemes 14-37 and 14-38). In the Negishi approach (Scheme 14-37), the 1:3 cross-coupling reaction between **188** and **189**, with the latter being derived *in situ* by DoM-transmetallation, affords (after hydrolysis) the target molecule **190** in good yield. In a more interesting and demanding synthesis, the dibromo-diMOM aromatic **192** undergoes clean 1:2 cross-coupling with phenylboronic acid **191** to afford **193** which, upon DoM – zinc transmetallation followed by a further 1:2 cross-coupling and hydrolysis, gives the structurally interesting **196** [144]. The synthesis of the 5-(dimethylamino)quinoline analogue **200** (Scheme 14-38) is initiated by use of the readily available 2-OMOM biaryl **198**, which is subjected to DoM-boronate conditions to give the corresponding boronic acid **199**. 1:2 cross-coupling with **197** followed by a nitro group reduction and reductive amination affords a good yield of the designed molecular receptor **200** [144].



Scheme 14-37 Synthesis of **190** and **196** as potential ion-receptor molecules.



Scheme 14-38 Synthesis of nitro-derived **200** as potential ion-receptor molecule.

14.5
Conclusions and Prognosis

The combination of directed *ortho* metallation (DoM) and transition metal-catalyzed Suzuki-Miyaura, Kumada-Corriu-Tamao, Stille, and Negishi cross-coupling reactions provides a useful methodology for the synthesis of polysubstituted aromatics and heteroaromatics, and a valuable strategy for the construction of corresponding bioactive molecules and natural products. The aim of this review was to provide a noncomprehensive survey of the DoM-cross-coupling link from which the following aspects would be, to various degrees, appreciated.

14.5.1
Synthetic Methodology

- The DoM-cross-coupling connections that can be favorably established using Li for B, Mg, Sn, and Zn transmetallation starting points in the context of the various carbon- (and heteroatom-) based directed metallation groups (DMGs) in both aromatic and heteroaromatic systems.
- DoM-cross-coupling methodologies for Ar-Ar and Ar-Z-Ar (Z = NR, O, S) bond motifs, as well as for HetAr systems, is the focus of this review.
- A sojourn into the DoM-cross-coupling link to directed remote metallation (DreM) is taken, albeit briefly in view of recent more extensive reviews on this topic [11b, 18].
- Tabular surveys are provided of selected synthetically useful cases, starting with biaryls, through to polyaryls, and considering heteroaryls in order of π-excessive and π-deficient systems.
- Convenience, stability, side reactivity factors of various ArMet (Met = B, Mg, Sn, Zn) species are considered.
- Qualitative relative rates of cross-coupling of various ArLG (LG = halogen, OTf, as well as newer $OCONR_2$ and SO_2NR_2) are considered in the context of the

currently incomplete mechanistic pictures for both DoM and cross-coupling reactions.
- Impact of steric effects and functional group compatibility for the named cross-coupling reactions are illustrated and compared as attainable from the current literature.
- **Experimental.** Selected experimental procedures for the preparation of the representative Ar-Ar and Ar-Z-Ar derivatives are provided in Section 14.6.

14.5.2
Synthetic Application

- Advantages gained from the use of the DoM-cross-coupling synthetic link are delineated: regioselectivity, brevity, and efficiency derived from both DoM and cross-coupling component reactions; pre- and post- DoM substituent introduction; interconnections, at all stages, with other synthetic methods; including the DreM connection.
- The DoM-cross-coupling strategies are illustrated by selected examples from the bioactive molecule, natural product, and, in small part, material science literature with attempts to enlighten how detection of DMGs and Ar-Ar and Ar-Z-Ar bonds in both simple and complex aromatic or heteroaromatic frameworks may lead to advantageous retrosynthetic analyses compared to alternative, many times, electrophilic substitution-based tactics.

14.5.3
Prognosis

Some 15 years have passed since the earliest DoM-cross-coupling sequence was reported [2]. Based on the discussions in this chapter, additional opportunities in synthetic methodology and applications are now evident, and further evolution of this strategy to achieve broader generality is anticipated. Whilst the coverage herein has been limited to connections to the Suzuki-Miyaura, Kumada-Corriu-Tamao, Migita-Stille, and Negishi Ar-Ar and Ar-Z-Ar bond-forming processes, links to other transition metal-catalyzed reactions, already indicated by preliminary studies, are ripe for development. Thus, the "departures" from the main DoM-cross-coupling terminal towards Heck, Sonogashira, Grubb metathesis, $S_{RN}1$ and, generally, nucleophilic aromatic substitution, carbonylative cross-coupling, ipso-E^{+}-induced desilylation, and …. "gates" are clearly ready for exploration and exploitation. Furthermore, cascade and/or domino processes, whereby selective transition metal tuning to influence rates of various combinations of couplings [145], will influence the thinking of organic chemists in their quest for increased efficiency, selectivity, and, not the least, environmental stewardship.

14.6
Selected Experimental Procedures

14.6.1
DoM-Suzuki-Miyaura Cross-Coupling for the Preparation of Benzo[*c*][2,7]naphthyridinone (125, Scheme 14-25).

A solution of NBoc aniline (1.8 g, 10 mmol) in anhydrous THF (40 mL) at –78 °C under argon, was treated with *t*BuLi (1.7 *M* solution in pentane, 14 mL, 24 mmol), and the solution was stirred for 15 min. The mixture was warmed to –20 °C and stirred for 2 h, after which trimethylborate (4.3 mL, 38 mmol) was added and the reaction mixture allowed to warm to ambient temperature. The reaction mixture was cooled to 0 °C and acidified to pH 6.5 by the addition of 10 % aqueous HCl. The aqueous phase was separated and extracted with CH_2Cl_2, the extracts were combined with the initial THF solution, and the combined extract was washed with brine (20 mL), dried ($MgSO_4$), and evaporated. The crude boronic acid **122** produced as a colorless powder was used without purification in cross-coupling reactions.

A heterogeneous mixture of 4-chloropyridine **121** (1.4 g, 8 mmol), $[Pd(PPh_3)_4]$ (0.4 g, 0.4 mmol), 2 *M* aqueous Na_2CO_3 (7.7 mL), and boronic acid **122** (4.2 g, 18 mmol) in DME (80 mL) was refluxed under nitrogen for 8 h. The reaction mixture was cooled and partially evaporated *in vacuo*. Addition of benzene (20 mL) and filtration gave 1.1 g (70 %) of **125**.

14.6.2
DoM-Kumada-Corriu-Tamao Cross-Coupling for the Preparation of *N,N*-diethyl-2-trimethylsilyl-3-phenylbenzamide (Table 14-9, entry 3).

To a solution cooled at 0 °C of *N,N*-diethyl-3-trifluoromethanesulfonyloxy-2-trimethylsilylbenzamide (350 mg, 0.88 mmol) and $[NiCl_2(dppp)]$ (30 mg, 0.055 mmol) in THF (10 mL) was added PhMgBr (0.60 mL, 3.0 *M*, 1.80 mmol). After 7 h, the reaction was treated with aqueous saturated NH_4Cl (10 mL) and extracted with ether (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was the purified by flash chromatography (3:1 hexane:EtOAc) and afforded the *N,N*-diethyl-2-trimethylsilyl-3-phenylbenzamide (200 mg, 70 %) as a colorless oil.

14.6.3
DoM-Migita-Stille Cross-Coupling for the Preparation of oligothiophene 185 (Scheme 14-36).

A flask was charged with compound **184** (1 g, 4 mmol), **183** (1.35 g, 2.04 mmol), 200 mg of tetrakis(triphenylphosphine)palladium(0), and toluene (15 mL). The reaction mixture was first purged with argon for 20 min, and then heated to 100–110 °C overnight before being poured into saturated NH_4Cl solution. The

aqueous layer was extracted with ether (2 ×10 mL), and the organic extracts were washed with saturated NH_4Cl solution and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the residue purified by flash chromatography (1 % ethyl acetate in hexane) to provide 320 mg (51 %) of **185** as yellow crystals.

14.6.4

DoM-Negishi Cross-Coupling in the Preparation of 5,5′-Diallyl-2,2′-bis(methoxymethoxy)biphenyl 173 (Scheme 14-34).

4-Allyl-2-iodophenyl methoxymethyl ether (**172**). A solution of 2.02 g (11.3 mmol) of 4-allyl-2-phenyl methoxymethyl ether in 10 mL THF was treated at –78 °C with 10 mL (17.0 mmol of a 1.7 *M* solution in hexane) of *tert*-butyllithium. After being stirred at –78 °C for 2 h, the mixture was treated with a solution of iodine (4.32 g, 17.0 mmol) in 15 mL THF. The mixture was stirred for 30 min, allowed to warm to r. t., poured into 10 mL of 20 % aqueous Na_2SO_3, and extracted three times with 10 mL of ether. The combined extract was washed with saturated NH_4Cl solution, dried over sodium sulfate, and the solvent was removed *in vacuo*. The crude product was purified by chromatography (hexane-EtOAc, 95:5) to give 3.1 g (90 %) of aryl iodide **172**.

5,5′-Diallyl-2,2′-bis(methoxymethoxy)biphenyl (**173**). A solution of *tert*-butyllithium in hexane (0.88 mL of a 1.7 *M* solution, 1.5 mmol) was added to 178 mg (1.0 mmol) of **172** in 1 mL THF at –78 °C. After 2 h, the mixture was warmed to –10 °C and transferred *via* a cannula to 1.0 mL (1.0 mmol, 1.0 *M* solution in ether) of zinc chloride at r. t.. The mixture was stirred for 1 h. The palladium catalyst was prepared in a separate flask by treating 22 mg (0.033 mmol) of $[PdC1_2(PPh_3)_2]$ in 1.0 mL THF with 0.066 mL (0.066 mmol) of DIBALH (1 *M* solution in hexane). To this catalyst solution was added 213 mg (0.70 mmol) of a solution of aryl iodide **172** in 2 mL THF, and the supernatant solution of the arylzinc chloride prepared above. The mixture was stirred for 2 h at r. t., and the reaction was then quenched with 5 mL saturated ammonium chloride solution. The aqueous layer was extracted with three 10-mL portions of ether. The combined extract was washed once with brine and dried over sodium sulfate. After removal of the solvent *in vacuo,* the crude product was purified by chromatography (hexane-EtOAc, 95:5) to give 169 mg (68 %) of biaryl **173**.

14.6.5

DoM-Ullmann Cross-Coupling. Synthesis of Ar-X-Ar′ (X = O, N, S) under Modified Ullmann Reaction Conditions (General procedure; Table 14-18**).**

A 0.5 *M* toluene/xylene solution of 2-halobenzamide, 1.5 equiv. of phenol (thiophenol or aniline), 2 equiv. of Cs_2CO_3 and 5 mol % of Cu(I)-catalyst was refluxed with intensive stirring for 19–48 h, monitoring the progress by GC. The reaction mixture was cooled to r. t. and filtered through a paper filter. The filter was washed with a sufficient amount of EtOAc and the filtrate was concentrated *in vacuo*. The pure product was isolated by Kugelrohr distillation or column chromatography.

14.6.6

Typical Buchwald-Hartwig Cross-Coupling Procedure. Synthesis of *N*,*N*-diethyl-*N*-phenylanthranilamide (Table 14-19, entry 4).

A thick-walled screw-cap glass tube was charged with a mixture of *N*,*N*-diethyl 2-bromobenzamide (505 mg, 1.97 mmol), aniline (0.21 mL, 2.30 mmol), NaO*t*Bu (266 mg, 2.77 mmol), $[Pd_2(dba)_3]$ (5 mg, 0.006 mmol), BINAP (11 mg, 0.017 mmol) and toluene (5 mL) under N_2 atmosphere. The tube was sealed and heated (90–100 °C) with stirring for 21 h, and then cooled to r. t.. The addition of aqueous NH_4Cl and a standard work-up, followed by flash column chromatography (10 % EtOAc/hexane) afforded *N*,*N*-diethyl-*N*-phenylanthranilamide (426 mg, 81 %).

Abbreviations

Ac	acetyl
acac	acetylacetonate
Ar	aryl
bn	benzyl
Boc	*tert*-butoxycarbonyl
dba	dibenzylideneacetone
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMG	directed metallation group
DoM	directed *ortho*-metallation
dppp	1,3-bis(diphenylphosphino)propane
DreM	directed remote metallation
FG	functional group
LDA	lithium diisopropylamide
LiTMP	lithium tetramethylpiperidide
MOM	methoxymethyl
PG	protecting group
Piv	pivaloyl
Pyr	pyridine
r. t.	room temperature
TBS	*tert*-butyldimethylsilyl
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Tf	triflate
THF	tetrahydrofuran
THP	tetrahydropyranyl
Ts	4-toluenesulfonyl

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15
Palladium- or Nickel-Catalyzed Cross-Coupling with Organometals Containing Zinc, Aluminum, and Zirconium: The Negishi Coupling

Ei-ichi Negishi, Xingzhong Zeng, Ze Tan, Mingxing Qian, Qian Hu, and Zhihong Huang

15.1
Introduction and General Discussion of Changeable Parameters

This chapter is a sequel to Chapter 1 in *Metal-Catalyzed Cross-Coupling Reactions* [1] which, in its First Edition, was published in 1998. This part of the Pd- or Ni-catalyzed cross-coupling process has received an enormous amount of attention among synthetic chemists, and its scope has expanded very significantly since the first edition was published. In both *The Merck Index,* 13th edition [2] and *Organic Syntheses Based on Name Reactions,* 2nd edition, by Hassner and Stumer [3], the topic of this chapter is listed as Negishi coupling, along with Suzuki and Stille couplings as well as Heck and Trost-Tsuji reactions. *The Merck Index* also lists the Buchwald-Hartwig amination reaction. Consequently, the use of these names has been widely practiced and, for the sake of convenience, is fully justified in this chapter.

In this chapter, a brief overview of the early history of Pd-catalyzed cross-coupling during the 1970s and a discussion of some of the basic aspects and parameters of Pd-catalyzed cross-coupling will be followed by a series of special topics of the current and future interest centered around Negishi coupling. As deemed appropriate, the corresponding Ni-catalyzed cross-coupling reactions will also be discussed. As it is not practical to try to cover the subject in an exhaustive manner, the presentation in this chapter is rather selective. For a more thorough discussion of Pd-catalyzed cross-coupling, as of a few years ago, the reader is referred to Part III of the *Handbook of Organopalladium Chemistry for Organic Synthesis* [4]. For discussions of more recent results, several recent reviews on specific topics cited throughout this book may be consulted. Within the area covered by this chapter, for example, a comprehensive review on Pd-catalyzed alkynylation was published in 2003 [5].

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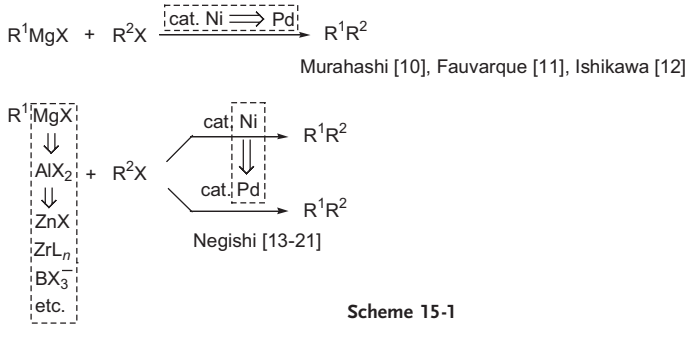
15.1.1 Genesis and Early Developments of Pd-Catalyzed Cross-Coupling

The early history of the discoveries and developments of Ni- and Pd-catalyzed cross-coupling has been documented in a special issue of the *Journal of Organometallic Chemistry*, published in 2002 [6], and in particular a chapter entitled "A Genealogy of Pd-Catalyzed Cross-coupling" by one of the present authors (E. N.) [7] included the following discoveries and developments which were made during the period between 1975 and 1978.

1. Following the discovery of the Ni-catalyzed cross-coupling of organomagnesium derivatives in 1972 by Tamao, Sumitani, and Kumada [8] as well as by Corriu and Masse [9], a few groups led by Murahashi [10], Fauvarque [11], and Ishikawa [12] seemingly independently reported the Pd-catalyzed version of Grignard cross-coupling between 1975 and 1976.
2. Negishi, on the other hand, reported in 1976 that both Ni- and Pd-catalyzed cross-coupling could be achieved with organoaluminums used in place of organomagnesiums [13,14] (Scheme 15-1).

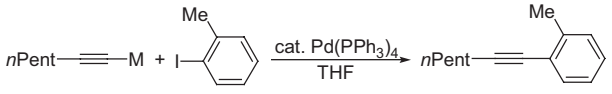


Scheme 15-1

3. During the period 1976 to 1978, the Negishi group made the following critical findings that have led to a number of significant subsequent discoveries and developments, including:

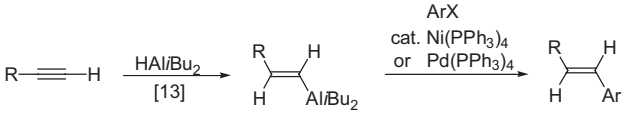
- The first systematic screening and discovery of Pd- or Ni-catalyzed cross-coupling reactions of organometals containing Al, B, Zn, and Zr [13–21], which clearly established the generality of Pd- or Ni-catalyzed cross-coupling with respect to the metal countercation (M) of the organometallic reagents (R^1M) (Schemes 15-2 and 15-3).
- The first demonstration of Pd- or Ni-catalyzed hydrometallation–cross-coupling [13,14,16,18,20,21] and carbometallation–cross-coupling [21] domino processes (Scheme 15-3).
- The first demonstration of double metal catalysis [21] with the use of second catalysts, such as $ZnCl_2$ and $ZnBr_2$ (Scheme 15-4).

With almost ten papers published by the Negishi group during this period [13–21], the basic foundation of the currently known Pd-catalyzed cross-coupling was reasonably well established.

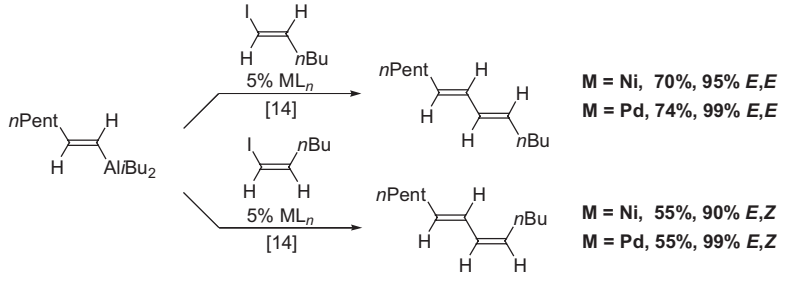


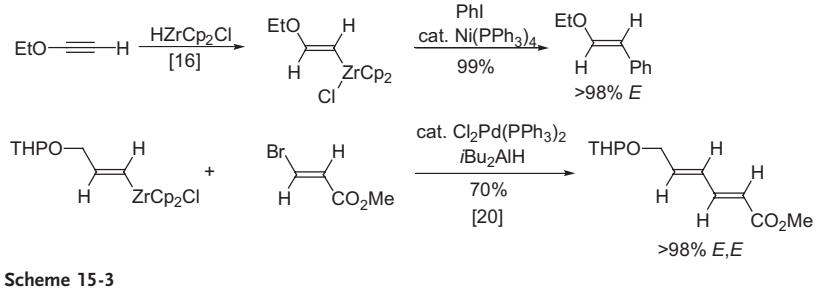
M	Temp.	Time [h]	Product Yield (%)	Starting Material (%)
ZnCl	room temp.	1	91	8
$^{-}$B*n*Bu$_3$	room temp.	3	10	76
$^{-}$B*n*Bu$_3$	reflux	1	92	5
Sn*n*Bu$_3$	room temp.	6	83	6

Scheme 15-2

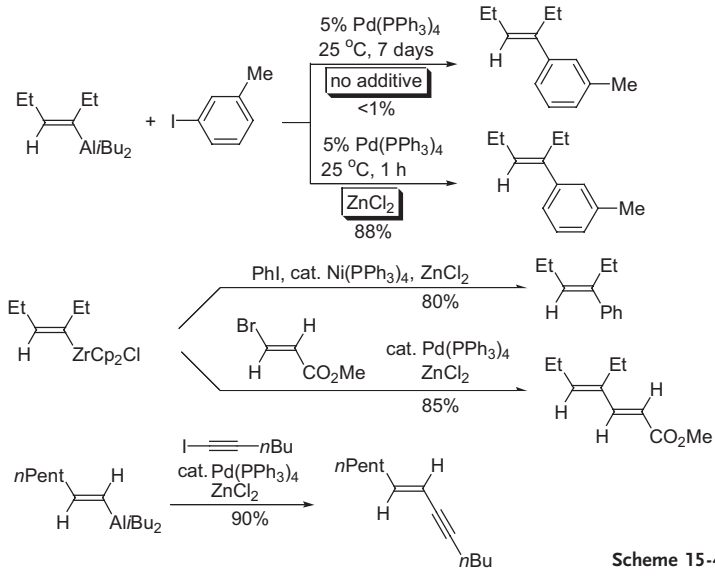


R = *n*Bu, ArX = 1-NaphBr: 93%. R = *c*Hex, ArX = *p*TolBr: 75%





Scheme 15-3



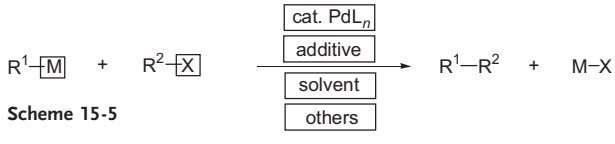
Scheme 15-4

15.1.2

An Overview of Recent Developments, and the Current Scope

All Pd-catalyzed carbon-carbon cross-coupling reactions can be represented by the general equation shown in Scheme 15-5.

For any given combination of R^1 and R^2, there are several parameters that can be changed and optimized, such as: (i) metal countercation (M); (ii) leaving group (X); (iii) Pd catalyst (PdL_n); (iv) additive or co-catalyst; (v) solvent; and (vi) others including temperature, time, concentration, and mode of addition. Thus, the main goal of the synthetic chemist is to identify the optimal set of these parameters for a given synthetic task.



Scheme 15-5

15.1.2.1 **Metal Countercations**

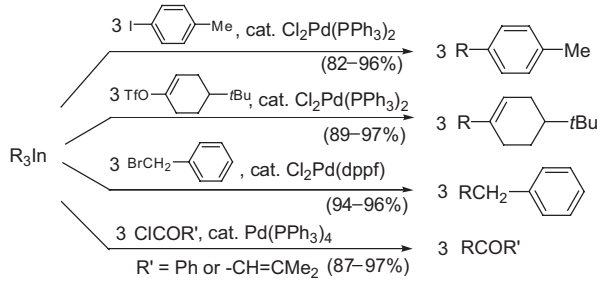
The first systematic screening of metal countercations reported in 1978 [18] employed various alkynylmetals as nucleophiles, and identified Zn, B, and Sn as three superior metals. This was despite Zn having already been shown to be a superior countercation in 1977 [15,17], when a couple of reports were also published on the Pd-catalyzed reaction of allylstannanes with aryl iodides [22,23]. It is noteworthy that these are the three most widely used metals today, and they correspond to Negishi, Suzuki, and Stille couplings, respectively. As discussed earlier, Al

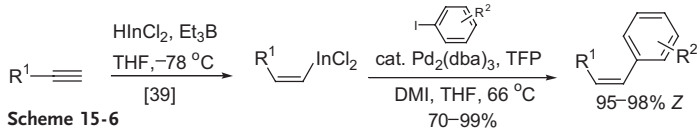
[13,14] and Zr [16,20] had been shown previously to be superior metal countercations of the respective alkenylmetals. These earlier studies also suggested that many other metals might be able to serve as metal countercations in Pd-catalyzed cross-coupling.

Even if all elements with atomic numbers higher than 83 as well as Tc and Pm are excluded for their radioactive property (except in the cases of Th, Pa, and U), there are 81 elements, of which H, C, and 18 group 15–18 elements may conveniently be considered as nonmetals. The remaining 61 metallic elements may be classified into 24 main group metals, 23 d-block transition metals, and 14 lanthanides including La. Of the 10 nonradioactive groups 1 and 2 metals, only Mg was shown during the 1970s to be of considerable utility in Pd-catalyzed cross-coupling [10–12,15,24–26]. Even so, the synthetic use of Mg has been limited by its generally low chemoselectivity and surprisingly low reactivity under Pd-catalysis conditions. Perhaps more surprising is the inability of organolithium compounds to participate widely in Pd-catalyzed cross-coupling [10,18,27,28], even though this has been shown to occur only in certain special cases [29]. Although further investigation is necessary, the inability of organolithium compounds to undergo Pd-catalyzed cross-coupling vis-à-vis their high reactivity under stoichiometric conditions may tentatively be interpreted in terms of catalyst inactivation or decomposition, i. e., "catalyst poisoning." The other members of groups 1 and 2 metals may also suffer from similar difficulties, and Be is known to be inherently toxic. Hence, organometals containing groups 1 and 2 metals will most probably continue to serve mainly as the first-generation organometals to be converted to other second-generation organometals for Pd-catalyzed cross-coupling. Otherwise, Mg may well be the only member of major synthetic utility.

By contrast, several of the twelve groups 12–14 metals, i. e., Zn, B, Al, and Sn, have been shown to be very useful in Pd-catalyzed cross-coupling, as discussed above. The heavier members of groups 12–14 metals, i. e., Cd, Hg, Tl, and Pb as well as Sn, are associated with a variety of toxic properties, and this should limit their synthetic utility. Organosilanes themselves are considered to be some of the least reactive organometals in Pd-catalyzed cross-coupling, and indeed, silyl groups are often used to protect various functional groups during the catalytic process. Nonetheless, a variety of methods for the selective activation of organosilanes has been devised to achieve Pd-catalyzed cross-coupling [30]. These reactions are discussed in Chapter 4, and will not be discussed at this point. Although significantly more expensive, Ge might be expected to show reactivities similar to those of Si, but very little appears to be known in this respect [30,31].

More than 20 years after the first systematic metal countercation screening [18], indium has recently emerged as a potentially useful metal in Pd-catalyzed cross-coupling. The Pd-catalyzed cross-coupling of R_3In reported in 1999 by Sarandeses [32] appears to be the seminal contribution. In addition to a series of papers from Sarandeses' group [32–34], those reported by others including Blum [35–37], Oshima [38–40], Lee [41–45], Fiaud [46], and Minehan [47] have also contributed to establish Pd-catalyzed organoindium cross-coupling as a potentially attractive and useful reaction, as indicated by the results summarized in Scheme 15-6.





Scheme 15-6

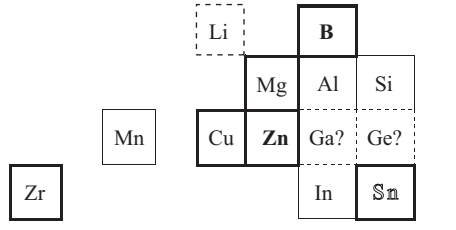
Although several of its neighboring elements are considered to be inherently toxic, In does not appear to be associated with any serious toxicity problems. The main drawback, however, is its relatively high cost, which appears to be about five to ten times that of $ZnCl_2$ on an equivalent basis. In this context, a recent finding in the authors' group that $InCl_3$ can serve as a better co-catalyst than $ZnCl_2$ or $ZnBr_2$ in promoting Pd-catalyzed cross-coupling of alkenylmetals containing Al or Zr [48] is noteworthy, and this reaction will be further discussed later. In view of the superior reactivity of In, it might appear worthwhile to investigate the Pd- or Ni-catalyzed cross-coupling of comparably priced organogallium compounds. At present, however, relatively little is known about the reaction [30,35–37], and preliminary results obtained in the authors' laboratories have not proved to be encouraging [48].

Little, if any, appears to be known about the Pd- or Ni-catalyzed cross-coupling of organometals containing group 3 metals including Sc, Y, and lanthanides. There does not appear to be any firm reason for categorically ruling them out, however. A round of systematic screening of at least some reasonably priced members might prove to be fruitful.

Of 23 d-block transition metals excluding radioactive Tc, a few (i.e., Zr and Cu) have been shown not only to participate in Pd- or Ni-catalyzed cross-coupling but also to offer some unique advantages that stem from their ability to undergo hydrozirconation [16,18,20,21] and carbocupration [49,50], respectively. A few other transition metals, such as Mn [51] and Ag [52,53], have been shown to undergo Pd-catalyzed cross-coupling, though additional positive and persuasive results would be needed to demonstrate their potential synthetic utility. In this context, the high costs of Ag compounds would pose a considerable barrier to their widespread use. This limitation also applies to the majority of the other d-block transition metals, except for several relatively inexpensive members such as Ti and Fe.

In summary, the current scope of Pd-catalyzed cross-coupling with respect to metal countercation (M) may be indicated as shown in Table 15-1. In the follow-

Table 15-1 Scope of Pd-catalyzed cross-coupling with respect to metal countercations (as of 2003)

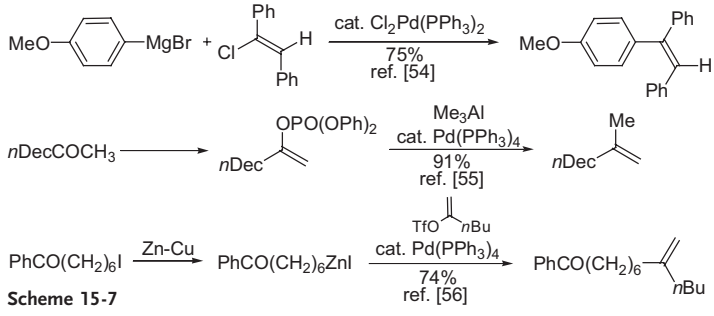


	Scope		Use			
Metal countercation	Widely applicable	Relatively limited	Widely used	Moderately used	Not yet widely used	Comments and concerns
Category I						
Zn	X		X			• Generally the most reactive.
B	X		X			• One of the most chemoselective.
Category II						
Sn	X		X			• Toxicity is a major concern.
Category III						
Cu						
	Catalytic (Sonogashira)	X	X			• Limited to alkynylation
	Stoichiometric	X			X	• Carbocupration-cross-coupling tandem promising.
Category IV						
Mg		X		X		• If satisfactory, it should be considered first.
Category V						
Al		X		X		• Specialty metals for alkenylation via hydro- and carbometallation.
Zr		X		X		
Category VI						
Si		X			X	• Low intrinsic reactivity may limit its scope.
In		X			X	• High cost is limiting.
Mn		X			X	• Promising.
Others						
Li		X			X	• Mainly to be transmetallated to other organometals
Ga						• Little is known about Ga or Ge.
Ge						

ing sections, attention will be mainly focused on the Pd-catalyzed cross-coupling reactions of organometals containing Zn, Al, and Zr – that is, the Negishi coupling.

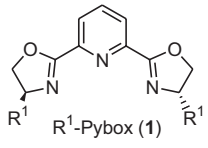
15.1.2.2 **Leaving Groups (X)**

During the 1970s, Pd-catalyzed cross-coupling was mostly performed with organic iodides, and less frequently with bromides. Organic chlorides were rarely used, and the use of fluorides was probably never reported. In the 1980s, the use of alkenyl chlorides as well as phosphates and sulfonates of phenols and enols were reported, as indicated by the results shown in Scheme 15-7.

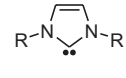


Scheme 15-7

In each example in Scheme 15-7, PPh_3 was used as a ligand in the Pd catalyst. Despite some favorable results, such as those shown in Scheme 15-7, the use of organic chlorides, phosphates, and even sulfonates (with the notable exceptions of triflates and higher fluoroalkylsulfonate derivatives) remained a generally difficult task. Over the past few years, however, a variety of "nonconventional" phosphines and other ligands, including sterically encumbered trialkylphosphines, such as tBu_3P and Cy_3P [57], variously substituted Pybox ligands represented by **1** [58], and *N*-heterocyclic carbenes (NHC) represented by **2** [59] have made it feasible to use generally and satisfactorily organic chlorides including even alkyl chlorides [58] in the Pd- or Ni-catalyzed cross-coupling. With $Ni(acac)_2$-NHC (R = 2,6-diisopropylphenyl) as a catalyst, even aryl fluorides were successfully cross-coupled with arylmagnesium bromides [60]. The use of these "nonconventional" ligands will be extensively discussed throughout this chapter.



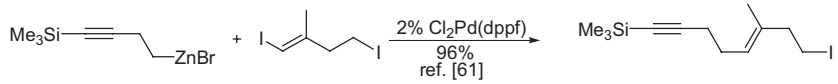
R^1-Pybox (**1**)



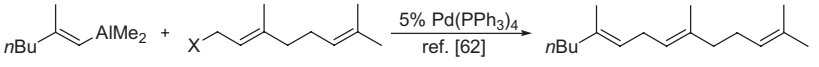
NHC (**2**)

It should be emphasized at this point that the reactivity of R-X bonds significantly depends not only on the leaving group (X) itself but also on the organic

group (R). One of the earliest examples which pointed eloquently to the significance of the organic group is shown in Eq. (1) of Scheme 15-8. The alkenyl-I bond is at least 100 times as reactive as the alkyl-I bond in this reaction [61]. In contrast to the relatively unreactive homoallyl iodide in Eq. (1), R-X bonds containing allyl and propargyl groups are substantially more reactive than alkenyl and aryl electrophiles. In fact, not only allylic chlorides but all oxygenated allylic derivatives including acetates and other carboxylates, free allylic alcohols protected in the form of alkoxyalanes, phosphates, and even trialkylsilyl derivatives tested in the authors' laboratories participated in the Pd-catalyzed reaction with alkenylalanes and arylzinc chlorides [62], as shown in Eq. (2). Similarly noteworthy are the highly contrasting reactivity profiles displayed by propargyl and allenyl derivatives having the same carbon framework and leading to the formation of the identical cross-coupling products [63] (Eqs. (3) and (4) in Scheme 15-8). These results clearly indicate that propargyl derivatives are much more reactive than the corresponding allenyl

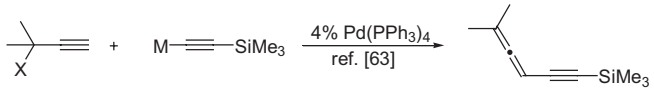


(Eq. 1)



(Eq. 2)

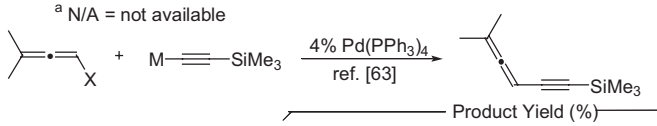
Leaving Group (X)	Product Yield (%) after 1 h	after 6 h	after 48 h
Cl	100	-	-
OAc	100	-	-
$OAlMe_2$	43	93	100
$OPO(OEt)_2$	33	43	-
$OSiMe_3$	18	41	94



(Eq. 3)

Leaving Group (X)	Product Yield (%) M = Li	M = MgCl	M = ZnCl	M = Cu	M = Ag
Br	0	70	98	N/A[a]	98
OAc	0	75	98	98	86
OSOMe	N/A[a]	90	98	98	<5
$OPO(OEt)_2$	20	98	98	N/A[a]	80

[a] N/A = not available



(Eq. 4)

Leaving Group (X)	Product Yield (%) M = Li	M = MgCl	M = ZnCl	M = Cu	M = Ag
Br	3	80	100	33	23
OAc	0	34	7	4	N/A[a]

[a] N/A = not available

Scheme 15-8

derivatives and suggest that the allenyl derivatives must act more like alkenyl derivatives rather than allyl derivatives.

With all other things being equal or comparable, the approximate order of reactivity of various carbon groups may tentatively be summarized as shown below (Scheme 15-9). Acyl derivatives are less reactive than allyl or propargyl but more reactive than alkenyl.

Allyl
Propargyl > Benzyl > Alkenyl > Aryl > Alkyl

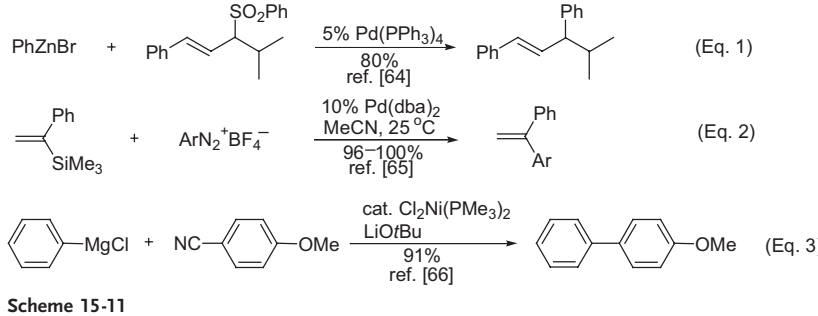
Scheme 15-9

With due considerations of (i) carbon group, (ii) ligand and Pd complexes, (iii) additive and co-catalyst, and (iv) solvent, the order of reactivity of various halogen and oxygenated leaving groups may tentatively be ranked as shown in Scheme 15-10. Organic fluorides are generally less reactive than the corresponding chlorides. The reactivity of sulfonates and phosphates can vary depending on their structural details. Consequently, these groups may not be readily ranked in Scheme 15-10.

I^+ > I > OTf ≥ Br > Cl > OOCR > OR > $OSiR_3$

Scheme 15-10

Some other nonmetals, notably S, N, and even C, have served as key atoms in leaving groups. A few representative examples are shown in Scheme 15-11.



Scheme 15-11

15.1.2.3 Ligands (L) and Pd Complexes (PdL_n)

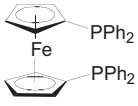
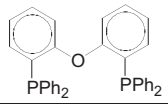
Over the past few years, a number of significant discoveries and developments that had previously been considered to be impossible have now been made in Pd- or Ni-catalyzed cross-coupling. In many cases, these new discoveries and developments were made through the consideration and use of "nonconventional" phosphines and other ligands. Since the number of conceivable ligands is literally endless, activities in this area may be expected to continue and grow in the future. In this

subsection, both conventional and "nonconventional" ligands and/or Pd complexes containing them will be listed as menus for use in synthesis and as stimuli for further research activities. Their applications will be found throughout this chapter.

In a recent review [67], a number of conventional phosphines and other ligands as well as their Pd complexes were catalogued, and a list of 10 phosphines shown in Table 15-2 was presented as a menu to be used for Pd-catalyzed reactions, including cross-coupling.

For most of the desired cross-coupling reactions, the menu presented in Table 15-2 would provide a reasonable starting point. For handling various demanding

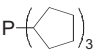
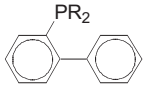
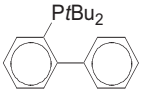
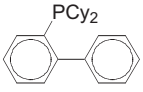
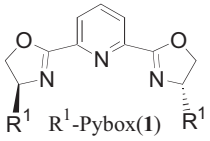
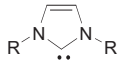
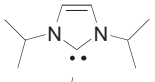
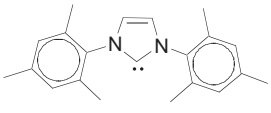
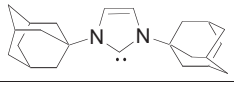
Table 15-2 A list of representative phosphines for Pd-catalyzed reactions

Monodentate Phosphines	Bidentate Phosphines	
PPh_3 (Referrence phosphine)	$Ph_2P(CH_2)_2PPh_2$	(dppe)
$PtBu_3$	$Ph_2P(CH_2)_3PPh_2$	(dppp)
PCy_3	$Ph_2P(CH_2)_4PPh_2$	(dppb)
$PTol_3$ (TTP)		(dppf)
$P(2\text{-Furyl})_3$ (TFP)	$iPr_2P(CH_2)_3PiPr_2$	(dippp)
		(DPEphos)

tasks of Pd- or Ni-catalyzed cross-coupling, and especially those cases with organic chlorides including alkyl chlorides [58, 69], it is desirable to add other "nonconventional" phosphines and *N*-containing ligands, as shown in Table 15-3 [58, 59, 68, 69].

Some of the "nonconventional" ligands listed in Tables 15-2 and 15-3 have recently been shown to exhibit not only rate acceleration but also remarkable abilities to alter stereoselectivity profiles, as detailed later [70–73]. Although these new ligands have made it possible to achieve various Pd- or Ni-catalyzed cross-coupling reactions that had until recently been considered very difficult or even impossible, they nevertheless have also been associated with some undesirable features. Their relative instability and high costs are two major concerns to be overcome. Since the cost-related problem in catalysis can be overcome by raising the turnover number (TON), which, in turn, depends on the stability of ligands and catalysts under catalytic conditions, both of the two problems mentioned above may be interrelated. Although relatively few investigations have been carried out on this subject, the preparation and use of phosphinous acids and their Pd complexes by Li [74] represent a step in the right direction. Many additional studies would be required to achieve overall optimization of various parameters including scope, rate, selectivity, cost, and safety.

Table 15-3 A list of additional "non-conventional" ligands

Class	Specific Examples		Reference
Trialkylphosphines	$PCyp_3$ = 		[69]
	$PtBu_2Me$		[69]
	$PiPr_3$		[69]
			[68]
			[68]
	*i*Pr-Pybox (R^1 = *i*Pr)		[58]
	*s*Bu-Pybox (R^1 = *s*Bu)		[58]
	*t*Bu-Pybox (R^1 = *t*Bu)		[58]
 *N*-Heterocyclic carbenes (NHC) (**2**)		(**2a**)	[59]
		(**2b**)	[59]
		(**2c**)	[59]

15.1.2.4 **Additives and Co-Catalysts**

A systematic screening of various metal salts including $ZnCl_2$ reported in 1978 [21] (Scheme 15-4) represents the first deliberate use of additives or co-catalysts. In this study, it was noted that alkenylzincs generated *in situ* by treating alkenylmetals containing Li or Mg with $ZnCl_2$ were significantly more reactive than the parent alkenylmetals and the corresponding organometals containing Al or Zr in the Pd- or Ni-catalyzed reactions. Furthermore, in cases in which sterically encumbered alkenylmetals containing Al or Zr failed to undergo the desired Pd- or Ni-catalyzed cross-coupling, addition of anhydrous $ZnCl_2$ accelerated such reactions as much as several thousand-fold or more. Significantly, these reactions were shown to be catalytic with respect to the added $ZnCl_2$. Although no detailed mechanistic studies were performed, it was thought that alkenylmetals containing Al or Zr would undergo reversible transmetallation with $ZnCl_2$ to generate equilibrium quantities of more reactive alkenylzincs.

During the early 1980s, zinc salts were shown to be similarly effective in promoting the Pd-catalyzed cross-coupling of alkenylcoppers [49, 50]. Likewise, some Pd-catalyzed cross-coupling reactions of organotins were shown to be accelerated by

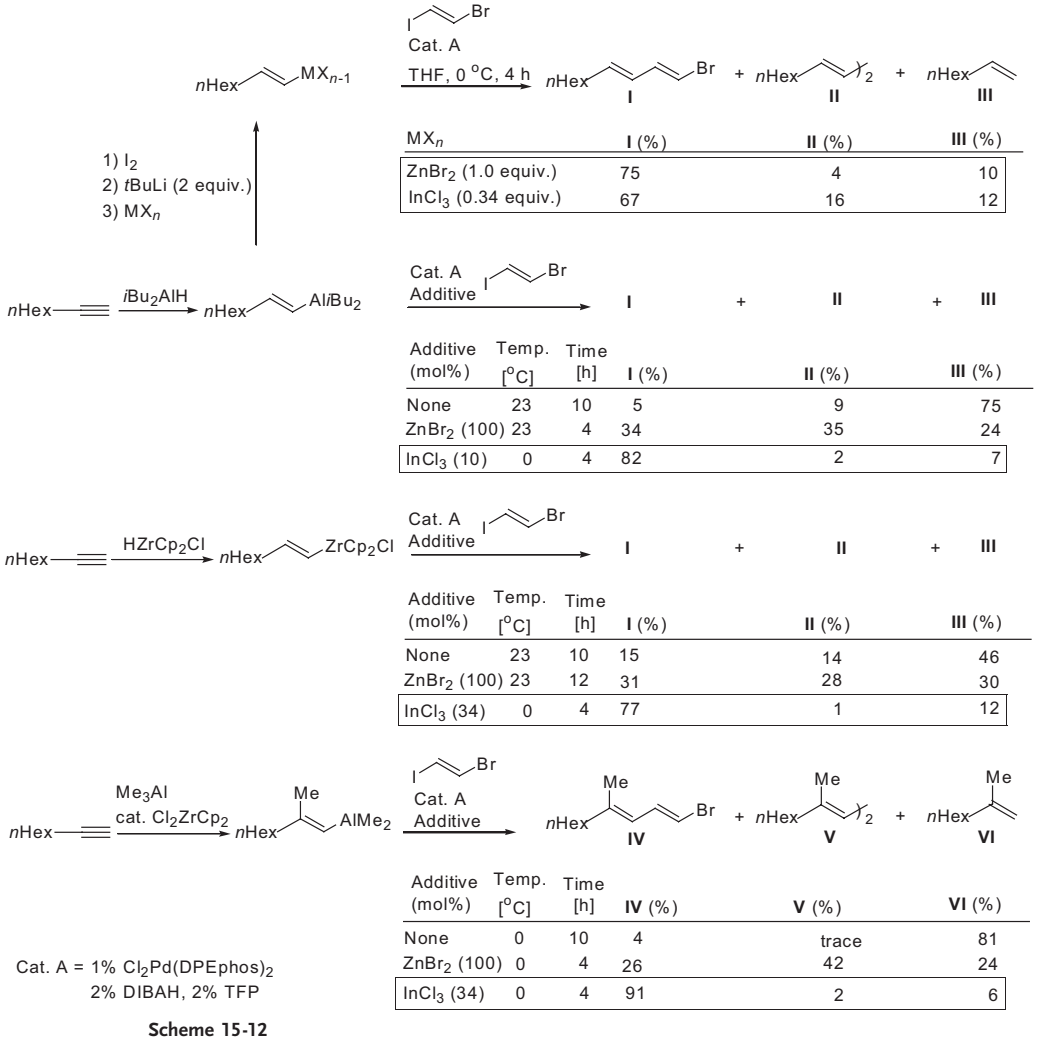
the addition of LiCl [75]. It was also noted between 1976 and 1978 that, whereas alkynylborates generated *in situ* by treating alkynyllithiums with trialkylboranes would undergo a slow but high-yielding Pd-catalyzed cross-coupling [18], alkenylboranes generated by hydroboration of alkynes would not [13,14]. Several years later, it was found that alkenylborates generated *in situ* by treating alkenyllithiums with trialkylboranes would undergo the desired cross-coupling in a manner similar to that of alkynylborates [76]. These results strongly suggested the desirability of using organoborates rather than organoboranes. In the intervening years, it was reported that the Pd-catalyzed cross-coupling with alkenylboranes could be achieved in the presence of bases, such as NaOEt, which presumably convert boranes into borates [77]. These early investigations clearly pointed to beneficial effects of additives, such ad $ZnCl_2$, LiCl, and NaOEt, which could be either stoichiometric or catalytic.

In principle, additives or co-catalysts may activate organometals (R^1M), organic halides (R^2X), and/or Pd catalysts (PdL_n), and they may be predominantly acidic, basic, or neutral. Although solvents, typically used in large excess, would not be called additives, many of them – especially polar solvents including DMF, NMP, amines, alcohols, and water – can significantly interact with organometals, organic halides, and Pd catalysts and can effectively serve as "additives". It is therefore advisable to consider additives including co-catalysts and solvents as the fourth and fifth parameters and attempt to optimize them, especially in cases where the desired cross-coupling is sluggish.

In Pd- or Ni-catalyzed cross-coupling reactions of organometals containing Al, Zr, and Cu, anhydrous $ZnCl_2$ and $ZnBr_2$ have proved to be two of the most effective co-catalysts. In fact, the widely observed rate acceleration by the addition of stoichiometric amounts of anhydrous $ZnCl_2$ or $ZnBr_2$ to organometals containing Li, Mg, and some other groups 1 and 2 metals may be interpreted in terms of effects of $ZnCl_2$ or $ZnBr_2$ as stoichiometric additives.

Until recently, no other metal compounds had been as effective as Zn salts in promoting the Pd-catalyzed cross-coupling of organometals containing groups 1 and 2 metals, Al, Zr, and Cu. Some 25 years after the discovery of beneficial effects of Zn salts as additives and co-catalysts, however, $InCl_3$ has recently been shown to be an effective co-catalyst that is superior to $ZnBr_2$ or $ZnCl_2$ in promoting the Pd-catalyzed cross-coupling reactions of alkenylmetals containing Al or Zr [48]. Although organoindiums have proved to be a widely favorable class of organometals in Pd-catalyzed cross-coupling, they themselves do not appear superior to organozincs. Thus, the favorable effects of $InCl_3$ on the Pd-catalyzed cross-coupling of alkenylmetals containing Al or Zr must be synergistic. Although further detailed comparisons are desirable, the results summarized in Scheme 15-12 [48] support the claims made above. The results observed with alkenylzinc derivatives preformed *in situ* by successively treating the corresponding alkenyl iodides with 2 equiv. of *t*BuLi and 0.5–1.0 molar equiv. of anhydrous $ZnBr_2$ are almost as good as those observed in $InCl_3$-co-catalyzed direct cross-coupling of alkenylmetals containing Al or Zr generated via either hydrometallation or carbometallation of alkynes. However, the latter is operationally much simpler and more convenient. The use of $GaCl_3$ in place of $InCl_3$ was much less effective.

In the reactions shown in Scheme 15-12, a novel – if puzzling – catalyst system (Cat. A) consisting of 1 % Cl_2Pd(DPEphos), 2 % DIBAH, and 2 % P(2-Furyl)$_3$ (TFP) was shown to be uniquely satisfactory. At this point, no clear mechanistic rationalization can be presented, but this may well represent the first demonstration that catalyst systems containing two different phosphines can be beneficial in Pd-catalyzed cross-coupling. Indeed, this catalyst system has also been shown to be



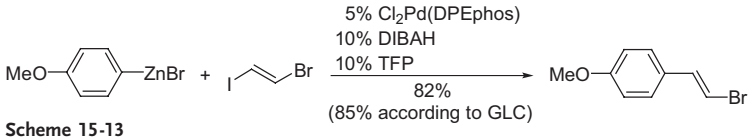
MX_n	I (%)	II (%)	III (%)
$ZnBr_2$ (1.0 equiv.)	75	4	10
$InCl_3$ (0.34 equiv.)	67	16	12

Additive (mol%)	Temp. [°C]	Time [h]	I (%)	II (%)	III (%)
None	23	10	5	9	75
$ZnBr_2$ (100)	23	4	34	35	24
$InCl_3$ (10)	0	4	82	2	7

Additive (mol%)	Temp. [°C]	Time [h]	I (%)	II (%)	III (%)
None	23	10	15	14	46
$ZnBr_2$ (100)	23	12	31	28	30
$InCl_3$ (34)	0	4	77	1	12

Additive (mol%)	Temp. [°C]	Time [h]	IV (%)	V (%)	VI (%)
None	0	10	4	trace	81
$ZnBr_2$ (100)	0	4	26	42	24
$InCl_3$ (34)	0	4	91	2	6

Scheme 15-12



Scheme 15-13

uniquely effective in the selective monoarylation of (*E*)-ICH=CHBr, as shown in Scheme 15-13. The omission of TFP or the use of other Pd complexes including $Pd_2(dba)_3$-TFP and $Pd_2(dba)_3$-dppf led to <20% yields of the desired product [48].

Although additives used in the past have been mostly metal salts and organometals, a variety of other types of compounds capable of interacting with R^1M, R^2X and/or Pd catalysts can serve as effective additives. *N*-Methylimidazole (NMI), for example, has been shown to be an effective additive in the Pd-catalyzed reaction of organozincs with primary alkyl halides [57]. Since it is readily conceivable that any stoichiometric or catalytic additives capable of interacting with R^1M, R^2X and/or Pd catalysts will affect, either positively or negatively, the kinetic profile of the reaction, the main task of synthetic chemists is to test such additives and identify those leading to favorable results. It may therefore be predicted that many additional and beneficial additives and co-catalysts will be found in the future.

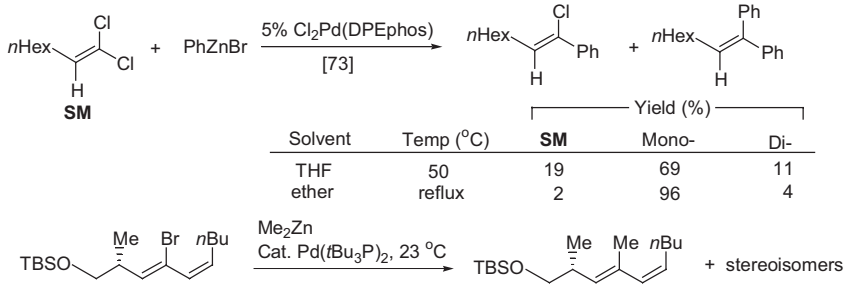
15.1.2.5 **Solvents**

At least 20 solvents have been used for various Pd-catalyzed cross-coupling reactions. Inasmuch as Pd catalysts and organometals (R^1M) can readily and significantly interact with donor solvents, such solvents should, in many cases, be considered as ligands or additives rather than mere liquid media for dissolving the reactants and catalysts. One frequently encountered question is which solvent should be chosen first for a given case of Pd-catalyzed cross-coupling. In the Pd- or Ni-catalyzed cross-coupling with organometals containing Zn, Al, and Zr as well as Mg, it is not unreasonable to consider first THF, as this solvent has been very satisfactory in a large number of cases. Likewise, it may be worth considering some or all of the solvents listed in Table 15-4, especially in cases in which the desired cross-coupling in THF is unsatisfactory.

Table 15-4 Representative solvents for Pd- or Ni-catalyzed cross-coupling

Hydrocarbons	*Halogenated Hydrocarbons*	*Ethers*	*Amines*	*Nitriles and Carbonyl Cpds.*	*Polar Aprotic Cpds.*	*Alcohols and Phenols*	*Water*
Toluene	CH_2Cl_2	THF	NEt_3	MeCN	FMF, DMA	EtOH	H_2O
Benzene	$CHCl_3$	Ether	Pyridine	Acetone	DMSO, HMPA	*t*BuOH	
		Dioxane	NMI	EtOAc	NMP	Phenol	

If it is desirable to accelerate a Pd-catalyzed cross-coupling reaction in THF, more polar solvents shown to the right of THF may be considered, although organometals containing Zn, Al, Zr, and Mg are generally not compatible with alcohols, phenols, and water. In general, polar aprotic solvents, such as DMF, DMA, and NMP, have been more favorable than THF in many cases of sluggish reactions. It is very important, however, to note that rate acceleration and product yields are just two of the several important factors in the Pd-catalyzed cross-coupling. Selectivities of various kinds, catalyst turnover numbers (TON), etc. must also be considered to globally optimize the reaction parameters. In a recent study on Pd-catalyzed selective disubstitution of 1,1-dibromoalkenes, for example, it was necessary to use ether or even toluene in place of THF to attain high stereo- and chemoselectivities in some cases, as shown in Scheme 15-14 [72, 73]. It is clearly advisable to consider the entire range of solvents including those shown in Table 15-4.



Solvent	Temp (°C)	SM	Yield (%) Mono-	Di-
THF	50	19	69	11
ether	reflux	2	96	4

Solvent	Combined Yield (%)	Composition (%) (3E,5Z)	(3E,5E)	(3Z,5E)	(3Z,5Z)
THF	91	87	7	4	2
ether	90	95	2	≤1	2

Scheme 15-14

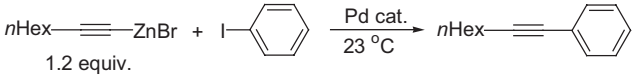
15.1.2.6 **Turnover Number (TON)**

Catalyst turnover numbers (TON) are not the sixth parameter to be optimized, as they represent some consequences of selection of various parameters discussed above. Nevertheless, TONs are discussed here, as their determination requires some deliberate planning and experimentation. If one arbitrarily chooses 5 mol % for the amount of a catalyst, the maximum TON is 20. In the past, Pd-catalyzed cross-coupling has been mostly performed with 1–5 mol % of Pd catalysts, limiting the TON range to 0 to 10^2, and evaluation of various protocols and procedures has been made mostly by comparing product yields with a range of 0–100 %. It is, however, much more meaningful additionally to compare TONs as well as turnover rates (TORs) in some cases. One reason is that it is highly desirable in most cases to attain TONs of at least 10^3, preferably 10^4–10^5 or even higher for reasons of economy. Another reason for determining TONs is that critical comparison of competing protocols and procedures can be made in a much more accurate and

unequivocal manner than mere comparison of product yields, yet very little effort has been made to adopt TONs as a criterion for comparison.

It has recently been observed in the authors' group [78] that TONs of 10^5–10^6 may be attainable in the reaction of *n*HexC≡CZnBr with PhI, provided that chelating phosphine-containing catalysts, such as Cl_2Pd(dppf) and Cl_2Pd(DPEphos), are used. On the other hand, monodentate ligands, such as PPh_3 and TFP led to TONs of up to 10^3–10^4. At the maximum TON level set at 10^5, the product yields observed with Cl_2Pd(dppf), Cl_2Pd(DPEphos), PPh_3, and Pd(tBu$_3$P)$_2$ were 99, 62, 0, and 0 %, respectively (Table 15-5). Provided that all of these experiments were properly executed, their comparative evaluation is unmistakable. Although many additional comparative data are desirable, it may tentatively be stated as a working hypothesis that bidentate or chelating phosphines with suitable tethers might be one key to attaining high TONs. As the protocols and procedures for Pd-catalyzed cross-coupling become increasingly complex and expensive to attain various desirable goals, it will be increasingly important to attain simultaneously high TONs. Thus, for example, even if a "designer" catalyst costs 10^2 times as much as the least expensive phosphine, most probably PPh_3, the use of the former would be readily justified, provided that it could lead to TONs that are 10^2 times as high as those attainable with PPh_3.

Table 15-5 Determination of turnover number (TON) for the Pd-catalyzed reaction of 1-octynylzinc bromide with iodobenzene



Catalyst	*Quantity (mol %)*	*Yield (%)*	*TON*
$Pd(PPh_3)_4$	5.0	97	1.94×10^1
	0.1	96	0.96×10^3
	0.001	0	–
Pd(tBu$_3$P)$_2$	5.0	80	1.6×10^1
	0.1	0	–
Cl_2Pd(DPEphos)	5.0	80	1.6×10^1
	0.1	82	0.8×10^3
	0.001	62	0.62×10^5
Cl_2Pd(dppf)	5.0	99	1.98×10^1
	0.1	99	0.99×10^3
	0.001	99	0.99×10^5
	0.0001	70	0.7×10^6

15.2
Recent Developments in the Negishi Coupling and Related Pd- or Ni-Catalyzed Cross-Coupling Reactions

In this section, some of the noteworthy recent developments made mainly during the past few years in Pd- or Ni-catalyzed cross-coupling involving Zn, Al, and Zr (Negishi coupling) will be discussed according to the cross-coupling carbon groups, i. e., R^1 and R^2. For the sake of convenience, the cross-coupling reaction of an arylmetal with an alkenyl electrophile, for example, is termed an aryl-alkenyl coupling. Conversely, the cross-coupling reaction of an alkenylmetal with an aryl electrophile is termed an alkenyl-aryl coupling. The topics to be covered in this section are divided into the five subsections indicated in Table 15-6, and their comprehensive discussion as of a few to several years ago may be found in those chapters in *Handbook of Organopalladium Chemistry for Organic Synthesis* indicated in Table 15-6 [79–93].

Additionally, a large number of natural products synthesized by applying Pd-catalyzed cross-couplings are listed in Chapter III.2.18 [94] of the same *Handbook*. Several topics of the Negishi coupling are not discussed in this chapter, and the reader is referred to those chapters in the *Handbook* indicated below. They include acylation (Chapter III.2.12.1 [90]), cyanation (Chapter III.2.14.1 [96]), α-substitution of metal enolate (Chapter III.2.14.1 [96]. See also Chapter V.2.1.4 [97]), asymmetric cross-coupling (Chapter III.2.16 [98]), mechanistic aspects (Chapter III.2.19 [99]), and homo-coupling (Chapter III.2.20 [100]).

Table 15-6 Detailed discussions of various Pd-catalyzed cross-coupling reactions

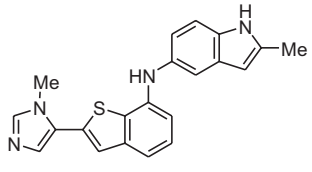
Subsection No.	*Cross-coupling type*	*Chapter in Ref. [4]*
15.2.1	Aryl-aryl coupling	III.2.5 [79], III.2.7 [80], III.2.17.2 [81].
15.2.2	Aryl-alkenyl, alkenyl-aryl, and alkenyl-alkenyl couplings	III.2.6 [82], III.2.17.1 [83], III.2.17.2 [84], III.2.13.2 [85], III.2.14.2 [86], III.2.15 [87].
15.2.3	Alkynylation with alkynylmetals	III.2.8.2 [88], III.2.7 [80], III.2.9 [89], III.2.12.1 [90], III.2.14.2 [86], III.2.15 [87]. See also [5].
15.2.4	Alkylation	III.2.11.1 [92], III.2.11.2 [93], III.2.14.2 [86].
15.2.5	Allylation, propargylation, and benzylation	III.2.9 [89], III.2.10 [91].

15.2.1
Aryl-Aryl Coupling

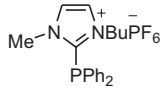
An overview of this topic dealing with various kinds of arylmetals as of a few to several years ago was presented in Chapter III.2.5 [79], as well as in a significant part of Chapter III.2.7 [80] and nearly all of Chapter III.17.2 [81] of Ref. [4]. Additionally, about 20 examples of the Pd-catalyzed aryl-aryl coupling employed in natural products syntheses are listed in Chapter III.2.18 [94] of the *Handbook*. In

addition to Mg, Zn, B, and Sn, several other metals including Al [79], In [32], Si [30], and Mn [51] have been shown to participate in the Pd-catalyzed aryl-aryl coupling. As the desired biaryls Ar^1-Ar^2 can be obtained by cross-coupling either between Ar^1M and Ar^2X or between Ar^1X and Ar^2M, it is important to consider both combinations before any negative conclusions will be drawn.

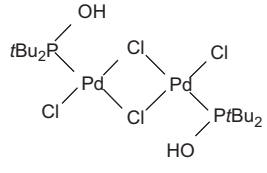
For the selection of an optimal protocol, the following guidelines might be considered. If one or the other arylmagnesium derivative should prove to be very satisfactory in the presence of either Pd or Ni catalysts, then Mg should be the first choice, because Grignard reagents are among the most easily prepared and least expensive arylmetals. If Mg should prove to be less than satisfactory, then Zn and B may be considered and compared. In cases in which aryllithiums or arylmetals containing Zn or B are directly and/or readily available from organic aryl derivatives, Zn and B may be considered first. Although Sn has been widely used in the past, its use must be carefully justified because of related toxicity and technological concerns for Sn compounds. Even in those cases in which Mg, Zn, and B should prove unsatisfactory, it is possible that other metals, such as those indicated above, might prove to be satisfactory. In a recent comparative study on the synthesis of a heterocyclic biaryl **3** [101], both Zn and Sn were found to be satisfactory on a small scale (<50 g), whereas Mg, B, and Si were unsatisfactory. On a larger scale (>50 g), however, the Sn reaction proved to be more satisfactory than the Zn reaction. At this point, it is still difficult to predict accurately the relative merits and demerits of various competing protocols, which are constantly changing, as different factors are optimized. The following recent developments are noteworthy.



3



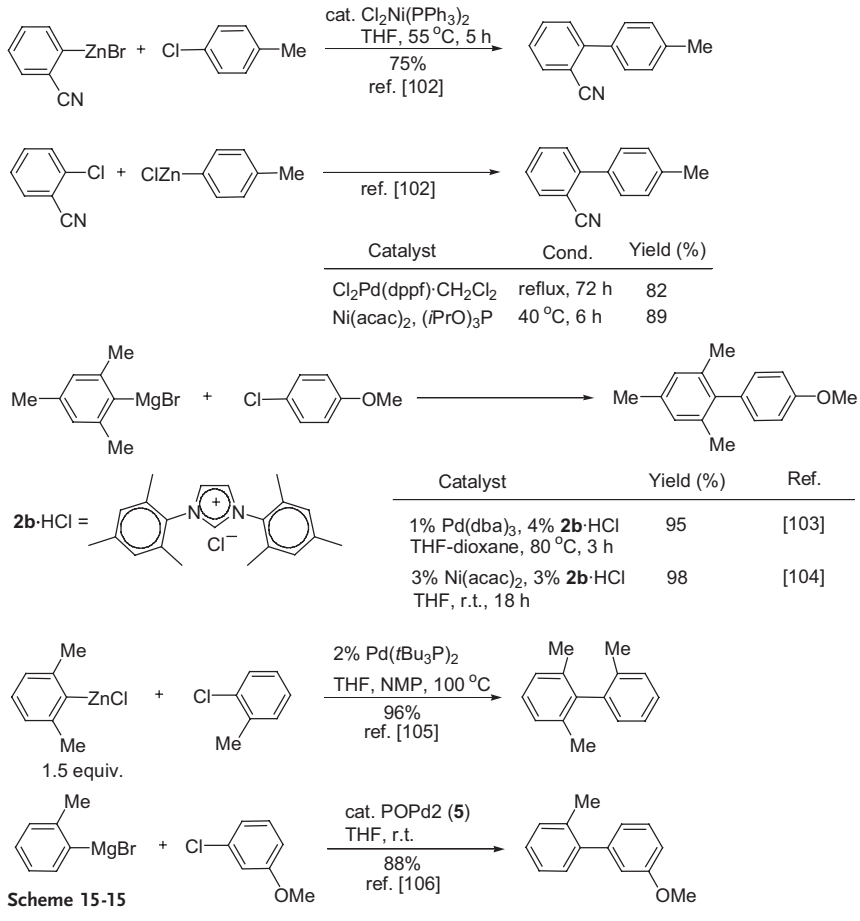
4



5 (POPd2)

15.2.1.1 Aryl-Aryl Coupling of Aryl Chlorides, Fluorides, and Cyanides

Until recently, Pd- or Ni-catalyzed aryl-aryl coupling involving Zn or Mg was performed mostly with aryl iodides and bromides. Over the past few years, however, Pd- or Ni-catalyzed reactions of aryl chlorides [102–106] and even fluorides [60] with arylmetals containing Zn [102, 105] and Mg [60, 102–104, 106, 107] have been found satisfactory under various optimized conditions. Some representative results are summarized in Scheme 15-15. These results clearly point to advantages in the use of "nonconventional" ligands, such as tBu$_3$P and NHCs **2**. Also noteworthy is the use of an ionic phosphine ligand **4** in the Pd-catalyzed reaction of arylzinc bromides with aryl iodides [108]. In addition to aryl chlorides and fluorides, aryl cyanides have also been shown to participate in the Ni-catalyzed aryl-aryl coupling with arylmagnesium derivatives [66, 109]. Addition of Li bases, such as LiOtBu appears to be essential.



Scheme 15-15

15.2.1.2 Heteroaryl-Containing Biaryls via Pd-Catalyzed Aryl-Aryl Coupling with Heteroaryl Reagents

Heteroaryl-containing biaryls have become increasingly important as components of a number of natural products and non-natural compounds of biological and medicinal interest, and Pd- or Ni-catalyzed aryl-aryl coupling involving arylzinc derivatives has emerged as one of the most favorable routes to these compounds along with related aryl-aryl coupling reactions of arylmetals containing B, Sn, and Mg. In general, arylzincs tend to be significantly more reactive than the other arylmetals under Pd-catalyzed conditions. However, there are a number of exceptions to this generalization. Although not yet well-established, electron-donating heteroatoms, such as N and S, in heteroaryl reagents may significantly interact not only with Pd catalysts but also with arylzinc derivatives. Such interactions may have either favorable or unfavorable effects on the desired cross-coupling, and it appears

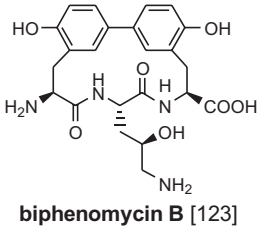
desirable to avoid or cope with unfavorable effects due to strongly interacting heteroatoms. Some of the recently reported examples of Pd-catalyzed syntheses of heteroaryl-containing biaryl with arylzinc reagents are presented below. Those examples involving the use of heterocycles containing one heteroatom are shown in Scheme 15-16, and the others are shown in Scheme 15-17. It appears reasonable to state that the Pd- or Ni-catalyzed syntheses of heteroaryl-containing biaryls with arylzinc derivatives is widely applicable. In some cases, it is more direct and more satisfactory than the B route.

15.2.1.3 **Miscellaneous Biaryls and Related Compounds**

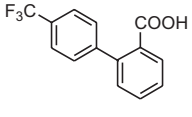
The Pd-Zn procedure has been satisfactorily applied to the synthesis of chiral ferrocene-containing biaryls [118] (Scheme 15-18). A novel C-B bond formation via a Pd-catalyzed cross-coupling reaction of iodocarboranes with various types of organozincs has been reported recently [119]. In this study, the other methods involving Mg, B, and Sn were found to be unsatisfactory. Two reports [120–122] on the Pd-catalyzed C-B bond formation through the use of diboronic esters, but not Zn reagents, have also been made.

15.2.1.4 **Natural and Non-Natural Biaryls of Biological and Medicinal Interest**

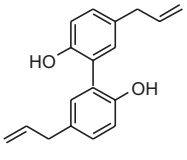
Biaryls of biological and medicinal interest synthesized over the past decade or so via Pd-catalyzed arylzinc cross-coupling include biphenomycin B [123], xenalepin [124], magnolol [125], (–)-monoterpenylmagnolol [125], and korupensamines A and B [126] in addition to eupomatenoid-15 [110] and cystine [113] shown in Scheme 15-16, PDE472 [116] and tasosartan [117] shown in Scheme 15-17, as well as losartan [117]. Also noteworthy is the synthesis of diazonamide-related biaryls [112] shown in Scheme 15-16.



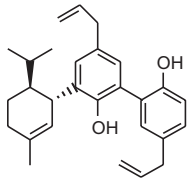
biphenomycin B [123]



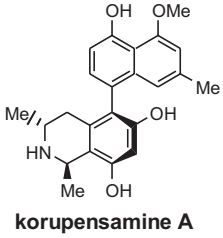
xenalepin [124]



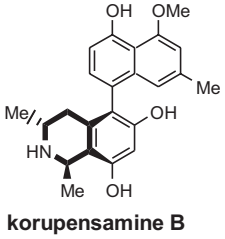
magnolol [125]



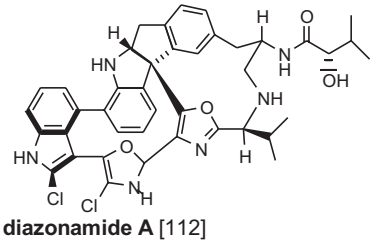
(−)-monoterpenylmagnolol [125]



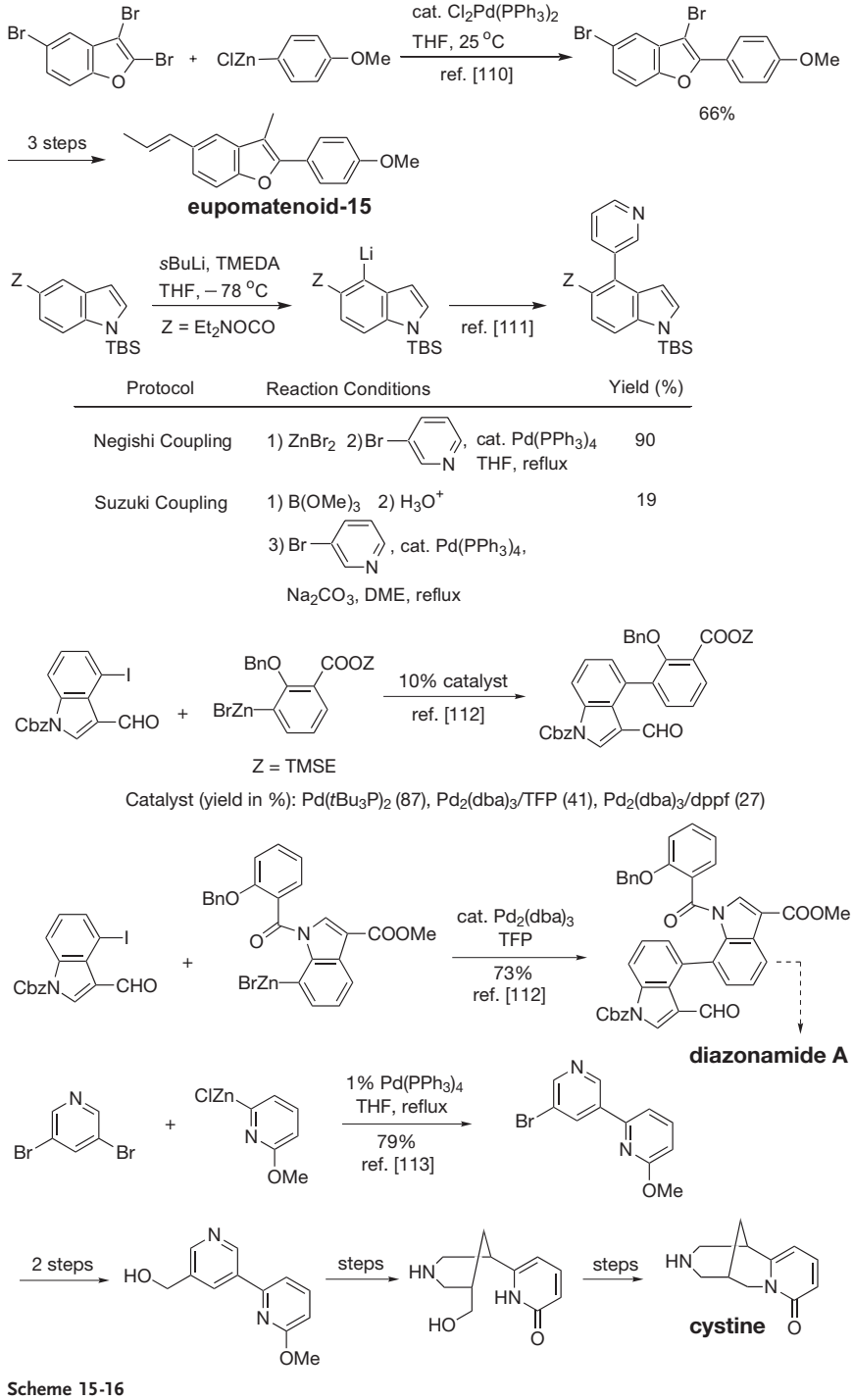
korupensamine A



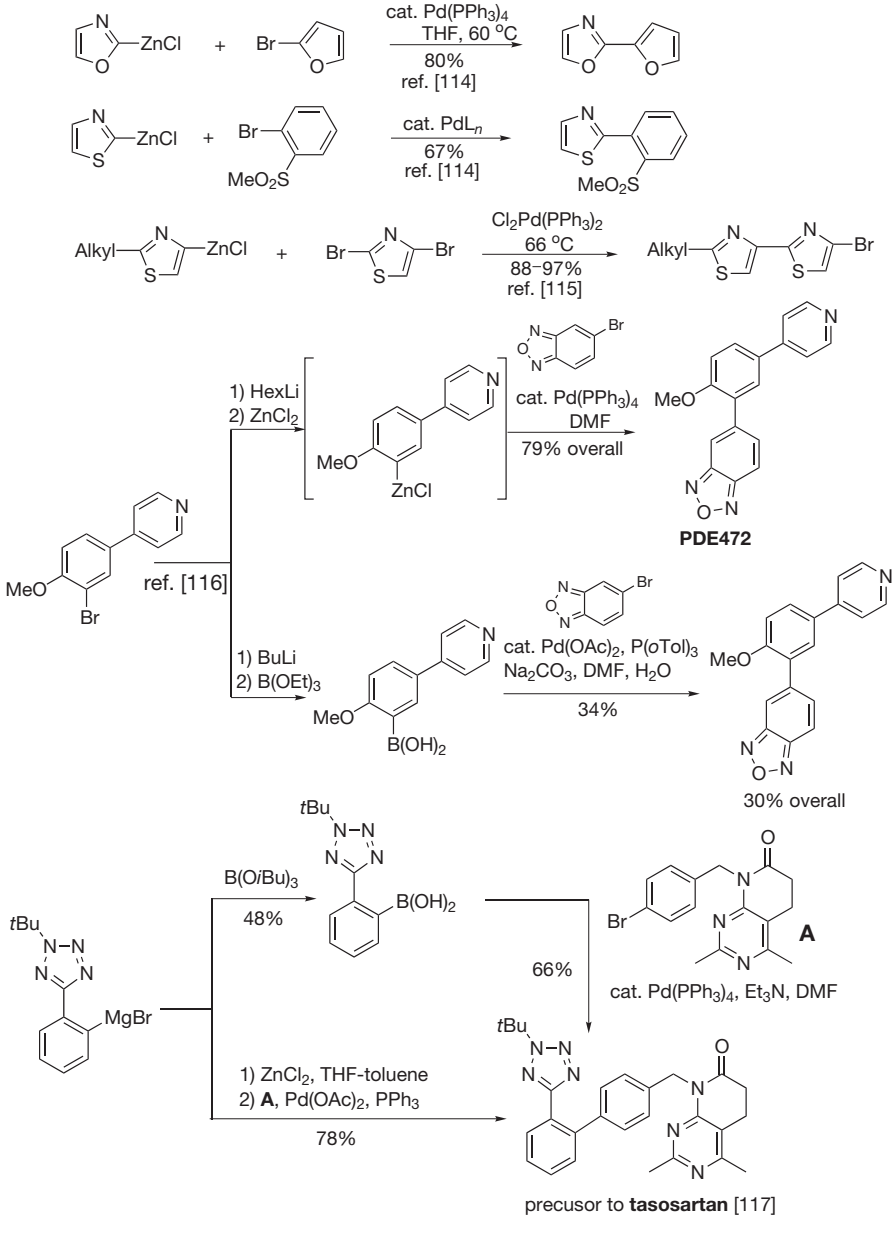
korupensamine B



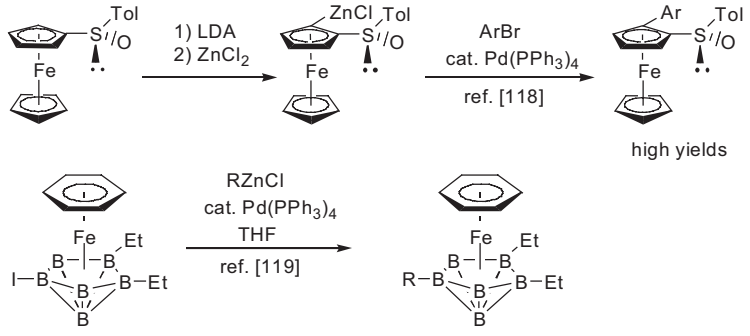
diazonamide A [112]


cat. Cl2Pd(PPh3)2
THF, 25 °C
ref. [110]
66%
3 steps
eupomatenoid-15
sBuLi, TMEDA
THF, – 78 °C
Z = Et2NOCO
ref. [111]
Protocol
Reaction Conditions
Yield (%)
Negishi Coupling
1) ZnBr2 2) Br
cat. Pd(PPh3)4
THF, reflux
90
Suzuki Coupling
1) B(OMe)3 2) H3O+
3) Br
cat. Pd(PPh3)4,
Na2CO3, DME, reflux
19
10% catalyst
ref. [112]
Z = TMSE
Catalyst (yield in %): Pd(tBu3P)2 (87), Pd2(dba)3/TFP (41), Pd2(dba)3/dppf (27)
cat. Pd2(dba)3
TFP
73%
ref. [112]
diazonamide A
1% Pd(PPh3)4
THF, reflux
79%
ref. [113]
2 steps
steps
steps
cystine

Scheme 15-16


cat. Pd(PPh3)4
THF, 60 °C
80%
ref. [114]
cat. PdLn
67%
ref. [114]
Cl2Pd(PPh3)2
66 °C
88–97%
ref. [115]
1) HexLi
2) ZnCl2
cat. Pd(PPh3)4
DMF
79% overall
PDE472
ref. [116]
1) BuLi
2) B(OEt)3
cat. Pd(OAc)2, P(oTol)3
Na2CO3, DMF, H2O
34%
30% overall
B(OiBu)3
48%
66%
cat. Pd(PPh3)4, Et3N, DMF
A
1) ZnCl2, THF-toluene
2) A, Pd(OAc)2, PPh3
78%
precusor to tasosartan [117]

Scheme 15-17



Scheme 15-18

15.2.2

Aryl-Alkenyl, Alkenyl-Aryl, and Alkenyl-Alkenyl Coupling Reactions

The Pd-catalyzed aryl-alkenyl, alkenyl-aryl, and alkenyl-alkenyl coupling reactions known as of a few to several years ago were comprehensively discussed and summarized in Chapters III.2.6 [82] and III.2.17.1 [83] as well as significant portions of Chapters III.2.12.2 [84], III.2.13.2 [85], III.2.14.2 [86], and III.2.15 [87] of Part III of *Handbook of Organopalladium Chemistry for Organic Synthesis* [4]. Additionally, close to 100 examples of natural products syntheses involving these alkenylation reactions are listed in Chapter III.2.18 [94].

The alkenyl-aryl and alkenyl-alkenyl coupling reactions require alkenylmetals, and those containing Zn and B have emerged within the past decade or so as the two most generally applicable and satisfactory alkenylmetals. Nevertheless, some other metals – mainly Al, Zr, and Cu as well as In, Si, and Sn – have displayed some unique advantages associated with each metal, including those indicated in Table 15-7. In fact, Sn had until recently been very widely used despite its toxicity and some technical concerns. In recent years, however, it has been shown repeatedly that the synthetic scope of the Pd-catalyzed cross-coupling of alkenyltins is considerably more limited than those of alkenylmetals containing Zn and B, as detailed later.

Since most of the metals mentioned above participate in hydrometallation, one may question the uniqueness associated with each metal. In this context, the following details summarized in Table 15-7 should be noted. In general, hydroboration displays the broadest scope with respect to alkene and alkyne structures, including their substitution patterns, while hydrozirconation is the most selective, cleanest, and satisfactory in cases where conjugated enynes and oligoenynes are used. Another advantage of Zr over B and Al is the relative ease with which a high level of regioselectivity can be attained through equilibration in cases where unsymmetrically substituted internal alkynes, especially 2-alkynes, are used. Although more limited in scope than those of B and Zr, hydroalumination is generally more economical than the others, and the synthesis of alkenyl

Table 15-7 Some unique advantages associated with various metals in the Pd-catalyzed alkenylation

Metal	*Unique Advantages*
Zn	• Generally most reactive under Pd-catalyzed conditions. • Zn salts can serve as co-catalysts.
B	• Hydroboration is the *syn*-hydrometallation of the broadest scope.
Al	• Synthesis of alkenyl halides and hydroalumination-cross-coupling domino process most facile and economical (promoted with Zn and In co-catalysts). • Zr-catalyzed carboalumination most satisfactory for Me-branched *E*-trisubstituted alkene syntheses (promoted with Zn and In co-catalysts).
Zr	• Hydrozirconation-cross-coupling domino process most selective and satisfactory with internal alkynes and conjugated enynes (promoted with Zn and In co-catalyst).
Cu	• Carbocupration-cross-coupling domino process is an attractive route to *Z* alkenes (promoted with Zn co-catalysts).
In	• *anti*-Hydroindation-cross-coupling domino process promising.
Si	• *syn*-Hydrosilation(Pt-catalyzed)–cross-coupling domino process promising.
Sn	• Selective *syn*- or *anti*-hydrostannation can be uniquely advantageous. • Ability to defer cross-coupling until completion of other Pd-catalyzed processes, such as carbopalladation and carbonylation, under one set of conditions is advantageous.

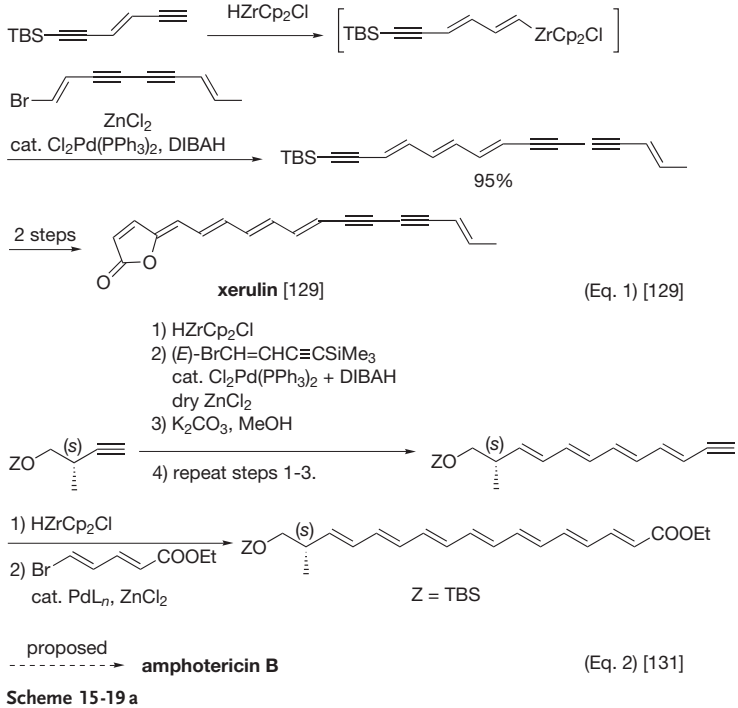
halides via hydrometallation of alkynes is more facile and economical with Al than with B or Zr. The usefulness of Al or Zr in the Pd- or Ni-catalyzed cross-coupling has been significantly enhanced by the use of Zn and In salts as co-catalysts, as discussed earlier. The Pt-catalyzed hydrosilation may be of broad synthetic applicability, but its usefulness in the Pd-catalyzed cross-coupling still lags behind that of B, Al, or Zr. Hydrostannation is capricious in that it may undergo selective *syn* and *anti* as well as stereorandom additions depending on substrate structures and other factors. In cases where the selectivity and other aspects are satisfactory, it can offer unique advantages that may not be readily matched with other metals.

The Zr-catalyzed carboalumination [127] and carbocupration[128] are the two most extensively developed *syn*-carbometallation reactions. The former is particularly useful in the single most important case of the synthesis of Me-branched *E*-trisubstituted alkenes, while the latter provides a satisfactory route to *Z*-di- and trisubstituted alkenes. The carbometallation–cross-coupling domino processes involving the above-mentioned reactions can be significantly promoted with Zn and/or In salts.

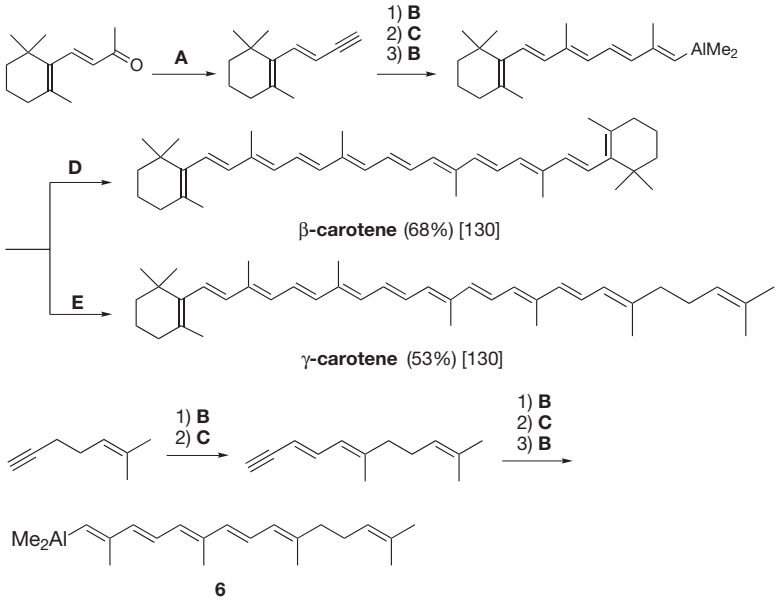
In this subsection, some of the noteworthy developments in those Pd-catalyzed alkenylation reactions that involve Zn, Al, and Zr reported over the past five to ten years will be highlighted, with emphasis placed on applications to highly demanding cases of alkenyl-alkenyl coupling, especially those employed in the synthesis of natural products.

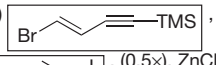
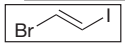
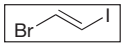
15.2.2.1 Iterative Hydrometallation–Cross-Coupling and Carbometallation–Cross-Coupling Domino Processes Involving the Use of (*E*)-ICH=CHBr and (*E*)-BrCH=CHC≡CSiR$_3$

A practical and satisfactory synthesis of (*E*)-ICH=CHBr from acetylene, IBr, and HBr was reported in 2000 [129], and it is now commercially available (Aldrich). Its Pd-catalyzed alkynylation with alkynylzincs (*vide infra*) provides (*E*)-1-bromoenynes including (*E*)-BrCH=CHC≡CSiMe$_3$ and (*E*)-BrCH=CHC≡CSiMe$_2$*t*Bu [129, 130]. These haloalkene derivatives have proved to be very convenient two- and four-carbon building blocks in oligoene and oligoenyne syntheses via Pd-catalyzed alkenyl-alkenyl coupling [129–131]. Some representative examples are shown in Scheme 15-19. As alluded to earlier, hydrozirconation was almost 100 % regioselective and high-yielding (ca. 95 %) in those cases shown in Scheme 15-19, whereas hydroboration with dialkylboranes produced minor amounts (5–10 %) of regioisomers. Hydroalumination with DIBAH under widely used conditions was accompanied by terminal alumination of enynes to a considerable extent, and was unsatisfactory.



Scheme 15-19 a



A: (i) LDA (ii) $ClPO(OEt)_2$ (iii) LDA (2.2×) **B**: (i) Me_3Al (2×), Cl_2ZrCp_2 (ii) evaporation
C: (i)  , $ZnCl_2$, $Pd_2(dba)_3$ + 2 TFP (ii) K_2CO_3, MeOH
D:  , (0.5×), $ZnCl_2$, $Pd_2(dba)_3$ + 2 TFP
E:  , (1.05×), $ZnCl_2$, $Pd(PPh_3)_4$ (ii) **6**, $ZnCl_2$, $Pd_2(dba)_3$ + 2TFP

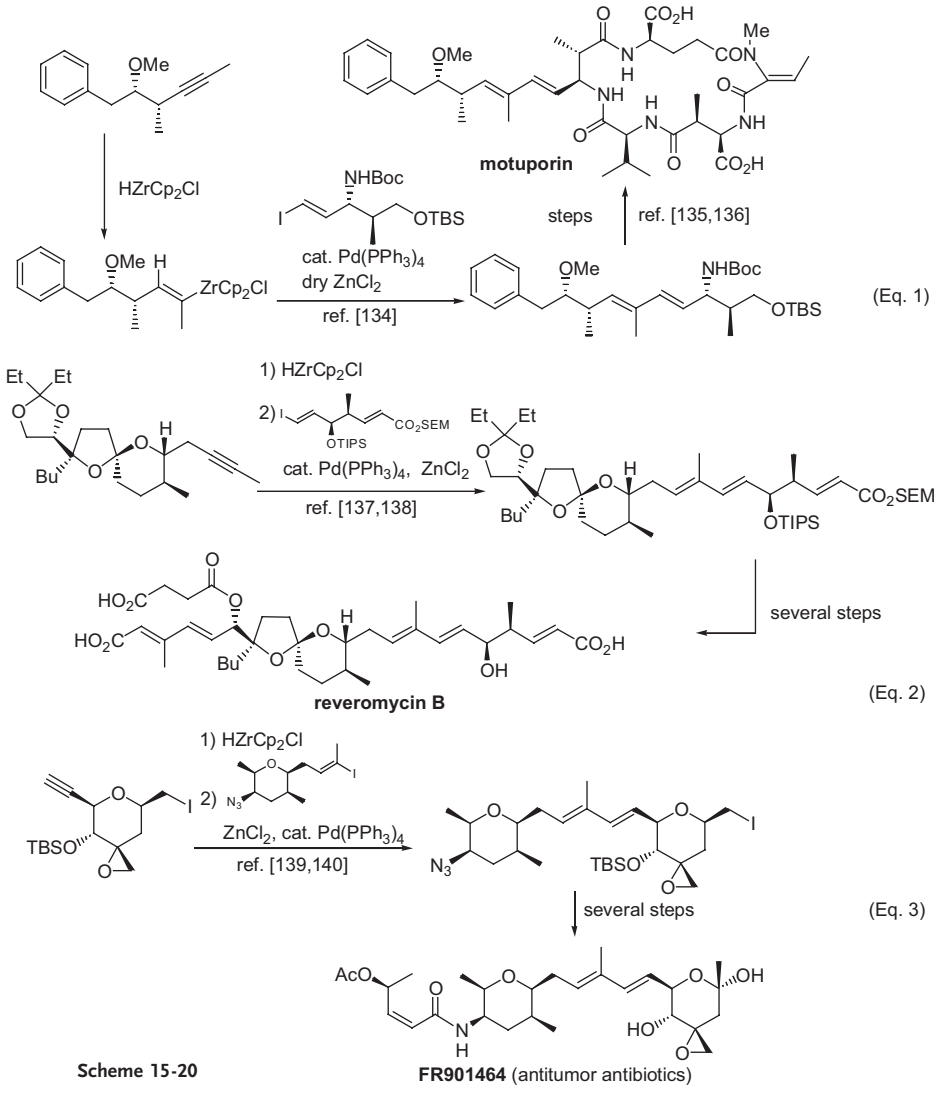
Scheme 15-19 b

15.2.2.2 Internal Alkyne Hydrozirconation–Cross-Coupling Domino Process

Regioselective hydrozirconation of internal alkynes in the presence of an excess of $HZrCp_2Cl$ [132] and alkenyl-alkenyl coupling co-catalyzed with Pd complexes and anhydrous Zn salts [21] have been combined to develop a very useful procedure for the synthesis of conjugated dienes containing trisubstituted alkene moieties [133]. This protocol has been successfully applied to stereoselective syntheses of various natural products or their fragments, as shown in Scheme 15-20.

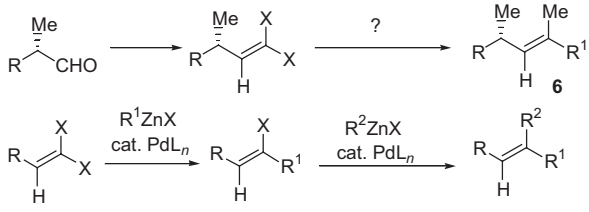
15.2.2.3 Pd-Catalyzed Aryl-Alkenyl and Alkenyl-Alkenyl Coupling Reactions with 1,1-Dihalo-1-alkenes

trans-Selective monosubstitution of 1,1-dihalo-1-alkenes containing Cl or Br was first performed in 1987 by using mostly arylmagnesium reagents and $Cl_2Pd(dppb)$ as a catalyst. The products yields were generally excellent (80–98 %), and the stereoselectivity was almost 100 % [54]. The second arylation also proceeded in 65–81 % yields to give triaryl-substituted alkenes. Since then, *trans*-selective mono-



Scheme 15-20

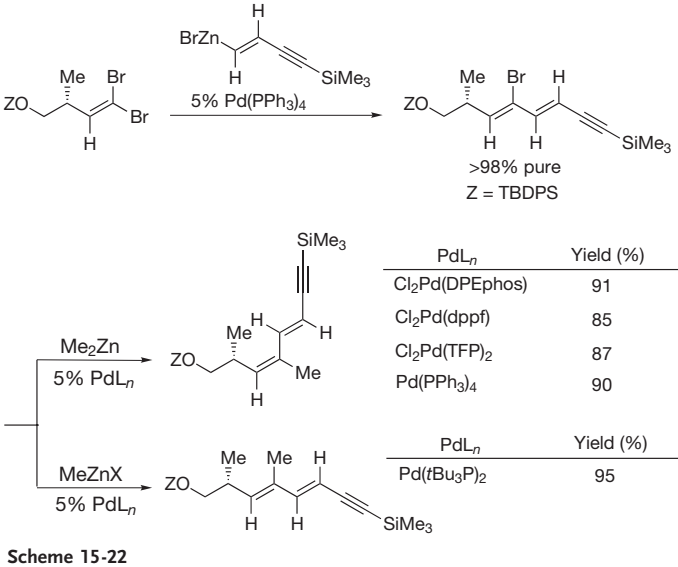
arylation and/or monoalkenylation have been achieved with organometals containing Zn [141–143], B [144, 145], Zr [142], and Sn [146]. As discussed later, *trans*-selective monoalkynylation under the Sonogashira conditions has also been reported recently [147, 148], so the *trans*-selective monosubstitution step has been reasonably well established. On the other hand, the scope of the second substitution has been mainly limited to arylation [54, 146], as well as a few examples each of alkenylation [146, 147], alkynylation [141, 147], and alkylation [54, 146, 147], including only one example of methylation of a bromostilbene derivative [146]. In view of the potential significance of stereoselective domino disubstitution of



X = Br or Cl. R = C group. R^1 = alkenyl, aryl, alkynyl. R^2 = alkyl. **Scheme 15-21**

1,1-dihalo-1-alkenes – especially those involving methylation and higher alkylation in the second step for stereoselective syntheses of trisubstituted alkenes represented by **6** – a systematic investigation of the Pd-catalyzed domino disubstitution with special emphasis on the second alkylation (Scheme 15-21) has recently been conducted [70–73].

The experimental results for the second substitution have turned out to be nothing but unexpected. The most unexpected of all is near-complete stereoisomerization in the second substitution of 2-bromo-1,3-dienes in cases where various conventional and even some recently developed phosphines were used, as represented by the results shown in Scheme 15-22 [71]. Although mechanistic details are not clear, the observed isomerization to the extent of ≥95–97 % must stem from the unique arrangement in the 2-bromo-1,3-diene framework, which simultaneously is both alkenylic and allylic. In this context, it is instructive to note that the corresponding reaction of 2-bromo-1-en-3-ynes undergoes synthetically unattractive partial stereoisomerization [70]. Despite mechanistic puzzles that remain to be solved,



PdL_n	Yield (%)	*Z,E* (%)
Cl_2Pd(DPEphos)	91	>97
Cl_2Pd(dppf)	85	>97
$Cl_2Pd(TFP)_2$	87	95
$Pd(PPh_3)_4$	90	95

PdL_n	Yield (%)	*E,E* (%)
$Pd(tBu_3P)_2$	95	>98

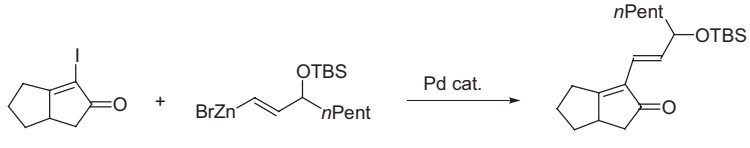
Scheme 15-22

the transformation shown in Scheme 15-22 provides a selective and attractive method for the synthesis of conjugated (*Z*,*E*)-dienes containing an adjacent chiral center that are otherwise difficultly accessible. The second pleasantly surprising and synthetically important finding is that, despite those results presented above, both full and partial stereoisomerization can be completely suppressed through the use of either Pd-phosphine complexes containing tBu$_3$P and some other bulky alkylphosphines or NHC (**2**) [70–73], as eloquently represented by the results shown in Scheme 15-22 [73]. These results clearly indicate that some of the more recently introduced "nonconventional" ligands not only accelerate a number of Pd- or Ni-catalyzed cross-coupling reactions, but also significantly affect the course of these cross-coupling reactions including stereochemistry. Furthermore, these "nonconventional" ligands have vastly widened synthetic options, as exemplified above by their ability to provide selectively either (*E*,*E*)- or (*Z*,*E*)-isomers, as desired.

15.2.2.4 α-Arylation and α-Alkenylation of α-Halo-α,β-unsaturated Enones and Related Carbonyl Derivatives

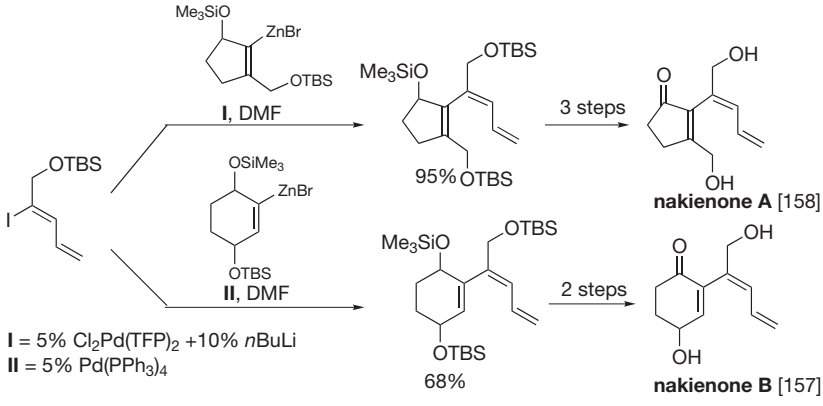
Despite extensive studies on α-alkylation of enolates, the corresponding α-arylation, α-alkenylation and α-alkynylation had until recently been difficult synthetic tasks. In order to achieve these goals with good control of regiochemistry, degree of substitution, and other desirable features, some indirect routes involving Pd-catalyzed α-substitution reactions of the corresponding α-halo-α,β-unsaturated enones and related derivatives were considered by the authors' group. The initially developed protocol involving Pd-catalyzed α-substitution of carbonyl-protected α-haloenones (Protocol I) [149] was superceded by a more direct protocol involving Pd-catalyzed direct α-substitution of unprotected α-iodoenones (Protocol II) [150]. This reaction has indeed proved to be widely applicable. In more demanding cases, such as that shown in Scheme 15-23, the use of Pd(dba)$_2$-TFP and DMF was s2hown to be particularly effective [150].

The seminal development with alkenyl- and arylzincs published in 1991 [150] was soon followed by other related developments with organotins [151] and organoboranes [152]. The Pd-catalyzed reaction of α-zinco-α,β-unsaturated enones with aryl and alkenyl halides was also developed [153]. Particularly attractive was



Pd Catalyst	Solvent	Temp [°C]	Time [h]	Yield (%)
$Cl_2Pd(PPh_3)_2$ + 2 *n*BuLi	DMF	25	1	13
$Pd(dba)_2$ + 2 TFP	THF	50	24	<5
$Pd(dba)_2$ + 2 TFP	DMF	20	3	87

Scheme 15-23

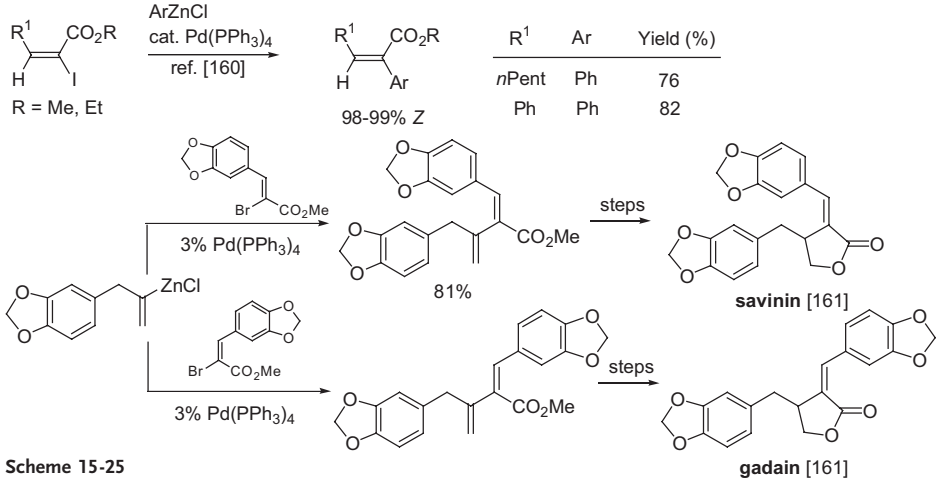


Scheme 15-24

the development of the Pd-catalyzed α-alkynylation of α-iodoenones either with alkynylmetals containing Sn [154] or Zn [155] or with alkynes themselves under the Sonogashira conditions [156], as discussed later in Section 15.2.3.

In some highly delicate and demanding cases, the use of carbonyl-reduced α-iodoenones, namely β-iodoallyl alcohol derivatives, proved to be more satisfactory than the use of α-iodoenones [157–159]. This indirect protocol (Protocol III) has been successfully applied to the synthesis of nakienones A [158] and B [157] (Scheme 15-24) as well as carbacyclin [159].

Many studies on the use of α-halo-α,β-unsaturated esters and amides have also been conducted [86]. Among those permitting stereo- and regioselective syntheses of trisubstituted alkenes via Pd-catalyzed cross-coupling with alkenyl- and arylzincs, the following reactions shown in Scheme 15-25 are particularly noteworthy.



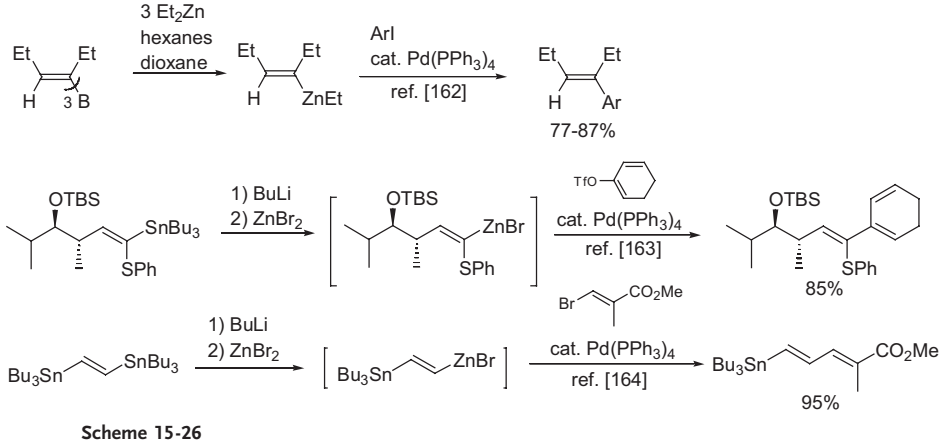
Scheme 15-25

15.2.2.5 Recent Developments in the Pd-Catalyzed Alkenylation and Arylation Promoted by Zn and In

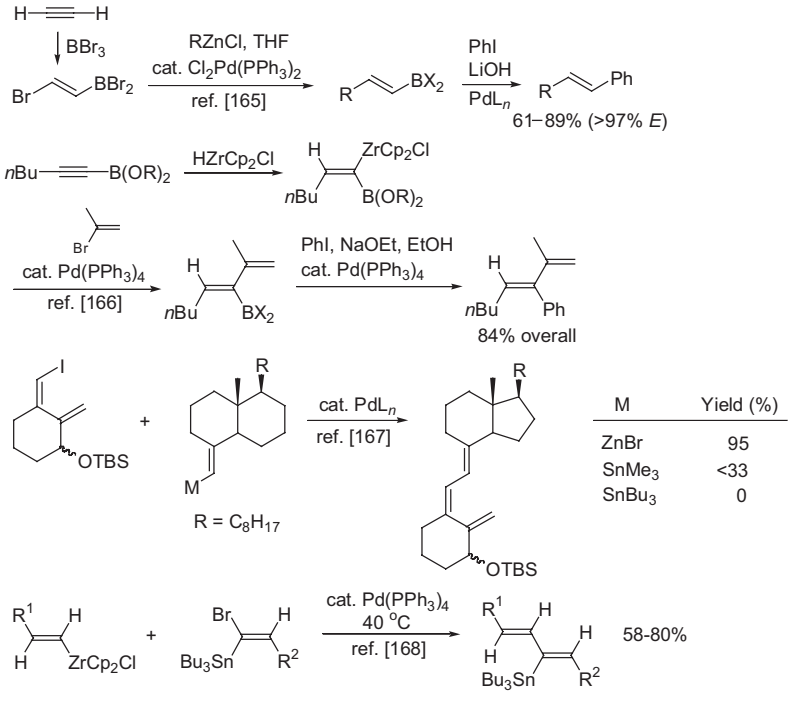
The beneficial effects of Zn (Zn effects) in the stoichiometric activation of organometals containing Li, Mg, and other group 1 and 2 metals as well as in either stoichiometric or catalytic activation of organometals containing Al, Zr, and Cu have been repeatedly discussed in this chapter. Also developed recently was the Pd-In co-catalyzed cross-coupling reaction of organometals containing Al and Zr (see Scheme 15-12).

Mainly during the past decade, even the Pd-catalyzed cross-coupling reactions of organoboranes [162] and organotins [163, 164] have also been promoted by the addition of Zn salts (Scheme 15-26). The results strongly point to the superior reactivity of Zn relative to B or Sn, and some studies have explicitly presented comparative results supporting this statement.

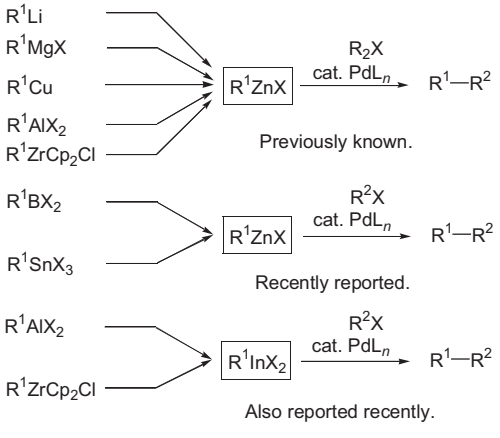
Some additional results revealing relative reactivities of metal countercations are shown in Scheme 15-27. The results presented above may be summed up by stating that the Pd-catalyzed cross-coupling reactions of most of the frequently used organometals may be profitably promoted by Zn salts, while $InCl_3$ has recently been shown to be a more effective co-catalyst than $ZnBr_2$ or $ZnCl_2$ in some cases (Scheme 15-28).



Scheme 15-26



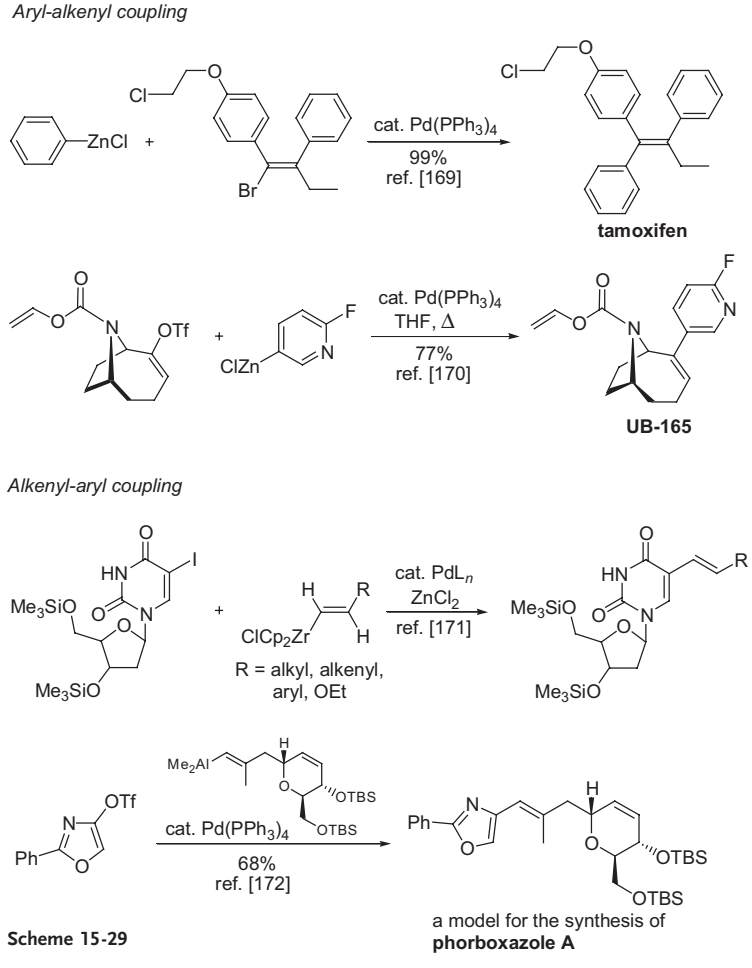
Scheme 15-27



Scheme 15-28

15.2.2.6 Synthesis of Natural Products and Non-Natural Compounds of Biological and/or Medicinal Interest via Pd-Catalyzed Aryl-Alkenyl and Alkenyl-Aryl Coupling Reactions

A dozen or more examples of the syntheses of complex natural and non-natural compounds of biological and/or medicinal interest involving Pd-catalyzed alkenyl-alkenyl coupling are shown in this section. The number of syntheses involving the use of Pd-catalyzed aryl-alkenyl and alkenyl-aryl couplings with organozincs is still rather modest. Nevertheless, the following examples (Scheme 15-29) indicate that these are indeed promising and potentially attractive, and many additional examples may be anticipated.



Scheme 15-29

15.2.3
Pd-Catalyzed Alkynylation

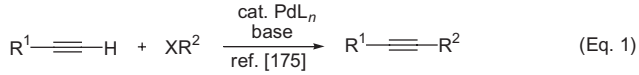
Alkynes contain highly strained, unstable, and reactive C≡C bonds and are indeed among the most reactive classes of organic compounds toward "soft" late transition metal complexes, such as those containing Cu, Ag, Ni, and Pd. Along with many synthetically useful reactions that are catalyzed by these late transition metals, alkynes can also readily undergo many other reactions that may be unwanted in a given synthetic task. One such reaction that can interfere with the desired alkynylation via cross-coupling is alkyne cyclotrimerization leading to the formation of arenes and other alkyne oligomers. This is indeed one of the main reasons why Ni complexes are generally inferior to Pd complexes and have therefore been rarely used, at least in the past, for alkynylation. Explosiveness is another potentially serious concern in dealing with alkynyl derivatives of transition metals. Although this matter has rarely been a serious concern in academia, where the scale of operation is generally very small, it should be carefully investigated for any large-scale operations.

Until about 30 years ago, the formation of a bond between a C≡C bond and an unsaturated carbon group had been performed mainly by Cu-promoted reactions represented by the Castro-Stevens reaction [173]. Today, alkynes containing such a bond are mostly prepared by one of the two types of the Pd-catalyzed alkynylations, namely: (i) Heck-type alkynylation, especially the Sonogashira version that employs Pd-Cu catalyst combinations [174], and (ii) cross-coupling using stoichiometric preformed alkynylmetals [88]. According to the definition of the Pd-catalyzed cross-coupling shown in Scheme 15-5, Heck-type alkynylations may not be classified as Pd-catalyzed cross-coupling reactions, though this is largely a matter of semantics. Although attention in this section is mainly focused on the cross-coupling reactions of preformed alkynylmetals, critical comparison between the two types of Pd-catalyzed alkynylation has become increasingly significant, and due attention will be paid to this matter.

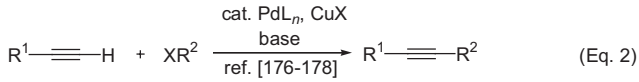
Both of the Pd-catalyzed alkynylation protocols were discovered during the period from 1975 to 1978. Heck [175] and Sonogashira [176] independently reported in 1975 their own versions shown in Eqs. (1) and (2), respectively. In many less-demanding cases, both protocols may be comparably satisfactory. In such cases, the simpler and less-involved Heck protocol should be favored. The Sonogashira protocol, however, has been shown to be of wider applicability than the Heck protocol. A report on the Pd-catalyzed alkynylation with alkynylsodiums [179] appears to be the first to describe the Pd-catalyzed alkynylation represented by Eq. (3) of Scheme 15-30, but this reaction has hardly been used. In view of the demonstrated inability of alkynyllithiums to undergo useful Pd-catalyzed alkynylation [28], other alkali metals including Na might also be expected to suffer from similar difficulties.

A systematic survey of various alkynylmetals conducted by the authors' group shown earlier in Scheme 15-2 [18] identified Zn, B, and Sn to be the three most satisfactory metals in the Pd-catalyzed alkynylation, and various representative

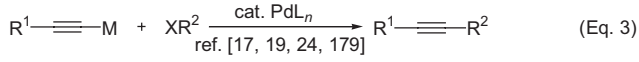
(i) Heck-type alkynylation



Sonogashira reaction



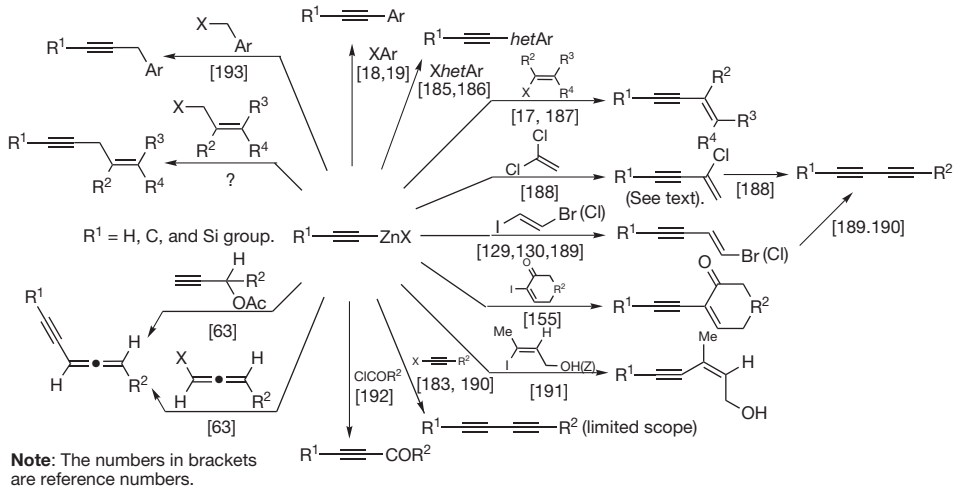
(ii) Cross coupling with preformed alkynylmetals



Scheme 15-30

examples of the Pd-catalyzed reactions of alkynylzincs with alkenyl halides [17] and aryl halides [19] were reported in 1977 and 1978, respectively. In the metal-screening study mentioned above [18], Mg and Al were also shown to undergo Pd-catalyzed alkynylation, but attempts to use Si and Zr were unsuccessful. In the meantime, the use of alkynylmagnesium derivatives was reported also by Linstrumelle [24]. More recently, a number of procedures involving activation of alkynylsilanes either via silicate formation or transmetallation into other alkynylmetals have been devised [5, 30]. Other promising metal countercations reported recently include Mn [51] and In [32]. At the present time, however, the Pd-catalyzed alkynylation with organozincs appears to be the protocol of widest synthetic utility among those that are represented by Eq. (3) of Scheme 15-30. A number of recent studies have further demonstrated that the alkynylzinc protocol is of considerably wider synthetic scope than even the Sonogashira alkynylation, as detailed below. Also noteworthy in this context are an increasing number of reports describing in-situ conversion of terminal alkynes into alkynylzincs in a manner similar to that of alkynylcoppers in the Sonogashira reaction [180–184]. In the following discussions of this subsection, attention will be focused on recent developments in the Pd-catalyzed alkynylation with alkynylzincs. For the other protocols and additional details of the alkynylzinc reaction, the reader is referred to Chapters III.2.8.1 [174], III.2.8.2 [88], parts of III.2.4 [30], III.2.7 [80], III.2.14.2 [86], and III.2.18 [94] of Ref. [4] as well as a very recent updating review on the Pd-catalyzed alkynylation [5].

The current scope of the Pd-catalyzed alkynylation with alkynylzincs is shown in Scheme 15-31. Some seminal and/or otherwise important works are referenced in the scheme. Essentially all types of unsaturated carbon electrophiles are shown to participate in the Pd-catalyzed alkynylation, but alkyl electrophiles are not shown, because little is known about them. For their alkynylation, alkynylmetals containing Li and Mg used either without catalysts or with Cu catalysts, such as Li_2CuCl_4, should be considered. Similarly, alkynylation of allyl and benzyl electrophiles may be more satisfactorily achieved by the Cu-catalyzed Grignard cross-coupling.



Scheme 15-31

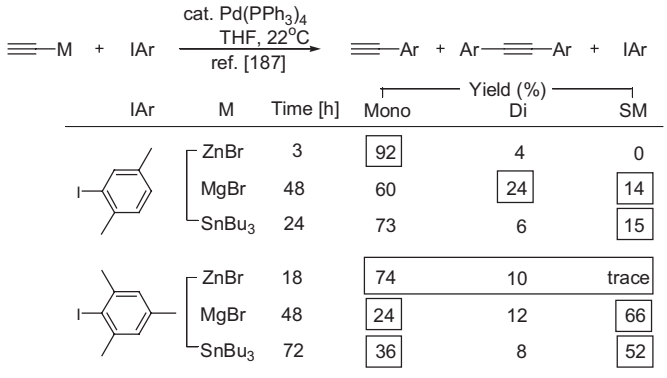
In many less-demanding cases of Pd-catalyzed alkynylation, most of the ten to a dozen protocols discussed above (including the Heck and Sonogashira protocols) would be satisfactory, and various factors including overall convenience, economy, and safety may prove to be more important than minor differences in chemical yields. In this context, the significance of TONs discussed earlier (see Table 15-5) should be re-emphasized, as TONs might prove to be a decisive factor in choosing one protocol over another.

Some notable aspects and features of the Pd-catalyzed alkynylzinc reactions with various unsaturated electrophiles are highlighted in the following discussions.

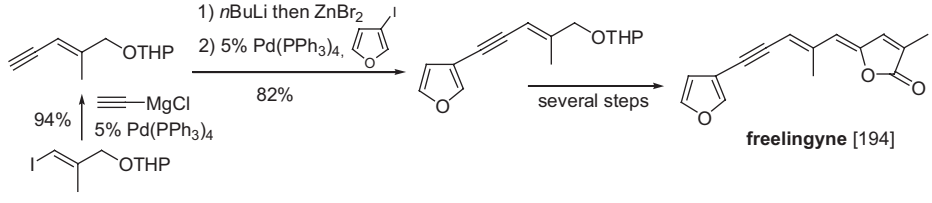
15.2.3.1 **Direct Synthesis of Terminal Alkynes**

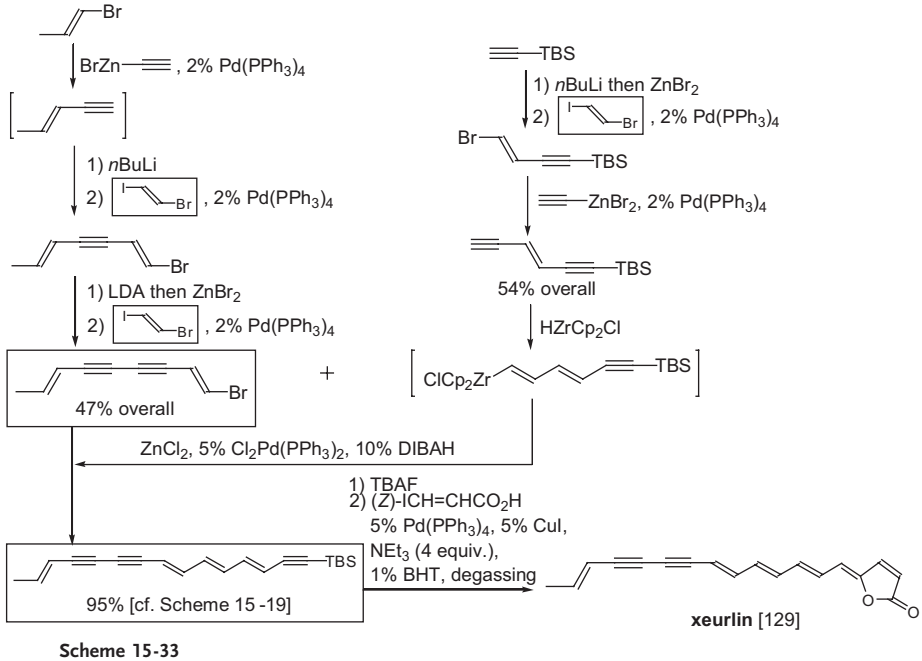
As has been well documented [176, 187], direct ethynylation without protection and deprotection cannot be satisfactorily performed by the Sonogashira reaction, as it tends extensively to produce disubstituted alkynes. On the other hand, the Zn, Mg, and Sn protocols have been shown to be satisfactory [187], but Zn is the most widely applicable and dependable [17, 186, 187]. The others tend to be sluggish in demanding cases, leading to the formation of unwanted disubstitution products and/or low product yields [186, 187] (Scheme 15-32).

The Pd-catalyzed direct ethynylation using ethynylmetals containing Zn or Mg has been exploited in devising highly efficient syntheses of natural products, such as freelingyne [194] and xerulin [129] (Scheme 15-33; see also Scheme 15-19). It should be noted that none of the several alkynylations – with the significant exception of the final lactone formation – can be satisfactorily performed by the Sonogashira reaction due to extensive side reactions. Some other serious limitations associated with the Sonogashira reaction include difficulties in the use of electron-deficient alkynes and sterically demanding electrophilic cross-coupling partners. The



Scheme 15-32





Scheme 15-33

alkynylzinc protocol, on the other hand, can readily accommodate a variety of electron-deficient alkynes with no major difficulties [182, 183] and cope with various sterically demanding cases, as shown in Scheme 15-32 [187]. For further discussions of these topics, the reader is referred to a recent review [5].

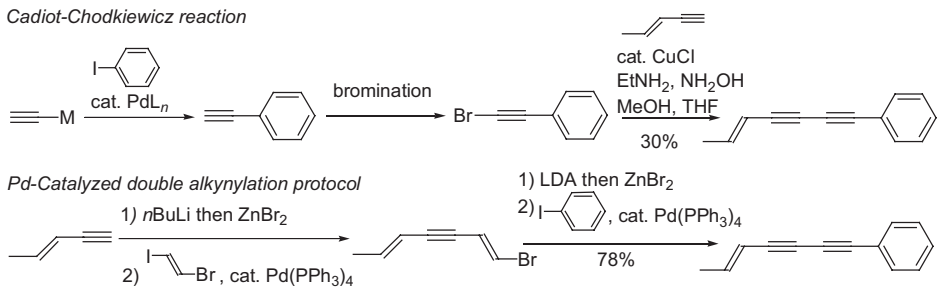
15.2.3.2 Pd-Catalyzed Alkynylation of 1,1- and 1,2-Dihaloalkenes. Pd-Catalyzed Route to Conjugated Diynes

In the xerulin synthesis shown in Scheme 15-33, (*E*)-ICH=CHBr was used three times as a two-carbon building block. Over the past 20–25 years, the Pd-catalyzed mono-alkynylation reaction of (*E*)-ClCH=CHCl [195], (*E*)-ICH=CHCl [189, 190], and (*E*)-ICH=CHBr [129–131,142,183,190] have been shown to proceed cleanly, with high yields in many cases. With (*E*)-ICH=CHBr, however, the Sonogashira reaction is not satisfactory [183]. Since the products of monoalkynylation of (*E*)-ICH=CHBr are sufficiently reactive in various second Pd-catalyzed cross-coupling reactions, these bromoenynes, especially (*E*)-BrCH=CHC≡CSiMe$_3$, have been shown to be useful reagents and intermediates for the synthesis of carotenoids [130], retinoids [130] and other conjugated oligoenes [131] and oligoenynes [129] as shown in Schemes 15-19, 15-22, and 15-33.

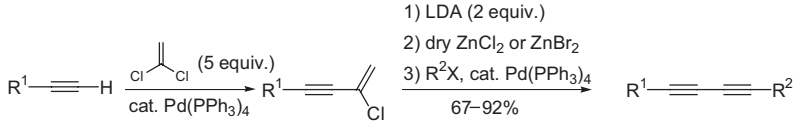
Caution should be heeded here that the Pd-catalyzed mono-substitution of (*E*)-ICH=CHBr with other classes of organozincs and other organometals has been much more capricious than the well-behaving alkynylation, and these reactions are currently under intensive investigation.

Another important application of the Pd-catalyzed alkynylation of 1,2-dihaloethylenes is the synthesis of conjugated diynes that has, in the past, been most frequently achieved by the Cadiot-Chodkiewicz reaction [196]. While the reaction is broadly applicable, it is often not sufficiently selective, producing significant amounts of undesired homo-coupled diynes. Similarly, the Pd-catalyzed reaction of alkynylmetals containing Zn and other metals with 1-halo-1-alkynes produces, more often than not, mixtures of the cross-coupled and two homo-coupled diynes, although some clean diyne formations have been reported [183]. In marked contrast, the Pd-catalyzed conjugated diyne synthesis via 1-halo-1-en-3-ynes is generally 100 % "pair"-selective and hence higher-yielding than either the Cadiot-Chodkiewicz reaction or the Pd-catalyzed alkynyl-alkynyl reaction. All of these protocols require roughly comparable amounts of synthetic efforts (Scheme 15-34). So, the Pd-catalyzed alkynyl-alkenyl coupling route is a distinctly superior choice in cases in which cross-homo-scrambling in the Cadiot-Chodkiewicz and other alkynyl-alkynyl coupling reactions is a serious side reaction.

A more economical synthesis of conjugated diynes was recently devised by replacing relatively expensive 1,2-dihaloethylenes with vinylidene dichloride [188]. Interestingly, the Sonogashira reaction has turned out to be considerably more satisfactory than the organometallic protocols for selective monoalkynylation of vinylidene dichloride. The products of monoalkynylation are in-situ converted into 1,3-diynylzincs that can be directly used for the second cross-coupling [188] (Scheme 15-35).



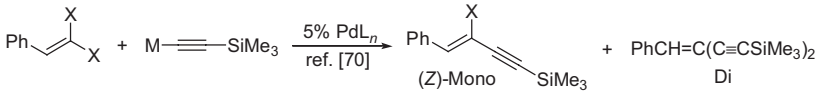
Scheme 15-34



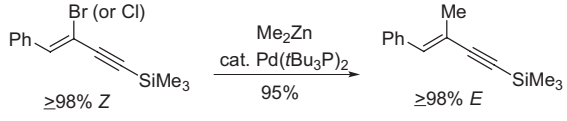
Scheme 15-35

Except for the rather isolated example of selective monoalkynylation of vinylidene dichloride discussed above, the Pd-catalyzed monoalkynylation of 1,1-dihalo-1-alkenes, where halogens are Br or Cl, can be satisfactorily achieved with either the Sonogashira [147] or the Negishi coupling [70]. In the great majority of cases, the reaction is ≥98 % *trans*-selective. Dialkynylation is a more serious and frequently encountered side reaction. It is possible that small amounts of *cis*-monoalkynylation products underwent second *trans*-alkynylation to deplete the undesired *cis*-monoalkynylation products through the formation of dialkynylation products. This can, however, be alleviated by the use of Cl_2Pd(DPEphos) or Cl_2Pd(dppf) as a catalyst. In the monoalkynylation of 1,1-dibromo-1-alkenes, both Sonogashira and Negishi coupling are generally satisfactory, provided that the above-mentioned catalysts containing bidentate phosphines are used. With 1,1-dichloro-1-alkenes, however, the Sonogashira protocol was shown to be much less satisfactory (Scheme 15-36]. In view of the significant difference between vinylidene dichloride and 2-substituted 1,1-dichloro-1-alkenes, however, further clarification of this point appears to be desirable.

As in the cases of the Pd-catalyzed alkenylation-alkylation domino process [71, 73] (Scheme 15-22), the stereochemistry of the second alkylation under Pd-catalyzed or, for that matter, under any other conditions [197] has proved to be rather capricious. Here again, however, bulky alkylphosphines, tBu_3P in particular, came to the rescue, and the second alkylation with Me_2Zn and Et_2Zn proceeded cleanly to give the desired disubstitution products of ≥98 % (*E*) in excellent yields [70]. However, clean inversion of configuration has not been achieved in the alkynylation-alkylation domino process.



X	M	PdL_n	Temp [°C]	Time [h]	Yield (%) (Z)-Mono	Yield (%) Di
Br	ZnCl	$Pd(PPh_3)_4$	23	24	84	14
Br	ZnCl	Cl_2Pd(DPEPhos)	0	1	90	8
Br	H	$Pd(PPh_3)_4$	23	20	15	18
Br	H	Cl_2Pd(DPEPhos)	0	1	89	8
Cl	ZnCl	$Pd(PPh_3)_4$	50	12	61	12
Cl	ZnCl	Cl_2Pd(DPEPhos)	23	6	84	13
Cl	H	Cl_2Pd(DPEPhos)	23	24	56	4

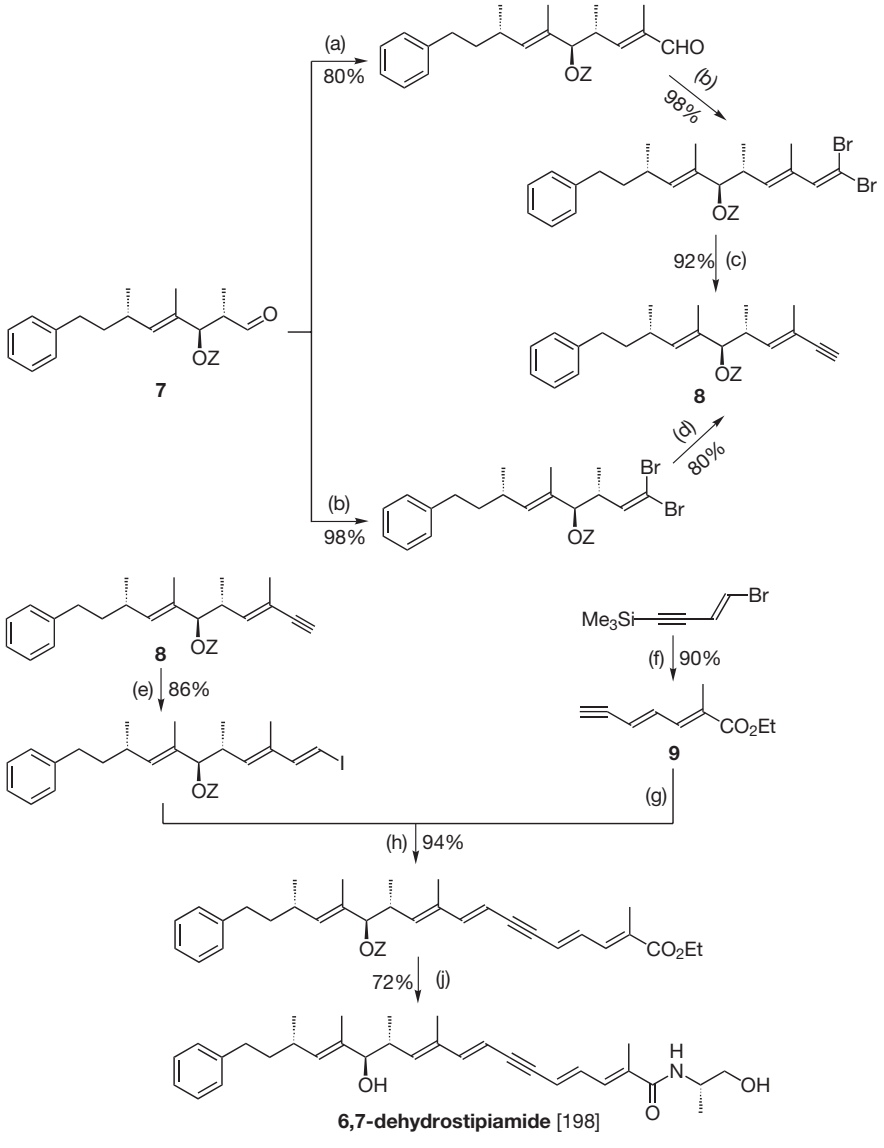


Scheme 15-36

In a recent synthesis of 6,7-dehydrostipiamide, conversion of **7** into another key intermediate **8** has been achieved in two different ways. The use of the Pd-catalyzed alkynylation-alkylation domino process has proved to be the more convenient and satisfactory of the two [198] (Scheme 15-37). The other required intermediate **9** was prepared in two steps from (*E*)-BrZnCH=CHC≡$CSiMe_3$ and (*E*)-BrCH=CH(Me)COOEt by Pd-catalyzed alkenyl-alkenyl coupling, followed by desilylation with TBAF in 90% yield.

15.2.3.3 *α*-Alkynylation of *α*-Halo-*α*,*β*-unsaturated Carbonyl Derivatives

A logical and significant extension of the development of Pd-catalyzed *α*-arylation and *α*-alkenylation of *α*-iodoenones discussed in Section 15.2.2 is that of the corresponding *α*-alkynylation, which has indeed been shown to be feasible by the use of Stille [154], Sonogashira [156], and Negishi [155] coupling reactions. This is a very significant development, as there was no satisfactory alternative prior to this development. All of the three alkynylation procedures have been applied to the synthesis of harveynone and tricholomenyn A [154b, 155, 156] (Scheme 15-38). Although no rigorous comparisons have been conducted, the data summarized in Scheme 15-42 suggest that the use of preformed alkynylmetals containing Zn or Sn would lead to more favorable results than the Sonogashira protocol. The Zn procedure has also been applied to the *α*-alkynylation of *α*-bromo-*α*,β-unsaturated esters [199] (Scheme 15-39).



6,7-dehydrostipiamide [198]

Z = TBS or TBDPS.

(a) (i) $Et_3Si(Me)CH{=}NCy$, (ii) CF_3CO_2H. (b) $Ph_3P/CBr_4/Zn$. (c) (i) *n*BuLi, (ii) H^+.

(d) (i) $BrZnC{\equiv}CSiMe_3$, $Cl_2Pd(DPEphos)$, (ii) Me_2Zn, $Pd(tBu_3P)_2$, (iii) K_2CO_3, MeOH.

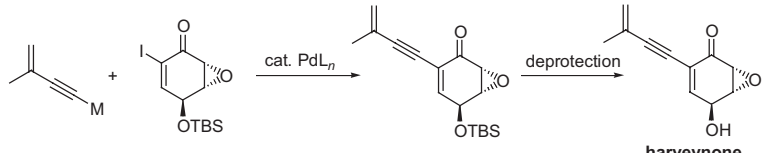
(e) (i) $Cp_2Zr(H)Cl$, (ii) I_2.

(f) (i) *t*BuLi, (ii) $ZnBr_2$, (iii) (*E*)-$BrCH{=}C(Me)CO_2Et$, $Cl_2Pd(PPh_3)_2$ + DIBAH, (iv) TBAF.

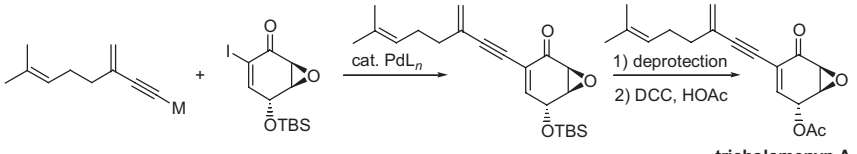
(g) (i) LDA, (ii) $ZnBr_2$. (h) $Cl_2Pd(PPh_3)_2$ + DIBAH.

(j) (i) TBAF, (ii) LiOH, (iii) iPr_2NEt, (*s*)-$H_2NCH(Me)CH_2OH$, PyBroP.

Scheme 15-37

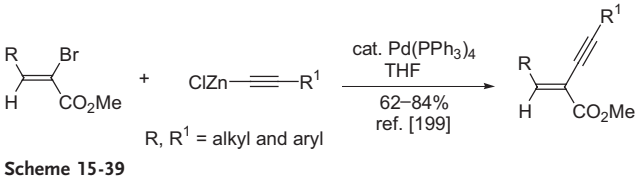


M	PdL$_n$	Cond.	Yield (%)	Ref.
Zn	$Pd(dba)_2$/TFP	DMF	73	[155]
Sn	$Cl_2Pd(PPh_3)_2$	cat. CuI, NMP	82	[154b]
H	$Cl_2Pd(PPh_3)_2$	cat. CuI, iPr$_2$NH	52	[156]



M	PdL$_n$	Cond.	Yield (%)	Ref.
Zn	$Pd(dba)_2$/TFP	DMF	80	[155]
Sn	$Cl_2Pd(PPh_3)_2$	cat. CuI, NMP	39	[154c]
H	$Cl_2Pd(PPh_3)_2$	cat. CuI, iPr$_2$NH	54	[156]

Scheme 15-38

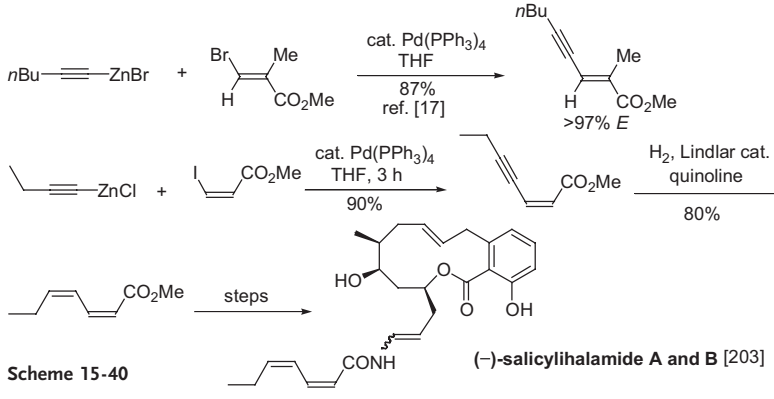


Scheme 15-39

15.2.3.4 β-Alkynylation of β-Halo-α,β-unsaturated Carbonyl Derivatives

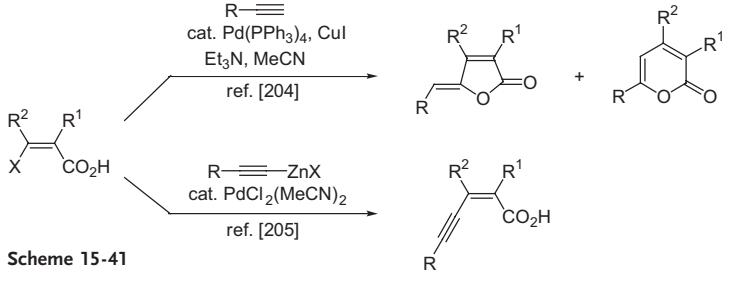
In contrast to the α-substitution of α-halo-α,β-unsaturated carbonyl derivatives, which generally is inherently difficult, the corresponding β-substitution of β-halo-α,β-unsaturated carbonyl derivatives, which may be conveniently termed *conjugate substitution* [87], is a fundamentally favorable process [5]. The reaction of 1-hexynylzinc chloride shown in Scheme 15-40 and reported in 1977 [17] appears to be the first example of the Pd-catalyzed β-alkynylation. Additional examples have since been reported by using the Zn protocol [200] and the Sonogashira reaction [201, 202]. A recent synthesis of salicylihalamide A and B [203] employed the Zn protocol (Scheme 15-40).

The reaction of terminal alkynes with (*Z*)-2-propenoic acid under the Sonogashira reaction conditions was reported to give (*Z*)-γ-alkylidenebutenolides along with α-pyrones [204] (Scheme 15-41). On the other hand, the corresponding reaction of alkynylzincs would merely produce the expected cross-coupling products [205] (Scheme 15-41).



Scheme 15-40

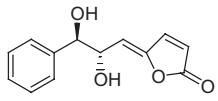
(−)-salicylihalamide A and B [203]



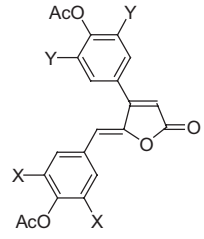
Scheme 15-41

The cross-coupling–lactonization domino process has provided an unprecedented, highly efficient one-pot procedure for the synthesis of biologically important (*Z*)-γ-alkylidenebutenolides [206]. After optimization of several reaction parameters, this has been applied to the synthesis of a wide range of naturally occurring (*Z*)-γ-alkylidenebutenolides, such as goniobutenolide A [207], rubrolides A, C, D, and E [208] (Scheme 15-42), freelingyne [194] (*cf.* Scheme 15-33), and xerulin [129] (*cf.* Scheme 15-19).

The inability of the alkynylzinc reaction to induce the same domino process has, in fact, turned out to be a blessing in disguise. Enynoic acids obtainable in high yields by this reaction can now be selectively converted into either five- or six-membered lactones by the use of a catalytic amount of either Ag_2CO_3 [209] or $ZnBr_2$, respectively, with ≥95 % selectivity. With enynoic acids derived from alkyl-substituted 1-alkynes, the cross-coupling–lactonization domino process has exhibited rather low regioselectivity figures [209] (Scheme 15-43). It does appear that successive application of the Negishi coupling and a Ag-catalyzed lactonization in two separate steps would be generally the best route to (*Z*)-γ-alkylidenebutenolides [210], except for cases in which the domino process under Sonogashira conditions proves



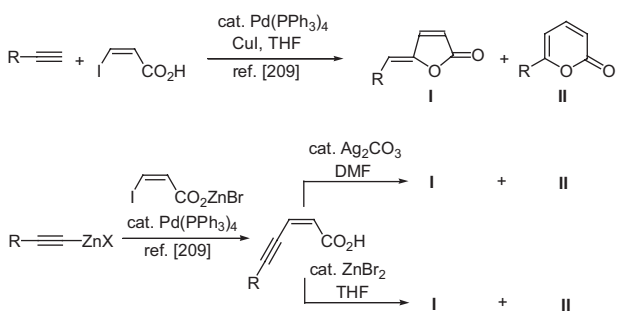
goniobutenolide A [207]



rubrolide diacetate [208]

Rubrolide diacetate	X	Y
A	Br	Br
C	Br	H
D	H	Br
E	H	H

Scheme 15-42



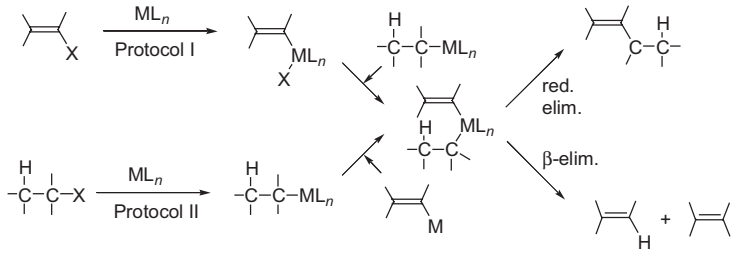
R	I + II (%)	I/II
*n*Hex	77	64/34
*i*Pr	75	80/20
*c*Hex	65	80/20
*t*Bu	76	97/3
*n*Hex	90	96/4
*i*Pr	93	95/5
*c*Hex	88	97/3
*t*Bu	86	98/2
*n*Hex	90	6/94
*i*Pr	92	4/96
*c*Hex	86	4/96
*t*Bu	86	34/66

Scheme 15-43

to be high-yielding and highly selective (Scheme 15-43). The Ag-catalyzed enynoic acid cyclization procedure has been successfully applied to the synthesis of lissoclinolide [142].

15.2.4
Pd- or Ni-Catalyzed Alkylation

Alkyl halides and related electrophiles lacking a β,γ-unsaturated alkyl group are among the least reactive carbon groups with regard to oxidative addition to Pd, Ni and other late transition metals. On the other hand, allyl, propargyl, and benzyl electrophiles are among the most reactive toward those transition metals mentioned above (Scheme 15-9). This striking contrast must be largely attributable to the absence of a β,γ-unsaturated bond in the former and its presence in the latter, strongly pointing to the significance of π-bonds in the β,γ-position. Despite the major difference in reactivities, all of these "alkyl" groups do share some common fundamental properties. In their orbital-controlled oxidative addition to late transition metals including Pd and Ni, they all must undergo Walden inversion, while alkenyl electrophiles discussed in preceding sections generally undergo oxidative



Scheme 15-44

M = Pd, Ni, or other transition metals

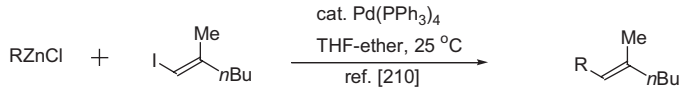
addition with retention with some notable exceptions, such as those shown in Scheme 15-22 [71]. With aryl, alkynyl, and acyl electrophiles, oxidative addition with retention is the only available option. Most of the alkyl derivatives are associated with another difficulty to be either avoided or overcome. In cases where alkyl groups contain one or more β-hydrogen atoms, their transition metal derivatives can often undergo facile β-dehydrometallation in which β-agostic interaction (or hyperconjugation) is thought to play a key role. This reaction can seriously interfere with Pd- or Ni-catalyzed cross-coupling with alkyl derivatives, as shown in Scheme 15-44 [210].

15.2.4.1 Discovery and Development of Pd-Catalyzed Alkylation with Alkylzincs

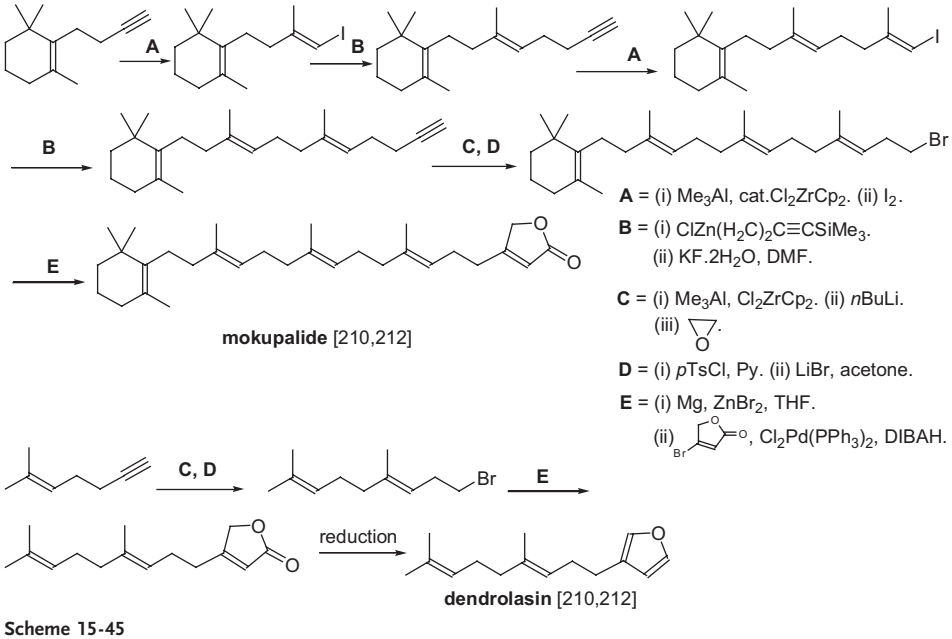
Although potentially more difficult than the Pd- or Ni-catalyzed cross-coupling reactions of unsaturated organic reagents, the discussion presented above does not rule out the possibility for Pd- or Ni-catalyzed cross-coupling according to the mechanisms shown in Scheme 15-44. After all, most of the chemical issues are matters of relative rates of various possible chemical processes. Fast reductive elimination processes coupled with slow β-elimination processes can favor cross-coupling over β-elimination. Closely related is the residence time of any transition metal alkylderivative. The shorter the time, the more favorable the desired cross-coupling would be. On this basis, Protocol I involving alkyl-alkenyl coupling should be more favorable than Protocol II involving alkenyl-alkyl coupling. As proposed earlier, the word before a hyphen represents the corresponding organometal, and that shown after a hyphen the corresponding electrophile. Indeed, until recently, essentially all reported cases were examples of Protocol I.

In 1979, two independent studies on Pd-catalyzed alkylation with alkylzincs were disclosed at the ACS Spring Meeting [211]. One was published in the same year, and the other in 1980. This reaction was soon applied to the stereoselective syntheses of terpenoids, such as farnesol [211(b)], dendrolasin [212], and mokupalide [211(b), 212] (Scheme 15-45).

The applicability of the Pd-catalyzed alkylation with alkylzincs even in the synthesis of tetrasubstituted alkenes has been demonstrated [213] and applied to the



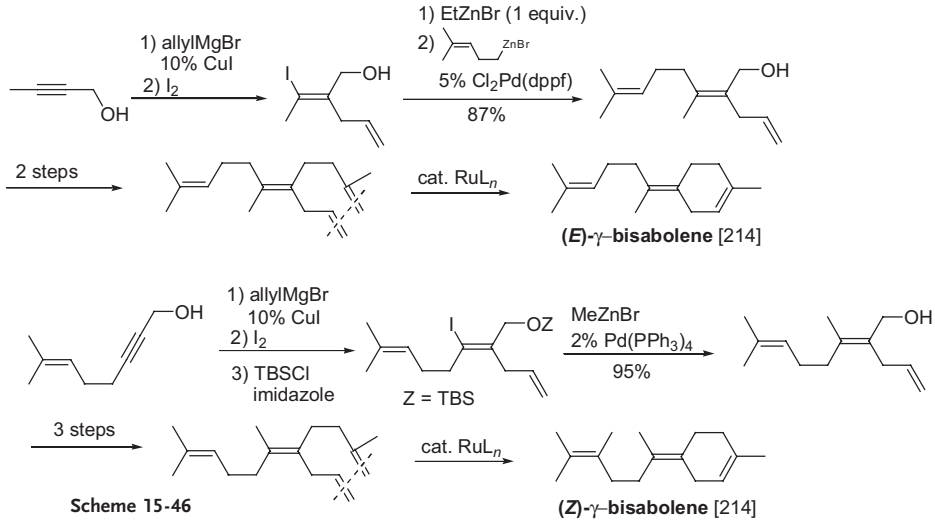
R	Time [h]	Yield (%)
*n*Bu	2	76
CH_2=CH(CH_2)$_2$	16	81
$Me_3SiC{\equiv}C(CH_2)_2$	2	91



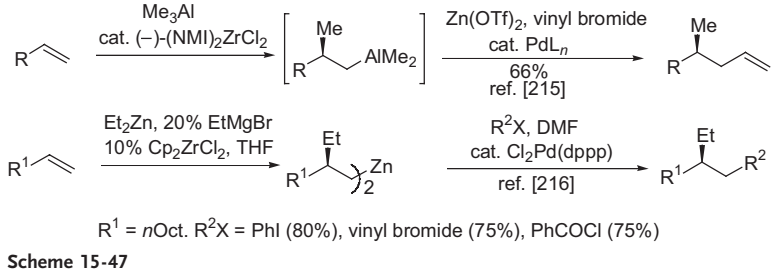
Scheme 15-45

synthesis of both (*E*)- and (*Z*)-γ-bisabolenes with ≥98 % stereoselectivity [214] (Scheme 15-46).

Although several other metals including Mg, B, Al, In, Sn and even Si [30] have been shown to participate in Pd-catalyzed alkylation, their current scopes (with the notable exception of B) are mostly limited to the use of alkylmetals containing Me, Et, and simple alkyl groups [92]. It is not unreasonable to state that the Pd-catalyzed alkylation represented by Protocol I (Scheme 15-44) is most satisfactorily achieved by using Zn or B at the present time [92]. The latter offers an advantage of being able to directly provide alkylboranes via alkene hydroboration. Similar advantages have also been observed with Al and Zn in their carboalumination-cross-coupling [215] and carbozincation-cross-coupling [216] domino processes, respectively (Scheme 15-47). It is, however, desirable to further develop these promising reactions.



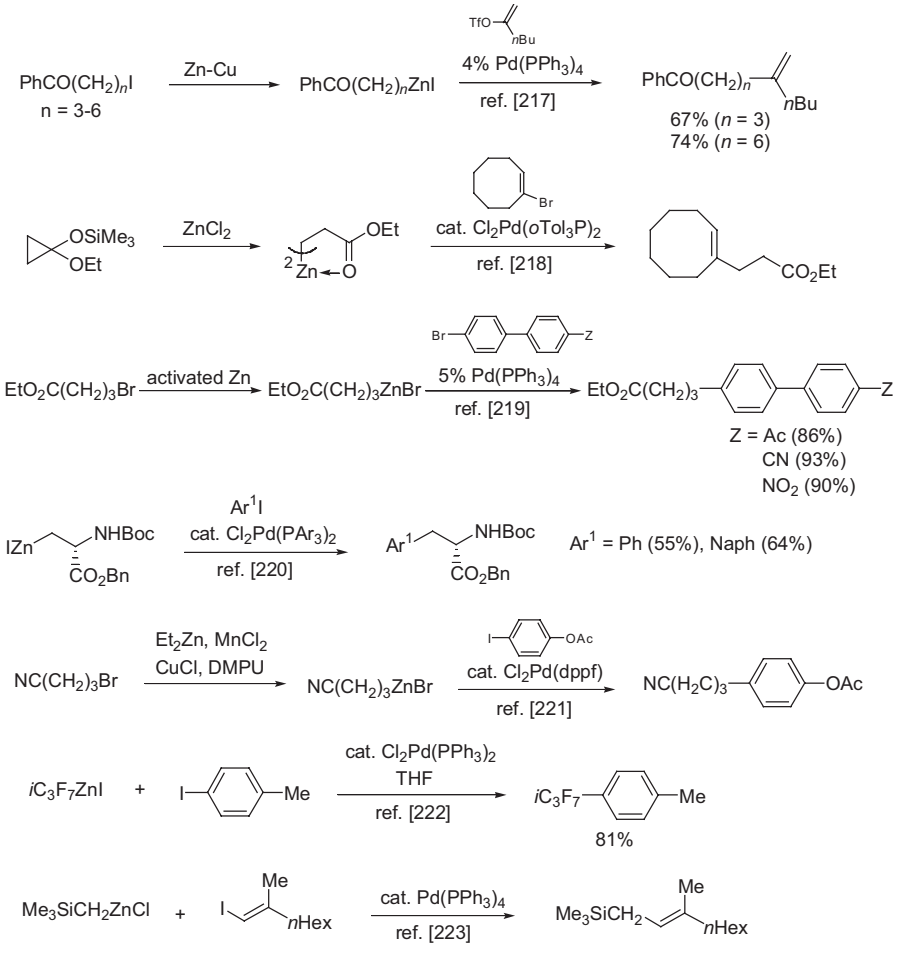
Scheme 15-46



Scheme 15-47

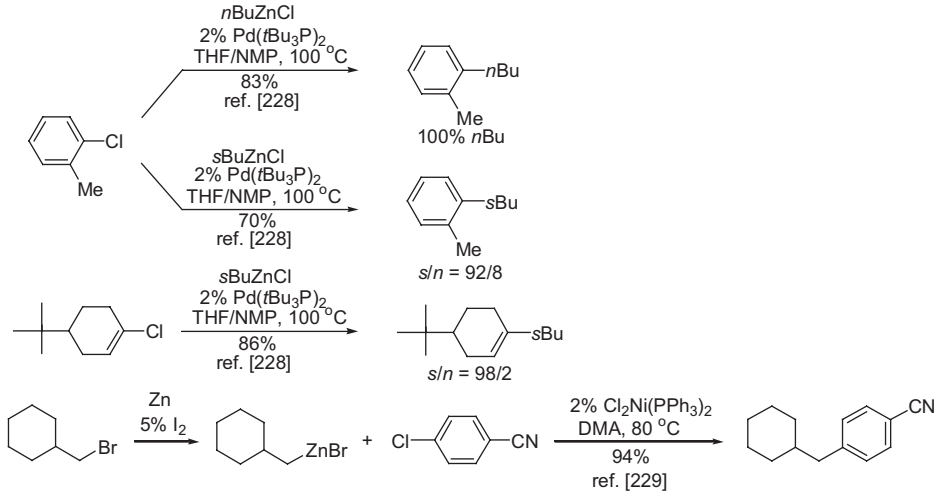
Another advantage that alkylzincs and, for that matter, any other types of organozincs offer is their chemoselectivity, which has often been very much underappreciated. The following examples clearly indicate that even alkylzinc reagents themselves may contain acyl [217], ester [218, 219], amino acid ester [220], nitrile [221], and fluoroalkyl [222] groups (Scheme 15-48). A highly stereoselective synthesis of allylsilanes by Pd- or Ni-catalyzed alkyl-alkenyl coupling is also noteworthy [223]. For additional discussions of various methods of preparation and use of functionalized organozincs, the reader is referred to two monographs [224, 225] and other extensive reviews [226, 227].

All examples of the Pd- or Ni-catalyzed alkylations presented above involve the use of aryl and alkenyl electrophiles containing I, Br or OTf, except for an acyl chloride shown in Scheme 15-47. One recent promising and potentially important development is the use of aryl and alkenyl chlorides in conjunction with $Pd(t\mathrm{Bu}_3\mathrm{P})_2$



Scheme 15-48

[228]. Also noteworthy is that the Ni-catalyzed alkylation of *p*-chlorobenzonitrile with alkylzincs proceeds in excellent yields [229] (Scheme 15-49). In view of the relatively high temperatures (80–100 °C) at which these reactions are performed, their further improvement is very desirable. An even more striking methodological development is the use of alkyl halides (Protocol II in Scheme 15-44) in the Pd- or Ni-catalyzed alkylation with organozincs. This topic will be discussed later in this section.



Scheme 15-49

15.2.4.2 Applications of the Pd-Catalyzed Alkylation with Alkylzincs to Natural Product Syntheses

In addition to relatively simple terpenoids, such as farnesol [211(b)], dendrolasin [212], mokupalide [211(b), 212], and (*E*)- and (*Z*)-γ-bisabolenes [214], discussed earlier, twenty or more complex natural products have been synthesized by using the Pd-catalyzed alkyl-alkenyl coupling with alkylzincs. Some of the earlier results including those indicated above were described in a few pertinent sections [92–94] of *Handbook of Organopalladium Chemistry for Organic Synthesis* [4]. Applications to the syntheses of complex natural products have been reported mostly over the past few years. In Table 15-8, most, if not all, of the examples known at this

Table 15-8 Natural products synthesized via Pd-catalyzed alkylation

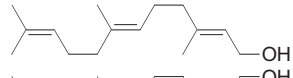
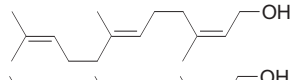
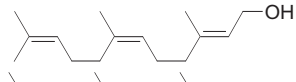
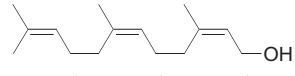
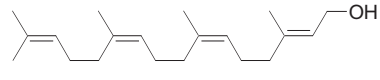
Natural product	*Structure*	*Major author*	*Ref.*
(2*E*,6*E*)-farnesol		E. Negishi	[211b]
(2*Z*,6*E*)-farnesol		E. Negishi	[61]
(2*E*,6*Z*)-farnesol		E. Negishi	[61]
(2*Z*,6*Z*)-farnesol		E. Negishi	[61]
(2*E*,6*Z*,10*E*)-geranyl geraniol		E. Negishi	[61]

Table 15-8 (continued)

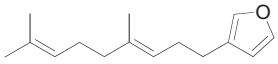
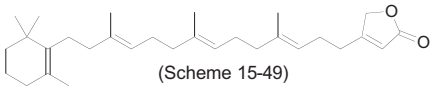
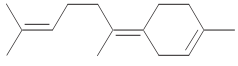
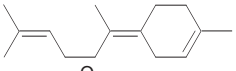
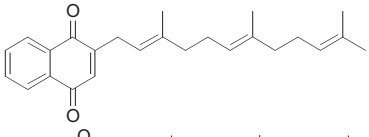
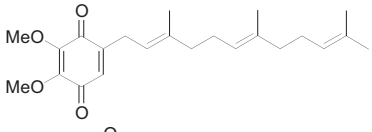
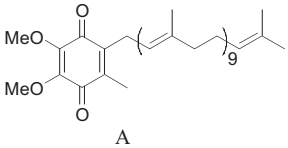
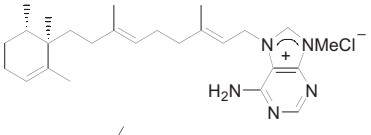
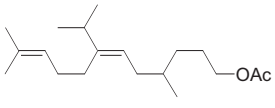
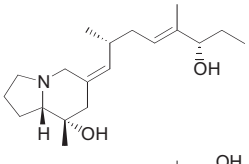
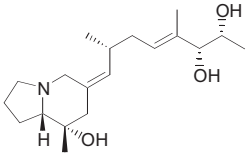
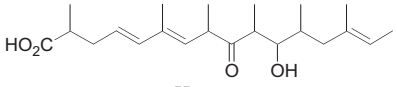
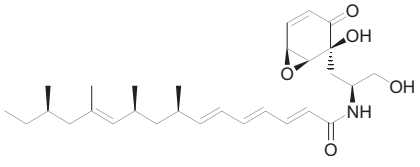
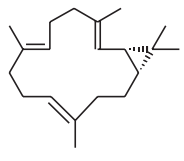
Natural product	*Structure*	*Major author*	*Ref.*
dendrolasin	 (Scheme 15-49)	E. Negishi	[212]
mokupalide	 (Scheme 15-49)	E. Negishi	[211b, 212]
(*E*)-γ-bisabolene	 (Scheme 15-50)	E. Negishi	[214]
(*Z*)-γ-bisabolene	 (Scheme 15-50)	E. Negishi	[214]
menaquinone-3		E. Negishi	[61]
coenzyme Q_3		E. Negishi	[61]
coenzyme Q_{10}		E. Negishi	[61, 231]
(+)-casbene	A	J. E. McMurry	[232]
ageline A		T. Tokoroyama	[233]
yellow seale pheromone		J. G. Millar	[234]
(+)-amphidinolide J	B	D. R. Williams	[235]
brevetoxin A	C	K. C. Nicolaou	[236]
(+)-pumiliotoxin A		C. Kibayashi	[237]
(+)-pumiliotoxin B		C. Kibayashi	[237]

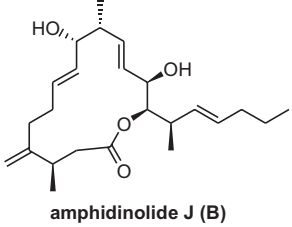
Table 15-8 (continued)

Natural product	*Structure*	*Major author*	*Ref.*
(+)-discodermolide	D	A. B. Smith III	[238] [239]
mycolactones A and B	E	Y. Kishi	[240]
oleandolide	F	J. S. Panek	[241]
epothilone A	G	K. H. Altmann	[242]
delactonmycin		R. A. Pilli	[243]
borrelidin	H	J. P. Morken	[244]
scyphostatin		T. Katoh E. Negishi	[245] [246]

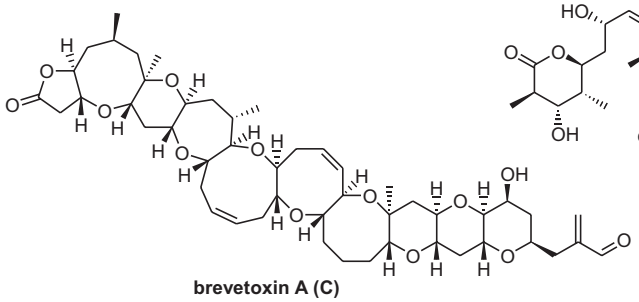
time are listed in a more or less chronological manner. For examples of natural products synthesized by Pd-catalyzed alkylation with alkylboranes, the reader is referred to an extensive recent review by Danishefsky [230].



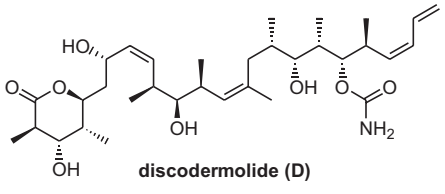
casbene (A)



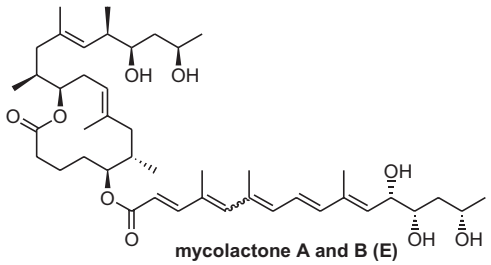
amphidinolide J (B)



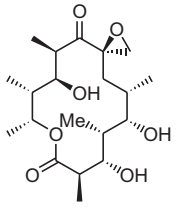
brevetoxin A (C)



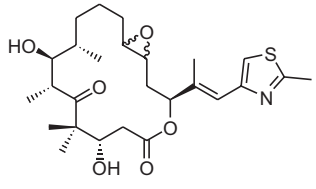
discodermolide (D)



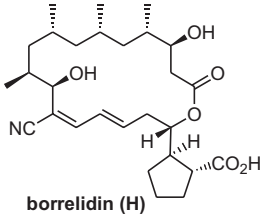
mycolactone A and B (E)



oleandolide (F)



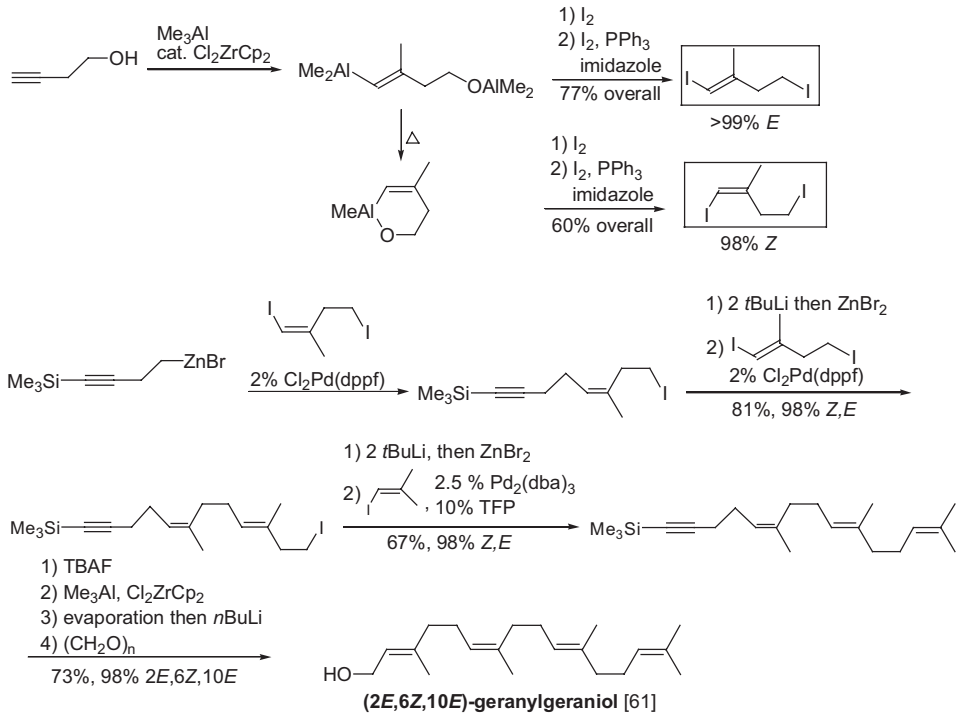
epothilone A (G)



borrelidin (H)

For the highly selective synthesis of 1,5-diene-containing terpenoids, development of the efficient and selective procedures for preparing (*E*)- and (*Z*)-1,4-diiodo-2-methyl-1-butenes as (*E*)- and (*Z*)-isoprene building blocks shown in Scheme 15-50 was crucially important. With these procedures, 1,5-diene-containing terpenoids of practically any stereochemical combinations can be prepared by an iterative one-pot metallation-cross-coupling process that is both high-yielding and highly stereoselective. The stereoselectivity level for each of the (*E*) and (*Z*) isoprene units are ≥99 and ca. 98 %, respectively. This method represents a substantial improvement not only over conventional methods involving capricious allyl-allyl coupling but also over the two-step protocol shown in Scheme 15-45. Although both (*E*) and (*Z*) alkene units can be constructed selectively and satisfactorily, there are some notable differences between *E* and *Z* isomers, the former syntheses being more favorable in a few critical respects than the latter.

The Pd-catalyzed alkylation of (*E*)-2-iodo-2-alkenes with isoalkylzinc derivatives has been successfully applied to the synthesis of complex natural products including discodermolide [238], mycolactones A and B [240], and borrelidin [244]. In these demanding cases, the use of one extra equivalent of *t*BuLi in the metallation of isoalkyl iodide has been reported to be beneficial [238]. Presumably, isoalkyl(*t*-butyl)zincs are generated as superior alkylzinc reagents. Even so, the yield of the desired isoalkyl-alkenyl coupling has often been modest. Further optimization of a few reaction parameters, such as ligands and solvents, appears to be desirable. For example, in a recent synthesis of the scyphostatin side chain, a closely related cross-coupling reaction was achieved in 94 % yield by using Cl_2Pd(DPEphos) [246], which might therefore prove to be a superior catalyst than those used in the past in many other cases.

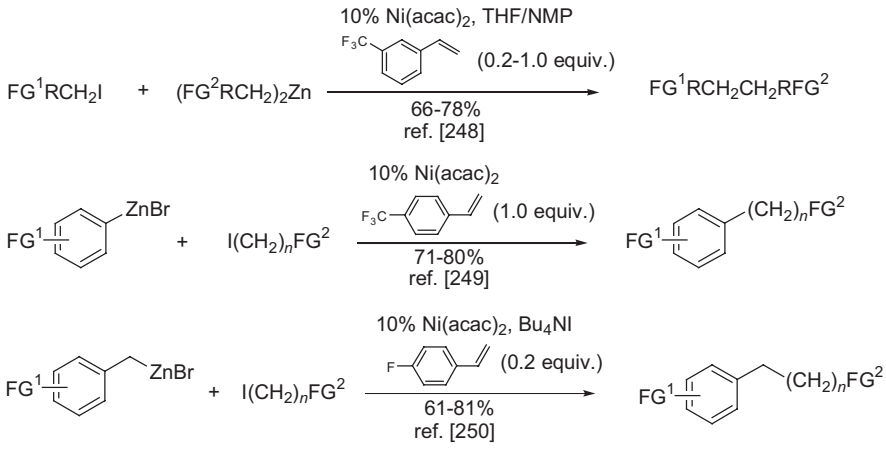


Scheme 15-50

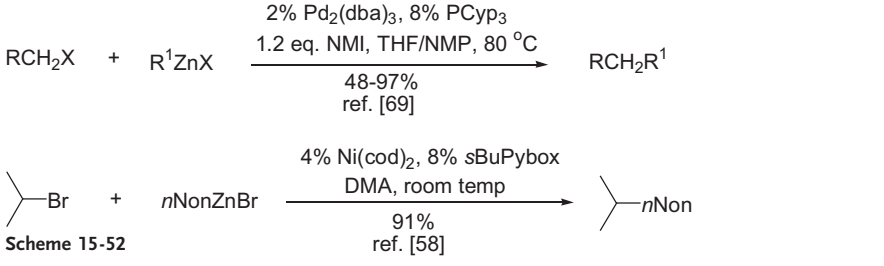
15.2.4.3 **Pd-Catalyzed Alkylation with Alkyl Electrophiles**

Although some scattered examples of Pd- or Ni-catalyzed cross-coupling reactions with alkyl electrophiles have been known for 10 or more years, relatively little attention had been paid to them until recently. In 1995, Knochel reported that various organozinc reagents would undergo Ni-catalyzed cross-coupling with primary alkyl iodides and bromides [247]. In a series of subsequent papers [248–251], the following noteworthy features were demonstrated. The most noteworthy is that addition of *m*- and *p*-CF_3-substitutued styrenes [248, 249], as well as *p*-fluorostyrene [250, 251] accelerates the desired cross-coupling reaction (Scheme 15-51). As might be expected, the reaction is compatible with a wide range of functional groups.

More recently, Fu et al. have reported that the Pd-catalyzed reaction of various organozincs with primary alkyl iodides, bromides, tosylates, and even chlorides can proceed well with $PCyp_3$ as a phosphine [69]. Even more striking is that, with a catalyst system consisting of 4 % $Ni(cod)_2$ and 8 % *s*Bu-Pybox **1** used in conjunction with DMA as a solvent, even secondary alkyl bromides and iodides can undergo alkyl-alkyl coupling with alkylzinc reagents [58] (Scheme 15-52). Similar studies of the Pd-catalyzed reaction of alkyl chlorides with Grignard reagents were also reported by Beller [252].



Scheme 15-51



Scheme 15-52

The results shown in Schemes 15-51 and 15-52 are not only striking but potentially useful. Clearly, a new chapter in Pd- or Ni-catalyzed cross-coupling has been opened. In this context, however, it should be clearly noted that either stoichiometric organocopper reactions or Cu-catalyzed reactions of Grignard reagents with alkyl halides and sulfonates [253] must still be viewed as the current benchmark, with which any new methods including those described above must be carefully compared to establish their pros and cons relative to the Cu-based methods. Further delineation of the scope and limitations of these new reactions is therefore highly desirable.

15.2.5
Pd-Catalyzed Cross-Coupling Using Benzyl, Allyl, and Propargyl Derivatives

As discussed earlier, benzyl, allyl, and propargyl derivatives that contain β,γ-unsaturated carbon-carbon bonds can readily interact with Pd complexes, and they can indeed participate in a wide variety of Pd-catalyzed cross-coupling and related reactions. A large number of examples of these reactions known as of a few years ago have been comprehensively documented in Chapters III.2.9 [89], III.2.10 [91],

III.2.16 [98], III.2.18 [94], and V.2.1.4 [97]. Although no extensive duplication is intended here, a brief summary of various possible protocols should be useful to minimize and clarify potential confusions associated with them. It is important to note that the organozinc-based methods are usually either the most satisfactory or among the most satisfactory options.

The Pd-catalyzed cross-coupling between an unsaturated group, i. e., aryl, alkenyl, or alkynyl, and a β,γ-unsaturated alkyl group, i. e., benzyl, allyl, or propargyl, provides nine different combinations of cross-coupling that may be carried out in 18 different organometal-electrophile combinations. Collectively, they can produce six different kinds of cross-coupling products. Each of the 18 processes is expected to display its own scope and limitations, and it is important to know the merits and demerits among either two or four available options for the synthesis of a given compound. To this end, the following summary should prove to be useful.

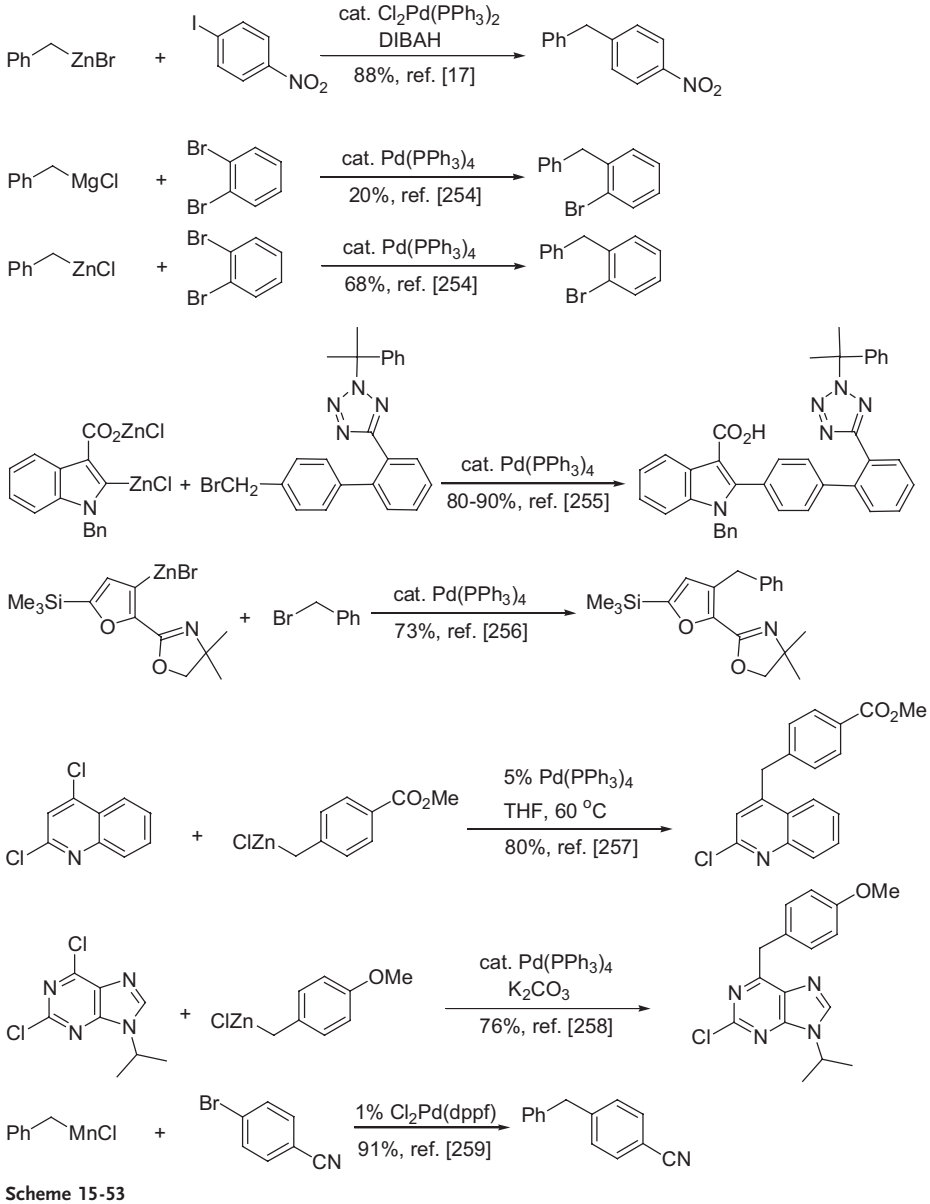
15.2.5.1 Benzyl-Aryl and Aryl-Benzyl Couplings

Both of these reactions produce diarylmethanes, and the first examples of the Pd-catalyzed benzyl-aryl coupling were reported in 1977 [17]. In many cases, however, Ni catalysts were similarly effective. Both types of reactions have since been successfully employed in a variety of cases, including those involving heteroaryl groups, as shown in Scheme 15-53. One recent example of benzyl-aryl coupling with benzylmanganese chloride is also noteworthy [259].

15.2.5.2 Synthesis of Allylated Arenes via Aryl-Allyl, Allyl-Aryl, Alkenyl-Benzyl, or Benzyl-Alkenyl Couplings

Synthesis of allylated arenes via Pd-catalyzed cross-coupling has been achieved by all four processes indicated above. Although the Pd-catalyzed reaction of allyl(tributyl)stannane with bromobenzene was reported in 1977 as the first Pd-catalyzed C-C coupling reaction of organotins [22], the allyl-aryl coupling protocol has not since been widely used for the synthesis of allylated arenes. In fact, allylmetals containing more electropositive metals, such as Zn, do not appear to be well-suited for Pd-catalyzed cross-coupling. Catalyst poisoning due to their intrinsically high reactivity may be suspected, although this point needs to be further clarified. For the Pd-catalyzed cross-coupling reaction of allyltins, a mechanism involving carbopalladation followed by destannylpalladation should be considered as a likely pathway.

Unlike the Pd-catalyzed allyl-aryl coupling, which appears to be limited with respect to metal countercations, the corresponding aryl-allyl coupling is widely observable with various metals including Zn and Mg. At present, Zn appears to be superior to the others in that arylzincs are not only more reactive than the others under the Pd- or Ni-catalyzed conditions but also readily available from both direct and indirect zincation. Direct zincation is attractive, since it can tolerate various heterofunctional groups that are sensitive to organometals containing Li, Mg, and other electropositive metals. Recent developments of direct syntheses of aryl-


Ph ZnBr + I NO2
cat. Cl2Pd(PPh3)2
DIBAH
88%, ref. [17]
Ph NO2
Ph MgCl + Br Br
cat. Pd(PPh3)4
20%, ref. [254]
Ph Br
Ph ZnCl + Br Br
cat. Pd(PPh3)4
68%, ref. [254]
Ph Br
CO2ZnCl
ZnCl + BrCH2
N
N
N
Ph
Bn
cat. Pd(PPh3)4
80-90%, ref. [255]
CO2H
Me3Si
ZnBr
O
N
O
+ Br Ph
cat. Pd(PPh3)4
73%, ref. [256]
Me3Si Ph
Cl
Cl N
+ ClZn CO2Me
5% Pd(PPh3)4
THF, 60 °C
80%, ref. [257]
CO2Me
Cl N
Cl
N
N
N
+ ClZn OMe
cat. Pd(PPh3)4
K2CO3
76%, ref. [258]
OMe
Ph MnCl + Br CN
1% Cl2Pd(dppf)
91%, ref. [259]
Ph CN

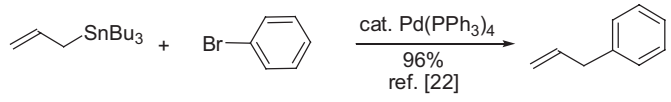
Scheme 15-53

zinc reagents through the use of I_2 [229] or Me_3SiCl [260] as promoters are noteworthy.

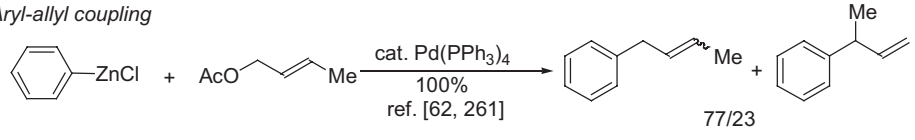
The main potential drawback of the aryl-allyl coupling is regiochemical and stereochemical isomerization of allyl groups. For strictly regio- and stereoselective construction of allylated arenes, benzyl-alkenyl and alkenyl-benzyl couplings should be considered. In cases where appropriate alkenylmetals are readily generated by regio- and stereoselective hydrometallation, carbometallation, and other related addition reactions of alkynes, the alkenyl-benzyl coupling process is operationally simpler and hence potentially more favorable than benzyl-alkenyl coupling. One seminal and/or representative example each of the four protocols discussed above are shown in Scheme 15-54.

The benzyl-alkenyl coupling processes have been successfully applied to the synthesis of coenzyme Q_n and menaquinones-*n* [61, 231, 263, 264], where *n* is an integer, such as 3 and 10 (Scheme 15-55). Both Pd [61, 262] and Ni [231, 263, 264] catalysts have been shown to be highly satisfactory, despite some conflicting comparative figures and results [262, 231]. Further critical comparison may be desirable, if the apparent discrepancy is to be resolved.

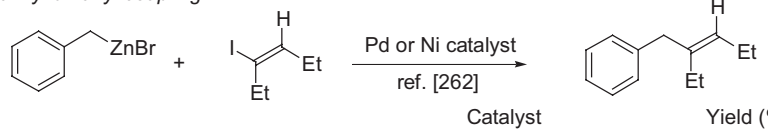
Allyl-aryl coupling



Aryl-allyl coupling

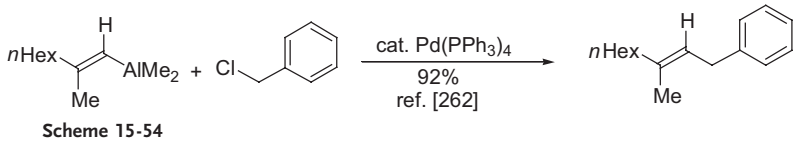


Benzyl-alkenyl coupling

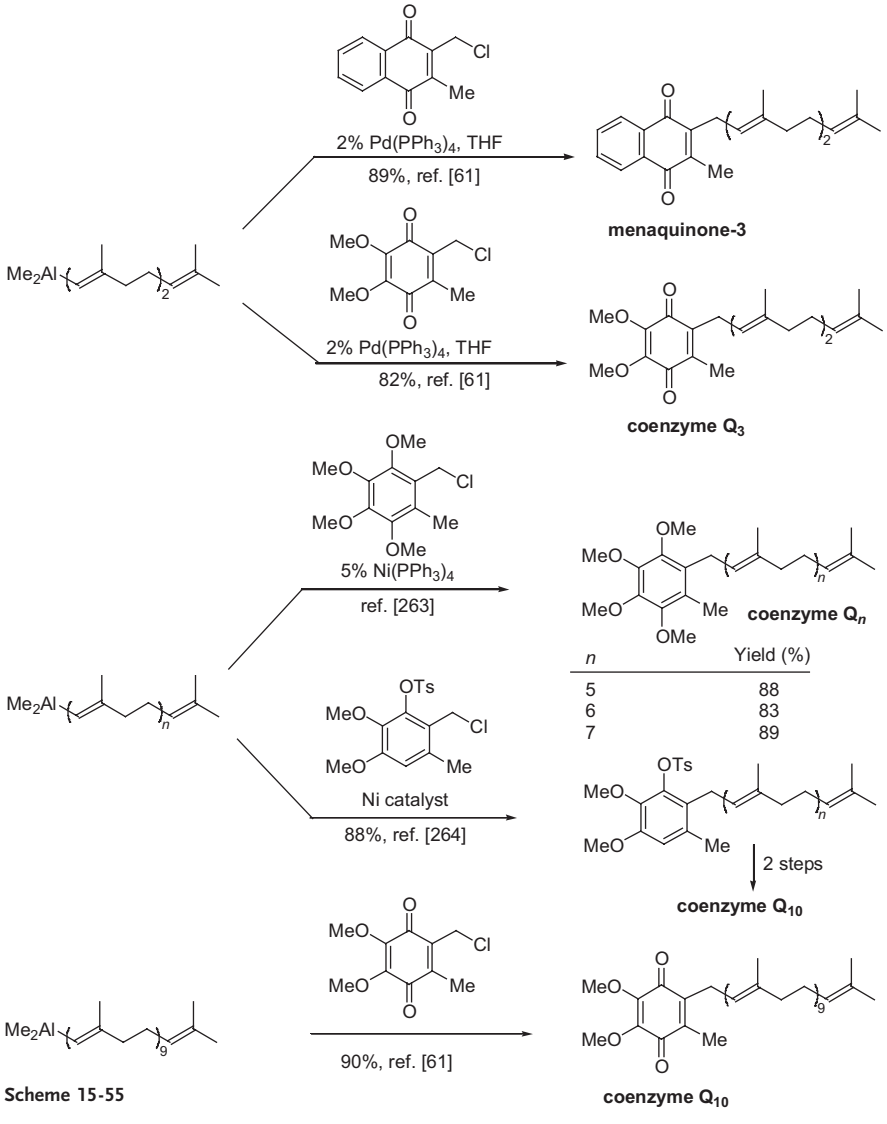


Catalyst	Yield (%)
$Cl_2Pd(PPh_3)_2$, DIBAH	86
$Ni(PPh_3)_4$	46

Alkenyl-benzyl coupling



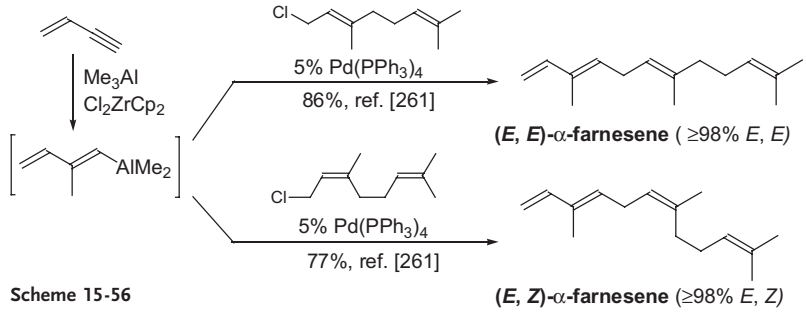
Scheme 15-54


2% Pd(PPh3)4, THF
89%, ref. [61]
menaquinone-3
2% Pd(PPh3)4, THF
82%, ref. [61]
coenzyme Q3
5% Ni(PPh3)4
ref. [263]
coenzyme Qn
n Yield (%)
5 88
6 83
7 89
Ni catalyst
88%, ref. [264]
2 steps
coenzyme Q10
90%, ref. [61]
coenzyme Q10

Scheme 15-55

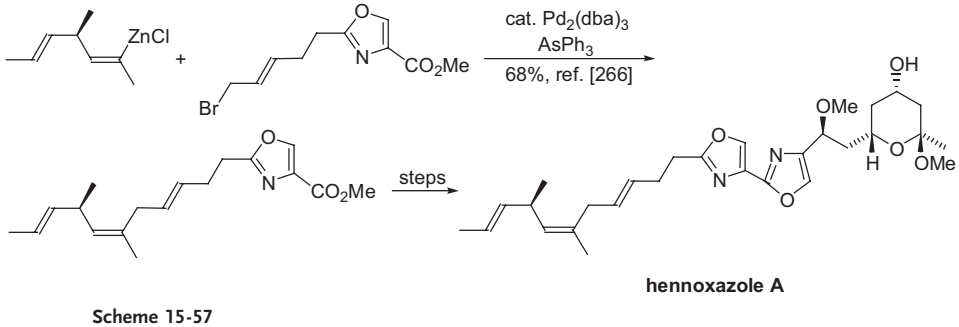
15.2.5.3 **Synthesis of 1,4-Dienes via Alkenyl-Allyl and Allyl-Alkenyl Couplings**

Alkenylmetals containing Zn, Al, or Zr can undergo Pd-catalyzed reactions with allyl electrophiles to give 1,4-dienes [62, 261, 265], while little is known about the Pd-catalyzed allyl-alkenyl coupling reaction of allylmetals containing Zn, Al, or Zr. Here again, possible catalyst poisoning may be suspected. One of the prototypical examples of alkenyl-allyl coupling is a highly selective one-step conversion of geranyl and neryl chlorides to (*E,E*)- and (*E,Z*)-*α*-farnesenes [261] (Scheme 15-56).



Scheme 15-56

In general, both regio- and stereochemistry can be almost fully retained in cases where *γ,γ*-disubstituted allylic electrophiles are used. In the corresponding reactions of *γ*-monosubstituted allylic electrophiles, the desired cross-coupling is usually accompanied by regio- and stereochemical scrambling to varying degrees [62]. Since the alkenyl-allyl coupling process is the only realistic Pd-catalyzed cross-coupling route to 1,4-dienes, optimization of various parameters in this reaction, especially ligands, additives, and solvents, might prove to be very fruitful. Even at the current level of perfection, the Pd-catalyzed reaction of an alkenylzinc chloride with a *γ*-monosubstituted allylic bromide has been successfully applied to the synthesis of some natural products, such as hennoxazole A [266] (Scheme 15-57). Further refinement of the Pd-catalyzed alkenyl-allyl coupling appears to be highly desirable.

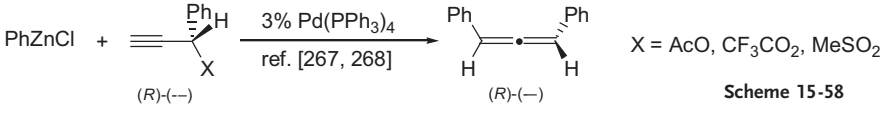


Scheme 15-57

15.2.5.4 Pd-Catalyzed Alkynyl-Benzyl, Benzyl-Alkynyl, Aryl-Propargyl, and Propargyl-Aryl Couplings

Until recently, little – if any – had been known about Pd-catalyzed alkynyl-benzyl and benzyl-alkynyl couplings. The Pd-catalyzed reaction of alkynylindiums with benzyl bromide reported in 1999 [32] (see Scheme 15-6) has provided a very promising method for Pd-catalyzed alkynyl-benzyl coupling. Earlier attempts by the authors' group with alkynylzincs, benzyl bromide, and $Pd(PPh_3)_4$ were met with disappointingly low product yields. However, a recent reinvestigation with the use of Cl_2Pd(DPEphos) has shown that the Pd-Zn procedure is not only highly satisfactory but is also superior to the Pd-In procedure, exhibiting a TON of about 8000 versus 3000 for In [193]. It should also be noted that, under the Sonogashira alkynylation conditions using 5 % $Pd(PPh_3)_4$ or $Cl_2Pd(PPh_3)_2$, 10 % CuI, and either Et_2NH or Cs_2CO_3, the corresponding alkynyl-benzyl coupling reaction did not produce the desired product in more than 8 % yield, the major byproduct being the alkyne homodimer [193]. It should also be pointed out that the preparation of alkynyl halides and related alkynyl electrophiles is almost always more involved and cumbersome than that of alkynylmetals. So, there does not appear to be any incentive for developing Pd-catalyzed benzyl-alkynyl coupling procedures.

The Pd-catalyzed reaction of PhZnCl with propargylic acetates and related electrophiles has produced Ph-substituted allenes, which proceeded with inversion at the propargylic carbon atom [267, 268] (Scheme 15-58). This reaction promises to provide a useful and selective route to stereodefined allenes. Little, if any, appears to be known about the Pd-catalyzed propargyl-aryl coupling.



Scheme 15-58

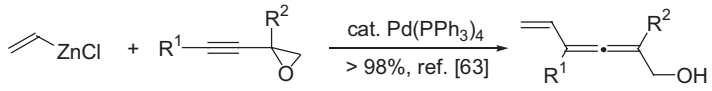
15.2.5.5 Pd-Catalyzed Alkynyl-Allyl, Allyl-Alkynyl, Alkenyl-Propargyl, and Propargyl-Alkenyl Couplings

These reactions can, in principle, lead to the formation of 1,4-enynes and/or conjugated enallenes. Although the currently available data are still rather scarce, the examples shown in Scheme 15-59 suggest that either enallenes or 1,4-enynes may be obtained selectively by using either propargylic electrophiles or propargylmetals, but it is premature to present any generalized statement based on the available data. Little, if any, appears to be known about Pd-catalyzed alkynyl-allyl and allyl-alkynyl couplings.

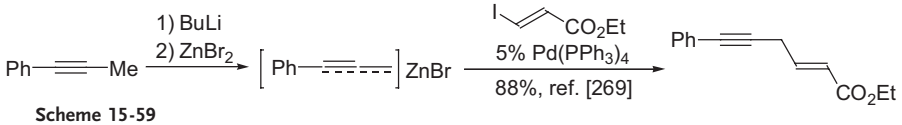
15.2.5.6 Pd-Catalyzed Alkynyl-Propargyl and Propargyl-Alkynyl Couplings

These reactions can, in principle, produce 1,4-diynes and/or allenynes. As indicated earlier in Scheme 15-8, the Pd-catalyzed alkynyl-propargyl and alkynyl-allenyl coupling reactions generally produce allenynes rather than 1,4-diynes [63]. The

Alkenyl-propargyl coupling

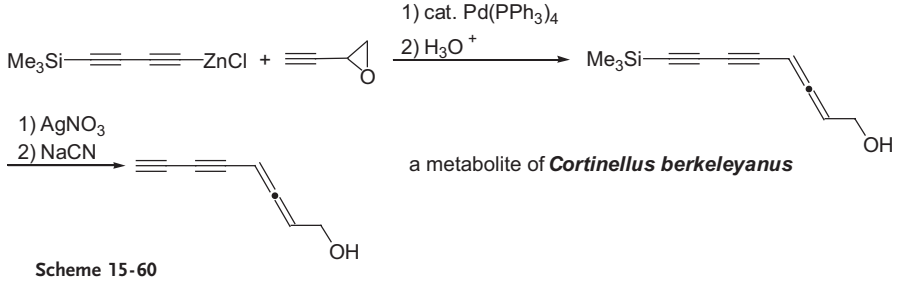


Propargyl-alkenyl coupling



Scheme 15-59

results shown in Scheme 15-8 also indicate that Mg, Zn, Cu, and Ag can produce the desired allenynes in excellent yields, but Zn is the most versatile with respect to leaving groups and most satisfactory. This reaction has been applied to the synthesis of 2,3-octadiene-5,7-diyn-1-ol, a metabolite from fungus *Cortinellus berkeleyanus* [63] (Scheme 15-60). There does not appear to be any reported example of the Pd-catalyzed propargyl-alkynyl coupling.



Scheme 15-60

15.2.5.7 Pd-Catalyzed Cross-Coupling Reactions Between a Benzyl-, Allyl-, or Propargylmetal and a Benzyl, Allyl, or Propargyl Electrophile

These reactions were exhaustively surveyed recently [91]. With the exception of the use of benzylzinc derivatives in benzyl-allyl and benzyl-benzyl coupling reactions [270], essentially all of the reported examples involve the use of allyltins and allenyltins that can be generated from propargylmetals. Most of the reactions are nonselective and/or low-yielding. Here again, virtual absence of the use of allyl- and propargylmetals containing Zn and other relatively electropositive metals might be linked with possible catalyst poisoning. In this context, it is important to notice that the desired products of these reactions are those that can be satisfactorily prepared with strict control of regio- and stereochemistry through the use of homoallyl-, homobenzyl-, and homopropargylmetals in conjunction with aryl and alkenyl electrophiles, as discussed in Section 15.2.4. However, the use of alkynyl halides in these reactions may not have been reported.

15.3
Summary and Conclusions

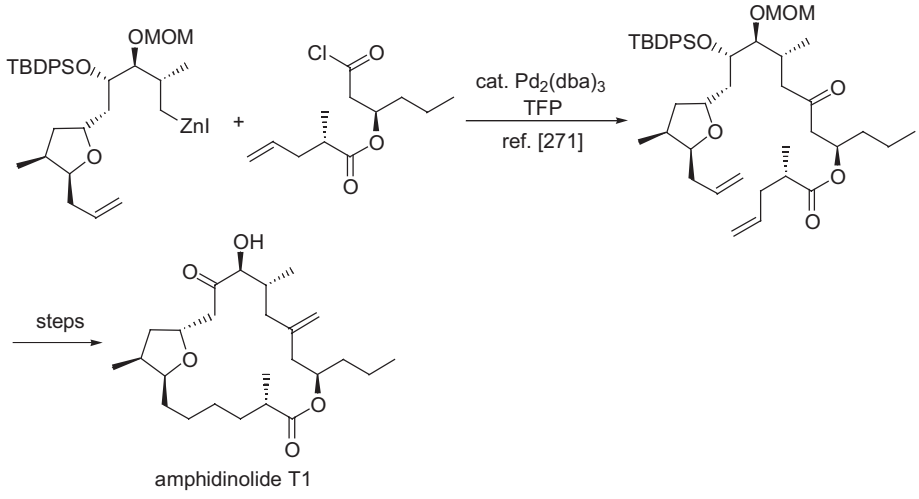
It was just a few years ago that Pd-catalyzed cross-coupling reactions were systematically and comprehensively discussed and summarized [4]. However, even before these surveys and reviews appeared in the market, it had already become abundantly clear that many of the chapters would have to be urgently updated and revised. This chapter has been written partially to fulfill this goal. In *Handbook of Organopalladium Chemistry for Organic Synthesis* [4], the overall scope of the Pd-catalyzed carbon-carbon cross-coupling was summarized as reproduced in Table 15-9. It indicates that most of all conceivable classes of the Pd-catalyzed cross-coupling reactions have been explored and well-developed with two notable exceptions, namely (1) those between an allyl-, benzyl-, or propargylmetal and an allyl, benzyl, or propargyl electrophile (Section 15.2.5), and (2) those involving the use of "ordinary" alkyl halides and related electrophiles. As discussed in Section 15.2.4, the latter may no longer be viewed as being categorically unfavorable.

In this chapter, Pd-catalyzed acylation [90], cyanation [95] and α-substitution of enolates [96] are not systematically discussed in order to keep this chapter within a reasonable length, and consequently some notable topics and examples may have been excluded. For example, the Pd-catalyzed acylation of organozincs [192] has been recognized as one of the most general and satisfactory methods of organometallic acylation reactions, which is compatible with many heterofunctional groups, as eloquently demonstrated by a recent synthesis of amphidinolides T1, T3, T4,

Table 15-9 Classification and current status of Pd-catalyzed cross-coupling reactions

R^1M \ R^2X	ArX						Alkyl X	RCOX
ArM	III.2.5 III.2.7	III.2.6 III.2.7	III.2.8(b)	III.2.9(a)				III.2.12.1
	III.2.6 III.2.7	III.2.6						
	III.2.8(a)							
	III.2.9(b)			III.2.10				
								
Alkyl M	III.2.11.1 and III.2.11.2							
N≡C−M	III.2.13.1(a)			III.2.13.1(b)				
—C=C—OH | |	III.2.14.1		V.2	III.2.14.1		V.2		

(a) The numbers in the frames indicate the pertinent sections. Bold-line frame: generally favorable and not highly demanding; broken-line frame: generally unfavorable; solid-line frame: others.
(b) Copied from *Handbook of Organopalladium Chemistry for Organic Synthesis* [4], p. 222.



Scheme 15-61

and T5 [271] (Scheme 15-61). For these topics known as of a few years ago, the reader is referred to the pertinent chapters in *Handbook of Organopalladium Chemistry for Organic Synthesis* cited above.

At present, there are approximately ten to a dozen protocols for Pd- or Ni-catalyzed cross-coupling reactions classified according to the metal countercations, and each appears to be capable of offering its own unique advantages. Even so, those involving the use of Zn and B may now be considered to be the two most versatile and satisfactory protocols with which the others are to be compared. Organotins have also been shown to be widely applicable. Moreover, they have displayed many unique features that cannot be readily matched by other organometals. In many cases where Sn competes with other metals, however, Sn has often been shown to be less satisfactory than Zn or B, and its toxicity is a major concern that should not be overlooked.

Another notable advantage that Zn offers is its ability to promote the Pd- or Ni-catalyzed cross-coupling reactions of other organometals containing Al, Zr, Cu, Sn and even B (see Scheme 15-26). With either stoichiometric or catalytic amounts of Zn, a wide variety of Pd-catalyzed cross-coupling reactions including aryl-aryl coupling (Section 15.2.1), alkenylation (Section 15.2.2), alkynylation (Section 15.2.3), alkylation (Section 15.2.4), as well as allylation, propargylation, and benzylation (Section 15.2.5) can now be satisfactorily performed.

In the meantime, efforts to search for additional superior metal countercations are being continued. Among main group metals, In has recently been identified as a very promising metal. Aside from some unique advantages, such as the *anti*-hydroindation-cross-coupling domino process [39] (Scheme 15-6), however, its straightforward cross-coupling reactions have not yet generated those kinds of results that urge its use in preference to Zn or B, especially in view of its relatively high cost. In this context, it is noteworthy that In has been shown to be distinctly

superior to Zn as a co-catalyst for promoting some hydrometallation-cross-coupling domino processes of Al and Zr [48] (Scheme 15-13). This promising lead is being pursued further. Although Si is intrinsically one of the least reactive metals, various procedures developed recently for promoting its Pd- or Ni-catalyzed cross-coupling have made it a respectable countercation component. Moreover, its usefulness may be predicted to increase with time. If its ability to serve as a key element in various protecting groups could be tightly coupled with superior cross-coupling processes, it would prove to be uniquely advantageous in such cases.

Among d-block transition metals as well as the group 3 metals and lanthanides, Mn seems promising in addition to Zr and Cu, the unique advantages of which have already been demonstrated and established. Clearly, additional studies with Mn that would demonstrate its superiority and/or unique advantages are desirable.

One question raised by synthetic chemists with increasing frequency is which protocol should be used for a given synthetic task. In this context, objective and wholesome comparison of various available protocols has become increasingly significant. Mere presentation of an assortment of ≥80–90 % product yields and/or differences in yield by 10 or even 20 % may no longer be considered as reliable bases for comparison. For this and other important reasons, TONs should be carefully determined, at least for some representative cases in addition to yield figures. After all, most – if not all – processes catalyzed by expensive transition-metal complexes should eventually be developed such that they display TON of 10^4–10^5 or higher, even though cross-coupling generating C-C bonds may well be collectively much more demanding than C-H and C-O bond formation in reduction and oxidation, respectively.

15.4
Representative Experimental Procedures

15.4.1
(3*E*,5*Z*,7*R*)-8-(*t*-Butyldiphenylsilyloxy)-5,7-dimethyl-1-trimethylsilyl-3,5-octadien-1-yne

(Scheme 15-22) [71].

To a mixture of (3*E*,5*Z*,7*R*)-5-bromo-8-(*t*-butyldiphenylsilyloxy)-7-methyl-1-trimethylsilyl-3,5-octadien-1-yne (526 mg, 1 mmol) and Cl_2Pd(DPEphos) (36 mg, 0.05 mmol) in THF (4 mL) was added Me_2Zn (1.0 mL, 2.0 *M* in toluene, 2 mmol) at 23 °C. The resultant mixture was stirred at room temperature and the reaction progress monitored by GLC analysis. After 20 h, the analysis indicated that the starting material had been completely consumed and that the title compound was formed in quantitative yield, with no indication of the formation of the configuration-retained *E*,*E* isomer or other byproducts in more than trace quantities. The reaction mixture was treated with aqueous NH_4Cl, extracted with ether (5 mL), washed with aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (silica gel, hexane:ethyl acetate, 99:1) afforded the title compound (419 mg, 91 %, stereoisomeric purity ≥97 %) as an oil.

15.4.2

(3*E*,5*E*,7*R*)-8-(*tert*-Butyldiphenylsilyloxy)-5,7-dimethyl-1-trimethylsilyl-3,5-octadien-1-yne (Scheme 15-22) [73].

To a mixture of (3*E*,5*Z*,7*R*)-5-bromo-8-(*tert*-butyldiphenylsilyloxy)-7-methyl-1-trimethylsilyl-3,5-octadien-1-yne (263 mg, 0.5 mmol) and $Pd(tBu_3P)_2$ (5.1 mg, 0.01 mmol) in THF (4 mL) was added Me_2Zn (0.25 mL, 2.0 *M* in toluene, 0.5 mmol) at 23 °C. The resultant mixture was stirred at 23 °C and the reaction progress monitored by GLC analysis. After 1 h, the analysis indicated that the starting material had been completely consumed, and that the title compound was formed in quantitative yield. The reaction mixture was treated with aqueous NH_4Cl, extracted with ether (5–10 mL), washed with aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (silica gel, hexane) afforded the title compound (438 mg, 95 %, stereoisomeric purity ≥98 %) as an oil.

15.4.3

Ethyl (*E*,*E*)-2-Methyl-2,4-heptadien-6-ynoate (9) (Scheme 15-37) [183].

(i) (*E*)-1-Bromo-4-trimethylsilyl-1-buten-3-yne

To a solution of (trimethylsilyl)acetylene (2.8 mL, 20 mmol) in THF (30 mL) was added via a syringe MeMgBr (8 mL of 3 *M* ethereal solution, 24 mmol). After the reaction mixture had been stirred at r. t. for 3 h, a solution of anhydrous $ZnBr_2$ (5.85 g, 26 mmol) in THF (10 mL) was added at 0 °C. The mixture was stirred at 0 °C for 30 min and added via a cannula to a solution of (*E*)-1-bromo-2-iodoethylene (5.12 g, 22 mmol) and $Pd(PPh_3)_4$ (0.46 g, 0.02 equiv.) in THF (15 mL). The resultant mixture was stirred at r. t. for 10 h, treated with aqueous NH_4Cl, and extracted with pentane. The pentane fraction was washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and distilled to afford 3.29 g (81 %) of the title compound of ≥98 % isomeric purity as a colorless liquid: b. p. 72–74 °C (15 mmHg).

(ii) Ethyl (*E*,*E*)-2-methyl-7-trimethylsilyl-2,4-heptadien-6-ynoate

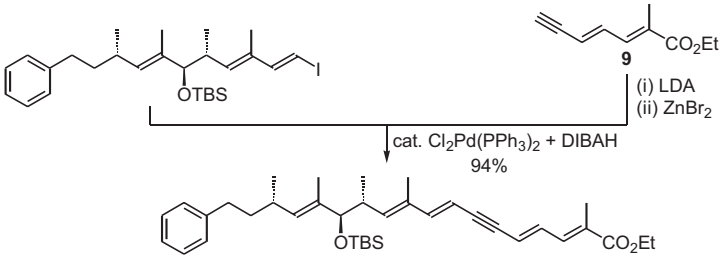
To a solution of (*E*)-1-bromo-4-trimethyl-1-buten-3-yne (487 mg, 2.4 mmol) in THF (3 mL) was added *t*BuLi (2.82 mL of 1.7 *M* solution in hexane, 4.8 mmol) at –78 °C. The solution was stirred for 1 h at –78 °C. To this was added via a cannula a solution of anhydrous $ZnBr_2$ (540 mg, 2.4 mmol) in THF (2 mL). The mixture thus obtained was stirred for 5 min at –78 °C, warmed to 0 °C over 25 min, and added via a cannula to a mixture of $PdCl_2(PPh_3)_2$ (70 mg, 0.1 mmol), DIBAH (0.2 mL, 1.0 *M* in hexane, 0.2 mmol), and ethyl (*E*)-3-bromo-2-methyl-2-propenoate (386 mg, 2 mmol) in THF (2 mL) at 0 °C. After stirring at 23 °C for 4 h, the reaction mixture was treated with water, extracted with ether, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (silica gel; pentane:EtOAc, 95:5) afforded 448 mg (95 %) of the title compound, which was ≥98 % (*E*,*E*), by ^{13}C- and ^{1}H-NMR analysis.

(iii) Ethyl (*E*,*E*)-2-methyl-2,4-heptadien-6-ynoate (**9**)

To a solution of ethyl (*E*,*E*)-2-methyl-7-trimethylsilyl-2,4-heptadien-6-ynoate (354 mg, 1.5 mmol) was added TBAF (1.7 mL, 1.0 *M* in THF, 1.7 mmol) at –78 °C. After 30 min, the flask was gradually warmed to 0 °C. After 30 min at 0 °C, the reaction mixture was quenched with water, extracted with ether (5 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (silica gel; pentane:EtOAc, 95:5) afforded 234 mg (95 %) of the title compound, which was ≥98 % (*E*,*E*), by ^{13}C- and ^{1}H-NMR analysis.

15.4.3

Ethyl (2*E*,4*E*,8*E*,10*E*,12*R*,13*R*,14*E*,16*S*)-13-(*tert*-Butyldimethylsilyloxy)-2,10,12,14,16-pentamethyl-18-phenyl-octadeca-2,4,8,10,14-pentaen-6-ynoate (Scheme 15-37) [198].



To iPr_2NH (53 µL, 39 mg, 0.38 mmol) in THF (2 mL) cooled to –78 °C was added *n*BuLi (0.15 mL, 2.5 *M* in hexane, 0.38 mmol). The resultant solution was stirred at –78 °C for 20 min and added dropwise via a cannula to a solution of ethyl (*E*,*E*)-2-methyl-2,4-heptadien-6-ynoate (63 mg, 0.38 mmol) in THF (1 mL) at –78 °C. After the reaction mixture had been stirred at –78 °C for 20 min, anhydrous $ZnBr_2$ (87 mg, 0.38 mmol) in THF (1 mL) was added. The mixture thus obtained was stirred at –78 °C for 5 min, warmed to 0 °C over 10 min, and added via a cannula to (1*E*,3*E*,5*R*,6*R*,7*E*,9*S*)-6-(*tert*-butyldimethylsilyloxy)-1-iodo-11-phenyl-3,5,7,9-tetramethyl-undeca-1,3,7-triene (174 mg, 0.32 mmol) in THF (1 mL) premixed with a solution of $Pd(PPh_3)Cl_2$ (11 mg, 0.016 mmol) and DIBAH (0.032 mL, 1.0 *M* in hexane, 0.032 mmol) in THF (1 mL). The resultant mixture was stirred at 23 °C for 3 h, quenched with aqueous NH_4Cl, filtered through Celite, washed, and extracted with ether (5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (silica gel; ethyl acetate:hexane, 1:99) afforded the title compound (175 mg, 94 %) as a colorless oil. ^{13}C- and ^{1}H-NMR spectra indicated that the product was ≥98 % isomerically pure.

15.4.4
Menaquinone-3 (Scheme 15-55) [61]

To a solution of Me_3Al (0.17 g, 2.4 mmol) and Cl_2ZrCp_2 (0.15 g, 0.5 mmol) in 1,2-dichloroethane (2 mL) was added at 23 °C (6*E*)-6,10-dimethyl-5,9-undecadien-1-yne (211 mg, 1.2 mmol). The reaction mixture was stirred for 4 h at 23 °C. To this reaction mixture were successively added at 0 °C THF (10 mL), 2-chloromethyl-3-methyl-[1,4]-naphthoquinone (0.22 g, 1 mmol), and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol). The reaction mixture was stirred for 1 h at 23 °C, diluted with ether, quenched with 1 *M* HCl, and extracted with Et_2O (10 mL). The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. Flash column chromatography (hexane:ethyl acetate, 10:1) afforded 0.335 g (89 %) of the title compound as a yellow oil. ^{13}C-NMR analysis indicated the compound was of ≥98 % stereoisomeric purity.

15.4.5
(*E*)-4-Methyl-3-decen-2-one [192]

To 2.52 g (10 mmol) of the (*E*)-2-methyl-1-octenyl iodide (≥99 % *E*) in 10 mL of diethyl ether were added sequentially *n*BuLi (4.8 ml of 2.3 *M* solution in hexane, –78 °C) and anhydrous $ZnCl_2$ (1.5 g, 11 mmol, –78 °C to 0 °C) in THF. After removal of the solvents at reduced pressure, THF (10 mL), AcCl (0.94 g, 12 mmol), and a mixture of $Cl_2Pd(PPh_3)_2$ (0.08 g, 0.1 mmol) and *i*Bu_2AlH (0.04 mL, 0.2 mmol) in 4 mL of benzene were added at 0 °C, and the reaction mixture was stirred for 30 min at 0 °C. Acidification (3 *M* HCl), extraction (hexane; 20–30 mL), washing (aq. $NaHCO_3$), drying ($MgSO_4$), and distillation provided 1.30 g (77 %) of (*E*)-4-methyl-3-decen-2-one (*E*/*Z* = 99/1): b. p. 55–57 °C (0.5 mmHg).

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