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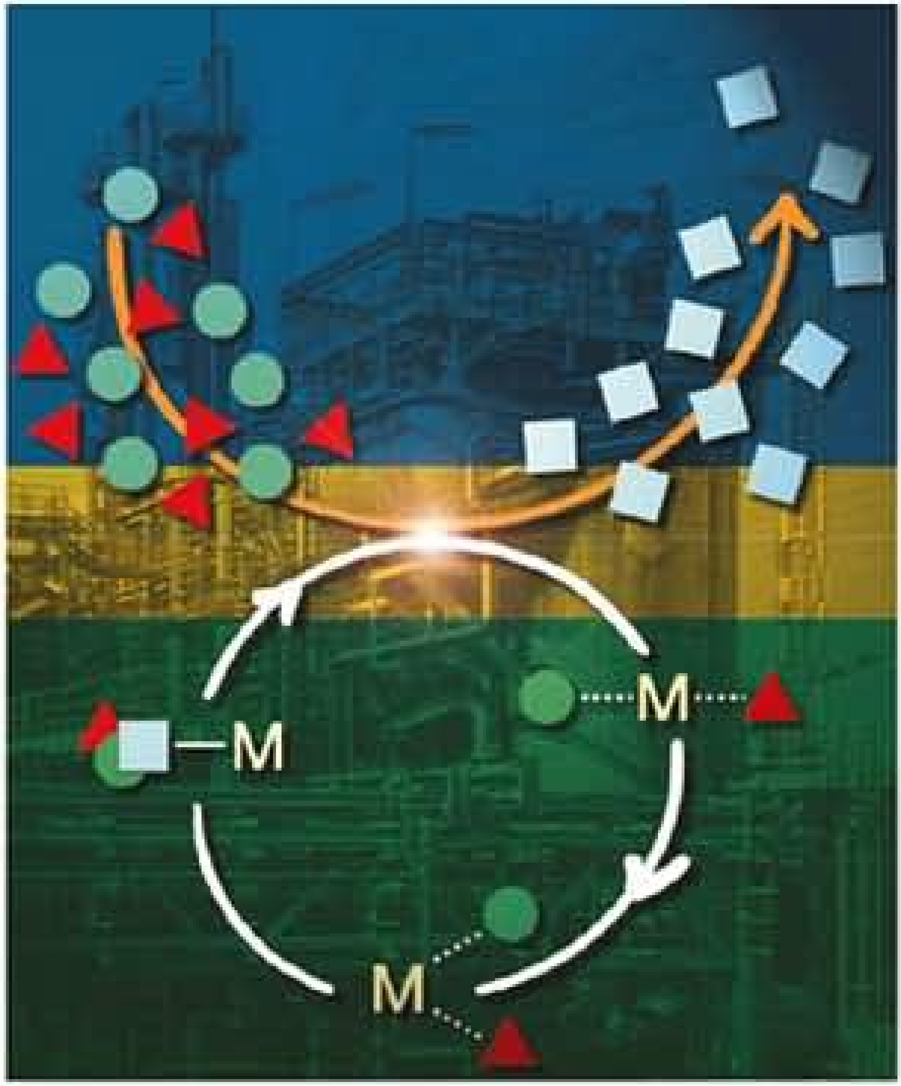

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Preface

This book describes for the first time all homogeneously catalyzed reactions in *multiphase* operation. Thus it summarizes the progress which became possible by the introduction of separate phases in the context of "homogeneous" catalysis: an apparent contradiction with far-reaching consequences. The book reviews all the realistic possibilities described so far using multiphase operation of homogeneous catalysis: processes with organic/organic, organic/aqueous, or "fluorous" solvent pairs (solvent combinations), nonaqueous ionic solvents, supercritical fluids, and systems with soluble polymers. The accounts concentrate on the modification and the handling of homogeneous catalysts under multiphase conditions in general, and the removal and subsequent recycling of the catalyst in particular.

Why multiphase systems? This goes back to the 1980s and the enormous impetus which was given to the homogeneous catalysis community by the first realization of Ruhrchemie/Rhône-Poulenc's aqueous-phase oxo process at the Oberhausen plant site. Astonishingly, this fact (and *not* the earlier SHOP process of Shell) sensitized the scene to the possibilities of multiphase action to imitate the decisive advantage of heterogeneous catalysis: the immediate separation of catalyst and substrates/products just after reaction which makes it possible to avoid additional separation steps post-reaction, such as distillations and other thermally stressing procedures.

All proposals have the same target: to enable the homogeneous catalyst to be bound to a suitable "support", i.e., another phase, without losing its superior homogeneous catalytic activity and selectivity. Within the scope of this book the editors define "phase" not only thermodynamically (as uniform states of matter of *one* substance which are separated (and separable) from each other by unequivocal phase boundaries; for example, water–ice or normal–supercritical states) but also as *different* states of aggregation of different compounds, such as systems consisting of water–organic liquids. Thus this book deals with the various possibilities of homogeneous catalysts on *liquid* supports. Additionally, the processes described imply two- or three-phase reactions.

The status of the different variants of multiphase homogeneous catalysis is described with the state-of-the-art as at the end of 2004.

The editors, as well-known players in their respective fields of homogeneous and homogeneously multiphase catalysis, have tried to portray the scene from the basic idea through the development stage up to commercial applications and the

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processes which are on the track to economical realization. Within the definitions as given in the introductory Chapter 1, the contents of the individual sections are the responsibility of the respective editor. Some contradictory statements within the various chapters of the book may arise from the fact that the authors started from very differing experiences and used different focal points to emphasize the importance of “their” multiphasic approach. All sections give outlooks about the developments to come.

Once more, we have to express our thanks not only to the authors and co-authors but also to the team at Wiley-VCH at Weinheim, especially Claudia Grössl and Melanie Rohn for the production and Elke Maase, the publishing editor. Diana Boatman from Redhill, Surrey (UK), served as freelance copy-editor and was an invaluable help for all of us who write in English, but not as our first language, during the difficult process of completion.

August 2005

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Multiphase Homogeneous Catalysis
Edited by Boy Cornils and Wolfgang A. Herrmann et al.

1
Introduction

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Stefan Mecking, Hélène Olivier-Bourbigou, and Dieter Vogt (Eds.)*

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1
Introduction

Boy Cornils, Wolfgang A. Herrmann, István T. Horváth, Walter Leitner,
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> "Sipping a cup of decaffeinated coffee the reader may wonder on the somewhat unusual classification of solvents as 'alternative': alternatives to what? And why would we need alternative media for doing chemistry or for any other purpose? These may be the first questions for those who are just starting to discover the existing new developments on using solvents other than volatile and often toxic organics for synthesis and especially for catalytic reactions. Yes, indeed, …" [1].

Yes, indeed, similarly to an opening cornucopia, the arsenal of methods and techniques in homogeneous catalysis has offered remarkable progress in recent years. Above all, these improvements concentrate on the modification and the handling of homogeneous catalysts in general and the removal and subsequent recycling of catalysts in particular. The progress to be dealt with in this book has been rendered essentially possible by the introduction of separate phases in the context of "homogeneous" catalysis: an apparent contradiction with far-reaching consequences. For the first time, this book reviews all the realistic possibilities described so far using multiphase operation of homogeneous catalysis: processes with organic/organic, organic/aqueous, or "fluorous" solvent pairs (solvent combinations), nonaqueous ionic solvents, supercritical fluids, and systems with soluble polymers. In Figure 1, the family tree of homogeneous catalysis proves that this recent research extends considerably the scope of the work.

Following the logic of this tree, the multiphase processes on the left-hand side belong among the operations with "immobilized catalysts" but on "liquid supports". The topics of this book are the processes with the liquid supports water, supercritical fluids, ionic liquids, organic liquids, soluble polymers, and fluorous liquids; among these, only two processes (Ruhrchemie/Rhône-Poulenc and Shell SHOP) are operative industrially so far. The more important "leaves" of the family tree are shaded in gray.

In Figure 2, demonstrating the genesis of homogeneous and heterogeneous catalysis, the topical processes are on the borderline between heterogeneous and homogeneous catalysis (and catalysts).

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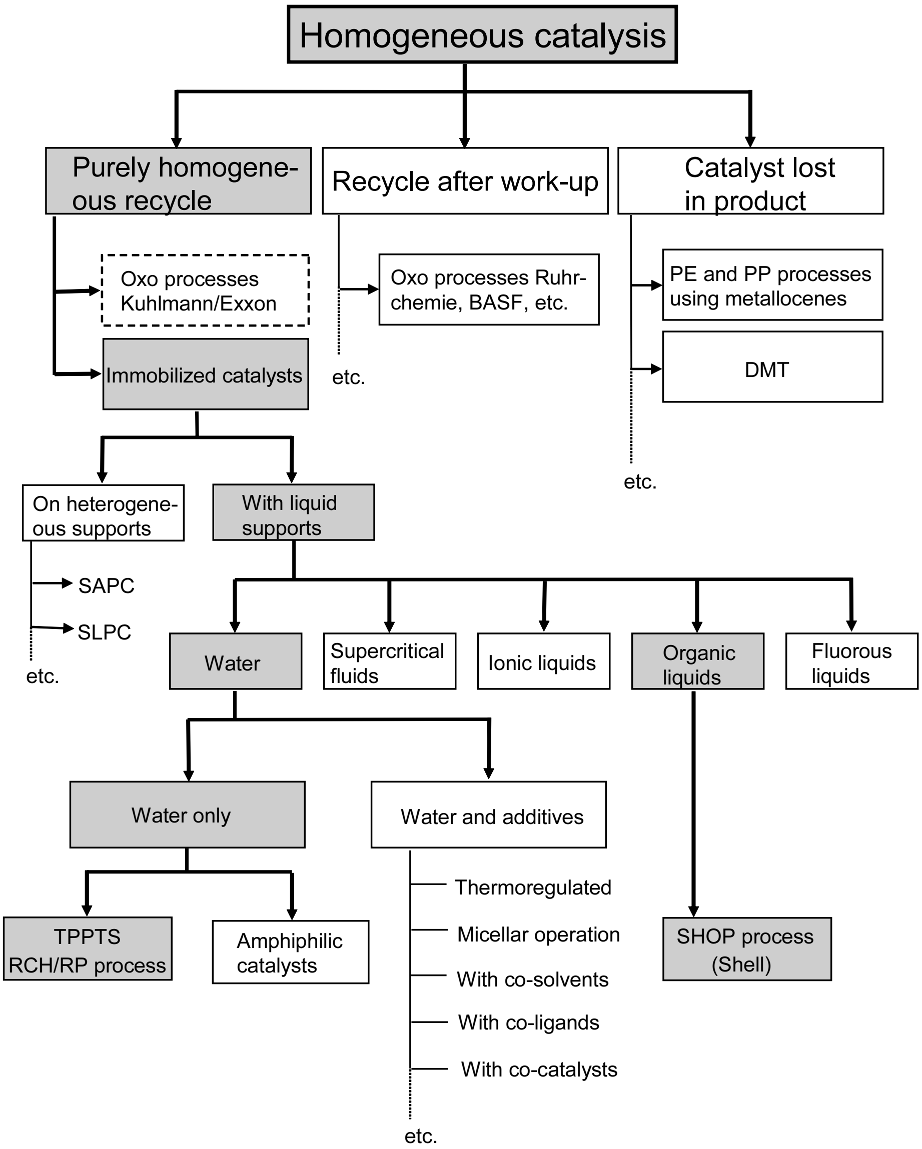

Figure 1 Family tree of homogeneous catalysis.

Why multiphase systems? This goes back to the 1980s and the enormous impetus which was given to the homogeneous catalysis community by the first realization of Ruhrchemie/Rhône-Poulenc's oxo process at the Oberhausen plant site. Astonishingly, it was this development (and *not* the earlier SHOP process of Shell) that sensitized the scene to the possibilities of multiphase action: only on the basis of the "aqueous" activities that so much widespread and multi-faceted research work, with effects on the newer areas mentioned has been accomplished success-

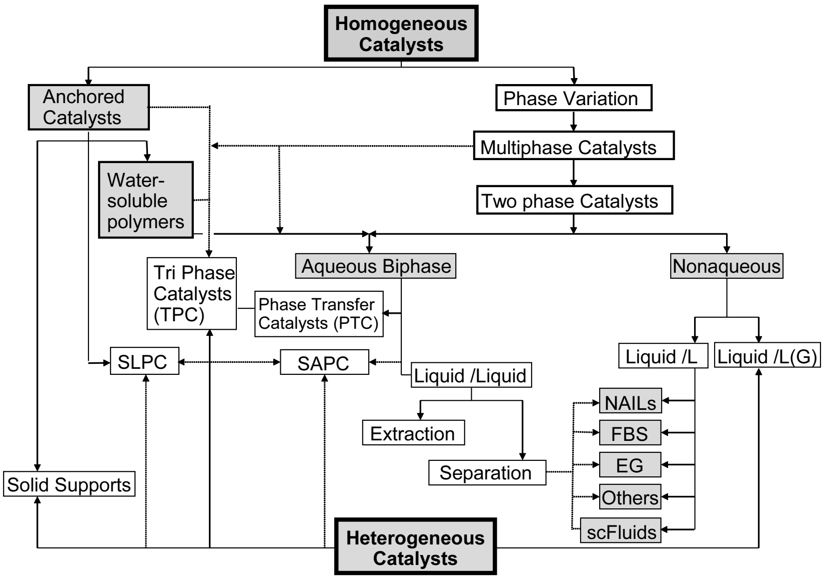

Figure 2 Genesis of homogeneous and heterogeneous catalysis.

fully. There was earlier work and proposals [2] to imitate the decisive advantage of heterogeneous catalysis: the immediate separation of catalyst and substrates/products just after reaction which makes it possible to avoid additional separation steps post-reaction, such as distillations and other thermally stressing procedures. All proposals have the same target: to enable the homogeneous catalyst to be bound to a suitable “support”, i.e., another phase, without losing its superior homogeneous catalytic activity and selectivity. Within the scope of this book the editors define “phases” not only thermodynamically (as uniform states of matter of *one* substance which are separated (and separable) from each other by unequivocal phase boundaries; for example, water–ice or normal–supercritical states) but also as *different* states of aggregation of different compounds, such as systems consisting of water–organic liquids. Thus this book deals with homogeneous catalysts on *liquid* supports. Additionally, the processes described imply two- or three-phase reactions (the latter is the case if gaseous reactants complete the reaction scheme, e.g., hydrogen in hydrogenations or syngas in hydroformylations).

The use of liquids in homogeneous catalysis thus means not only a liquid support and from there a basic intervention in the handling and the operation of the catalyst, but also a modern separation technique for efficient work-up in organic synthesis [3]. Figure 3 illustrates the enormous importance of the biphasic technique for homogeneous catalysis: the catalyst solution is charged into the reactor together with the reactants A and B, which react to form the solvent-dissolved reaction products C and D. The products C and D have different polarities than the catalyst solution and are therefore simple to separate from the catalyst phase (which may be recycled in a suitable manner into the reactor) in the downstream phase separation unit.

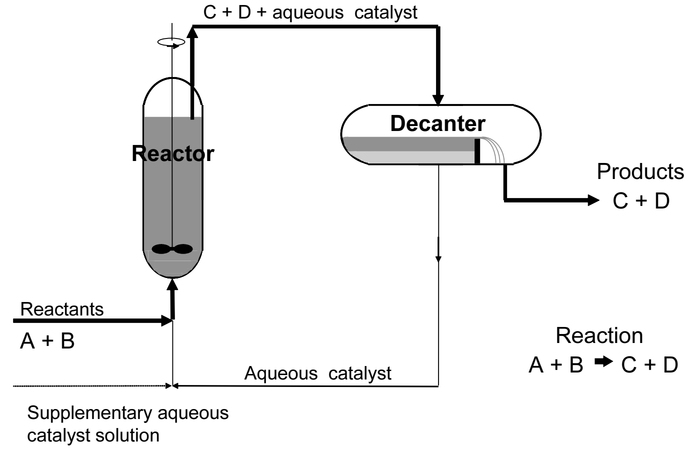

Figure 3 Principle of two-phase catalysis illustrated for the aqueous-phase reaction A + B → C + D (cf. also Chapter 2).

This double meaning of the multiphasic approach is specially visible in the case of fluorous liquids, where organic chemists are at least as interested as the catalytic community in the use of these fluids.

The ability of different combinations of solvent pairs to enable biphasic operation can be estimated on the one hand according to the principle of "like dissolves like" (*"similia similibis solvuntur"*, as the old alchymists used to say) in respect to the solvent for the catalyst and, on the other hand, with the help of diagrams as shown in Figure 4 [4] and of fundamental investigations.

The fundamentals of miscibility (solvation power, E_T^N) of various solvents from nonpolar, aprotic tetramethylsilane (TMS; with $E_T^N = 0$ as defined) to polar water ($E_T^N = 1$) are given by the solvent polarity scale in Figure 5 [5].

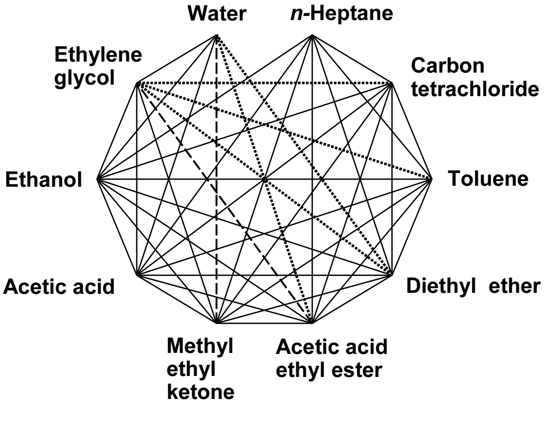

Figure 4 Miscibility of organic solvents: —— miscible in all proportions; – – – limited miscibility; ····· little miscibility; no line: immiscible.

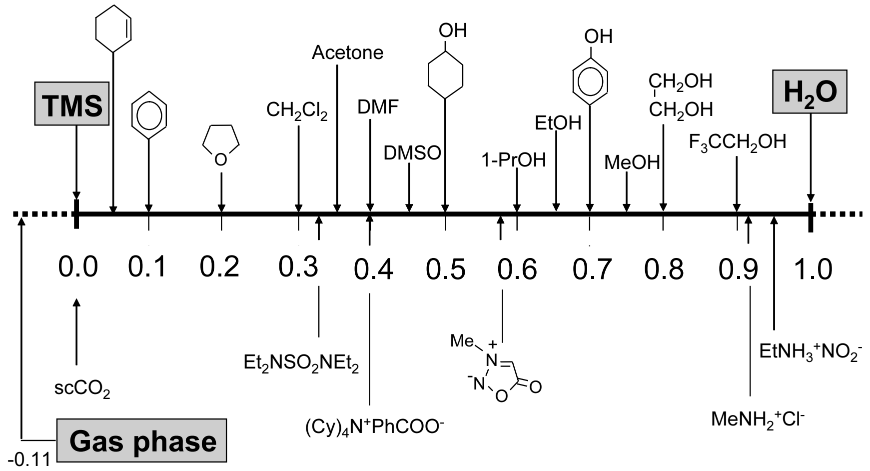

Figure 5 Empirical polarity values E_T^N.

This graph gives a selection of 14 (out of approximately 360) of the usual solvents above the baseline and seven more exotic solvents (supercritical CO_2 and ionic liquids included) below. The 14 compounds, from left to the right with increasing solvent polarity, include apolar, aprotic (such as TMS, cyclohexene, or benzene), bipolar (such as acetone or DMF), and eventually bipolar, protic solvents (cyclohexanol, ethanol, phenol). Using the E_T^N values, numerous solvent-dependent processes may be correlated with each other. Other measures that can be used for the estimation of miscibility/solvent power are the cohesive pressures, solubility parameters, dispersive forces, Kamlet–Taft parameters, etc. [6a,b]. Solvent combinations of exotic members and systems with more than two members are known and have been recommended, but their application has been concentrated in the lab because of economic disdavantages with their handling and recyclability/separability [6b–e].

A recent proposal concerns mixed organic–aqueous tunable solvents (OATS) such as dimethyl ether–water, the solubility of which for substrates can be influenced by a third component such as carbon dioxide. CO_2 acts as a “antisolvent” and as a switch to cause a phase separation and to decant the phases from each other (preferably under pressure). This behavior makes the operation of bi- or multiphase homogeneous catalytic processes easier and more economic: the preferential dissolution at modest pressure of carbon dioxide causes phase separation which results in large distribution coefficients of target molecules in biphasic organic–aqueous systems. This extraordinary behavior lead to a sophisticated flow scheme (Figure 6) [7].

This operation, which needs at least two internal recycles, may be economic for special purposes (e.g., highly prized applications) such as enzyme–catalyst conversions. Indeed, it has been tested for the ADH-catalyzed reduction of hydrophobic ketones coupled with regeneration of the cofactor NADH. Another possibility discussed recently is the use of surface polarity-modified (heterogeneous) catalysts and their distribution between two immiscible solvents which occurs against gravity [8].

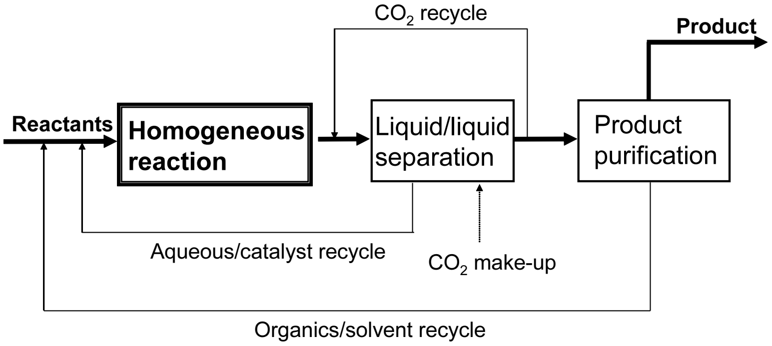

Figure 6 Schematic of the OATS procedure with a CO_2 switch for catalyst recycle.

It might be added that the multiphase operation offers more than the decisive separation between desired products and catalyst, although there are differences between the various multiphase liquids [9]. It cannot be emphasized enough that the use of polar multiphase liquids also separate the byproduct "heavy ends" from the catalyst in the system, thus avoiding a build-up in the catalyst recycle. In other processes (and probably also if very apolar fluorous liquids are used) an additional purge is needed to remove the high boilers from the catalyst, which then requires a further (and costly) separation or purification [10].

It is also worth mentioning that the multiphase approach has been used as a strategy to avoid undesired consecutive reactions [11a–c] or even to segregate two different and incompatible catalysts in one-pot or in tandem syntheses. In a typical example, Chaudhari et al. described the combination of a hydroformylation step – catalyzed by phosphine-modified rhodium complexes – with the Mannich reaction of the oxo aldehydes formed, catalyzed by tertiary amines. Thus the manufacture of methacrolein according to Figure 7 proceeds best in two different phases: the organic phase for hydroformylation and the aqueous phase in which the Mannich reaction is achieved (Figure 8) [11d].

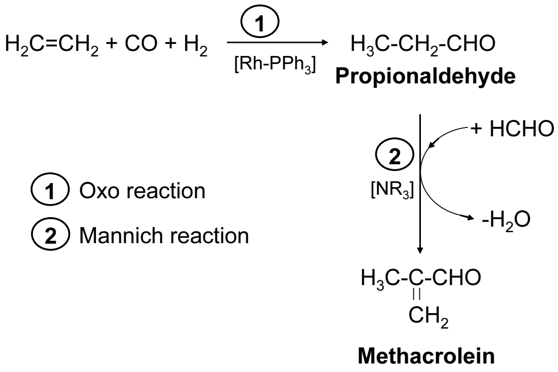

Figure 7 Overall reaction in two phases.

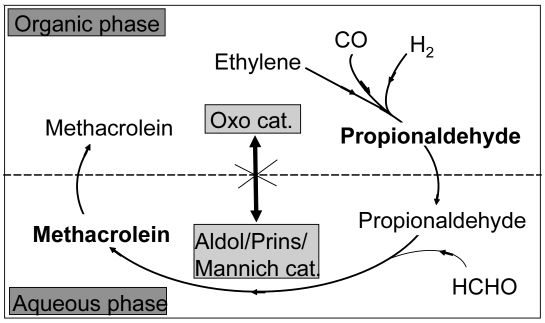

Figure 8 Tandem two-phase catalysis with incompatible catalysts.

Our definitions of phases or multiphases, respectively, include interfacial events, but it must be emphasized that the engineer's definition of "interphases" or "interfacial engineering" concentrates more on solid–solid phase boundaries such as in the manufacture of chips, photographic films, polymer composites, advanced ceramics, etc. [12], or on processes with heterogeneous catalysts and other phases [13]. Last, but not least, the possibility of placing the emphasis on "greener" techniques and thus so-called "sustainable" operations [14] may be mentioned in passing.

Although they also are "biphasic", this book does not include immobilized, modified homogeneous catalysts on *solid* supports ("anchored catalysts" [15]). There is little mileage in looking for ostensibly more and more effective ligands and better and better optimization of the solid support and/or catalyst precursor to ensure, on the one hand, adequate immobilization on the support (sufficient stability of the covalent bond between the support matrix and the central atom) and, on the other, adequate mobility for the catalytically active catalyst constituents (sufficient lability of the modified ligand sphere). All the results so far allow only the conclusion that with the heterogenizing techniques used significant problems remain to be solved. The reason for this is that the various catalyst species undergo changes in spatial configuration as they pass through the catalytic cycle typical of a homogeneous process.

The constant "mechanical" stress on the catalyst's central atom↔ligand bonds and the constant change in the bond angles and lengths ultimately lead also to a weakening of the central atom↔support bond. In hundreds of publications this is conveniently demonstrated using the hydroformylation reaction catalyzed by heterogenized cobalt or rhodium carbonyls as an example. The catalyst passes through the two forms of a trigonal-bipyramidal and a tetrahedral metal carbonyl, which overstresses and weakens the heterogenizing bond between the metal and the support – ending up with a considerable "leaching" of the catalysts's active components. This leaching always affects not only the usually costly central atoms but also the (frequently more costly) ligands of homogeneous metal complex catalysts. Therefore, it might be no coincidence that – apart from lab or pilot plant work [18] and apart from enzymatic techniques – no homogeneously catalyzed reaction attained large-scale, commercial status. Processes including the reaction in biphasic operation but on heterogeneous catalysts (as, for example, in [16]) are also not included.

According to our definition, homogeneous catalysis includes catalysts which, inter alia,

- are molecularly dispersed "in the same phase" or between two suitable phases (see above),
- are unequivocally characterized chemically and spectroscopically and can be synthesized and manufactured in a simple and reproducible manner,
- can be tailor-made for special purposes according to known and acknowledged principles and based upon a rational design, and
- permit unequivocal reaction kinetics related to each reactant catalyst molecule, in general each metal ion [17].

These definitions allow the well-known compilation of the advantages/disadvantages of both catalytic regimes (Table 1).

Entry 7 of Table 1 is the reason for the application of the idea to use multiphase techniques, probably first articulated and systematized by Manassen [19] and Joó [20]. In 1972, Manassen suggested

> "... the use of two immiscible liquid phases, one containing the catalyst and the other containing the substrate ..."

and hence the general form of biphase catalysis, which constitutes a logical development of the work in "molten salt media" (further developed and known today as "ionic liquids"; this term used to refer to high-melting, inorganic or organic/inorganic salts or salt mixtures [21]; cf. Chapter 5). The inventors of Shell's SHOP

Table 1 Homogeneous versus heterogeneous catalysis.

		Homogeneous catalysis	***Heterogeneous catalysis***
1	Activity	high	variable
2	Selectivity	high	Variable
3	Reaction conditions	mild	harsh
4	Service life of catalysts	variable	extended
5	Sensitivity against catalyst poisons	low	high
6	Diffusion/mass transfer problems	low	important
7	Catalyst recycling[a)]	expensive	not necessary
8	Variability of electronic and steric properties of catalysts	possible	not possible
9	Mechanistic understanding	plausible under random conditions	extremely complex

a) *Catalyst recycling* has to be distinguished from *catalyst (or catalytic) cycle*. While the first-mentioned describes the way in which a catalyst is formed, employed, separated or deposited, made up, and regenerated or recovered, the "catalytic cycle" is the visual interpretation of a complex reaction mechanism by subdividing the overall reaction into a series of ad- and desorption steps (with heterogeneous catalysts) or arranging the intermediates of a homogeneously catalyzed reaction in a logical sequence to form a closed cycle [18].

process, who had already worked on soluble, homogeneous complex catalysts in a biphase system some years earlier [22], cited the special method without particular emphasis. Some years later, Joó concentrated on hydrogenations and Kuntz [23] published his work on aqueous-phase hydroformylation, i.e., reactions of commercial interest. Other historical roots may be found in [24].

Looking back, it must be stated that Manassen and Beck/Joó's ideas were developed independently of each other. Remarkably, the fundamental papers of Joó and Kuntz created little interest and only found a wider echo in academic research once Shell and Ruhrchemie had managed to achieve industrial scale-up of their biphase catalyses in organic/organic or in aqueous systems. In a drastic departure from the normal pattern, here basic research lagged considerably behind industrial research and application [25]. This has changed with the introduction of other liquid phases such as ionic liquids (as defined today), supercritical liquids, polymeric fluids, and fluorous liquids.

As a last definition the book concentrates on *organometallic* catalysts as one of the bases of homogeneous catalysis, although the introduction of strange additives like water and other immiscible ingredients such as other organic liquids, carbon dioxide, nonaqueous ionic liquids, solvent-miscible polymers, or even perfluorinated compounds was originally regarded as disturbing if not poisoning. So Cintas wrote in respect of the “additive” water [26]:

> “At first, the idea of performing organometallic reactions in water might seem ridiculous, since it goes against the traditional belief that most organometallics are extremely sensitive to traces of air and moisture and rapidly decompose in water”.

Other statements voice people's doubts about the same fact [27]. Acid–base catalysts, the other well developed category of homogeneous catalysts, are mentioned when their action is typical or decisive for the demonstration of the respective multiphase action.

Besides one book summarizing *Chemistry in Alternative Reaction Media* [6a], which concentrates more on physical aspects rather than applications, the above-mentioned multiphase media have so far been dealt with only in monographs such as

- *Aqueous-Phase Organometallic Catalysis* [24, 26],
- *Applied Homogeneous Catalysis with Organometallic Compounds* [17],
- *Handbook of Fluorous Chemistry* [28],
- *Ionic Liquids in Synthesis* [29],
- *Chemical Syntheses Using Supercritical Fluids* [30],
- *Emulsion Polymerization and Emulsion Polymers* [31].

Except for transitions from heterogeneous to homogeneous catalysis, there is also common ground for the various methodologies described here: the application of $scCO_2$ is described in the presence of ionic liquids [32a] or of fluorous solvents [32b,c] as well in aqueous operation [33a–d]; and aerobic epoxidations have been attained in fluorous biphasic systems using ionic liquids [33e]. On the other hand, ionic liquids [34] or fluorous solvents [35a,c] have been used together with aqueous operations; and water-soluble polymers are the focal point of the application of

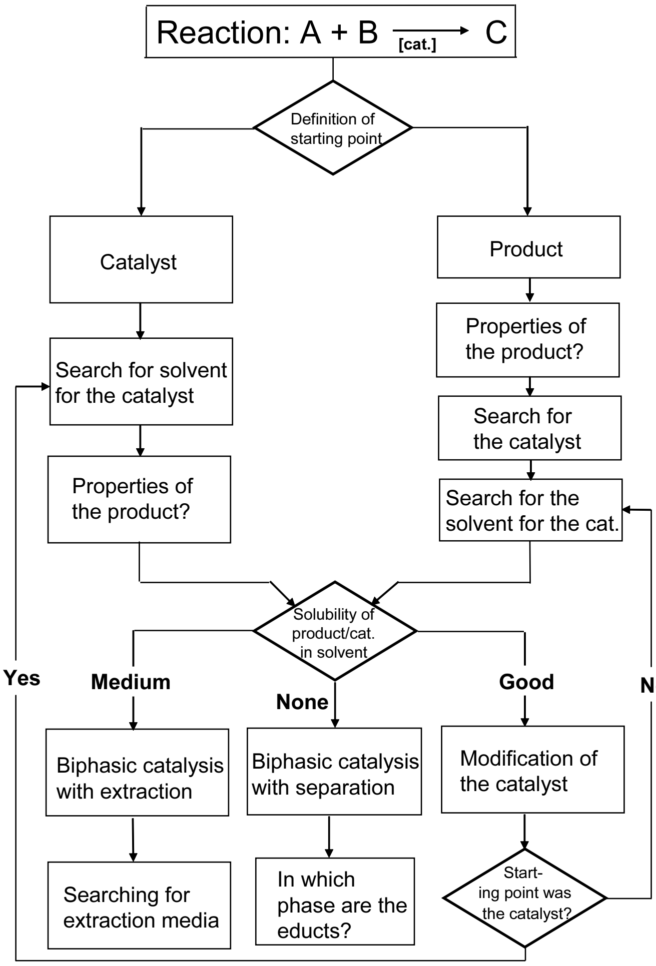

Figure 9 Decision-making for multiphase reactions in respect to the adjustment of their properties as far as catalyst, phase, and solvent are concerned.

polymers in homogeneous catalysis (see Chapter 7). Some of these hybrid systems are described in more detail, for instance in Sections 5.2.1.1 or 5.2.1.2. Membrane techniques, as described for aqueous applications in Chapter 2, may be applied to all other techniques where solvent-resistant membranes can be developed [35b,c] (Section 2.3.3). This is of decisive importance for the use of soluble, polymer-supported catalysts (cf. Chapter 7). Keeping in mind the intentions which underlie the use of nonmiscible solvents, as a paradox the development of supported ionic liquids may be mentioned [36].

Considering the transferability of conventional chemical processes to a multiphase technology, Behr [37] made proposals for a formal decision-making process on whether, and how, this transition could be achieved (Figure 9).

There are some examples of industrial applications of aqueous-phase homogeneous catalysis which will be described in Section 2.5.

The other process based on Manassen/Joò's ideas of liquid supports [19, 20] goes back to Keim's developments of *organic–organic biphase systems* for the Ni-catalyzed conversion of olefins to medium- and long-chain alpha- and internal olefins [38] by a combination of various process steps, among them oligomerization, metathesis, and isomerization. This is described in Chapter 3.

Based on Ziegler's work at the MPI für Kohlenforschung in Mülheim/Germany, Wilke and co-workers learned how to control the selectivity of nickel-catalyzed reaction by use of ligands. Keim, then at Shell at Emeryville, introduced P–O chelate ligands and carried out the basic research for the oligomerization process. The whole process was developed in a collaboration between Shell Development in the US and the Royal Shell Labs in Amsterdam/The Netherlands. Today there are two locations producing nearly 1 MMt of α-olefins per year.

Within the scope of this book, the first step of the organic–organic biphasic oligomerization is of interest. This process step is carried out in a polar solvent in which the nickel catalyst is dissolved but the nonpolar products – the α-alkenes – are almost insoluble. Preferred solvents are alkanediols, especially 1,4-butanediol (BDO). The nickel catalyst is prepared in situ from a nickel salt by reduction with $NaBH_4$ in BDO in presence of an alkali hydroxide, ethylene, and a chelating P–O ligand such as *ortho*-diphenylphosphinobenzoic acid.

The oligomerization is carried out in a series of reactors at 80–140 °C and pressures of 7–14 MPa. The α-alkenes produced have a distribution of up to 99% linearity. In a high-pressure separator the insoluble products and the catalyst solution as well as unreacted ethylene are separated; the catalyst is recycled into the oligomerization reactor.

Although a genuinely homogeneous reaction takes place without mass transfer limitation at the liquid–liquid phase boundary (as far as is known to date), it is noteworthy that the Shell SHOP process is up to now the only example of the biphasic organic/organic technology. This curious status may be the result of the fact that aqueous-biphasic processes received more attention or – at least – it is a consequence of the fact that the search for other applicable couples of organic/organic liquids was ineffective. It is only very recently that academic groups became interested again in this concept. One reason might be the fact that much more empirical data and knowledge are required for a thorough description of such a process (i.e., phase diagrams considering all the components of the system envisaged). Because there are only occasional publications (and no precise or informative ones) by Shell, the economics of organic/organic processes remain doubtful, at least if the first steps of the reaction sequence are not in the hands of the producers of petrochemicals (with their possibilities of cost distribution).

But once more, and similarly to aqueous-biphase operation, basic academic research also lagged behind the industrial research and application.

Even the use of perfluorinated alkenes, dialkyl ethers, etc., forming *fluorous biphase systems* because of their low miscibility with common organic solvents such as acetone, toluene, THF, and alcohols, is a subdivision of biphasic catalysis and,

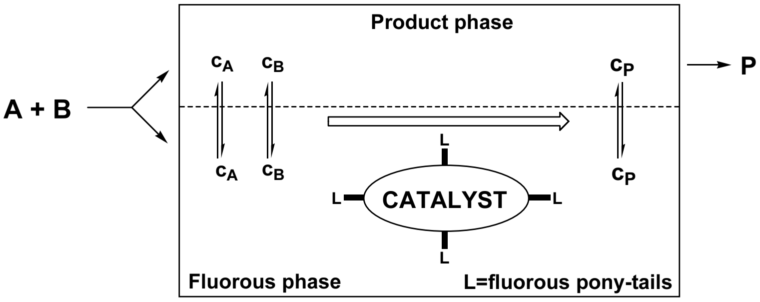

Figure 10 The fluorous-biphase concept for the catalytic reaction of substrates **A** + **B** → **P**. The attachment of appropriate fluorous ponytails **L** to a homogeneous catalyst ensures that the fluorous catalyst remains in the fluorous phase.

eventually, the application of Manassen/Joó's principle (see Chapter 4). The term *fluorous* was introduced as the analogue to the term *aqueous* to emphasize the fact that one of the phases of a biphase system is richer in fluorocarbon than the other. Such systems can be used in catalytic chemical transformations by immobilizing catalysts in the liquid, i.e., fluorous, phase. A fluorous catalyst system consists of a fluorous phase containing a preferentially fluorous-soluble catalyst and a second product phase which may be any organic or inorganic solvent with limited solubility in the fluorous phase.

The characteristic of fluorous phase operation is (like using supercritical carbon dioxide; see Chapter 6) that the catalysts have to be made fluorous-soluble by incorporating fluorocarbon moieties in their structure in appropripate size and number (Figure 10). The most effective fluorocarbon moieties are linear or branched perfluoralkyl chains with high carbon numbers that may contain other heteroatoms (the "fluorous ponytails"). The best fluorous solvents are perfluorinated alkanes, perfluorinated dialkyl ethers, and perfluorinated trialkylamines [28, 39].

A fluorous-biphase reaction can proceed either in the fluorous phase or at the interphase of two phases, depending on the solubilities of the substrates in the fluorous phase. It should be emphasized that a fluorous-biphase system might be converted to a one-phase system by increasing the temperature. Thus fluorous catalysis could combine the advantages of *monophasic* catalysis with *biphasic* product separation by running the reaction at higher temperatures and separating the products at lower temperatures (Figure 11).

In this respect, fluorous-phase operation is similar to temperature-regulated phase transfer catalysis (see Section 2.3.5) and to special versions of soluble polymer-bound catalysis (see Chapter 7). Alternatively, the temperature-dependent solubilities of *solid* fluorous catalysts in liquid substrates or in conventional solvents containing the substrates could eliminate the need for fluorous solvents.

Up to a certain degree the properties of fluorous solvents can be calculated and thus "tuned", especially when observing the strong electron withdrawing effects of "insulating" groups between the fluorous ponytails and the basic molecule [40] –

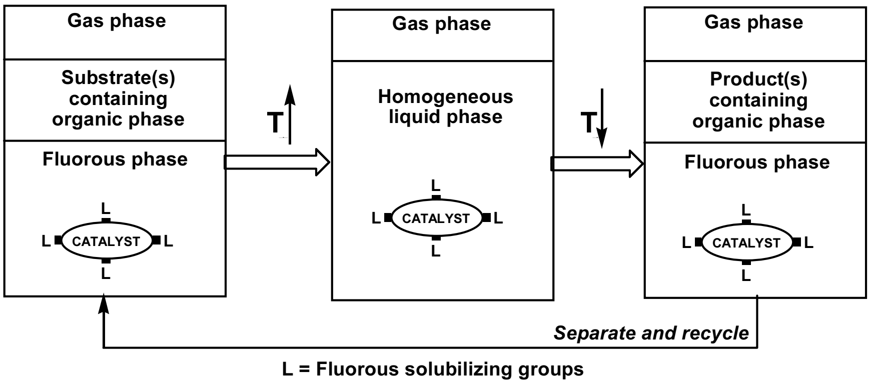

Figure 11 The temperature-dependent fluorous-liquid/liquid-biphase concept.

a great advantage for well-aimed tuning to a special application and a disadvantage for the production of larger-scale tonnages of bulk chemicals.

Fluorous catalysis is now regarded by some specialists as a well-established area providing complementary approaches to aqueous (see Chapter 2) or ionic-biphase (see Chapter 5) catalysis. So far, no economical application of fluorous-biphase catalysis is known (except for highly specialized lab uses); but fluorous-biphasic separation techniques without catalytic reactions involved may be the trailblazers of later catalytic uses.

As far as *nonaqueous ionic liquids* (more shortly but erroneously also called "ionic liquids", or ILs) are concerned, they were just considered as potential alternatives for multiphase reactions and were mentioned in forward-looking chapters of books dealing with this area, while water was already in key transition metal-catalyzed processes; see, for example, [6a, 17, 24, 29] (cf. also Chapter 2). Ionic liquids also have recently attracted much interest: it is now possible to buy them, which probably promotes their use, and there are more and more physical data available for these solvents. The range of reactions that have been described in IL media is probably wider than in $scCO_2$ (and surely wider than in fluorous liquids). But it would not be realistic to say that all catalyzed reactions can be transferred to ionic liquids with benefits. The advantages of using ILs have been well described for some reactions which will be reported later in this book and just a few of them have been run on micro-pilot or pilot plant scale.

The main interest in ionic liquids was first to offer "green" alternatives to volatile organic solvents. But not only this: because of their unique set of physico-chemical properties they are very different from conventional organic solvents. They may give the opportunity to promote reactions that are not possible in other solvents. For example, they offer a nonaqueous environment to substrates and can be poorly miscible with organic compounds (cf. Section 5.2.1). But one would expect more than just a physical solvent: "new chemistry" may be foreseen. Indeed, it has been proven that the nature of the ionic liquid may influence the outcome of chemical reactions [41]. In many cases, ILs contribute to improving reaction rates and selectivities. This is the case for biphasic systems in which the organic reactants are more soluble in the catalyst ionic phase than are the products of reaction intermediates. Consecutive side reactions of products can be minimized (cf., for example, Sections 5.2 or 5.3).

Product separation can be made easier and less energy consuming. ILs may also stabilize catalysts and prevent their deactivation, leading to less catalyst consumption and waste. The overall process may be simplified if the ILs act simultaneously as solvent *and* as catalyst.

From an engineering point of view, ILs offer a huge potential (similar to the aqueous variants as described in Chapter 2) for separating reaction products and recycling the catalyst. New reactors may be smaller than in conventional homogeneous catalysis (e.g., the Difasol or Basil processes), which contributes to making processes “environmentally friendlier”.

Their physical properties, such as viscosity, density, thermal stability, or surface tension, are important to consider during the design phase of new processes. The demonstration of the thermal and chemical stability of ILs and the recyclability can only be proven through continuous pilot plant runs. On the other hand, the sensitivity to feed impurities that can accumulate in the ionic phase requires feed pretreatments or guard beds for some scheduled applications.

Examples of commercial applications are scarce up to now (cf. Section 5.3; use of ILs has been considered for a series of specific questions). The scaling-up of IL synthesis procedures is normally without problems; however, the commercialization and/or transport of the ionic liquids raise the question of their registration (EINECS for Europe or equivalents; see Section 5.4). Disposal and recycle of ILs are important concerns and have to be considered on a case-by-case basis. And: “Ionic liquids are not always green” – as has been stated by Rogers et al. [42]. From the standpoint of “life cycle assessment” and “hazard analysis” ILs are clearly not recommendable for industrial use, especially if those with PF_6 or BF_4 as anions are concerned. And it is obviously no wonder that recent new developments such as BMIM octylsulfate have been emphasized as “even greener” ionic liquids [43].

Supercritical (sc) fluids have received considerable attention recently as new reaction media for chemical syntheses [30]. In particular, carbon dioxide in its supercritical state ($scCO_2$; $T_c = 31\,^\circ C$, $p_c = 7.37$ MPa) appears to be a very attractive “green” solvent, owing to its lack of toxicity and ecological hazards, the mild critical data, and the unique combination of gas-like and liquid-like properties. The possibility of tuning its solubility properties by variation of pressure and temperature gives access to a wide range of fascinating applications. In particular, it opens the way to new methodologies for the immobilization of transition metal catalysts either solely with CO_2 or in multiphase combinations [32, 33]. In multiphase approaches, $scCO_2$ can be envisaged either as the substrate/product phase (mobile phase) or as the catalyst phase (stationary phase) [44]. The existent technology platform for use of CO_2 in natural product extraction and materials processing may serve as a promising basis for the development of integrated production schemes combining reaction and separation stages. So far, only one application of (heterogeneous) catalysis in $scCO_2$ phase operation has been described (see Section 6.5).

As a possible alternative to immobilized or heterogenized homogeneous catalysts, the binding of metal complexes to *soluble polymers* and other colloidally dispersed systems is interesting. The concept of binding catalytically active metal complexes to soluble metal complexes was brought forward by Manassen as early as the 1970s [45]. First results of homogeneously catalyzed reactions with rhodium complexes bound to phosphine-modified soluble polystyrenes were communicated by Bayer and Schurig soon afterward [2a]. It was not until ten years later that Bergbreiter initiated a broader investigation of the topic [2f], and since the mid-1990s the field has begun to attract a wider interest in academia as well as industry.

The separation of polymer-bound catalysts from a (single-phase, homogeneous) reaction solution after catalysis by means of properties specific to macromolecules is an alternative to homogeneous two- or multiphase catalysis. Such specific properties, allowing for differentiation between the polymer-bound catalysts and low molecular weight compounds in the reaction mixture (products, substrates, and solvent), can be the dependence of polymer solubility on solvent composition or temperature. Another option is the separation based on the large difference in "size" of the dissolved species by means of ultrafiltration. These approaches, the subject of Chapter 7, can be differentiated from the use of polymers as mere solubility-impeding groups in ligands for two- or multiphase catalysis. An example of the latter is the replacement of the sulfonate groups in the archetypical TPPTS by nonionic poly(ethylene glycol) chains.

In linear polymers, catalyst binding can occur by coordination of the metal centers with two functional end groups or with functional moieties (S) pendant to the polymer backbone chain (Figure 12). The latter approach obviously offers the advantage of higher possible loadings. A somewhat less common case is the

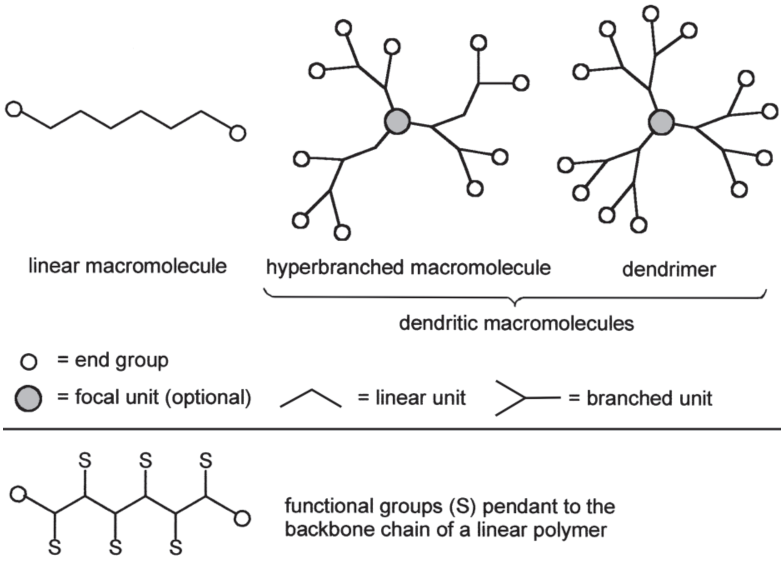

Figure 12 Schematic structures of linear and branched polymers.

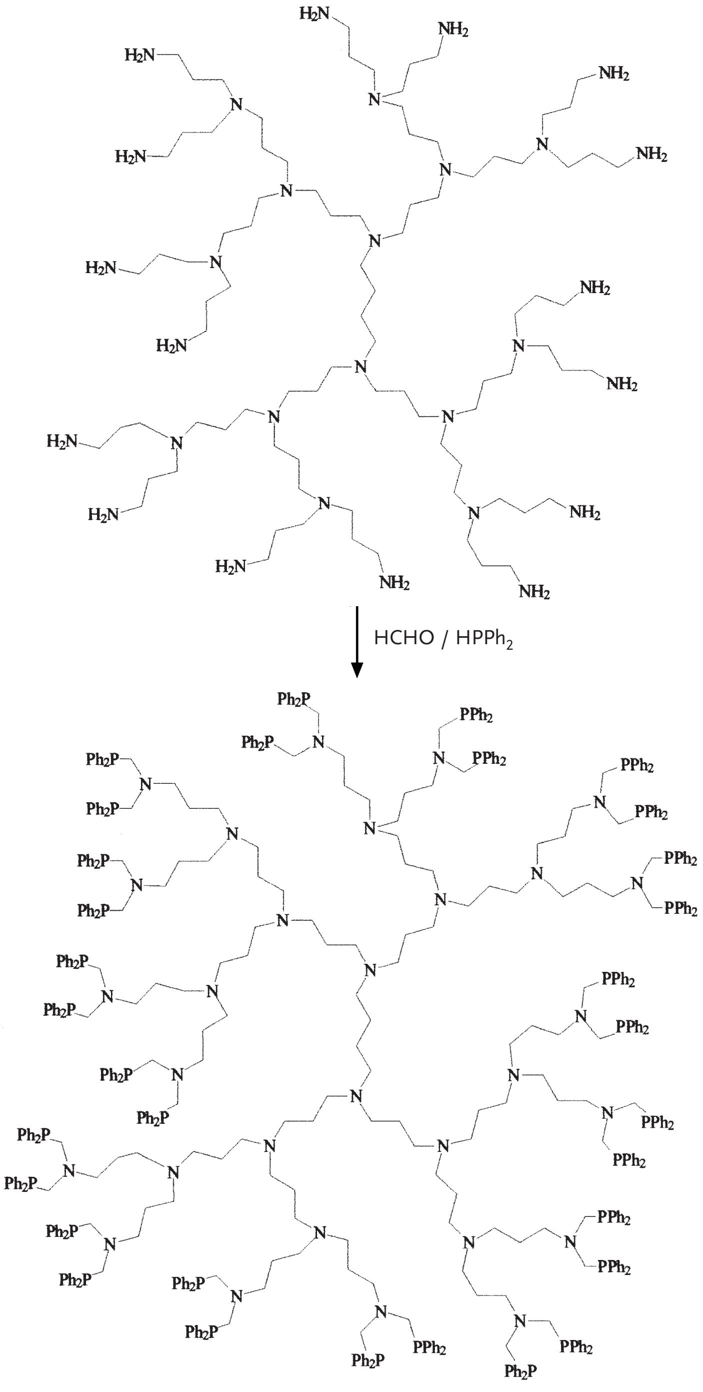

Figure 13 Synthesis of a diphosphine G2 polypropyleneimine dendrimer by polymer-analogous modification [46].

coordination of the metal centers by heteroatoms which are directly part of the polymer backbone. The most prominent example of the latter are (linear or branched) polyethylene imines with $-CH_2CH_2NR-$ repeat units.

A variety of linear polymers have been employed as catalyst supports with functional groups serving as ligands covalently attached as end groups or to the polymer backbone, e.g., polystyrene, low molecular weight polyethylenes, and also polymers which can be water-soluble such as poly(ethylene glycol)s or poly(*n*-alkylacrylamides). In addition to these organic polymers, polymers with an inorganic backbone have also been studied, most notably polysiloxanes.

Concerning polymer synthesis in general, the functional groups which will represent the ligands for the metal center at a later stage in catalysis can be introduced by homo- or copolymerization of corresponding substituted monomers, or by post-polymerization functionalization reactions of preformed polymers (also termed polymer-analogous reactions). Whereas linear polymers have been employed mostly, recently highly branched dendrimers (Figure 13) have also aroused considerable interest as soluble supports for metal complex catalysts.

By contast to dendrimers, hyperbranched polymers can be obtained in one-step procedures. As a drawback, molecular weight distributions are often extremely broad. However, certain hyperbranched polymers can be prepared with reasonably narrow molecular distributions if suitable reaction conditions are employed. Hyperbranched polyethyleneimine is produced on a large scale industrially (e.g., Lupasol from BASF). Hyperbranched polyesteramides with, e.g., terminal OH groups (tradename Hybrane® by DSM) and hyperbranched polyglycerol, a polyetherpolyol with terminal OH groups, are available as a specialty product on a kilogramm scale currently. For molecular weights around M_n 5000 g mol^{-1}, polyethyleneimine and polyglycerol are available routinely with polydispersities of $M_w/M_n \leq 1.3$; higher molecular weight samples are more broadly distributed.

The attachment of metal complexes to the polymer most often occurs via coordinating functional groups (ligands) bound to the polymer in a covalent fashion as outlined in the earlier chapters of this book, but various types of noncovalent attachment are also well documented. The latter can be achieved, for instance, by means of electrostatic interactions, physisorption by amphiphilic polymer micelles (either as common association micelles or as unimolecular micelles), by hydrogen bonding, or by specific interactions of proteins with a molecule (Figure 14).

Noncovalent attachment can offer the advantage of lower synthetic effort in the catalyst preparation. On the other hand, it can be assumed that the resulting catalysts will often be restricted to a comparatively narrow range of organic solvents for reasons of solubility (electrostatic interactions) or leaching (physisorption and hydrogen bonding), and an enhanced sensitivity to temperature and changes in the solvent composition of the latter two types of binding compared with covalent attachment or electrostatic interactions must be considered.

Metal colloids, i.e., colloidally stable dispersions of metal particles in the size range 1–10 nm, are often considered to be an intermediate between classical homogeneous and heterogeneous catalysts. On the one hand, like heterogeneous catalysts such colloids contain more than one phase, i.e., the solid nanoparticle

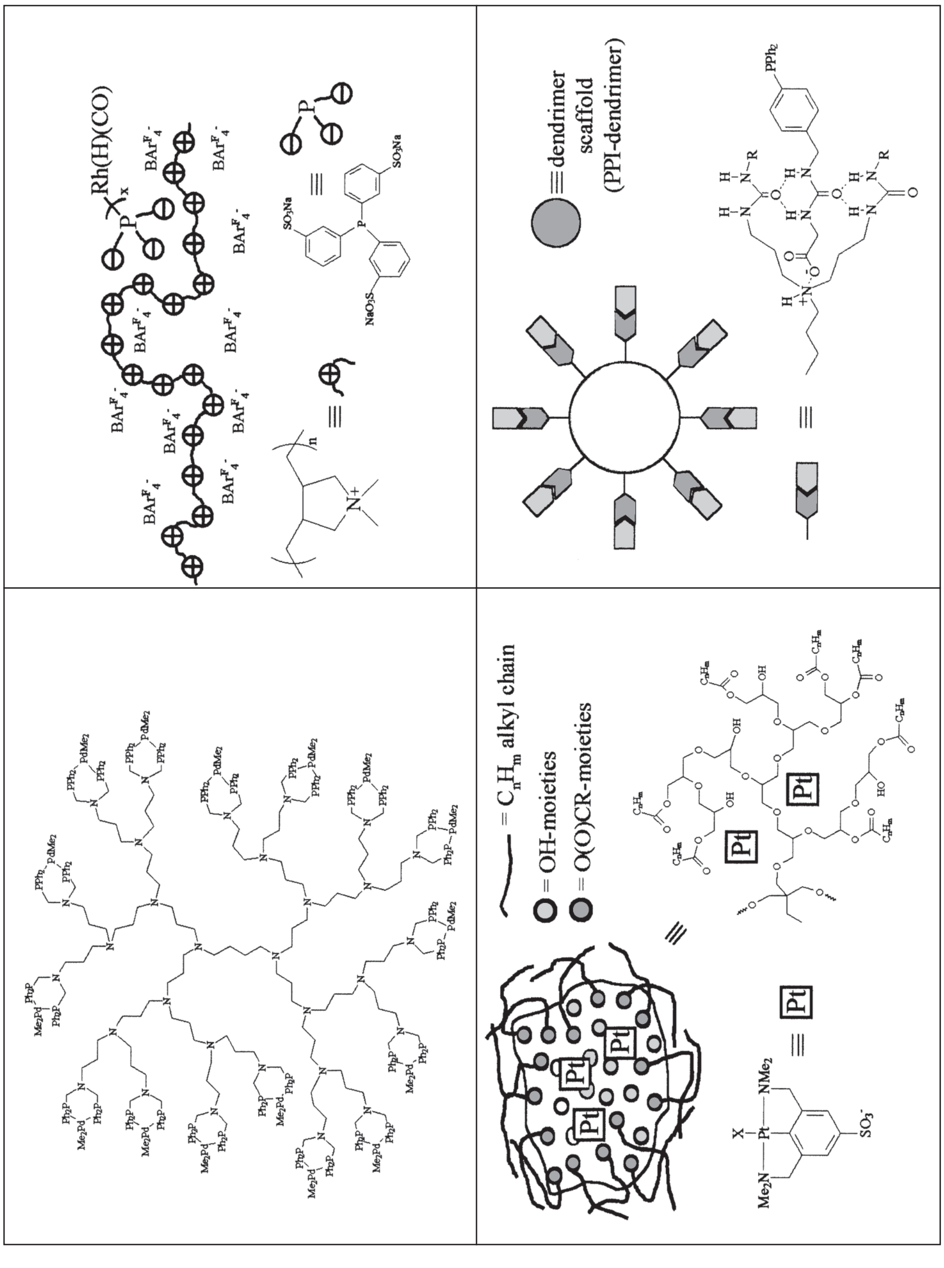

Figure 14 Schematic representation of various modes of attachment of catalytically active complexes to soluble polymers.

dispersed in a liquid medium. On the other hand, in terms of practical handling they are more similar to homogeneous catalysts in resembling single-phase "solutions". In terms of catalytic reactivity, metal colloids are known to catalyze a variety of reactions. Most interest to date has certainly been devoted to catalytic hydrogenation with metal colloids. Generally speaking, the reactivities and activities observed are roughly similar to hydrogenations with standard heterogeneous catalysts, albeit in detail colloids can offer advantages in some cases. In terms of reaction mechanisms, hydrogenation by soluble metal colloids does not appear to differ from the well-known mechanism of hydrogenation on metal surfaces of heterogeneous catalysts.

By comparison to homogeneous catalysts based on metal complexes, the properties of which can be tuned via the ligands coordinating to the metal center, the scope of reactions and viable substrates is certainly less broad for metal colloids.

Given the similarities to homogeneous complexes in some aspects, involving catalyst recovery, and the major importance of soluble polymers for the stabilization of metal colloids, the latter will also be considered throughout Chapter 7 where appropriate.

It is likely that the spread of biphase (multiphase) processes as described here will increase the proportion of homogeneously catalyzed reactions and hence the importance of homogeneous catalysis in general. It will then also be possible to demonstrate in full the great advantages of homogeneous catalysis over the rather empirical methods of heterogeneous catalysis and answer Heinemann's 1971 question, "Homogeneous and heterogeneous catalysis – common frontier or common territory?" [47], clearly in favor of the homogeneous version.

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2
Aqueous-Phase Catalysis

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Multiphase Homogeneous Catalysis
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2.1
Introduction

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Figures 1 and 2 of the Introduction to this book (Chapter 1) have given the orientation of aqueous-phase catalysis within the overall picture of homogeneous catalysis. Together with the other possibilities of multiphase operation as defined there, the aqueous option is one step toward the release of homogeneous catalysis from its system-immanent restriction, especially the necessity of costly catalyst recycling. It is no wonder that these limits were particularly disturbing in the upcoming and rapidly growing hydroformylation reaction [1] (current yearly output approx. 9 MM tons [2]). Thus it is also no wonder that the impressive advantages and the tremendous progress of the biphasic processes were first used commercially with aqueous- and aqueous/organic-phase operation [3]. Table 1 demonstrates that when using the aqueous-phase technique the expenditure for catalyst removal and recycling of homogeneous and of heterogeneous operations are for the first time at the same level.

The advantages of anchoring homogeneous catalysts on "liquid" supports (and thus the biphasic techniques) are obvious and render possible – besides the organic/organic operation; cf. Chapter 3 – the utilization of the principle which was expressed by Manassen ([5]:

> "… the use of two immiscible liquid phases, one containing the catalyst and the other containing the substrate …",

Table 1 Catalyst removal in homogeneous and heterogeneous catalysis (according to [4]).

	Homogeneous catalysis		***Heterogeneous catalysis***	
	In general	***Aqueous-phase***	***Suspension***	***Fixed bed***
Separation of catalyst/product	Expensive[a)]	Decantation	Filtration	Simple
Additional equipment required?	Yes	No[b)]	No[b)]	No
Catalyst recycling	Expensive	Easy	Easy	Not necessary
Cost of catalyst losses	High	Minimal	Minimal	Minimal
Service life of catalyst	Just one cycle	——— Depending on conditions ———		

a) The normal recycling requires filtration or chemical/thermal deposition, distillation, evaporation, extraction, or similar means.
b) Except for decanter or filtrator.

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and

> "The two phases can be separated by conventional means and high degrees of dispersion can be obtained through emulsification. The ease of separation may be particularly advantageous in situations where frequent catalyst regeneration is required."

Figure 1 illustrates the enormous importance of the biphase technique for homogeneous catalysis: the aqueous catalyst solution is charged in the reactor together with the reactants A and B, which react to form the reaction products C and D. C and D are less polar than the aqueous catalyst solution and are therefore simple to separate from the aqueous phase (which is recycled directly into the reactor) in the downstram phase separator (the decanter).

The advantage of the "liquid support" water and of its high affinity toward homogeneous catalysts is evident. The catalyst is "heterogenized" with respect to the organic reaction products C and D and therefore can not only be separated from the products "in the other phase" (possibly including unconverted reactants A and B), but also immediately thereafter can start a new cycle of the catalytic cycle process. Aqueous biphase catalysis is therefore – intentionally – located between heterogeneous and homogeneous catalysis, as demonstrated in Figure 2 of Chapter 1. Special attention may be drawn to the somewhat confusing and ambiguous use of the terms "homogeneous" and "heterogeneous" in the context of homogeneous/heterogeneous *catalysis* and homoge-neous/heterogeneous *phase variation*: the catalytic system works mechanistically homogeneously although it is in heterogeneous phase.

The immobilization of the homogeneous catalyst with the aid of the liquid support water leads to appreciable technical – and consequently commercial [6] – simplifications, as illustrated for the example of large-scale oxo processes in Figure 2.

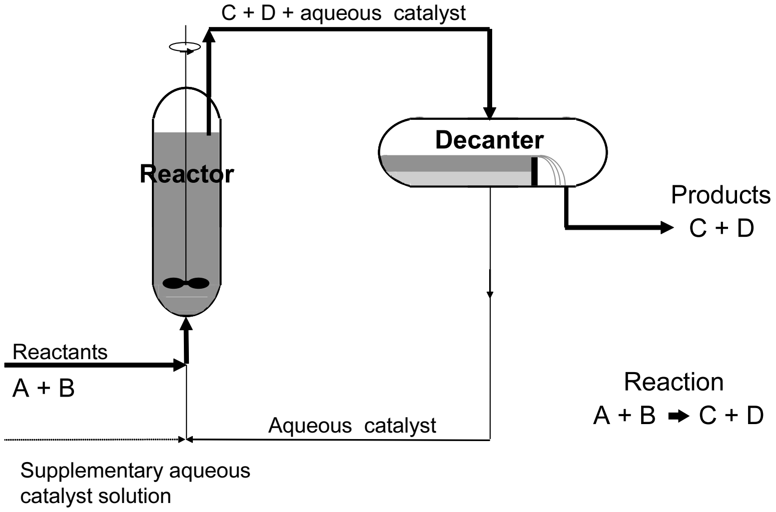

Figure 1 Principle of aqueous-phase catalysis illustrated for the reaction A + B → C + D.

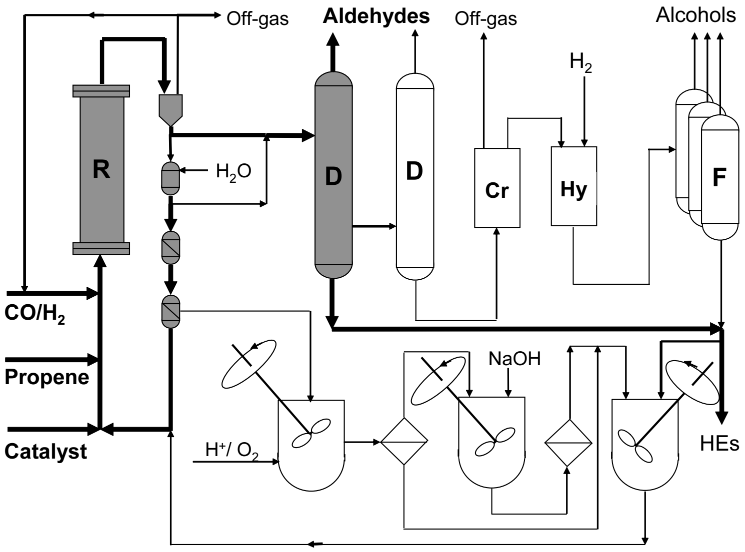

Figure 2 Schematic flowsheet of a “classical” oxo process, the earlier Ruhrchemie oxo process [7]. Those parts of the process and equipment which are dispensed with in the new RCH/RP process (with an aqueous catalyst system) are unshaded [6].

Table 1 predicts that, of the biphase processes, the aqueous version will attain particular importance because of the many advantages of water as the medium of the “liquid support”. As a solvent, water has many anomalies (e.g., the density anomaly, being the only nontoxic and liquid “hydride” of the nonmetals, the pressure dependence of the melting point, the dielectric constant, etc.), and its two-/three-dimensional structure is still not well understood. The most important properties are listed below [8a]; recent results given in [8b–h].

1. Polar and easy to separate from apolar products; additionally, the polarity may influence (improve) reactivity (cf. Sections 2.2.1 and 2.2.2).
2. Nonflammable, not combustible, and nontoxic: a decisive advantage in terms of safety and occupational health (see Section 2.3.6).
3. Ubiquitous and widely available of suitable quality.
4. Odorless and colorless, making contaminations easy to recognize.
5. Forms a hexagonal two-dimensional surface structure, a tetrahedral three-dimensional molecular network, or clusters which influence the mutual (in)solubility significantly; chaotropic compounds lower the order by H-bond breaking.
6. High Hildebrand parameter as the unit of solubility of nonelectrolytes in organic solvents.
7. The density of 1.00 g cm^{-3} provides a sufficient difference from most organic substrates/products.

8. Very high dielectric constant.
9. High thermal conductivity, high specific heat capacity, and high evaporation enthalpy of water predestine it as a heat removal fluid; see Section 2.4.
10. Low refractive index n_D.
11. High solubility for many gases, specially CO_2.
12. Formation of hydrates and solvates with sometimes surprising properties (e.g., gas hydrates).
13. Highly dispersible and high tendency toward micelle and/or microemulsion formation, which can be stabilized by additives such as surfactants.
14. Amphoteric behavior in the Brønsted sense.
15. Advantageously influences chemical reactions.

For homogeneously catalyzed reactions of chemical compounds in a biphasic, aqueous manner, most of these properties are used advantageously. Except for the positive influence of water on the chemical reaction (no. 15; see also Sections 2.2.1 and 2.2.2) the peculiarities of water with direct significance for the aqueous-biphasic processes are the physiological (2, 4), economic (1, 3, 7), ecological (2, 3, 4), technical/engineering (1, 6, 7, 9, 11, 12, 13, 14), and special physical properties (1, 5, 6, 8, 10, 12, 14). The various properties have multiple effects and are mutually reinforcing. Astonishingly, the quality and significance of the properties listed above is debatable: some count the low solubility of organic substrates (and thus the basis for the aqueous-biphasic approach for homogeneously catalyzed processes) among the disadvantages. The different pros and cons of water as a reaction fluid are compiled in Table 2, which includes the alternative views of others on the whole picture.

Table 2 Pros and cons of water as liquid support [9].

Advantages	***Disadvantages***
Nonflammable	Large heat of evaporation[a)]
Nontoxic	Difficult to detect in the case of leakage[b)]
No smell[c)]	Low solubility of many nonpolar substrates
Good separation with many organics	Hard to collect in the case of spills[d)]
Cheap	No incineration of bleed streams[e)]
Stabilization of certain organometallic complexes	Decomposition of water-sensitive compounds [f)]

a) Which is an advantage within the economics of the heat compound.
b) Which – in contrast – is an advantage since contaminated water smells strongly in certain syntheses (for example, the manufacture of butyraldehydes).
c) See: the difference between "no smell" and the smell of "contaminated bleed streams is important and advantageous".
d) Which is true for all "solvents" and all organic liquids and is not a specific disadvantage of water.
e) Which in contrast is advantageous when containing the water-soluble catalysts: the system is self-extinguishing.
f) This is true but a matter of evaluation: nobody will recommend water in the case of decomposition of water-sensitive substrates or products.

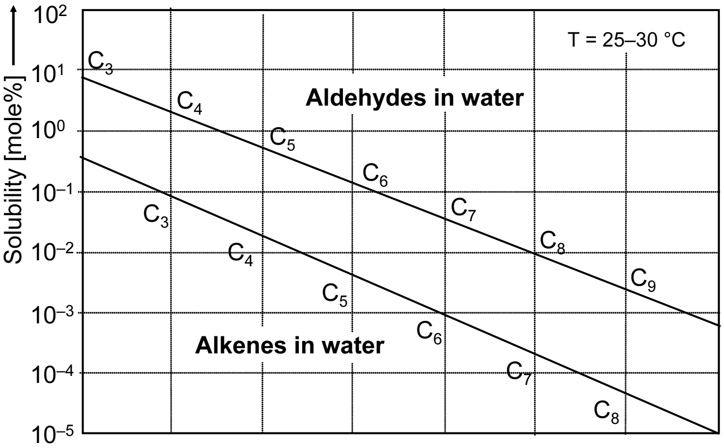

Figure 3 Solubility of alkenes and of the aldehydes obtained therefrom by hydroformylation in water [10].

Obviously, "misunderstandings continue to prevail", as van Leeuwen cautiously put it into words [9] although water does not ignite, does not burn, is odorless and colorless, and is ubiquitous: important prerequisites for the solvent of choice in homogeneous catalytic processes. The favorable thermal properties make water doubly exploited as a mobile support and as a heat-transfer fluid.

There is an important restriction regarding the general use of water in homogeneously catalyzed processes. This is that to attain adequate chemical reaction, there has to be a minimum solubility of the organic substrates in the aqueous catalyst phase. Normally, this solubility decreases with increasing carbon number of the substrates. This is illustrated in Figure 3 for the dependence of the solubilities of alkenes and aldehydes in water on their C number – thus an example is the homogeneously catalyzed conversion of alkenes to aldehydes (via oxo synthesis; cf. Section 2.4.1).

The differences in reactivity of the hydroformylation of the alkenes C_3 up to C_9 are readily explained by the solubility differences between the various olefins. This is also the case for other examples of aqueous-biphasic operation. All proposals to enhance the reactivity of higher alkenes by addition of solvents, co-ligands, co-solvents, tensides, counter ions, micelle-forming agents, surface-active ligands, etc. [11] (as a single measure or in combination: the record holder used three! [12]) are based on the improvement of the solubility of the feed alkene in the bulk of the aqueous catalyst solution. This is also important for the idea of reactivity, as shown in Figure 4.

On the one hand, the reaction can occur in the bulk of the liquid phase: the gaseous reactants have already become uniformly distributed in the liquid phase owing to the rapid mass transfer somewhat before the actual and slower chemical reaction commences. This model A contrasts with the idea of a relatively rapid chemical reaction as opposed to mass transport.

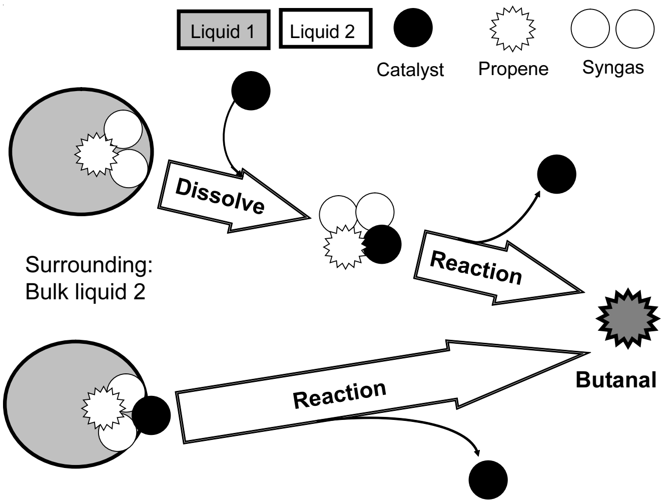

Figure 4 Comparison of the two models A (above: reaction in the bulk of the liquid) and B (below: reaction at the interfacial boundary) [13c].

The fact that the gaseous substrates react very quickly means that, in practice and according to model B, the reaction takes place at the phase boundary or in an interfacial layer with a relatively small thickness [13]. The latter has been proven and – via process modeling on the basis of appropriate kinetic models – renders possible a more optimal reactor and mixing design (cf. also Section 2.3.1). The dependence of the reactivity of aqueous systems on the solubility of the reactants in the aqueous catalyst solution is of appreciable importance for the problem of universal applicability.

Using water as the solvent not only has the advantage of employing a “mobile support” and hence of a de facto “immobilization” of the catalyst while retaining a homogeneous form of reaction, but also has positive repercussions on the environmental aspects of the different reactions to which it is applied, e.g., hydroformylation (see Section 2.4.1.1).

Aqueous processes will become more important in the future because of the immense advantages of this version of homogeneous catalysis in the multiphase version. In addition to the syntheses already utilized now, an enormous laboratory study has been done to convert conventional syntheses to the aqueous-multiphasic mode (see Section 2.5.2). A selection of recent work covering a multitude of reactions and and catalysts based on various transition metals is presented in Table 3.

Various protocols describe aqueous-phase processes with heterogeneous catalysts such as the reforming of oxygenated hydrocarbons over Sn-modified Ni catalysts [22a], the epoxidation of alkenes over zeolites [22b], etc. [22c–i,l,m].

Some authors reported commercial applications [22n] but this is rather uncertain, and in any case this would not be a “green application” as claimed.

Obviously, there are beneficial effects but the reason for this combination is not that heterogeneous catalysis is made much easier by bi- or multiphase operation.

Table 3 Research work in aqueous–phase reactions.

Type of reaction/Metal involved	*References*
Additions to alkynes/Pd,Rh,organo[a)]	[19c], [20i], [21c,l]
Aldolization/Sc,In,Cu,Ln	[14a–d]
Alkylation/K,Pd,organo[a)]	[14e,f], [18l]
Alkyl radical addition/In	[21o]
Alkynylation of acid chlorides/Pd	[23s]
Allylation/Ru,Pd,Zn	[14d,y,z], [17b], [20x]
Allylic amination	[23k]
Allylic benzoylation/Cu	[21m]
Amination/Pd	[14g], [21a]
Carbonylation/Pd,Rh	[14h–l]
Condensation reactions/heteropolyacids, Mo,W	[20s], [21d]
Conjugate addition/Rh	[20w]
Copolymerization/Pd	[20f], [23y]
Cross-couplings/Pd	[23v]
Cyanation/Pd,Ln	[14m,n]
Cycloaddition, cyclotrimerization/Co,Rh	[14o,p], [17v], [20m,n]
Dihydroxylation/Os	[17m], [20v]
Electrocatalysis/Mo	[21i]
Ene reactions/Pd,Rh,Ni	[19b]
Epoxidation/W,Re,Mn,Cr,Al,ionic liquids	[14q–u], [20o,p], [23n,z]
Hydration/Au,Pt,Rh	[14v], [17y], [18b]
Hydroaminomethylation/Rh,Ir	[14w]
Hydroamination/Ni	[20r]
Hydrocarboxylation/Pd	[14h], [15a–e], [18d]
Hydrodesulfurization/Ru,Rh	[15f,g]
Hydroformylation/Rh, Rh-α-CD	[23p,q,w]
Hydrogenation/Ru,Rh,Pd,Ir, Pt–Pd	[13a,b], [15h–t], [18m], [19a,d], [20j]
Hydrogenation of CO_2/Ru,Rh	[20a,u], [21j]
Hydrosilylation/Pt	[15u]
Hydroxycarbonylation/Pd,Ni	[20t]
Hydroxymethylation/organo[a)]	[23l]
Isomerization/Ni,Ru,Rh,Pd,Ir	[15v,w], [21b,k,n,q]

Table 3 (continued)

Type of reaction/Metal involved	***References***
Metallo–ene reactions	[19b]
Metathesis/Ru,In	[15x–z], [16a]
Nucleotides/Fe	[23u]
Oligomerization/Pd,Al	[15c], [16b–f]
Oxidation/Ru,Pd,Os,W,Mn,Cu	[16g–l], [18a,e,h], [20b,d,q]
Oxidative dimerization/Pd	[20l]
Phenol synthesis/Fe	[16m]
Polymerization/Cu,Ti,Ni,Pd,Rh,Co,Ru	[16n–r], [21p]
Syntheses of various heterocycles/Rh,Ni	[16s], [18c,k]
Telomerization/Pd,Ni	[16t–v], [20e,y]
Thiolysis/In	[16w]
Transfer hydrogenation/Rh	[20k]
Use of carbene complexes/Ru	[23x]
Wacker reaction/Pd	[16x]
Water–gas shift reaction/Ru	[17t], [23r]
Examples of name reactions	
• Barbier-type allylation/In,Sn	[16y,z]
• Claisen rearrangement/Al	[17a]
• Diels–Alder/Si,Cu	[14d], [17c], [18j]
• Friedel–Crafts/Sc,Ga	[17d], [20h]
• Grignard/Sn, Sn–Rh	[17e]
• Heck/Pd,Rh	[17f–i], [18g], [23o]
• Kharasch/Pd	[17j]
• Knoevenagel/La	[23m]
• Mannich/Zn,Brønsted acid,NaOTf	[14d], [20c,z]
• Michael/Sc,Ag	[14d], [17k]
• Pauson–Khand/Rh	[14x], [17z]
• Reformatsky/Zn	[17l]
• Sharpless/Os	[17m–o], [18i]
• Sonogashira/Pd	[21f]
• Suzuki/Pd, organo[a)]	[17p,q,x], [21g,r]
• Tsuji–Trost/Pd	[23t]
• Ullmann/Pd,Rh,Ni,Cu	[17u,w], [20g], [21e]
• Wittig/organic[a)]	[17r]

a) Organocatalysts, cf. [17s].

The same is true for combinations of two or more measures to ensure biphasic homogeneous catalysis, such as aqueous-biphase + supercritical solvents [23a–d], aqueous-biphase + fluorous solvents [23e–h], supercritical solvents + ionic liquids [23i], fluorous + supercritical solvents [23j], or other combinations. By the way, some papers argue a new concept for the separation of heterogeneous catalysts by usage of two different and immiscible solvents. Against gravity, surface polarity modified catalysts are located only in one of the two phases. The catalyst phase can be separated by simple decantation [22j,k].

The application of aqueous-phase processes requires the rule over some new techniques. Systematic studies on the examples hydrogenation and hydroformylation have shown the vast improvements which can be achieved through variation of the ligands (cf. Section 2.2.3.2). Sections 2.2.3.1 and 2.4.8 prove the great variety of the central atoms that have been applied. Especially in the case of the ligands, it is true that a multitude of water-soluble compounds have been developed (and applied) but it is only TPPTS which is both active and inexpensive. With more exotic ligands, activity, productivity, and selectivity may be enhanced further but at the expense of a more costly and uneconomic operation. This is not true for enantioselective reactions, which are just to be applied. Last but not least, aqueous-phase operation requires some more techniques from the chemical engineering side. Except for the proven oxo process (see Sections 2.4.1.1.1 and 2.4.1.1.3 [24]) the developments under way will be described in Sections 2.3.1 through 2.3.5.

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24 See references in [3].

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2.2
State-of-the-Art

2.2.1
Organic Chemistry in Water

André Lubineau, Jacques Augé, and Marie-Christine Scherrmann

2.2.1.1
Introduction

Since the seminal contributions in the 1980s of Breslow [1a] for the Diels–Alder reaction and Kuntz and Ruhrchemie for hydroformylation reactions [1b], there has been an upsurge in interest in using water as the solvent, not only to enhance the reaction rates, but also to perform organic reactions that would otherwise be impossible, or to elicit new selectivities. Several reviews have been devoted specially to such a use [2], which nevertheless does not exclude the possibility of further catalyzing the reactions with Lewis acids [3] or the use of Lewis acid–surfactant-combined catalysis (LASC) [4].

As the most abundant liquid that occurs on Earth, water is very cheap and, more importantly, not toxic, so it can be used in large amounts without any associated hazard. In this medium, reactions can be carried out under mild conditions and yields and selectivities can therefore be largely improved. Furthermore, water-soluble compounds, such as carbohydrates, can be used directly without the need for the tedious protection–deprotection sequences. Finally, water-soluble catalysts can be reused after filtration, decantation, or extraction of the water-insoluble products [1b].

A remarkable feature of water-promoted reactions is that the reactants only need to be sparingly soluble in water and, most of the time, the effects of water occur under *biphasic* conditions (cf. Sections 2.1 and 2.3.1). If the reactants are not soluble enough, co-solvents can be used as well as surfactants. Another possibility for inducing water solubility lies in grafting a hydrophilic moiety (a sugar residue or carboxylate, for instance) onto the hydrophobic reactant.

This contribution encompasses the main concepts supporting the origin of the reactivity in water, along with some applications in organic synthesis.

2.2.1.2
Origin of the Reactivity in Water

The combination of a small size and a three-dimensional hydrogen-bonded network system is responsible for the complexity of the structure of water, which results in a large cohesive energy density (550 cal mL^{-1} or 2200 MPa), a high surface tension and a high heat capacity. These three attributes give water its unique structure as a liquid, and give rise to the special properties known as hydrophobic effects, which

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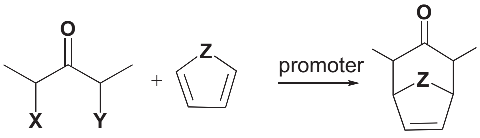
play a critical role in the folding of biological macromolecules, in the formation and stabilization of membranes and micelles, or in the molecular recognition processes, such as antibody–antigen, enzyme–substrate, and receptor–hormone binding. Since Breslow's discovery that the Diels–Alder reaction, which is known as insensitive to solvent effects, can be dramatically accelerated in aqueous solution, special attention was focused on the origin of the aqueous acceleration. Of interest was the observation of good correlations between solubilities of the reactants and Diels–Alder rate constants [5a]. The influence of hydrophobic effects on solubilities, reaction rates, and selectivities could be interpreted by the use of prohydrophobic and antihydrophobic additives [5b]. In 1986, Lubineau assumed that a fundamental issue is the high cohesive energy of water; he postulated then that a kinetically controlled reaction between two nonpolar molecules for which $\Delta V^{\neq}$ is negative must be accelerated in water [6]. The importance of the cohesive energy density to Diels–Alder reactions and Claisen rearrangements, both displaying a negative activation volume, was demonstrated by Gajewski [7]. By measuring standard Gibbs energy of transfer from organic to aqueous solvents, Engberts and co-workers showed that enforced hydrophobic interaction due to a decrease in the overall hydrophobic surface area during the activation process plays an important role in the rate acceleration in water [8]. This effect was considered to be a consequence of the high cohesive energy density of water [2a] and should be expressed in terms of pressure (cohesive pressure), but one must avoid any confusion with the internal pressure of water, which is small compared with other solvents [9]. The importance of hydrophobic effects was emphasized in Monte Carlo simulated Diels–Alder reactions especially when both reactants are nonpolar; when one of the reactants is a hydrogen-bond acceptor, enhanced hydrogen bonding interaction and hydrophobic effects contribute equally to the rate enhancement [10]. With methyl vinyl ketone as a dienophile model in Diels–Alder reactions, computed partial charges displayed greater polarization of the carbonyl bond in the transition state and consequently enhanced hydrogen bonding to the transition state; on the basis of Monte Carlo simulations [11a] and molecular orbital calculations [11b], hydrogen bonding was proposed as the key factor controlling the variation of the acceleration for Diels–Alder reactions in water. Monte Carlo simulations showed enhanced hydrogen bonding to the oxygen in the transition-state envelope of water molecules for Claisen rearrangements as well [12]. Such an enhanced hydrogen bonding effect was invoked to explain the experimental differences of reactivity between dienophiles in some Diels–Alder reactions [13a–c] and to understand the acceleration in water of the retro Diels–Alder reaction, a reaction with a slightly negative activation volume [13d].

In summary, the acceleration in water of reactions between neutral molecules arises from an enforced hydrophobic effect (especially when apolar reactants are involved), and a charge development in transition states in particular when one of the reactants is a hydrogen donor or acceptor. In both cases a negative volume of activation is expected. The two contributions (hydrophobic effects and polarity) could be active in the same reaction, which means a greater destabilization of the hydrophobic reactants in the initial state than in the transition state, and a greater stabilization of a more polar transition state.

2.2.1.3
Pericyclic Reactions

In his pioneering work [1a], Breslow studied the kinetics of the cycloaddition between cyclopentadiene and methyl vinyl ketone. The implication of the hydrophobic effect in Diels–Alder reactions was extensively supported by the effect of cyclodextrins [14] and additives, such as lithium chloride (salting-out agent) or guanidinium chloride (salting-in agent), which respectively increases or decreases the rate of the reaction [15]. By measuring activation parameters, it has later been shown that the acceleration arises from a favorable change of activation entropy, which is an indication of the implications of the hydrophobic effect [16]. Another aspect of the influence of water as the solvent in Diels–Alder reactions is the higher *endo* selectivity observed by comparison with organic solvents. Indeed, the Diels–Alder reaction has a negative activation volume and of the two possible transition states, the *endo* one is the more compact and therefore should be favored. An improvement in the rate of the aqueous Diels–Alder reaction came with the use of Lewis acid in aqueous media [17] also in the presence of micelles [18]. Use of metallo-vesicles or metallo-micelles was found to be very efficient [19].

The hetero Diels–Alder reaction has also been carried out efficiently in water. For instance, glyoxylic acid undergoes cycloadditions with various dienes [20] although the carbonyl function is almost exclusively present as its hydrate form. Other pericyclic reactions such as 1,3 dipolar [21] or [4+3] cycloadditions [Eq. (1), Table 1], and Claisen rearrangement [22] gave better results when conducted in aqueous media than in organic solvents.



(1)

Table 1 Conditions and results for Eq. (1).

X	*Y*	*Z*	*Solvent*	*Promoter*	*Time*	*Temp. [°C]*	*Yield [%]*	*Ref.*
Br	Br	CH_2	Benzene	$Fe_2(CO)_9$	25 h	25	81	[23a]
Br	Br	CH_2	H_2O	Fe (powder)	13 h	20	60	[23b]
Br	Br	O	H_2O	Fe (powder)	34 h	20	82	[23b]
Cl	H	O	EtOH	Et_3N	330 d	20	70	[23c]
Cl	H	O	H_2O	Et_3N	5 h	20	88	[23b]
Cl	H	CH_2	H_2O	Et_3N	12 h	20	76	[23b]

2.2.1.4
Carbonyl Additions

Surprisingly enough, the reaction between a silyl enol ether, a potentially hydrolyzable compound, and an aldehyde can be performed in water without catalyst. In this solvent, contrary to what is obtained in $TiCl_4$-catalyzed reactions, the formation of the *syn* adduct is favored, as observed for the aldolization in CH_2Cl_2 under high pressure (10 000 atm). The *syn* selectivity is due to the smaller activation volume of the corresponding transition state ($\Delta V^{\neq}_{syn} < \Delta V^{\neq}_{anti}$). This is an indication of the implication of hydrophobic effects during the activation process [6, 24]. The use of lanthanide triflates [3a, 25] as water-tolerant catalysts substantially improved the yields of the addition and allowed a good enantioselective control [26]. Similarly, the Henry [27], Reformatsky [28], Mannich [29], and Mannich-like reactions [30] were successfully performed in aqueous media.

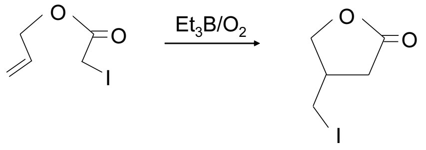
The use of water as a solvent in the conjugate addition was first reported for 1,3-diketones [31] and then applied to β-unsubstituted enones [32], other conjugated enones [33], methyl vinyl ketone [34], α,β-unsaturated nitriles [35], and dehydroalanine amides [36]. Also a related reaction, the Baylis–Hillman coupling, was found to be greatly accelerated in water compared with usual organic solvents [37].

The allylation of aldehydes via organotin reagents displays a negative activation volume [38], therefore it is accelerated by addition of water [39]. The reaction was extended to various aldehydes and ketones and to various allylic organotin dichlorides [40] or tetra-allyltin in acidic aqueous medium [41]. With scandium triflate as a catalyst, tetra-allyltin [42] or tetra-allylgermane [43] react smoothly in mixed aqueous solvents, providing high yields of the corresponding homoallylic alcohols. The aqueous Barbier-type allylation reaction was found to be mediated by zinc [44a–b] and tin [39, 44c, 45a], and also applied to unprotected carbohydrates to prepare diastereoselectively higher-carbon sugars [45b]. A major improvement was realized with the use of indium, a metal with a very low first ionization potential (5.8 eV) which works without ultrasonic radiation even at room temperature [46]. The reactivity and the diastereoselectivity are compatible with a chelation-controlled reaction [45a, 47]. Indeed, the methodology was used to prepare 3-deoxynonulosonic acids such as KDN [48], Neu5Ac [48b, 49a] and analogues [49b], and *C*-disaccharides [50].

2.2.1.5
Radical Reactions

Although significant solvent effects have been observed for radical reactions in water, the use of an aqueous medium for this type of chemistry remains, nowadays, rare. Oshima's group has reported a remarkable improvement for the triethylborane-mediated radical cyclization reactions of allyliodoacetates in butyrolactones [51a,b] [Eq. (2)]. Some other studies by the same group have recently been reviewed [51c]. Miyabe et al. described the indium- [52a] or triethylborane-mediated [52b] radical addition of alkyl iodide to electron-deficient C=N bonds and C=C bonds in water.

The same group reported indium-mediated tandem radical addition–cyclization–trap reactions in aqueous media [52c]. The use of water-soluble radical initiator 2,2′-azobis[2-(2-imidazolin-2-yl)propane], water-soluble chain carrier 1-ethylpiperidinium hypophosphite (EPHP) and surfactant cetylammonium bromide (CTAB) allowed the C–C bond-forming radical reactions of highly hydrophobic substrates in water [53]. Similarly, the use of CTAB and EPHP in presence of 4,4′-azobis(4-cyanovaleric acid) promoted the indium-mediated radical addition to β-substituted conjugated alkenes in water [54].



(2)

Solvent/yield (%): Water/78; DMSO/37; MeCN/13; EtOH/13; CH_2Cl_2/<1; THF/<1

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2.2.2
Organometallic Chemistry of Water

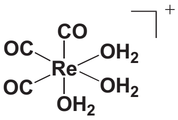
Fritz E. Kühn and Wolfgang A. Herrmann

2.2.2.1
Introduction

Water plays a fundamental role in coordination chemistry. Not only do many, if not all, metals bind water molecules to fill their coordination sphere; it has been through the kinetics of water-exchange processes at metal ions that the basics of the theory of coordination chemistry have been conveyed [1]. By way of contrast, not so much is known about aqueous organometallic chemistry, because of the notorious lability of organometallics toward water. It has to be noted, however, that particularly in recent years the organometallic chemistry of water has gained increasing attention, particularly with water as the polar phase in multiphase systems, as can be seen in the appearance of an increasing number of original articles and several review articles in this field [2]. This section focuses on the key features of water in both aspects, i.e., coordination and organometallic chemistry.

2.2.2.2
Water as a Solvent and Ligand

Water as a solvent offers several opportunities as compared with organic solvents. It favors ionic reactions because of its high dielectric constant ($\varepsilon_{25\,°\mathrm{C}} = 78.5$) and the ability to solvate cations as well as anions. Beyond that, water is the ideal solvent for radical reactions since the strong O–H bonds (enthalpy 436 kJ mol^{-1}) are not easily attacked [1g]. Furthermore water displays particularly high enthalpy changes during the solid–liquid ($\Delta H_{\text{melt}} = 6.003$ kJ mol^{-1}) and particularly the liquid–gaseous ($\Delta H_{\text{vap}} = 40.656$ kJ mol^{-1}) transfer, since the phase transfers are associated with the formation or breaking of hydrogen bridges. Additional advantages of water as a solvent are its high heat capacity, its strong pressure dependency of the viscosity, and the high cohesive energy density (c.e.d. = 2.303 kJ cm^{-3}) [2]. Classified as a ligand for metal ions, water has decent crystal field splitting properties, standing between oxygen-bound anions and nitrogen donors such as pyridines in the spectrochemical series. The water molecule is a good σ-donor ligand, while π back-bonding is negligible. For this reason, higher-valent transition metals form the more stable metal complexes, but the nature of the metal itself is important, too. For first-row metals (+2), an extra destabilization due to electrons in e_g orbitals accounts for a ligand labilization. This effect is commonly referred to as "crystal field activation energy" (CFAE) [1a–c]. From these properties it is concluded that low-valent metals do not favor water in the ligand sphere. Note that $Cr(CO)_6$ is a stable compound because of the outstanding π back-bonding of carbon monoxide, while $\{Cr(H_2O)_6\}$ does not exist – quite contrary to the common occurrence of $[Cr(H_2O)_6]^{3+}$. On the other hand, trivalent chromium does not form the (hypothetical) cationic carbonylchromium complex $\{[Cr(CO)_6]^{3+}\}$. This is, in short, one major reason why so little is known about typical organometallic water complexes. Comparatively few organometallic aquo complexes have been isolated in fact. Examples are the carbonylrhenium(I) and (π-benzene)ruthenium(II) complexes **1** and **2**, respectively, and their congeners **3**–**5** [3–6]. They can be used as convenient starting materials for complexes exhibiting the respective organometallic backbones, e.g., the $[Re(CO)_3]^+$ cation from **1** which is otherwise available only with difficulty [6]. The synthesis of aquo complexes from metal carbonyls proceeds via photolysis from the anhydrous parent compounds. The air-stable (!) rhenium complex **1** is conveniently generated from $[ReO_4]^-$ or $[ReOCl_4]^-$ and $[BH_3 \cdot \text{solvent}]$ in the presence of carbon monoxide [6a,b]. It is an outstanding precursor of products like $[L_3Re(CO)_3]^+$, with L = N- or P-donors [6].



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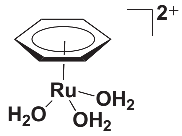

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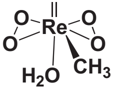

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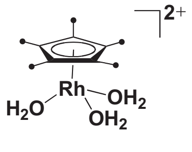

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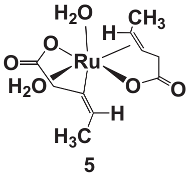

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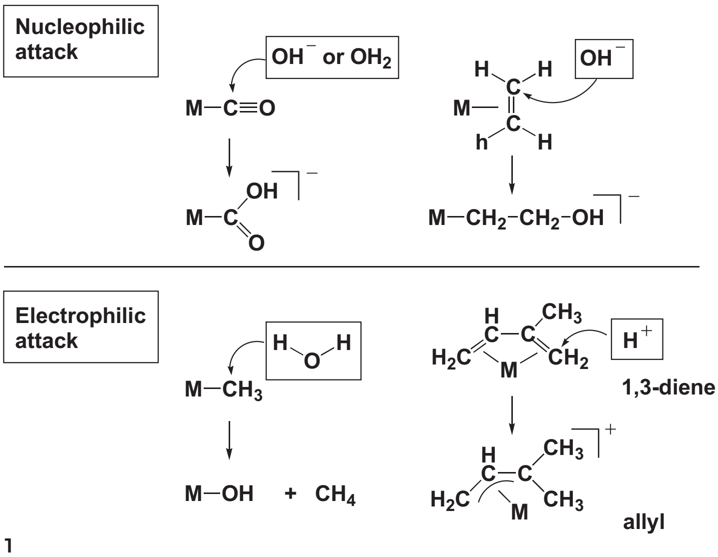
2.2.2.3
Organometallic Reactions of Water

Metal–carbon (M–C) bonds are thermodynamically unstable with regard to their hydrolysis products. Water can attack M–C bonds either by proton transfer (H^+, electrophilic reaction) or via the oxygen (OH_2 or OH^-, nucleophilic reaction). Examples are shown in Scheme 1. Ligands such as carbon monoxide and ethylene are activated toward nucleophilic attack upon coordination to (low-valent) metals, e.g., Pd^{2+}. A number of C-C bond-forming reactions derive from this activation. Allyl ligands are generated by proton attack at the terminal 1,3-diene carbon groups (Scheme 1). In other cases, protonation of heteroatoms of metal-attached ligands is followed by elimination steps; for example, the allyl alcohol ligand $H_2C{=}C(CH_3)CH_2OH$ (η^2) is converted by $H[BF_4]$ into the allyl cation $[H_2CC(CH_3){=}CH_2]^+$, which is a standard route of making metal–allyl complexes [3]. High bond polarity yields increased reactivity with water. Thus, $Al(CH_3)_3$ and $In(CH_3)_3$ hydrolyze quickly. $Sb(CH_3)_3$ and $Sn(CH_3)_4$ are inert because of low bond polarity and efficient metal shielding (electron pair at Sb, coordination number 4 at Sn). $Si(CH_3)_4$ is water-stable (low bond polarity, good steric shielding), while SiH_4 hydrolyzes quickly due to inefficient shielding and nucleophilic attack, probably via 3d orbitals of the silicon. However, metal hydrides hydrolyze only if they are ionic or coordinatively unsaturated. For example, NaH (ionic) instantaneously extrudes hydrogen upon contact with water whereas the covalent hydrides $Mn(CO)_5H$, $(\eta^5\text{-}C_5H_5)Fe(CO)_2H$, and $(\eta^5\text{-}C_5Me_5)ReH_6$ remain unchanged.

Since the M–R bond is normally polarized toward an anionic organyl group ($R^{\delta-}$), a metal hydroxide forms along with the respective hydrocarbon from metal alkyls [Eq. (1)].



Scheme 1

$$\overset{\delta^+}{\mathrm{M}}\!-\!\overset{\delta}{\mathrm{R}} + H_2O \rightarrow \mathrm{M{-}OH} + \mathrm{R{-}H} \tag{1}$$

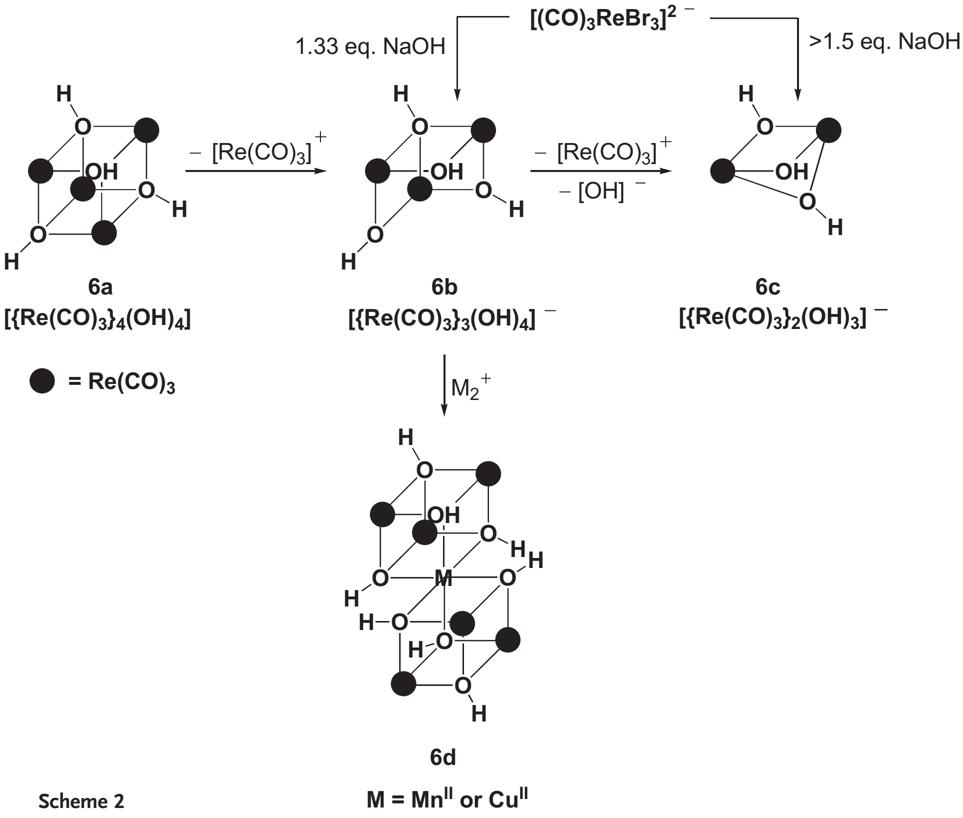
$$2\ \mathrm{M{-}OH} \rightarrow \mathrm{M{=}O} + H_2O\mathrm{{-}M} \tag{2}$$

$$2\ \mathrm{M{-}OH} \rightarrow \mathrm{M{-}O{-}M} + H_2O \tag{3}$$

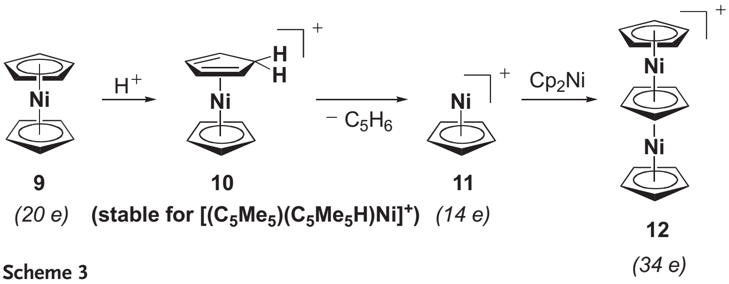
$$2\ Re_2(CO)_{10} + 4\ H_2O \xrightarrow[-8\ CO]{h\nu} [(CO)_3ReOH]_4 + 2\ H_2 \tag{4}$$

Follow-up products may include metal oxides, be it in a mononuclear or in a di- or oligonuclear form [Eqs. (2)–(4)]. The tetranuclear rhenium(I) complex formed by photolysis [Eq. (4)] has a cubane-type structure [7]. Related complexes **6a–d** were made according to Scheme 2 [8].

Since many organometallics behave as Lewis bases due to electron-rich metals, protonation is a common reaction. For example, the tungsten hydride **7** undergoes reversible protonation at the metal, forming the water-soluble cationic hydride **8** [Eq. (5)]. In nickelocene **9**, a 20e$^-$ complex, protonation occurs at the π-bonded cyclopentadienyl ligand; the intermediate **10** has a stable, isolable counterpart in

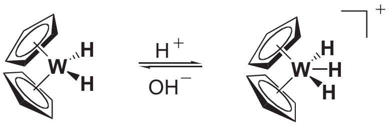


Scheme 2



Scheme 3

the fully methylated derivative. Consecutive loss of cyclopentadiene forms the cation **11**, which adds to unchanged nickelocene forming the tripledecker sandwich **12** (Scheme 3). Pronouncedly oxophilic metals such as the rare-earth elements are particularly sensitive to water. There are numerous cases where an oxo ligand has been introduced by accidental moisture present under the conditions of reaction [9]. Chemistry of this type of metals has therefore to be performed under rigorous glove-box conditions.



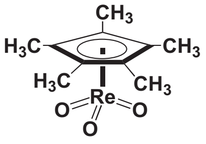
(5)

7 **8**

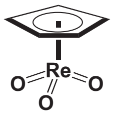
$$L_nRh–P(C_6H_5)_3 + H_2O \rightarrow O{=}P(C_6H_5)_3 + \ldots \quad (6)$$

$$(CO)_4CO–H + H_2O \rightarrow [CO)_4)Co]^- + H_3O^+ \quad (7)$$

There are also cases where the *ligand* reacts with water. Organic phosphanes, for example, may show up as phosphane oxides under certain circumstances [cf. Eq. (6)]. The oxidant is not always obvious in these cases, but it can be water. Strong metalla-acids undergo protonation of water to form the corresponding anion; $HCo(CO)_4$ is such an example [Eq. (7)]. There are cases where the M–C bonds withstand cleavage. The organorhenium(VII) oxide **13** (pentamethyl(cyclopentadienyl)trioxorhenium) does not exchange its terminal oxo ligands with water, while the sterically less hindered and more electron-deficient cyclopentadienyltrioxorhenium **14** exchanges its oxo ligands slowly [10].

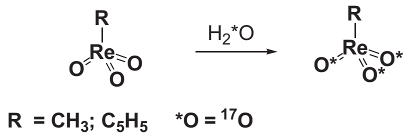


13

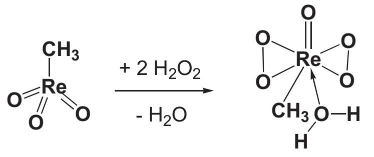


14

The water-soluble (ca. 30 g L^{-1}) methyltrioxorhenium(VII) (MTO) **15** [5] exchanges its oxo ligands quickly with water [Eq. (8)] [10] and it has been assumed that it possibly forms octahedral water adducts prior to undergoing aggregation to “polymeric MTO”. Mainly steric but also electronic reasons are likely to account for this difference between the organorhenium(VII) oxides **13** and **14**, and **15**. MTO is also an example of a water-stable metal organyl: even in boiling water, only a few of the methyl groups are lost (as methane) after several hours [5, 11]! The reaction product of MTO with excess hydrogen peroxide, a highly reactive and catalytically active organometallic bisperoxo complex (**16**) can be stabilized – among other possibilities – and isolated with a coordinating water molecule [Eq. (9)] [6e, 12]. Water can also oxidize organometallic complexes. For example, the platinum(IV) complex cation $[(C_6H_5)_2Pt(OH)]^+$ is generated from divalent platinum by reaction with water [13].



(8)



(9)

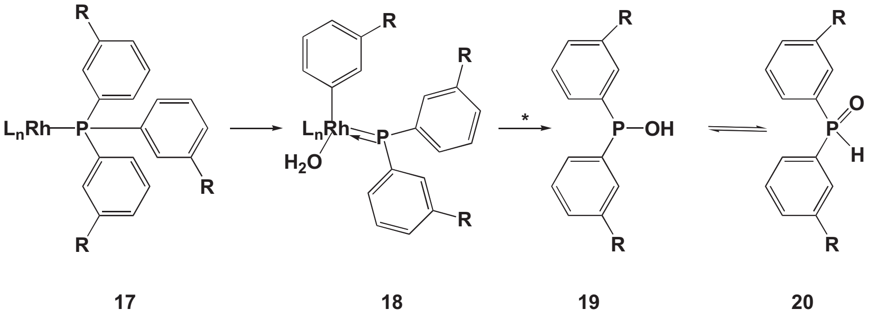
15 **16**

2.2.2.4
Water-Soluble Metal Complexes

Following the pioneering work in the area of biphasic catalysis [14, 15], a steady demand for water-soluble and, at the same time, water-compatible metal complexes has been recognized. Despite a broad array of solubilizing ligands, sulfonated derivatives of ligands containing aryl groups have proven most successful, mostly because of the outstanding solubility in water. Notably, the standard tris(*m*-sulfonatophenyl)phosphine [$P(C_6H_4$-*m*-SO_3-$Na^+)_3$; TPPTS] has a solubility of ca. 1.1 kg L^{-1} upon which the success of the catalyst system Rh/TPPTS depends in biphasic aqueous hydroformylation [15] (cf. Section 2.4.1.1). Numerous ionic organometallics, e.g., $Na[Re(CO)_5]$ or $[(\eta^5\text{-}C_5H_5)Fe(CO)_2\text{–}\{P(C_6H_5)_3\}]^+I^-$, are soluble in water and can be precipitated by large counter-ions (e.g., $[P(C_6H_5)_4]^+$, $[B(C_6H_5)_4]^-$, $[(C_6H_5)_3P{=}N{=}P(C_6H_5)_3]^+$). Basic ions such as $[Re(CO)_5]^-$ give hydrido complexes upon protonation, e.g., $HRe(CO)_5$.

2.2.2.5
Perspectives

Organometallic entities display a variety of reactions with water, following their commonly observed thermodynamic instability. However, in many cases, kinetic barriers prevent these reactions from occurring, making organometallics seemingly stable toward water and, often, even toward protic aqueous acids and hydroxides. Even in cases where highly charged metal ions coordinate water, further degradation of the (organic) ligand sphere does not necessarily occur. Therefore, water is much more compatible with organometallic compounds than has previously been assumed. The organic chemistry in water is just beginning to gain wider attention, too [2, 16]. Specific reaction modes arising from the reactivity of water have to be taken into account. Consider, for example, the sulfonated hydroformylation catalyst **17**, which undergoes slow but significant P–C bond cleavage (Scheme 4). The resulting phosphinidene intermediate **18** can react with water to give the phosphinous acid **20** via tautomerization of the hydroxyphosphine **19** [15a]. Thus, one must be aware of oxygenated (side) products when working with aqueous organometallics. The field is far from being fully explored.



R = SO_3Na

Scheme 4

Supercritical water (the critical point of water is reached at $T = 374.2$ °C and $p = 22.1$ MPa) offers opportunities in selectivity for organometallic reactions. The behavior of supercritical water is in several aspects (e.g.) heat capacity, viscosity, dissociation constant, quite different from water under normal conditions. This behavior change is due to the loss of hydrogen bridging. The dielectric constant, for example, changes from 78.5 to 6.0 in supercritical water and becomes quite similar to the dielectric constants of some organic solvents, such as tetrahydrofuran (THF) ($\varepsilon_{THF} = 7.4$). Several applications of supercritical water have been reported [17] during recent years. An example is the cyclotrimerization of certain alkynes, which is very selective for benzene derivatives in supercritical water at 374 °C [18]. Organometallic, water-soluble anticancer reagents, normally in the context of amino acid ligands, are also appearing more frequently in the literature now [19]. Important C–C coupling reactions, such as the Heck and Suzuki reactions, have been successfully transferred to aqueous media recently [20], the use of polymer-fixed homogeneous catalysts which can be dispersed in the aqueous phase is also becoming more widespread, and a particularly interesting development is the use of surface- or polymer-fixed catalysts which are reversibly released into the aqueous solution only in certain defined temperature intervals [21].

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2.2.3
Catalysts for an Aqueous Biphasic Catalysis

2.2.3.1
Central Atoms

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2.2.3.1.1
Introduction

As has been discussed in some detail in the previous section, organometallic complexes are usually regarded as water-sensitive and several of these compounds are indeed very instable toward moisture and decompose readily in the presence of even minor amounts of water. Nevertheless, the use of water as a solvent in many catalytic reactions is of the utmost interest, due not only to its unique properties (high dielectric constant, ability to solvate both cations and anions, etc.) but also to environmental and cost–benefit reasons, when it replaces toxic, explosive, or flammable organic solvents on an industrial scale (see Sections 2.1 and 2.3). Because of these advantages, catalysis by transition metals in aqueous media has become increasingly attractive, it has received much attention, and much effort has been put into research on suitable active complexes [1]. The solubility of the transition metal complexes can be brought about by using water-solubilizing ligands or it can be due to the direct interaction of the metal center with water. Organometallic complexes are usually viewed with respect to the fields of their (potential) applications in catalysis or from the point of view of their ligands, enabling solubility and providing the right environment for particular reaction pathways. In this section a different perspective is chosen. Here, we treat the organometallic complexes enabling catalytic reactions in the aqueous phase with respect to their metal atom, giving a very brief but general overview of the most recent developments; we then turn in more detail to organometallic catalysts in a stricter sense (compounds with an M–C bond) and discuss one particular example with respect to the behavioral changes of potential catalysts if the metal atoms are changed within one group of transition metals.

2.2.3.1.2
Overview of the Metal Complexes Involved in Aqueous Catalysis

This section is not intended to give a detailed description of the applications of organometallic complexes in aqueous catalysis. In Table 1 some recent catalytic applications for different metals are presented as examples. The complexes here are considered to be organometallic in a broader context. The comparatively few examples described with organometallic compounds in a stricter sense (containing an M–C bond) will be dealt with in the following paragraph. Since only the most recent applications are mentioned, for further information see the References.

Table 1 Selected transition metal complexes described recently as catalysts in the aqueous phase.

Central atom	***Catalyst***	***Type of reaction***	***Ref.***
W	$\{PO_4[WO(O_2)_2]_4\}^{3-}$	Oxidation of fatty acids	[2]
Ru	$RuCl_2(PPh_3)_3$	Allylic C–H activation	[3]
Ru	$[RuCl_2(p\text{-cymene}]_2L^{*}$[a]	Cyclopropanation	[4]
Ru	$Na[\{O_3S(C_6H_4)CH_2C(CH_2PPh_2)_3Ru\}_2(\mu\text{-}Cl)_3]$	Hydrogenation of alkenes	[5]
Ru	$[RuCl_3(NO)(TPPMS)_2]/[RuCl_3(NO)(TPPTS)_2]$[b]	Hydrogenation of CO_2	[6]
Ru	$[RuCl_2(PTA)_4]$[c]	Hydrogenation of olefins	[7]
Os	$[Os(CO)_3Cl_2]_2$	Hydration of acetonitrile	[8]
Co	$Co(CO)_8$[d]	Pauson–Khand reaction	[9]
Rh	$Rh_2(COD)_2Cl_2$	Carbonylation, conjugated addition	[3]
Rh	$Rh_2(COD)_2BF_4$	Carbonylation, conjugated addition	[3]
Rh	$Rh(acac)(CO)_2/PNS$[e]	Hydroformylation	[10]
Rh	$Rh(COD)BF_4/\alpha,\alpha\text{-}\ \beta,\beta$-trehalose	Asymmetric hydrogenation	[4]
Rh	$RhCl(CO)(PPh_2\text{-PS-PEG-}PPh_2)$[f]	Hydroformylation of alkenes	[11]
Rh	$[RhCl(m\text{-TPPMS})_3]$	Hydrogenation	[7]
Ni	$Ni(COD)_2/CF_3COOH/L$[g]	Isomerization of allylic alcohols	[12]
Pd	Pd/C	Synthesis of asymmetric biaryls	[3]
Pd	$Pd(TTPTS)_3$	Copolymerization CO/olefins	[13]
Pd	$PdCl_2/TPPTS$	Hydrocarboxylation of styrenes	[14]
Pd	$Pd(OAc)_2$ or $PdCl_2/(bpy)$[h]	Oxidation of alcohols	[15]
Pd	$Pd(OAc)_2/m\text{-TPPTC}$[i]	Heck reaction	[16]
Pd	$PdCl_2(PhCN)_2$	Kharasch reaction	[17]
Pd	$Pd(OAc)_2/BINAS$[j]	Amination of aromatic halides	[18]
Pt	*cis*-$PtCl_2(TPPTS)_2$[k]	Alkyne hydration	[19]
Cu	$Cu(NO_3)_2$/L-abrine[l]	Chiral Diels–Alder reaction	[20]
Ag	$AgNO_3$/(S)-Tol-BINAP[m]	Allylation	[4]
Ce	$Ce(Otf)_4L^{*}$[n]	Allylation	[4]

Even a short look at Table 1 reveals that Ru, Rh, and Pd, the "classical" catalyst metals, are still more frequently examined than other transition metals in catalysis. These "classical" catalyst metals, however, are quite expensive, so the use of cheaper metals seems desirable if this is possible without a significant loss of activity. Nevertheless, in cases where the (organic) starting materials for the reactions to be catalyzed are relatively expensive or where significant excesses of co-ligands are used, the price of the catalyst metal may not be decisive. Anyway, changing the catalyst metal is usually only desirable when significantly higher selectivities and/or turnovers are reached or the new catalyst is – with similar catalytic results – much more stable than its alternative/established competitors. Such general rules, however, are not strictly applicable for nonindustrial research where mechanistic or fundamental research may justify the use of complexes which are not applicable for industrial purposes.

It is also evident from Table 1 that seemingly a variety of ligands and even metal oxidation states may be applied for similar catalytic purposes. However, changes of both the surrounding ligands and the metal center make comparisons often difficult and generalizations dangerous.

2.2.3.1.3
Complexes Containing an M–C Bond in Aqueous Catalysis

Compounds containing one or more metal–carbon σ- or π- bonds (organometallic complexes in a strict sense) are still not so frequently used as catalysts in aqueous phase, despite the fact that their applications in aqueous systems are increasing. A more general account of organometallic complexes in water is given in Section 2.2.2, referring particularly to the role of water. However, the limited number of truly organometallic complexes applied in water containing organometallic catalytic systems are usually not systematically examined with respect to the influence of a change of the central atom (metal) on the behavior of the catalytic system. Ligand changes usually seem to provide an easier and subtler means of change in catalyst behavior than a change of the metal. In low oxidation state transition metal com-

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Footnotes to Table 1

a) L* = bis(hydroxymethyldihydroxyoxazolyl)pyridine.
b) TPPMS = P(m-$C_6H_4SO_3Na$)Ph_2.
c) PTA = 1,3,5-triaza-7-phospha-adamantane.
d) Water was used as reaction promoter; worse yields were obtained with water as solvent.
e) PNS = $Ph_2PCH_2CH_2C(O)NHC(CH_3)_2CH_2SO_3Li$.
f) PS-PEG = polystyrene-poly(ethyleneglycol).
g) 1,4-bis(diphenylphosphanyl)butane.
h) bpy = substituted 2,2′-bipyridine.
i) m-TPPTC = P(m-$C_6H_4CO_2Li$)$_3$.
j) BINAS = sulfonated 2,2′-bis(diphenylphosphinomethyl)-1,1′-binaphthyl.
k) TPPTS = P(m-$C_6H_4SO_3Na$)$_3$.
l) *N*-(α)-methyl-L-tryptophan.
m) BINAP = 2,2′-bis(diphenylphosphino)-1.1′-binaphthyl.
n) L* = (*S*,*S*)-2,6-bis(4-isopropyl-2-oxazolin-2-yl)pyridine.

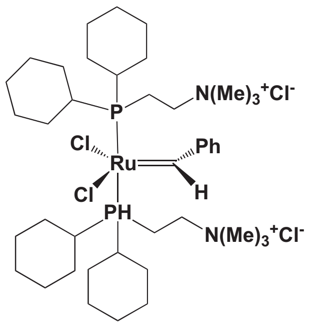
plexes, changes of the metal are usually regarded as of less significant influence than in high oxidation states, but such general statements should be regarded with great caution. Changes of both metal (often including its formal oxidation state) and (at least some of the) ligands are of course applied as well. In this case it is very hard to ascribe reliably and accurately the observed behavior changes to a defined source (such as the changed metal alone). In this section recent applications of complexes containing a metal–carbon bond in aqueous-phase catalysis are described briefly.

Molybdocene compounds have been known since the 1960s and have a very rich reaction chemistry. Recently, detailed investigations dealing with $[Cp_2MoCl_2]$ ($Cp = \eta^5\text{-}C_5H_5$) have been reported, mainly due to its potential as anti-tumour agent [21]. This has led to a particular interest in the study of the aqueous chemistry of molybdocenes and to the discovery of new catalytic properties of these compounds. $[Cp'_2Mo(\mu\text{-}OH)_2MoCp'_2](OTs)_2$ (**1**) ($Cp' = \eta^5\text{-}C_5H_4CH_3$, OTs = *p*-toluenosulfonate) was prepared from $[Cp'_2MoCl_2]$ and HOTs in aqueous acetone [22]. This compound was found to catalyze intra- and intermolecular H/D exchange with alcoholic substrates, through the intermediacy of a π-carbonyl complex, and was therefore capable of activating C–H bonds in aqueous solution.

The reaction of nitriles with water to form amides was also found to be catalyzed by complex **1** [23]. This is a commercially relevant reaction since amides are used as lubricants, detergent additives, drug stabilizers, etc. [24]. In aqueous solution this complex was found to be in equilibrium with $[Cp'_2Mo(OH)(H_2O)]^+$ (**2**), and this monomer was proposed to be the active hydration catalyst. The hydration was proposed to occur by an intramolecular attack of a hydroxide ligand on a coordinating nitrile. The reaction occurred under mild conditions, preventing the autocatalytic formation of acrylamide. Although this system allows the hydration of simple and functionalized nitriles, including acrylonitrile, which is hydrated exclusively at the C≡N position, its major drawback resides in the fact that the reactions are subject to product inhibition.

With the work by Grubbs et al. [27] and Herrmann et al. [28], the use of ruthenium carbene complexes as homogeneous catalysts for the ROMP (Ring-Opening Metathesis Polymerization) of olefins was established (see Section 2.4.4.3). The development of catalysts that can catalyze living polymerization in water was an important goal to achieve, especially for applications in biomedicine. In this context, two water-soluble ruthenium carbene complexes (**3** and **4**) have been reported that act as initiators for the living polymerization of water-soluble monomers in a quick and quantitative manner [29].

The polymerization must be conducted in the presence of an acid (that leaves the ruthenium–alkylidene bond intact) that eliminates any hydroxide ion present that would lead to catalyst decomposition. In solution under acid conditions, one of the phosphines is protonated; the monophosphine species formed is surprisingly stable. This species is not formed stoichiometrically, but always coexists with the biphosphine species, which is less reactive. No surfactants or organic solvents are needed. The same research group also presented a Ni(II) system [30] capable of producing high molecular weight polyethylene, polymerizing functionalized olefins, and requiring no co-catalyst. One of the compounds was tested in a toluene/water



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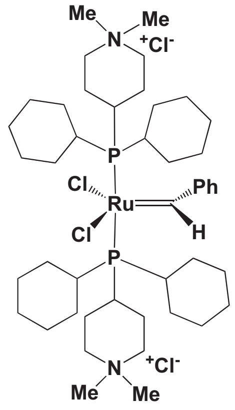

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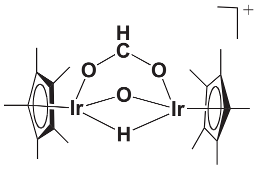
biphasic system, and the presence of water was found not to decrease the catalytic performance.

The compound $[Cp^*Ir(H_2O)_3]^{2+}$ ($Cp^* = \eta^5$-C_5Me_5) was found to be an efficient catalyst precursor for the hydrogenation of water-soluble compounds [25]. Such organometallic aqua complexes are very interesting, since their properties change drastically with variations of the solution pH, due to deprotonation of the aqua ligands [26]. The active catalyst was found to be a binuclear μ-hydride complex $[(Cp^*Ir)_2(\mu\text{-H})(\mu\text{-OH})(\mu\text{-HCOO})]^+$ (**5**) that could be isolated and characterized.



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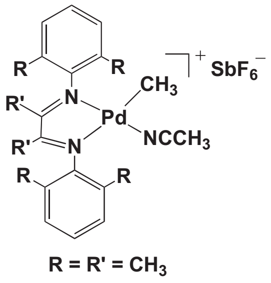
The pH-dependent transfer hydrogenation of water-soluble carbonyl compounds in the presence of a hydrogen donor (HCOONa) was studied for a different series of carbonyl compounds, namely straight-chain aldehydes, cyclic aldehydes, ketones, aldehyde-acids and keto-acids. The reaction rates were found to be higher for aldehydes than for ketones. Furthermore there was a strong pH dependence of the reaction, the best results being obtained at pH 3.2. This value corresponds to the higher yield of the catalyst formed from the catalyst precursor and HCOONa.

A Pd(II) complex bearing a diimine ligand (**6**) [31] was also found to catalyze the polymerization of ethylene in aqueous conditions. Highly branched or linear polyethylenes can be obtained at high rates. It is interesting to note that an aqueous suspension of the precursor complex displays a high activity and stability, but solutions in acetone/water mixtures are inactive toward ethylene. The polymers obtained have a higher molecular weight and are in general less branched than the ones obtained in organic solvents under otherwise identical conditions.



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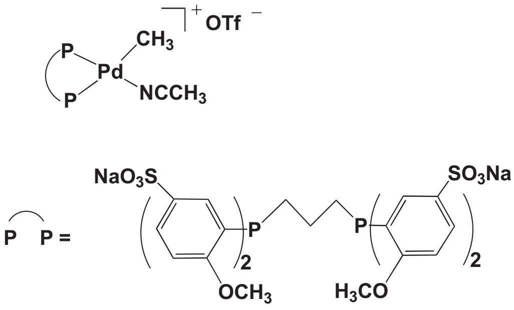
A further example of the application of an organometallic palladium complex as polymerization catalyst was presented by Sheldon et al. [32]. The active complex can be obtained by reacting [PdCl(CH_3)COD] (**7**) in methanol with a tetrasulfonated diphosphane, under abstraction of a chloro ligand by AgOTf. The complex can be isolated as an air-stable white solid and shows a remarkable activity on the copolymerization of ethylene and CO in water. In fact, activities of 32.2 kg copolymer per gram Pd are reached, corresponding to TOFs > 61 000 h^{-1}.



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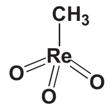
2.2.3.1.4
Mn, Tc, Re Complexes $H_3C–MO_3$ as an Example of Metal Variation in Potential Catalysts for Aqueous Systems

Methyltrioxorhenium(VII) (MTO, **8**) has been established as a powerful catalyst for a broad variety of organic transformations [33]. MTO has also found several applications in catalytic reactions performed in the aqueous phase, due to its pronounced stability to both water and temperature. A more detailed description of the application of MTO in aqueous systems is given in Section 2.4.3.3. When the particular importance of the presence of the Re–C bond in MTO was noted, the question arose of whether it would be possible to synthesize similar transition metal complexes derived from metals cheaper than Re, which would be applicable for the same purposes and would have comparable stabilities (**8**–**10**) [34]. Furthermore, would the lower homologues of Re parallel the chemistry of MTO and its derivatives, or differ principally as found within group 8 transition metals? Not much was known of the organometallic chemistry of technetium in the high valencies in the late 1980s [35].



MTO

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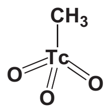

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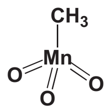

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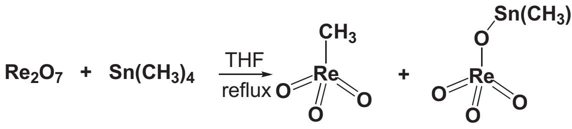
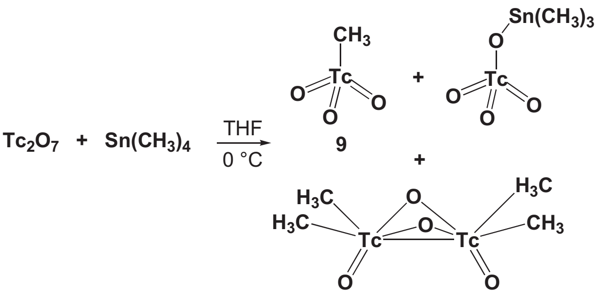
The reasons for this fact were manifold. Technetium is an artificial element and accordingly rare and not readily available. Therefore it was not examined in great detail with respect to its organometallic chemistry in the early days of this research field. However, since one of the isotopes, Tc-99(m), possesses interesting decay characteristics for application in nuclear medicine coordination chemistry in aqueous systems, it was investigated thoroughly with the goal of yielding compounds to be applied in life sciences. The main focus during this exploration was originally put on classical Werner-type complexes rather than on organometallics. During the late 1980s, growing interest arose in the high oxidation state chemistry of Tc, following the exploration of the chemistry of $(C_5(CH_3)_5))ReO_3$ and the finding of the catalytic usefulness of MTO [36]. In 1990, the synthesis of $H_3C–TcO_3$ was reported, starting from Tc_2O_7 and $Sn(CH_3)_4$, a pathway seemingly similar to the preparation of MTO [Eqs. (1) and (2)] [37]. However, while the reaction of Re_2O_7 with $Sn(CH_3)_4$ takes place in boiling THF and is completed under these conditions after ca. 4 h, the synthesis of CH_3TcO_3 (**9**) has to be performed below room temperature to avoid decomposition of the product, which is quite sensitive to both temperature (decomposition above ca. 20 °C) and moisture (formation of pertechnetium acid). Besides the desired product and the synthetically (in this particular procedure) unavoidable byproduct $(CH_3)_3Sn–O–TcO_3$, a dimer of composition $(CH_3)_2OTc(\mu\text{-}O)_2TcO(CH_3)_2$ is formed, due to reduction of Tc(VII).



MTO

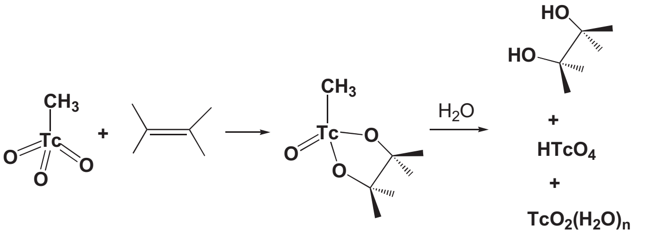
8

(1)



(2)

An analogous by-product is not formed during the synthesis of MTO. CH_3TcO_3 does not form stable adducts with N-donor Lewis bases, such as bipyridine and quinuclidine, a reaction that is quite characteristic for MTO and also of importance for its application in olefin epoxidation catalysis [38]. Vibrational spectroscopic investigations of CH_3TcO_3 indicate much weaker M=O interactions than in the case of its Re congener. In other reactions, MTO and CH_3TcO_3 differ not only marginally but also fundamentally. Olefins such as cyclohexene add to the Tc complex to form a glycolate Tc(V) compound. In the presence of water and acids this complex decomposes to yield the 1,2-diol and the disproportionation products $TcO_2(H_2O)_x$ and $[TcO_4]^-$ [Eq. (3)]. As observed for OsO_4, this reaction sequence occurs catalytically [39]. Based on these results it has been concluded that the even more powerful olefin-cleaving oxidizing agent RuO_4 might correspond to the still unknown $H_3C–MnO_3$ [37a].



(3)

It is interesting to note the attempts to synthesize $(C_5(CH_3)_5)TcO_3$ in this context. The Re homologue was originally prepared from $(C_5(CH_3)_5)Re(CO)_3$ and H_2O_2 [40]. The synthesis of "$(C_5(CH_3)_5)TcO_3$" was reported to work likewise; the reported structure of the product, however, was unparalleled in Re chemistry: "$(C_5(CH_3)_5)TcO_3$" was described as a linear polymer of formal composition $[(C_5(CH_3)_5)Tc(\mu\text{-}O)_3Tc]_n$, having an unusually short Tc–Tc distance [41]. Despite the fact that the structure has been rationalized theoretically [42] after it was described, its validity has been questioned, particularly since the published synthesis proved to be irreproducible and problems with the published structure became evident [37a]. A subsequent re-examination of the structural data of the Tc compound and a detailed examination of the structure of its Re congener (which suffers from both twinning and disorder phenomena) by Cotton et al. revealed that the compound of composition $[(C_5(CH_3)_5)Tc(\mu\text{-}O)_3Tc]_n$ was very likely in reality to be its Re congener (!) and "$(C_5(CH_3)_5)TcO_3$" possibly never existed in fact [43]. Nevertheless, the existence of $(C_5(CH_3)_5)TcO_3$ has been predicted on the basis of theoretical calculations [44].

Theoretical investigations (density functional investigations studying the influence of relativistic effects on the reactivity of the metal center) have been performed to account for the differences in chemical behavior of MTO and its Tc congener, which should be isostructural with their different behavior therefore originating solely or at least overwhelmingly from electronic reasons [45]. In order to quantify the Lewis acidity of the central metal atom, adduct formation with NH_3 as a probe molecule has been examined. MTO was calculated to form stable base adducts, which is in accordance with experimental results. The calculation for the

Tc complex yielded longer M–N bond distances and lower M–N stretching frequencies indicating fairly small association energies, also in accord with the above-mentioned experimental result that CH_3TcO_3 does not form Lewis adducts. From the calculated NH_3 adduct formation energies supported by an analysis of the charge distribution it was concluded that Re is a somewhat stronger Lewis acidic center than Tc in the MO_3 moiety. According to an analysis of Mulliken populations and of core and valence level shifts, charge transfer from NH_3 occurs preferentially to the Re center in the case of MTO and to the oxo ligands in CH_3TcO_3. From the charge distribution in CH_3MO_3 and in the corresponding NH_3 adducts it can be concluded that Re is the stronger and more reactive Lewis acidic metal center, as it withdraws electronic charge from all its ligands, including the electronegative oxygens. The hardness, calculated from the HOMO–LUMO splitting and from the M–O displacement derivatives of the charges as well as of the dipole moment, increases in the order $CH_3TcO_3 < OsO_4 < CH_3ReO_3$. This result rationalizes the fact that CH_3TcO_3 and OsO_4 preferentially react with softer bases, whereas MTO prefers to react with hard bases. Accordingly, MTO reacts with the harder Lewis base H_2O_2 to form mono- and bisperoxo complexes. Instead of oxidizing olefins directly, it even exhibits reactivity with epoxides to react further to glycolate complexes if no H_2O_2 is present. On the other hand, the MO_3 moiety of CH_3TcO_3 and OsO_4 has been calculated to be more polarizable. Therefore, the preferred reaction partners are soft Lewis bases, e.g., olefins through their π-bonds [45]. In fact, CH_3TcO_3 takes a place between MTO and the dihydroxylating agent MnO_4^- [46]. Based on Hartree–Fock results, $H_3C–MnO_3$ has been predicted to be unstable [44]. Considering the stability discussed above and sensitivity differences observed between MTO and CH_3TcO_3 this might really be the case. When considering $CpMnO_3$, it turned out by a DF theory approach [47] that the Cp ligand should be bound in a η^1 fashion, not in a η^5 fashion as observed for $CpReO_3$ [48]. It has to be noted, however, that $CpReO_3$ shares neither the water solubility nor the temperature stability of MTO and seems also to be much less applicable to catalytic reactions. However, despite the fact that in theoretical examinations it is usually regarded as an more easily calculated substitute for the experimentally much better examined Cp^*ReO_3, the chemical behavior of these two complexes seem to be surprisingly different [48]. $CpReO_3$ seems to decompose under formation of η^3- and η^1-intermediates at elevated temperatures [49]. Accordingly, $CpTcO_3$ and $CpMnO_3$ might be even more unstable than their CH_3MO_3 congeners and should therefore not be applicable as catalysts in an aqueous medium in a comparable fashion to MTO.

In summary, the theoretical and experimental results obtained for CH_3MO_3 (M = Mn, Tc, Re) clearly show that the Tc complex is much more prone to reduction than the Re complex MTO. While the Tc(VI) complex $(CH_3)_3OTc(\mu\text{-}O)_2TcO(CH_3)_2$ forms as a byproduct of the synthesis of CH_3TcO_3 from Tc_2O_7 and $Sn(CH_3)_4$ even below room temperature, the Re(VI) congener $(CH_3)_3ORe(\mu\text{-}O)_2ReO(CH_3)_2$ is only made available by means of the much stronger methylation/reducing agent $Zn(CH_3)_2$ [50]. CH_3TcO_3 is very sensitive to water, while MTO is water-stable and only sensitive to basic reaction conditions, forming perrhenate as a reaction product [51]. While MTO forms peroxo complexes with H_2O_2, which are also water-stable and react with olefins under epoxide formation, CH_3TcO_3 reacts with olefins directly under formation of glycolate, Tc being a softer Lewis acid than Re in the MO_3 moiety. CH_3MnO_3 has been predicted to be far more sensitive than the Tc compound and has accordingly not been isolated to date.

This subsection shows that at least for certain transition metal complexes, such as high oxidation state compounds of group VII, a change of the metal in otherwise identical complexes may have severe consequences for their behavior in both catalysis and reaction chemistry, turning complexes from stable, water-soluble and catalytically very versatile, e.g., MTO- to temperature- and moisture-sensitive ones with very different chemical behavior, such as (CH_3TcO_3), or even to ones that do not exist, such as (CH_3MnO_3). When changing from CH_3TcO_3 to OsO_4 the differences in reaction chemistry are seemingly less pronounced, but a change of the metal alone is also not straightforwardly feasible. Cases where the changes from metal to metal cause less pronounced changes in the chemistry, however, are also known. Examples are some cases of low oxidation state transition metal chemistry and several aspects of the chemistry of the rare-earth complexes.

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2.2.3.2
Ligands

2.2.3.2.1
Phosphorus-Containing Ligands

Othmar Stelzer (†), Stefan Rossenbach, Dietmar Hoff, Marcel Schreuder-Goedheijt, Paul C. J. Kamer, Joost N. H. Reek, and Piet W. N. M. van Leeuwen

a) Monophosphines

General Features, Scope, and Limitations

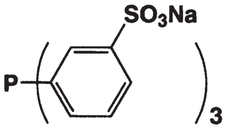
The water solubility of the catalysts in aqueous two-phase catalysis can be achieved by appropriate modification of the phosphine ligands with polar groups such as SO_3^-, COO^-, NMe_3^+, OH, etc. [1a]. First attempts to carry out transition metal catalyzed reactions using water-soluble phosphine ligands date back to 1973 [1b]. The monosulfonated derivative of Ph_3P had already been synthesized in 1958 [1c], and the well-known standard ligand TPPTS (trisulfonated triphenylphosphine) was reported by Kuntz in 1975 [2]. The development of new types of hydrosoluble phosphine ligands with "tailor-made" structures for highly active and selective two-phase catalysts is an ongoing challenge to chemists working in this field. Aspects of the topic under review have been covered in the literature by review articles [3–6] and monographs [7].

Anionic Phosphines

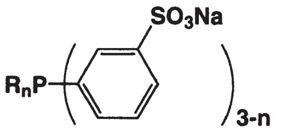
Phosphines Containing Sulfonated Aromatic and Aliphatic Groups

Water-soluble phosphines of this type reported in the literature so far are collected as Structures **1**–**6**. Direct sulfonation of the neutral "mother phosphine" with oleum, introduced originally by Kuntz in 1975 [2] for the preparation of TPPTS (**1a**), is still the most important procedure; it has also been used for the syntheses of an extended series of TPPTS-type catalyst ligands, e.g. **1b** (R = Ph [8], C_6H_{13} [9]), **1c** (R = alkyl, CYHex; R′ = Me, OMe [10]), **1d** (R = 4-F-C_6H_4 [11]), **1e** [12]. Sulfonated tris (ω-phenylalkyl)phosphines **5a** [13] and their *p*-phenylene analogues **5b** [14] as well as the bicyclic phosphine **4** [15] were obtained in an analogous manner. Triarylphosphines containing activated aryl groups, e.g., the dibenzofuran system, can be sulfonated with concentrated sulfuric acid under mild conditions (**1g**) [16c]. The kinetics of PPh_3 sulfonation have been investigated by Lecomte and Sinou [16a]. The selectivity has been studied by Chaudhari [16b].

The formation of phosphine oxides, which is a serious disadvantage inherent to this synthetic procedure [17], may be suppressed by addition of boric acid to the reaction mixtures [18].

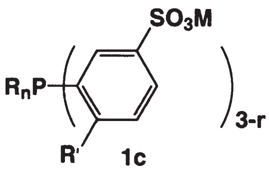


1a (TPPTS)



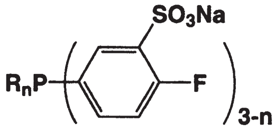
1b

R = Ph; n = 1, 2 (TPPDS, TPPMS); R = Me; n = 1;
R = C_6H_{13}; n = 1



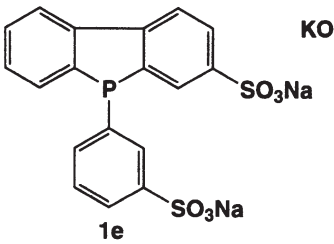
1c

R = Me, Et, Pr, Bu, Cy;
R'= Me, OMe; n = 0-2

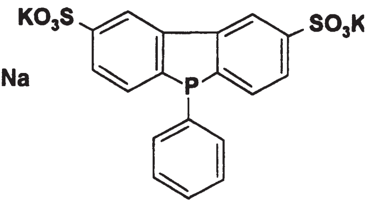


1d

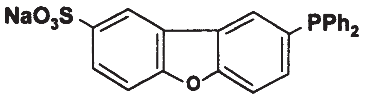
R = 4-F-C_6H_4; n = 0–2



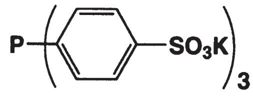
1e



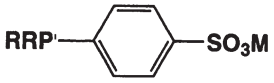
1f



1g

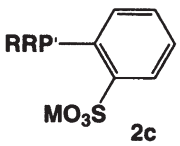


2a



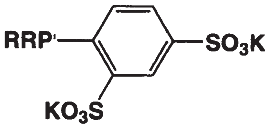
2b

R = R' =Ph, 3-Py; R = H;
R'= Ph; R = 2-Py;
R'= 4-SO_3K-C_6H_4;
M = Li, Na, K



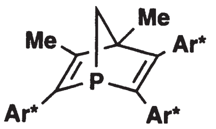
2c

R =R'=Ph; M = Li, K;
R = H; R'=Ph; M = K, Na



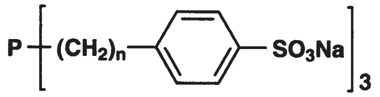
3

R = R'= Ph, 3-Py;
R = H; R'= Ph, Ar*;
R = 2-Py, Ph; R'= Ar*;
R = CH_2Ph, nBu; R'= Ar*;
R = CH_2Ph; R'= Mes;
Ar* = 2,4-$(SO_3K)_2C_6H_3$

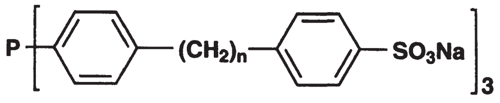


4

Ar* = 4-SO_3Na-C_6H_4
(NORBOS)



5a (n = 1–3, 6)



5b (n = 3, 6)

Figure 1 Water-soluble phosphines containing sulfonated aryl and alkyl side chains.

Ruthenium complexes of TPPTS and TPPMS [19–22] have been employed as catalysts or catalyst precursors for the hydrogenation of α,β-unsaturated carbonyl compounds in biphasic systems [19–23a]; cf. Section 2.4.2. Other ligands **7**–**13** are known and have been described [20, 23b, c].

The technically most important biphasic process in the Ruhrchemie/Rhône-Poulenc hydroformylation of propene uses the *in-situ* Rh(I) catalyst HRh(CO)-$(TPPTS)_3$ [6, 24]. Its formation from $Rh(CO)_2(acac)$ and TPPTS in a syngas atmosphere has been studied in detail [25, 26]. The BINAS-Na (**10**)/Rh catalyst showed an outstanding performance in propene hydroformylation [15]. Binuclear thiolato-bridged rhodium complexes **11** have been used in 1-octene hydroformylation as precatalysts [41]. For details of the hydroformylation, see Section 2.4.1.1 [15, 27, 28].

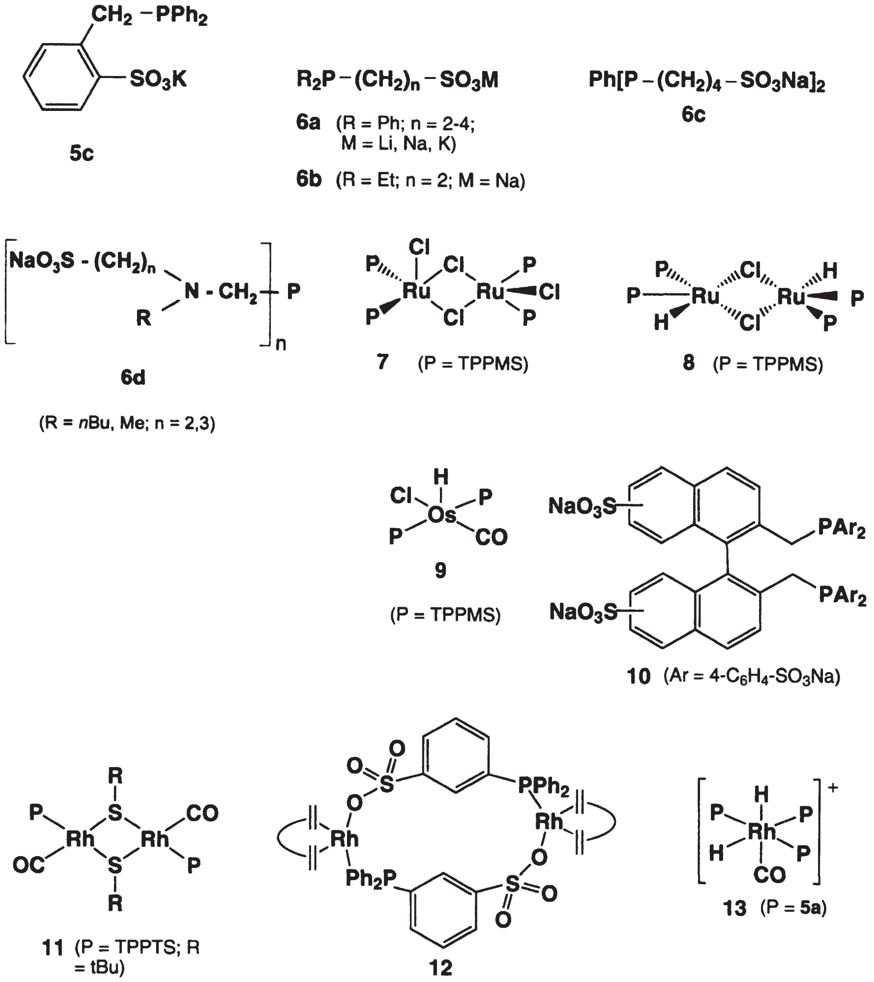


Figure 2 Structure of catalysts, ligands, and intermediates.

Rh(I) catalysts containing TPPTS-type ligands with electron-withdrawing groups in the aromatic rings show higher *n*/*i* selectivity in hydroformylation reactions. Thus *para*-fluorinated derivatives of TPPTS and TPPDS (**1d**), which are weaker bases and stronger π-acids than TPPTS and TPPDS [29], in 1-hexene hydroformylation gave *n*/*i* selectivities of 93 : 7, compared with 86 : 14 for the nonfluorinated ligands [11]. The application of aqueous two-phase catalysis in hydroformylation of longer chain olefins is hampered, however, in most cases by their low solubility in water. This problem has been overcome by using phosphine ligands like **5b**, showing a more pronounced surface-active character than TPPTS.

High ionic strengths stabilize the hydration sphere by minimizing the electrostatic repulsions between the sulfonate groups. As a consequence the dissociation energy for TPPTS with formation of the active species $\{HRh(CO)(TPPTS)_2\}$ will be increased, thus lowering the activity of the catalyst. In agreement with this reasoning a value of 30.6 or 22.4 kcal mol^{-1} has been calculated for the barrier of exchange at high or low ligands and complex concentration, respectively [30].

Palladium complexes of TPPTS and TPPMS have been employed extensively as catalysts for carbonylation, hydroxycarbonylation, and C–C cross-coupling reactions. Hydroxycarbonylation of bromobenzene in a biphasic medium using $Pd(TPPTS)_3$ as catalyst yields benzoic acid, which remains in the aqueous phase, thus avoiding the direct recycling of the catalyst [31]. The formation of $Pd(TPPTS)_3$ from $PdCl_2$ and TPPTS in aqueous solution has been studied in detail by ^{17}O, $\{^1H\}^{31}P$, and ^{35}Cl NMR spectroscopy. The complex $[PdCl(TPPTS)_3]^+Cl^-$ obtained initially is reduced by excess TPPTS, TPPTSO being formed. A more attractive synthesis of $Pd(TPPTS)_3$ involves the facile reduction of $[PdCl(TPPTS)_3]^+Cl^-$ with CO [32].

Ni(0) complexes of TPPTS have been employed as catalysts for the hydrocyanation of dienes and unsaturated nitriles. Product linearity and catalyst lifetimes can be improved if the catalysis is performed in a xylene/water biphasic system by using TPPTS as co-catalyst [33]. The Ni(0)/TPPTS complexes employed may be obtained by electrochemical reduction of $Ni(CN)_2$ in water in presence of TPPTS [34].

Dual metal Rh/Ir/TPPTS catalysts have been employed in the hydroaminomethylation of 1-pentene with synthesis gas ($CO/H_2 = 1 : 5$) and ammonia in an aqueous two-phase system [35]. With this catalyst system good *n*/*i* selectivities and a rapid hydrogenation of the imine to amine have been observed. Both primary and secondary amines can be formed with high selectivity by variation of the olefin/NH_3 ratio.

Rhodium(I) complexes $HRh(CO)L_3$ of alkali metal phenylphosphinoalkylsulfonates (L = **6a**, $n = 3, 4$; **6c**) have been used as catalysts for hydroformylation of higher olefins (e.g., *n*-1-tetradecene) in methanolic solution. The catalyst could be recovered with loss of activity by extraction of the isolated product with water.

Phosphines Containing Carboxylated Aromatic Groups and Side Chains

Structures **14**–**22** (Figure 3) are hydrophilic phosphine ligands bearing carboxylic groups. In contrast to their alkali metal salts, the free acids show only moderate

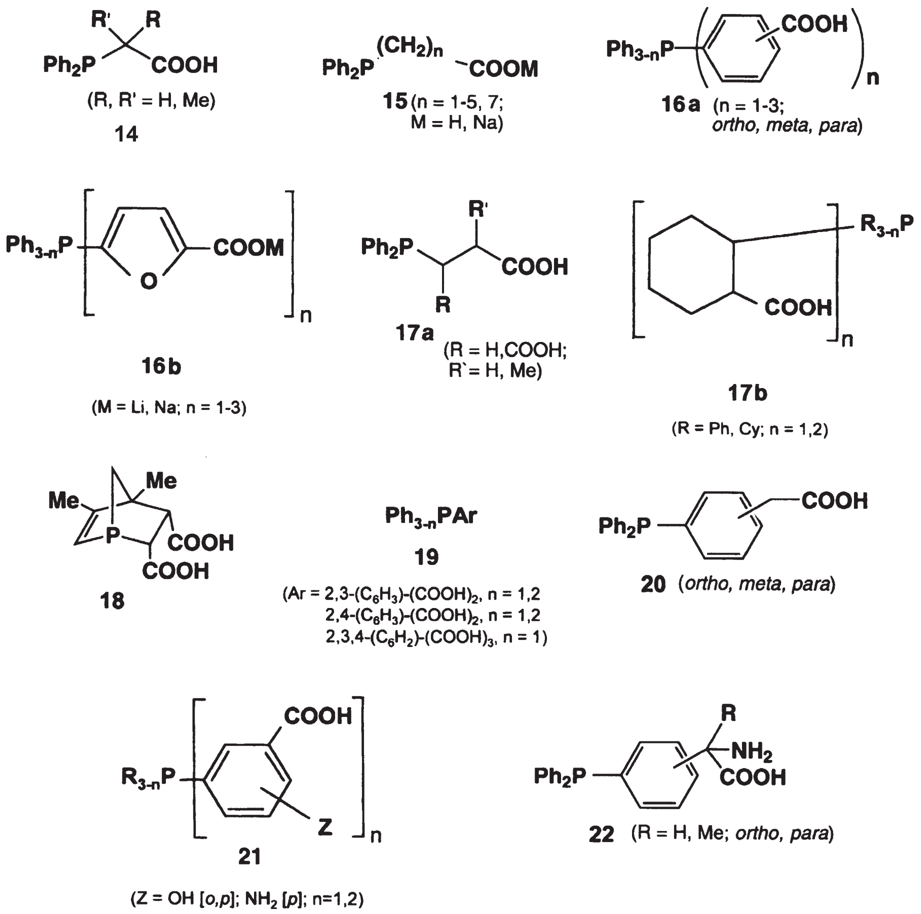


Figure 3 Carboxylated phosphines.

solubilities in water. The ligands **15**–**17a** have been obtained by standard preparative methods comprising alkylation and arylation of alkali metal organophosphides in organic solvents (THF, DME, dioxane) [36–38]. Improved synthetic procedures based on the nucleophilic phosphination of fluorobenzoic acids [39] or Pd-catalyzed P–C coupling reactions of bromo- and iodobenzoic acid with primary or secondary phosphines [40] are known. These methods are of broad applicability and can be used also for the syntheses of multiply functionalized phosphinocarboxylic acids (**19**, **21**) including the diphenylphosphinophenylacetic acids (**20**) and the novel phosphine ligands containing amino acid moieties (**22**) [41].

Compared with their sulfonated analogues, phosphine ligands containing carboxylic acid moieties have been much less investigated as catalyst components, although some of them (e.g., Ph_2PCH_2COOH, **14**) have already been applied at an early stage in the Shell Higher-Olefin Process (SHOP; cf. Section 3.3) [42], the first large-scale industrial biphasic but nonaqueous catalytic process.

Phosphines Containing Phosphonated Aromatic Groups and Alkyl Side Chains

The water-soluble phosphonate-functionalized phosphines have been obtained by halogen–metal exchange on bromophenyldiphenylphosphines with *n*BuLi followed by reaction with diethyl chlorophosphate and subsequent hydrolysis [43].

Catalytic applications have been described [44–48].

Cationic Phosphines

The synthesis of AMPHOS, the prototype of cationic phosphines, requires intermediate protection of the phosphorus in $Ph_2P–(CH_2)_2–NMe_2$ by oxidation or coordination to a transition metal before N-quaternization [49, 50a]. In the case of the ligands **23a** and **23b** (Figure 4), borane was used as the protecting group.

Ligands **25** and **26a** containing guanidinium moieties constitute a novel type of cationic phosphine ligand showing extreme solubilities in water. The guanidinium groups were introduced into the corresponding aminoalkyl- and aminoarylphosphines by addition of cyanamides $R_2N–CN$ (R = H, Me) or 1*H*-pyrazole-1-carboxamidine [50b,c].

Catalytic applications have been described [40b,c, 51–53].

Rhodium(I) and cobalt(0) complexes of AMPHOS, $[(nbd)Rh(AMPHOS)_2]^{3+}$, and $[Co(CO)_3(AMPHOS)]_2(PF_6)_2$, were already being used in the early 1980s for the hydrogenation and hydroformylation of maleic and crotonic acid or styrene and 1-hexene in water or aqueous biphasic systems [49]. The lower effectiveness of the Co catalyst was attributed to the lighter metal's proclivity to oxidation and phosphine

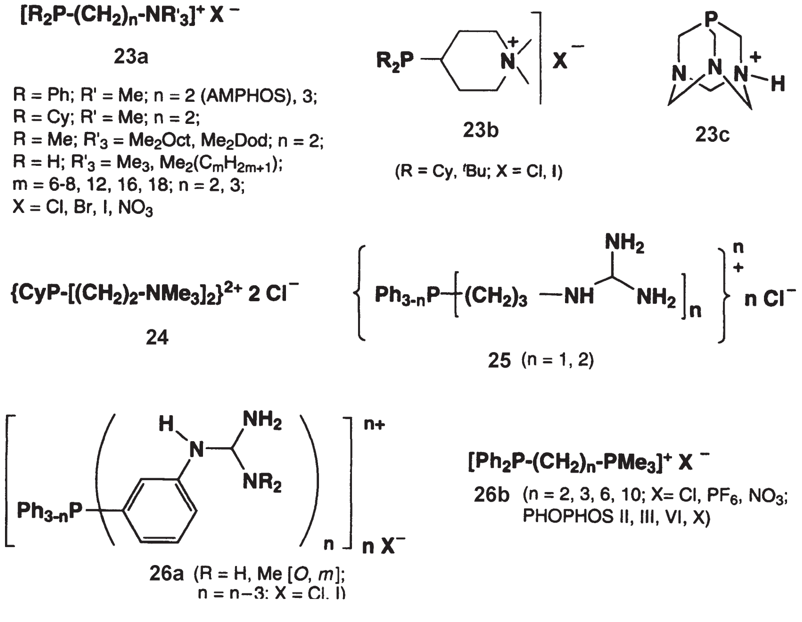


Figure 4 Cationic phosphine ligands.

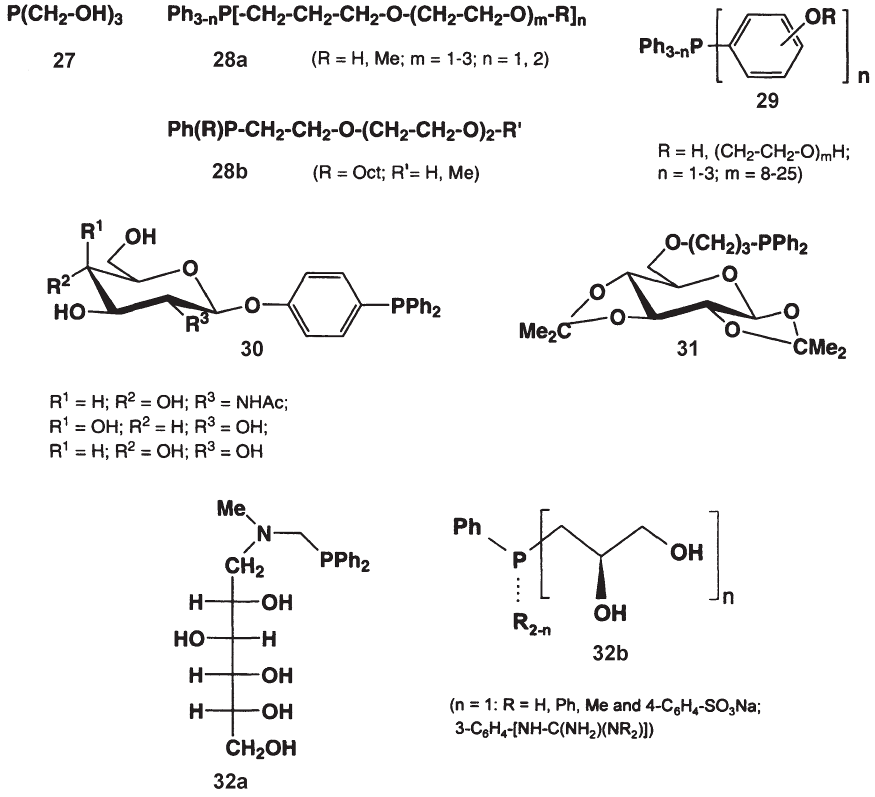


Figure 5 Nonionic water-soluble phosphines.

dissociation. Binuclear thiolato-bridged Rh(I) complexes, $[\mathrm{Rh(CO)(AMPHOS)}(t\mathrm{BuS})]_2^{2+}2[\mathrm{BPh}_4]^-$ are highly active catalysts for the hydrogenation of unsaturated alcohols and acids [106]. Water-soluble Rh(I) complexes of monoprotonated 1,3,5-triaza-7-phosphaadamantane (PTA), $[\mathrm{Rh(PTA)}_2\mathrm{(PTAH)Cl]Cl}$(PTAH = **24c**), have been used as catalysts for the regioselective reduction of unsaturated to saturated aldehydes with sodium formate in an aqueous biphasic system or dihydrogen in presence of ethanol as co-solvent.

Nonionic Water-Soluble Phosphines

The concept of attaining water solubility by incorporation of hydroxylic groups into the ligand periphery has either to attracted little attention. Large-scale syntheses for **27** [54] based on K_2PtCl_4-catalyzed addition of aqueous formaldehyde to PH_3 or decomposition of commercially available $[P(CH_2OH)_4]^+Cl^-$ have been published recently [55]. Ligands of type **28a** have been obtained by addition of $Ph_{3-n}PH_n$ to ethylene glycol monoallyl ethers [56]. Chiral ligands of this type, e.g., **28b**, showing unprecented η^3-mode bonding to transition metals, were prepared by Mathieu and co-workers [57]. The hydroxyphenylphosphines **29** are accessible by multistage syntheses [58] or by making use of the Pd-catalyzed P–C coupling reaction employing iodophenols as starting materials [40]. Ethoxylation of mono-, di- and tris-*p*-hydroxytriphenylphosphines with ethylene oxide yields polyether-substituted triphenylphosphines (PETPPs) designed for use in micellar [59, 60] and thermally regulated [61] phase-transfer catalysis. Ligands whose water solubility is inversely dependent on temperature were first reported by Bergbreiter et al. [62]. This subject will be discussed in more detail in Chapter 7.

Ligands incorporating the diphenylphosphine moiety into sugar structures have been reported by a number of authors [68, 64]. In most cases, however, the hydroxyl functions were fully (e.g., **31**) or at least in part protected, the solubilities of these ligands in water being low [56]. By two-phase glycosidation of acetyl-protected halopyranoses with *p*-hydroxyphenyldiphenylphosphine at ambient temperature and subsequent O–Ac deprotection the aryl-*β*-*O*-glycosides of glucose, galactose, and glucosamine (**30**) could be obtained [65]. There are scattered examples of applications in catalysis [66, 67]. The same is true for **32**.

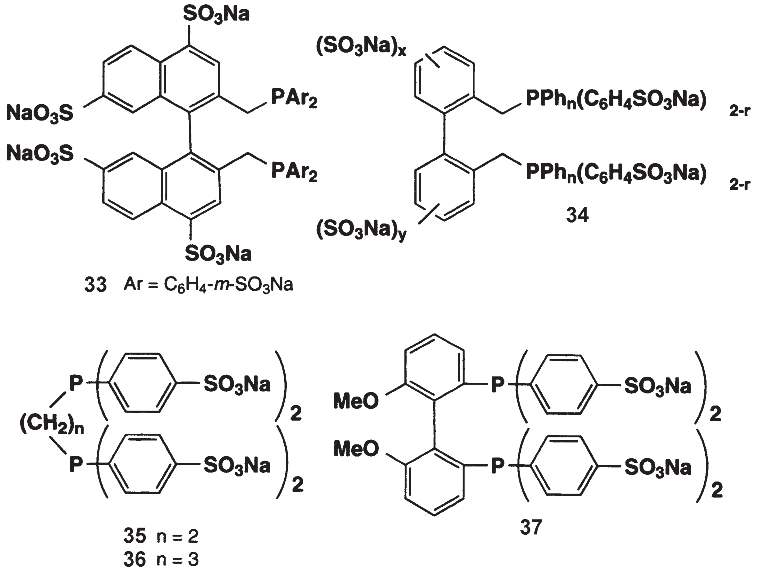
b) Diphosphines and Other Phosphines

Diphosphines: Introduction of Sulfonate Groups by Direct Sulfonation

Water-soluble diphosphines have been synthesized by controlled sulfonation in oleum (**33**–**37**). Although the number of chiral diphosphines reported is ever increasing, the number of sulfonated achiral diphosphines remains limited and includes BINAS-8 (**33**) [68] and BISBIS (**34**) [69], both of which contain an aromatic bridge between the two phosphino moieties, and the alkyl-bridged bidentates 1,2-bis[di(3-sulfonatophenyl)phosphino]ethane (**35**) [70] and 1,3-bis[di(3-sulfonatophenyl)phosphino]propane (**36**) and some analogues [71]. Sulfonated analogs of Xantphos have also been prepared using this strategy and these water-soluble ligands from rhodium complexes that are very selective in the hydroformylation of alkenes [72].

The precise control of the number and position of the sulfonate groups remains a challenge. The concentration of SO_3 and reaction temperature have a major effect on the degree of sulfonation [73]. Oxidation of phosphorus may be avoided using a method developed by Herrmann et al., which makes use of a superacidic medium derived from orthoboric acid and anhydrous sulfuric acid [74a]. In that manner, BINAP was sulfonated almost without formation of phosphine oxides (≤ 3 mol%).

The diphosphines **33** and **34** were tested as ligands in the rhodium-catalyzed *biphasic* hydroformylation of propene. Both catalysts were found to exhibit higher activities and gave rise to higher *l*/*b* ratios [68] than TPPTS. Furthermore, it was shown that displacement of the *biphenyl* unit of **34** by a *binaphthyl* unit in **33** leads to an increase of the catalytic activity which was ascribed to electronic effects.



33 Ar = C_6H_4-*m*-SO_3Na

34

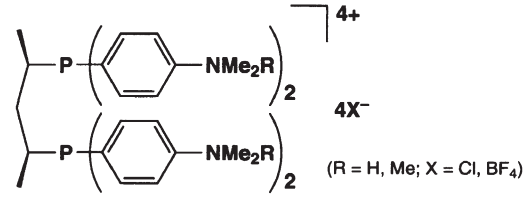
35 n = 2
36 n = 3

37

Figure 6 Directly sulfonated diphosphines.

Diphosphines with Quaternized Aminoalkyl or Aminoaryl Groups

Quaternization of nitrogen atoms of aminoalkyl or aminoaryl diphosphines opens up another route to water-soluble diphosphines. One of the first (chiral) diphosphines that has been synthesized by this method was shown to be very soluble in water [75], which stimulated several others to use similar procedures to prepare chiral water-soluble diphosphines [76]. Before quaternization, the phosphorus atom has to be protected either by oxidation (e.g., with hydrogen peroxide) or by coordination to a metal. Subsequent reduction or decomplexation then affords the water-soluble diphosphine; for example, the *chiral* diphosphine **38** (Figure 7) [77]. Stelzer and co-workers used a strategy involving a palladium-catalyzed P–C coupling reaction to introduce water-soluble groups in (di)phosphine ligands [78], which can be used to prepare guanidinium-modified (di)phosphines [79].

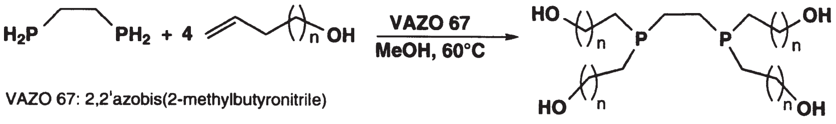


38

Figure 7 Chiral water-soluble quaternized diphosphine.

Diphosphines with Hydroxyalkyl or Polyether Substituents

After initial prelineary reports [80–82], the synthesis of 1,2-bis(di(hydroxyalkyl)-phosphino)ethans (**39**) was described [83a] [Eq. (1)].

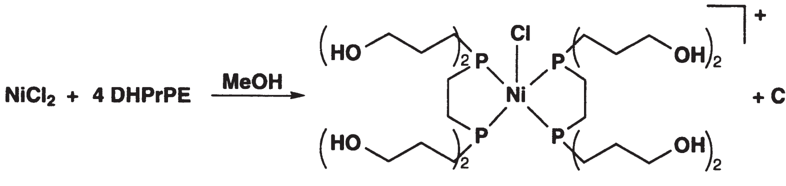


(1)

VAZO 67: 2,2'azobis(2-methylbutyronitrile)

39 n = 0, 2, 3, 4

Several metal complexes were prepared and characterized. For example, the reaction of **39** with $NiCl_2$ in a 2 : 1 ratio in methanol gave an orange product identified as $Ni(DHPrPE)_2Cl$ [**40**; Eq. (2)]. The solubility of the metal complexes in water can be attributed to the hydrophilic hydroxyl groups, which surround the outside of the complexes, but even more to the charges on the molecules [84].



(2)

40

Substituting a phosphine with a polyether chain may also make the phosphine water-soluble. However, diphosphines of the type **41** (**41**–**43**) are only soluble in water when $n > 15$ [85]. This type of material can also be used to prepare thermally responsive catalysts [86].

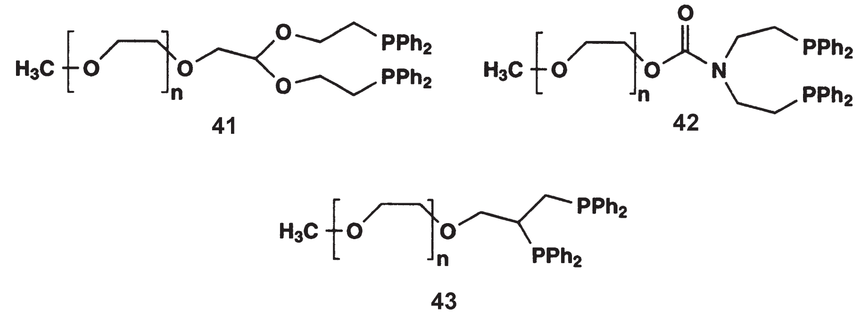
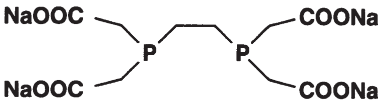


Figure 8 Diphosphines containing polyether chains.

Carboxylated Diphosphines

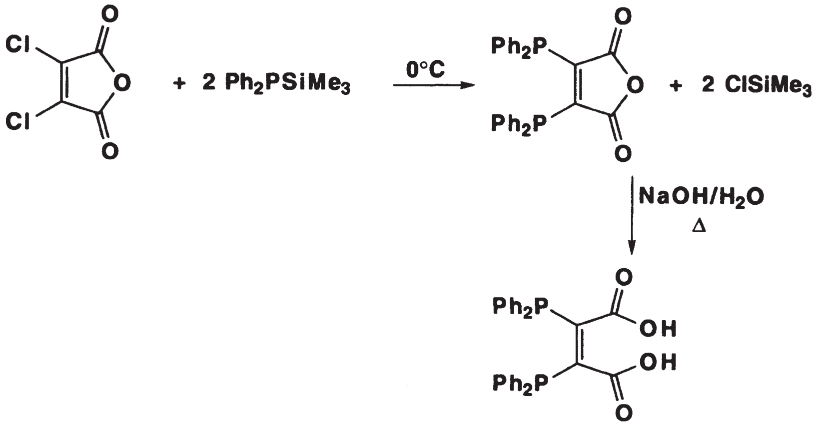
Phosphines with carboxylic groups were some of the earliest water-soluble phosphines investigated (see also p. 70) [87]. The Podlahová's group prepared a diphosphine, the phosphine analogue of ethylenediaminetetraacetic acid, which is obtained as a monohydrate of the tetrasodium salt (**44**) [87]. Jegorov and Podlahová published a short review on the catalytic uses of these carboxyalkylphosphines [88].



44

Van Doorn developed a water-soluble diphosphine based on 2,3-bis(diphenylphosphino)maleic anhydride, which was converted into the biscarboxylic acid **45** with sodium hydroxide (Scheme 1) [89a]. The compound was also described by Tyler and co-workers in 1993 [89b].

An advantage over other methods for the preparation of water-soluble phosphines is that diphosphine **45** could easily be purified by extraction followed by crystallization from diethyl ether. The structure of **35** was confirmed by X-ray crystallography. The ligand is readily soluble in aqueous solution at pH 5 or higher. For example, the solubility is > 1 M at pH 7. At this pH the ligand is deprotonated.



45

Scheme 1 Synthesis of the water-soluble diphosphine **45** based on 2,3-bis(diphenylphosphino)maleic anhydride.

Amphiphilic Diphosphines

Another approach to water-soluble phosphines with the emphasis on metal recycling has been reported [90]. The ligands synthesized are based on BISBI and **46–48**, and hydroformylation (for example) can be conducted in a homogeneous (organic) phase [90a]. After it has been used in the hydroformylation of olefins the catalyst can be removed by acidic extraction. It has been established that these novel diphosphines form active and highly selective catalysts.

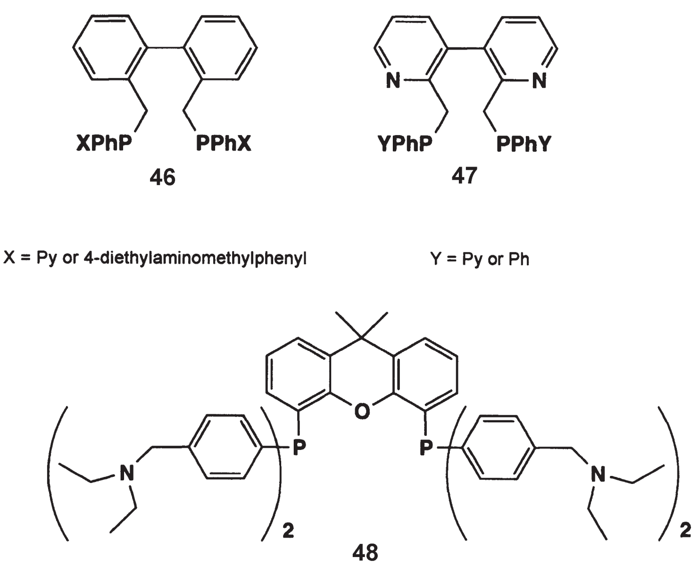
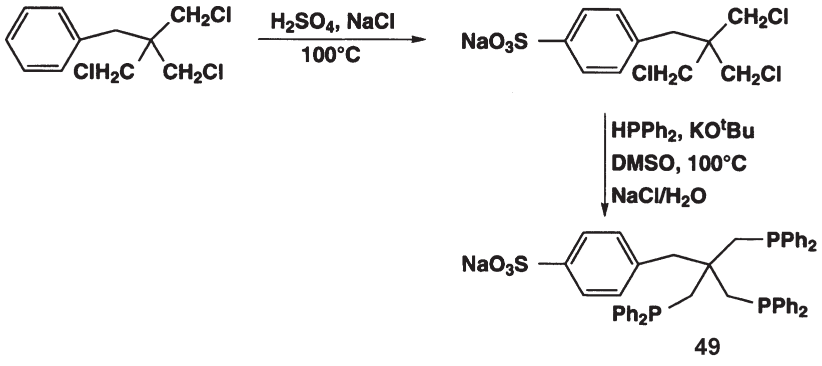


Figure 9 Amphiphilic diphosphine ligands.

Other Phosphines

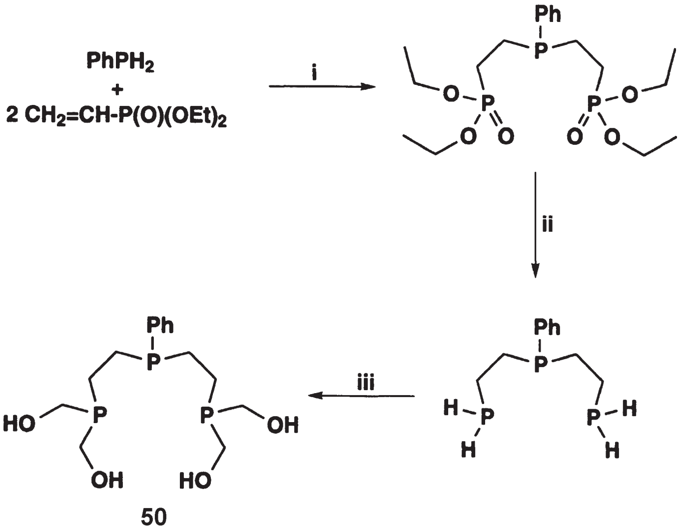
Water-soluble mono- and diphosphines represent the major class of phosphines used in aqueous-phase homogeneous catalysis. However, some new types of water-soluble phosphines have been developed, including phosphines containing sugar substructures [91] or phosphonate chains [92], and chiral sulfonated phosphines for the asymmetric hydrogenation of dehydropeptides [93] and phosphines with amino acid moieties [94].



Scheme 2 Synthesis of SULPHOS (**54**).

Bianchini et al. [95] synthesized another water-soluble triphosphine, $NaO_3S(C_6H_4)CH_2C(CH_2PPh_2)_3$, the so-called SULPHOS (**49**; Scheme 2). This ligand is a TRIPHOS ligand [96] with a hydrophilic tail attached to the bridgehead carbon atom. It has been developed to facilitate catalyst separation in biphasic but aqueous systems. The synthesis involves the treatment of benzyltris(chloroethyl)-methane with concentrated sulfuric acid at 100 °C, which results in the regioselective *para* sulfonation of the phenyl ring. Reaction of $NaO_3S(C_6H_4)CH_2C(CH_2Cl)_3$ with $KPPh_2$ in DMSO at 100 °C gives **49**. The complexes (**49**)Rh(cod) and (**49**)$Rh(CO)_2$ were used in biphasic catalysis as hydrogenation and hydroformylation catalysts respectively.

Katti et al. have developed the new water-soluble triphosphine $PhP[CH_2CH_2P(CH_2OH)_2]$ (**50**) [97]. This triphosphine, upon interaction with $[Rh(cod)Cl]_2$ under biphasic (water/dichloromethane) conditions, produces a water-soluble rhodium(I) complex in which the rhodium center is tripodally coordinate via the PPh and $P(CH_2OH)_2$ functionalities, as established by NMR spectroscopy. The presence of PPh and $P(CH_2OH)_2$ groups of disparate basicities makes it unusual in comparison with the traditional triphosphines (e.g., TRIPHOS: $PhP(CH_2CH_2PPh_2)_2$). They suggested that the different basicities in **50** may aid the development of catalytically useful transition metal complexes in which the weaker of the two different M–P bonds may be reversibly cleaved in the presence of a substrate molecule.



50

Scheme 3 Synthesis of water-soluble triphosphine **50**.
Reagents: (i) $KOBu^t$, THF; (ii) $LiAlH_4$, Et_2O; (iii) HCHO, EtOH.

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2.2.3.2.2

Nitrogen- and Sulfur-Containing Water-Soluble Ligands

Philippe Kalck and Martine Urrutigoïty

Introduction

Biphasic catalysis involving the organometallic complex immobilized in the aqueous phase is concerned exclusively with transition metal complexes coordinated by water-soluble ligands which act as ancillary ligands to tune the coordination sphere of the metallic center and confer to it a good solubility in water. As catalysis is devoted to the functionalization of the substrate, the complex will contain ligands like hydride, carbonyl, allyl etc., arising from the activation of the substrate and the reactants. It is thus important that the water-soluble ligand maintains the various complexes and intermediates of the catalytic cycle in the aqueous phase. The various strategies that have been developed to modify a ligand with appropriate functionalities recall to some extent the methodology of incorporating protecting groups in organic syntheses. For instance, nitrogen-containing groups have been reviewed recently [1].

Nitrogen-Containing Ligands

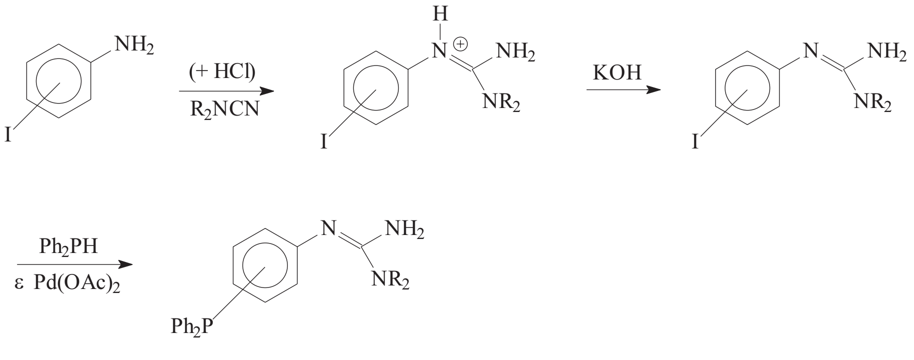
Ethylenediaminetetraacetic acid or its sodium salt (EDTA) is a well-known complexing agent which can form an abundant variety of water-soluble complexes with all metals. EDTA is widely used in industry and environmental studies are concerned with the degradation of its complexes [2] or the bioaccumulation of platinum group metals [3]. Directly related to the aim of this book is the catalytic activity in various carbonylation reactions of the precursor [Ru(EDTA)(H_2O)], as reported by Taqui Khan and co-workers [4]. In fact the two nitrogen and three carboxylate functions bind the ruthenium(III) center, and under a CO atmosphere this complex is reduced to the ruthenium(II) species [Ru(EDTA)(CO)]$^-$ in which only one carboxylate group is not bonded to the metal. Apart the water gas shift reaction, which transforms CO/H_2O into CO_2 and H_2, this complex catalyzes carbonylation of terminal alkenes, cyclohexenes, primary or secondary amines, and aryl halides. Similarly triethanolamine, $N(CH_2CH_2OH)_3$, can bind a metal center, as in $[MoO_4(TEA)]^{2-}$, and confer to it some solubility in water, although some compatibility with organic solvents has been noted [5].

Bidendate ligands containing the bipyridine framework have been synthesized by introduction of one or two sulfonate substituents onto the pyridine rings, or even of two carboxylate groups [6]. The corresponding water-soluble complexes have been prepared [7], and extension to carboxylato- or sulfonatopyridines [8], as well as to pyridineimine ligands, have been reported [9].

Chiral diamine ligands bearing hydrophilic substituents in the two *para* positions of (1*R*,2*R*)-(+)-N,N′-dimethyl-1,2-diphenylethylene diamine have been designed (hydroxy-, methoxy- or methoxytriethyleneglycol) and coordinated to a cationic iridium species to perform the enantioselective hydrogenation of phenylglyoxate methyl ester and acetophenone. Catalysis in water increases both the activity and the enantioselectivity (up to *ee* = 68%) and an encouraging recycling efficiency has been obtained [10].

Initial studies by Baird et al. have shown that quaternization of the nitrogen atom of an aminophosphine induces an amphiphilic character: the prototype is thus $Ph_2P(CH_2)_2NMe_3^+$ (AMPHOS), which has been coordinated to rhodium and tested in hydrogenation or hydroformylation [11]. The two phenyl groups have been substituted with long carbon chains containing C_8 or C_{10} frames and the resulting ligands coordinated to palladium [12], or with trimethylammoniumphenyl groups in chiral diphosphines which have been introduced in the coordination sphere of rhodium in order to study the asymmetric hydrogenation of dehydroamino acid derivatives [13].

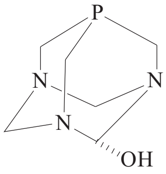
Interestingly, the synthesis of guanidiniumphenylphosphines has been accomplished by reaction of Ph_2PH with *meta*- or *para*-iodophenylguanidine in the presence of catalytic amounts of palladium acetate. This is prepared in a straightforward way from iodoaniline, as shown in Scheme 1.



Scheme 1 Synthesis of guanidinium phenyl phosphines.

The corresponding complexes with molybdenum and palladium have been prepared; particularly, the Suzuki and Sonogashira reactions have been examined using the protonated form $[PhP(GuaH)_2]^{2+}$, and the results in the latter reaction show better yields than with monosulfonated triphenylphosphine [14].

Introduction in the *para* position on one phenyl group of triphenylphosphine of a $CH_2N(CH_2CH_2NEt_2)_2$ substituent containing three amino functions provides a ligand with a good solubility in water and particularly in water/toluene mixtures. The catalytic activity for the hydroformylation of 1-hexene with rhodium is rather modest [15]. Phosphatriazaadamantane (PTA); **1** shows some solubility in water and various ruthenium or rhodium complexes bearing the PTA and $PTAH^+$ ligands have been prepared by Darensbourg and co-workers and evaluated in catalysis, more particularly in regioselective hydrogenations [16].



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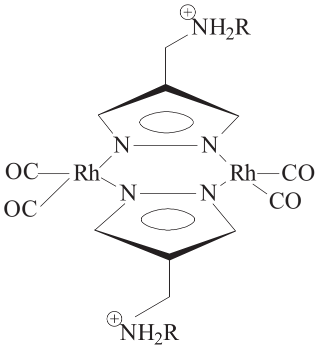
Structure 1 The phosphatriazaadamantane (PTA) molecule.

Concerning pyrazoles, substitution of a in the 4-position by an (ethylamino)methyl or an (isopropylamino)methyl group provides the ligand and the bridged dirhodium complexes with a good solubility, presumably because the ammonium function introduced does not interact with the rhodium centers as represented for the tetracarbonyl complex (**2**) [17].



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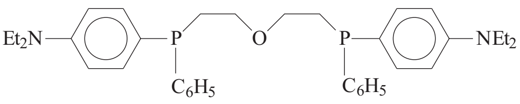
Structure 2 $[Rh(Pz)CO_2]_2$ complex (Pz = pyrazolate ammonium) (adapted from [17]).

Finally, simultaneous introduction of amines and ether functions allows diphosphine ligands to gain some solubility in water. The two ligands (**3** and **4**) have been described by van Leeuwen et al. and their behavior as ancillary ligands of rhodium has been examined in the hydroformylation reaction of terminal alkenes [18].



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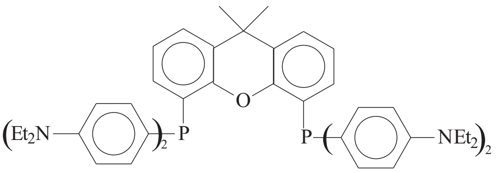
Structure 3 POPam ligand (adapted from [18]).



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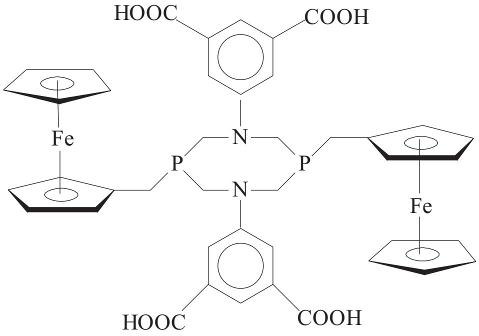
Structure 4 Xantham ligand (adapted from [18]).

Potential catalysts which would be immobilized in an aqueous phase have been built up from air-stable, water-soluble phosphino amino acids [19]. Heterobimetallic $[Fe_2Pd]$ and $[Fe_2Pt]$ complexes have been prepared with the assembling ligand 1,5-bis(*meta*-dicarboxyphenyl)-3,7-bis(ferrocenylmethyl)-1,5-diaza-3,7-diphosphacyclooctane (**5**).



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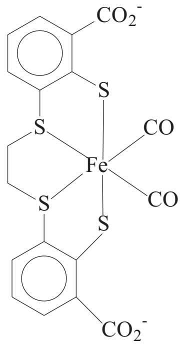
Structure 5 1,5-bis(meta-dicarboxyphenyl)-3,7-bis(ferrocenylmethyl)-1,5-diaza-3,7-diphosphacyclooctane ligand.

Sulfur-Containing Ligands

Sulfur plays a central role in enzymatic catalysis and metal sulfido enzymes can activate various small molecules in biological conditions [20]. Much work has been devoted to the isolation and understanding of the intimate mechanisms of activation of biomimetic sulfur-containing complexes [21]. However, these systems do not present significant solubility in water under the studied conditions. We can nevertheless refer to the Sellman group's work in which the authors isolated sulfur-containing representative [FeMo] complexes of the cofactor of [FeMo] nitrogenases [22, 23], and were able to produce water-soluble complexes by introduction of carboxylic acid functions. The corresponding iron and ruthenium compounds gain solubility in water by deprotonation of the carboxylic groups, as for instance in the anionic species (**6**) [23].



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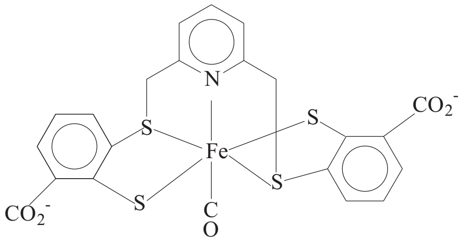
Structure 6 Sulfur-water-soluble iron complex (adapted from [23]).

More recently, various ligands have been designed to produce water-soluble iron complexes which can bind CO or NO as extra ligands [24]; e.g., **7**.



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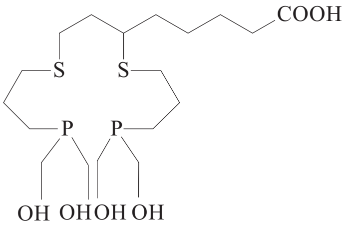
Structure 7 $[Fe(pyCO_2S_4)]^{2-}$ complex (adapted from [24]).

Thiolato ligands bearing a dimethylaminopropyl chain, which can be protonated by diluted sulfuric acid, induces water solubility to the dinuclear complexes $[Rh_2(\mu\text{-}S(CH_2)_3NMe_2)_2(CO)_2(PR_3)_2]$, especially after catalysis to separate the rhodium complex from the organic products [25]. The water solubility of the related rhodium–TPPTS complex (PR_3 = TPPTS) can be raised by using the same bridging ligand in acidic media [26].

Chiral aminosulfonamide ligands containing a phenylsulfonic acid substituent display a significant solubility in water and have been engaged directly with a ruthenium precursor to reduce enantioselectively aromatic ketones to the corresponding alcohols [27].

Interestingly, although no catalytic activity has been examined, novel dithiabisphosphine ligands have been designed (one example is shown in **8**) and coordinated to ^{99m}Tc to produce water-soluble radiolabeling complexes [28]. The authors are extending their investigations on the capacity of coordination of such ligands to new systems containing nitrogen in place of the sulfur atoms [29].



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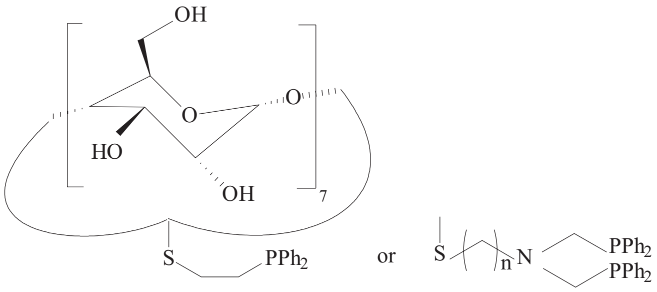
Structure 8 Structure of Dithia(bishydroxymethyl)bisphosphine "P_2S_2-COOH" (adapted from [28]).

Cyclodextrins can be modified by thiol substituents and further attachment to phosphine or aminophosphine ligands (see **9**) allows the coordination to rhodium catalysts [30]. The activity in the hydroformylation reaction of 1-octene is interesting since turnover frequencies near to 180 h^{-1} can be reached with a selectivity in C_9-aldehydes higher than 99% [31].



9

Structure 9 Cyclodextrin modified by thiophosphine or thioaminophosphine ligands (adapted from [30].

Conclusion

In fact, various ligands which coordinate a metal center through a nitrogen-, a sulfur-, or a phosphorus-donating atom are made water-soluble by introduction of various functionalities. Apart from the sulfonated phosphines which have been largely studied, presumably due to their great capacity to dissolve in water, especially TPPTS (cf. Section 2.2.3.2.1), these ligands, bearing various hydrophilic groups, can provide a good way to tune the coordination sphere of the metal center while still being able to control water solubility.

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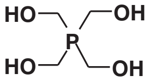
2.2.3.2.3
Other Concepts: Hydroxyphosphines

Mandy-Nicole Gensow and Armin Börner

Apart from sulfonate, carboxylate and ammonium groups, hydroxy groups incorporated in phosphorus ligands also increase the solubility of the catalyst in water. Several members of this large class of ligands have been synthesized [1] and were tested in catalysis in organic solvents as well as in water [2]. Particular attention has been given to the special effect of the hydroxy group in acting as a hemilabile ligand or establishing secondary interactions with a suitable substrate [3].

Katti et al. synthesized polyhydroxyphosphines (Structures **1–5**) by the nucleophilic addition of PH_3 or primary phosphines to formaldehyde or other carbonyl compounds [4]. The utility of such ligands in the formation of water-soluble transition metal complexes was evidenced in several cases [5]. It should be noted that besides the phosphorus(III) atom, hydroxy groups also can coordinate with "soft" transitions metals [3, 6].



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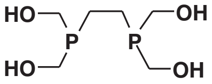

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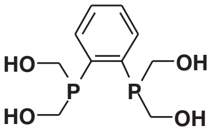

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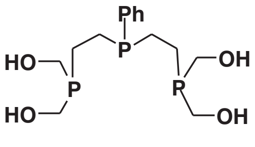

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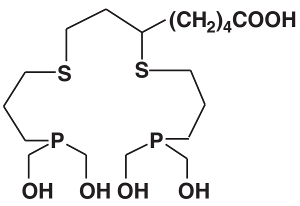
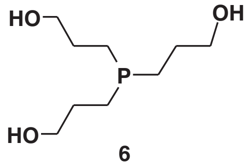


5

By addition of PH_3 or 1,2-ethylenediphosphine to allyl acetate [7] or allyl alcohol, 1,3-polyhydroxyalkylphosphines **6** and **7** can be prepared [8].

Related 1,3-polyhydroxyphosphines **8** and **9** were synthesized by Lindner et al. by photochemical addition of 1,3-propylenediphosphine to the relevant alkenes [9]. Pd(II) complexes of the new ligands were successfully employed for the copolymerization of CO and ethylene in water.

Carbohydrates represent one of the most versatile tools for the synthesis of *P*-ligands bearing hydroxy groups [1, 10]. Thus, Beller et al. used *β*-*O*-glycoside ligands **10** bearing a phenylphosphine group as aglycones for the Pd-catalyzed Suzuki coupling and Heck reaction in an aqueous two-phase system [11].



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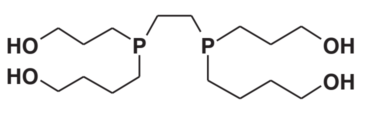

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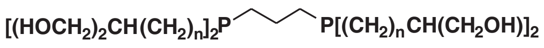
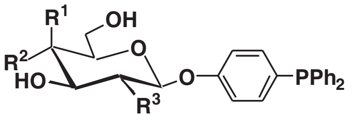
8 (n = 1-8)



9 (n = 3-6)



$R^1 = H$, $R^2 = OH$, $R^3 = NHAc$
$R^1 = OH$, $R^2 = H$, $R^3 = OH$
$R^1 = H$, $R^2 = OH$, $R^3 = OH$

10

In comparison to the application of PPTS, with ligands of type **10** improved catalyst activities and yields were noted. These effects were rationalized by the higher catalyst concentration in the nonpolar phase.

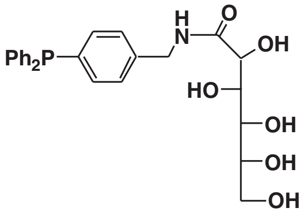
Similarly superior results in comparison to the application of sulfonated phosphine ligands were achieved in the Pd-catalyzed biaryl coupling of arylboronic acids in aqueous media by use of the ligand **11** (glcaPHOS) [12].

Selke et al. advantageously used rhodium(I) precatalysts **12a**,**b** based on Ph-*β*-glup-type ligands bearing two hydroxy groups in the sugar backbone for the asymmetric hydrogenation of *Z*-acetamidocinnamic acid derivatives in water [13]. Strong effects upon the enantioselectivity were noted which depended on the orientation of the hydroxy groups at the pyranose (besides D-glucose derivatives of D-galactose were used also). By addition of amphiphiles the enantioselectivity could be considerably enhanced in comparison to the reactions in a water blank.

Ohe and Uemura investigated the asymmetric hydrogenation of several enamides and itaconic acid in water in the presence of a Rh(I) catalyst based on disaccharide (e.g., trehalose) diphosphinite ligands **13a**,**b** [14]. When sodium dodecyl sulfate (SDS) was used as an additive the amount of catalyst could be significantly reduced. Simultaneously the enantioselectivity in the product was enhanced.

Evidence for a synergistic effect of internal hydroxy groups and amphiphiles on the Rh-catalyzed asymmetric hydrogenation in water was given by Selke and Börner. Thus, incorporation of a single hydroxy group in the DIOP-analogue ligand **14** increased the enantioselectivity by up to 70% *ee* in comparison to the blank experiment [15].

Such an effect was absent in the trial with the parent ligand (DIOP). It is noteworthy that the enantioselectivity achieved under optimized conditions distinctly exceeded that in pure methanol.



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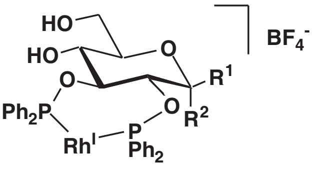
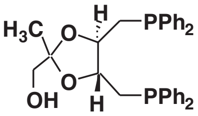


12a: R^1 = H; R^2 = OPh, OMe
12b: R^1 = OPh, OMe; R^2 = H
13a: R^1 = H; R^2 = 1-α-D-glucopyranose
13b: R^1 = 1-β-D-glucopyranose; R^2 = H

The chiral Rh(I) complex **15** bearing the tetrahydroxydiphospholane $(HO)_4$-BASPHOS was prepared by Holz and Börner [16]. In comparison to the strongly related Et-DuPHOS-Rh precatalyst, the four hydroxy groups increased the water solubility of the complex by a factor of four [17]. In the asymmetric hydrogenation of acetamidoacrylate in water with this cationic $(HO)_4$-BASPHOS catalyst, (*S*)-*N*-acetylalanine was obtained in quantitative yield and in more than 99% *ee*. Noteworthy is the unusually short time necessary in order to get complete conversion of the substrate. Later, RajanBabu and co-workers succeeded in the preparation of the free ligand, $(HO)_4$-BASPHOS [18]. This method was revealed to be more advantageous than the cleavage of HO-protective groups with acids in aqueous solutions affording mainly phosphonium salts [19].

Polyhydroxyphospholanes of the RoPHOS type [20] were prepared by Zhang and co-workers [19, 21]. With the ethyl-substituted ligand **16b** in the Rh(I)-catalyzed asymmetric hydrogenation of itaconic acid in a water–methanol mixture as solvent, 100% conversion and > 99% *ee* were achieved.



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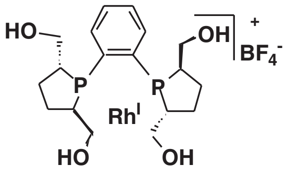

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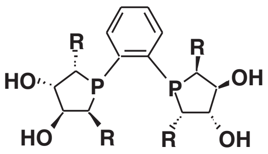
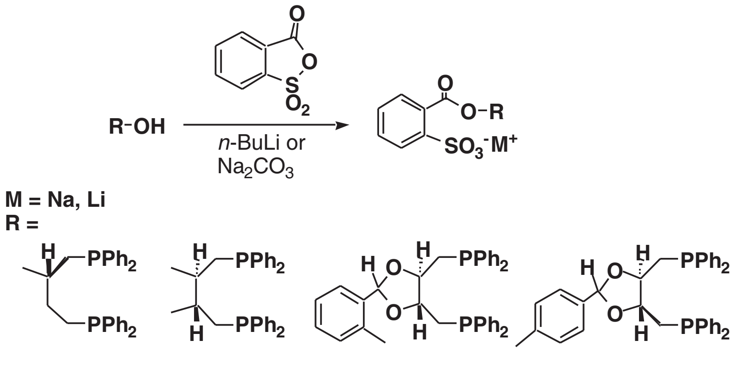


16a: R = Me
16b: R = Et

It should finally be noted that hydroxyphosphines can be converted under very smooth conditions into sulfonated phosphines by acylation with *o*-sulfobenzoic anhydride, as shown by Börner et al. [Eq. (1)] [22]. With this methodology in hand the severe conditions commonly used for the incorporation of sulfonate groups in phosphines can be avoided. Acid-labile functional groups like acetals survive under these conditions.

In comparison to the parent hydroxyphosphines the water solubility of the relevant Rh catalysts was strongly enhanced [23]. In the asymmetric hydrogenation of prochiral olefins, moderate enantioselectivities were achieved.



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2.2.3.3

Water-soluble Receptor as Mass Transfer Promoter

Eric Monflier

Solubilization of water-insoluble substrate in the aqueous phase containing the organometallic catalyst can be achieved by using catalytic amounts of water-soluble receptors such as cyclodextrins [1] or calixarenes [2]. The beneficial effect of these water-soluble host compounds on the mass transfer is ascribed to their complexing properties and it is postulated that these compounds operate like inverse phase-transfer catalysts according to Figure 1.

In this mechanism the receptor, which is represented by a truncated cone, forms a host/guest complex with the substrate at the liquid/liquid interface and transfers the water-insoluble substrate (**S**) into the aqueous phase where it reacts with the water-soluble organometallic catalyst. After reaction, the product (**P**) is released in the organic phase and the transfer cycle can go on.

Cyclodextrins are the most used host compounds so far. Native cyclodextrins are effective inverse phase-transfer catalysts for the deoxygenation of allylic alcohols [3], epoxidation [4], oxidation [5], or hydrosilylation [6] of olefins, reduction of α,β-unsaturated acids [7], α-keto ester [8], conjugated dienes [9] or aryl alkyl ketones [10]. Interestingly, chemically modified cyclodextrins like the partially *O*-methylated β-cyclodextrin (RAME-β-CD) show a better catalytic activity than native cyclodextrins in numerous reactions such as the Wacker oxidation [11], hydrogenation of

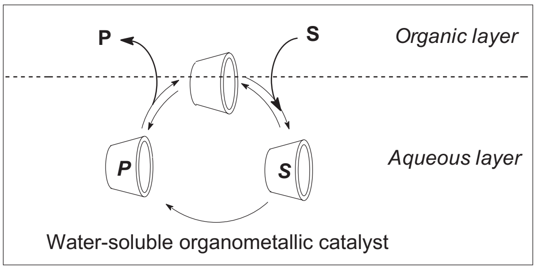

Figure 1 Cyclodextrins as water-soluble host compounds.

aldehydes [12], the Suzuki cross-coupling reaction [13], hydroformylation [14] or hydrocarboxylation [15] of olefins. This outstanding effect of RAME-β-CD on reaction rate was attributed to its slight surface activity and to the presence of a deep hydrophobic host cavity that accommodates the substrate properly. RAME-β-CD was also used successfully to perform substrate-selective reactions in a two-phase system [16]. Thus, in the presence of a mixture of isomers, the water-soluble catalyst reacts with the isomer that preferentially interacts with the cyclodextrin cavity, inducing substrate selectivity. For instance, a 97 : 3 product ratio was observed during the palladium-catalyzed cleavage of a 50 : 50 mixture of *N*-dodecyl-*O*-allylurethane and *N,N*-dihexyl-*O*-allylurethane [17]. Surprisingly, it was found that the cyclodextrins can form inclusion complexes with the hydrosoluble phosphine used to dissolve the catalyst in the aqueous phase [18]. These complexes were responsible for the decrease in the linear/branched aldehydes ratio during the rhodium-catalyzed hydroformylation reaction [19], the modification of the catalyst structure [20], and the drop in cyclodextrin activity in some experimental conditions [21]. Interestingly, more sophisticated approaches involving covalent attachment of the phosphane ligand to the cyclodextrin through a spacer have also been performed to combine molecular recognition, phase-transfer properties and aqueous organometallic catalysis [5d, 22, 23]. Reetz et al. have reported the synthesis of rhodium complexes with β-cyclodextrin modified by diphosphanes as ligands [22]. Numerous substrates including internal olefins have been hydrogenated or hydroformylated successfully in a biphasic medium. Unfortunately, the catalytic systems cannot be recovered quantitatively due to partial transfer of the catalyst into the organic phase during the reaction [22, 23].

Recently, the use of water-soluble calixarenes as inverse phase-transfer catalysts has also been reported to overcome mass transfer limitations in aqueous organometallic catalysis. In the Suzuki cross-coupling reaction, the efficiency of these synthetic macrocycles was higher than that observed for β-cyclodextrins [13, 24]. Water-soluble sulfonated calixarenes modified by phosphine [25]- or nitrile [26]-containing groups are efficient ligands for the hydroformylation or Wacker oxidation of olefins, respectively. Contrary to the cyclodextrins modified by phosphine groups, no decrease in the catalytic activity was observed during recycling experiments, suggesting that the rhodium catalyst is stable and quantitatively immobilized in the aqueous phase. Unfortunately, the selectivity in aldehydes (55–80%) was notably lower than selectivities observed with systems described by Monflier (95%) [14] or Reetz (99%) [22].

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2.3
Homogeneous Catalysis in the Aqueous Phase as a Special Unit Operation

2.3.1
Fundamental Reaction Engineering of Aqueous Biphasic Catalysis

Zai-Sha Mao and Chao Yang

2.3.1.1
Introduction

Several considerations invoke the association, or incorporation, of the general catalytic study with the relevant chemical engineering study. Many chemists have been aware of such intrinsic connections between chemistry and chemical engineering, but there is still misunderstanding or neglect of chemical engineering factors in the study of catalysis. Among the most important aspects are the following ones.

Firstly, chemical engineering measures need to be taken to guarantee hydroformylation, especially biphasic hydroformylation, in a well-defined and controlled physico-chemical environment. For example, the reaction rate and conversion of olefins to aldehydes is largely dependent on the mass transfer rate between the gas (syngas consisting of CO and H_2) and the liquid phase (aqueous phase containing a water-soluble transition metal complex catalyst, and organic phase of long-chain olefins and solvent), and the mass transfer rate itself is in turn the product of the interfacial mass transfer coefficient and the specific interfacial area. It is usually believed intuitively that the mass transfer rate or the specific interfacial area will reach an asymptotic value as the agitation speed is increased to a sufficiently high value, beyond which little further increase in the conversion or TOF of olefins would be observed, and that under such a condition the limitation of interphase mass transfer to chemical reaction is eliminated. For example, Zhang et al. [1] examined the effects of the stirring speed on the conversion of biphasic hydroformylation of 1-dodecene catalyzed by a water-soluble rhodium complex and the normal/iso (n/i) ratio of the product aldehydes. The experimental results presented in Figure 1 were very typical, and the speed of $N = 15$ rps was selected for the rest of the hydroformylation experiments. However, rigorous analysis according to the principles of chemical engineering suggests that such selection is not fully justified. To reduce the mass transfer boundary layer thickness as much as possible so as to eliminate the mass transfer resistance, motion of the bulk phase relative to gas bubbles and droplets needs to be maximized, but this may not be accomplished by simply increasing the rotational speed of the stirrers. At a higher stirring speed, the bubbles and drops would follow closely the bulk liquid phase flow, and the relative motion would not be increased as effectively as expected. Therefore, achievement of the maximum or the asymptotic conversion is not an indication that conclusions on the intrinsic kinetics are guaranteed, and this may give an

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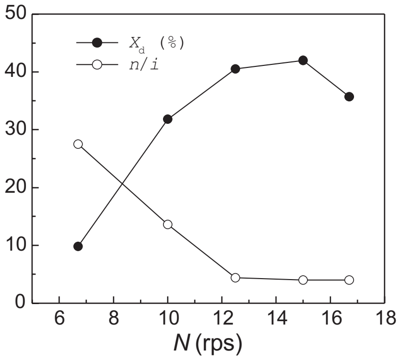

Figure 1 Variation of X_d and n/i of hydroformylation of 1-dodecene versus stirrer speed (N) [1].

inconsistent basis for comparison of similar studies. Chemical engineers would suggest using an autoclave with standard wall baffles to enhance the relative motion between phases and to standardize the reactor/agitator configuration to ensure a consistent basis for quantifying and comparing catalytic studies. In Figure 1 the decrease of conversion at above $N = 15$ rps suggests further complications caused by chemical and engineering factors, which have to be analyzed by the principles of two crosslinked disciplines, chemistry and chemical engineering.

Secondly, the theory incorporated with chemical engineering principles is necessary so as to offer means to elucidate the phenomena and data in catalytic research. It is now generally accepted that the surfactant added to the biphasic hydroformylation system causes the formation of micelles so that the associated solubilization, etc., promotes the reaction rate and influences the *n*/*i* ratio (see Section 2.3.4 [2, 3]. Chen et al. [2] suggested that the hydroformylation of 1-dodecene in biphasic systems occurred at the interface between aqueous and organic phases; the micelle structure formed was favorable for the *n*/*i* ratio; the key factor to the enhancement of reaction rate was the enrichment of catalytic species by the static electric attraction between the negatively charged active rhodium anion species and the positively charged cationic ends of surfactant solubilized in the organic phase. The data also supported the proposition of solubilization of olefin in micelles [4]. Van Vyve and Renken [3] also reported that the reaction rate and normal aldehyde selectivity were improved for the hydroformylation of C_6–C_{16} olefins in reverse micellar systems. To thoroughly and quantitatively understand the surfactant-enhanced hydroformylation, a chemical engineering study on the formation of micelles and the quantitative formulation of their physico-chemical properties is necessary. This should be incorporated into the chemical research and process development of hydroformylation of olefins, in particular the heterogeneous hydroformylation of long-chain olefins. To date no report is available about the hydroformylation of olefins based on quantitative mathematical models of micellar systems.

Thirdly, chemical engineering studies are very important to commercial exploitation of the results of homogeneous and biphasic hydroformylation, but it seems that chemical and chemical engineering studies constitute two separate periods of an originally indivisible research program. Thus, chemists should be alerted to plan their study and analyze the results with due consideration of the relevant chemical engineering factors; it is anticipated that close cooperation of chemists and chemical engineers would bring more benefits in efficiency and productivity in research and development of biphasic hydroformylation.

2.3.1.2
Chemical Engineering Factors

Many engineering factors have a profound influence on the performance of catalysts in hydroformylation, and their effects are demonstrated in terms of reaction indices such as conversion and selectivity. More concretely, these factors influence the mass transfer rate, phase dispersion, emulsification and demulsification, catalyst distribution, product separation, etc. (Table 1).

No comprehensive investigation is available to elucidate all the facets of the effects listed in Table 1. From the point of view of chemical engineering, some of them may be addressed only qualitatively, although some interesting experimental evidence has appeared. The mechanistic representation in Figure 2 [2] illustrates several factors listed in Table 1. When the biphasic system consisting of 1-dodecene (organic phase) and an aqueous solution of water-soluble rhodium catalyst precursor $RhCl(CO)(TPPTS)_2$ and surfactant cetyltrimethylammonium bromide (CTAB) is agitated sufficiently, the reduction in liquid–liquid surface tension due to the presence of CTAB makes the formation of fine gas bubbles and 1-dodecene droplets much easier, leading to higher specific gas–liquid and liquid–liquid interfacial areas. This would be favorable to the dissolution of gaseous reactants in the liquid phases and to a greater area for the hydroformylation reaction. If the concentration of CTAB is above the critical micelle concentration (CMC), micelles with organic kernels would be formed, and the interfacial liquid–liquid area would be increased

Table 1 Chemical engineering factors influencing the performance of biphasic hydroformylation.

Factor	*Influencing mechanism*	*Target index*	*Ref.*
Number of phases	Phase dispersion, dispersion uniformity, mass transfer resistance	Conversion	–
Phase ratio	Dispersion type (O/W, W/O), dispersion uniformity	Conversion *n*/*i* ratio	[5]
Stirring speed	Interphase mass transfer coefficient, specific interfacial area, uniformity of phase dispersion, emulsification	Conversion *n*/*i* ratio	[1, 2, 5, 6]
Stirrer type	Specific interfacial area, uniformity of phase dispersion, emulsification	Conversion *n*/*i* ratio	[5]
Surfactant	Formation of micelles, catalyst distribution, specific interfacial area	Conversion *n*/*i* ratio	[2]

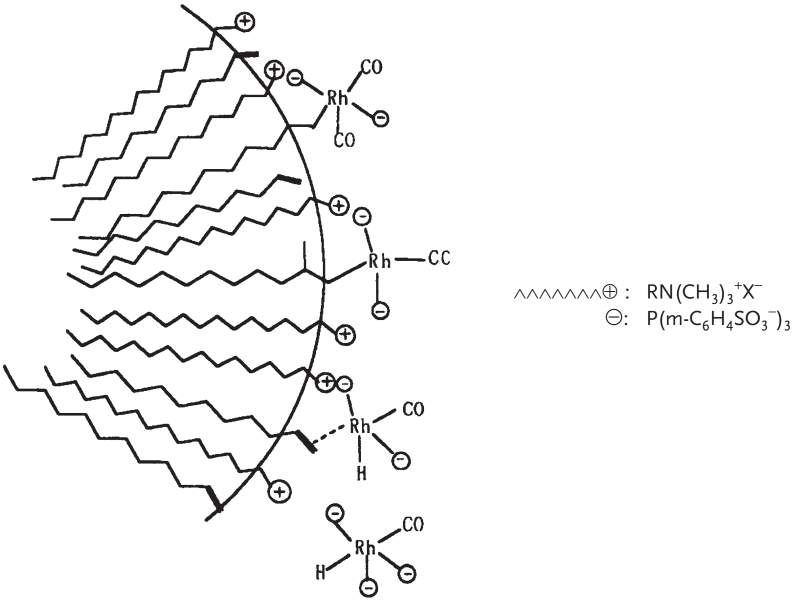

Figure 2 Catalytic active species in the interfacial layer of a cationic micelle [2].

further. Besides, the micelles probably solubilize the water-soluble catalyst species and this becomes the second factor in favor of a higher hydroformylation rate, in addition to a higher area for the reaction to occur. The orderly assembly formed by the long hydrophobic cetyl ends of CTAB at the liquid–liquid interface induces an orderly orientation of 1-dodecene molecules, thus contributing a higher selectivity of terminal aldehyde (higher *n*/*i* ratio). The contribution of static electric attraction between positive CTA ions and negative Rh complex ions, which results in enrichment of catalyst species at the interface, is also illustrated by Figure 2. Although the formation of a relatively stable emulsion makes the gravitational phase separation more difficult than just a simple decantation, high activity, high regioselectivity, and much lower ligand costs for the hydroformylation of higher olefins render it attractive and feasible for potential commercialization.

It has been found that the *n*/*i* ratio is significantly determined by the intensity of agitation [2, 5], and this was conjectured to be related to stability of the ordered assemblies of surfactant hydrophobic ends at the liquid–liquid interface. Violent disturbance of the interface and a less orderly surfactant arrangement make possible more diversified steric routes of hydroformylation of linear olefin molecules. This relationship of the *n*/*i* ratio with the intensity of agitation has not been elucidated in a quantitative and mechanistic sense so far.

Moreover, the above physico-chemical concept of multiphase reaction mechanisms has not been formulated into a quantitative mathematical model as a tool to predict better the performance of biphasic hydroformylation of long-chain olefins and explore efficiently the provisos of industrialization.

2.3.1.3
Gas–Liquid–Liquid Three-Phase Hydroformylation

Industrial homogeneous hydroformylation with a water-soluble complex catalyst has been commercialized successfully for propylene (Ruhrchemie/Rhône-Poulenc process) [7, 8] and butylene [9], because they have significant water solubility and the reaction proceeds at a reasonable rate in the bulk aqueous phase. For long-chain substrates such as 1-dodecene with low solubility in the aqueous phase, the rate of biphasic reaction is slow. In addition to finding novel more active catalysts and catalytic systems, many chemical engineering efforts have been devoted since the mid-1990s to improving the interphase mass transfer between the organic and aqueous phases; the proposed approaches depend on the chemists' and chemical engineers' understanding of the mechanisms of biphasic hydroformylation. Different chemical engineering measures were proposed to enhance the rate and regioselectivity of hydroformylation reactions.

Purwanto and Delmas [10] proposed the addition of co-solvent (ethanol) to enhance the solubility of 1-octene in the aqueous phase so that the overall reaction rate was increased, and their kinetic study led to a rate model similar to that in homogeneous liquid systems consistently from the point of view of bulk reaction mechanism. Chaudhari et al. [11] reported the improvement of the hydroformylation rate by addition of a small amount of PPh_3 to the biphasic system to enrich the effective catalyst species at the liquid–liquid interface. Kalck et al. [12] tested two more approaches to improve the mass transfer rate of biphasic hydroformylation of 1-octene and 1-decene with catalyst precursor $[Rh_2(\mu\text{-S}^tBu)_2(CO)_2(TPPTS)_3]$: use the phase-transfer agent β-cyclodextrin to transport the substrate into the aqueous phase to react there (see Section 2.2.3.2.2), and the supported aqueous-phase (SAP) catalyst to increase the reaction area due to the high specific surface area of porous silica (see Section 2.6). The improved conversion and TOF gave informative suggestions for the reaction mechanisms.

Wachsen et al. [13] presented a chemical engineering analysis of typical biphasic hydroformylation, the RCH/RP process using propylene, to demonstrate that the reaction occurred at the gas–liquid interface. With the comparison of the model of bulk liquid-phase reaction and that of reaction in the interphase region with experimental data, it was found that only the latter model elucidated the experimental measurements on the gas-phase pressure and the flux of reaction heat. This model is instructive in further efforts to improve the biphasic hydroformylation performance.

However, the analysis did not clearly state at which interface the reaction took place: gas–aqueous, or gas–organic phase. Also there exists a possibility that the hydroformylation takes place at the liquid–liquid interface, where gaseous propylene and syngas first dissolve largely in the organic phase and are then transported to the reaction location. When surfactants were added to accelerate the catalytic reaction, the performance indicated that the biphasic reaction might occur mainly in the interface of the aqueous–organic phases instead of in the bulk of the liquid mixture [2, 14].

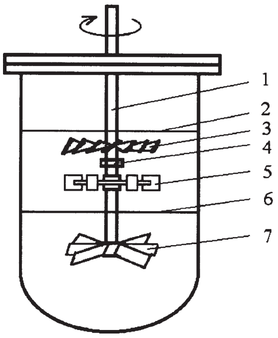

Figure 3 Hydroformylation autoclave with a patented composite surface aeration configuration: 1 Shaft; 2 Gas–liquid interface; 3 Self-rotating floating baffle (SRFB); 4 Annulus for position limiting; 5 Standard Rushton disk turbine (DT); 6 Liquid–liquid interface; 7 Pitched blade turbine upward (PBTU) [5, 18].

Previous studies [12, 15, 16] indicated that the intensity and mode of stirring and the reactor configuration affected dramatically the reaction rate and selectivity of biphasic hydroformylation of 1-dodecene catalyzed by water-soluble rhodium complexes. Yang et al. [5] further investigated several key engineering factors, including intensity of agitation, reactor configuration, and the technological conditions of reaction on hydroformylation of 1-dodecene as a typical higher olefin using $RhCl(CO)(TPPTS)_2$ complex catalyst and cationic surfactant. Hydroformylation of 1-dodecene was carried out in a 500 mL stirred stainless steel autoclave (Figure 3) in the $RhCl(CO)(TPPTS)_2/TPPTS/CTAB$ system. Both a six-blade Rushton disk turbine (DT) and a six-blade pitched blade turbine upward (PBTU) were used as surface aerators for entraining gaseous reactants into the liquid solution phases and for avoiding the recovery, recompression, and recycle of unreacted gases. A home-made baffle called a self-rotating floating baffle (SRFB) [17] was also applied for improvement of gas and liquid dispersion and pumping capability.

2.3.1.3.1
Effect of Agitation Speed

Agitation is certainly an important engineering factor that is strongly relevant to the performance of hydroformylation. In addition to the evidence presented in Figure 1, Yang et al. [5] also reported a significant influence of the agitation speed on the initial rate, conversion, and *normal/iso* aldehyde ratio of biphasic hydroformylation of 1-dodecene in a preliminary study. As shown in Figure 4, the initial rate and conversion increased with the agitation speed, but the regioselectivity to n-C_{13} aldehyde decreased. These data demonstrated that violent stirring was unfavorable for the formation of linear aldehyde in the presence of cationic surfactant CTAB. The data presented by Chen identified a similar trend [2]. The opposite trends of the conversion and regioselectivity versus agitation make the conventional way of choosing the experimental agitation speed disputable, and it is suggested that a thorough understanding of the role of agitation is lacking, and that the laboratory experiments are not sufficient to advise on a proper compromise between the hydroformylation rate and the regioselectivity. However, the simple trend of a monotonic approach to an asymptotic level of hydroformylation

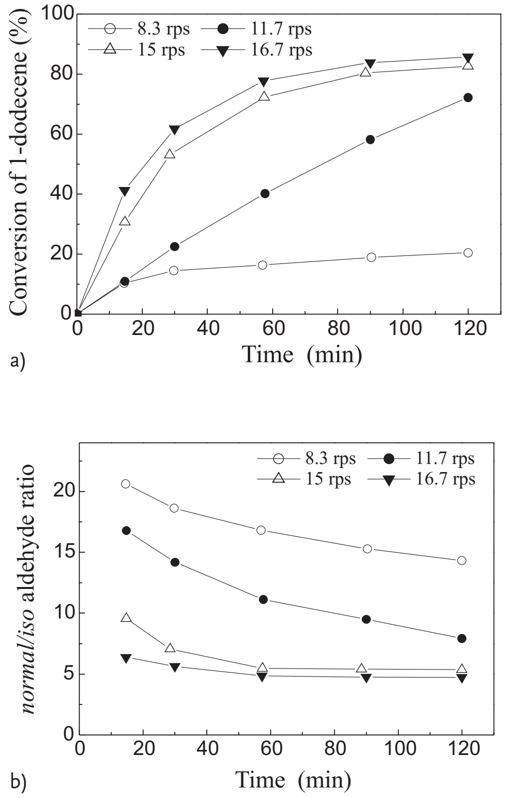

Figure 4 Influence of agitation speed on the conversion and regioselectivity of 1-dodecene hydroformylation [5].
(a) Conversion of 1-dodecene, (b) *n*/*i* aldehyde ratio.

conversion is frequently the case in simple biphasic systems without surfactant. For example, Lekhal et al. [6] observed that in the biphasic system with a co-solvent and without surfactant the reaction rate of 1-octene hydroformylation increased with the stirrer speed, but the selectivity of linear aldehyde was not affected and always close to 0.75. Only in such a case is it acceptable to select the stirrer speed corresponding to the stabilized hydroformylation conversion.

2.3.1.3.2
Orthogonal Experiment on Engineering Factors

Several chemical engineering factors affect the biphasic hydroformylation of 1-dodecene in a gas–liquid–liquid three-phase reaction system. In previous research [1], effects of temperature, total pressure, H_2/CO molar ratio, catalyst and ligand concentration, olefin concentration, surfactant concentration, and organic/aqueous-phase volume ratio on the hydroformylation kinetics were studied with

Table 2 Orthogonal table of L_{12} $(3^1 \cdot 2^4)$ for experimental design and the experimental results [5].

No.	*N (rps)*	V_O/V_W	C_{CTAB} a) $\cdot 10^3$	*Stirrer type*	C_d a)	r_L b) $\cdot 10^3$	r_O b) $\cdot 10^3$	*n/i* c)	*x* c) [%]	*P* [W]
1	1 (8.3) d)	1 (3/7)	1 (11.0)	2 (PBTU)	2 (4.4)	0.0577	0.192	14.3	20.5	0.18
2	1	2 (1/1)	1	2	1 (2.2) e)	0.0393	0.079	8.71	37.2	0.10
3	1	1	2 (12.3)	1 (DT)	1	0.0262	0.087	12.7	57.8	0.20
4	1	2	2	1	2	0.0865	0.173	9.13	33.3	0.39
5	2 (11.7)	1	1	1	2	0.135	0.451	5.17	77.3	0.48
6	2	2	1	2	1	0.131	0.263	6.37	58.7	0.42
7	2	1	2	2	2	0.208	0.695	9.08	68.5	0.35
8	2	2	2	1	1	0.134	0.268	4.87	54.3	0.43
9	3 (15.0)	1	1	1	1	0.192	0.640	4.37	77.0	1.05
10	3	2	1	1	2	0.233	0.467	4.22	68.1	1.04
11	3	1	2	2	1	0.176	0.586	4.75	78.6	0.91
12	3	2	2	2	2	0.357	0.713	4.85	72.5	1.45

Other reaction conditions: $T = 100$ °C, $p = 1.1$ MPa, $\gamma_{H2}/\gamma_{CO} = 48.3/51.7$, [TPPTS]/[Rh] = 18, $C_{cat} = 1.5 \cdot 10^{-3}$ kmol m^{-3}, 2 h reaction time.

a) C_{CTAB} and C_d in kmol m^{-3}.
b) r_L and r_O in kmol m^{-3} s^{-1}; r_L was based upon total liquid volume, and r_O on the organic phase volume.
c) Observed values after 2 h reaction time.
d) Parameter values at different levels.
e) *n*-Decane was used as the organic diluent for adjusting the concentration of 1-dodecene to 2.2 kmol m^{-3}.

an orthogonal experiment of L_{18} $(2^1 \cdot 3^7)$. The preliminary optimal reaction conditions were found to be $T = 100$ °C, $p = 1.1$ MPa, $V_O/V_W = 3/7$, $\gamma_{H2}/\gamma_{CO} = 1/1$, $C_{cat} = 1.5 \cdot 10^{-3}$ kmol m^{-3}, [TPPTS]/[Rh] = 18, $C_d = 2.2$ kmol/m^3 and $C_{CTAB} = 11.0 \cdot 10^{-3}$ kmol m^{-3}. Then Yang et al. [5] adopted another orthogonal experimental design to further investigate several key parameters: stirrer speed, CTAB concentration, 1-dodecene concentration, stirrer type, and the of organic/aqueous-phase volume ratio. The orthogonal design table of L_{12} $(3^1 \cdot 2^4)$ and the experimental results are tabulated in Table 2.

The margin analysis based on the experimental results in Table 2 suggests that the most important factor investigated is the agitation speed *N* and the second most important is the V_O/V_W ratio, as far as the maximum initial reaction rate, *normal/iso* aldehyde ratio and conversion are concerned (Table 3). The effect of surfactant concentration was the least important in the selected range of reaction

Table 3 Results of marginal analysis of orthogonal tests [16].

	N [rps]	*V_O/V_W*	*C_{CTAB} [mol m^{-3}]*	*Stirrer type*	*C_d [kmol m^{-3}]*
r_{O1a}	0.133	0.467	0.390	0.390	0.367
r_{O2a}	0.417	0.333	0.420	0.422	0.450
r_{O3a}	0.617				
R_{ro}	0.484	0.134	0.030	0.032	0.083
n/i_{1a}	11.22	8.40	6.79	6.75	6.60
n/i_{2a}	6.37	6.36	7.57	7.95	7.79
n/i_{3a}	4.51				
$R_{n/i}$	6.71	2.04	0.78	1.20	1.19
P_{1a}	0.26	0.71	0.726	0.78	0.70
P_{2a}	0.49	0.75	0.732	0.67	0.76
P_{3a}	1.29				
R_p	1.03	0.04	0.006	0.11	0.06
x_{1a}	37.17	65.24	59.38	63.56	62.93
x_{2a}	64.69	53.99	60.82	55.98	56.68
x_{3a}	74.64				
R_x	37.47	11.25	1.44	7.58	6.25
r_{L1a}	0.052	0.133	0.131	0.135	0.115
r_{L2a}	0.152	0.163	0.164	0.161	0.149
r_{L3a}	0.240				
R_{rL}	0.188	0.030	0.033	0.026	0.034

Note: Analysis was based on the results in Table 2.
r_{Oja} ($j = 1, 2, 3$) is the average value of r_O at level j of factor i ($i = 1, 2, \ldots, 5$),
$R_{rO} = \max(r_{Oja}) - \min(r_{Oja})$.
n/i_{ja} ($j = 1, 2, 3$) is the average value of n/i at level j of factor i ($i = 1, 2, \ldots, 5$),
$R_{n/i} = \max(n/i_{ja}) - \min(n/i_{ja})$.
P_{ja} ($j = 1, 2, 3$) is the average value of P at level j of factor i ($i = 1, 2, \ldots, 5$),
$R_P = \max(P_{ja}) - \min(P_{ja})$.
x_{ja} ($j = 1, 2, 3$) is the average value of x at level j of factor i ($i = 1, 2, \ldots, 5$),
$R_x = \max(x_{ja}) - \min(x_{ja})$.

conditions [16]. The results of variance analysis were similar to the margin analysis, except for a minor difference in the sequence of importance of influence of two less important factors: the importance of the concentrations of CTAB and 1-dodecene to the index of conversion. The main result was that when the agitation speed was increased, the power consumption, conversion, and initial rate all increased, whereas the regioselectivity to *n*-tridecylic aldehyde decreased. It is somewhat surprising that a seemingly irrelevant factor, the V_O/V_W ratio, plays a significant role in the hydroformylation performance: the reaction rate based on organic phase volume and regioselectivity was enhanced by a decrease in V_O/V_W. This is possibly attributable to easy and stable formation of micelles and O/W emulsion as well as a greater amount of catalyst, but the exact mechanism awaits quantitative interpretation.

Although the optimal set of variable levels corresponding to each index was not completely coincident, the optimal reaction conditions for a compromise between high productivity and selectivity and low power consumption were suggested to be $N = 11.7$ rps, $V_O/V_W = 3/7$, $C_d = 4.4$ kmol m^{-3}, $C_{CTAB} = 12.4 \cdot 10^{-3}$ kmol m^{-3} and the stirrer type PBTU [5]. It is noticeable that the optimal value of the organic/aqueous-phase volume ratio agrees with that obtained by Zhang et al. [1]. It is also reported that low volume ratio (V_O/V_W) was in favor of conversion and TOF frequency in hydroformylation of 1-dodecene [19]. However, no chemical engineering model is available for a quantitative account of the influence of this factor.

2.3.1.3.3
Influence of Agitation Configuration

Biphasic hydroformylation of 1-dodecene indexed by the chemical conversion and regioselectivity can be optimized by exploration of the appropriate agitation configuration and intensity of agitation, which affects the hydrodynamics of mixing and dispersion correlated with interphase mass transfer. Five cases of agitation configuration were tested [5, 15]. Cases 1 and 2 were standard surface aeration configurations using single DT and PBTU, respectively. Novel composite impeller configurations were featured with a self-rotating floating baffle (SRFB) located between the gas–liquid interface and a DT impeller (Case 3) or a PBTU impeller (Case 4) to improve surface aeration. As shown in Figure 3, a dual impeller including an upper DT used as a surface aerator and a PBTU fixed in the middle of the reactor for circulating the reaction mixture was combined with an SRFB placed above the DT, and this composite agitation configuration was Case 5 [18].

As shown in Table 4 and Figure 5, the single PBTU impeller (Case 2) achieved a better performance with a higher initial rate and n/i aldehyde ratio accompanied by a lower power consumption than the single DT impeller (Case 1) under the same conditions of operation. This was possibly due to the better capability for overall circulation and lower agitation intensity of the PBTU impeller, which favored maintenance of the orderly micelle structure. When the novel SRFB was used (Cases 3 and 5), the initial rate of the biphasic hydroformylation increased remarkably from $0.630 \cdot 10^{-3}$ kmol m^{-3} (Case 1) to $1.24 \cdot 10^{-3}$ and $2.03 \cdot 10^{-3}$ kmol m^{-3} respectively, by a factor of almost 2–3. However, the conversion and regioselectivity after 2 h of reaction were almost the same. Therefore, it is clear that an SRFB can increase the initial rate of 1-dodecene hydroformylation, but fails to further enhance

Table 4 Effect of agitation configuration on hydroformylation of 1-dodecene [5].

Case	*Stirrer type*	$r_L \cdot 10^3$ [kmol m^{-3} s^{-1}]	$r_O \cdot 10^3$ [kmol m^{-3} s^{-1}]	n/i $^{a)}$	x $^{a)}$ [%]	*P* [W]
1	DT	0.189	0.630	6.39	84.0	0.42
2	PBTU	0.208	0.695	9.08	68.5	0.35
3	DT + SRFB	0.372	1.24	6.24	83.0	0.56
4	PBTU + SRFB	0.0620	0.207	10.5	42.8	0.41
5	DT + PBTU + SRFB	0.609	2.03	6.06	84.2	–

a) Observed values after 2 h reaction time.

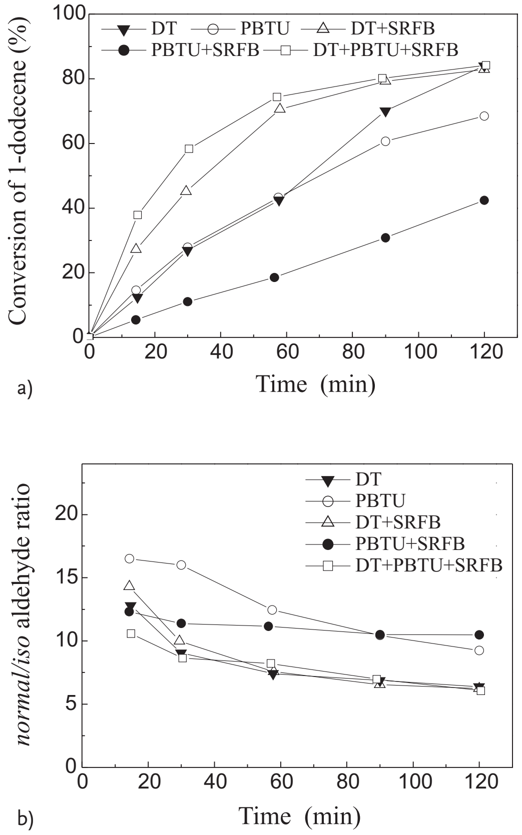

Figure 5 Hydroformylation conversion and regioselectivity versus reaction time with different agitation configurations [5]. (a) Conversion of 1-dodecene, (b) *n*/*i* aldehyde ratio.

the conversion and selectivity over a full 2 h run. The poor performance in Case 4 was probably caused by the failure to self-rotate and float of the SRFB placed above the PBTU, with the consequence that normal contact, circulation, and mixing of gas and liquid streams were weakened.

Yu et al. [17] demonstrated that the composite surface aeration configurations with an SRFB were effective in enhancing the gas–liquid volumetric mass transfer coefficient by intensifying turbulence in gas–liquid–liquid flow and in generating more small gas bubbles by stronger shear. Since the gas–liquid mass transfer of biphasic hydroformylation systems may be limiting [6], the composite agitation configuration displays a better performance in promoting the reaction rate and is recommended for stirred autoclaves. From the above results, it can be concluded that improving the agitation configuration and choosing a suitable agitation intensity in gas–liquid and gas–liquid–liquid systems require as much attention as the catalytic chemistry itself.

2.3.1.3.4
Emulsification of Reaction Mixture

It is observed from Figures 4 and 5 that the molar ratio of *normal* to *iso* aldehyde products decreased significantly with time, and it obviously varied with the agitation intensity and stirrer type. This phenomenon, closely related to the mechanisms of biphasic hydroformylation, is difficult to explain even in a qualitative manner. At the same time, significant variation of emulsification of the reaction mixture occurred in correlation with the hydroformylation system, surfactant addition, and agitation.

It is believed that the extent of emulsification is a reflection of the operating conditions and physicochemical properties of the reaction system. Because it is very difficult to characterize quantitatively, the extent of emulsification, a simple but somewhat subjective and fuzzy index was proposed to represent the extent of emulsification [15]. The defined fuzzy index ranges from 0 (significant phase settlement in less than 1 min after sample withdrawal from the reactor) to 5 (severe emulsification and no phase separation by gravity observed over 4 h at ambient temperature); for intermediate values, 1 is assigned to the situation with significant phase separation in 1–5 min, 2 for 5–20 min, 3 for 20–60 min and 4 for 1–4 h.

As shown in Figures 6 and 7, the extent of emulsification was observed to develop as the hydroformylation reaction proceeded, and to be intensified with the agitation intensity and CTAB concentration. The agitation configuration leading to higher olefin conversion resulted in more severe emulsification (Figure 8). It is obvious that emulsification favors the hydroformylation conversion and disfavors the regioselectivity (Figure 9). It may be conjectured that the oscillating microstructure of micelles accompanied by severe emulsification was not kept as orderly and compact as that at the beginning of the reaction, and this effect not only increased the difficulty of product separation at the end of hydroformylation, but was also unfavorable for the formation of linear aldehyde. It seems that the correlation of the extent of emulsification with hydroformylation indices must be interpreted from the chemical and chemical engineering point of view, and more work on

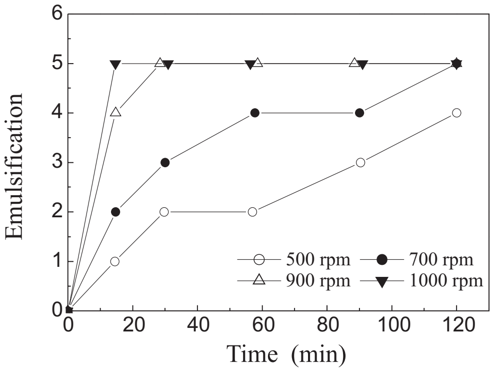

Figure 6 Influence of agitation speed on emulsification [5].

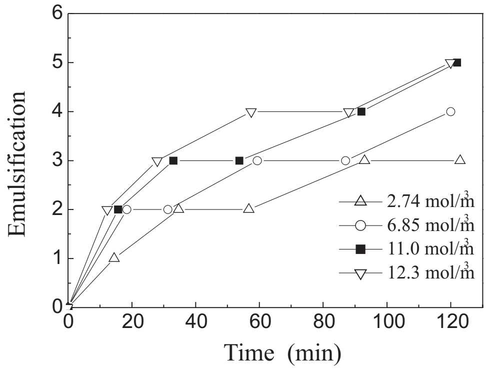

Figure 7 Influence of surfactant concentration on emulsification [5].

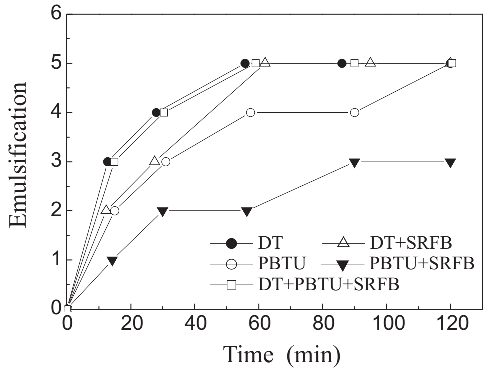

Figure 8 Influence of agitation configuration on emulsification [5].

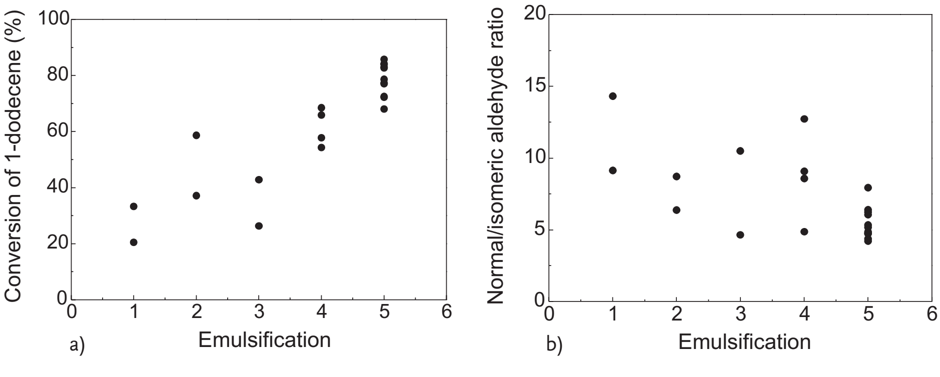

Figure 9 Conversion and regioselectivity versus emulsification extent of hydroformylation mixture in 2 h under different reaction conditions based on the experimental data in Table 2 and Figures 6–8 [5].
(a) Conversion of 1-dodecene, (b) *n*/*i* aldehyde ratio.

physicochemical properties of the emulsification, such as optical refraction, droplet size and interface features, micelle microstructure, etc., is required so as to facilitate further and in-depth understanding of the underlying mechanism of biphasic hydroformylation.

2.3.1.3.5
Kinetics of Biphasic Hydroformylation

Biphasic hydroformylation is a typical and complicated gas–liquid–liquid reaction. Although extensive studies on catalysts, ligands, and catalytic product distributions have appeared, the reaction mechanism has not been understood sufficiently and even contradictory concepts of the site of hydroformylation reaction were developed [11, 13, 20]. Studies on the kinetics of hydroformylation of olefins are not only instructive for improvement of the catalytic complexes and ligands but also provide the basic information for design and scale-up of novel commercial reactors. The kinetics of hydroformylation of different olefins, such as ethylene, propylene, 1-hexene, 1-octene, and 1-dodecene, using homogeneous or supported catalysts has been reported in the literature. However, the results on the kinetics of hydroformylation in aqueous biphasic systems are rather limited and up to now no universally accepted intrinsic biphasic kinetic model has been derived, because of the unelucidated reaction mechanism and complicated effects of multiphase mass transfer (see also Section 2.4.1.1.2).

The kinetics of low-carbon olefins, ethylene [21] and propylene [22], in aqueous systems was reported and different rate models proposed. Wachsen et al. [13] proved that aqueous biphasic hydroformylation of propylene took place at the interfacial region, in contrast to two preliminary kinetic models that incorporate mass transport.

The biphasic hydroformylation of 1-octene was studied in the presence of ethanol as a co-solvent and a proposed kinetic rate expression was nearly identical to that of the homogeneous system [10, 23]. A further kinetic study of this biphasic hydroformylation system was conducted by Lekhal et al. [6] to analyze the experimental data by coupling kinetics to a pseudo-homogeneous gas–liquid–liquid macroscopic conservation model; the authors proved that gas–liquid mass transfer was the only limitation.

Borrmann et al. [24] reported the kinetic data of the biphasic hydroformylation of several long-chain and branched olefins using a water-soluble rhodium polyethylene glycolate catalyst, with first-order reaction for 1-dodecene and 2,4,4-trimethylpent-1-ene and zero-order for styrene. The activation energy of the biphasic hydroformylation in a polyethylene glycol (PEG) solvent is higher than that in water as solvent (cf. Section 2.3.5). Based on some conjecture about the mechanism of 1-dodecene hydroformylation, Zhang et al. [1, 25] investigated the macro-kinetics of 1-dodecene hydroformylation catalyzed by a $RhCl(CO)(TPPTS)_2$ complex in the presence of CTAB, and analyzed the influence of interphase mass transfer by a computational fluid dynamics method. Several complicated kinetic and regioselectivity models, including the influence of concentrations of higher olefin and

Table 5 Activation energy of biphasic hydroformylation of olefins.

Olefin	*Catalyst*	*E [kJ mol^{-1}]*	*Ref.*
1-Octene	$[Rh(COD)Cl]_2$TPPTS/ethanol	66	[23]
1-Hexene	Supported Rh/P4VP	18–59	[26]
Cyclohexene		22–93	
1-Hexene	Rh(PEG_x)water/PEG	23–71	[24]
1-Octene		94–106	
1-Dodecene		95–105	
Diisobutene		30–51	
Propylene	$RhCl(CO)(TPPTS)_2$	77–83	[22]
1-Dodecene	$RhCl(CO)(TPPTS)_2$	62–73	[1]

catalyst, partial pressures of H_2 and CO, molar ratios of ligand to catalyst, volume ratios of organic/aqueous phases, weight percentages of surfactant and temperature, were presented. The macro-kinetic data reflecting the intrinsic chemical reaction and mass transfer under practical technological conditions provide the necessary basis for modeling and designing multiphase reactors.

Summarizing results reported in literature, the kinetic rate of biphasic hydroformylation was found to be influenced positively by increasing the concentration of catalyst, olefin, and hydrogen, whereas a higher carbon monoxide pressure exerted a negative effect. It seems that regioselectivity has not been approached by kinetic analysis to date. The apparent activation energy for hydroformylation was found to be in the range from 20 to 100 kJ mol^{-1} (Table 5), which covers the lower range of usual chemical reactions. Thus, the influence of mass transfer on the intrinsic kinetics of biphasic hydroformylation is not completely eliminated, though many precautions were taken to minimize the resistance of mass transfer in kinetic experiments. The mass transfer resistance depends largely on the solubility of the reactants, the thermodynamic phase equilibrium, and the interfacial properties, as well as the hydrodynamics of gas–liquid–liquid dispersion, agitation, and mixing. In practice, for improved performance of a gas–liquid–liquid hydroformylation reaction in a multiphase reactor, it is necessary to study and combine the intrinsic kinetics, mass and heat transfer, residence time distribution, and reactor configuration in an appropriate mathematical model.

2.3.1.4
Mathematical Model for Biphasic Hydroformylation Reactor

It is rather difficult to establish a reasonably accurate mathematical model of a gas–liquid–liquid three-phase reactor for biphasic hydroformylation, because of the complexity in formulating all the necessary mechanisms such as phase dispersion and distribution, multiphase flow, interphase mass transfer, micromixing, and the hydroformylation reaction. Besides, the task is further complicated by turbulence in multiphase flow and the complex domain of stirred-tank reactors.

Although a chemical engineering study is in rapid progress toward this goal, only a few simpler but still rather difficult models, aimed at part of the chemical engineering process taking place in the reactor, have been proposed for application in the biphasic hydroformylation of olefins.

Lekhal et al. [6] proposed a pseudo-homogeneous gas–liquid–liquid model based on the Higbie penetration theory to account for simultaneous absorption of two gases into the liquid phases. Because of the assumption of rapid liquid–liquid mass transfer of reactants leading to the equilibrium between two liquid phases, the model was simplified greatly and the detail of phase dispersion and distribution and multiphase flow was avoided. Reasonable success was achieved and the results of analysis suggested that the only limitation to the conversion of hydroformylation of 1-octene was the gas–liquid mass transfer of CO and H_2.

Van Elk et al. [27] used a similar mathematical model, based on the penetration model for three reactants in an ideally stirred reactor, to study the dynamic behavior of the gas–liquid homogeneous hydroformylation process. The influence of mass and heat transfer on the reactor stability in the kinetically controlled regime was analyzed and it brought to mind the existence of a dynamically unstable (limit circle) state under certain operating conditions. This model needs to be extended to account for the presence of a second liquid phase in biphasic hydroformylation.

In fact, a complete mathematical model of a hydroformylation reactor includes many sub-models. At present, the kinetics reported in the literature seems to contain uncertainty due to incomplete elimination of interphase mass transfer resistance in conventional experimental studies. In view of this, Zhang et al. [25] tried to use a reactor of simple geometry (a regular cylinder) in combination with a numerical approach to account accurately for the gas–liquid and liquid–liquid mass transfer in determining the interfacial hydroformylation kinetics and removing the possible uncertainty of estimating effective reactant concentrations. As for the multiphase flow in stirred reactors, great success in numerical simulation of gas–liquid flow has been achieved [28–31], but the turbulent interphase mass transfer is not resolved yet. Therefore, tremendous efforts are required before the mathematical model of a hydroformylation reactor as a predicting tool can be used for the purpose of commercial biphasic hydroformylation.

2.3.1.5
Prospect of Reaction Engineering Study on Hydroformylation

It is gradually being recognized by chemists that the engineering aspects indeed have important relevance to the chemical study of homogeneous and heterogeneous hydroformylation. In a series of regular reviews on yearly progress in hydroformylation research, a subtitle “Engineering aspects” started to appear in the contents [32] but the discussion was less voluminous. Meanwhile, several developments open new routes for effectively conducting hydroformylation of higher molecular weight olefins, in particular for facilitating the catalyst separation. Horváth et al. [33a,b] proposed fluorous biphasic systems (FBSs) which consist of a fluorous phase containing dissolved reagent or catalyst and a product phase with limited solubility in the fluorous phase (see Chapter 4). Based on nonionic phosphine ligands, the concept of thermoregulated phase transfer catalysis (TRPTC) was developed and applied in aqueous/organic biphasic hydroformylation of higher olefins [34, 33] (cf. Section 2.3.5). The separation of catalyst from substrate and product phase can also be achieved by using the special properties of ionic liquids, as suggested by Webb et al. [38], who conducted hydroformylation of 1-dodecene in a continuous flow system consisting of ionic liquid and supercritical CO_2 to effect downstream separation of products from reaction solvent and catalyst (cf. Chapters 5 and 6). The improved SLP-catalyst technology, combined with flow reversal and artificial unsteady operation, approaches steadily the same target along the same lines [39, 40]. Leitner [36] also devoted effort to understanding the role of engineering aspect factors on the performance and kinetics of hydroformylation of olefins. Here we use the conclusion from Leitner as the final remark, i.e., "Increasing research efforts are urgently needed to improve our fundamental knowledge and to broaden the scope of the basic methodology. At the same time, reaction engineering becomes more and more important to evaluate various process designs in terms of efficiency and costs. Interdisciplinary efforts involving preparative chemists, researchers in catalysts, physico-chemists, and chemical engineers appear to have the highest chances to meet this challenge."

Symbols

C	concentration of various component, kmol m^{-3}
E	activation energy, kJ mol^{-1}
N	agitation speed, rps
n/i	ratio of *normal*/*iso* aldehydes
P	power consumption for agitation, W
p	total pressure, MPa
r	initial rate of hydroformylation reaction, kmol m^{-3} s^{-1}
T	reaction temperature, °C
V_O/V_W	volume ratio of organic/aqueous phases
W	weight percentage in water, %
x	conversion of olefin
y	molar fraction of gas component

Subscripts

a	average value
cat	rhodium complex catalyst
CO	carbon monoxide
CTAB	cetyltrimethylammonium bromide
d	1-dodecene
H_2	hydrogen
L	total liquid phase based
O	organic phase volume based

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2.3.2
Technical Solutions

Arno Behr and Joachim Seuster

2.3.2.1
Introduction

A question that applies generally in homogeneous catalysis using organometallic catalysts is how to separate the catalyst from the product. In homogeneous catalysis this problem can become the most critical point in the technical realization of a chemical process. One benefit of the aqueous-phase chemistry is the possible formation of a second nonpolar phase by organic products, thus enabling the separation of the catalyst from the products. The use of two liquid phases with the aim of separating the homogeneous catalyst is called the liquid–liquid two-phase technique (LLTP).

A further benefit of this LLTP technique is the suppression of consecutive reactions. This advantage is described by the general equation (1), in which starting components A and B usually yield the products C and D, but also an undesired consecutive product E. If the catalyst and the products C and D form only one phase, a further reaction to E cannot be avoided. If, however, the catalyst is dissolved in the aqueous phase and the products C and D in the second organic phase, no further reaction can proceed. Consequently, by using the LLTP-technique, the products C and D are formed with high selectivity.

$$A + B \xrightarrow{[cat]} C + D \xrightarrow{[cat]} E \qquad (1)$$

2.3.2.2
Technical Realization

Table 1 gives a brief overview of the industrially realized polar-phase organometallic-catalyzed reactions together with some related reactions which are still under development.

The most important process worldwide is the “Shell higher-olefin process” (SHOP) in which ethylene is oligomerized to higher molecular mass, linear α-olefins. The nickel catalyst, containing a phosphorus/oxygen chelate ligand, is dissolved in the polar solvent 1,4-butanediol, which is not miscible with the α-olefins (see Chapter 3 [1–5]).

A very important process with the solvent water is the hydroformylation of propene to butyraldehydes, known as the Ruhrchemie/Rhône-Poulenc process. The reaction is catalyzed by a rhodium complex containing the water-soluble ligand triphenylphosphine trisulfonate (TPPTS) (see Section “Lower Alkenes” [6–11]).

All other industrial applications are still on a smaller scale. The Kuraray telomerization of butadiene with water is carried out at 5000 t y^{-1} (see Section 2.4.4.2

Table 1 Examples of organometallic-catalyzed reactions.

Company or University	*Reaction*	*Catalyst*	*Solvent*	*Ref.*
Shell (SHOP)	Oligomerization of ethene	Ni	1,4-Butanediol	[1–5]
Ruhrchemie/ Rhône-Poulenc	Hydroformylation of olefins	Rh	Water	[6–11]
Rhône-Poulenc	Co-oligomerization with myrcene	Rh	Water	[12–14]
Rhône-Poulenc	Hydrogenation of unsaturated aldehydes	Ru	Water	[15–18]
Wasserscheid/ Univ. Erlangen	Hydrogenation of sorbic acid	Ru	Ionic liquids	[19]
Kuraray	Telomerization of butadiene with water	Pd	Water/sulfolane	[20–28]
Behr/Univ. Dortmund	Telomerization of isoprene with methanol	Pd	Methanol	[29]
Behr/Univ. Dortmund	Telomerization of butadiene with glycol	Pd	Acetonitrile	[30–31]
Driessen-Hölscher/ Univ. Paderborn	Telomerization of butadiene with ammonia	Pd	Water	[32–33]
Keim/ Univ. Aachen	Telomerization of butadiene with phthalic acid	Pd	Acetonitrile	[34]
Keim/ Univ. Aachen	Dimerization of butadiene	Pd	DMSO	[34]

[20–28]); the Rhône-Poulenc reactions have been developed into bulk processes [12–18]. The investigations at the Universities of Dortmund, Aachen, Paderborn, and Erlangen (Germany) are still on laboratory or mini-plant scale.

After the reaction, the products have to be separated from the catalyst. This can be done by separation either of the product or of the catalyst from the residue. The separation methods can be varied: simple separation of two liquid phases, extraction with an additional solvent, or chemical treatment with additional bases or acids.

In all these cases a reaction is combined with a separation step. This can be done in the same unit (simultaneously) or in separate units (successively).

In total, by combining all variations there are 12 cases which will be discussed in more detail using the general reaction [Eq. (1)]. To simplify the discussion it is assumed that the expected products are organic nonpolar compounds. Of course, analogous considerations apply if the products are polar. In these cases the terms “polar” and “nonpolar” in the following sections have to be interchanged.

2.3.2.2.1
Reaction and Product Separation

The simplest way to combine catalysis in a polar medium and product separation is shown in Figure 1, where both operations proceed in one unit. The nonpolar phase can be separated at the top of the column while the polar catalyst phase remains in the reactor. This principle is realized in the SHOP process using 1,4-butanediol with a nickel catalyst as the catalytic phase.

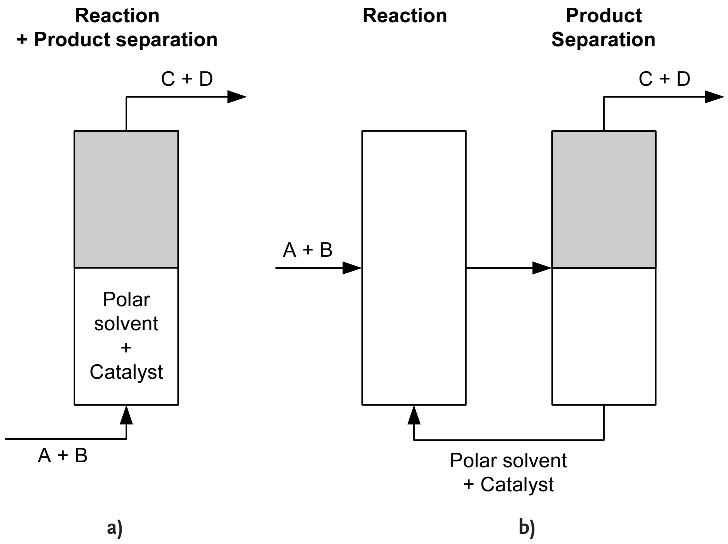

Figure 1 Simultaneous (a) and successive (b) reaction and product separation.

The simultaneous process shown in Figure 1 (a) can be divided into two sequential units, shown in Figure 1 (b), as realized in the Rhône-Poulenc/Ruhrchemie hydroformylation process of propene. The reaction takes place in a continuous stirred tank reactor (CSTR) while the phase separation is carried out in a decanter.

2.3.2.2.2
Reaction and Product Extraction

Unlike the processes described above, the processes in this section use an additional organic nonpolar solvent for the product extraction. Figure 2 shows the simultaneous reaction and product extraction also called “in-situ extraction”. The nonpolar extractant absorbs the reaction product in the reactor and is separated from the polar catalyst phase in the following separation step. Due to the subsequent solvent distillation this process is somewhat more complex.

An application of this principle is in the telomerization of butadiene with ethylene glycol. One-phase reactions yield both mono- and ditelomers, while the two-phase system using a water/glycol phase containing a polar palladium catalyst avoids the

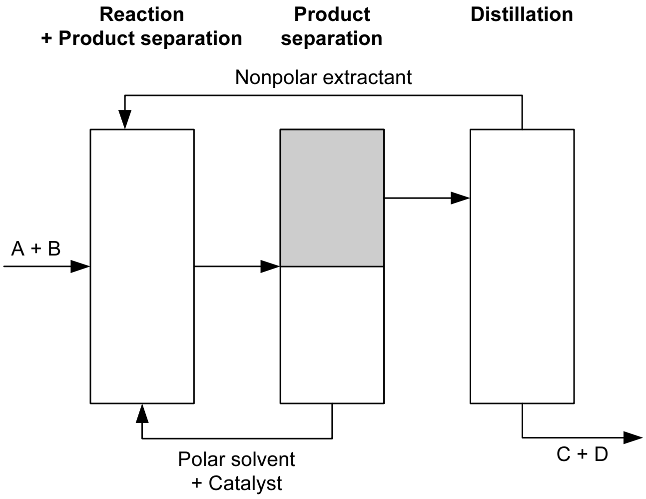

Figure 2 Simultaneous reaction and product extraction.

consecutive reaction to the ditelomer, thus yielding the desired monotelomers with high selectivity [30–31].

The successive process alternative, shown in Figure 3, divides the combined reaction/extraction step into a reaction unit with a single polar phase and the product extraction unit.

The practicability of this concept will be demonstrated by two examples. In the first, the dimerization of butadiene to 1,3,7-octatriene in the presence of a catalyst containingg a palladium precursor and triphenylphosphine as well as the alcohol $PhC(CF_3)_2OH$ is carried out favorably in the solvent acetonitrile. The following

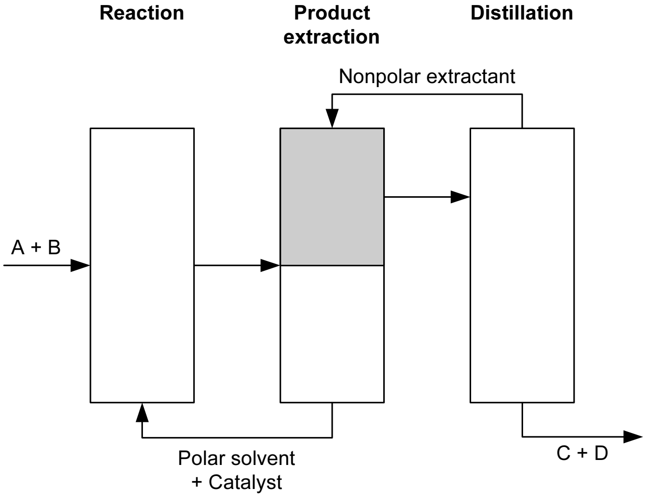

Figure 3 Successive reaction and product separation.

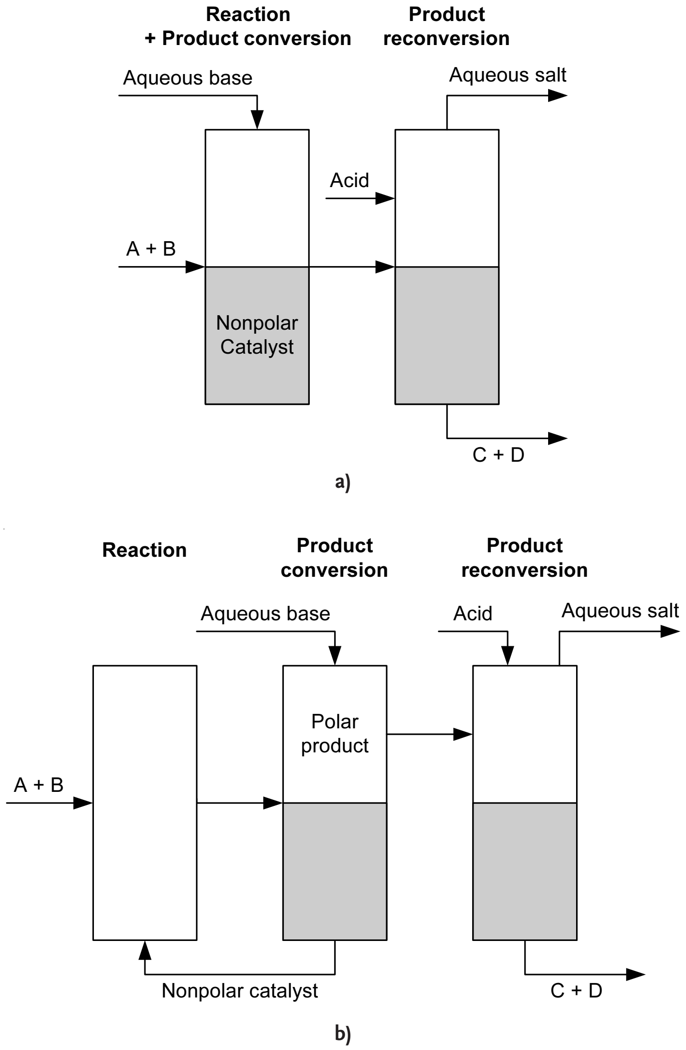

Figure 4 Simultaneous (a) and successive (b) reaction and product treatment.

extraction with isooctane separates the product from the acetonitrile phase, which still contains the catalyst and alcohol. Finally, the isooctane is distilled from the product and recycled into the extraction unit. In a continuously working miniplant 3 kg of octatriene per gram Pd could be produced.

The second example is the telomerization of phthalic acid with butadiene yielding bis(octadienyl) phthalates, which can be used as plastic softeners after hydrogenation. The polar solvent dimethyl sulfoxide contains the palladium catalyst formed from $Pd(acac)_2$ and tris(*p*-methoxyphenyl)phosphite. This extraction uses isooctane as well [34].

2.3.2.2.3
Reaction and Product Treatment

An interesting concept is the synthesis of an organic nonpolar product with a nonpolar catalyst, and the parallel conversion of the nonpolar product into a polar one and its separation with the polar phase from the catalytic nonpolar phase as shown in Figure 4 (a).

An example is the synthesis of nonpolar long-chain carboxylic acids, which are transformed into the polar carboxylic salts by addition of an aqueous base. In a second unit the carboxylic salt is reconverted into the nonpolar product and a salt solution which can easily be separated. The production of salt waste is one of the disadvantages of this and related chemical separation techniques.

The alternative process of successive reaction and product treatment, where the reaction and product conversion is split into two units, is shown in Figure 4 (b).

2.3.2.2.4
Reaction and Catalyst Separation

Another alternative for catalyst separation is the filtration after the catalyst has been precipitated. An interesting application is given by Fell and co-workers [35] for the hydroformylation of higher olefins by a methanol- and water-soluble rhodium catalyst. As shown in Figure 5, the reaction is carried out in a homogeneous methanol solution. After distillation of the methanol the catalyst is precipitated, filtered off, and again prepared with the distilled methanol. The products leave the process after the filtration step.

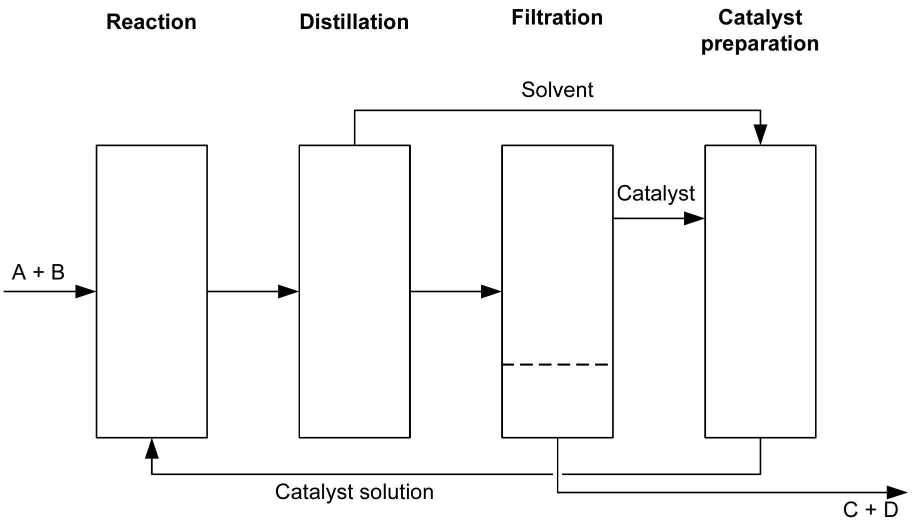

Figure 5 Successive reaction and catalyst separation (using catalyst filtration).

2.3.2.2.5
Reaction and Catalyst Extraction

The simultaneous reaction and catalyst extraction shown in Figure 6 (a) is not favorable, due to the fact that the catalyst leaves the reaction medium during the reaction. The successive reaction and catalyst extraction shown in Figure 6 (b), where reaction and extraction are carried out in two different units, is however much more favorable.

The most important point is the complete separation of the catalyst and the products. The Union Carbide process proposal for the hydroformylation of higher olefins solves this problem [36, 37]. The catalyst leaching is lower than 20 ppb of the rhodium catalyst.

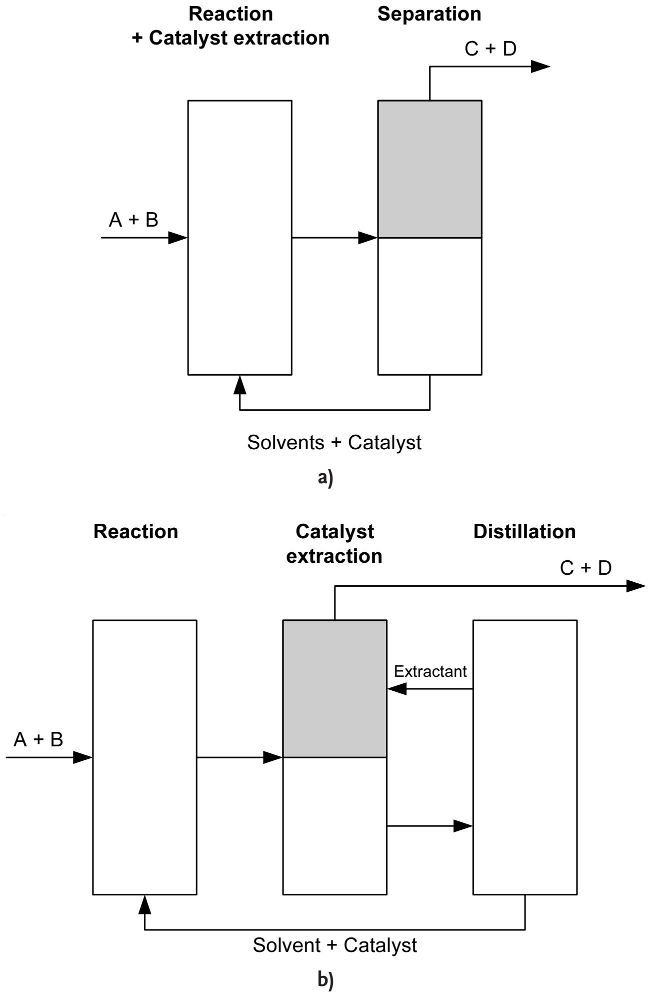

Figure 6 Simultaneous (a) and successive (b) reaction and catalyst extraction.

2.3.2.2.6
Reaction and Catalyst Treatment

Analogously to the process described in Section 2.3.2.2.3, where the product is treated with bases or acids, the catalyst also can be treated in this way. As discussed in the previous section, removal of the catalyst while the reaction is occurring is not favorable.

Figure 7 shows the successive reaction and catalyst treatment. After the single-phase reaction using a nonpolar solvent and catalyst, the nonpolar catalyst is converted into a polar one. In the third step, the catalyst is reconverted into a nonpolar one and recycled to the reaction unit. The conversions can be processed by using a catalyst containing anionic ligands with higher alkylammonium cations. Addition of sodium hydroxide will cause the alkylammonium cation to be exchanged by the sodium cation and leave the nonpolar phase. Of course, this process can be reversed by adding an acid and new ammonium ions.

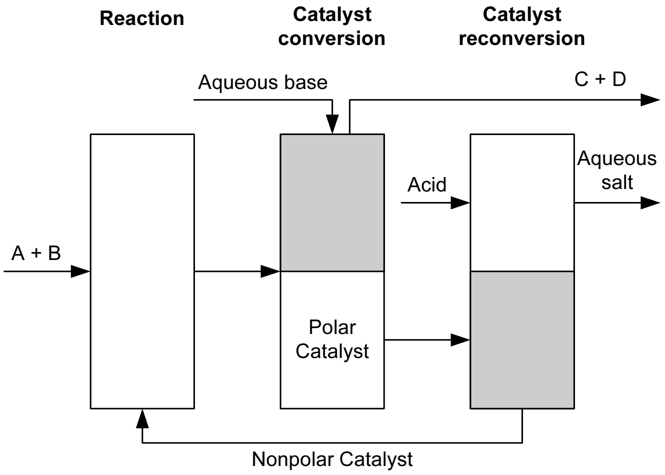

Figure 7 Successive reaction and catalyst treatment.

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2.3.3
Membrane Techniques

José Sanchez Marcano

2.3.3.1
Membrane Separation Processes

Today, membrane separation processes are finding an extensive and ever-increasing use in the pharmaceutical, food, and petrochemical industries, as well as in environmental applications. Membrane separation processes present some advantages over more classical separation processes since they are less energy-consuming and more compact, and generally require less initial capital investment.

A membrane is a permeable or semi-permeable thin film made of a variety of different materials, from inorganic porous solids to different types of polymers. The main function of the membrane is to control the exchange of materials between two adjacent fluids (the phases can be similar or different). To do so, the thin film acts as a barrier, which separates different species either by sieving or by controlling their relative rate of transport through itself. Transport processes through the membrane are the result of a driving force typically associated with a gradient of concentration, pressure, temperature, electric potential, etc. The ability of a membrane to separate mixtures is determined by two parameters: permeability and selectivity. Permeability is defined as the flux (molar or volumetric flow per unit area) through a membrane scaled with respect to the membrane thickness and driving force. Thus, when the gradient involved is the partial pressure, the units of permeability are mol (or m^3) m m^{-2} Pa^{-1} s^{-1}. Selectivity is the second important parameter which characterizes the capability of a membrane to separate two species. "Ideal selectivity" is then defined as the ratio between the individual permeabilities of the two species.

Membranes can be classified according to the type of material their film is made of (organic or inorganic materials) or to the porosity of the thin layer (porous or dense). Choosing between a porous or a dense film as well as choosing the type of

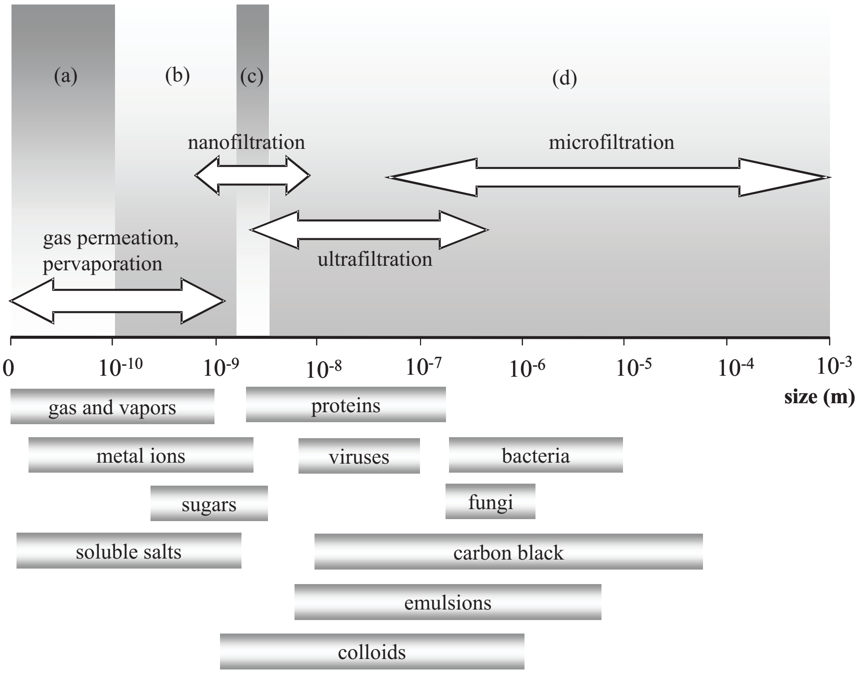

Figure 1 Membrane processes, different types of membranes and the sizes of species: (a) dense and ultramicroporous, (b) microporous, (c) mesoporous, (d) macroporous.

material depends on the separation process, the operating temperature, and the driving force. In addition, for applications concerning membrane reactors (MRs), where the reaction is coupled with the separation process, the thin film has also to be stable under reaction conditions.

Porous membranes can be made of polymers (polysulfones, polyacrylonitrile, polypropylene, silicones, perfluoropolymers, polyimides, polyamides, etc.), ceramics (alumina, silica, titania, zirconia, zeolites, etc.) or microporous carbons. Dense organic membranes are commonly used for molecular-scale separations involving gas and vapor mixtures, whereas the mean pore sizes of porous membranes is chosen considering the size of the species to be separated. Current membrane processes include microfiltration (MF), ultrafiltration (UF), nanofiltration (NF), gas and vapor separation (GS), and pervaporation (PV). Figure 1 indicates the types and sizes of species typically separated by these different separation processes.

Membranes are manufactured in a wide range of geometries; they include flat, tubular, and multi-tubular, hollow-fiber, and spiral-wound. The type of geometry of the membrane depends on the material the membrane is made of. Ceramic membranes generally come in tubular, multi-tubular and flat geometries, whereas most spiral-wound and hollow-fiber membranes are made of polymers.

2.3.3.2

The Coupling of a Membrane Separation Process with a Catalytic Reaction: the MR Concept

In MR processes, separation and reaction are combined into a single unit. The coupling of both processes therefore results in a continuous separation/feed of reactants/products, which often results in enhanced selectivity and/or yield. The MR concept was first applied in reactions in which the continuous extraction of products would enhance yield by shifting equilibrium. The catalytic reactions of this type that have been investigated include dehydrogenation and esterification. However, reactive separations also appear to be interesting for other reactions, such as hydrogenation and partial oxidation. Since the 1980s, many studies have been published on the application of membrane separations in catalytic processes. Reaction yield and selectivity have been reported to be strongly dependent not only on operating conditions but also on membrane permeability and selectivity. Detailed descriptions of the state-of-the-art of catalytic membrane reactors have already been published [1–4].

In the early stages of MRs, the two functions were coupled by connecting two distinct units – the reactor and the membrane separator – in series (Figure 2a). The membrane reactor design, shown in Figure 2 (b), which combines both process units into a single one, was the result of the development of the first process design into the second.

The design configuration of Figure 2 (b) results in obvious advantages over the first design: it is more compact, while capital and operating savings are realized by the elimination of intermediate steps. Other beneficial effects can result from the synergy between separation and reaction. Indeed, for reactions limited by thermo-

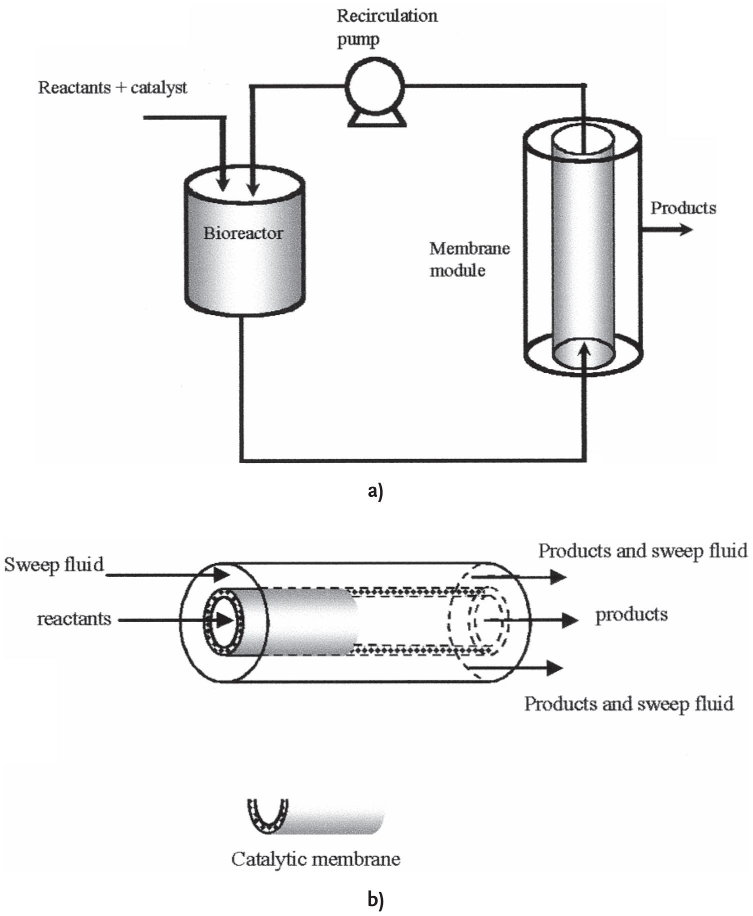

Figure 2 (a) A conventional system (reactor and membrane separator) and (b) a catalytic membrane reactor.

dynamic equilibrium, as is frequently the case with catalytic hydrocarbon dehydrogenation, it is obvious that the continuous and selective separation of hydrogen from the reaction vessel will result in better yields. Despite the advantages of the catalytic membrane reactor (CMR) of Figure 2 (b), the more conventional design of Figure 2 (a) is still frequently used, because of its simplicity and the easy control of its different operating parameters. In both MR designs shown in Figure 2, the membrane (in any configuration, whether tubular, hollow-fiber, or plate) defines two different chambers. These are the retentate chamber, where the reactants are fed and the reaction often takes place, and the permeate chamber, where the products are separated.

The impressive progress in the area of MRs since the 1980s has been associated with the development of membrane manufacturing and processes. In quite a short time, the field has progressed far beyond such initial applications as dehydrogenation reactions. A multitude of different configurations have been proposed in the literature in order to combine the membrane separation module and the reactor into a single unit. Sanchez and Tsotsis [1] have classified the catalytic MR into six basic configurations:

- the *packed-bed membrane reactor* (PBMR), in which the membrane provides only a separation function and where the reaction is provided by a packed bed of catalyst placed in the permeate or retentate sides;
- the *catalytic membrane reactor* (CMR), where the membrane simultaneously provides separation and reaction functions, to achieve which one could use either an intrinsically catalytic membrane (e.g., a zeolite or metallic membrane) or a membrane that has been made catalytic through impregnation or by ion exchange;
- the *packed-bed catalytic membrane reactor* (PBCMR), where a PBMR contains a catalytically active membrane in order to provide an additional reactive function;
- the *fluidized-bed membrane reactor* (FBMR) in which the packed bed has been replaced by a fluidized bed when good control of the process temperature is necessary;
- the *fluidized-bed catalytic membrane reactor* (FBCMR), with the same functional advantage as the FBMR;
- the *catalytic nonpermselective membrane reactor* (CNMR), in which the membrane is not selective, but is only used to provide a well-defined reactive interface [1].

Membrane reactors can also be classified according the role the membrane plays with respect to the removal/addition of species [1–5]. Indeed, MRs could be classified as reactive *membrane extractors* when the membrane's function is to remove one or more products; such action could result in an increased equilibrium yield, as in the catalytic dehydrogenation reaction applications previously described. In *membrane distributors,* the membrane is used as the distributor of one of the reactants. Such MRs find application for consecutive and parallel reactions (in the partial oxidation of hydrocarbons, for example). Controlling the addition of the oxidant through the membrane lowers its partial pressure and generally results in a better yield of the intermediate oxidation products. Another advantage obtained with this type of MR is the potential to avoid the thermal runaway phenomena that are typically associated with highly exothermic reactions. In some other reactions, the membrane is not even required to be selective; it only acts as a *membrane contactor* providing a controlled reactive (or extractive) interface between reactants (or products) flowing on the opposite sides of the membrane [6, 7]. In this configuration, the membrane is used to improve the contact between the different reactive phases that are fed separately into either side of the membrane; reactions requiring a precise stoichiometry and phase-transfer catalytic reactions are examples of such an application. Intimate contact between the reactants can also be carried out by forcing them to flow together through a membrane, which is endowed with catalytic sites for the reaction. This "flow-through" configuration can also be used, to decrease the internal diffusion limitations of the reaction rate. Indeed, the process enhancement is attributed to the intensification of the intraporous mass transfer, which is the result of the reactants being forced to flow through the membrane's pores. Multiphase reactions involving a catalyst with liquid and gaseous reactants can also be studied in reactive membrane contactors. As in the previous example, the primary advantage of the use of a membrane reactor consists in decreasing the mass-transfer limitations frequently encountered with such reactions in slurry- or trickle-bed reactors.

2.3.3.3
Application of the MR Concept to Homogeneous Catalytic Reactions (HCRs)

Since 1990 the MR concept has not been applied so intensively in HCR as in heterogeneous catalysis. Nevertheless, the application of the MR concept in this area seems to be a thrilling new topic, which opens enormous possibilities of research and development. Indeed, one of the major problems existing in HCR (in many forms, including transition metal catalyzed reactions and phase-transfer catalysis) is the separation of reaction products from catalysts (see Chapter 1). Therefore, the application of UF or NF in HCR for the separation and recycling of a soluble catalyst from the reaction mixture and/or for the continuous separation of the reaction products, as well as for the use of hollow-fiber membrane contactors in multiphase reactions (aqueous/solvent, aqueous/supercritical, solvent/gas, etc.), are some of the most exciting ideas in this area. The coupling of membrane techniques with multiphase HCR has been made possible with the recent development of membranes which are resistant to organic solvents. Indeed, this type of coupled process has already been performed in enzymatic reactions at laboratory and industrial scale [1]. The principle of this coupling is illustrated in Figure 3.

In general, homogeneous catalysts, such as soluble metal complexes, are expensive and their presence in the final product is often undesirable. One of the most frequently adopted solutions is the separation of the homogeneous catalysts from the reaction mixture by immobilization on a support. Nevertheless, immobilization is an arduous process, which often results in decreased catalytic activity and increasing leaching. Among the different membrane processes, NF, which presents a very low cut-off, is a very suitable technique to separate homogeneous catalysts from reaction products or to recuperate solvents.

Nair and co-workers [8] have coupled of semi-continuous NF with the Heck reaction. The objective was the synthesis of *trans*-stilbene from styrene and iodobenzene using $Pd(OAc)_2(PPh_3)_2$ as catalyst and $P(o\text{-tolyl})_3$ as stabilizing agent. They used solvent-resistant membranes and different aqueous/solvent systems (ethyl acetate and acetone/H_2O; methyl *tert*-butyl ether and acetone/H_2O; tetrahydrofuran/H_2O). The best conversion was obtained with the first-mentioned solvent mixture. A selectivity of 100% of *trans*-stilbene with a cumulative turnover number of 1200 was reported, where the rejection of the catalyst turned out to be as high as 97%. Therefore, the authors concluded that NF was a convenient technique to run catalytic reactions with catalyst recycling, since this method saves the catalyst, prevents the metal contamination of the products, and increases reactor productivity.

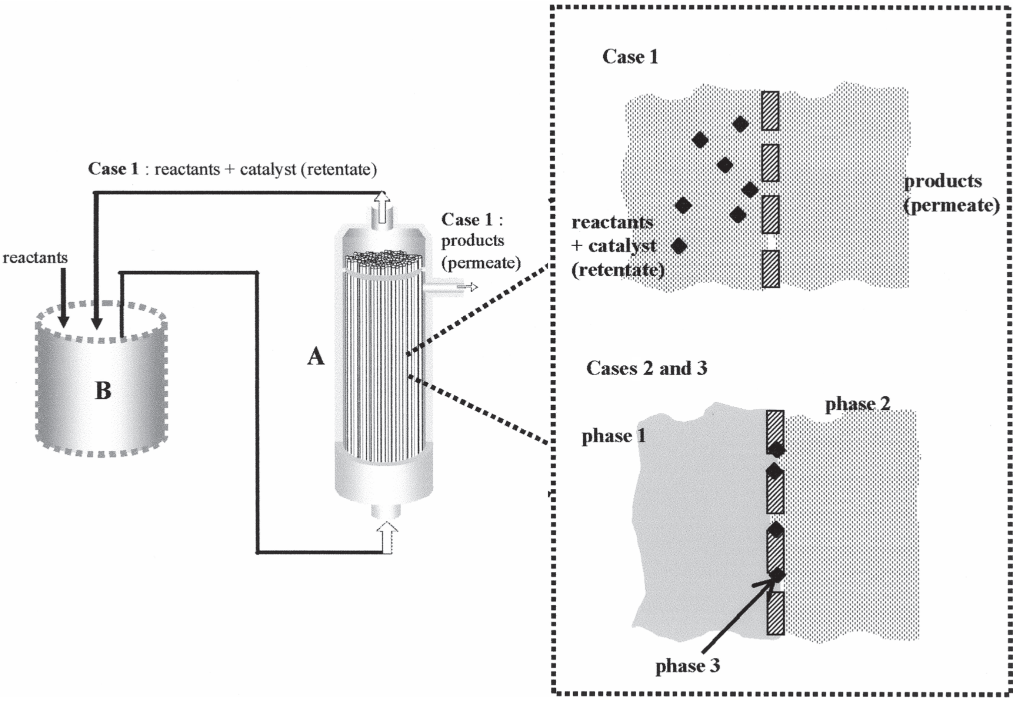

Figure 3 Some examples of the principle of coupling a membrane technique with an HCR. (a) Hollow-fiber membrane module; (b) reactor. Case 1, separation of a soluble catalyst by NF; case 2, MR contactor in two-phase reaction (only phase 1 and 2); case 3, MR contactor in three-phase reaction (phases 1, 2, and 3).

Some authors have grafted homogeneous catalysts to macromolecules in order to increase the kinetic size and thus avoid losses during UF or NF. Dwars et al. [9] used a micellar enlarged Rh-(*2S,4S*)-*N-tert*-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine catalyst in a membrane reactor, equipped with a UF membrane for the enantioselective hydrogenation of α-amino acids. The chiral *α*-amino acid derivatives were thus obtained with good enantioselectivity and yield. The catalyst, embedded in micelles, obtained from triblock copolymers as surfactants, was retained and reused several times without any loss of activity and enantioselectivity. The authors observed a minimal leaching of the catalyst components when they used a regenerated cellulose acetate UF membrane from Amicon. Giffels et al. [10] used oxazaborolidines enlarged with soluble polymers as catalysts for the enantioselective reduction of ketones in a continuously operated MR equipped with an NF membrane. The amount of chiral product per mole of catalyst was enhanced from 10 (batch) up to 560 moles (MR). The chiral alcohols were obtained in good to excellent enantiomeric excess and space–time yield. Smet et al. [11] combined the hydrogenation of dimethyl itaconate with Ru-BINAP as a homogeneous chiral catalyst with an NF process. Two different configurations have been utilized, one in which the membrane was inserted into the reactor itself, and another in which the membrane was extraneous to the reactor. The polymeric membranes tested were shown to separate the Ru-BINAP catalyst completely. The hybrid reactor system was tested for about a month, and showed very stable activity and enantioselectivity. Laue et al. [12] attached a homogeneous hydrogenation catalyst onto a polymer. They used a membrane reactor with a UF membrane, which was capable of retaining the soluble, polymer-bound catalyst. Their membrane reactor achieved high space–time yields of up to 578 g L^{-1} day^{-1}, and enantioselectivities of up to 94%.

Ilinitch et al. [13, 14] have studied the catalytic oxidation of sulfides. For this reaction, macroporous polymeric membranes, impregnated with a sodium salt of tetra(sulfophthalocyanine)cobalt(II) (Co-TSPC), were used. The MR utilized included macroporous membranes and operated in a “flow-through” configuration.

A recent application reported by Vankelecom et al. [15] concerns the use of polydimethylsiloxane membranes in which an active catalyst ([5,10,15,20-tetrakis-(2,6-dichlorophenyl)porphyrinato]manganese(III)chloride) was incorporated. The membranes are not permselective but only act as interfacial contactors to carry out the epoxidation (but also hydrogenation and hydroformylation) of various organic compounds. In this case, the thin film also gives additional advantages such as allowing the reaction to take place without any co-solvent, which prevents loss of the catalyst. The catalytic membrane was then tested for 3-penten-2-ol epoxidation using hydrogen peroxide. The results showed that selectivity dramatically increased (from approximately 20 to 100%) when the catalytic membrane was used instead of the free catalyst. This result was explained by the reduced mobility of the ligand in the membrane, when compared with its free form in a solution. Langhendries et al. [16] used the same concept for the oxidation of cyclohexane, cyclodecane, and *n*-dodecane using *t*-butyl hydroperoxide as oxidant, and zeolite-encaged iron phthalocyanine as catalyst (embedded in a polymeric membrane). During he *n*-dodecane oxidation in the CMR, the alcohol and ketone products are exclusively recovered with the organic *n*-dodecane phase, which is another advantage of the CMR configuration.

Frusteri and co-workers [17] have studied the activation of alkanes (CH_4, C_2H_6, C_3H_8) under mild conditions (80–120 °C, 140 kPa) in a three-phase CMR containing superacid catalytic membranes. In this reactor, they studied the functionalization of the C_1–C_3 alkanes to oxygenate on superacid catalytic films mediated by the Fe^{2+}/H_2O_2 Fenton oxidation system. The Nafion®-based membrane is sandwiched between two porous Teflon plates with the catalytic side toward the liquid phase, which consists of a solution of H_2O_2 and [Fe^{2+}] or [Fe^{3+}]. The gas phase consists of a mixture of hydrocarbon and N_2. The two half-cells of the three-phase MR operate as batch reactors with separate recirculation for the two phases. The authors present a reaction pathway which involves the activation of the C–H bond of the alkane molecule on the superacid membrane sites and the subsequent reaction of the activated alkane with primary reactive intermediates, generated from the Fe^{2+}/H_2O_2 system.

Catalysts supported on polymeric membranes have also been applied for hydroformylation reactions. Feldman et al. [18], for example, have reported the synthesis of a cellulose acetate membrane containing $HRh(CO)(PPH_3)_3$, which was incorporated in the thin film by introducing it into the cellulose acetate solution before the casting procedure. The membranes thus obtained were tested in the hydroformylation of ethylene and propylene [19], and were shown to be very active (turnover rate numbers with the film-supported catalyst were about five times higher than those observed with the corresponding homogeneous catalysts). The n/i ratio was reported to be higher as well. Hydroformylation of ethylene has also been studied in a membrane reactor by Kim and Datta [20]. These authors utilized a three-layer membrane, which consisted of a porous matrix supporting a liquid-phase catalyst dissolved in a high boiling point organic solvent, which was sandwiched between two different hydrophobic polymeric membranes. The reaction was studied using a flat-disk membrane. In this configuration, the reactants (C_2H_4, CO, H_2) were fed into one compartment of the membrane reactor, and a sweep gas was used in the second compartment in order to eliminate the product continuously. The experimental results were in good agreement with the theoretical model presented and showed that very high separation factors and good conversion were possible for this type of CMR. More recently, Naughton and Drago [21] reported the hydroformylation of 1-hexene by using a water-soluble rhodium complex incorporated in a PEG thin film. The catalytic activity of the supported catalyst was then better than that observed with the unsupported rhodium complex. The experimental results obtained with the supported catalysts indicate that the CMR technique is promising for this application.

The coupling of membrane techniques with the technology of supercritical fluids is an emerging topic which begins to be intensively explored for extraction and reaction purposes [22, 23]. This concept offers the advantages of using benign high-density gases, i.e., the possibility of achieving a high concentration of gaseous reactants in the same phase as the substrates and catalyst (see also Chapter 6). In addition, the membrane is also used to recycle the catalyst as explained above. Goetheer et al. [24] have recently reported the hydrogenation of 1-butene using a fluorous derivative of Wilkinson's catalyst [$RhCl\{P\text{–}(C_6H_4\text{-}p\text{-}SiMe_2CH_2CH_2C_8F_{17})_3\}_3$]. The membrane was made of porous silica/alumina, an inorganic material which is resistant to supercritical CO_2.The silica top layer had an average pore diameter of 0.6 nm whereas the fluorous derivative of Wilkinson's catalyst, obtained from RhCl(*cis,cis*-1,5-cyclooctadiene) and $P[C_6H_4\text{-}p\text{-}SiMe_2(CH_2)_2C_8F_{17}]_3$, had a mean molecular size between 2 to 4 nm. The difference in size resulted in a retention of the catalyst higher than 99.9%. The authors reported stable operation and continuous production of *n*-butane at 353 K and 20 MPa (see also Chapter 4).

2.3.3.4
Conclusion

To conclude this chapter, as the preceding discussion has – hopefully – indicated, there is considerable interest today and significant emerging potential for the application of membrane reactors in catalytic homogeneous reactions. The effectiveness of the MR concept in HRC at laboratory scale has been improved in many cases by considering the separation of the reaction products from the reaction mixture containing the soluble catalyst (grafted or not). Other possible applications which concern the membrane contactors in phase-transfer catalysis will also have to be taken in consideration in a near future. Mixed-matrix membranes incorporating the catalyst into the membrane matrix are promising for a variety of applications. The main remaining challenge concerns the development of membranes that have to be sufficiently resistant toward the solvents and high pressures encountered in supercritical conditions. Nevertheless, before commercial success is achieved, the key challenge that remains is to prove the long-term resistance of the membranes.

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2.3.4
Micellar Systems

Günther Oehme

2.3.4.1
Introduction

Micelles are spherical supramolecular assemblies of amphiphilic compounds with surface-active properties (surfactants, tensides) in a colloidal dimension [1] (see also Section 2.3.1). Typical micelle-forming molecules carry a hydrophilic headgroup and a hydrophobic tail. This is shown schematically in Figure 1.

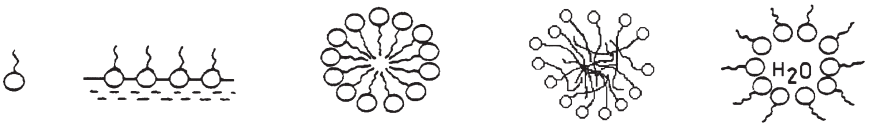


Figure 1 Formation of aqueous micelles and reverse micelles.

Examples of such surfactants are cetyltrimethylammonium bromide (CTAB, $9.2 \cdot 10^{-4}$ M), polyoxyethylene(22)hexadecanol (Brij 58, $7.7 \cdot 10^{-5}$ M), and sodium dodecyl sulfate (SDS, $8.1 \cdot 10^{-3}$ M). The actual formation of micelles begins above a certain temperature (Krafft's point) and above a characteristic concentration (critical micelle concentration, CMC) which is given in parentheses. Driving forces for the formation of aqueous micelles are the solvation of the headgroup and the desolvation of the alkyl chain ("hydrophobic effect") [2]. The association–dissociation process is very fast and occurs within milliseconds, faster than the rate of the most thermally initiated reactions. Because of a very high polarity gradient between surface and core, micelles can enclose different organic species from the surrounding aqueous phase [3]. This incorporation can be described by an equilibrium constant as a basis for kinetic treatments and creates a micro-heterogeneous multiphase system [4]. Encapsulation of reactants in micelles often enhances or inhibits the reaction rates. Any reaction promotion has been called "micellar catalysis". The rate enhancement of organic reactions in micelles can be a combination of the following effects [5]:

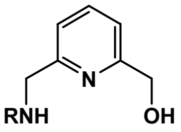
- a medium effect caused by a lower dielectric constant in the interior;
- a stabilization of the transition state owing to an interaction with the head group;
- concentration of the reactants by incorporation into the micelle.

Because of the relatively high regularity in the micellar core some asymmetric reactions occur with an enhanced stereoselectivity. Other typical effects of organized surfactants are the alteration of chemical and photophysical pathways, of quantum efficiency and ionization potentials, of oxidation and reduction properties, and finally of products and charges [6]. The morphology of micelles can change to rod-like structures at increasing concentrations of surfactants. The suitability of micellar solutions as reaction media, depending on the structure of the surfactants and environmental influences, is discussed in a review by Taşcioğlu [7].

Depending on the structure of the amphiphiles and the composition of the solvent mixture, other types of aggregates are possible, such as vesicles, reverse micelles, and microemulsions [8]. Because of the presence and proximity of polar and apolar regions in the interior of surfactant assemblies, there are some similarities to enzymes and natural membranes. Supramolecular aggregates of surfactants have a membrane-mimetic chemistry [9].

2.3.4.2
Selected Reactions in Aqueous Micelles

Important topics include solvolytic reactions, oxidations, reductions, and C–C coupling reactions. The saponification of activated esters in aqueous micelles is a model for an enzyme-mimetic reaction. The influence of the micellar medium on the reaction rate and on the stereoselectivity has been investigated. Models of metalloenzymes were developed with the ligands **1–3** and metal ions like Ni^{II}, Cu^{II}, Zn^{II}, and Co^{II} [10]. The amphiphilic ligands which were embedded in micelles enhanced the reaction rate in comparison with a dispersion in surfactant-free water. The use of optically active ligands (e.g., **2**) led to a moderate kinetic resolution of α-aminoesters.



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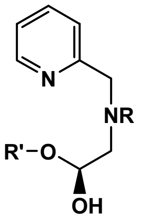

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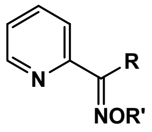


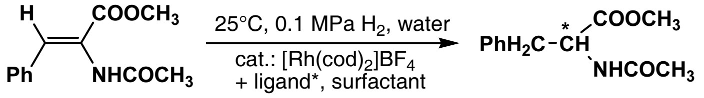
3

R = CH_3, C_nH_{2n+1} n = 8, 12, 13, 16

Pioneering work in micellar catalysis was described by Menger et al. [11] in 1975: the oxidation of piperonal to the corresponding carboxylic acid by means of $KMnO_4$ in presence of CTAB.

An example of micellar oxidation is a biomimetic system of cytochrome P450 investigated by Monti et al. [12], who found in the epoxidation of styrene with NaOCl a significant influence of the type of surfactant: cetylpyridinium chloride promoted the reaction more than cetyltrimethylammonium bromide. One explanation could be a specific noncovalent interaction between catalyst, substrate and surfactant.

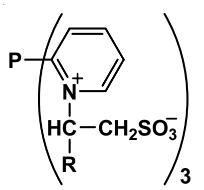
The asymmetric hydrogenation of dehydro-α-amino acid derivatives catalyzed by chiral rhodium–phosphine complexes is a successful example of an aqueous micellar system [Eq. (1)]. Normally, activity and selectivity are decreased by changing from an organic solvent to water but the addition of a small amount of a micelle-forming amphiphile leads to a significant increase in the reaction rate and in the enantioselectivity [13, 14].



(1)

Yonehara et al. [15] recently extended the scope of surfactant-promoted enantioselective hydrogenation to simple enamides.

The formation of C–C bonds is one of the most important reaction types in organic chemistry. This field has advanced rapidly due to the introduction of transition metal catalysts. Most C–C coupling reactions utilizing carbon monoxide are of industrial significance. In hydroformylation of long-chain olefins especially, a phase-transfer reagent or a micellar system is required when aqueous conditions are employed [16]. Fell and Papadogianakis [17] synthesized surface-active phosphines starting from tris(2-pyridyl)phosphine and different long-chain β-sultones **4**.



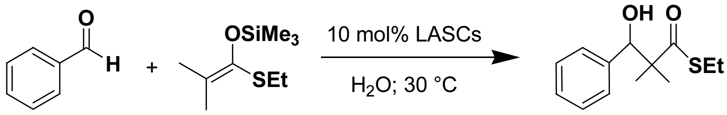
4

R = C_3H_7 to $C_{11}H_{23}$

New types of amphiphilic phosphines used by Hanson [18] and van Leeuwen as ligands resulted in high activities and satisfying regioselectivities (up to *n*/*i* ~50 for aldehydes with a xanthen-derived amphiphilic diphosphine [19]). A systematic investigation of surfactants during the hydroformylation of higher olefins by water-soluble Rh-TPPTS complexes was conducted by Chen et al. [20]. They found that only cationic amphiphiles gave a significant effect on yield and regioselectivity.

Suzuki-type C–C coupling reactions with palladium–phosphine complexes as catalysts can also be promoted by surfactants [21] in a toluene/water biphasic system.

Water-stable Lewis acids as catalysts for aldol reactions were developed by Kobayashi and co-workers [22]. A high promotion could be observed by combination of Lewis acid and surfactant (LASCs = Lewis acid–surfactant combined catalysts as shown in Eq. (2)). The surfactant is here the anion of dodecanesulfonic acid.



(2)

In the same manner Engberts and co-workers [23] used the copper(II) salt of SDS as the catalyst in a Diels–Alder reaction of 3-(*p*-substituted phenyl)-1-(2-pyridyl)-2-propen-1-ones with cyclopentadiene in water as medium, and observed a spectacular enhancement of the reaction rate.

The palladium-catalyzed asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate could be influenced in activity and enantioselectivity by the surfactant cetyltrimethylammonium hydrogen sulfate [24].

2.3.4.3
Reactions in Reverse Micelles

Reverse micelles are formed by association of surfactants with colloidal drops of water in an organic medium (see Figure 1). A favored surfactant seems to be AOT (sodium bis(2-ethylhexyl)sulfosuccinate) but SDS and tetraalkylammonium salts have also proved to be useful. Like aqueous micelles, reverse micelles exist in highly diluted systems [25].

The hydrogen transfer reaction from 1,2-cyclohexanedimethanol to *E*-4-phenyl-3-buten-2-one is catalyzed by [RuCl(*S*-binap)(benzene)]Cl and accelerated by SDS [26]. The surfactant is essential for the rate enhancement and the authors proposed the existence of reverse micelles. Interesting new experiments on CH activation in *n*-heptane or methylcyclohexane were communicated by Elsevier and co-workers [27]. In a reverse micellar system containing $NaPtCl_4$ in D_2O, AOT, and the substrate, CH/CD exchange occurs under mild conditions (80 °C) regioselective in the methyl group. One of the main fields of application of reverse micelles is the entrapment of enzymes in the water cavity [28].

2.3.4.4
Perspectives

The solubilization of reactants in aqueous micelles and the achievement of rate and selectivity enhancement are sometimes unexpectedly high, but the main problem has been the separation of products, amphiphile, and catalyst after the reaction. One solution should be the immobilization of micelle-like structures on polymers [29] (cf. also Chapter 7). An early proposal to use immobilized amphiphiles like micelles was made by Brown and Jenkins [30]. Regen [31] used amphiphilic polymers for the first time in phase-transfer catalysis. A variety of different amphiphilized and amphiphilic polymers were successfully applied in the asymmetric hydrogenation of amino acid precursors [32]. The simplest type of immobilized surfactant is an admicelle [33]; this means that the surfactant (SDS) is adsorbed on alumina, thus forming a bilayer on its surface, which is stable against washing with water or other polar solvents. In analogy to admicelles, Milstein and co-workers [34] adsorbed the amphiphilic complex [Rh(4,4′-diheptadecyl-2,2′-bipyridine)-(1,5-hexadiene)]$^+PF_6^-$ on hydrophobic or hydrophilic porous glass particles and observed under the conditions of a Langmuir–Blodgett film, a high catalytic activity and selectivity for the hydrogenation of acetone in an aqueous medium. The complex was almost inactive in solution.

It should be concluded that catalysis with surfactant assemblies is an active and successful area of research. In the case of emulsion polymerization, phase-transfer processes, and analytical applications, micellar methods are of practical importance.

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2.3.5
Thermoregulated Phase-Transfer Catalysis

Zilin Jin and Yanhua Wang

2.3.5.1
Introduction

The most severe drawback in homogeneous catalysis is the separation of the catalyst from the reaction mixture. The industrial success of the aqueous two-phase hydroformylation of propene to *n*-butanal [1] in Ruhrchemie AG in 1984 represents the considerable progress in this field. However, aqueous/organic biphasic catalysis has its limitations when the water solubility of the starting materials proves too low, as in hydroformylation of higher olefins (see Chapter 1). To solve this issue, a variety of approaches have been attempted. Additions of co-solvents [2] or surfactants [3, 4] to the system or application of tenside ligands [5, 6] and amphiphilic phosphines [7, 8] are ways to increase the reaction rates. Other approaches such as fluorous biphase system (FBS; see Chapter 4) [9], supported aqueous phase catalysis (SAPC; see Section 2.6) [10], supercritical CO_2 (cf. Chapter 6) [11] and ionic liquids (cf. Chapter 5) [12] have also been introduced to deal with this problem.

Recently, a new aqueous biphasic catalytic system based on the cloud point of nonionic tensioactive phosphine, termed “thermoregulated phase-transfer catalysis” (TRPTC) has been developed [13]. The concept of TRPTC as a “missing link” could not only provide a meaningful solution to the problem of catalyst/product separation, but also extricate itself from the limitation of low reaction rates of water-immiscible substrates.

2.3.5.2
Thermoregulated Ligands and Thermoregulated Phase-Transfer Catalysis

It is well known that the water solubility of nonionic surfactants with polyoxyethylene moieties as the hydrophilic group is based on the hydrogen bonds formed between poly(ethylene glycol) (PEG) chains and water molecules (Figure 1). The solubility of this type of surfactant decreases with a rise in temperature, and their aqueous solutions will undergo an interesting phase separation process (a miscibility gap) on heating to a low critical solution temperature – the “cloud point”. A reasonable explanation attributes this phenomenon to the cleavage of hydrogen bonds. In addition, it is worth mentioning that such a process is a reversible one since the water solubility could be restored on cooling to a temperature lower than the cloud point [14]. A thermoregulated ligand (TRL) [15] is generally defined as a kind of nonionic surface-active phosphine ligand containing PEG chains as the hydrophilic group in the molecular structure, which demonstrates a special property of inverse temperature-dependent solubility in water. Bergbreiter et al. [16] firstly reported a “smart ligand” with a phosphorus-bonded block copolymer of ethylene oxide and

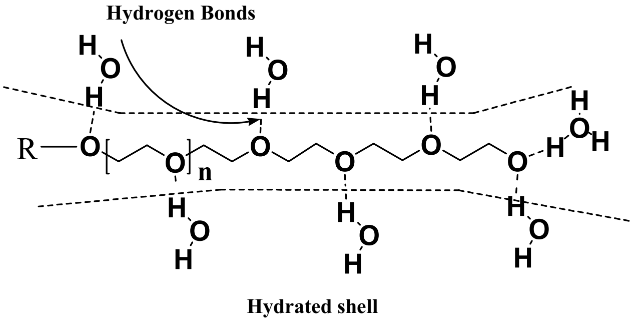
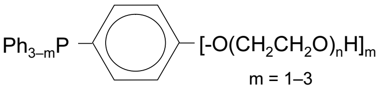
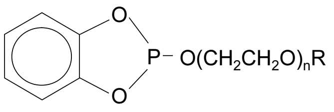


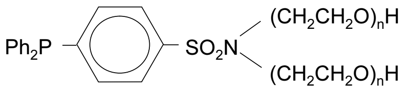
Figure 1 Hydrogen bonds formed between a polyether chain and water.

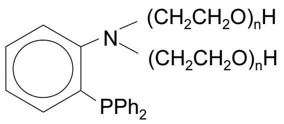
propylene oxide, which exhibits a property of inverse temperature-dependent solubility. Jin et al. synthesized a series of TRLs (**1**–**5**) by introducing PEG chains to phosphines [17–21] and investigated their water solubility and cloud point (C_p) [18].


PETPP 1

$[RO\text{-}(CH_2CH_2O)_n]_mPPh_{3-m}$ m = 1, 2 **AEOPP 2**


OPGPP 3


PEO-DPPSA 4


PEO-DPPPA 5

TRPTC system based on the C_p of TRLs has been proposed [13]. The general principle of TRPTC is depicted in Figure 2. The TRPTC process can be described as follows: at a temperature lower than the cloud point, the catalyst is soluble in the aqueous phase. On heating to a temperature higher than the cloud point, however, the catalyst transfers from the aqueous phase into the organic phase. Thus, the catalyst and the substrate are in the same phase and the reaction proceeds in the

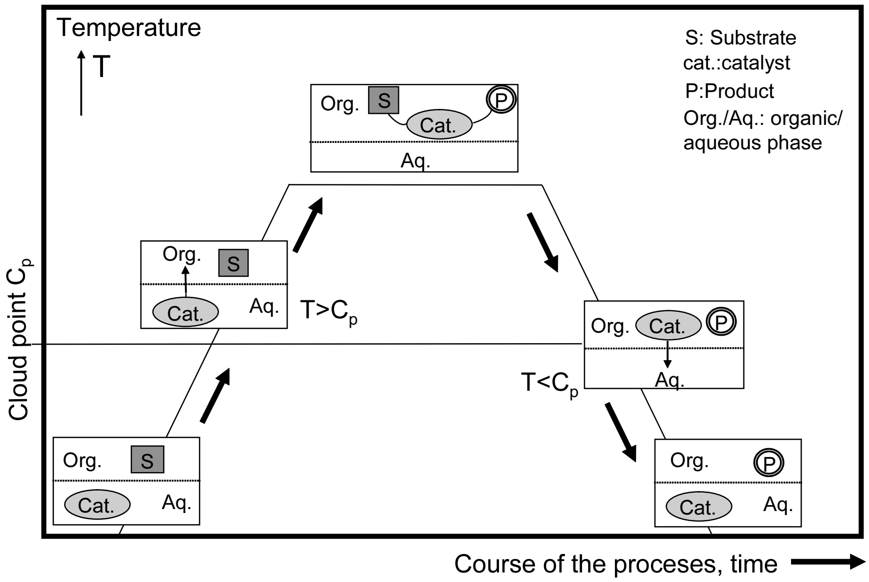


Figure 2 The general principle of TRPTC.

organic phase. As soon as the reaction is completed and the system is cooled to a temperature lower than the cloud point, the catalyst returns to the aqueous phase. The introduction of TRPTC is free from the shortcomings of classical biphasic catalysis, in which the scope of application is restrained by the water solubility of substrate. Moreover, the thermoregulated phase-transfer catalyst can be separated and recycled by simple phase separation.

The thermoregulated phase-transfer function of TRLs has been proven by means of the aqueous-phase hydrogenation of sodium cinnamate in the presence of an Rh/AEOPP complex as the catalyst [18]. As outlined in Figure 3, an unusual inversely temperature-dependent catalytic behavior has been observed.

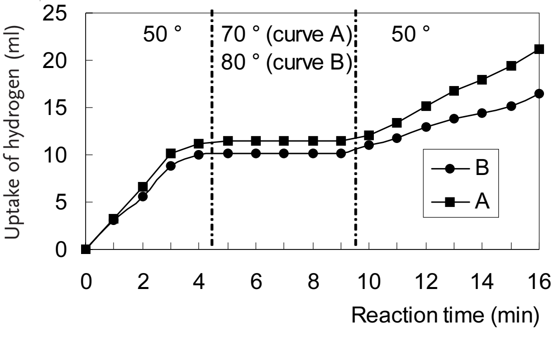


Figure 3 Hydrogenation of sodium cinnamate in water.
The cloud point of A is 64 °C and the cloud point of B is 72 °C.

2.3.5.3
Applications of Thermoregulated Phase-Transfer Catalysis

TRPTC has already been applied successfully in the hydroformylation of higher olefins and the CO selective reduction of nitroarenes, both on a laboratory scale.

2.3.5.3.1
Hydroformylation of Higher Olefins

Approaches in which surfactants [22, 23] and surface-active water-soluble phosphines [5, 6] are used to accelerate the rate of hydroformylation of high olefins in the aqueous two-phase system have been reported. Surface-active materials tend to make it possible for hydrophobic higher olefins to “enter” the aqueous phase through micellar solubilization (see Sections 2.3.1 and 2.3.4).

Thermoregulated phase-transfer catalysis has been used successfully for the aqueous biphasic hydroformylation of higher olefins [13, 18]. A reasonable explanation for the satisfactory catalytic reactivity is that it results from the thermoregulated properties of Rh/TRL complexes. As shown in Table 1, average turnover frequencies (TOFs) of 250 h^{-1} for 1-dodecene and 470 h^{-1} for styrene have been achieved. Even the hydroformylation of oleyl alcohol, an extremely hydrophobic internal olefin, exhibits a yield of 72% [24].

The recycling effect of the catalyst was also examined. Aqueous phase containing the Rh/PEO-DPPPA catalyst after phase separation was re-used 20 times in the hydroformylation of 1-decene [21]. It should be pointed out that leaching of Rh into the organic phase might be diminished with difficulty to less than the ppm level by means of a single-phase separation.

Breuzard et al. [25] prepared chiral polyether ligands derived from (*S*)-binaphthol and combined with the $[Rh(cod)_2]BF_4$ complex. This system has been used in the catalytic enantioselective hydroformylation of styrene in thermoregulated phase-transfer conditions, but the *ee* value is less than 25%.

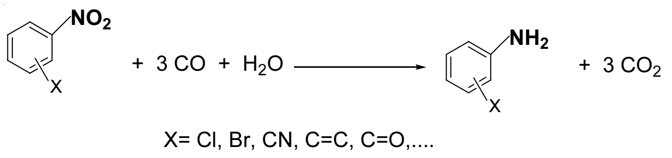
Table 1 Two-phase hydroformylation of olefins catalyzed by nonionic phosphine-modified rhodium complexes.

Olefin	*Ligand (PETPP)*	*N*[a)]	*P/Rh*	*P [MPa]*	*T [°C]*	*Yield [%]*	*n/i*	*TOF [h⁻¹]*
1-Hexene	$m = 3$	18	5	5.0	100	85	2.0	–
1-Octene	$m = 3$	18	5	5.0	100	88	2.8	–
1-Dodecene	$m = 3$	18	5	5.0	100	84	1.8	250
Styrene	$m = 1$	25	12	3.0	80	94	0.5	470
p-Chlorostyrene	$m = 1$	25	12	3.0	80	92	0.6	460
p-Methoxystyrene	$m = 1$	25	12	3.0	80	95	0.5	480
Cyclohexene	$m = 1$	25	5	6.0	120	82	–	140
Oleyl alcohol	$m = 1$	16	5	6.0	120	72	–	70

a) N = average number of ethylene oxide units per molecule of ligand.

2.3.5.3.2
Selective Reduction of Nitroarenes

Selective reduction of nitroarene to aromatic amine by the basic aqueous route using CO as the reducting agent leads to fine chemicals, due to the selective reduction of the nitro group while the other groups, like halogen, –C=C, –C=O, and –CN, could be kept free from hydrogenation or dehalogenation [Eq. (1)].



(1)

Tafesh et al. [26] first began using water-soluble Pd complexes with TPPTS or BINAS as ligands in the CO selective reduction of nitroarenes, obtaining a yield less than 65%.

Recently, the CO selective reduction of nitroarenes catalyzed by $Ru_3(CO)_9(PETPP)_3$ [27] and $Ru_3(CO)_9$(PEO-DPPSA) [28] has been reported by Jin et al. The results are listed in Table 2. After being used four times, the activity of the catalyst is not evidently decreased.

Table 2 CO selective reduction of several aromatic nitro compounds catalyzed by $Ru_3(CO)_9(PETPP)_3$.[a)]

Reactant	*Product*	*Conversion [%]*	*Yield [%]*
o-$ClC_6H_4NO_2$	*o*-$ClC_6H_4NH_2$	99.2	99.0
m-$ClC_6H_4NO_2$	*m*-$ClC_6H_4NH_2$	99.6	99.4
p-$NO_2C_6H_4CN$	*p*-$NH_2C_6H_4CN$	97.4	97.0
p-$NO_2C_6H_4COCH_3$	*p*-$NH_2C_6H_4COCH_3$	95.8	95.4

a) Reaction conditions: $T = 140$ °C, $P_{CO} = 4.0$ MPa, $V_{toluene}/V_{water} = 4:4$, $Ru_3(CO)_9(PETPP)_3 = 0.01$ mmol.

2.3.5.4
Conclusion

Although the development of aqueous/organic two-phase catalysis has only occurred more than 20 years since its emergence, crucial advantages of this methodology have been proven as it overcomes the immanent problem of catalyst/product separation associated with homogeneous catalysis. Compared with classical aqueous/organic two-phase catalysis, the process of TRPTC is more "homogeneous" to some extent because the catalyst and substrate remain in the same organic phase at the reaction temperature. TRPTC is also quite different from FBS. While the initial fluorous/organic biphase of FBS becomes a single phase at an appropriate higher temperature, TRPTC maintains the aqueous/organic two-phase system throughout the reaction. It is the mobile catalyst that "transfers" between the two phases without any additive in response to temperature changes; the possibility of changing the status of the phase is one of the properties of the ligand.

The introduction of TRPTC to aqueous/organic two-phase is free from the shortcomings of classical aqueous two-phase catalysis, in which the scope of application is more or less restrained by the water solubility of the organic reactants. Obviously, the core of TRPTC is to use TRL with the cloud point in water. Therefore, to design and prepare ligands with higher catalytic reactivity at lower cost will be a main topic of scientific research and industrial exploitation of this strategy in the future. Just as Cornils remarks in Ref. [29]: "since the agent responsible for the merger and subsequent separation of the phases is the appropriately custom-designed ligand itself, there is no call for investing extra effort in the removal and recycling of a foreign additive, and this must therefore be regarded as a promising avenue for further exploration on a commercially realistic scale."

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2.3.6
Environmental and Safety Aspects

Boy Cornils and Ernst Wiebus

Although the use of water as a liquid support in homogeneous processes has raised controversy in academia [1], twenty years of experience prove the decisive advantages of this aqueous technology. None of the predictions from "false prophets" arrived – there have been no problems with "detection in case of leakage" or with "incineration of bleed streams", with the tremendous heat of evaporation of water, or with the decomposition of water-sensitive compounds. Spills are hard to collect – but what liquid is easy to handle in that case? (see also p. 30) [2]. On the contrary, water does not ignite, does not burn, is odorless and colorless, and is ubiquitous: important prerequisites for the solvent of choice in homogeneous catalytic processes. Additionly, the favorable thermal properties make water doubly exploited as a mobile support and as a heat-transfer fluid. The only restriction regarding the general use of water in homogeneously catalyzed processes results from the fact that to attain adequate chemical reaction, there has to be a minimum solubility of the organic substrates in the aqueous catalyst phase – but this is a chemical engineering limitation, not one which has to be addressed to water as a catalyst support! Twenty years of experience with the most important aqueous-phase process, the Ruhrchemie/Rhône-Poulenc (RCH/RP) hydroformylation process and its production of some five millions of tons of butyraldehydes provide unequivocal results: the process is extremely favorable to the environment and there have been no accidents as a consequence of using water.

The details and the background of RCH/RP's developments have been described elsewhere. The work of Kuntz (then at RP; see Section 2.4.1.1.1) on trisulfonated triphenylphosphine (TPPTS) and the industrial implementation and improvements developed by Ruhrchemie eventually laid the foundation for the subsequent successful commercialization [3]. TPPTS is the ideal ligand modifier for the oxo-active $HRh(CO)_4$. Without any expensive preformation steps, three of the four CO ligands can be substituted by the readily soluble (1100 g L^{-1} water) and nontoxic (LD_{50}, oral: > 5000 mg kg^{-1}) TPPTS, which yields the hydrophilic oxo catalyst $HRh(CO)[P(3\text{-sulfophenyl-Na})_3]_3$. The trisulfonation, in particular, permits the fine adjustment of TPPTS and thus of the hydrophilic versus the hydrophobic properties; hydrophilicity is ranked in the order TPP*T*S > TPP*D*S > TPP*M*S, from the trisulfonated through to the monosulfonated species.

Because of the solubility of the Rh(I) complex in water and its insolubility in the oxo products, the oxo unit is essentially reduced to a continous stirred tank reactor followed by a phase separator (decanter) and a stripping column. This simplification (see Figure 3, Section 2.4.1.1.1) is a “green” improvement – speaking in the terms of the sustainability supporters – which contributes considerably to the favorable reduction in manufacturing costs of the new process. Propene and syngas are added to the noncorrosive catalyst solution, they react, and the reaction products and the catalyst phase pass into the decanter. While being degassed, they are thus separated into the aqueous catalyst solution and the organic butyraldehyde phase. The catalyst solution exchanges heat and produces steam in the heat exchanger, is replaced by the same amount of water (not catalyst solution!) dissolved in the crude aldehyde, and is returned to the oxo reactor. The crude aldehyde passes through a stripping column in which it is treated with fresh syngas in countercurrent and, if necessary, it is freed from unreacted alkene. No side reactions occur which decrease the selectivity and yield of the aldehyde, since stripping of the aldehydes is carried out in the absence of the oxo catalyst, a distinctive feature of RCH/RP’s process. The reboiler of the subsequent “*n*/*i*” column, separating *n*- from isobutytaldehyde, is designed as a heat-absorbing falling-film evaporator incorporated into the oxo reactor, thus providing a neat, efficient method of recovering heat by transferring the heat of reaction from the reactor to cold *n*-butanal, which subsequently heats the *n*/*i* column. Whereas other oxo processes are steam consumers, the RCH/RP process including the distillation unit exports steam [4] – in energy terms a drastic improvement and even “a greener replacement” [5].

The catalyst is not sensitive to sulfur or other oxo poisons, which is another environmental advantage. Together with the simple but effective decantation, which allows the withdrawal of organic and other byproducts at the very moment of separation, accumulation of activity-decreasing poisons in the catalyst solution is prevented. Therefore no special treatment or purification step is necessary. This reduces the environmental burden still further. For a considerable time the oxo units at Ruhrchemie’s plant site were even supplied with syngas derived from coal produced by the TCGP (Ruhrchemie/Ruhrkohle’s version of the Texaco coal gasification process). In various cases this can be an important factor as far as local resources are concerned.

The oxo catalyst $[HRh(CO)(TPPTS)_3]$, its formation from suitable precursors, and its handling and operation are described under “Lower Alkenes” in Section 2.4.1.1.3. The reaction system is self-adjusting – an important consideration for safety reasons – and thus control analyses are needed only at prolonged intervals. Owing to the high degree of automation, only two employees per shift supervise two or more oxo units with a total capacity of over 600 000 tons y^{-1}. The design obviates the need for certain equipment (e.g., feed and cooling pumps); the on-stream factor of the whole system exceeds 98%. Typical reaction conditions, crude product compositions of the RCH/RP process averaged out over a 20-year period, and a discussion of selectivities and activities are given in Ref. [6].

The high selectivity of the C_3 conversion toward C_4 products makes fractional distillation after aldehyde distillation unnecessary, reduces expenditure, and thus also minimizes the monetary and environmental load. The manufacture of the byproducts advantageously becomes part of the 2-EH (2-ethylhexanol) process since the heavy ends consist mainly of 2-ethyl-3-hydroxyhexanal, which, during downstream processing, is also converted to 2-EH. This (and the avoidance of the formation of butyl formates) is the reason for the considerable simplification of the process flow diagram compared with other process variants (cf. Figure 2 in Section 2.1).

The RCH/RP process exhibits considerable improvements in respect of environmental conservation, conservation of resources, and minimization of pollution. This can be demonstrated by various criteria and proved very convincingly by means of Sheldon's environmental factor *E* [7], which is far more suitable and constructive than Trost's "atom effiency" [8]. Sheldon defined the *E* factor as the amount of waste produced per kilogram of product, and specified the *E* factor for every segment of industry (Table 1).

Table 1 Environmental acceptability: the *E* factor.

Segment of chemical industry	***Product tonnage***	***Byproducts/product [w/w]***
Oil refining	10^8–10^9	< 0.1
Bulk chemicals	10^4–10^6	< 1–5
Fine chemicals	10^2–10^4	5–50
Pharmaceuticals	10^1–10^3	25–100+

As expected and as shown in Table 2, this environmental quotient for conventional oxo processes (using cobalt catalysts) and the production of the bulk chemical *n*-butyraldehyde is actually about 0.6–0.9, depending on the definition of the term "target product". This range indicates that the main byproduct of propene hydroformylation, isobutyraldehyde, is processed by a number of producers (e.g., to isobutanol, isobutyric acid, or neopentyl glycol) so that isobutyraldehyde is not always and everywhere a byproduct; thus when it becomes a target product the *E* factor falls from 0.9 to 0.6.

Table 2 *E* factors for oxo processes.

Process	***Byproducts/products [w/w]***	
	Isobutyraldehyde as product	***Isobutyraldehyde as byproduct***
Cobalt-high pressure	> 0.6	< 0.9
Rhodium RCH/RP process	< 0.04	< 0.1

Strictly speaking, this observation is included in Sheldon's wider statement, according to which the *E* factor is refined and becomes the "environmental quotient" *EQ*, depending on the nature of the waste. Since such quotients "are debatable and will vary from one company to another and even from one production to another" [7], they will not be discussed here. The crucial point is that, on the same basis (taking into account all the byproducts, including those used in ligand manufacture, etc. – i.e., as for life cycle assessment) conventional oxo processes have an *E* factor of 0.6–0.9, which falls to below 0.1 in the RCH/RP process: an important pointer to the enviromental friendliness of this technology. The low *E* factor of < 0.04 indicates that the utilization of material resources is improved more than tenfold: according to Sheldon's assessment, production of the bulk chemical "butyraldehyde" is classified alongside the highly efficient products of oil refining processes.

Whereas this important quotient is calculated solely from the product spectrum, process simplifications are a consequence of combining the Rh catalyst with the special biphasic process: as indicated in Figure 2 in Section 2.1, the reaction sequence and the procedure of separation and work-up of the products is considerably simplified. As stated in Ref. [9], the capital expenditure for the old Co technology is at least 1.9 times higher than for the RCH/RP process. The conservation of energy resources with the RCH/RP process is dramatic: the steam consumption figures for the Co process are very much higher than those for the Rh process and power consumption is twice as high as that of the RCH/RP process. For example, the compression costs alone for the required syngas are in a ratio (Co process/Rh process) of 1.7 : 1, and the volume of waste water from the RCH/RP process is 70 times lower. The fact that the water-soluble catalyst does not leave the oxo reactor and its immediate surroundings is an important reason why the Rh losses are in the ppb range. The reduced probability of leaks also increases effectiveness and safety.

The "solvent" water reliably averts the risk of fire inherent in the old Co processes as a result of leaking highly flammable metal carbonyls. The reaction system with its "built-in extinguishing system" reliably prevents such fires, and the painstaking measuring and monitoring procedure necessitated by the valuable catalyst metal rhodium, accompanied by constant simultaneous balancing of the RCH/RP process, permits any leaks from the aqueous system to be detected much earlier than was ever possible previously. This also applies to the cooling system, in which any leak from the falling-film evaporator would be noticed after a loss of only a few ppm of rhodium. The solvent water is available instantly everywhere; it is not odor-free, since because of its residual solubility for butyraldehydes it is as certain to be detected by the sensory/olfactory organs as are the product streams of other oxo processes.

Taking all the criteria into consideration, the RCH/RP biphasic oxo process is probably the soundest and "best-natured" variant in terms of the environment: it is a "green" and "sustainable" process which, in addition to its enviromental compatibility, has the advantage of being extremely cost-effective and reduces the manufacturing costs by a sensational 10%. During the manufacture of more than 5 MM tons of *n*-butyraldehyde the plants experienced no serious accident which could be attributed to the use of water as the "mobile support".

On the other hand, there are the advantages of a successful waste management system which ultimately lead to higher cost-effectiveness: the aqueous-biphase process is a typical example of "cleaner technology" or "soft chemistry" – and both expressions are involved here in the non-ideological meaning of the word [10].

Thus it can be taken for granted that among the homogeneously catalyzed processes the aqueous-biphase variants will be in the forefront of further development.

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2.4
Typical Reactions

2.4.1
Syntheses with Carbon Monoxide

2.4.1.1
Hydroformylation

2.4.1.1.1
Historical Development

Boy Cornils and Emile G. Kuntz

The history of biphasic homogeneous catalysis starts with Manassen's statement [1]:

> "... the use of two immiscible liquid phases, one containing the catalyst and the other containing the substrate, must be considered. The two phases can be separated by conventional means and high degrees of dispersion can be obtained through emulisification."

Roughly at the same time (in contradiction to a misleading statement by Papadogianakis [2]) and parallel to work done by Shell [3] (concerning nonaqueous systems) and by Joó [4] and others [5], one of us (EK, then at Rhône-Poulenc) devoted time and effort to starting practical work on aqueous biphasic catalysis with organometallic catalysts (mainly for hydroformylations), developing the basic principle and the currently well-known standard ligand triphenylphosphine trisulfonate, TPPTS (cf. Section 2.2.3.2).

At that time the general basis for industrial hydroformylation was the monophasic operation with cobalt or with modified Co catalysts [6]. The Wilkinson school of thought opened up a new field of rhodium chemistry by applying the remarkable catalytic properties of ligand-modified (especially triphenylphosphine-substituted) Rh carbonyls [7]. The high activity, productivity, and selectivity of Rh catalysts promised economically operated plants with only some (or some dozens of) kilograms of precious metals needed on the inventory. The Monsanto acetic acid process proved that the amount of precious metals involved represents only a minor part of the investment and the manufacturing costs – provided the "handling" of commercial amounts of precious metal catalysts would be feasible, especially with a "biphasic" approach for the separation of catalyst and substrate/products by decantation (cf. Section 2.3).

This was the starting point of Kuntz's work at Rhône-Poulenc, trying to transfer rhodium catalysts from the organic monophase to the aqueous biphase not by triphenylphosphine *mono*sulfonate (which had been tried by Joó or Wilkinson [4, 8]) but by TPPTS. From 1974 onward, the scope of different reactions using biphasic catalyst systems was tested in laboratory-scale experiments. Among these were

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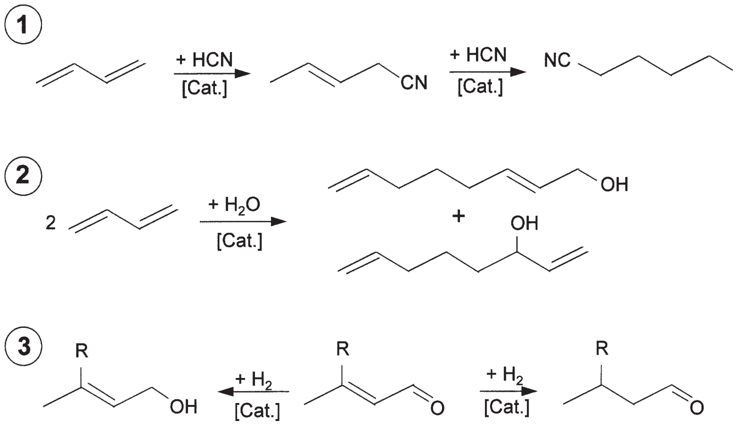


Figure 1 Industrially relevant reactions filed in Rhône-Poulenc's patents ([Cat.] = catalyst + TPPTS) [10]. ① Hydrocyanation; ② Telomerization; ③ Partial hydrogenation of unsaturated aldehydes.

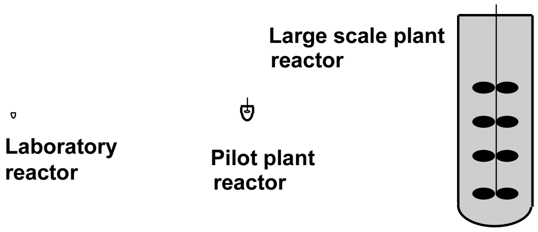
butadiene hydrodimerization, hydrogenation, and hydroformylation (Figure 1 [9]). Even during this initial stage of experimental work it was shown that only a small fraction of the precious metal (less than 0.1 ppm Rh) is leached by the organic (product) phase. Various patent applications were filed to protect Rhône-Poulenc's main fields of interest. One of these was hydroformylation although Rhône-Poulenc was not an oxo producer.

Following earlier contacts, in 1982 Ruhrchemie (RCH) and Rhône-Poulenc (RP) joined forces to develop a continuously operated hydroformylation process for the manufacture of *n*-butyraldehyde from propene. On the basis of the ideas documented in RP's patent applications, RCH used its own long-standing expertise with its own biphasic catalytic cracking process and its long experience in converting laboratory-scale syntheses to commercial processes – as Ost observed [11] as long ago as 1907 in *Z. Angew. Chem.*, the forerunner of *Angewandte*:

> "... For it is one thing to invent a process that is right in principle but a very different thing to introduce it on the industrial scale."

In many cases, RCH was very successful at transferring new laboratory-scale processes to the industrial dimension. Between 1982 and 1984, in a period of less than 24 months, RCH developed and tested a completely new process for which no prototype was available and for which various new apparatuses had to be invented. Using an scale-up factor of 1 : 24 000 the first production unit employing the "Ruhrchemie/Rhône-Poulenc oxo process" (RCH/RP) went on stream in July 1984 with an initial capacity of 100 000 tons per year (Figure 2).

Because of Ruhrchemie's commitment and status as an important oxo producer, development was primarily driven by product and commercial considerations. It was not until the 1990s that further development became science-driven, including especially all the scientific research work currently being conducted at universities as a result of the successful implementation of the RCH/RP process.



	Laboratory	OT-pilot plant	Plant
Temp. [°C]	125	125	122
Press. [bar]	30	50	50
Volume	5 L	50 L	120 m^3
Scale-up factor	1	1 : 10	1 : 24.000
TON	3,1 x 10^6	3,6 x 10^6	>> 5 x 10^6
n/*iso*-ratio	94 : 6	95 : 5	96 : 4

Figure 2 Development work at Ruhrchemie: the different stages of reactor design [12].

Focal points of RCH's work are described using Figure 3 as a schematic flowsheet.

Some of the conditions of the new process were based on RP's patents but all had to be adjusted to the rougher operation conditions of a commercial plant, to different qualities and purities of commercially available feedstocks (alkenes of different origin, syngas [from oil or coal], catalyst precursors, etc.), to a normal operation of 8760 h y^{-1}, and to the finely tuned relationships between, e.g., temperatures, pressures/partial pressures, concentrations of various organic and inorganic components in different phases, mass and heat transfer, and flow conditions of a continuous process. The economics of cooling and heat recovery

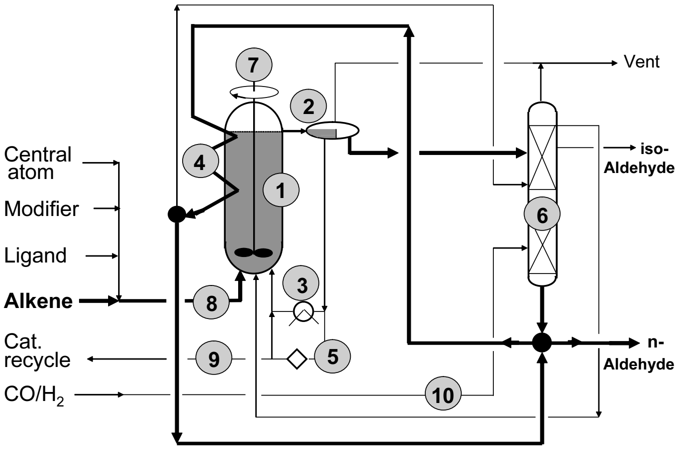


Figure 3 General Ruhrchemie design of the aqueous-biphasic hydroformylation process as the realization of Kuntz's inventions; focal points of R&D work as indicated.

and the utilization of unreacted substrates in off-gases or vents are of special importance.

Extensive chemical engineering work (including many details) comprised the following items: reactor design (**1** in Figure 3) together with the details of mass transport, behavior of phases/decanter (**2**), heat recovery/steam generation (**3**, **4**); rhodium and ligand recycle (**5**), fractionation (**6**), control units (**7**), feed (**8**, **10**), and catalyst work-up (**9**) [13]. Preceding work revealed the basic dependencies as far as pH values, addition of CO_2, salt effects, ionic strengths of solutions, the influence of catalyst modifiers, spectator effects, or microwave irradation and sonochemical treatment are concerned.

All the development work included the full work-up of the reactants, sidestreams, and products, reflecting the characteristics of the biphasic system, the testing of reaction parameters (even under random conditions), the dynamic responses of both the reactor and the catalytic system, product qualities, etc. Apart from the handling of the new aqueous catalyst system, a virtually new design of the hydroformylation process had to be prepared, involving much detailed work. Most of the engineering solutions to new questions arising from the Figure 3 system and numerous important variants have been patented. This included the preparation of TPPTS in commercial amounts and superior quality, which was also solely RCH's responsibility (see, for example, Ref. [14]).

All's well that ends well: the first commercial plant of RCH/RP's process went on stream in summer 1984, and today they produce approximately 890 000 metric tons per year of aldehydes, mainly C_4s from propene besides some C_5 (from butene) at two different locations. Typical reaction conditions, experiences, and performances over a 20-year average are given in Sections 2.3.6 and 2.4.1.1.3 (under "Lower Alkenes") and in Ref. [15].

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2.4.1.1.2
Kinetics

Raghunath V. Chaudhari

Introduction

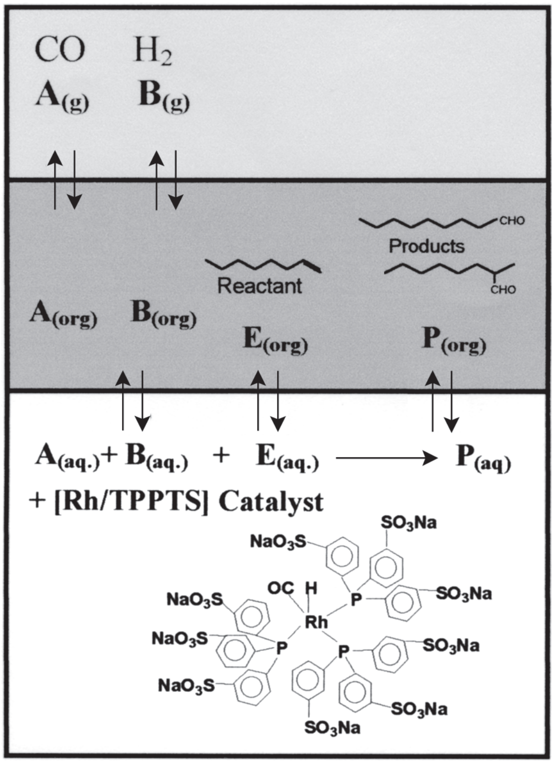
Homogeneously catalyzed processes often involve multiphase contacting due to the presence of reactants or products in gaseous, liquid, and solid phases, though the principal catalytic reaction occurs in a single phase in which the catalyst exists in a dissolved state. The most important aspects concerning the commercial viability of such processes are an understanding of the overall rate behavior, selectivity engineering, and catalyst recycle. In spite of several important developments in homogeneous catalysis, their applications in industry have been limited due to difficulties in identifying an economic and industrially feasible separation of products and catalysts. In order to solve this problem, numerous approaches to the immobilization of homogeneous catalysts have been explored. It is well known that several attempts to heterogenize homogeneous catalysts, which include polymer anchoring, encapsulation/tethering [1, 2] supported liquid-phase catalysis [3], and use of organometallic catalysts on mineral supports [4, 5], have not led to industrially viable alternatives. In this context, biphasic catalysis using water-soluble metal complexes has been the most significant development in recent years, in which the aqueous-phase catalyst is contacted with the immiscible organic phase containing reactants and products with or without gaseous reactants in a multiphase system (gas–liquid–liquid), thus allowing a simple catalyst-product separation. It was after the work of Kuntz [6] on the synthesis of the triphenylphosphine trisulfonate (TPPTS) ligand and its application in the hydroformylation of olefins that the research on water-soluble catalysis gained momentum. The concept has been proven on a commercial scale in the Ruhrchemie/Rhône-Poulenc process for the hydroformylation of propene to butyraldehyde [7]. The roles of different water-soluble ligands, their synthesis and stability, as well as other means of intensifying these gas–liquid–liquid catalytic reactions, have been extensively studied and the subject has been reviewed by Kalck and Monteil [8], Herrmann and Kohlpaintner [9], Cornils [10], and Beller et al. [11] among others. Herrmann and Kohlpaintner

[9] have shown that Rh complexes with other water-soluble ligands, such as BISBIS (sulfonated (2,2′-bis(diphenylphosphinomethyl)-1,1′-biphenyl) and NORBOS, give exceptionally high activities and n/i ratios. Uses of cationic [12], nonionic [13], and surface-active [14, 15] phosphines as water-soluble ligands have also been proposed. Of all the catalyst systems studied, Rh-TPPTS is the most suitable and commercially proven catalyst system for biphasic hydroformylation. Several modifications of the water-soluble catalysts using co-solvents [15], surfactants and micelle-forming reagents [16], a supercritical CO_2–water biphasic system [17], supported aqueous-phase catalysis [18], and catalyst-binding ligands (interfacial catalysis) [19] have been proposed to overcome the lower rates observed in biphasic catalysis due to poor solubilities of reactants in water (see Sections 2.2.3.2 and 2.3.3.3). So far, endeavors have been centered on innovating novel catalyst systems from the viewpoint of efficient catalyst recycle and rate enhancement, but limited information is available on the kinetics of biphasic hydroformylation.

The understanding of the overall rate of biphasic catalytic reactions is an equally important aspect in the evolution of an economical process. In the case of aqueous biphasic hydroformylation reactions, the rate will be governed by several factors, which include dissolution of CO, H_2, and olefins in organic and aqueous (catalyst) phases, their solubility, their partition coefficients, and the intrinsic kinetics of the reactions occurring in the aqueous phase [20]. The most important of these is knowledge of the kinetics, which is also essential to understand the reaction mechanism and elucidation of the rate-controlling step. The aim of this contribution is to present a review of the current status on the kinetics of hydroformylation of olefins using water-soluble catalysis and catalyst recycle studies (see also Section 2.3.1). The role of ligands, pH, co-solvents, and surfactants on the rate behavior will be discussed.

Overall Rate of Reaction

Hydroformylation of olefins using aqueous biphasic catalysts is an example of a gas–liquid–liquid catalytic system in which a reaction of two gaseous reactants (carbon monoxide and hydrogen) and gaseous or liquid-phase olefin occurs in the presence of a water-soluble catalyst in a liquid–liquid dispersion. The reaction of dissolved gases and olefins occurs in the aqueous (**bulk**) phase or organic aqueous interface (Figure 1). The overall rate of reaction in such multiphase catalytic systems depends on gas–liquid and liquid–liquid mass transfer, the solubility of gas-phase reactants in the organic and aqueous phases, the liquid–liquid equilibrium properties, and the intrinsic kinetics of the reaction in the aqueous phase. In addition, the dispersion characteristics of the droplets, the droplet size, and the bubble size can also influence the rate of reaction. Depending on the fractional hold-up of the aqueous phase, it will be either a continuous aqueous phase with dispersed organic droplets or a dispersed aqueous phase in a continuous organic medium. The coupled influence of mass transfer with chemical reaction is expected to be quite different in these two situations. To determine of intrinsic kinetics of such reactions, it is necessary to ensure that the experimental data are obtained



Gaseous Reactants
($CO + H_2$)

Organic Phase
(Reactant + Products + Solvent)

Aqueous Phase
(Catalyst + Water)

Figure 1 Schematic representation of biphasic hydroformylation.

under a kinetically controlled regime and the contributions of the interphase mass transfer and hydrodynamics of the liquid–liquid dispersion are not significant. The criteria for significance of gas–liquid and liquid–liquid mass-transfer steps for such systems have been described by Mills and Chaudhari [21]. In this section, examples of hydroformylation reactions using aqueous biphasic catalysts will be reviewed with a focus on kinetic studies, the effect of additives, co-solvents and surfactants, and catalyst recycle studies.

Kinetic Studies Without Additives

Hydroformylation of olefins using water-soluble catalysts in two-phase systems has been extensively studied [22, 23], the role of different types of water-soluble ligands and metal complexes in the activity, selectivity, and stability has been discussed for a variety of olefinic substrates. A few case studies in which kinetics and rate behavior have been addressed are reviewed here.

The hydroformylation of 1-octene using a water-soluble Rh-TPPTS catalyst in a biphasic medium was studied in the absence of any additive or co-solvent by Bhanage [24]. The experiments were carried out under conditions such that the aqueous phase containing the Rh-TPPTS catalyst was dispersed in the continuous organic phase consisting of 1-octene and toluene. The results indicated absence of hydrogenation products and the selectivity to hydroformylation products was greater than 98%, with the *n*/*i* ratio in the range 1–2 : 1. The aqueous Rh complex catalyst was found to retain its activity even after ten recycles, indicating negligible deactivation. The effects of the concentration of catalyst precursor, TPPTS, and of 1-octene, and the partial pressure of CO and hydrogen, were studied in a temperature range of 353–373 K. The rate of reaction was found to be first order with respect to catalyst concentration and hydrogen partial pressure. This was explained as a consequence of oxidative addition of hydrogen to acyl-carbonyl rhodium species as the rate-determining step [25]. The reaction rate was found to be 0.7th order with respect to CO partial pressure, in contrast to the CO inhibition observed for homogeneously catalyzed hydroformylation [26]. For a water-soluble catalyst, the concentration of dissolved carbon monoxide in the aqueous phase is very low compared to that in the organic phase; hence, formation of a dicarbonyl Rh species [$(RCO)Rh(CO)_2(TPPTS)_2$], which is believed to be responsible for a negative-order dependence [25], is not very likely. Therefore, this difference in the trends is not truly due to any change in the reaction mechanism. In the homogeneous catalytic reaction, the rate varies linearly with carbon monoxide pressure in the lower region and only beyond a certain pressure of CO is rate inhibition observed. The 1-octene concentration dependence on the rate of hydroformylation showed an apparent reaction order of 1.7 (Figure 2), but this was due to an inappropriate account of the solubility variation with changes in 1-octene concentrations. Bhanage [24] has shown that if the variation in solubility is accounted for, the rate of reaction shows first-order dependence on 1-octene concentrations. A rate model [Eq. (1)], derived from

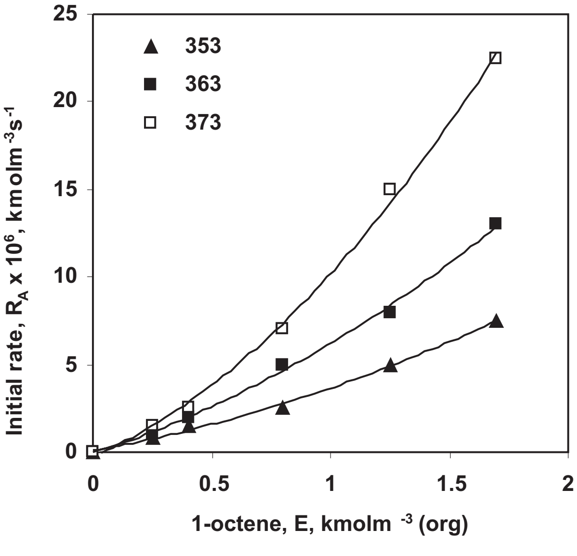


Figure 2 Effect of 1-octene concentration on hydroformylation rate.

the well-known mechanism of hydroformylation [25] assuming oxidative addition of hydrogen to acyl-carbonyl rhodium species as a rate-determining step, was found to represent the rate data satisfactorily:

$$R = \frac{k\, K_1\, K_2\, K_3\, A\, B\, C\, D}{1 + \alpha\, B} \tag{1}$$

where A = partial pressure of hydrogen, MPa; B = partial pressure of carbon monoxide, MPa; C = concentration of catalyst, kmol m^{-3}; D = concentration of olefin, kmol m^{-3}; k = reaction rate constant, s^{-1}; and K_1, K_2, K_3, K_4 and α are constants.

The effect of aqueous phase hold-up on the rate of hydroformylation for 900 and 1500 rpm is shown in Figure 3. At 1500 rpm, the rate versus ε_{1a} (aqueous phase hold-up) plot shows a maximum. For kinetic control, the rate is expected to vary linearly with catalyst loading. However, in a case where the reaction occurs essentially at the liquid–liquid interphase, it would depend on the liquid–liquid interfacial area even though liquid–liquid mass transfer is not rate limiting. For $\varepsilon_{1a} > 0.4$, phase inversion occurs and the interfacial area would be determined by the dispersed phase, which would be the organic phase. Since, for $\varepsilon_{1a} > 0.5$, ε_1 will decrease with an increase in ε_{1a}, a reduction in liquid–liquid interfacial area is expected. Hence, the observed results of a decrease in the rates with an increase in ε_{1a} indicate a possibility of interfacial reaction rather than a bulk aqueous-phase reaction [7]. For $d_1 < 0.3$ mm, a very large interfacial area ($a_1 = 6\ \varepsilon_1\ d\ /\ d_1$) in the range (4–5) · 10^4, l/m is likely to exist compared to the volume of the aqueous phase.

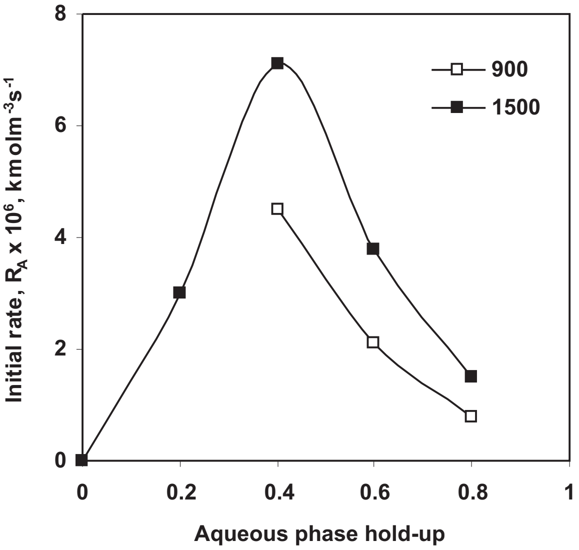


Figure 3 Effect of aqueous phase hold-up on hydroformylation rate.

Hydroformylation of ethylene using a water-soluble Rh-TPPTS catalyst has been investigated [27] using a toluene–water solvent system at 353 K. The effect of TPPTS concentration on rate shows a maximum at a P/Rh ratio of 8 : 1. The rate of reaction first increases with catalyst concentration, and above a certain value it remains constant. The effect of aqueous-phase hold-up shows a maximum in the rate at $\varepsilon_{1a} = 0.4$. The apparent reaction orders for the partial pressures of hydrogen and ethylene were found to be one and zero respectively. A strong inhibition in the rate with an increase in P_{CO} was observed. An interesting example of tandem synthesis of methacrolein in an aqueous biphasic system has been reported by Deshpande et al. [28], in which hydroformylation of ethylene and aldol condensation reactions occur in two immiscible liquid phases with a high yield of the product. Use of a two-phase system prevents contact of the hydroformylation and aldol catalysts, the interaction of which leads to deactivation.

Herrmann et al. [29] have reported the hydroformylation of propene using a Rh-BISBIS catalyst system in a continuous stirred reactor. The activity of this catalyst (45.5 mol g^{-1} min^{-1}) was found to be three times higher than that of a Rh-TPPTs catalyst (15 mol g^{-1} min^{-1}). The n/i ratio also improved from 94 : 6 (TPPTS) to 97 : 3 (BISBIS). They have also studied the hydroformylation of 1-hexene at 5 MPa CO/H_2 pressure in the temperature range 395–428 K, and observed that the activity increased from 0.73 to 10.73 (mol g^{-1} min^{-1}) when the temperature was raised from 395 to 428 K whereas the n/i ratio decreases from 97 : 3 to 94 : 6. The catalyst was found to be stable even after 16 h of a continuous run. Wachsen et al. [30] have shown that hydroformylation of propene using a Rh-TPPTS catalyst operates under conditions of significant gas–liquid mass-transfer resistance. A detailed analysis of the engineering aspects supported with experimental validation is necessary to understand the critical scale-up issues. The kinetics of hydroformylation of styrene using a biphasic $HRh(CO)(TPPTS)_3$ catalyst [31] showed that the rate was first order with respect to catalyst loading, H_2, CO, and styrene concentrations. The rate was found to be limited by transport of styrene from the organic to the aqueous phase under certain conditions.

The development of supported aqueous-phase catalysis (SAPC; see Section 2.6) opened the way to hydroformylating hydrophobic alkenes such as oleyl alcohol and octene [14]. SAPC involves dissolving an aqueous-phase $HRh(CO)(TPPTS)_3$ complex in a thin layer of water adhering to a silica surface. Such a catalyst shows a significantly high activity for hydroformylation. For classical liquid–liquid systems, the rate of hydroformylation decreases in the order 1-hexene > 1-octene > 1-decene; however, with SAP catalysts, these alkenes react at virtually the same rate and the solubility of the alkene in the aqueous phase is no longer the rate-determining factor [32]. The loss of catalytic activity due to depletion of water in the aqueous film is a major drawback of the SAPC catalysts.

Co-Solvent Effect

It has been shown that by using co-solvents such as ethanol, acetonitrile, methanol, ethylene glycol, and acetone, the rate of hydroformylation can be enhanced by

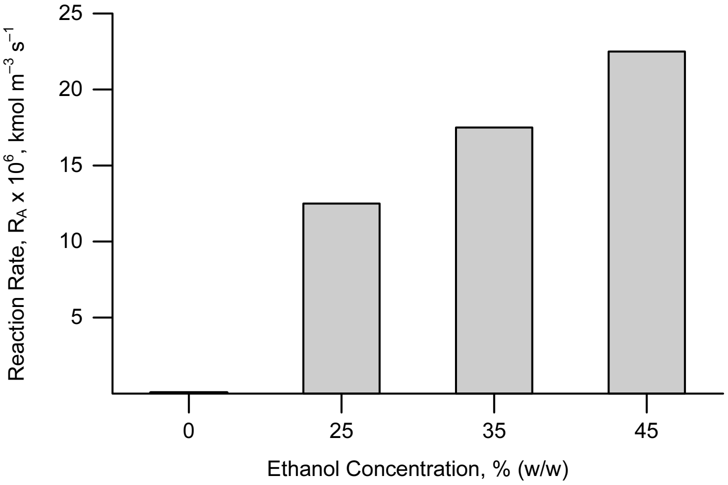


Figure 4 Effect of co-solvent on 1-octene hydroformylation.

severalfold [33, 34]. However, in some cases, a lower selectivity is obtained due to interaction of the co-solvent with products (e.g., formation of acetals by the reaction of ethanol and aldehyde). The hydroformylation of 1-octene with dinuclear $[Rh_2(\mu\text{-}SR)_2(CO)_2(TPPTS)_2]$ and $HRh(CO)(TPPTS)_3$ complex catalysts using various co-solvents has been investigated by Monteil et al. [33], who showed that ethanol was the best co-solvent. Purwanto and Delmas [34] have shown that the hydroformylation rate increases eight-fold in the presence of ethanol as a co-solvent (Figure 4) and studied the kinetics of hydroformylation of 1-octene using $[Rh(COD)Cl]_2$-TPPTS catalyst in the temperature range 333–343 K. First-order dependence was observed with respect to the concentration of catalyst and 1-octene. The effect of the partial pressure of hydrogen indicates a fractional order (0.6–0.7) and substrate inhibition was observed with a partial pressure of carbon monoxide. Equation (2) was proposed as the rate equation

$$R = \frac{k\,A\,B\,C\,D}{(1 + K_1\;A)\,(1 + K_2\;+ B)^2} \tag{2}$$

The kinetics of hydroformylation of 1-octene using $[Rh(COD)Cl]_2$ as a catalyst precursor with TPPTS as a water-soluble ligand and ethanol as a co-solvent was further studied by Deshpande et al. [15] at different pH values. The rate increased by two- to fivefold when the pH increased from 7 to 10, while the dependence of the rate was found to be linear with olefin and hydrogen concentrations at both pH values. The rate of hydroformylation was found to be inhibited at higher catalyst concentrations at pH 7, in contrast to linear dependence at pH 10 (Figure 5). The effect of the concentration of carbon monoxide was linear at pH 7, in contrast to the usual negative-order dependence. At pH 10, substrate-inhibited kinetics was observed with respect to CO (Figure 6).

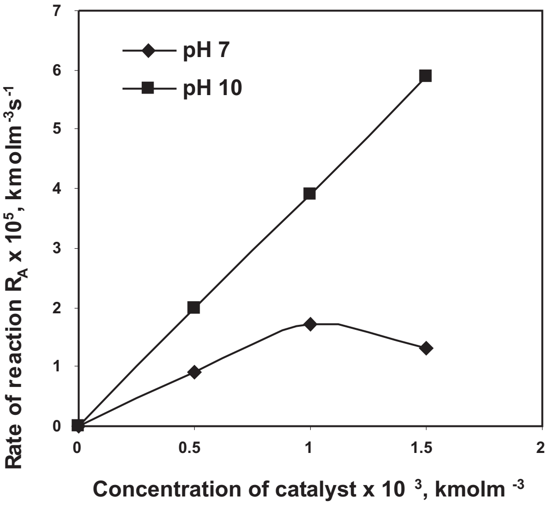


Figure 5 Effect of catalyst concentration on 1-octene hydroformylation rate at different pH values.

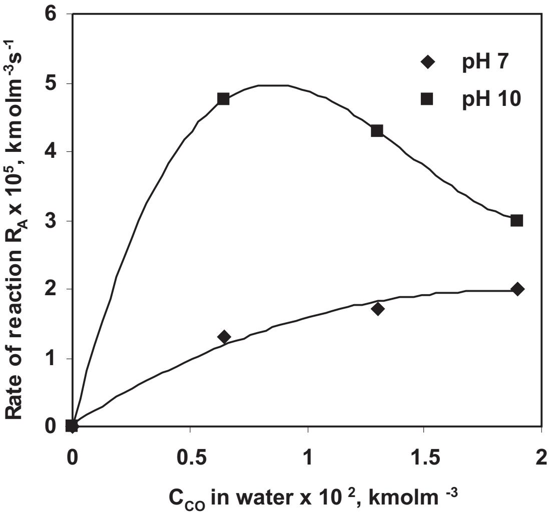


Figure 6 Effect of partial pressure of CO on 1-octene hydroformylation rate at different pH values.

Smith et al. [35] have reported a drop in the activity when the pH of the reaction medium was reduced from 6.8 to 5 for a Rh nitrate/AMPHOS catalyst system (AMPHOS = 1-*N,N,N*-trimethylamino-2-diphenylphosphinoethane iodide). Hydroformylation of 1-tetradecene with a water-soluble Rh-NABSDPP (NABSDPP: Na-butylsulfonated diphenylphosphine) catalyst gave poor rates in acidic (pH 2.5 to 6) medium. A seven- to eight-fold increase in the rates was observed when the pH was increased from 6 to 10 [36].

The kinetics of hydroformylation of styrene using $HRhCO(TPPTS)_3$ catalyst in a biphasic system with various co-solvents was investigated by Nair [31]. *N*-Methylpyrrolidone (NMP) and ethanol were found to enhance the rate by 7–9-fold compared to that in the absence of any co-solvent. However, with ethanol as a co-solvent, the aldehyde selectivity observed was 80% with acetals as side products. With NMP co-solvent the aldehyde selectivity was > 99%. A kinetic study at 373 K revealed that the rate was first-order dependent on catalyst concentration, fractional-order on CO, and first-order tending to zero-order on styrene concentration.

Surfactant Effect

The addition of various surfactants and micelle-forming agents in the biphasic hydroformylation of olefins was also considered as a tool for enhancement of the reaction rates (see Section 2.3.4). Whereas the presence of a surfactant leads to a lower droplet size in the dispersed phase, thus increasing the liquid–liquid interfacial area and hence the mass-transfer rate, the formation of emulsions is considered as a major drawback of this system. Mass-transfer effects in biphasic hydroformylation of 1-octene in the presence of cetyltrimethylammonium bromide (CTAB) was studied by Lekhal et al. [37]. A mass-transfer model based on Higbie's penetration theory was proposed to predict the rate of hydroformylation in a gas–liquid–liquid system.

Hydroformylation of 1-dodecene in the presence of various micelle-forming agents with aqueous $[RhCl(CO)(TPPTS)_2]$ catalyst was studied by Li et al. [38]. The solubility of 1-dodecene was enhanced in the presence of mixed micelles due to a decrease in the critical micelle concentration (CMC), and higher conversion and selectivity were observed in the mixed micellar solution compared to that for a single micelle type. For biphasic hydroformylation of 1-dodecene in the presence of CTAB, Yang et al. [39] reported several agitator configurations for improving the mixing, dispersion, and interphase mass transfer. An empirical form of macrokinetic equation [Eq. (3)] was found to represent the initial rate data as well as the n/i ratio of aldehydes.

$$R = k\, N^m\, {C_{\mathrm{CTAB}}}^n\, D^p \left(\frac{V_{\mathrm{O}}}{V_{\mathrm{W}}}\right)^q \qquad (3)$$

In another report a semi-empirical rate equation has been proposed combining mechanisms of homogeneous catalysis and interfacial parameters for biphasic hydroformylation of 1-dodecene with a water-soluble Rh complex catalyst [40].

Promoting Interfacial Catalysis

Chaudhari et al. [19] have shown that the rate of biphasic hydroformylation can be enhanced severalfold by using a catalyst-binding ligand to promote interfacial catalytic reaction. This approach involves the use of a ligand that is insoluble in the aqueous catalyst phase but has a strong affinity for the metal complex catalyst. The

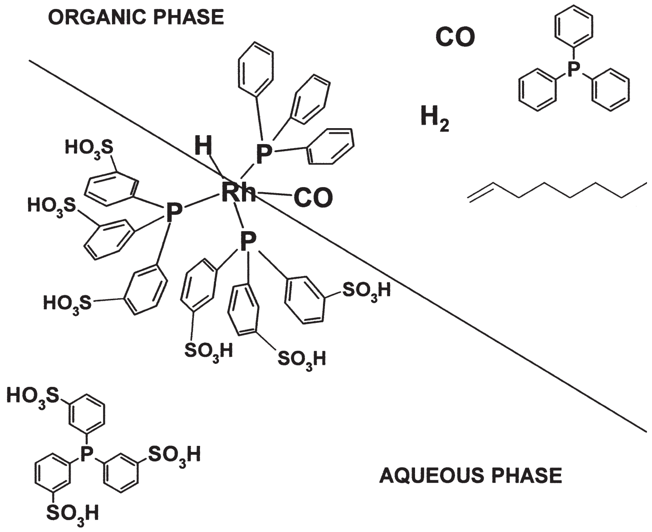


Figure 7 Schematic representation of interfacial catalysis.

interaction of the ligand and the catalyst takes place essentially at the liquid–liquid interface (Figure 7); thus the concentration of the catalytic species will be enriched at the interface, where it can access the reactants present in the organic phase in significantly higher concentrations with respect to the aqueous phase. This results in a dramatic increase in the rate of such a biphasic catalytic reaction, as indicated by experimental data on the hydroformylation of 1-octene using a Rh-TPPTS complex catalyst with triphenylphosphine as a catalyst-binding ligand [19]. The rate of the reaction was enhanced by 10–50-fold in the presence of catalyst-binding ligands when compared with the biphasic hydroformylation reaction (Figure 8).

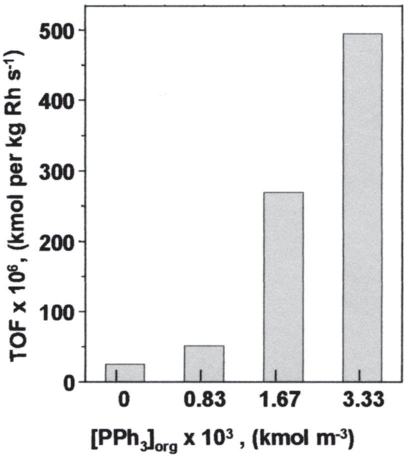


Figure 8 Enhancement of hydroformylation rate by promoting interfacial catalysis.

This concept has also been demonstrated in reverse for the hydroformylation of a water-soluble olefin (allyl alcohol) with the organic phase containing a catalyst, $HRh(CO)(PPh_3)_3$. In this case, the catalyst is present in the organic phase, whereas the catalyst-binding ligand (TPPTS) is added to the aqueous phase.

The effect of reaction parameters, such as the concentrations of catalyst and olefin and the partial pressures of CO and hydrogen, on the rate of reaction has been studied at 373 K [24]. The rate varies linearly with catalyst concentration, olefin concentration, and partial pressure of hydrogen. A typical substrate-inhibited kinetics was observed with the partial pressure of carbon monoxide. Further, a rate equation [Eq. (4)] to predict the observed rate data has been proposed.

$$R = \frac{k\ A\ B\ D}{(1 + K_1\ B^2)\,(1 + K_2\ D)} \tag{4}$$

It is important to note that the kinetic trends for carbon monoxide were completely opposite to those without a catalyst-binding ligand. Since, under conditions of interfacial catalysis, a higher CO concentration is accessible to the catalytic species, substrate inhibition is observed. The aqueous-phase catalyst could be recycled several times without loss of activity.

Conclusions

The kinetics of hydroformylation of olefins using aqueous biphasic catalysts demonstrates that the rate behavior varies significantly for biphasic catalytic reactions depending on the ligands, additives, and co-solvents. In particular, the kinetics with respect to CO shows a variation for different systems. A major limitation to the rate of biphasic hydroformylation is the solubility of the olefin in the aqueous catalyst phase. Using co-solvent, catalyst-binding ligands, micelle-forming agents, supercritical CO_2–water biphasic systems, and SAPC, the rates are enhanced significantly. Although sufficient information on the intrinsic kinetics is now available, further studies on understanding of the role of gas–liquid and liquid–liquid mass transfer, the influence of dispersed-phase hold-up, drop size, and phase equilibrium properties are necessary. Interface mass-transfer parameters under gas–liquid–liquid hydroformylation conditions also need to be investigated.

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2.4.1.1.3
Conversion of Alkenes

Carl-Dieter Frohning and Christian W. Kohlpaintner

a) Lower Alkenes

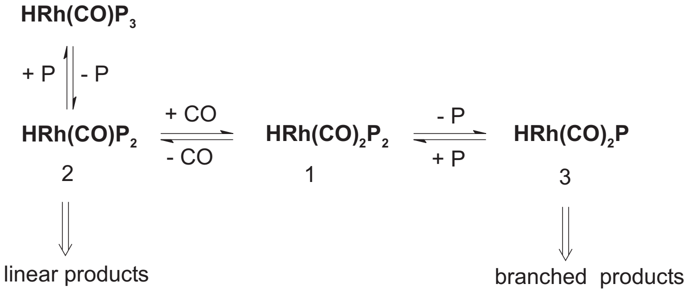
Introduction

Although olefins with variable chain lengths have been successfully hydroformylated in aqueous two-phase reactions, a distinction between lower and higher olefins is reasonable. The solubility of ethylene (C_2), propene (C_3), and C_4 olefins, herein referred to as lower olefins, in the aqueous catalyst phase is high enough to assure chemical reaction without phase-transfer limitations. Olefins with chain lengths greater than C_4 have a significantly lower solubility, thus making special means necessary to overcome such limitations (see under “Mechanism”, below).

We will describe the basics of aqueous two-phase hydroformylation with TPPTS and rhodium complexes thereof [1] as they apply to C_3 and C_4 olefins according to the Ruhrchemie/Rhône-Poulenc process. Emphasis will be put on the commercial applications and the basic description of the processes.

Mechanism

The mechanism of the oxo reaction has been extensively studied in the past. A comparative study of the two commercially applied oxo catalysts $HRh(CO)(TPP)_3$ (TPP = triphenylphosphine) and $HRh(CO)(TPPTS)_3$ was performed by Horváth [2]. The latter, which is water-soluble, is considered to react according to the dissociative mechanism. However, remarkable differences exist in the catalytic activity and the selectivity of the organic and the water-soluble catalyst. The latter shows much lower specific activity but an increased selectivity to linear products in the hydroformylation of propene. From an Arrhenius plot it is concluded that the dissociation energy of TPPTS from $HRh(CO)(TPPTS)_3$ is about 30 ± 1 kcal mol^{-1} (1 kcal mol^{-1} = 4.18 kJ mol^{-1}). Compared with the dissociation energy of TPP from $HRh(CO)(TPP)_3$ (19 ± 1 kcal mol^{-1} [3]) the difference is greater than 10 kcal mol^{-1}, thus explaining the lower catalytic activity at comparable reaction conditions. Additionally, it was shown that $HRh(CO)(TPPTS)_3$, in contrast to its organic-soluble derivative, does not form $HRh(CO)_2(P)_2$ (P = TPPTS; **1**) at syngas pressures up to 200 bar. By dissociation of either carbon monoxide or TPPTS the unsaturated species $HRh(CO)(TPPTS)_2$ (**2**) and $HRh(CO)_2(TPPTS)$ (**3**) are generated, which are responsible for the formation of linear or branched aldehydes (Scheme 1). As $HRh(CO)(TPPTS)_2$ is formed by dissociation of TPPTS from $HRh(CO)(TPPTS)_3$ and $HRh(CO)_2(TPPTS)$ is obtained through an equilibrium reaction from $HRh(CO)_2(TPPTS)_2$, the observed increased selectivity to linear products becomes explicable.



Scheme 1 Alternative paths of the oxo reduction.

Kinetics

Limited data are available for the kinetics of the oxo synthesis with HRh(CO)-(TPPTS)$_3$. The hydroformylation of 1-octene was studied in a two-phase system in the presence of ethanol as a co-solvent to enhance the solubility of the olefin in the aqueous phase [4]. A rate expression was developed which was nearly identical to that of the homogeneous system, the exception being a slight correction for low hydrogen partial pressures [Eq. (1)]; see also Section 2.4.1.1.1.

$$R_0 = k \frac{[\text{octene}]_0[\text{cat}][\text{H}_2][\text{CO}]}{(1 + K_{\text{H}_2}[\text{H}_2])\,(1 + K_{\text{CO}}[\text{CO}])^2} \tag{1}$$

A rigid reaction rate model, established under idealized conditions, becomes complex and complicated when it is transferred to the hydroformylation of lower olefins under conditions relevant to industrial practice, as the mass-transfer phenomena involved in a triphasic system (gas/liquid/liquid) in large reactors have to be taken into account. The resulting algorithm in general is limited to a narrow bandwidth of operating conditions, thereby diminishing the applicability and reliability of such models. The substitution of rigid models by data-driven models (e.g., so-called artificial neural networks) has been under consideration for some years by one of the authors (CDF).

Recent Developments

In order to develop highly active and selective catalysts for propene hydroformylation, several ligands based on biphenyl or binaphthyl structures were synthesized and have been applied in the oxo synthesis [5]. A mixture of six-, seven- and eightfold sulfonated NAPHOS, called BINAS, together with rhodium is the most active water-soluble oxo catalyst known today. Even at very low phosphine to rhodium ratios (P/Rh), *n*/*i* selectivities of 98 : 2 are achieved.

A challenge in synthesizing new water-soluble ligands is the direct functionalization of new or previously known organic phosphines. The plethora of functionalized phosphines available today have been categorized and discussed in

[6]. In the particular case of sulfonated phosphines the introduction of the sulfonato group is difficult as the phosphines tend to oxidize during treatment with oleum (sulfur trioxide dissolved in concentrated sulfuric acid) and require specific synthesis methods [7]. Some information about special phosphines and their manufacturing conditions are given in [8].

Commercial Applications

The industrial hydroformylation of short-chained olefins such as propene and butenes is nowadays almost exclusively performed by so-called LPO (LPO = low-pressure oxo) processes, which are rhodium-based. In other words, the former high-pressure technology based on cobalt has been replaced by the low-pressure processes, which cover more than 80% of the total C_4 capacity due to their obvious advantages [9, 30].

Two basic variants of LPO processes exist: the homogeneous processes, e.g., the catalyst and the substrate are present in the same liquid phase; and the two-phase process (Ruhrchemie/Rhône-Poulenc process, RCH/RP) applying a water-soluble catalyst. The homogeneous processes dominate the field by far, a consequence as much of their early development as of the licensing policy for the two-phase process. Both types of process use rhodium as the catalyst metal in combination with a suitable phosphine as ligand. More precisely, the ligand is triphenylphosphine (TPP) in most cases, applied as such in the homogeneous case and in its water-soluble (sulfonated) variant (TPPTS) in the RCH/RP process. Some phosphite ligands have also gained commercial importance for LPO processes recently [10, 11], but no metal other than rhodium has been successfully applied commercially in this technology.

Economic and Ecological Aspects

The RCH/RP process has been in operation since the early 1980s, producing some 5 million tonnes of *n*-butanal [12, 13]. The water-soluble catalyst $HRh(CO)(TPPTS)_3$ combines the advantages of a homogeneous catalyst (high activity, high selectivity) with those of a heterogeneous one. These advantages, in addition to a highly efficient recovery of process heat, lead to a superior technology which also results in a cost advantage compared with the classical homogeneous processes. The RCH/RP process has its strengths in the efficiency of material usage (raw materials, energy and byproduct credits) along with smaller fixed costs due to the ease of operation. The overall cost advantage is estimated to be roughly 10% compared with the standard processes (see Section 2.5.1).

The ecological benefits of this modern process are obvious and can be summarized as follows:

- usage of water as a nontoxic, nonflammable solvent;
- efficient usage of C_3 raw material (propene);
- high selectivity toward the desired products;
- excellent atom economy;

- energy consumption minimized, e.g., net steam exporter;
- efficient recovery of catalyst (loss factor = $1 \cdot 10^{-9}$);
- ligand toxicity is not critical (LD_{50}, oral > 5 g kg^{-1});
- almost zero environmental emissions (cf. also Section 2.3.6).

Along with other water-based reactions the RCH/RP process has been critically reviewed with respect to its environmental attractiveness by Sheldon [14]. Overall the RCH/RP process, besides a technical success, is an outstanding example for the impact of modern technology on both economic and ecological aspects at the same time.

C_3 Process Description

Ruhrchemie AG was the first to seize upon the idea of applying a water-soluble rhodium catalyst and thus commercializing a process which had been elaborated on a laboratory scale by Rhône-Poulenc earlier [15, 16].

It took only two years of intensive research to develop the technical concept and to erect the first plant, which went on stream in 1984 [17]. By 1987 the second unit was already built, followed by a third unit in 1997. Today the total estimated capacity in *n*-butanal amounts to more than 400 000 t y^{-1} having been 350 000 t y^{-1} in 1995 [18, 19]. An additional plant for the production of *n*-pentanal from *n*-butene was brought on stream in 1995.

Basically, the requirements for a process using an aqueous catalyst phase are the same as for the homogeneous processes. The reaction of propene, hydrogen, and carbon monoxide takes place in the first liquid phase, the aqueous catalyst solution. The second, organic, layer is formed by the reaction product, e.g., butanals. Intimate contact between the catalyst solution and the gaseous reactants has to be provided by intensive gas dispersion at the bottom of the reactor together with sufficient stirring. The two liquid phases form an intimate admixture (emulsion) upon stirring which occupies most of the reactor volume, leaving only a small headspace as an internal reservoir for the gaseous reactants. A heating/cooling device is necessary in order to enable start-up of the reactor and to control the exothermic hydroformylation reaction (about 28 kcal mol^{-1} or 118 kJ mol^{-1}). Finally, the mixture of liquid and gaseous products has to be withdrawn from the reactor, products and catalyst have to be separated, and the latter has to be recycled.

A simplified scheme for the RCH/RP unit is presented in Figure 1 [1, 12, 13]. The reactor (1) is essentially a continuous stirred tank reactor equipped with a gas inlet, a stirrer, a heat exchanger and a catalyst recycle line. Catalyst and reactants are introduced at the bottom of the reactor. Vent gas is taken from the head of the reactor and from the phase separator. Control of the liquid volume inside the reactor is simple: the liquid mixture, composed of catalyst solution and aldehydes, leaves via an overflow and is transferred to a phase separator (2), where it is partially degassed. The separation of the aqueous catalyst solution (density of the catalyst solution ≈ 1100 g L^{-1}) and the aldehydes occurs rapidly and completely, favored by the difference in densities (density of aldehyde layer ≈600 g/L due to dissolved gases).

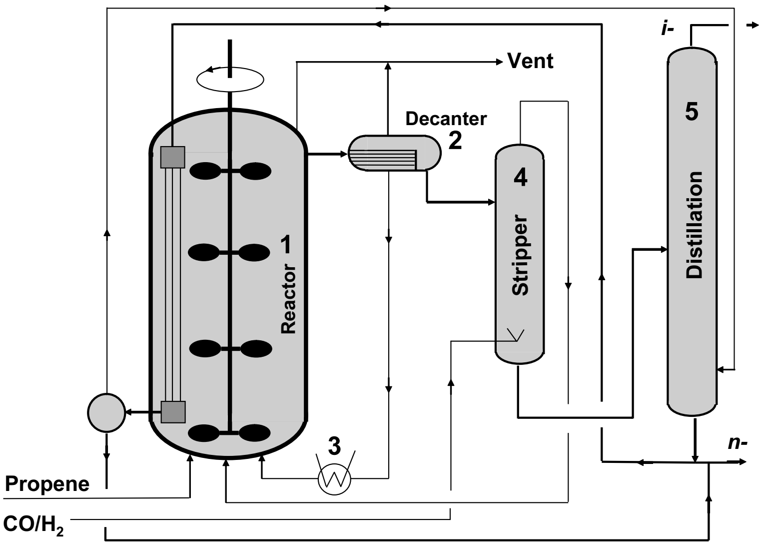


Figure 1 The RCH/RP unit.

The catalyst solution passes through a heat exchanger (3) and produces process steam that is consumed in downstream operations. Some water is extracted from the catalyst solution by its physical solubility in the aldehydes (about 1.3% w/w) which may be replaced before the catalyst solution reenters the reactor.

The subsequent stripping column (4) is important. From the raw organic phase coming from the phase separator and entering at the top of the stripping column, the dissolved reactants are removed by a fresh countercurrent stream of synthesis gas. The pressure inside the stripping column is kept slightly higher than the pressure in the reactor; e.g., no additional mechanical compression nor heating is necessary to recycle unconverted reactants. The resulting crude aldehydes are virtually free of propene as well as propane and contain only minimum amounts of dissolved synthesis gas. The head gas from the stripping column is fed back into the reactor.

The crude aldehydes are split into *n*- and isobutanals in the distillation column (5). The heat required is supplied by the hydroformylation itself: the reboiler of the distillation is a falling-film evaporator which is incorporated in the synthesis reactor using *n*-butanal as the heat carrier. This system has clear advantage over the classical hydroformylation processes, as the RCH/RP process not only uses the heat of reaction efficiently but is also a net steam exporter.

The favorable combination of stripping column, distillation, and heat recovery system is closely linked with the properties of the catalyst solution. The raw aldehydes are virtually free from ingredients of the catalyst solution, thus avoiding any of the well-known side reactions which take place in the presence of even traces of catalyst during thermal treatment. The fact that highly reactive *n*-butanal may be used as a heat-transfer medium well underlines this statement.

Table 1 RCH/RP process: typical data.

	Range	*Typical value*
Reaction conditions		
Temperature [°C]	110–130	120
Pressure [bar]	40–60	50
CO/H_2 ratio	0.98–1.03	1.01
Propene conversion [%]	85–99	95
Propene purity [%]	85–99.9	95
Product composition [%]		
Isobutanal	4–8	4.5
n-Butanal	95–91	94.5
Isobutanol	< 0.1	< 0.1
n-Butanol	0.5	0.5
Butyl formates	traces	traces
Heavy ends	0.2–0.8	0.4
Selectivity to C_4 products	> 99	> 99.5
Selectivity to C_4 aldehydes	99	99
n/*i* ratio	93 : 7–97 : 3	95 : 5

The active catalyst species $HRh(CO)(TPPTS)_3$ is generated during the start-up of the reactor. Rhodium is introduced in any suitable form, e.g., as an acetate or as the salt of another organic acid. The resulting solution, with a rhodium concentration in the range of 200–350 ppm, is brought to reaction temperature under synthesis gas pressure, leading to the formation of the active yellow complex. No induction period is observed when the reaction is started immediately by adding propene and synthesis gas after the reaction temperature of about 120 °C has been reached, making start-up and close-down operations extremely easy. Some typical data for the hydroformylation of propene are summarized in Table 1 [8].

C_4 Process Description

It is an intrinsic characteristic – not only in the presence of aqueous catalyst solutions – that the rate of the oxo reaction in comparable conditions declines with increasing chain length of the olefin. This fact is attributed, inter alia, to the decreasing solubility of higher olefins in the aqueous catalyst solution, which correspondingly leads to low olefin concentrations and thus reduced reaction rates [20]. There are not too many options of ways to overcome the problem: an increase in temperature (with a negative impact on long-term ligand stability and *n*/*i*-ratio), an increase in rhodium concentration (cost factor), or addition of substances improving the solubility of the olefins (complicating the simple basic process). For the hydroformylation of *n*-butene a slight increase in rhodium concentration is sufficient to ensure appreciable space–time yields in industrially relevant conditions.

The cheapest source for *n*-1-butene is "raffinate II", a C_4 cut from which butadiene (by extraction) and isobutene (by conversion into methyl *t*-butyl ether) have been removed. The remaining mixture of C_4 hydrocarbons contains about 50–65% of *n*-1-butene, the remainder consisting of *cis/trans* *n*-2-butene and saturated butanes. A high concentration of *n*-1-butene in the raffinate is desirable, for obvious reasons. On the other hand the price of “raffinate II” is directly proportional to its content in *n*-1-butene. Therefore it is an unconditional requirement that the process be compatible with different concentrations of *n*-1-butene in the feedstock.

The most valuable product of C_4 hydroformylation is *n*-pentanal, whereas the isomers 2-methylbutanal and 3-methylbutanal are less in demand and lower in value. A catalyst with high selectivity should not catalyze the hydroformylation of 2-butene and convert 1-butene predominantly to *n*-pentanal. Both requirements are fulfilled by the Rh/TPPTS system [21]. However, despite the high regioselectivity in hydroformylation, a side reaction occurs which diminishes the overall selectivity. Part of the *n*-1-butene isomerizes under reaction conditions parallel to the hydroformylation reaction to *n*-2-butene, which is not hydroformylated in the presence of Rh/TPPTS under regular reaction conditions.

The reaction temperature to be chosen depends on several aspects. High temperatures favor the activity of the catalyst system and increase the partial pressure of *n*-1-butene (b.p. –6.1 °C) but have a negative impact on the long-term stability of the ligand. As a compromise, a reaction temperature 5–10 °C higher than in the hydroformylation of propene is acceptable. Also, with respect to the partial pressure of *n*-1-butene the overall pressure is lower: about 40 bar has been proven suitable. The stripping column, as the central unit in the process, deserves special attention: in order to remove dissolved butenes and butane completely from the oxo crude product a balance between temperature and pressure conditions has to be established.

The process design corresponds to the RCH/RP process for the hydroformylation of propene; for example, by slight adjustment of the conditions propene as well as *n*-1-butene may be processed in the same unit [21].

Deactivation Phenomena

All commercially applied rhodium/phosphine catalysts deactivate with time, for different reasons and in several ways. The most obvious is a decline in activity, as it directly reduces the unit capacity and frequently also leads to increased consumption of materials as unconverted olefins have to be vented. The reasons are found in the rhodium inventory: there are always some losses which decrease the rhodium concentration in the reaction medium, either by carry-over with the products during thermal separation from the catalyst (homogeneous systems), or by being swept out with the products from the two-phase system. Although these losses normally are in the ppb range with respect to the rhodium concentration in the products, they may well accumulate into substantial losses if the lifetime of the catalyst charge exceeds months or even years. In most kinetic expressions for the reaction rate the rhodium concentration is first-order or close to, thus directly influencing that rate. On the other hand, the formation of inactive rhodium species may leave the rhodium inventory virtually unchanged, although the catalyst loses activity [22]. Finally, the formation of modified phosphines has been proven to occur under reaction conditions, e.g. TPPTS can be converted to propyldisulfophenylphosphine (PDSPP), which acts as a stronger electron donor than TPPTS and thus occupies coordination sites on the rhodium [6].

The deactivation mechanism for TPPTS has been elucidated in some detail. The primary idea of *ortho*-metallation of the phenyl ring has been abandoned in the meantime as it definitely plays no role. Instead the deactivation is initiated by the oxidative insertion of the rhodium metal into the P–C bond of the triphenylphosphine ligand. An analogous mechanism for the TPPTS degradation has been outlined for the homogeneous system with TPP as ligand [23].

In continuous operation phosphorus-containing consecutive products are formed which also influence the activity of the rhodium center and thus contribute to the catalyst deactivation. One of the main degradation products from TPPTS is the sodium salt of *m*-formylbenzene sulfonic acid, which indicates the insertion of the rhodium atom into the P–C bond.

The aryl–rhodium species in which rhodium has replaced one phosphorus atom presumably exists as a phosphido-bridged dimer which is inactive. This compound may subsequently be converted to a series of consecutive products, e.g., alkyldiarylphosphines, which act as catalyst poisons.

Besides the degradation reactions, all phosphines are oxidized by traces of oxygen, which are always present in the olefins introduced. Synthesis gas, generated mainly by partial oxidation of hydrocarbons, may well contain small amounts of oxygen which are removed by special gas purification systems. Nevertheless, oxidation also plays a role in the losses of ligand in long-term operation. A certain concentration of “active” ligand, e.g. phosphorus in the oxidation state +III, is necessary to ensure stability of the rhodium and a sufficiently high n/i ratio; maintenance of this concentration is achieved best by adding small portions of ligand at short intervals over the whole run rather than adding greater quantities of fresh ligand now and then.

At the very beginning it was noticed that some sulfur dioxide together with sulfur-containing components was swept out with the butanals formed, causing partial poisoning of the catalysts in the subsequent hydrogenation steps. The source of the sulfur dioxide is clearly identified today: during sulfonation of TPP with oleum, i.e., in the presence of a surplus of sulfur trioxide, some of the TPP is oxidized to TPPO, yielding sulfur dioxide as a reduced product, which in part is preserved in the neutralized catalyst solution. The problem was resolved by treating the acidic aqueous solution of TPPTS with some inert gas (nitrogen, carbon dioxide), thus leading to complete removal of the sulfur dioxide [24].

The TPPTS catalyst system itself is not sensitive toward sulfur and most of the other common poisons for hydroformylation catalysts. One reason is the continuous withdrawal of organic and other byproducts with the product phase and the vent stream from the decanter (see Figure 1), avoiding the accumulation of poisons in the catalyst solution.

Outlook and Future Developments

The hydroformylation of propene and butene in the presence of an aqueous catalyst phase has proven successful since the early 1980s. In particular, the hydroformylation of propene has acquired merit from the very beginning in 1984 and has encountered virtually no problems, even in large-scale units. Comparison with other hydroformylation processes based on the conventional homogeneous principle has shown some distinct technical and economic advantages:

- phase separation is an elegant and efficient method to recover catalyst and oxo crude;
- space–time yields in biphasic and homogeneous processes are on a comparable level;
- the n/i ratio is very high (95 : 5) and can be shifted if desired;
- losses in rhodium and TPPTS are negligible;
- the absence of thermal strain reduces the formation of high-boiling byproducts;
- the technical equipment is extremely simple and reliable;
- the energy usage system is process-integrated (net energy exporter);
- selectivity is high overall with respect to propene input;
- there are no environmental emissions.

However, despite the advantages cited for the hydroformylation of propene and butene it has to be admitted that the biphasic system also nears its limits when olefins with increasing chain lengths are considered. Due to the decreasing solubility of the olefins in the aqueous catalyst phase, the reaction rate slows down, leading to an unacceptably low space–time yield (please see Figure 3 in Section 2.1).

Several proposals have been published to solve this problem, e.g., by using polyether-substituted triphenylphosphines [25–27] (see also Section 2.2.3.3). These types of phosphines show inverse temperature-dependent solubility in water that enables them to act as thermoregulated phase-transfer ligands [25] (see Section 2.3.5). So far, little is known about their applicability in technical operation. On the other hand, the homogeneous systems are also facing problems with long-chain olefins, but at a different process stage: whereas the hydroformylation still proceeds acceptably, the recovery of the oxo crude by distillation from the catalyst residue generates byproducts and destroys the catalyst or the ligand, respectively. These facts explain the survival of “ancient” cobalt hydroformylation processes for the hydroformylation of C_6–C_{10} olefins until a convenient solution has been found for one or the other variant. It may be noted that Celanese operates a ligand-modified homogeneous rhodium catalyst for hydroformylation of C_6 and C_8 olefins very successfully at its Bay City (TX, USA) plant.

The extension of the biphasic principle to higher olefins may be accomplished by changing the ligand [29], e.g., from TPPTS to bisphosphines, some of which have already proven to be valuable tools to increase the specific activity combined with high n/i selectivity [4]. Increasing the specific (or better: intrinsic) activity of rhodium in the aqueous two-phase system may be coupled with understanding of the relevant mass-transport phenomena. In this case the role of the phase boundaries as a potential barrier for the chemical reaction will have to be carefully analyzed (see Sections 2.3.1, 2.3.4, and 2.4.1.1.2).

The potential of the biphasic system has not been fully elucidated so far, and there is still a broad field for research activity with this simple but highly efficient technique.

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b) Higher Alkenes

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Introduction

The Ruhrchemie/Rhône-Poulenc [1] process for the hydroformylation of short-chain alkenes such as propene and butene (cf. Section 2.4.1.1.3) combines a facile catalyst recycling with high selectivity and sufficiently high conversion rates to provide a commercially viable large-scale manufacturing process for butanal [2] and valeraldehyde [3]. Higher alkenes (> C_8) are not suitable for the RCH/RP process as run in Oberhausen.

Here, we summarize briefly investigations into the two-phase hydroformylation of higher alkenes with aqueous rhodium–triphenylphosphine bisulfonate (Rh–TPPTS) catalyst systems.

Two-Phase Hydroformylation of Higher Alkenes with Rh–TPPTS as Catalyst System

The Unmodified Ruhrchemie/Rhône-Poulenc Process

Few data are available in the academic literature on the Rh–TPPTS catalyst system. This section will provide some information on the effect of various reaction parameters (pressure, P/Rh ratio, rhodium concentration, alkene chain length, etc.) in the two-phase hydroformylation of higher alkenes with the aqueous catalyst system Rh–TPPTS. The alkene *n*-1-hexene was most thoroughly investigated.

Preparation and Effects of the Basic Catalyst $HRh(CO)(TPPTS)_3$ [4]

The conversion versus time diagram (Figure 1) illustrates the dependence of the reaction rate on the chain length of the alkene. The reaction proceeds according to first-order kinetics, i.e., the consumption rate of the substrate alkene is proportional to the concentration of the substrate.

Severe effects have also been determined for the reaction pressure, but especially for the P/Rh ratio: *n*/*iso* selectivities from 38 : 62 to 98 : 2 were observed. A review was recently published [5].

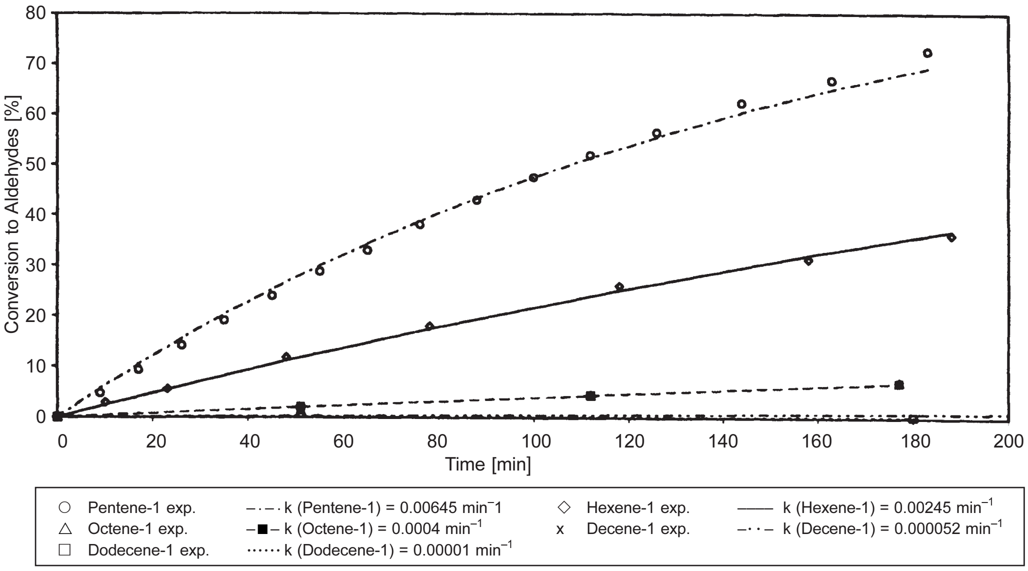

Figure 1 Dependence of reaction rate on chain length of alkenes.

Other Water-Soluble Phosphines

BINAS and BISBIS

Special chelating ligands, such as BINAS (sulfonated 2,2′-bis(diphenylphosphinomethyl)-1,1′-binaphthylene) [6, 7] and BISBIS (sulfonated 2,2′-bis(diphenylphosphinomethyl)-1,1′-biphenyl) [8], were found to be very useful ligands for the twophase hydroformylation of higher alkenes. Under standard conditions with BINAS a relatively high conversion of 36% is achieved (Table 1). In the presence of only 0.24 wt.% of tetradecyltrimethylammonium BINAS in the catalyst phase, the conversion rate rises to 77% (3 h) or 84% (6 h). In addition it should be mentioned that no decrease of the excellent *n*/*iso* ratio of 99 : 1 is observed with BINAS, as opposed to TPPTS.

A high selectivity toward linear aldehydes at a low P/Rh ratio could also be achieved with sulfonated fluorophosphine [tris(*p*-fluorophenyl)phosphine] [9].

Dinuclear rhodium(I) complexes with TPPTS, containing thiolato bridging ligands in aqueous phase, were found to be transformed into the monomer $HRh(CO)(TPPTS)_3$ under reaction conditions [10].

Recycable catalysts based on Rh complexes and xanthene diphosphine ligands were used in the hydroformylation of 1-octene. Amphiphilic diphosphines spontaneously form aggregates that are remarkably stable at elevated temperatures and are specially suitable for the aqueous two-phase catalytic process. The observed TOF in the hydroformylation of 1-octene using ligands that form vesicles was up to 14 times higher compared to ligands that do not form aggregates [11]. Electron microscopy experiments showed that these ligands and their complexes form

Table 1 Comparison of TPPTS and BINAS.

	No additive		***$C_{14}Me_3N$ action***		
	BINAS[a]	***TPPTS***	***BINAS[a]***		***TPPTS***
	3 h	***3 h***	***3 h***	***6 h***	***3 h***
Additive [%]	–	–	0.24	–	0.86
Rate of conversion [%]	36	22	77	84	74
n/i rate[b]	99 : 1	98 : 2	99 : 1	99 : 1	91 : 9

P/Rh ratio 15 : 1.

a) Relative to the whole catalyst solution.

b) Average values from 3 to 30 single experiments (standard conditions; $T = 125$ °C, $p = 2.5$ MPa, Ru concentration = 300–400 ppm, P/Rh ratio = 80–100 : 1, reaction time = 3 h).

There are several methods for the preparation of the active hydroformylation catalyst HRh(CO)(TPPTS)$_3$. In analogy to its homogeneous counterpart , it is possible to synthesize the catalyst directly from RhCl$_3$ and TPPTS under syngas pressure.

vesicles in H_2O if the hydrophobic part of the ligand is large enough. The formed aggregates are stable at elevated temperatures (90 °C), and their presence leads to a significant enhancement of the solubility of 1-octene in aqueous solution. Furthermore, recycling experiments show that the TOF and the high selectivity toward the more valuable linear aldehyde remains the same in four consecutive runs. The aggregates stay intact during the recycling and the active Rh complex is retained in the H_2O-phase quantitatively [12].

Two novel phosphines, tris[*p*-(10-phenyldecyl)phenyl]phosphine and 2,2′-bis{di}-[*p*-(10-phenyldecyl)phenylphosphinomethyl]-1,1′-biphenyl, were successfully synthesized and sulfonated in H_2SO_4. The resulting water-soluble surface active phosphines were applied to the rhodium-catalyzed hydroformylation of higher alkenes. It is found that these two ligands are not only excellent for octene hydroformylation, but catalyze tetradecene hydroformylation under biphasic conditions as well. Rates and selectivities are superior to TP PTS-modified rhodium catalysts under the same reaction conditions [13].

Nonionic tensioactive water-soluble phosphines that act as ligands for rhodium-catalyzed hydroformylation of higher alkenes under biphasic conditions have been tested, too. Phosphines discussed are $P[p\text{-}C_6H_4(OCH_2CH_2)_nOH]_3$ ($n = 18, 25$) and $Ph_2P[p\text{-}C_6H_4(OCH_2CH_2)_nOH]$ ($n = 16, 25$). The rhodium catalyst combined with these ligands gave an average turnover frequency of 182 h^{-1} for 1-hexene. More importantly, recovery and re-use of catalyst is possible because of the inverse temperature-dependent water solubility of the phosphines [14].

Phosphonated Ligands

New and efficient routes to modify phosphines with phosphonic acid groups have been developed. Phosphonate-phosphines showed high solubilities in water and were used to immobilize rhodium catalysts in the aqueous phase of biphasic systems. In the two-phase hydroformylation of propene, some of the novel catalysts showed activities and regioselectivities similar to those of Rh/TPPTS. Amphiphilic Rh/phosphonate-phosphine catalysts were found widely superior to Rh/TPPTS in the hydroformylation of 1-octene [15].

The Combination of Triphenylphosphine Monosulfonate (TPPMS) and Polar Solvents

Several processes for the hydroformylation of higher alkenes have been suggested on the basis of the water-soluble ligand TPPMS. In contrast to TPPTS, which is almost exclusively soluble in water, TPPMS can be used in both aqueous and polar organic media.

Abatjoglou et al. from the Union Carbide Corporation (UCC) presented a homogeneous process for the hydroformylation of higher alkenes, combined with an aqueous two-phase catalyst recovery [16]. The key discovery is that alkali-metal salts of monosulfonated triphenylphosphine form reverse micelles in organic media in the presence of certain solubilizing agents which are stable under the reaction conditions. These systems can easily be induced to separate into a nonpolar product phase and a polar catalyst phase, thereby providing the catalyst recovery typical of two-phase reactions. The separation of the micelles can be accomplished by either raising the temperature or cooling the reaction mixture. In the case of *N*-methylpyrrolidine (NMP)-solubilized systems the addition of water brings about a sharp separation into an organic phase and a catalyst phase. The product phase, however, has to be extracted with water to eliminate traces of catalyst components completely.

Fell et al. published a simplified version of the above-mentioned process design of UCC in which the hydroformylation reaction of 1-tetradecene is performed homogeneously with a Rh/Li–TPPMS catalyst system in the presence of methanol. When the methanol is distilled off after almost complete conversion, the catalyst complex precipitates and can be separated by filtration or extraction with water [17].

The idea of using monosulfonated or monocarboxylated triphenylphosphines in a biphasic reaction medium in the presence of amphiphilic reagents has already been patented, in 1981, by the Johnson–Matthey Corporation. However, the recycling of the catalyst complex published in this patent was not complete so that no technical process could be established in those early days of two-phase hydroformylation [18].

Outlook

What are the major challenges for the two-phase hydroformylation of higher alkenes?

The most important applications of higher oxo products are plasticizer alcohols in the C_8–C_{11} range and synthetic detergent alcohols in the C_{12}–C_{18} range, with a worldwide consumption of 1.5 million tons [19] and 1.2 million tons in 1995, respectively. Compared with cobalt, rhodium as catalyst metal is favorable with respect to the raw material economy and the energy balance in the hydroformylation of higher alkenes. A biphasic hydroformylation process would bear the advantage that the long-chain aldehydes can be separated from the catalyst simply by phase separation. For alkenes above C_{10} the crude aldehyde cannot be separated from the unreacted alkene by distillation. Therefore, such a process would be required to achieve complete conversion in continuous operation.

Since the major raw materials for higher plasticizer alcohols are internal alkenes from polygas units (e.g., diisobutene, tripropenes), this market requires the development of even more efficient biphasic catalyst systems for internal and branched alkenes.

Scientifically, another major challenge is the development of a biphasic hydroformylation process for internal alkenes combining isomerization and hydroformylation of linear internal alkenes and affording predominantly terminal hydroformylation products. Such a technology would be of primary interest for the fine chemical and the detergent alcohol markets.

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19 This figure does not include 2-ethylhexanol. *n*-Butyraldehyde-derived 2-ethylhexanol is by far the most important plasticizer alcohol, with an estimated worldwide consumption of 2.4 million t.

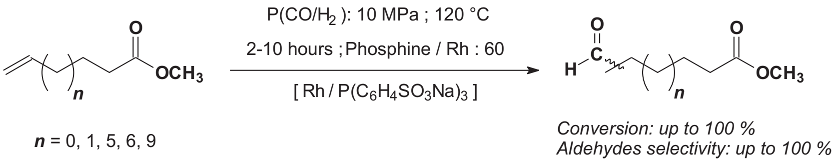
c) Functionalized Alkenes

Eric Monflier

Functionalized olefins can be classified in two groups: the δ-functionalized olefins in which the functional group is not directly branched on the double bond but on an alkyl chain of the olefin as in the case of oct-7-en-1-al or linoleic alcohol, and the α-functionalized olefins in which the functional group is directly branched on the double bond as in the case of methyl acrylate or phenyl vinyl ether. The results described for these two groups will be discussed separately. Hydroformylation of water-soluble olefins in two-phase system with water-insoluble catalysts is far beyond the scope of this chapter and will not be discussed here [1, 2].

Biphasic Hydroformylation of *d*-Functionalized Olefins

Hydroformylation of ω-alkene carboxylic acid methyl esters catalyzed by a Rh/TPPTS system was initially investigated by Fell et al. [Eq. (1)]. As expected in a biphasic medium, low molecular ω-alkene carboxylic acid methyl esters such as methyl 4-pentenoate can be hydroformylated efficiently without any additives whereas methyl esters of higher ω-alkene carboxylic acids such as methyl 13-tetradecenoate require the presence of mass-transfer promoters such as surfactants [3] or chemically modified β-cyclodextrins [4].

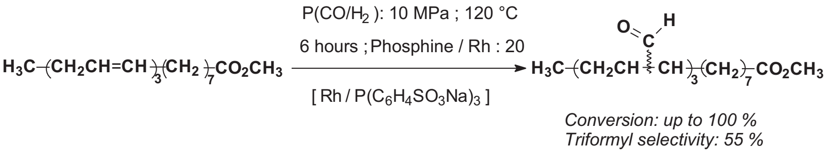


(1)

n = 0, 1, 5, 6, 9

Conversion: up to 100 %
Aldehydes selectivity: up to 100 %

Unsaturated fat chemicals can also be hydroformylated in the presence of surfactants. For instance, the Johnson-Matthey Co. has reported that oleic acid methyl ester or linoleic acid methyl ester can be hydroformylated in micellar media using a water-soluble rhodium complex of monocarboxylated triphenylphosphine as catalyst [5]. Interestingly, linolenic acid methyl ester can be hydroformylated to the triformyl derivative with a selectivity of 55% with a Rh/TPPTS catalytic system in the presence of hexadecyltrimethylammonium bromide [Eq. (2)] [6].

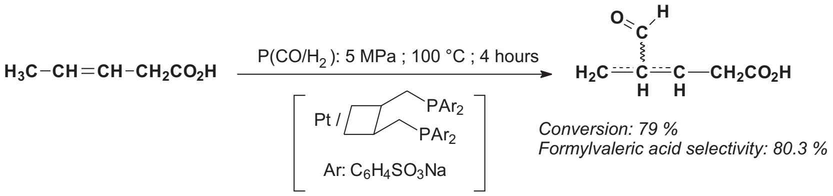


$$\mathrm{H_3C{-}(CH_2CH{=}CH)_3(CH_2)_7CO_2CH_3} \xrightarrow[\mathrm{[\,Rh\,/\,P(C_6H_4SO_3Na)_3\,]}]{\substack{\mathrm{P(CO/H_2):\ 10\ MPa\ ;\ 120\ ^\circ C}\\ \mathrm{6\ hours\ ;\ Phosphine\ /\ Rh\ :\ 20}}} \mathrm{H_3C{-}(CH_2\overset{\overset{O=C-H}{|}}{CH}{-}CH)_3(CH_2)_7CO_2CH_3} \quad (2)$$

Conversion: up to 100 %
Triformyl selectivity: 55 %

Hydroformylation of oleyl alcohol into formylstearyl alcohol has been successfully achieved with a 96.6% yield by using a Rh/TPPTS complex dissolved in an aqueous film supported on a high surface area silica gel [7]. This supported catalyst also made it possible to hydroformylate allyl 9-decenyl ether and 3-methyl-2-(2-pentenyl)-2-cyclopenten-1-one (*cis*-jasmone). However, with the latter substrate, the aldehyde yields did not exceed 38% [8].

The DSM Co. has described an attractive approach for the synthesis of adipic acid or 6-aminocaproic acid precursors by claiming the hydroformylation of 3-pentenoic acid into 5-formylvaleric acid in biphasic medium [Eq. (3)].



(3)

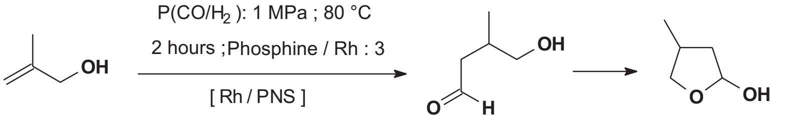
Conversion: 79 %
Formylvaleric acid selectivity: 80.3 %

With a water-soluble platinum complex of tetrasulfonated *trans*-1,2-bis(diphenylphosphinomethylene)cyclobutane as catalyst, the 5-formylvaleric acid selectivity reached 62% [9]. The same catalytic system allows also the hydroformylation of *trans*-3-pentenenitrile with 91.4% selectivity.

Rhodium/poly(enolate-*co*-vinyl alcohol-*co*-vinyl acetate) catalysts have been developed for the selective biphasic hydroformylation of functionalized olefins [10]. Although the conversions were low (< 25%), excellent selectivities for the hydroformylation of methyl 3,3-dimethylpenten-4-onate can be achieved with such water-soluble polymer-anchored rhodium catalysts (see Chapter 7). Indeed, only the linear aldehyde was obtained during the hydroformylation of methyl 3,3-dimethylpenten-4-onate.

To our knowledge, the only industrial application of the water-soluble catalyst for the hydroformylation of δ-functionalized olefins has been developed by Kuraray [11]. In this process, oct-7-en-1-al is hydroformylated into 1,9-nonanedial by using a rhodium catalyst and the monosulfonated triphenylphosphine (cf. also Section 2.4.4.2).

Hydroformylation of various unsarurated alcohols with different catalytic systems has been investigated by two research groups. Ziolkowski et al. have reported the hydroformylation of 1-buten-3-ol, 2-methyl-2-propen-1-ol and 2-buten-1-ol with a catalytic system containing Rh(acac)$(CO)_2$ and the water-soluble phosphine $Ph_2PCH_2CH_2CONHC(CH_3)_2CH_2SO_3Li$ (PNS). In all cases, the main products of the hydroformylation were 2-hydroxytetrahydrofuran derivatives formed via a hydroxyaldehyde cyclization [Eq. (4)] [12].



(4)

Conversion: 93 %
Yield: 91 %

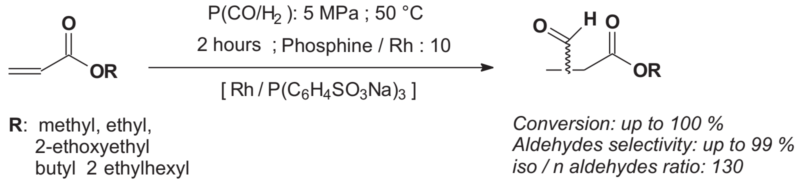
As described by Paganelli et al., hydroformylation of 1,1-diarylallyl alcohols such as 1,1-bis(*p*-fluorophenyl)-2-propenol can be carried out conveniently in a biphasic system using a water-soluble complex formed by a mixture of $[Rh(COD)Cl]_2$ and TPPTS [13, 14] or sulfonated Xantphos [14]. Interestingly, the retroaldolization reaction leading to byproducts seems to take place with more difficulty in a biphasic medium.

A beneficial effect of water on the reaction rate and aldehyde selectivity was observed during the Rh/TPPTS-catalyzed hydroformylation of the water-soluble *N*-allylacetamide. Thus, the reaction rates and aldehyde selectivities in water are much higher than those observed in organic solvents with a Rh/PPh_3 catalyst. Unfortunately, the linear/branched aldehydes ratios were rather low and the water-soluble catalyst cannot be recovered [2].

Surprisingly, 2,5-dimethoxy-2,5-dihydrofuran did not form the expected aldehydes under CO/H_2 pressure (3 MPa) in the presence of the Rh/TPPTS system. Instead of hydroformylation, hydrogenation was the main reaction path in water, where 2,5-dimethoxytetrahydrofuran and its hydrolysis product were obtained. However, hydroformylation occurred when the surface-active phosphine $Ph_2P(CH_2)_{10}PO_3Na_2$ was used [15].

Biphasic Hydroformylation of α-Functionalized Olefins

The first work on α-functionalized olefins was focused on the hydroformylation of acrylic esters [Eq. (5)] [16–19].



(5)

As in the case of *N*-allylacetamide, immobilization of the catalyst in the aqueous phase results in an enhancement of the catalytic activity [17]. Indeed, hydroformylation rates of acrylic esters that are soluble in water were much higher in a biphasic system than those observed under comparable homogeneous conditions. Except for 2-ethylhexyl acrylate, the initial rate was increased by a factor of 2.4, 12, 2.8, and 14 for methyl, ethyl, butyl, and 2-ethoxyethyl acrylate, respectively [18]. The peculiar enhancement of the catalytic activity for the hydroformylation of water-soluble acrylates was attributed to the formation of hydrogen bonding between water and the carboxyl group of the acrylate [19]. The decrease in the activity with 2-ethylhexyl acrylate was due to mass-transfer limitation. As a matter of fact, the hydroformylation of this substrate can be achieved by using an aqueous phase supported rhodium catalyst [18] or chemically modified cyclodextrins [20]. More surprising is the unprecedented observation that immobilizing of the Rh/TPPTS catalyst on a wet silica gel yields an extremely active supported aqueous-phase catalyst for the hydroformylation of a series of acrylic esters [20]. Such an increase in the reaction rate was not observed when the Rh/TPPTS complex was immobilized on polyelectrolyte-coated latex particles [21].

Rhodium-catalyzed hydroformylation of aryl vinyl ethers can be achieved efficiently in the presence of TPPTS [13], water-soluble polymers [10, 22], or human serum albumin as ligand [23]. The conversions were comparable with those reached in a homogeneous medium but the chemoselectivities can be lower. Indeed, at 100 °C, aryl vinyl ethers can be cleaved into the corresponding phenols (up to 11%).

Finally, water-soluble phosphorylated BINAPs were tested as ligands in aqueous biphasic rhodium-catalyzed hydroformylation of vinyl acetate. Compared with catalysts prepared with the parent ligand in a homogeneous medium, the chemo-, regio- and enantioselectivities were markedly lower [24].

Conclusion

Although the scope of the aqueous biphasic hydroformylation of functionalized olefins still needs to be deeply investigated, these few studies demonstrate clearly that functionalized olefins can be hydroformylated efficiently in an aqueous biphasic medium. However, it should be kept in mind that water is not only an inert mobile phase. Water can also act as a reactant or a coordinating solvent that modifies catalytic species. So, in some cases, unexpected increases or decreases in the activity or selectivity can be observed.

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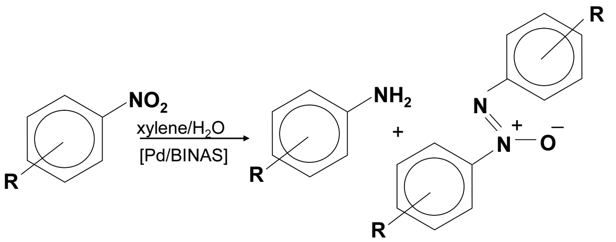
2.4.1.2
Carbonylations

Matthias Beller and Jürgen G. E. Krauter

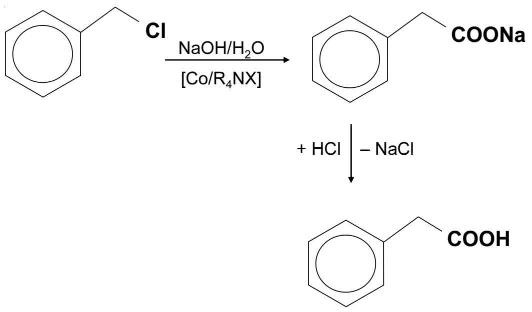
Apart from hydroformylations, the potential advantages of two-phase catalysis for other carbonylation reactions have not been thoroughly evaluated. Only a few examples of carbonylation reactions under biphasic conditions have been described.

Metal-catalyzed *reductive* carbonylation of nitroaromatics using CO has been the subject of intensive investigation in recent years because of the commercial importance of amines, urethanes, and isocyanates [1]. Biphasic operation could offer interesting horizons regarding the ease of catalyst recycling. Thus, palladium catalysts have been applied in the presence of water-soluble ligands such as TPPTS or BINAS [2] for the carbonylation of substituted nitroaromatics (Scheme 1).

Interestingly, the nitro group can be selectively reduced to an amino group at TONs of some thousands, even in the presence of halide substituents or a vinyl group [3] although recycling of the catalyst was not possible due to decompsition. The reductive carbonylation of 5-hydroxymethylfurfural under aqueous biphasic conditions yields the 5-methyl derivative instead of dicarbonylation [4].



Scheme 1 Biphasic reaction of nitroaromatics.

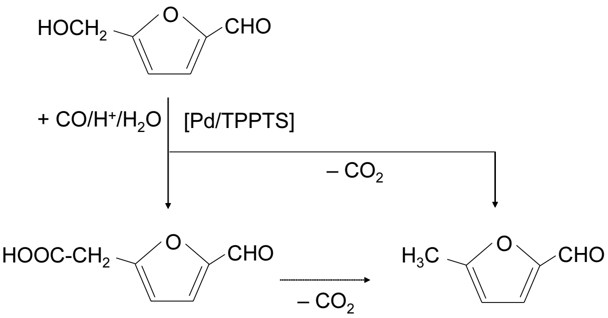


Scheme 2 Hydrocarbonylation of benzyl chloride.

Mechanistically closely related are hydroxycarbonylations (or carboxylations) of alkyl, ary, benzyl, or allyl halides [5]. Thus, aryl iodides have been carbonylated with various Pd salts in water – lacking phosphine ligands. With TONs of 100 000 the results are remarkable although the reaction is not truly biphasic. When ligands such as TPPTS are used the activity of the Pd catalyst was decreased considerably. The hydrocarbonylation of chloroarenes to the corresponding carboxylic acids, especially the commercially interesting phenylacetic acids, proceeds via the Na salts with $Co_2(CO)_8$ and a benzyltrialkylammonium surfactant in a biphasic medium employing diphenyl ether and aqueous 40% NaOH as a solvent (Scheme 2).

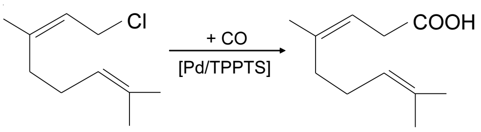
Another proposal from the industry used a Pd catalyst dissolved in aqueous TPPTS, yieding turnover frequencies (TOFs) of 135 h^{-1} [6]. Apart from aryl–X derivatives and, more interestingly from an industrial point of view, metal-catalyzed carbonylation of substituted benzyl halides to give the corresponding phenylacetic acids has been investigated [7]. Two-phase systems are applied with the catalyst and substrate being dissolved in the organic phase and the product formed is dissolved in an excess of alkaline aqueous solution. Despite significant disadvantages such as indispensable addition of phase-transfer agents and additional salt as a byproduct, the carbonylation of benzyl chloride to give phenaylacetc acid for use in perfume constitutents and pesticides has been reported to be practiced on a commercial scale by Montedison [8]. Other metal catalysts besides Co carbonyl which have been utilized for biphasic carbonylation of benzylic halides to carboxylic acids under phase-transfer conditions include Pd(0)– and Ni–carbonyl complexes [9]. It is assumed that catalysis takes place in the organic phase in all these reactions. However, by the use of the water-soluble ligand TPPMS (see Section 2.2.3.2) a Pd catalyst which is active in the water phase is formed [10]. Nevertheless, the addition of surfactants is effective in accelerating this reaction. This effect is attributed not to a simple surface activation but to a counterphase-transfer catalysis.

On the bases of the Pd-catalyzed carbonylation of benzylic halides Sheldon et al. investigated the functionalization of 5-hydroxymethylfurfural to 5-formylfuran 2-acetic acid in an aqueous medium in the presence of a water-soluble Pd/TPPTS catalyst (Scheme 3) [4]. They found that the hydroxy group displays similar reactivity under acidic conditions as the benzylic halides.



Scheme 3 Carbonylation of 5-hydroxymethylfurfural.

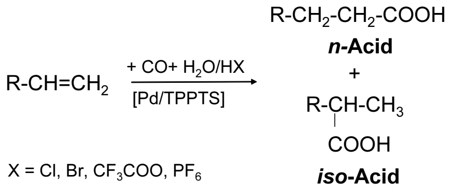
In general, for carbonylations, Pd is preferable to Ni as the catalyst metal with respect of catalyst efficiency. Thus Okano et al. [10] described some other efficient Pd-catalyzed carbonylations of allyl chloride and substituted allylic halides (e.g., Scheme 4).



Scheme 4 Carbonylation of allylic chlorides.

In greater detail, the water-soluble Pd complex [$PdCl_2TPPMS$] has been used in a two-phase system consisting of aqueous NaOH/benzene. Clearly, the isomerization depends on the concentration of the base and was therefore suppressed by a method of continuous addition to the aqueous medium.

Biphasic hydrocarboxylations of alkenes yield carboxylic acids with a typical linear to branched (*n/i*) ratio which ranges from 1 to 1.4 (Scheme 5).



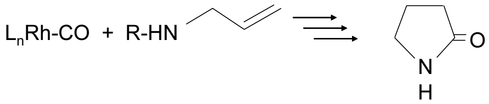
$$\text{R-CH=CH}_2 \xrightarrow[\text{[Pd/TPPTS]}]{\text{+ CO+ H}_2\text{O/HX}} \underset{\textbf{\textit{n}-Acid}}{\text{R-CH}_2\text{-CH}_2\text{-COOH}} + \underset{\textbf{\textit{iso}-Acid}}{\underset{\text{COOH}}{\text{R-}\underset{|}{\text{C}}\text{H-CH}_3}}$$

X = Cl, Br, CF_3COO, PF_6

Scheme 5 Hydrocarboxylations of alkenes.

A Brønsted acid HX may be used as a co-catalyst. Long-chain alkenes give only insufficient conversion due to low solubility and isomerization side reactions. In order to overcome these problems the addition of co-solvents (such as *β*-cyclodextrins; cf. Section 2.2.3.3) was recommended. Their advantageous effect was rationalized by a host–guest complex of the cyclic carbohydrate and the alkene feed which prevents isomerization of the double bond [5].

The biphasic carbonylation of isopropylallylamines leads to *N*-isopropylbutyrolactam, whereas with syngas the competitive hydroformylation yields the *N*-isopropylpyrrolidine (Scheme 6) [11]. In this case, water under the conditions of the water-gas shift reaction serves as a hydrogen source.



Scheme 6 Carbonylation of isopropylallyamine.

So far, nearly all the reported reactions in two-phase systems suffer similarly to their homogeneous counterparts from low catalyst efficiency. Thus it was predicted for the future that careful design of water-soluble catalyst sytems will make it possible to overcome these problems, and indeed some recent protocols describe the formation of phenylacetic acid or ibuprofen on a semi-technological scale [5, 12].

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2.4.2
Hydrogenation and Hydrogenolysis

2.4.2.1
Hydrogenation

Ferenc Joó and Ágnes Kathó

2.4.2.1.1
Introduction

Hydrogenation has been *the* prototype reaction of homogeneous catalysis by transition metal complexes [1].The number of papers and patents on homogeneous hydrogenation is enormous and this reaction is treated in detail in numerous reviews and monographs [2–4].

Being a highly polar solvent, water is *not* a good medium in which to dissolve molecular hydrogen and the usual substrates of catalytic hydrogenations, mostly apolar organics. Conversely, its immiscibility with many of the common organic solvents makes possible the realization of hydrogenation processes in biphasic solvent systems. A specific value of water as solvent lies in the fact that there are catalysts (such as $K_3[Co(CN)_5]$) and substrates (e.g., carbohydrates) which do not dissolve in common nonpolar organic solvents.

Recent research concerning the application of supercritical (sc) fluids and ionic liquids (IL) as solvents in homogeneous catalysis, [5, 6] opened the way to the development of biphasic water/$scCO_2$ [7] and water/IL [8] systems for the hydrogenation of various substrates with water-soluble catalysts (see also Chapters 5 and 6).

2.4.2.1.2
Catalysts and Mechanisms of Hydrogenation in Aqueous Solution

Solubility of the catalysts in water can be due either to their *overall* charge or to their water-soluble ligands. Most frequently, derivatives of well-known tertiary phosphines (modified by sulfonation, carboxylation, phosphonation, etc.) serve as such ligands (structures **1**–**16**). Among these, *sulfonated* arylphosphines are easily available, stable and well soluble in water over a wide pH range.

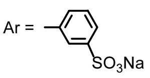
Obviously, there is a great deal of analogy between the mechanisms of hydrogen activation and hydrogenation in aqueous and nonaqueous systems. The most common made of activation of dihydrogen is its homolytic splitting by oxidative addition [Eq. (1)].

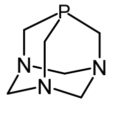
$$[RhCl(TPPMS)_3] + H_2 = [H_2RhCl(TPPMS)_3] \qquad (1)$$

Aqueous organometallic catalysis, however, is not a mere duplication of what had already been observed in organic solvents, and indeed, special effects of the

Ph_nPAr_{3-n}

n=2; TPPMS, **1**
n=0; TPPTS, **2**

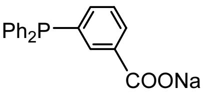




3

$Ph_2P\text{-}(CH_2)_n\text{-}COONa$

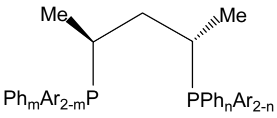
n=5 HEXNa, **4**
n=7 OCTNa, **5**

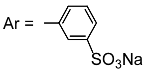


6

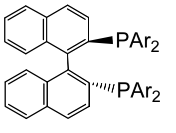
$P[CH_2CH_2O(CH_2CH_2O)_nCH_2CH_2OCH_3]_3$

n=33, **7**

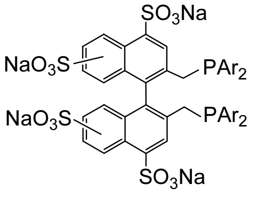




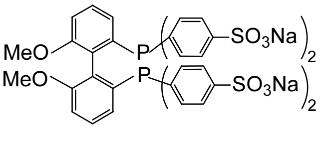
m=2 n=2 BDPP, **8**
m=2 n=1 $BDPP_{MS}$, **9**
m=1 n=1 $BDPP_{DS}$, **10**
m=0 n=1 $BDPP_{TRS}$, **11**
m=0 n=0 $BDPP_{TS}$, **12**



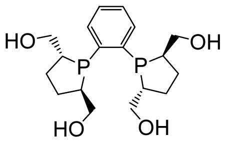
$BINAP_{TS}$ **13**



BINAS, **14**



MeO-BIPHEP-S, **15**



BASPHOS **16**

aqueous solvent can be encountered. For example, in the oxidative addition of H_2 to *trans*-[IrCl(CO)(TPPMS)$_2$] yielding *trans*-[H_2IrCl(CO)(TPPMS)$_2$] a change of the solvent from toluene to water brought about a 50-fold increase in the reaction rate [9]. Such a great increase in rate should be a consequence of water favoring a polar transition state.

Many transition metal hydrides are sufficiently acidic to undergo proton dissociation in the presence of bases or in solvents of suitable solvation power [10]. Whereas in benzene solutions formation of [HRuCl(PPh$_3$)$_3$] takes place only in the presence of an added base such as triethylamine [Eq. (2)], reactions of $[RuCl_2(TPPMS)_2]_2$ with H_2 in water are spontaneous [Eqs. (3)–(5)]. In addition to the temperature and phosphine excess, positions of equilibria (3)–(5) depend critically on the pH of the solution [11].

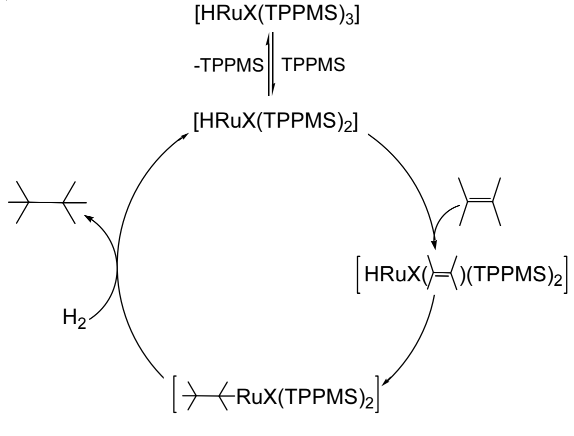
$$[RuCl_2(PPh_3)_3] + H_2 + Et_3N \rightarrow [HRuCl(PPh_3)_3] + Et_3NH^+ + Cl^- \tag{2}$$

$$[RuCl_2(TPPMS)_2]_2 + 2\ H_2 \rightleftharpoons [HRuCl(TPPMS)_2]_2 + 2\ H^+ + 2\ Cl^- \tag{3}$$

$$[RuCl_2(TPPMS)_2]_2 + 2\ H_2 + 2\ TPPMS \rightleftharpoons 2\ [HRuCl(TPPMS)_3] + 2\ H^+ + 2\ Cl^- \tag{4}$$

$$[RuCl_2(TPPMS)_2]_2 + 4\ H_2 + 4\ TPPMS \rightleftharpoons 2\ [H_2Ru(TPPMS)_4] + 4\ H^+ + 4\ Cl^- \tag{5}$$

$[RuCl_2(TPPMS)_2]_2$ is an active catalyst (precursor) for the hydrogenation of water-soluble olefins, such as maleic, fumaric, and crotonic acids. For these hydrogenations detailed kinetic studies [12] revealed the same reaction mechanism as had been suggested earlier for the hydrogenation of maleic acid in DMF solutions catalyzed by $[RuCl_2(PPh_3)_3]$ [4] (Scheme 1). It could be concluded that neither the sulfonation of the phosphine ligand nor the replacement of an organic solvent by water had any effect on the reaction mechanism of alkene hydrogenation by the Ru(II)–phosphine catalysts.



Scheme 1 Mechanism for $[HRuX(TPPMS)_2]_2$-catalyzed hydrogenation of water-soluble olefins.

2.4.2.1.2
Hydrogenation of Alkenes, Alkynes, and Arenes

Several copper, silver, ruthenium, rhodium, and cobalt compounds (such as $RuCl_3 \cdot aq$, $[RuCl_4(bipy)]^{2-}$ (bipy = 2,2′-bipyridine), $RhCl_3 \cdot aq$, bis(dimethylglyoximato)cobalt derivatives (cobaloximes), etc.) have been found to catalyze hydrogenations in aqueous solutions [4]. Although important for the early research into homogeneous catalysis, these catalysts did not gain synthetic significance.

$[HCo(CN)_5]^{3-}$ is readily formed under mild conditions from $Co(CN)_2$, KCN, and H_2 [Eqs. (6) and (7)]. It is an active catalyst for the hydrogenation of a variety of unsaturated substrates but the catalysis suffers from several drawbacks such as the rapid "aging" of the catalyst with a loss of activity, and the necessity of using highly basic aqueous solutions.

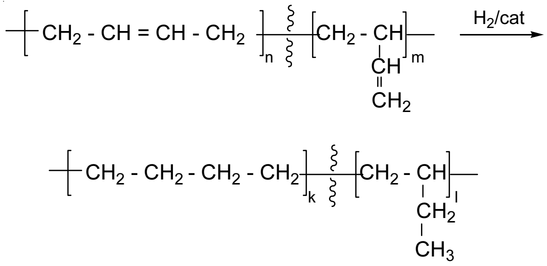
$$Co(CN)_2 + 3\ KCN \rightleftharpoons K_3[Co(CN)_5] \tag{6}$$

$$2\ K_3[Co(CN)_5] + H_2 = 2\ K_3[HCo(CN)_5] \tag{7}$$

Conjugated dienes (such as 2,4-hexadienoic acid or sorbic acid) and polyenes can be selectively hydrogenated to monoenes; unactivated alkenes are totally unreactive [13]. Unfortunately, the possibilities for modification of the catalyst by ligand alteration are very restricted [14].

Selective hydrogenation of sorbic acid to *trans*-3-hexenoic acid was also achieved with a $[Ru(CO)(Cp^*)\{P(CH_2CH_2CH_2OH)_3\}][CF_3SO_3]$ ($Cp^* = \eta^5$-C_5Me_5) catalyst [15].

Hydrogenation of polymers results in improved thermal and oxidative stability. In the hydrogenation of polybutadiene using the $[RhCl(\mathbf{4})_2]_2$ and $[RhCl(\mathbf{5})_2]_2$ catalysts, the pendant (terminal) vinyl units were hydrogenated preferentially over the internal double bonds [Eq. (8)] [16].



(8)

The catalytic modification of lipid membranes, either in model systems (liposomes) or in living cells [17], is a special application of homogeneous hydrogenation of olefins in aqueous media. An ideal catalyst efficiently reduces the unsaturated fatty acid units in the polar lipids at low temperatures (0–40 °C) in an aqueous environment, does not effect transformations other than hydrogenation, can be totally removed from the cell after the reaction is completed, and has no "self-effect", such as toxicity. So far the most investigated homogeneous catalyst for biomembrane hydrogenation is $[Pd(QS)_2]$, QS = 1,2-dioxy-9,10-anthraquinone-3-sulfonic acid (Alizarin Red) [18]. Such biological conversions are treated in more detail in Section 2.4.7.

In aqueous solution *mer*-$[Ir(H)(H)Cl(PMe_3)_3]$ catalyzed the hydrogenation of various alkynes to alkanes [19].

Hydridoarene clusters of Rh and Ru are moderately active catalysts of hydrogenation of simple olefins [20]. Conversely, benzene and monosubstituted benzenes can be efficiently hydrogenated in aqueous biphasic systems with hydridoareneruthenium cluster catalysts, such as $[Ru_3(\mu_2\text{-}H)_2(\mu_2\text{-}OH)(\mu_3\text{-}O)(\eta^6\text{-}C_6H_6)(\eta^6\text{-}C_6Me_6)_2]^+$ [21].

Lignin phenols were hydrogenated to the corresponding cyclohexanols with Ru(II)/TPPMS or TPPTS catalysts, resulting in the inhibition of the light-induced yellowing of lignin and lignin-rich wood pulps [22]. A recent study [23] called attention to the possible formation of metal colloids in aqueous arene hydrogenations.

The reaction rates and selectivities of enantioselective hydrogenations in water are often much inferior to those of analogous systems using organic solvents [24]. Among the tertiary phosphine ligands for enantioselective hydrogenation in aqueous solutions are structures **8**–**16** (above).

The water-soluble variants of the highly successful Ru(II)–BINAP catalyst have been prepared using the 5,5′-disulfonato-BINAP [25], and the tetrasulfonate $BINAP_{TS}$ (**13**) ligands [26]. In water, $[Ru(R\text{-}BINAP_{TS})Cl_2]$ catalyzed the hydrogenation of (*Z*)-α-acetamidocinnamic and (*Z*)-α-acetamidoacrylic acid with 87.7% (*R*) and 68.5% (*R*) *ee*, respectively. The water-soluble catalyst showed the same dependence on hydrogen pressure as the parent $[Ru(BINAP)Cl_2]$ (a sharp decline of *ee* with increasing p_{H2} [26]). The cationic [Rh(BASPHOS, **16**)(COD)]$[BF_4]$ catalyst showed 99.6% *ee* in the hydrogenation of (*Z*)-α-acetamidoacrylic acid [27].

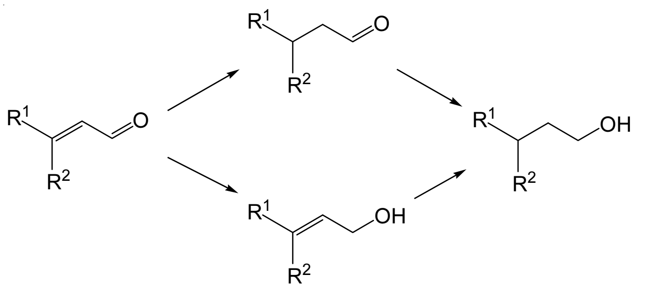
Water-soluble atropisomeric diphosphines, such as the (*S*)-(+)- and (*R*)-(–)-MeO-BIPHEP tetrasulfonate (15) were used as components of Ru(II)- and Rh(I)-based hydrogenation catalysts [28]. In some cases high substrate/catalyst ratios could be used (up to 10 000 : 1), a strong requirement for practical applications [29].

The solubility of hydrogen in water is $8 \cdot 10^{-4}$ M, which is about 20% of the solubility in MeOH, $3.86 \cdot 10^{-3}$ M (both at 20 °C, 0.1 MPa total pressure [30]). The limited solubility of H_2 may influence both the chemoselectivity (hydrogenation versus isomerization of olefins) [31] and the enantioselectivity [26, 32] of a given reaction.

2.4.2.1.3
Hydrogenation of Compounds with C=O and C=N Bonds

Several water-soluble ruthenium complexes, with P = TPPMS, TPPTS, or PTA ligands (cf. Section 2.2.3.2), catalyze the selective reduction of crotonaldehyde, 3-methyl-2-butenal (prenal), and *trans*-cinnamaldehyde to the corresponding unsaturated alcohols (Scheme 2) [33–36]. Chemical yields are often close to quantitative in reasonable times and the selectivity toward the allylic alcohol is very high (> 95%). The selectivity of the reactions is critically influenced by the pH of the aqueous phase [11] as well as by the H_2 pressure [37]. The hydrogenation of propionaldehyde, catalyzed by Ru(II)/TPPTS complexes, was dramatically accelerated by the addition of inorganic salts [38], too. In sharp contrast to the Ru(II)-based catalysts, in hydrogenation of unsaturated aldehydes rhodium(I) complexes preferentially promote the reaction of the C=C double bond, although with incomplete selectivity [33, 39].

Both aliphatic and aromatic unsaturated aldehydes were reduced exclusively to unsaturated alcohols by hydrogen transfer from aqueous sodium formate in a two-phase system with or without an organic solvent. The reactions proceeded smoothly with either $[RuCl_2(TPPMS)_2]$ [40] or $[RuCl_2(PTA)_4]$ catalyst [35].

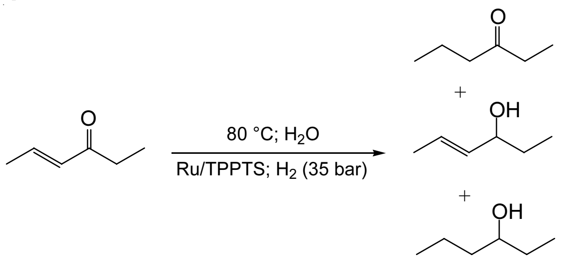


e. g. $R^1 = R^2 = Me$; $R^1 = Ph$, $R^2 = H$

Scheme 2 Selective reduction of unsaturated aldehydes to alcohols, catalyzed by water-soluble Ru complexes.

Hydrogenation of ketones is less facile and less selective than the reduction of aldehydes. $[H_2Ru(TPPTS)_4]$ proved to be an active catalyst in hydrogenation of 2-butanone, cyclohexanone, and benzylacetone (80 °C, 3.5 MPa H_2) [34]. The same catalyst was also rather selective toward the formation of the saturated ketone in the hydrogenation of *trans*-4-hexen-3-one [Eq. (9)], yielding only 2–7% of 3-hexanol. Similar C=C/C=O selectivity was found with the $[(C_5R_5)RuCl(PTA)_2]$ (R = H or CH_3) catalysts, too [41].

Importantly, ethyl and methyl acetoacetate were hydrogenated with Ru(II)/5,5′-disulfonato-BINAP and Ru(II)/MeOBIPHEP-S (**15**) with 91% *ee* and 93% *ee*, respectively [28].



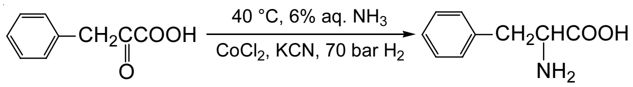
(9)

The organometallic aqua complex $[Ir(Cp^*)(H_2O)_3]^{2+}$ served as a suitable catalyst precursor for the hydrogenation of water-soluble aldehydes, ketones, and olefins [42]. $[Ru(bipy)(\eta^6\text{-}C_6Me_6)(H_2O)]^{2+}$ [43] and $[Ir(bipy)(Cp^*)(H_2O)]$ [44] were active in the hydrogenation of various ketones by hydrogen transfer from aqueous sodium formate. In hydrogen-transfer reductions of acetophenone derivatives in aqueous or biphasic systems 96% *ee* was obtained with $[Ru(p\text{-cymene})Cl]_2$ + (*S*)-proline amides [45], 94% *ee* with $[MCl_2(Cp^*)]_2$ (M = Rh, Ir) + water-soluble aminosulfonamides [46], and 84% *ee* with phosphonated N,N′-dimethyl-1,2-diphenylethane-1,2-diamine ligands [47].

Efficient hydrogenations of carbohydrates such as fructose, D-glucose, and D-mannose was achieved with $[HRuCl(TPPTS)_3]$ and with Ru(II)/TPPMS and Ru(II)/TPPTS catalysts prepared in situ [12, 48, 49].

Imines, such as *N*-benzylacetophenoneimine, are relatively stable to hydrolysis and were hydrogenated in water/ethyl acetate two-phase solvent mixtures [50, 51]. In a benzene – AOT – water reverse micellar solution (AOT = bis(2-ethylhexyl)-sulfosuccinate), $[Rh(NBD)(BDPP)]^+$ catalyzed the reaction with 82% *ee*, compared to the 68% *ee* in neat benzene [52].

Ketoximes and oximes of 2-oxo acids are hydrogenated to amines [53]. 2-Amino acids can be prepared in high yields by reductive amination of 2-oxo acids in an aqueous NH_3 solution [Eq. (10)] [54]. Aromatic aldehydes were converted with high selectivity to benzylamines by reductive amination with aqueous ammonia catalyzed by a Rh(I)/TPPTS catalyst prepared in situ [55]. In a related, ingenious one-pot process, alkenes were directly converted to primary amines by sequential hydroformylation, condensation with aqueous ammonia, and hydrogenation of the resulting imines [56].

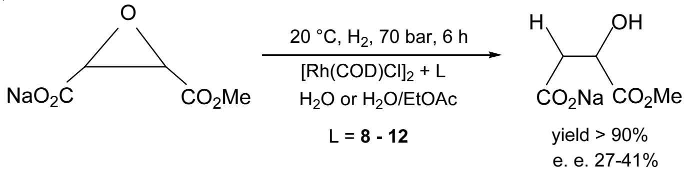


(10)

2.4.2.1.4
Hydrogenolysis of C–O, C–N, C–S, and C–Halogen Bonds

Hydrogenolysis of allyl acetate with $[PdCl_2L_2]$ (L = **1**, **6**, **7**) catalyst proceeded smoothly in heptane/aqueous sodium formate mixtures at 80 °C [57]. The catalyst, formed in situ from $[Pd(OAc)_2]$ and TPPTS, could be used for the selective removal of allylic protecting groups; such closely related protecting groups as dimethylallylcarbamates and allyloxycarbonates could also be distinguished [58, 59].

Asymmetric hydrogenolysis of sodium *cis*-epoxysuccinates leads to malic acid derivatives which are useful building blocks in natural product synthesis [Eq. (11)] [60].



(11)

The removal of sulfur from petroleum is commonly achieved by hydrogenation on heterogeneous catalysts (in a hydrodesulfurization, or HDS, process) but a few homogeneously catalyzed reactions are also known [61, 62]. For biphasic processes, see Section 2.4.2.2.

Hydrogenolysis of the carbon–halogen bond is an important reaction, both from synthetic and from environmental points of view. The results of the early experiments with $[HCo(CN)_5]^{3-}$ as catalyst are summarized in Ref. [4]. A variety of organic halides could be effectively dehalogenated with aqueous sodium formate with $[PdCl_2L_2]$ (L = various sulfonated phosphines) [57], $[RuCl_2(TPPMS)_2]_2$ and $[Ru(H_2O)_3(PTA)_3]^{2+}$ [63], and $[Ir(bipy)(Cp^*)(H_2O)]$ [64] catalysts.

2.4.2.1.5
Miscellaneous Hydrogenations

Hydrogenation of nitro compounds to amines can be achieved with $[HCo(CN)_5]^{3-}$ as catalyst; the reaction is often accompanied by reductive dimerization [4]. The complexes prepared from $PdCl_2$ and TPPTS or BINAS (**14**) catalyzed the selective hydrogenation of nitroarenes to anilines at 100 °C under 2 MPa CO [65]. Catalytic hydrogenation of chloronitroaromatics often leads to dehalogenation. Importantly, in DMSO-containing water, the $[Pd(OAc)_2]$ + TPPTS catalyst hydrogenated 5-chloro-2-nitrophenol to 5-chloro-2-aminophenol with outstanding selectivity [66]. Anilines can be obtained from nitroarenes under water-gas shift (WGS) conditions, too [Eq. (12)] [67]. $[Rh_6(CO)_{16}]$ [68] and $[Ru_3(CO)_{12}]$ (with added aliphatic amines [69]) are among the most active catalysts.

$$PhNO_2 + 3\ CO + H_2O \rightarrow PhNH_2 + 3\ CO_2 \tag{12}$$

Hydrogenation of carbon dioxide, bicarbonates, and carbonates can also be achieved in aqueous solutions [70–73]. Up till now, however, only formic acid and/or formate salts were observed as the sole products of these hydrogenations. An application as a CO_2 sink is not in sight.

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2.4.2.2

Hydrogenation, Hydrogenolysis, and Hydrodesulfurization of Thiophenes

Claudio Bianchini and Andrea Meli

2.4.2.2.1

Introduction

Hydrodesulfurization [HDS, Eq. (1)] is the process by which sulfur is removed from fossil materials upon treatment with a high pressure of H_2 (3.5–17 MPa) at high temperature (300–425 °C) in the presence of *heterogeneous* catalysts, generally transition metal sulfides (Mo, W, Co, Ni) supported on alumina [1]. About 90% of the sulfur in fossil materials is contained in thiophenic molecules, which comprise an enormous variety of substituted thiophenes, and benzo[*b*]thiophenes, dibenzo[*b,d*]thiophenes as well as other fused-ring thiophenes, most of which are generally less easily desulfurized over heterogeneous catalysts than any other sulfur compound in petroleum feedstocks (e.g., thiols, sulfide, and disulfides).

$$C_aH_bS + c\,H_2 \rightarrow H_2S + C_aH_d \qquad (1)$$

The current HDS technologies are capable of reducing the sulfur contents in gasoline and diesel fuel to the marketing limits (< 50 ppm in 2005) [2]. This achievement requires a high consumption of energy, with consequent emission of greenhouse gases, and large quantities of hydrogen.

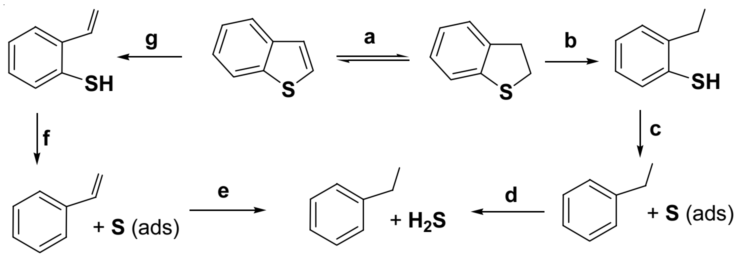
Since all the problems affecting HDS are destined to get worse, due to the increase in sulfur levels in the global supplies of crude over the next decade [3], intensive research efforts are being devoted to both improve traditional hydrotreating catalysis and develop alternative strategies for achieving low and ultra-low sulfur in fuels.

Most alternative approaches to desulfurization of sulfur compounds contained in raw oils involve multiphase systems and reactors for processes such as: oxidation to water-soluble sulfones catalyzed by either metal compounds or protic acids [4]; ultrasonic degradation, using shock waves to break carbon–sulfur bonds [5]; biodesulfurization using a series of enzyme-catalyzed reactions [3]; liquid–liquid extraction using substrates capable of forming hydrocarbon-insoluble adducts with thiophenes [6]; degradation by means of supercritical water [7]; or hydrogenation in multiphase systems using homogeneous or heterogenized single-metal sites [8].

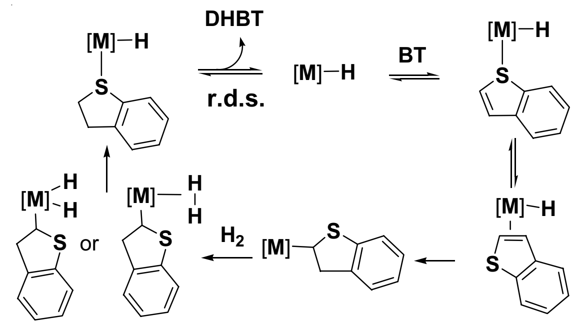
Reference to important work is provided in this section, which, however, is exclusively concerned with hydrogenation reactions of thiophenes either in aqueous biphasic systems, wherein the metal catalyst resides in the aqueous phase and can be recycled by phase separation, or in liquid–solid systems wherein the solid phase is constituted of a heterogenized metal catalyst that can be recycled by filtration.

2.4.2.2.2
Hydrogenation Reactions

The principal mechanisms proposed for the heterogeneous HDS of a prototypical thiophenic molecule, namely benzo[*b*]thiophene (BT), are illustrated in Scheme 1. The hydrogenation of C–C double bonds occurs in step **a**, involving the regioselective reduction of BT to dihydrobenzo[*b*]thiophene (DHBT), as well as in step **e**, where styrene is reduced to ethylbenzene [1].



Scheme 1 Heterogeneous HDS of benzo[*b*]thiophene.



Scheme 2 Hycrogenation of benzo[*b*]-thiophene catalyzed by metal complexes (r.d.s. = rate determing step).

Irrespective of the phase system (homogeneous, aqueous biphasic, heterogeneous single-site), the hydrogenation mechanisms of thiophene (T) or BT catalyzed by metal complexes comprise the usual steps of H_2 oxidative addition, η^2-C,C coordination of the substrate, hydride transfer to form dihydrobenzothienyl, and elimination of DHBT by hydride/dihydrobenzothienyl reductive coupling (Scheme 2) [8].

Hydrogenation in Aqueous Biphasic Systems with Water-Soluble Metal Catalysts

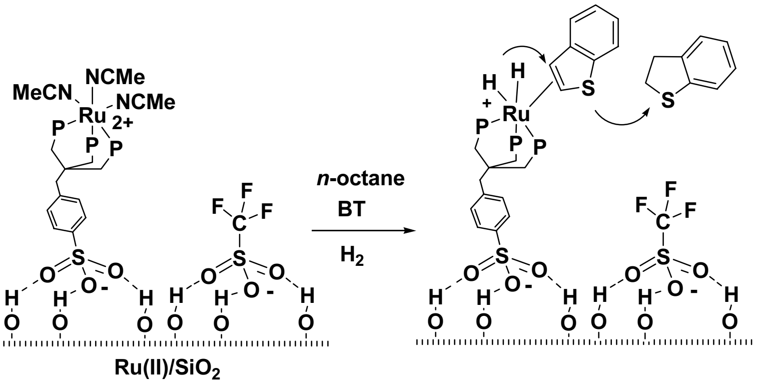
The aqueous biphasic hydrogenation of T or BT to the corresponding cyclic thioether was primarily achieved with the use of water-soluble ruthenium(II) catalysts supported by triphenylphosphine trisulfonate (TPPTS) or triphenylphosphine monosulfonate (TPPMS) ligands [9] (see Section 2.2.3.2). The reactions were performed in water/decalin under relatively harsh experimental conditions (130–170 °C, 7–11 MPa H_2) leading to the selective reduction of the heterocyclic ring. It was observed that nitrogen compounds did not inhibit the hydrogenation of either T or BT. In some cases, in fact, a promoting effect was observed.

Efficient and robust rhodium and ruthenium catalysts for the hydrogenation of BT to DHBT have been obtained using the backbone-sulfonated polyphosphines $NaO_3S(C_6H_4)CH_2)_2C(CH_2PPh_2)_2$ (Na_2DPPPDS) [10] and $NaO_3S(C_6H_4)CH_2C(CH_2PPh_2)_3$ (NaSULPHOS) [11]. The ruthenium(II) binuclear complex Na[{Ru(SULPHOS)}$_2$(μ-Cl)$_3$] [12] and the mononuclear complex [Ru(MeCN)$_3$(SULPHOS)](SO_3CF_3) [13] showed comparable activity in water/decalin or water/*n*-heptane, suggesting the formation of the same catalytically active species.

Hydrogenation in Liquid–Solid Systems with Heterogenized Metal Catalysts

The first attempts to hydrogenate sulfur heterocycles with a supported metal catalyst date back to 1985 when Fish reported that $Rh(PPh_3)_3Cl$ tethered to 2% crosslinked phosphinated polystyrene-divinylbenzene was able to selectively hydrogenate various heteroaromatics, including BT to DHBT (benzene, 85 °C, ca. 2 MPa H_2) with rates three times faster than those observed in homogeneous phase with $Rh(PPh_3)_3Cl$ [14]. This rate enhancement was attributed to steric requirements surrounding the active metal center in the tethered complex, which would favor the coordination of the heterocycles by disfavoring that of PPh_3.

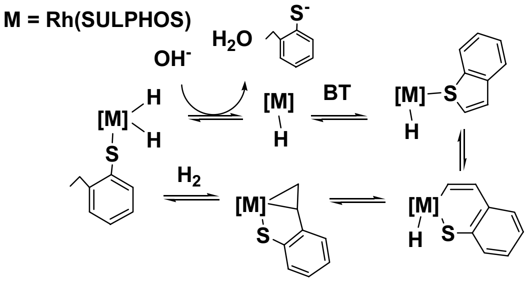
The most active and fully recyclable single-site catalyst for the hydrogenation of thiophenes in naphthas or model hydrocarbon solvents is still the silica-supported single-site complex [Ru(NCMe)$_3$(SULPHOS)](OSO_2CF_3)/SiO_2 [15]. Upon hydrogenation (3 MPa H_2), this Ru(II) complex forms a very active catalyst for the selective hydrogenation of BT to DHBT with a TOF as high as 2000 mol of BT converted (mol of catalyst · h)$^{-1}$ (Scheme 3). Remarkably, the TOF did not practically change even when a new feed containing 2000 equiv of BT in 2 ml of *n*-octane was injected into the reactor after 1 h reaction, showing that DHBT does not compete with BT for coordination to ruthenium. Unlike BT and T, DBT was not hydrogenated by any of the catalysts investigated irrespective of the metal oxidation state or the phase system.



Scheme 3 Activation of the silica-supported Ru(II) complex catalyst and hydrogenation of BT.

2.4.2.2.3
Hydrogenolysis/Desulfurization Reactions

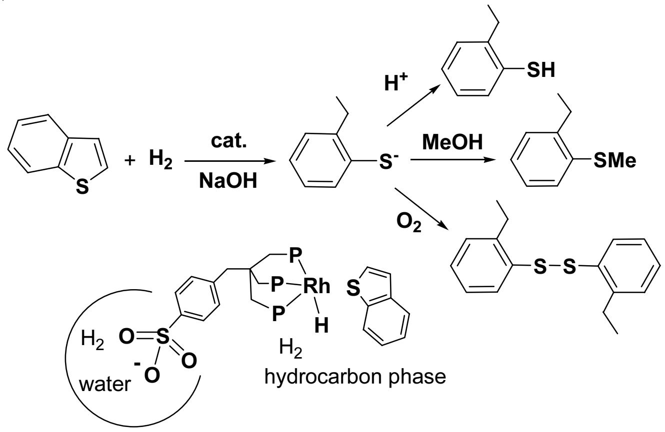
The reaction which transforms a thiophenic substrate into the corresponding thiol is referred to as hydrogenolysis (Scheme 4). Highly energetic metal fragments with filled orbitals of appropriate symmetry are necessary to lower the barrier to C–S insertion which occurs via dπ(metal) → π*(C–S) transfer [8, 16]. The steric crowding at the metal center must be great enough to disfavor the η^2-C,C bonding mode of the substrate, but not so great as to impede the coordination of the substrate via the sulfur atom.



Scheme 4 Catalytic mechanism in hydrogenolysis of thiophenes.

Hydrogenolysis in Aqueous Biphasic Systems with Water-Soluble Metal Catalysts

The aqueous biphasic hydrogenolysis of BT has been accomplished in either water/*n*-decalin or water/naphtha mixtures with the rhodium(I) precursor [Rh(COD)-(SULPHOS)] (COD = cycloocta-1,5-diene) [17]. Rather harsh reaction conditions (160 °C, 3 MPa H_2) and an equivalent amount of NaOH were required for high conversions of BT to 2-ethylthiophenolate. In these conditions, the thiolate product was totally recovered in the aqueous phase, leaving the hydrocarbon phase formally "desulfurized" (Scheme 5).

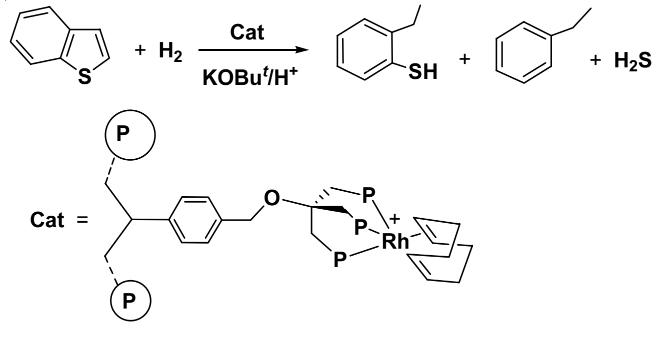


Scheme 5 Aqueous biphasic hydrogenolysis of benzo[*b*]thiophene.

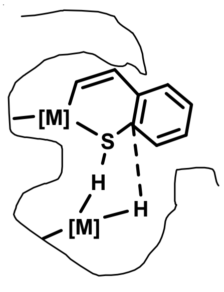
Hydrogenolysis in Liquid–Solid Systems with Heterogenized Metal Catalysts

The tripodal triphosphine moiety –$C(CH_2PPh_2)_3$ was anchored to a crosslinked styrene-divinylbenzene polymer yielding a polymeric material, POLYTRIPHOS, which reacted with a CH_2Cl_2 solution of $[RhCl(COD)]_2$ in the presence of $AgPF_6$ to give the polystyrene-supported complex $[Rh(COD)(POLYTRIPHOS)]PF_6$ (Rh 0.94 wt.%) (Scheme 6) [18].

Upon hydrogenation with 3 MPa H_2, this supported rhodium complex generated an effective catalyst for the hydrogenolysis of BT to 2-ethylthiophenol (TOF 48) and ethylbenzene (TOF 2), which still represents the first evidence of a successful single-site catalyst in the desulfurization of a thiophenic substrate. Indeed, under rather harsh experimental conditions (THF, $KOBu^t$, 160 °C, 3 MPa H_2), BT was mainly converted to a mixture of 2-ethylthiophenol and ethylbenzene (ET). No trace of the hydrogenation product DHBT was observed. As well, no rhodium leaching was observed, while the catalyst was recycled several times with no loss of catalytic activity. The surprising desulfurization of BT to ET has been interpreted in terms



Scheme 6 Hydrogenolysis and desulfurization of benzo[*b*]thiophene with a supported Rh complex.



1

of the concomitant action of two metal sites kept in close proximity by the flexible polystyrene matrix (**1**). Evidence showing the need for at least two metal sites to promote the desulfurization of a thiophenic substrate has several precedents in the literature [19].

2.4.2.2.4
Perspectives

Nowadays, deep desulfurization of gasoline and naphtha can be achieved by traditional hydrotreating, yet with technologies that require an exceedingly high energy consumption and cause a strong environmental impact. The future in the production of clean fuels from fossil materials is represented by multiphase catalysis as well as other multiphase absorption/extraction techniques [1–8]. Multiphase catalysis will involve both reduction and oxidation processes whereby sulfur removal can be achieved by well-defined metal sites capable of lowering the energy barriers to both C–S bond cleavage and disruption of the thiophene-ring aromaticity.

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2.4.3
Oxidations

2.4.3.1
Partial Oxidations

Roger A. Sheldon

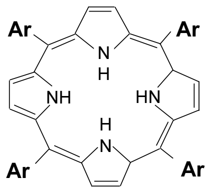
2.4.3.1.1
Introduction

Metal-catalyzed hydrogenations, carbonylations, hydroformylations, etc. involve transition metals in low oxidation states coordinated to soft ligands, e.g., phosphines, as the catalytically active species and organometallic compounds as reactive intermediates. Performing such reactions in aqueous/organic biphasic media generally involves the use of water-soluble variants of these ligands, e.g., sulfonated triarylphosphines such as **1** (see Section 2.2.3.2). In contrast, catalytic oxidations involve transition metals in high oxidation states as the active species, generally coordinated to relatively simple hard ligands, e.g. carboxylate. Reactive intermediates tend to be coordination complexes rather than organometallic species.

Water often has an inhibiting effect on catalytic oxidations owing to strong coordination to the hard metal center hampering coordination of a less polar substrate, such as a hydrocarbon (cf. Sections 2.2.1 and 2.2.2). Coordination of complex nitrogen- and/or oxygen-containing ligands can lead to the generation of more active oxidants by promoting the formation of high oxidation states. For example, in heme-dependent oxygenases and peroxidases the formation of active high-valent oxo-iron complexes is favored by coordination to a macrocyclic porphyrin ligand. Hence, we have limited our frame of reference to systems in which the reaction takes place in the aqueous phase using transition metal complexes of water-soluble ligands as catalysts.

2.4.3.1.2
Water-Soluble Ligands

Much of this research falls into the category of biomimetic oxidations. Hence, water-soluble porphyrins and the structurally related phthalocyanines have been widely used (see structures **1–4** for examples).



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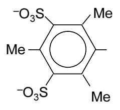
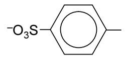
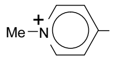
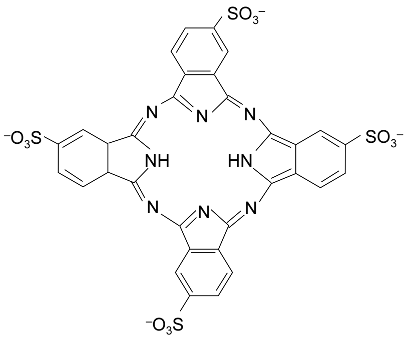


2 TSPP Ar =



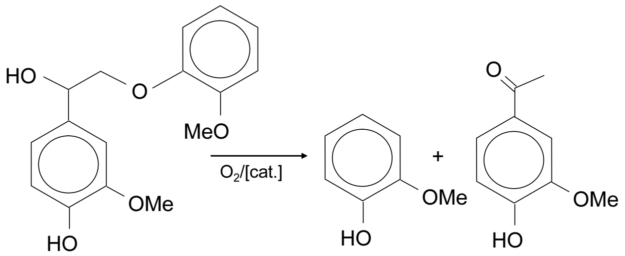
3 T2PyP Ar =





PcTS **4**

Such complexes have been studied as catalysts in environmentally friendly O_2-based delignification of wood pulp in paper manufacture. Conventional processes involve the use of Cl_2 or ClO_2 as oxidants and produce effluents containing chlorinated phenols. For example, Wright and co-workers [1] oxidized lignin model compounds such as **5** with O_2 [Eq. (1)] in the presence of Na_3Fe(III) (PcTS), Na_3Co(III) (TSPP), and Na_3Rh(III) (TSPP) catalysts. The latter gave the highest rates and selectivities.



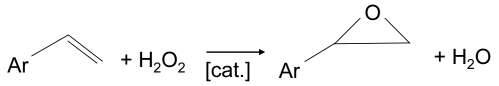
5

(1)

Similarly, Hampton and Ford [2] studied the Fe(PcTS)-catalyzed autoxidation of 3,4-dimethoxybenzyl alcohol as a model for delignification. They concluded, however, that the catalyst degrades too fast to be useful for delignification. In this context it is worth mentioning that water-soluble polyoxometallates such as $Pv_2Mo_{10}O_{40}{}^{5-}$ have also been used as catalysts for delignification with O_2 [3].

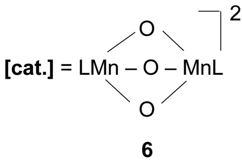
Fe(PcTS) [4] and Fe(TMPS) [5] have also been examined as catalysts for the oxidative destruction of chlorinated phenols in waste water, using H_2O_2 or $KHSO_5$ as the oxidant. For example, 2,4,6-trichlorophenol underwent facile oxidation to 2,6-dichloro-1,4-benzoquinone with Fe(PcTS)/H_2O_2 [4] or Fe(TMPS)/$KHSO_5$ [5]. Similarly, Fe(III) and Mn(III) complexes of T2MPyP catalyzed the oxidation of phenols with $KHSO_5$ [6].

Water-soluble manganese complexes of 1,4,7-trimethyl-1,4,7-triazacyclononane (**6**) and related ligands are highly effective catalysts for low-temperature bleaching of stains [7]. Polyphenolic compounds were used as appropriate models for tea stains. The same complexes were shown to catalyze the selective epoxidation of styrene and 4-vinylbenzoic acid with aqueous H_2O_2 [Eq. (2)] in aqueous MeOH or water, respectively. However, large amounts of H_2O_2 (10 equiv.) were required, indicating that considerable nonproductive decomposition occurs. Subsequently, it was shown that nonproductive decomposition of the hydrogen peroxide could be largely suppressed by the addition of oxalate [8] or ascorbic acid [9] as co-catalysts, or by anchoring the ligand to a solid support [10]. More recently, the use of glyoxylic acid methyl ester hemiacetal as a co-catalyst was shown to afford an even more effective epoxidation catalyst, enabling high conversions with only a 30% excess of



(2)

Ar = Ph, 4-(COOH)Ph



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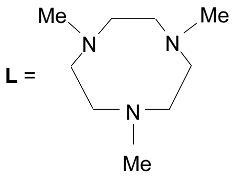
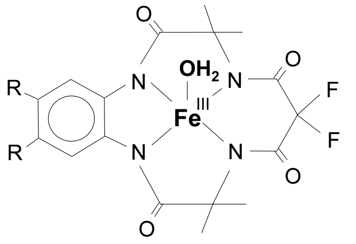


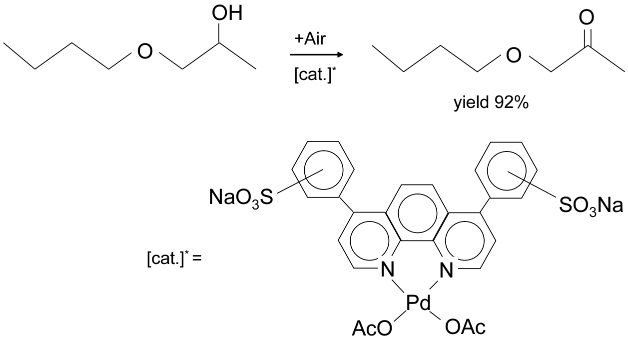
hydrogen peroxide [11]. Interestingly, the corresponding *cis*-diols were observed as byproducts in many cases and a concerted mechanism via a manganese(III)–*cis*-diol complex was proposed to explain their formation. The binuclear manganese complex of **6** also catalyzed the oxidation of benzylic alcohols, to the corresponding benzaldehydes, with aqueous hydrogen peroxide [12].

Collins and co-workers [13] have developed a series of iron(III) complexes of macrocyclic tetradentate nitrogen ligands, so-called TAML oxidant activators, with greatly enhanced stability toward oxidative and hydrolytic degradation (**7**). They are efficient, water-soluble activators of hydrogen peroxide, over a broad pH range, with a wide variety of potential applications, e.g., to replace chlorine bleaching in the pulp and paper industry and for use in water effluent treatment in the textiles industry. Applications in organic synthesis have not, as yet, been explored.



7

Recently, we described [14–16] the use of a water-soluble palladium(II) complex of sulfonated bathophenanthroline (**8**) as a stable, recyclable catalyst for the aerobic oxidation of alcohols in a two-phase aqueous–organic medium [e.g. Eq. (3)]. Reactions were generally complete in 5 h at 100 °C/3 Mpa air with as little as 0.25 mol% catalyst. No organic solvent is required (unless the substrate is a solid) and the product is easily recovered by phase separation. The catalyst is stable and remains in the aqueous phase, facilitating recycling to the next batch.



(3)

A wide range of primary and secondary alcohols were oxidized with TOFs ranging from 10 to 100 h^{-1}, depending on the structure and the solubility of the alcohol in water (since the reaction occurs in the water phase the alcohol must be at least sparingly soluble in water). Secondary alcohols afforded the corresponding ketones in > 99% selectivity in virtually all cases studied. Primary alcohols afforded the corresponding carboxylic acids via further oxidation of the initially formed aldehyde, e.g., 1-hexanol afforded 1-hexanoic acid in 95% yield. It is important to note that this was achieved without the necessity to neutralize the carboxylic acid product with 1 equiv. of base. When the reaction was performed in the presence of 1 mol% of the stable free radical, TEMPO (2,2,6,6-tetramethylpiperidinoxyl), over-oxidation was suppressed and the aldehyde was obtained in high yield, e.g. 1-hexanol afforded hexanal in 97% yield.

Compared to most existing systems for the aerobic oxidation of alcohols, the Pd–bathophenanthroline system is an order of magnitude more reactive, requires no organic solvent, involves simple product isolation and catalyst recycling, and has a broad scope in organic synthesis.

A catalytic cycle was proposed [15] for the reaction in which, consistent with the observed half-order in palladium, the active catalyst is formed by initial dissociation of a hydroxyl-bridged palladium(II) dimer. This is followed by coordination of the alcohol and β-hydrogen elimination affording the carbonyl product and palladium(0). The latter is reoxidized to palladium(II) by dioxygen. More recently, electronic [17] and steric [18] effects of substituents in the phenanthroline ligands on the rates and substrate scope of these reactions were studied. Results were in accordance with the proposed mechanism and afforded an optimized catalyst which was highly active (turnover frequencies > 1500 h^{-1}) and tolerated a wide variety of functional groups in the alcohol substrate.

2.4.3.1.3
Concluding Remarks

Important advances have been made in the last few years in the design of water-soluble, oxidatively stable ligands. In combination with appropriate metal ions they afford stable, water-soluble catalysts for oxidations with dioxygen or hydrogen peroxide in aqueous–organic biphasic systems. Up till now synthetic applications have generally been limited to olefin epoxidations with hydrogen peroxide (Mn) and aerobic oxidation of alcohols (Pd). These methodologies constitute green alternatives – clean oxidants, no need for organic solvents, facile product separation and catalyst recycling – for traditional oxidations. In the future we expect that these methodologies will be further applied in organic synthesis. In particular, iron complexes offer significant advantages from both an economic and an environmental viewpoint.

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2.4.3.2
Wacker-Type Oxidations

Eric Monflier

The Wacker-type oxidation of olefins is one of the oldest homogeneous transition metal-catalyzed reactions [1]. The most prominent example of this type of reaction is the oxidation of ethylene to acetaldehyde by a $PdCl_2/CuCl_2/O_2$ system (Wacker–Hoechst process). In this industrial process, oxidation of ethylene by Pd(II) leads to Pd(0), which is reoxidized to Pd(II) via reduction of Cu(II) to Cu(I). To complete the oxidation–reduction catalytic cycle, Cu(I) is classically reoxidized to Cu(II) by O_2 [2, 3]. The use of bidentate ligands [4], bicomponent systems constituted of benzoquinone and iron(II) phthalocyanine [5] or chlorine-free oxidants such as ferric sulfate [6], heteropoly acid [7], and benzoquinone [8], make it possible to increase the selectivity reaction by avoiding the formation of chlorinated products.

The Wacker reaction has been applied to numerous simple olefins such as α-olefins and cycloalkenes, or to functionalized olefins such nitroethylene, acrylonitrile, styrene, allyl alcohol, or maleic acid [3]. The carbonyl group is formed at the carbon atom of the double bond where the nucleophile would add in a Markovnikov addition. Reversal of the regioselectivity has only been observed with particular substrates such as 1,5-dienes [9]. Conversion and selectivity for the oxidation of these olefins were found to be very dependent on the water solubility of the olefin. Indeed, high molecular weight olefins do not react under the standard biphasic Wacker conditions due to their low solubility in water. Furthermore, the products obtained are often highly contaminated by chlorinated products and isomerized olefins [8, 10, 11]. In order to overcome these problems, numerous studies have been undertaken. Only the most significant approaches for the oxidation of higher α-olefins (1-hexene and above) will be developed here.

2.4.3.2.1
Co-Solvents or Solvents

The use of a co-solvent or solvent is the simplest solution to overcome mass-transfer limitations [8, 11, 12]. Among the different solvents described in the literature (DMSO, acetone, THF, dioxane, acetonitrile, ethanol), dimethylformamide appears to be the most suitable. Indeed, oxidation of 1-dodecene into 2-dodecanone can be achieved with yields greater than 80% in water–DMF mixtures.

2.4.3.2.2
Phase Transfer Catalysis

Phase-transfer catalysis constitutes another alternative to increase oxidation rates of water-insoluble terminal alkenes [13]. Although some results in the literature are contradictory [14], it seems that only quaternary ammonium salts containing at least one long-chain alkyl group are suitable as phase-transfer catalysts. Interestingly, rhodium and ruthenium complexes can also be used instead of palladium for the oxidation of terminal olefins [15]. With these catalysts, symmetrical quaternary ammonium salts such as tetrabutylammonium hydrogen sulfate are effective. The rate of palladium-catalyzed oxidation of terminal olefins can also be improved by using polyethylene glycol (PEG) instead of quaternary ammonium salts [16]. Thus, the rate of PEG-400-induced oxidation of 1-decene is three times faster than cetyltrimethylammonium bromide-catalyzed oxidation under the same conditions (see also Section 2.3.5).

2.4.3.2.3
Microemulsion Systems

These systems have also been proposed for the oxidation of sparingly water-soluble olefins [17]. The microemulsion system consisted of formamide, 1-hexene, 2-propanol as co-surfactant and C_9H_{19}–C_6H_4–$(OCH_2CH_2)_8OH$ as surfactant. In such a medium, the oxidation rates of 1-hexene to 2-hexanone were three times faster than those observed in the water–DMF mixture under similar condition.

2.4.3.2.4
Immobilized Catalysts

Immobilized catalysts have also been described for the oxidation of water-insoluble olefins. Most work has been done with polymer-anchored palladium catalysts [18].

For instance, palladium supported on a highly rigid cyanomethylated polybenzimidazole produces a highly effective catalyst for the oxidation of 1-decene, with activity higher than homogeneous systems in some cases [19]. The use of palladium and copper salts dissolved in an aqueous film supported on a high surface-area silica gel has also been proposed by Davies et al. to perform the oxidation of higher olefins (the SAPC concept; see Section 2.6). Unfortunately, the ketone yields are rather low (< 25%) and significant isomerization of the olefin occurred [20].

2.4.3.2.5
Inverse Phase-Transfer Catalysis

The principle of inverse phase-transfer catalysis (cf. Section 2.2.3.3) has been successfully applied to the oxidation of higher olefins [21]. The success of this oxidation is mainly due to the use of β-cyclodextrin functionalized with hydrophilic or lipophilic groups. The best results have been obtained with a multicomponent catalytic system constituted of $PdSO_4$, $H_9PV_6Mo_6O_{40}$, $CuSO_4$, and randomly O-methylated β-cyclodextrin [22]. Interestingly, β-cyclodextrin modified by nitrile-containing groups was found to be more efficient than native β-cyclodextrin to perform 1-octene oxidation [23]. The rate increase was attributed to the formation of a ternary inclusion complex between the olefin, the palladium salt, and the modified cyclodextrin. Recently, the effect of other inverse phase-transfer catalysts such as sulfonated calixarenes was also investigated [24]. Interestingly, the sulfonated calixarenes displayed substrate selectivity, confirming that internal cavity of the calixarenes recognizes the substrates.

2.4.3.2.6
Summary

Although the Wacker-type oxidation of olefins has been applied since the early 1980s, processes involving higher olefins are still the subject of investigations due to their poor solubility in water. Particularly interesting in this context is the inverse phase-transfer catalysis using water-soluble host molecules. Indeed, upon a careful choice of the substituent, these receptor molecules avoid the isomerization into internal olefins or make it possible to perform substrate selective oxidations that cannot be achieved a biphasic medium with conventional transition metal catalysts.

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2.4.3.3
Methyltrioxorhenium(VII) in Oxidation Catalysis

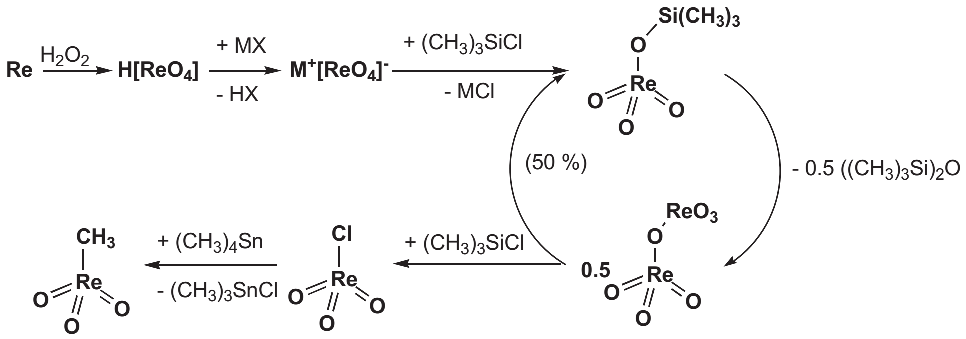
Fritz E. Kühn

2.4.3.3.1
Introduction

Since 1989 organorhenium(VII) oxides, especially the very stable methyltrioxorhenium (MTO), have proven to be excellent catalyst precursors for a surprisingly broad variety of processes, among them various oxidation reactions [1–3]. This section gives a brief summary of the behavior of MTO and its peroxo derivatives in aqueous multiphase systems. Particular emphasis is given to the well-examined olefin epoxidation reactions.

2.4.3.3.2
Synthesis of Methyltrioxorhenium(VII)

MTO was first synthesized in 1979 in a quite time-consuming (weeks) and low-scale (milligrams) synthesis [4]. The breakthrough toward possible applications came only about ten years later [5]. An additional improvement was the prevention of any significant Re loss as unwanted byproducts [6, 7]. A further modification of the synthesis avoids the moisture-sensitive and expensive dirhenium heptaoxide as starting material, using instead Re powder or perrhenates [8, 9]. This method is of particular additional interest since it allows recyclization the catalyst decomposition products from reaction solutions (Scheme 1).



Scheme 1 Synthesis of methyltrioxorhenium(VII).

2.4.3.3.3
Behavior of Methyltrioxorhenium in Aqueous Solutions

MTO hydrolyzes rapidly in basic aqueous solutions and much more slowly in acidic media. At low concentrations (σ_{MTO} (concentration) < 0.008 M) the formation of methane gas and perrhenate was detected. At higher concentrations a second reaction, a faster reversible polymerization–precipitation, takes place to yield a golden-colored solid of the empirical composition $\{H_{0.5}[(CH_3)_{0.92}ReO_3]\}$ (poly-MTO) in about 70% yield [Eq. (1)] [10–15]. The reaction follows first-order reversible kinetics. The rate of polymerization–precipitation is independent of the concentration of H^+, and the reaction does not occur in the presence of oxidants [10]. The structure of the crystalline domains of poly-MTO can be described as double layers of corner-sharing CH_3ReO_5 octahedra (AA′) with intercalated water molecules (B) in an ...AA′BAA′... layer sequence. It adopts the three-dimensional extended ReO_3 motif in two dimensions as a $\{ReO_2\}_n$ network. The oxo groups of two adjacent layers are face to face with the intercalated water layer. Hydrogen bridges are formed between the oxo groups and the water molecules, enhancing the structure of the polymer. The double layers are interconnected by van der Waals attractions generated by the nonpolar methyl groups, which are orientated inside the double layer (Figure 1). These structural features explain the observed lubricity of poly-MTO.

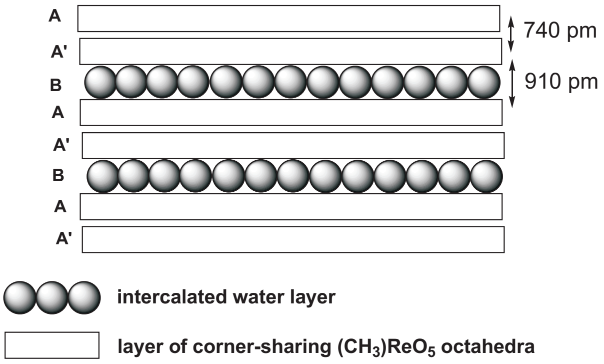
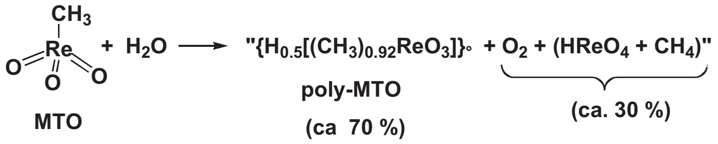


Figure 1 Structure of the crystalline domains of poly-MTO.

Substoichiometry with respect to the CH_3/Re ratio of 4.6 : 5 and partial reduction by extra hydrogen equivalents are responsible for a high electric conductivity of poly-MTO [13, 14]. Poly-MTO also contains amorphous areas with a defect stacking of double layers and with a smaller content of water. The conductivity of poly-MTO is attributed to occasional demethylation and to the inclusion of extra hydrogen in the lattice. A theoretical study of MTO dimers, trimers, and tetramers has been performed. The tetramer already provides a good model for the interpretation of the IR and Raman spectra of poly-MTO and assigns the bridging oxygen atoms as the best candidates to bind the excess protons present in poly-MTO [16]. The terminal oxygens of monomeric MTO seem to be easily available for the formation of bridging oxygens [17].



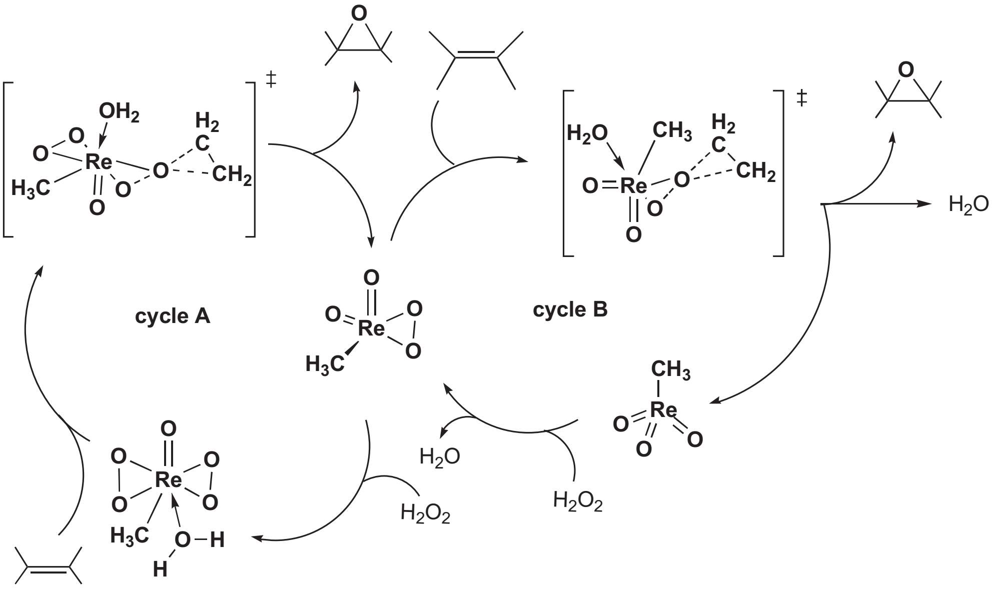
(1)

2.4.3.3.4
Catalyst Formation and Catalytic Applications

An important step in the understanding of the role of MTO in epoxidation and oxidation catalysis was the isolation and characterization of the reaction product of MTO with excess H_2O_2, i.e., a bisperoxo complex of stoichiometry $(CH_3)Re(O_2)_2O \cdot H_2O$ [18, 19]. This reaction takes place in any organic solvent or water. The structures of $(CH_3)Re(O_2)_2O \cdot H_2O$ and $(CH_3)Re(O_2)_2O \cdot (O{=}P(N(CH_3)_2)_3)$ (X-ray diffraction) were determined; the structure of ligand-free complex $(CH_3)Re(O_2)_2O$ is known from the gas phase [19, 20].

Experiments with the isolated bis(peroxo) complex $(CH_3)Re(O_2)_2O \cdot H_2O$ have shown that it is an active species in olefin epoxidation catalysis and several other catalytic reactions [19, 20]. In-situ experiments show that the reaction of MTO with

1 equiv. of H_2O_2 leads to a monoperoxo complex of the composition $(CH_3)Re(O_2)O_2$ [21, 22]. $(CH_3)Re(O_2)O_2$ has not been isolated and exists solely in equilibrium with MTO and $(CH_3)Re(O_2)_2O \cdot H_2O$. The monoperoxo complex is also catalytically active in oxidation processes. Kinetic experiments indicate that the rate constants for the transformation of most substrates into their oxidation products by catalysis with the mono- and bisperoxo complexes are of a comparable order of magnitude [21–23]. These results are supported by density functional calculations [24–26]. The transition states in the olefin epoxidation process starting from $(CH_3)Re(O_2)O_2$ and $(CH_3)Re(O_2)_2O \cdot H_2O$ are not different enough in energy to exclude one of these two catalysts totally from the catalytic process. The activation parameters for the coordination of H_2O_2 to MTO have also been determined. They indicate a mechanism involving nucleophilic attack. The protons lost in converting H_2O_2 to a coordinated O_2^{2-} ligand are transferred to one of the terminal oxygen atoms, which remains on the Re as the aqua ligand L. The rate of this reaction is not pH-dependent [27]. Two catalytic pathways for the olefin epoxidation may be described, depending on the concentration of the hydrogen peroxide used. With 85% hydrogen peroxide, only $(CH_3)Re(O_2)_2O \cdot H_2O$ appears to be responsible for the epoxidation activity (Scheme 2, cycle A). When a solution of 30 wt.% or less H_2O_2 is used, the monoperoxo complex, $(CH_3)Re(O_2)O_2$, is also taking part in the epoxidation process and a second catalytic cycle is involved as shown in Scheme 2, cycle B. For both cycles, a concerted mechanism is suggested in which the electron-rich double bond of the alkene attacks a peroxidic oxygen of $(CH_3)Re(O_2)_2O \cdot H_2O$. It has been inferred from experimental data that the system may involve a spiro arrangement [24–29].



Scheme 2 MTO-catalyzed oxidation of olefins.

The most important drawback of the MTO-catalyzed process is the concomitant formation of diols instead of the desired epoxides, especially in the case of more sensitive substrates [30]. It was quickly detected that the use of Lewis base adducts of MTO significantly decreases the formation of diols due to the reduced Lewis acidity of the catalyst system. However, while the selectivity increases, the conversion decreases [30–32]. It was found that biphasic systems (water phase/organic phase) and addition of a significant excess of pyridine as Lewis base not only hamper the formation of diols but also increase the reaction velocity in comparison to MTO as catalyst precursor [33, 34].

Additionally it was shown that 3-cyanopyridine and especially pyrazole as Lewis bases are even more effective and less problematic than pyridine itself, while pyridine N-oxides are less efficient [35–37]. The Brønsted basicity of pyridines lowers the activity of hydronium ions, thus reducing the rate of opening the epoxide ring [38]. MTO forms trigonal-bipyramidal adducts with monodentate N-bases and (distorted) octahedral adducts with bidentate Lewis bases [39–41]. The monodentate Lewis-base adducts of MTO react with H_2O_2 to form mono- and bisperoxo complexes analogous to that of MTO, but coordinated by one Lewis-base molecule instead of H_2O. From the Lewis-base–MTO complexes to the bisperoxo complexes a clear increase in electron deficiency at the Re center can be observed by spectroscopic methods. The activity of the bisperoxo complexes in olefin epoxidation depends on the Lewis bases, the redox stability of the ligands, and the excess of Lewis base used. The peroxo complexes of the MTO–Lewis bases are, in general, more sensitive to water than MTO itself [40].

Furthermore, in the presence of olefins which are not readily transformed to their epoxides, 2,2′-bipyridine can be oxidized to its N-oxide by the MTO/H_2O_2 system [42]. Low to moderate stereo induction values (up to about 40% *ee* with conversions of around 10% at –5 °C reaction temperature) can be achieved when prochiral olefins, e.g., *cis*-β-methylstyrene or α-pinene are epoxidized with chiral amine adducts of MTO [43].

MTO has also been successfully applied as an olefin epoxidation catalyst in ionic liquids ([44, 45]; see also Chapter 5).

Alternative strategies to improve MTO-catalyzed oxidations have made use of host–guest inclusion chemistry [46–51].

A particularly important role of water and pH values becomes evident when looking at the catalyst deactivation processes. While MTO and its peroxo complexes are quite stable in acidic media, basic conditions lead to significantly reduced catalyst stabilities. In spite of the extraordinarily strong Re–C bond [52], characteristic of MTO, the cleavage of this bond plays a prominent role in the decomposition processes of these complexes [10, 53–55]. Concerning MTO, the full kinetic pH profile for the base-promoted decomposition to CH_4 and ReO_4^- was examined. Spectroscopic and kinetic data give evidence for mono- and dihydroxo complexes of formulae $CH_3ReO_3(OH^-)$ and $CH_3ReO_3(OH^-)_2$ prior to and responsible for the decomposition process. In the presence of hydrogen peroxide, $(CH_3)Re(O_2)O_2$ and $(CH_3)Re(O_2)_2O \cdot H_2O$ decompose to methanol and perrhenate with a rate that is dependent on $[H_2O_2]$ and $[H_3O]^+$. The complex peroxide and pH dependencies are explained by two possible pathways: attack of either hydroxide on $(CH_3)Re(O_2)O_2$ or HO_2^- on MTO. The bisperoxo complex decomposes much more slowly to yield O_2 and MTO [55]. Thus critical concentrations of strong nucleophiles have to be avoided; a great excess of hydrogen peroxide stabilizes the catalyst. It turned out to be advantageous to keep the steady-state concentration of water during the oxidation reaction as low as possible to depress catalyst deactivation.

Quite recently the possibility of MTO-catalyzed reactions utilizing dioxygen from the air instead of H_2O_2 as the oxidizing agent has been reported for some special cases [56, 57].

2.4.3.3.5
Summary

In summary, epoxidations with the MTO/H_2O_2 display several advantages. MTO is easily available, active in low concentrations of both MTO (0.05 mol%) and H_2O_2 (< 5 wt.%), it works over a broad temperature range (–40 to +90 °C) and is stable in water under acidic conditions as well as in basic media in special cases. Furthermore, the MTO/H_2O_2 system works in a broad variety of solvents, ranging from highly polar ones (e.g., nitromethane, water) to ones with low polarity (e.g., toluene). However, the reactions between MTO/H_2O_2 and alkenes are ca. one order of magnitude faster in semi-aqueous solvents (e.g., 85% H_2O_2) than in methanol. The rate constants for the reaction of MTO/H_2O_2 with aliphatic alkenes correlate closely with the number of alkyl groups on the alkene carbons. The reactions become significantly slower when electron-withdrawing groups such as –OH, –CO, –Cl, and –CN are present in the substrates.

A major advantage of MTO is that it does not decompose hydrogen peroxide. This is in striking contrast to many other oxidation catalysts. Turnover numbers of up to 2500 mol product per mole catalyst (reaction conditions: 0.1 mol% MTO, 5 mol% pyrazole) and turnover frequencies of up to 14 000 mole product per mole catalyst per hour have been reported, with typical MTO concentrations of 0.1–1.0 mol%. However, these impressive results have only been reached in perfluorinated alcohols as solvents with cyclohexene as substrate [58].

High selectivity (epoxide versus diol) can be adjusted by temperature control, trapping of water, or the use of certain additives, such as aromatic Lewis-base ligands, which additionally accelerate the epoxidation reactions. Selectivities of > 95% can be reached.

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2.4.4
Addition Reactions

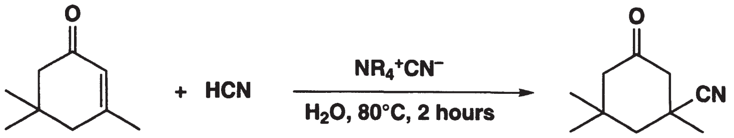
2.4.4.1
Hydrocyanation

Henry E. Bryndza and John A. Harrelson Jr.

Hydrogen cyanide is a remarkably versatile C_1 building block. Its use, however, has been limited by its relatively difficult synthesis/purification as well as by its high flammability, its tendency toward base-catalyzed explosive polymerization, and its toxicity. Most of the recent hydrocyanation literature comes from industry rather than academic laboratories.

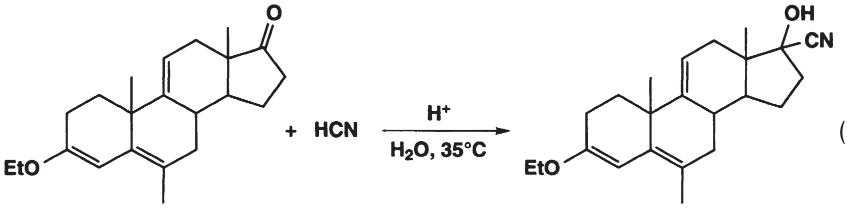
If toxicity and handling difficulties are the drawbacks of HCN as a feedstock, the versatility of the nitrile functional group as a synthon is a significant advantage. Moreover, the full miscibility of HCN with water at 25 °C offers a potential advantage to pursuing hydrocyanation catalysis in aqueous media. Therefore, hydrocyanation reactions offer the potential for generating new nitrogenous products which are useful intermediates, including the addition of HCN to C=C, C=O, and C=N double bonds to generate new alkyl nitriles, cyanohydrins, and aminonitriles, respectively. All of these reactions have commercial impact today [1], although aqueous hydrocyanation catalysis remains an emerging area of technology.

The addition of HCN to activated alkenes, as in Michael additions, has been known and commercially practiced for many years. Addition of HCN to isophorone [Eq. (1)] is an example [2].



(1)

More common is the general acid- or base-catalyzed addition of HCN to ketones and aldehydes to give cyanohydrins [Eq. (2)] [1]. Because of the propensity of HCN to spontaneously and exothermically polymerize under basic conditions, general acid catalysis is sometimes favored over basic media, as was the case in the recent Sumitomo [3] and Upjohn work [4, 5]. Applications of aqueous media have been reported to lead to asymmetric hydrocyanation catalysis [Eq. (3)] [6, 7].



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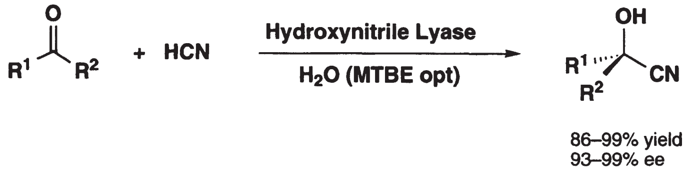
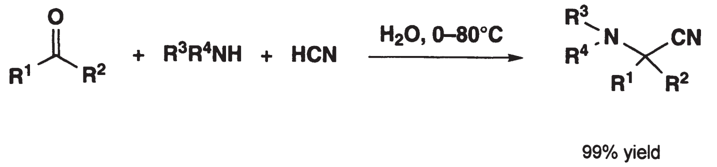


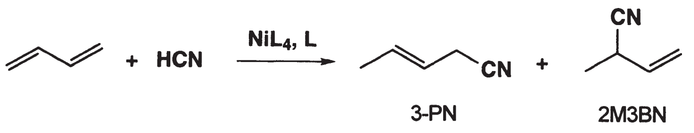
(3)

Another variant of this HCN addition to polar C=X bonds is the Strecker synthesis of aminonitriles from ketones or aldehydes, HCN, and ammonia [Eq. (4)] [8]. A number of patents to Distler and co-workers at BASF do teach the use of aqueous media to facilitate isolation of pure products [9], and researchers at Grace [10], Stauffer [11], Mitsui [12], and Hoechst [13] have reportedly used aqueous media to control the rates of formaldehyde aminohydrocyanation to isolate intermediate addition products in good yields. The use of aqueous media has also proven advantageous when amides, rather than nitriles, are the desired products.



(4)

The addition of HCN to C=C double bonds can be effected in low yields to produce Markovnikov addition products. However, through the use of transition metal catalysts, the selective anti-Markovnikov addition of HCN to alkenes can take place. The most prominent example of the use of aqueous media for transition metal-catalyzed alkene hydrocyanation chemistry is the three-step synthesis of adiponitrile from butadiene and HCN [Eqs. (5–7)]. First discovered by Drinkard at DuPont [14], this nickel-catalyzed chemistry can use a wide variety of phosphorus ligands [15] and is practiced commercially in nonaqueous media by both DuPont and Butachimie, a DuPont/Rhône-Poulenc joint venture. Since the initial reports of Drinkard, first Kuntz [16] and, more recently, Huser and Perron [17, 18] from Rhône-Poulenc have explored the use of water-soluble ligands for this process to facilitate catalyst recovery and recycle from these high-boiling organic products.



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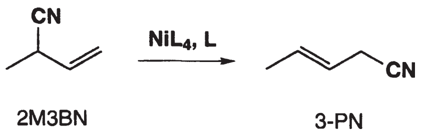

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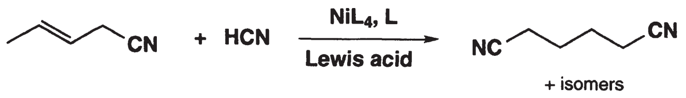
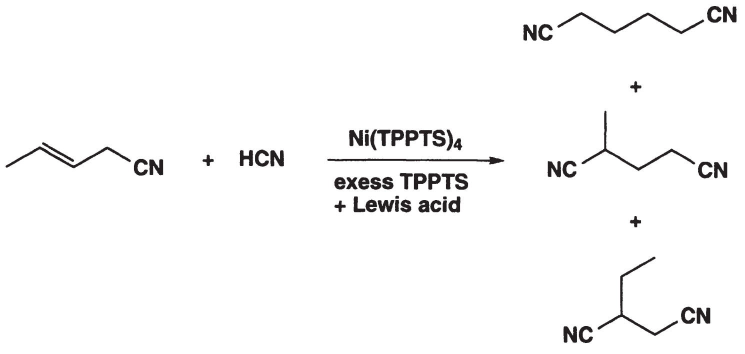


(7)

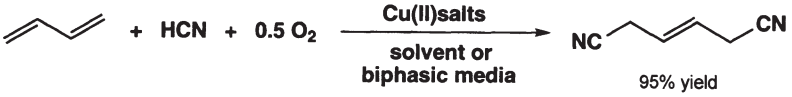
Huser et al. have extended Kuntz's work to the isomerization of 2-methyl-3-butenenitrile (2M3BN) to 3-PN (isomerization step; Eq. (6) 92% yield) [17–19].

A final example of aqueous media used in the hydrocyanation of butadiene is provided by Waddan at ICI [20]. In this chemistry, copper nitrate salts in aqueous media (among many others) are used for the oxidative dihydrocyanation of butadiene to dicyanobutenes [Eq. (8)].



(8)

Another type of aqueous cyanide chemistry is the oxidative coupling of cyanide to produce oxamide [Eq. (9)]. Both batch and continuous reaction have been demonstrated at Hoechst by Riemenschneider and Wegener [21], who report advantages of aqueous media not only in concurrently hydrolyzing the coupled products but also in facilitating product isolation from the reaction medium. This clever combination of reactive solvent is reportedly the basis for the commercial production of oxamide [2].



(9)

Even from the limited examples of hydrocyanation reactions, it is clear that HCN is a versatile reagent and that its chemistry is generally compatible with aqueous media. Some traditional advantages which recommend the use of aqueous or biphasic media include the high solubility of HCN in water, the facility in removing products from catalysts, the ability to control rates of reactions more finely and the concomitant hydrolysis of nitrile functional groups to amides along with C–C bond formation. Commercial applications of aqueous hydrocyanations have been emerging, and improved catalysts and separation technologies coming into play in the chemical industry.

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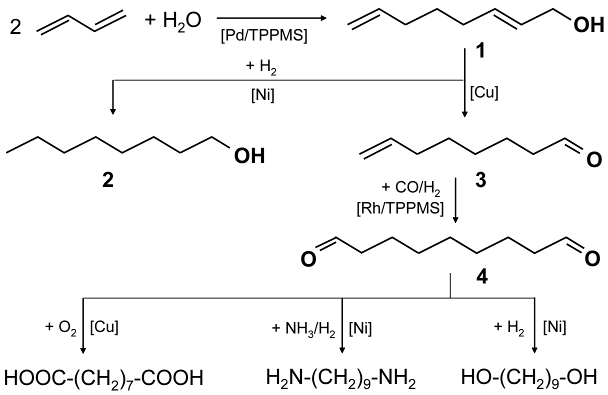
2.4.4.2
Hydrodimerization

Noriaki Yoshimura

The linear telomerization reaction of dienes (the taxogen) with nucleophiles such as alcohols, amines, carboxylic acids, water, etc. (the telogen), catalyzed by ligand-modified Pd or Ni complexes, provides an elegant method for the synthesis of useful compounds. With water as telogen, the telomerization becomes a hydrodimerization. In the case of butadiene as taxogen, the reaction product is the versatile 2,7-octadien-1-ol (**1**) which may the basis for a series of various derivatives (Scheme 1).



Scheme 1

2,7-Octadien-1-ol (**1** in Scheme 1) is a highly reactive compound which on the one hand can be hydrogenated over a fixed- bed Ni catalyst at 130–180 °C and a pressure of 3–8 MPa to 1-octanol (**2**). This octanol has a considerable market as a raw material for plasticizers for PVC and is produced with a capacity of approximately 5000 t y^{-1}. On the other hand, **1** can be hydrogenated/dehydrogenated over a copper chromite catalyst at 220°C to yield 7-octenal (3). This aldehyde is hydroformylated to the dialdehyde **4** which is then hydrogenated to give 1,9-nonanediol. The dialdehyde can also give, on air oxidation in an acetic solvent with a copper catalyst, azelaic acid and, on reductive amination in ammonia in the presence of a nickel catalyst, 1,9-nonanediamine. The hydroformylation step mentioned is a variant of the RCH/RP process using TPP*M*S instead of TPP*T*S (cf. also Sections 2.2.3.2.1 and 2.4.1.1).

The hydrodimerization reaction to 1-octanol was developed commercially in 1991 by Kuraray using an aqueous homogeneous catalyst [1, 2], i.e., a ligand-modified palladium catalyst (Figure 1).

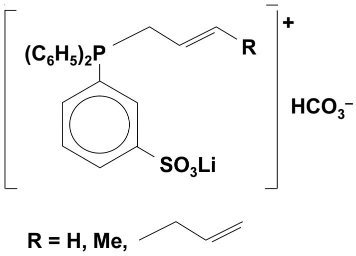


Figure 1 The TPPMS-modified Pd catalyst.

The catalyst is the phosphonium salt of the Li salt of TPPMS (cf. Section 2.2.3.2). This catalyst shows, as desired, sufficient activity at a high P/Pd ratio and no appreciable time-dependent deterioration of the activity after repeated catalyst cycles. The formation of phosphine oxides by traces of oxygen in the feed is also minimized. It has been demonstrated that the catalyst is stabilized at high levels if carbonate anions are present along with monoamines or tertiary ammonium carbonates.

To ensure a continuous operation and the separability of the reaction products from the catalyst solution, the use of sulfolane (tetrahydrothiophene-1,1-dioxide) is advantageous. Compared to other tested solvents, only sulfolane gives high yields (> 90%) and high selectivities (92%) with a ratio of 92 : 8 of the desired 2,7-octadien-1-ol versus the other isomer 1,7-octadien-3-ol.

For the telomerization of butadiene, distillation methods cannot be employed to separate the product from the reaction mixture containing the catalyst because the palladium complex has a lower thermal stability and high-boiling compounds would accumulate in the catalyst-containing solution that has been recycled. Therefore the extraction method with hexane as extraction agent (cf. Section 2.3.2) has been chosen (Figure 2).

In the present reaction, water acts as a nucleophile and the product hardly dissolves in it. Therefore, the process is capable of retaining the catalyst component

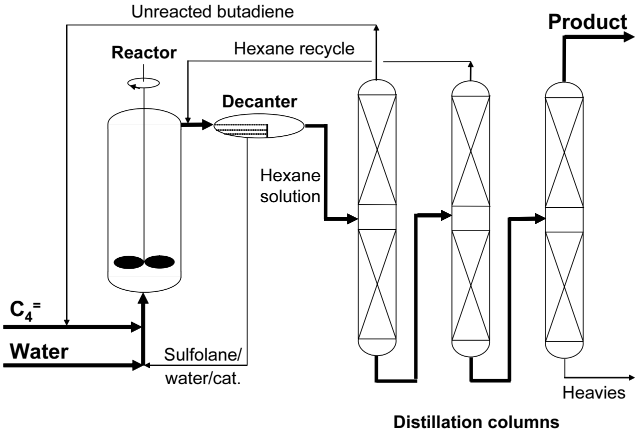
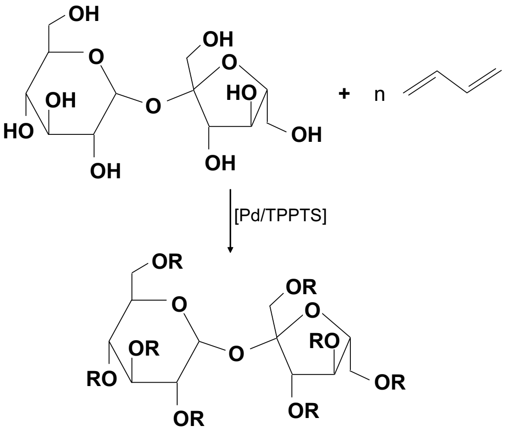


Figure 2 Extraction method for separating butadiene hydrodimerization products from the aqueous catalyst solution.

in the aqueous solution being used, and of extracting the product selectively. Thus, in order to solubilize the catalyst components in the aqueous sulfolane solution used, a hydrophilic group (e.g., a sulfonic acid salt) has been introduced into the phosphonium salt ligand and the procduct is extracted with an aliphatic saturated hydrocarbon such as hexane. This method has the advantages that (1) the catalyst and product can be separated without heating; (2) the extraction equilibrium is achieved for all compounds so that the accumulation of catalyst poisons and high-boiling byproducts is minimal. The catalyst lifetimes and the elution losses of catalyst components are within commercially acceptable ranges.

The total process consists thus of four steps: hydrodimerization, extraction, hydrogenation, and distillation [3]. The catalyst is separately prepared from a Pd salt, the phosphonium salt ligand, and a solution of triethylammonium hydrogen carbonate in aqueous sulfolane. Butadiene and water react at temperatures of 60–80 °C under a total pressure of CO_2 of 1–2 MPa, to achieve a 2,7-octadien-1-ol selectivity of 90–91%. In the following extraction step, 50–70% of the reaction products are extracted with hexane, and the aqueous sulfolane containing the catalyst, parts of the product, and the triethylammonium hydrogen carbonate returns to the reactor. The loss of catalyst is only in the range of a few ppm. After unreacted butadiene and hexane have been recovered from the extraction mixture, 2,7-octadien-1-ol is purified by distillation and subsequently hydrogenated.

According to Scheme 1, one of the products is 1-octanol, a valuable linear alcohol based on cheap butadiene instead of expensive 1-octene in combination with its hydroformylation (cf. Section 2.4.1.1). Alternatively, 2,7-octadien-1-ol can readily be converted to 7-octenal in a yield of at least 80%. This unsaturated aldehyde is then hydroformylated to a linear C_9 dialdehyde (**4** in Scheme 1). The dialdehyde may be converted by hydrogenation to 1,9-nonanediol, by hydrogenative amination to a nonanediamine, or by oxidation to azelaic acid: quite a whole, interesting product range.



Scheme 2 Biphasic etherification of carbohydrates.

It may be noted that other homogeneous telomerization reactions of butadiene with ammonia lead to trioctadienylamines. When carried out in an aqueous two-phase operation with Pd/TPPTS, primary and secondary octadienylamines are obtained [4]. Telomerization of butadiene with formic acid or its salts using the above-mentioned process can produce 1,7-octadiene [5]. Substituting isoprene for butadiene leads to dimethyloctadiene. The biphasic Pd-catalyzed telomerization of butadiene with carbohydrates in aqueous operation is also an important reaction and yields the desired ethers (Scheme 2) [6].

As known from other publications [7], no other processes have been realized so far.

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2.4.4.3
Olefin Metathesis

Wolfgang A. Herrmann

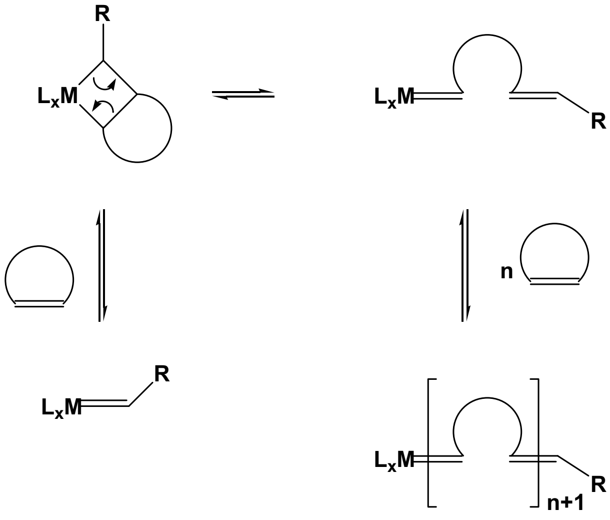
2.4.4.3.1
Introduction

Olefin metathesis is a most charming and curious, yet industrially useful C–C bond-forming reaction: alkylidene groups are exchanged at catalytic metal centers to form new olefins [1–3]. Thus, the most stable bonds in olefins undergo cleavage, initiated by metal-alkylidene species (Scheme 1).

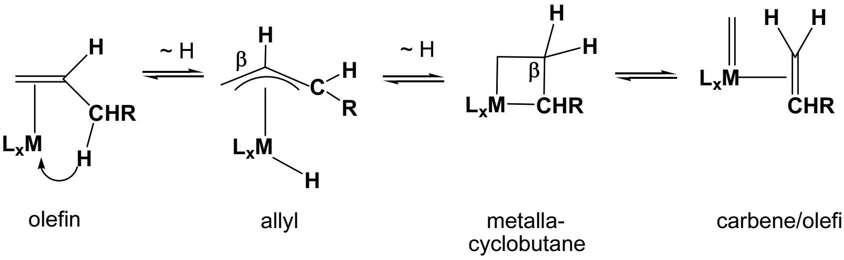
While the mechanistic principles were settled some time ago [4], structurally defined, tailored catalysts came along only recently, especially for functionalized olefins. Olefin metathesis, previously a most parameter-sensitive reaction, is no longer restricted to simple olefins, and it can now also be conducted in polar solvents. Ring-opening metathesis (ROMP), acyclic α,ω-diene metathesis (ADMET), ring-closure metathesis (RCM), and just simple metathesis are the main applications.

Famous examples are the well-established Norsorex® process (using RuX_3 catalysts), the *S*hell *h*igher-*o*lefins *p*rocess (SHOP), and the cyclooctene ROMP to form Vestenamer® rubber products [3, 5, 6].

Many industrial processes employ multiphase catalysis, predominantly gas-phase reactions at heterogeneous catalysts [1–6]. The nature of the active catalytic site is speculative in most of these cases. However, the generation of metal-attached carbenes is likely, even starting from simple olefins carrying active hydrogen; cf. Scheme 2. In other cases, activators containing carbene precursor groups, such as $Sn(CH_3)_4$, are used to generate the active sites at the surface, e.g. via the equilibrium



Scheme 1

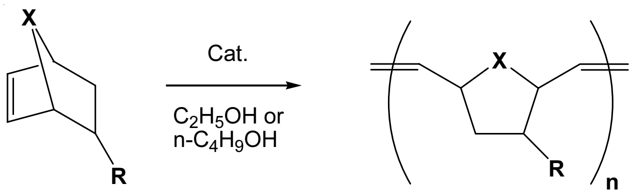


Scheme 2

$M{-}CH_3 \rightleftharpoons HM{=}CH_2$. Well-defined, single-component catalysts initiate living polymerization of olefins [7].

2.4.4.3.2
Ruthenium Catalysts

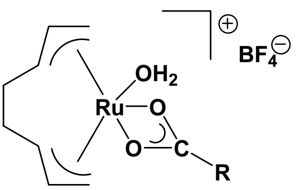
Water as a co-catalyst was early reported in the ROMP of (strained) cycloolefins, with the catalysts being the hydrates of $RuCl_3$, $OsCl_3$, and $CrCl_3$ in refluxing ethanol [Eq. (1)] [8]. Redox equilibria to generate Ru(II) active catalysts seem to be engaged but the mode of metal carbene formation finally remains unclear. These catalysts, however, initiate the aqueous-phase polymerization of substituted norbornenes in the presence of anionic emulsifiers and suitable reducing agents [9], even though the overall yield of polymers is still low.



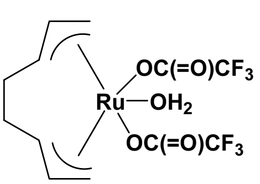
(1)

R = H, CH_2Cl, CH_2OH, CO_2H
X = CH_2, O

Water-soluble bis(allyl)ruthenium hydrate catalysts (**1** and **2**) initiate emulsion polymerization of norbornene, yielding surprisingly specific *cis* polymers (85–90% *cis*) [10].



1

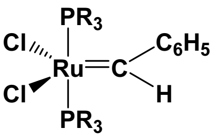


2

The polymers made by use of the other water-soluble catalysts normally have no defined stereochemistry, with the *cis/trans* ratio varying considerably from catalyst to catalyst. As a rule, the *trans* products are preferred.

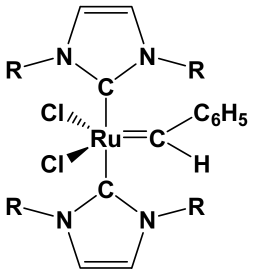
This lack of selectivity changes with the structurally defined Ru(II)-carbene catalysts **3** introduced by Grubbs [11, 12]. The breakthrough, however, was achieved by the Herrmann strategy using N-heterocyclic carbenes (NHC instead of, or in addition to, phosphanes) in catalysts **4** and **5** [13–15]. Catalyst **5** first exemplified the principle of combining a strongly metal-attached NHC ligand with a phosphane ligand that undergoes dissociation to make a vacant coordination site available for the initial step. A wide array of now easily available NHCs is possible, including the C–C-saturated derivatives **6** and **7** that, in metathesis, are more active but of shorter catalyst lifetime. Larger-ring systems have also been employed, yielding different polymer properties than conventional poly(dicyclopentadiene) [16].

No initiation periods are observed with the new catalysts, in contrast to the "classical" RuX_3– and related catalysts. Living polymerization has been observed by NMR spectroscopy. The polydispersity of products formed from hydrophilic or hydrophobic monomers is typically very narrow (PD 1.10).



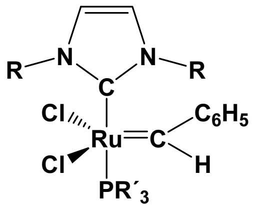
3

R = C_6H_5, c-C_6H_{11}



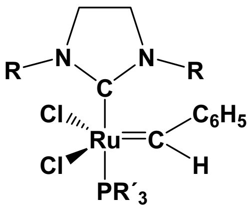
4

R = alkyl, aryl

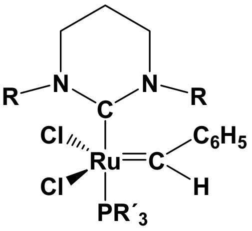


5

R = alkyl, aryl
R′ = CH_3, c-C_6H_{11}

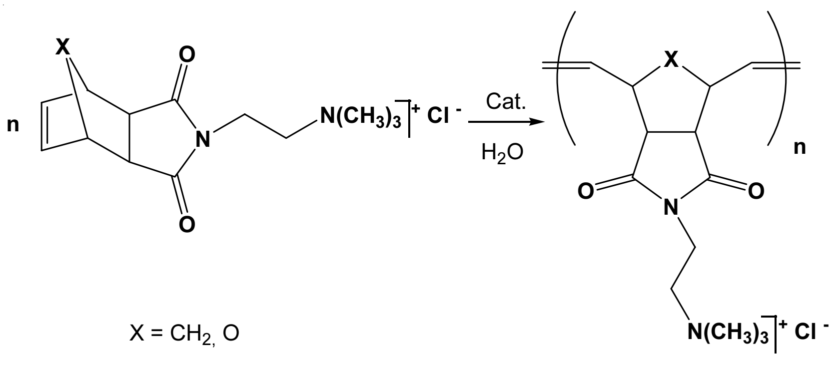


6



7

R = alkyl, aryl
R′ = CH_3, c-C_6H_{11}



10

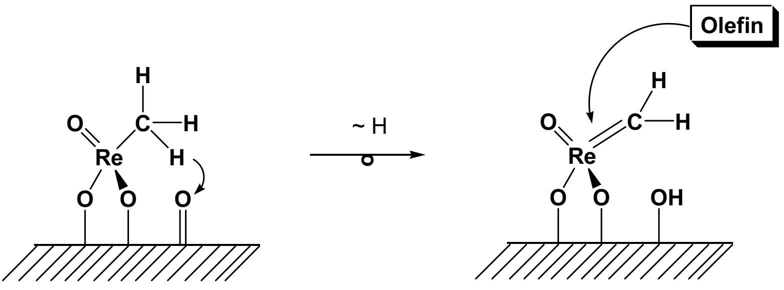
(2)

Well-defined block copolymers have been obtained via sequential monomer addition. Water-soluble, biologically active glycopolymers have also been made by this type of Ru(II) catalyst [18].

Replacement of PR_3 in compounds **3** by $P(C_6H_5)_2(C_6H_4\text{-}m\text{-}SO_3^-Na^+)$ ("TPPMS") and $[P(c\text{-}C_6H_{11})_2\{CH_2CH_2N(CH_3)_3\}]^-Cl$ gives water-soluble catalysts (e.g., **8**). While TPPMS is not electron-donating enough to act as an active catalyst [20], the alkyl-derived species **8** gives quick ROMP of the water-soluble monomers **9** to yield the polymer **10** at 45–80% conversion [Eq. (2)] [21].

2.4.4.3.3
Rhenium Catalysts

A novel class of metathesis catalysts derives from methyltrioxorhenium, CH_3ReO_3 (MTO) [22]. Combined with certain solid supports such as SiO_2/Al_2O_3 or Nb_2O_5, highly active catalysts are generated [23, 24]. They even tolerate functional groups such as ketones, esters, and carboxylic acids. Based upon NMR spectroscopic evidence [25] and in accord with theoretical studies, surface-attached $Re{=}CH_2$ species initiate metathesis via a novel type of tautomerism [Eq. (3)].



(3)

The catalyst precursor MTO was previously difficult to make, but it is now available from cheap starting materials on a multi-kilogram scale [26]. It is thus the ideal candidate for industrial uses, be it in metathesis or in oxidation [22].

2.4.4.3.4
Conclusion

In the meantime, olefin metathesis is applicable to all kinds of substrates, including those bearing functional and protic groups. The tailoring of structurally defined metal-carbene initiators allows for a defined stereochemistry of products. In many cases, metathesis occurs in two-phase processes: either as gas-phase reactions of simple olefins on heterogeneous catalysts, or as ring-opening polymerization with organic- or aqueous-phase catalysts.

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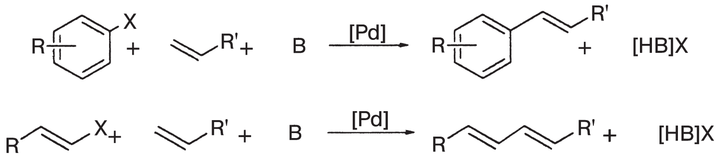
2.4.4.4
Heck and Other C–C Coupling Reactions

Wolfgang A. Herrmann, Claus-Peter Reisinger, and Peter Härter

2.4.4.4.1
Introduction

Here, the term “Heck-type reaction” is taken to include palladium-catalyzed C–C coupling processes where vinyl or aryl derivatives are functionalized with olefins, alkynes, or organometallic reagents [see Eqs. (1) and (2)] [1]. Aryl and vinyl chlorides are most reluctant to undergo Pd-catalysed activation, as expected from the C–X bond dissociation energies [2].



(1)

(2)

X = I, Br, N_2, BF_4 B = base: NR_3, K_2CO_3, NaOAc

Although most applications of Heck-type reactions are carried out in polar aprotic media, there are several successful approaches using partially or completely aqueous solution and aqueous–organic biphasic systems. Furthermore, the methodology was expanded to N–C and P–C bond-forming reactions; in addition, cross-coupling reactions will also be discussed here. In most cases, the recovery and re-use of the water-soluble catalyst is of minor importance, because the procedures are developed for the laboratory scale with respect to fine chemical synthesis. The main advantage of this approach may be the significant change in thermodynamics, resulting in milder reaction conditions and improvements in chemo- and regioselectivity. Recently, a novel type of biphasic system has been introduced using fluorous hydrocarbons/organic phases as solution media [43]. The main impetus for the employment of the fluorous biphase concept (FBS) is the easy recovery of the catalyst, a subject which is of crucial importance in industrial applications [44]. This methodology also provides a possibility of performing reactions under biphasic conditions with substrates which are labile toward water (see Chapter 4).

2.4.4.4.2
Catalysts and Reaction Conditions

Palladium is one of the most versatile and efficient catalyst metals in organic synthesis. Solubility in water is achieved by utilization of simple palladium(II) salts or water-soluble ligands, such as TPPTS and TPPMS. The active catalysts for heck-type reactions are zerovalent palladium(0) species [3], which are often generated in situ by thermal decomposition of a Pd(II) precursor or by the application of a reducing agent, e.g., 1–6 equiv. of a phosphine in the presence of base generates Pd(0) and the phosphine oxide [4].

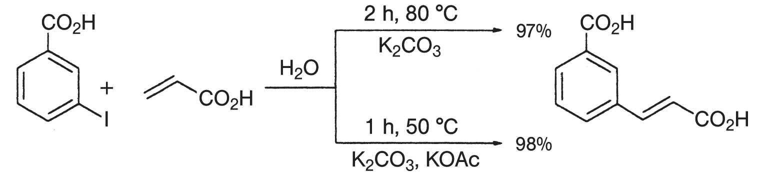
The isolation of water-soluble palladium (0) complexes was achieved by gel-permeation chromatography for $Pd(TPPTS)_3$ [5]; an X-ray determination by Casalnuovo and Calabrese for $Pd(TPPMS)_3$ [6] is the first published structure of a transition metal complex containing a sulfonated phosphine.

Furthermore, the combination of palladium(II) salts with tetrabutylammonium halide additives, called “Jeffery conditions”, is an efficient system for Heck-type reactions [7a], but the mechanistic implications are unknown. Also, nonionic phosphine ligands, such as triphenylphosphine which yields $Pd(PPh_3)_4$, are applied in water-miscible organic solvents, like DMF and acetonitrile. In these cases, the application of water is of crucial importance, but the role is often not well investigated.

2.4.4.4.3
Olefination

Since the pioneering work by Beletskaya and co-workers [8] the intra- and (more commonly) intermolecular arylation of olefins has been shown to proceed very smoothly in aqueous medium in the presence of palladium acetate. At the beginning, the methodology seemed to be limited to aryl iodides under a strong influence of the base: it was shown that the presence of potassium acetate instead of carbonate yielded lower reaction temperatures and higher rates [Eq. (3)].

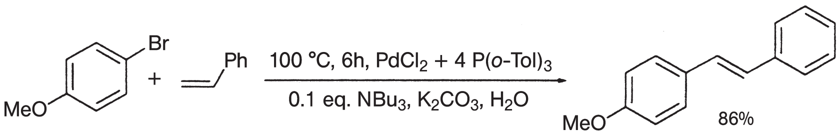
Several years later, a similar approach succeeded even in the application of deactivated bromoanisole [9]. Further investigations by Jeffery indicated the rate- and selectivity-enhancing ability of tetraalkylammonium salts in Heck-type reactions [7].



(3)

This approach was adopted by Daves for the coupling of iodo derivatives of nitrogen heterocycles with cyclic enol ethers and furanoid glycals in a water/ethanol mixture, using tetrabutylammonium chloride as a promoter [10]. Surprisingly, the use of absolute ethanol as reaction solvent was ineffective.

Furthermore, comparative studies with arylphosphine ligands in aqueous organic media demonstrated the superior activity of palladium tri(*o*-tolyl)phosphine complexes [11] with an unusual combination of 10 mol% tributylamine with 1.5 equiv of potassium carbonate in water [Eq. (4)] [9].



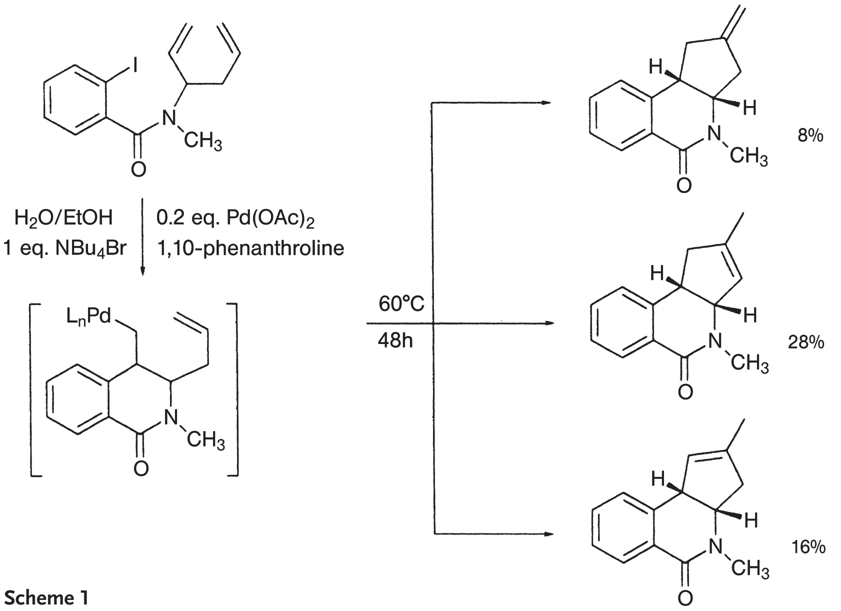
(4)

If water-soluble phosphine ligands are applied, extremely mild reaction conditions can be achieved. Especially, Pd(TPPMS)$_3$, which converts 4-iodotoluene, is tolerant of a broad range of functional groups, including those present in unprotected nucleotides and amino acids [6]. Interestingly, even the coupling of a donor-substituted iodoarenes and cyclic olefins can be conducted by palladium acetate with TPPTS at only 25 °C in aqueous acetonitrile. However, the low rates observed require a reaction time of up to 48 h for high conversions [12].

The application of ethylene in Heck reactions often shows different activities from other olefins, because of Wacker-type side reactions. It was found, however, that iodo- and acceptor-substituted bromoarenes are cleanly converted in aqueous media to the corresponding styrenes utilizing a palladiium–TPPMS complex [13]. Furthermore, high-purity *o*- and *p*-vinyltoluenes were prepared in a dimethylformamide/water mixture with palladium tri(*o*-tolyl)phosphine complexes [14]. Here, the role of water may be the dissolution of the inorganic base (potassium carbonate) in the organic media.

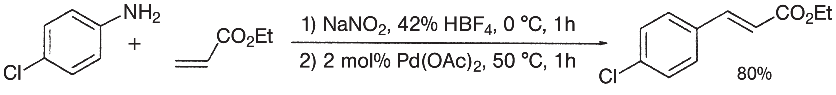
Even superheated (to 260 °C) or supercritical (to 400 °C; see Chapter 6) water was employed in the Heck reaction with several catalyst precursors and aryl halides with styrene. However, all conversions show large amounts of side products and the yields were in the 5–30% range, indicating radical intermediates and byproducts from decomposition of the arene starting material [15].

The progress of tandem Heck reactions in organic synthesis [16] led to their first application in the aqueous phase. Hence, a double Heck reaction on a substrate for which β-hydride elimination is possible results in three tricyclic products (Scheme 1) [17].



Scheme 1

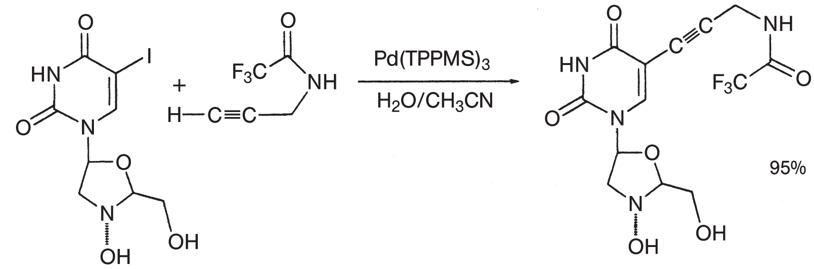
Surprisingly, the application of 1,10-phenanthroline as a ligand suppresses β-hydride elimination completely and raises the total yield of double cyclization products to 52% [18]. In addition, an efficient one-pot procedure for Heck reactions starting with aniline derivatives, forming arenediazonium salts with sodium nitrite in 42% aqueous HBF_4, was reported [Eq. (5)] [19]. The process has several advantages: short reaction times, high catalytic turnover frequency, superior reactivity of the diazonium nucleofuge, and, most significantly, the use of aqueous reaction conditions. Therefore, this route toward ring-modified phenylalanine and tyrosine was used via a ring nitration and reduction sequence, thus expanding the field of artificial amino acids [20].



(5)

2.4.4.4.4
Alkyne Coupling

The palladium-catalyzed coupling of terminal acetylenes with aryl and vinyl halides is a widely used reaction in organic synthesis [21]. Hence, the application of water-soluble palladium complexes was first reported in aqueous acetonitrile with $Pd(TPPMS)_3$ and CuI as promoter, but was limited to aryl iodides [6]. The advantages of this catalyst already mentioned are low reaction temperatures and short reaction times with high yields [Eq. (6)]. Further ligand variations with TPPTS [12] and guanidino-functionalized phosphines [22] revealed that this methodology works also without any CuI promoter, when higher amounts of palladium (10 mol%) are used.



(6)

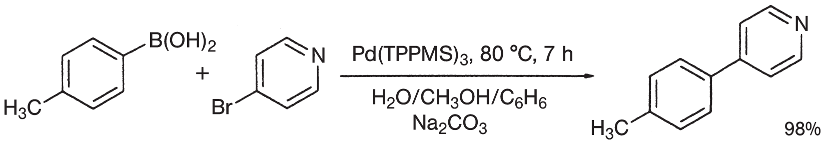
Furthermore, Bumagin and Beletskaya reported the first coupling in neat water in the presence of a small amount tributylamine and potassium carbonate as base [23]. Surprisingly, the catalyst system consists of water-insoluble triphenylphosphine with $PdCl_2$ and CuI at room temperature, resulting in high yields with aryl iodides and phenylacetylene. The role of cuprous iodide was noted to be important to facilitate the reaction, which may be rationalized by two connected catalytic cycles.

In addition, the application of "Jeffery's conditions" by Sinou and co-workers, with extra triphenylphosphine and tetrabutylammonium hydrogen sulfate, confirmed that CuI is not essential to success in alkyne coupling reactions [24]. Moreover, they reported the most efficient coupling of bromoanisole with propargyl alcohol in 81% yield.

2.4.4.4.5
Cross-Coupling Reactions

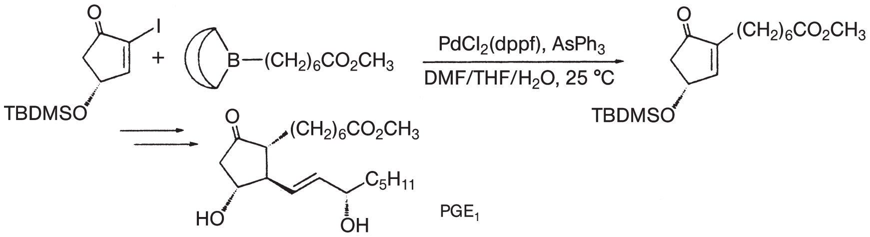
Suzuki Coupling

The Suzuki coupling is defined by the presence of boron-containing coupling reactions. Thus, the palladium-catalyzed reaction of aryl or alkenyl halides with alkenylboronates or arylboronic acids is a regio- and stereoselective bond formation affording, in particular, unsymmetrical substituted biaryls [25]. Once again, the first application of this approach in the aqueous phase was reported by Casalnuovo and Calabrese, demonstrating the high efficiency of their $Pd(TPPTS)_3$-based catalyst system. Thus, 4-bromopyridine was coupled with *p*-tolylboronic acid in a water/methanol/benzene solvent mixture in 98% yield [Eq. (7)] [6].



(7)

Later, the same methodology was applied by Wallow and Novak for the synthesis of water-soluble poly(*p*-phenylene) derivatives via the "poly-Suzuki" reaction of 4,4′-biphenylylene bis(boronic acid) with 4,4′-dibromodiphenic acid in aqueous dimethylformamide [26]. These aromatic, rigid-chain polymers exhibit outstanding thermal stability (decomposition above 500 °C) and play an important role in high-



Scheme 2

TBDMSO = t - butyldimethylsilyl
dppf = 1,1 - bis (diphenylphosphinoferrocene)

performance engineering materials [27], conducting polymers [28], and nonlinear optical materials [29] (see also Section 7).

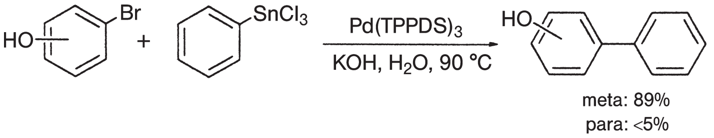
Furthermore, this regio- and stereoselective bond formation between unsaturated carbon atoms was applied to the synthesis of functionalized dienes under extremely mild conditions. Thus, even vinylic boronic esters containing an allylic acetal moiety and alkenylboronate having a chiral protected allylic alcohol were obtained successfully with vinylic iodides under aqueous conditions [30]. In addition, an exceptionally simple and efficient synthesis of a prostaglandin (PGE_1) precursor was reported by Johnson, by applying a DMF/THF/water solvent mixture with a 1,1-bis(diphenylphosphino)ferrocene palladium catalyst [31]. It is curious that the presence of water is an absolute necessity in order to succeed in this approach (Scheme 2).

It is noteworthy that 9-alkyl-9-BBN (9-BBN = 9-boracyclo[3.3.1]nonyl) reagents are easily prepared by hydroboration of the corresponding olefin, demonstrating the high variability of this approach in organic synthesis.

Stille Coupling

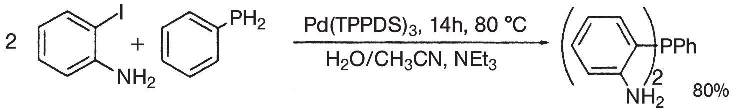
The Stille coupling depends on tin-containing reagents. Although the cross-coupling of organotin reagents with organic halides proceeds under extremely mild conditions, it seems to be the most unexplored field of palladium-catalyzed reactions [32], because of the high toxicity of the volatile tetraorganotin compounds. Thus, the first application in an aqueous medium was reported by Daves in 1993, describing the synthesis of a pyrimidine derivative formed by in-situ hydrolysis of the intermediate enol ether [33].

In 1995, Beletskaya [34] and Collum [35] reported independently the application of alkyltrichlorostannanes instead of tetraorganotin compounds, overcoming the disadvantage of three inert anchoring groups and technologically more important, because of their lower toxicity and availability via economic direct synthesis from tin(II) compounds [36]. Furthermore, the hydrolysis of the tin–halide bond in water results in higher water solubility, activation of the C–Sn bond toward electrophiles (e.g., in transmetallation) and less toxic byproducts. The reaction may be accomplished via intermediate anionic hydroxo complexes [37] produced in situ in aqueous alkaline solution, and proceeds in most cases in 3 h at 90–10 °C [Eq. (8)].



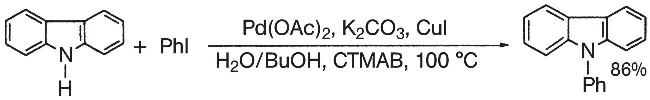
(8)

For insoluble development in Heck-type reactions is P–C and N–C bond formation, which results from coupling of aryl halides with phosphorous compounds [38] and amines [39]. The first application in aqueous medium was achieved by coupling of a dialkyl phosphite with an aromatic iodide to give an arylphosphonate in 99% yield. In 1996, Stelzer and co-workers presented a P–C cross-coupling reaction between primary and secondary phosphines and functional aryl iodides to water-soluble phosphines [Eq. (9)], which are potentially applicable as ligands in aqueous-phase catalysis [40].



(9)

A rather unusual procedure has been published for the palladium- and copper-catalyzed synthesis of triarylamines, using an alkaline water–ethanol emulsion stabilized by cetyltrimethylammonium bromide [41]. Anyway, this method overcomes the problem in the synthesis of *N*-aryl carbazoles [Eq. (10)], which are not accessible by the method developed by Hartwig and Buchwald [42].



(10)

2.4.4.4.6
Conclusion

The advantages of Heck-type reactions in the aqueous phase are demonstrated by the large number of successful approaches presented here. The change in the thermodynamics caused by using water as the reaction medium results in milder reaction conditions, higher yields, and improvements in chemo- and regioselectivity. The trend in the last few years has moved toward systems which are designed to improve the catalyst recovery. The results reported in this field give great promise for powerful catalyst systems in the near future.

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2.4.4.5
Aminations

Birgit Drießen-Hölscher (†)

2.4.4.5.1
Introduction

All kinds of amines are of great importance for synthetic chemists in basic research as well as for the chemical industry. But the synthesis of amines in terms of an optimum material balance, short sequences, and selectivities is still a challenge. In recent years, great efforts have been made worldwide to develop new amination reactions [1].

This section deals with catalyzed aminations in aqueous phases, so the developments discussed here must have some water in the reaction mixture. All reactions known to synthesize amines via catalysts in the presence of water can be divided into four categories and are discussed in the following order: Hartwig–Buchwald aminations, telomerization to yield amines, reductive aminations/hydroaminomethylations, and allylic aminations.

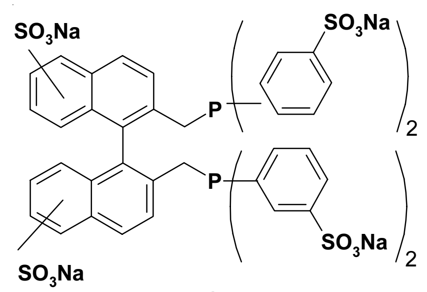
2.4.4.5.2
Hartwig–Buchwald Aminations

The palladium-catalyzed amination of aryl halides and sulfonates has emerged as a valuable method for the preparation of aromatic amines [2]. Numerous ligands and catalysts have been reported to effect this type of cross-coupling. This reaction, known as the Hartwig–Buchwald amination, is shown in Eq. (1).

$$\mathrm{ArX} + \mathrm{HNNR^1} \xrightarrow[\text{toluene, 80–100 °C}]{\text{PdL, NaOBu}^t} \mathrm{ArNRR^1} \qquad (1)$$

$$\mathrm{X = Cl, Br, I, OSO_2CF_3} \qquad \mathrm{R = H, alkyl, aryl} \qquad \mathrm{R^1 = aryl}$$

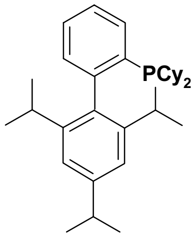
Under such conditions re-use of the palladium catalyst would be difficult. This was the motivation of Boche et al. to use a two-phase protocol by dissolving the six-fold sulfonated BINAS-6 (**1**) and palladium acetate in water [3].



1

The reaction of 4-bromoacetophenone with *N*-methylaniline in water using NaOH as the base and the aforementioned catalyst afforded the tertiary amine in 36% yield. By adding co-solvents, such as methanol, the yield can be increased to 91%. In conclusion, the advantages are the facile catalyst/product separation, the reusability of the water-soluble palladium catalyst, and the use of NaOH instead of the expensive NaOBu^t as the base.

Aqueous aminations with palladium catalysts that are not soluble in water have recently been described by Buchwald et al. [4]. The use of **2**/Pd_2dba_3 and KOH in water without co-solvent gives excellent results in the amination of aryl chlorides containing nitro, trifluoromethyl, or pyridyl groups. Indoles and hindered aryl nonaflates can be aminated in good yields. In summary, co-solvents and phase-transfer catalysts are not necessary.

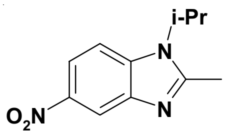


2

Aminations that occur in the presence of inexpensive and air-stable bases have become more important. Hartwig et al. demonstrated that low-cost alkali metal hydroxides can serve as stoichiometric base for the palladium-catalyzed cross-coupling of various amines with aryl chlorides and bromides [5].

Acceptable reaction rates and high yields are obtained with the combination of phase-transfer catalyst and 1 equiv of water and KOH, or with the combination of phase-transfer catalyst and concentrated aqueous NaOH or KOH. In summary, the new base system performed as well as $NaOBu^t$ in certain reactions. In a recent paper, K_3PO_4 was delivered as an aqueous solution which was approximately 17% of the total volume of the reactions [6]. The coupling of a complex bromoarene and a fluorophore was tested with [CpPd (allyl)] as palladium source. Mixtures of dioxane and xylene gave much higher yields compared to $NaOBu^t$ as the base in this medium.

Intramolecular palladium–catalyzed aryl amination chemistry is used to synthesize benzimidazoles. When NaOH in toluene is used as a base, the reaction rate is very slow. But aqueous reaction conditions (20% water/xylene) led to complete conversion of an amidine to benzimidazole **3** after two hours at reflux [7].



3

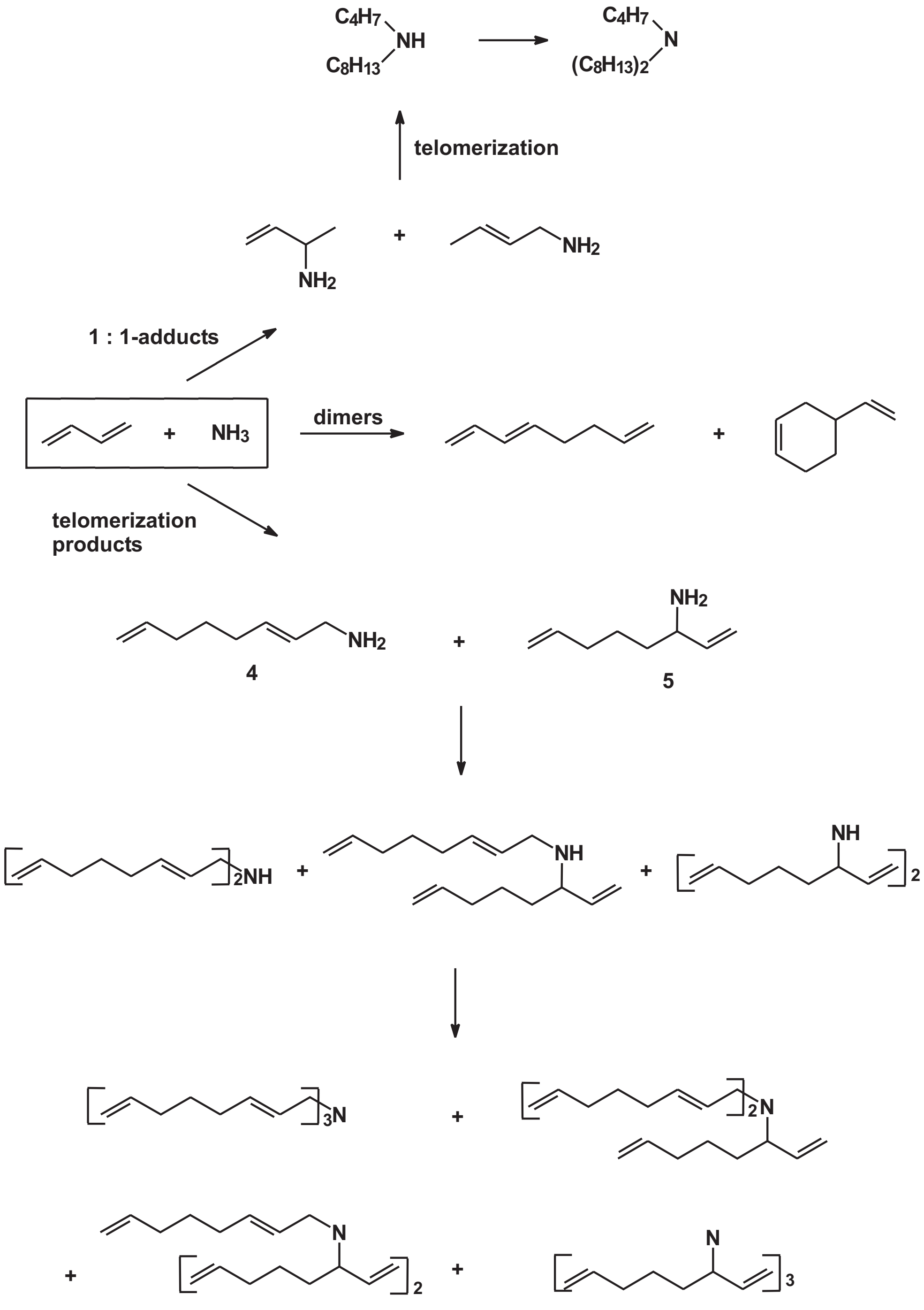
When this chemistry was attempted with microwave heating, a quantitative conversion to **3** occurred in just 20 min at 200 °C. But 10 mol% of a phase-transfer catalyst was necessary. The reaction conditions were optimized, leading to lower catalyst concentrations and shorter reaction times.

2.4.4.5.3
Telomerization to Yield Amines

Telomerizations have proven to be of great industrial value [8] and the products obtained play an important role as intermediates for the production of fine and bulk chemicals (see Section 2.4.4.2). The telomerization of ammonia and butadiene (Scheme 1) has been extensively studied using homogeneously catalyzed one-phase reactions [9]. In this case the main products obtained are the tertiary octadienylamines. The nucleophilicity increases in the order ammonia, primary octadienylamine, secondary octadienylamine so that the reaction cannot be stopped. A summary of all observed and possible products is given in Scheme 1.

These consecutive reactions can be avoided by using the biphasic method [10], which allows the selective production of the primary amines **4** and **5**. The reaction takes place in an aqueous catalyst phase ($Pd(OAc)_2$ + TPPTS) and the primary products are extracted in situ by a second organic phase (e.g., toluene, methylene chloride, butadiene) which is immiscible with water.

In order to optimize and better understand the regioselectivity and the rate of product formation, the kinetics of this reaction were determined. The kinetic experiments led to a model of the reaction that also explains the different regioselectivities. By ligand variations the regioselectivity of the reaction can be controlled. The ligand with the highest π-acceptor properties (*p*-F-TPPTS) gives the lowest selectivity to the terminal amine **4** whereas the ligand with the highest σ-donor properties (TOM-TPPTS) leads to the terminal amine **4** with a selectivity of 94%.



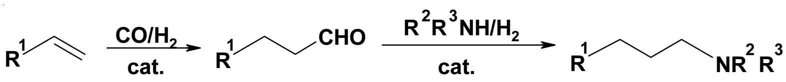
Scheme 1 Possible reactions of butadiene with ammonia.

By lowering the π-acceptor properties of the ligand, the activity of the catalyst system decreases [11].

2.4.4.5.4
Reductive Aminations/Hydroaminomethylations

The reductive amination of carbonyl compounds constitutes a convenient and practical approach to synthesizing primary amines and is generally performed by heterogeneous catalysts [12].

Reductive amination is the last step in a domino reaction called hydroaminomethylation (Scheme 2). One-phase hydroaminomethylations with primary and secondary amines have been described in particular by Eilbracht [13].



Scheme 2 Hydroaminomethylations of olefins.

The hydroaminomethylation of 1-pentene and ammonia, with a Rh/Ir/TPPTS catalyst in an aqueous/organic two-phase system, was developed by Beller et al. [14]. Under standard hydroformylation conditions (130°C, 12 MPa) amines could be isolated in 75% yield. By increasing the ammonia/olefin ratio and by using the extraction effect of the organic solvent as in Ref. [10], the selectivity for primary amines could reach more than 90%. This method could also be used for propene and 1-butene to give butylamine and pentylamine as main products.

Organometallic aqua complexes of iridium such as $[Cp^*Ir(H_2O)_3]^{2+}$ are slightly active catalysts in reductive amination of *n*-butanal when $HCOONH_4$ is utilized as the hydrogen and amine donor [15]. The rate of the reductive amination is dependent on the concentration of $HCOONH_4$ and on pH. The initial TOF is 2 h^{-1}. Recently, an unprecedented ruthenium-catalyzed reductive amination of aldehydes with tertiary amines in an aqueous medium was reported [Eq. (2)] [16]. Treatment of benzaldehyde with tributylamine afforded benzyldibutylamine in 43% yield and dibenzylbutylamine in 7% yield. Several other ruthenium complexes were ineffective for this reaction, and performing the reaction in pure dioxane gave much lower yields.

$$RCHO + NR_3' \xrightarrow[\substack{\text{dioxane/H}_2\text{O1} \\ 180\,°\text{C, 12 h}}]{[Ru_3(CO)_{12}],\ CO} RCH_2NR_2' + R(CH_2)_2NR' \tag{2}$$

The synthesis of primary amines in biphasic operation has been developed via selective reductive amination of aromatic and aliphatic carbonyl compounds using aqueous ammonia in the presence of water-soluble transition metal catalysts [17]. The use of $[Rh(cod)Cl]_2$ with TPPTS as catalyst and ammonium acetate in water/THF afforded benzylamine from benzaldehyde in 86% yield. This method is also feasible for the synthesis of aliphatic primary amines from aliphatic aldehydes in

45–47% yield. Byproducts are secondary amines as well as aldol condensation products, but the formation of alcohol is negligible.

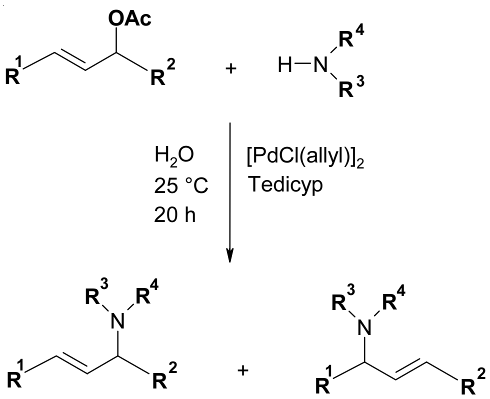
Aqueous ammonia was found to increase the yield of the alcohol but not of the amine in the highly enantioselective hydrogen-transfer reductive amination of acetophenone, as recently described by Kadyrov et al. [18]. All these reactions were performed in methanol/NH_3 with [((*R*)-tol-binap)$RuCl_2$] as catalyst with a best asymmetric induction of 98% *ee*.

2.4.4.5.5
Allylic Aminations

Allylic substitutions in water were described a few years ago by the groups of Genet and Sinou [19] (see also Section 2.4.5.1), but few results have been obtained so far for allylic amination in water.

A new tetrapodal phosphine ligand, *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane (Tedicyp), in association with $[PdCl(C_3H_5)]_2$, is an extremely efficient catalyst for allylic amination [20]. Addition of diisopropylamine to an allyl acetate [Eq. (3)] is suprisingly higher in water than in THF.

The complex seemed to be very stable in water. A conversion of 98% was observed when a substrate/catalyst ratio of 1.000 was used.



(3)

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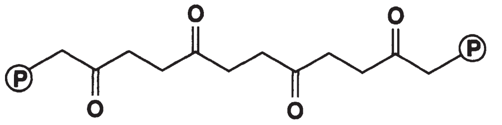
2.4.4.6
Alternating Copolymers from Alkenes and Carbon Monoxide

Eite Drent, Johannes A. M. van Broekhoven, and Peter H. M. Budzelaar

2.4.4.6.1
Introduction

The copolymerization of ethylene and carbon monoxide to give alternating copolymers has attracted considerable interest in both academia and industry over recent decades [1, 2]. Attention was focused on aliphatic polyketones such as poly(3-oxotrimethylene) (**1**) because of the low cost and plentiful availability of the simple monomers. The new family of thermoplastic, perfectly alternating olefin/carbon monoxide polymers commercialized by Shell provides a superior balance of performance properties not found in other commercial materials; the an ethylene/propene/CO terpolymer is marketed by Shell under the tradename Carilon®. About the history of polyketones see Refs. [3–11].

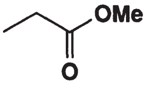


1 polyketone

2.4.4.6.2
Copolymerization of Ethylene and CO

The discovery of efficient catalysts for the copolymerization of alkenes originated from a study of the alkoxycarbonylation of ethylene in methanol (MeOH) to methyl propionate [Eq. (1)].

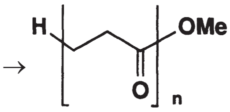
$H_2C{=}CH_2 + CO + MeOH \rightarrow$



(1)

The catalysts were cationic palladium–phosphine systems prepared from palladium acetate, an excess of triphenylphosphine (PPh_3), and a Brønsted acid of a weakly or noncoordinating anion (e.g., *p*-tosylate (OTs^-); methanol was used as both the solvent and a reactant. An unexpected change in selectivity was observed upon replacement of the excess of PPh_3 by a stoichiometric amount of the *bidentate* 1,3-bis(diphenylphosphino)propane (dppp). Under the same conditions, these modified catalysts led to perfectly alternating ethylene/CO copolymers with essentially 100% selectivity [Eq. (2)] [12–14].

$n\ H_2C{=}CH_2 + n\ CO + MeOH \rightarrow$



(2)

A typical reaction rate would be about 10^4 mol of converted ethylene/mol Pd per hour, to give a polymer with an average molecular weight (M_n) of ~20 000. Under suitable conditions the catalysts are highly stable and total conversions of more than 10^6 mol of ethylene per mol of Pd can be obtained. The product is high-melting (~260 °C) and is insoluble in most organic solvents; it crystallizes and precipitates during copolymerization as a snow-white solid.

Variation of the bidentate ligand results in significant changes in both the reaction rate and the molecular weight of the product. Figure 1 shows the effect of changing the chain length *n* of the diphosphine, of general formula $Ph_2P(CH_2)_nPPh_2$, on the rate and molecular weight. Many patents deal with more subtle variations of the diphosphine. In addition, several other types of *chelating* ligands (bipyridines [15], bisoxazolines [16], thioethers [17]) can be used. The counteranions also affect reaction rates; highest catalyst activities are obtained with weakly or noncoordinating anions (OTs^-, triflate (OTf^-), trifluoroacetate (TFA^-), BF_4^-, ClO_4^-, and "organic" anions such as certain tetraaryl borates). Best results are observed in protic solvents, such

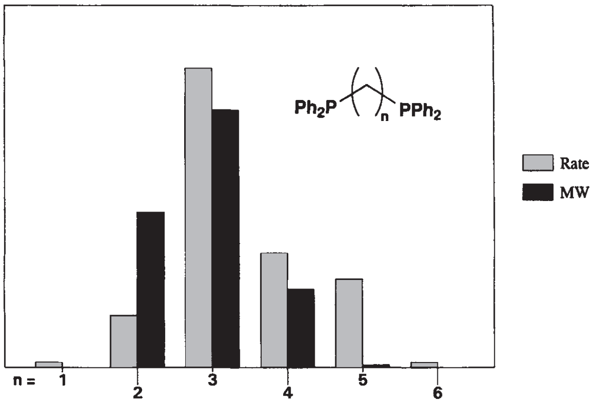


Figure 1 Influence of chain length of ligand $Ph_2P(CH_2)_nPPh_2$ on polymerization rate and molecular weight of polyketone.

as lower alcohols, but the polymerization also proceeds well in some aprotic solvents. The anions can, generally, conveniently be introduced by adding a Brønsted or Lewis acid, as anion source, to palladium acetate [Eq. (3)].

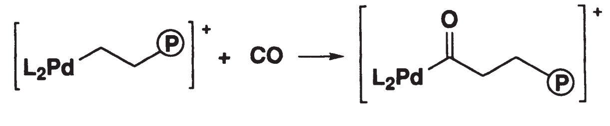
$$L_2Pd(OAc)_2 + 2\ HX \rightarrow L_2PdX_2 + 2\ HOAc \qquad (3)$$

Instead of the free acid it is sometimes advantageous to use a metal salt (e.g., of Cu(II) of Ni(II)) to introduce the anions. Preformed complexes of the type L_2PdX_2 [18] and $L_2Pd(R)X$ [19], where L_2 represents a chelating ligand, X a weakly coordinating anion, and R a hydrocarbyl group (e.g., methyl), have also been tested as catalysts. The results are, generally, very similar to those obtained with catalysts prepared in situ.

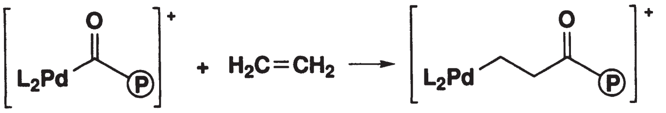
a) Mechanism of Polymerization

Propagation

The catalytically active species in polyketone formation is thought to be a d^8 square-planar cationic palladium complex $L_2Pd(P)^+$, where L_2 represents the bidentate ligand and Ⓟ is the growing polymer chain. The fourth coordination site at palladium may be filled with an anion, a solvent molecule, a carbonyl group of the chain (vide infra), or a monomer molecule. The two alternating *propagation* steps are migratory insertion of CO in the palladium–alkyl bond [Eq. (4)] [20] and subsequent migratory insertion of ethylene in the resulting palladium–acyl bond [Eq. (5)]. Propagation "errors" (double CO or ethylene insertion) are not observed.



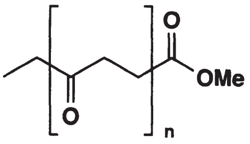
(4)

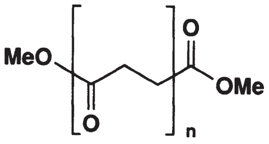

(5)

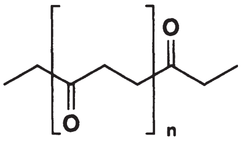
Carbon monoxide insertion in a palladium–carbon bond is a fairly common reaction [21]. Under polymerization conditions, CO insertion is thought to be rapid and *reversible*. Olefin insertion in a palladium–carbon bond is a less common reaction, but recent studies involving cationic palladium–diphosphine and –bipyridyl complexes have shown that olefin insertion also, particularly in palladium–acyl bonds, appears to be a facile reaction [22]. Nevertheless, it is likely that olefin insertion is the slowest (rate-determining) and *irreversible* step (vide infra) in polyketone formation.

Initiation and Termination

End-group analysis by ^{13}C-NMR of the ethylene/CO copolymer produced in methanol generally shows the presence of 50% ester (–COOMe) and 50% ketone (–$COCH_2CH_3$) groups, in accordance with the average overall structure of the polymer molecule as depicted in Eq. (2). It is not clear a priori which group is the "head" and which is the "tail" of the molecules. Moreover, GC and MS analyses of oligomers produced with certain catalysts [13] show, in addition to the expected keto-ester product (**2**), the presence of diester (**3**) and diketone (**4**) compounds.


2
keto-ester
n ≥ 0

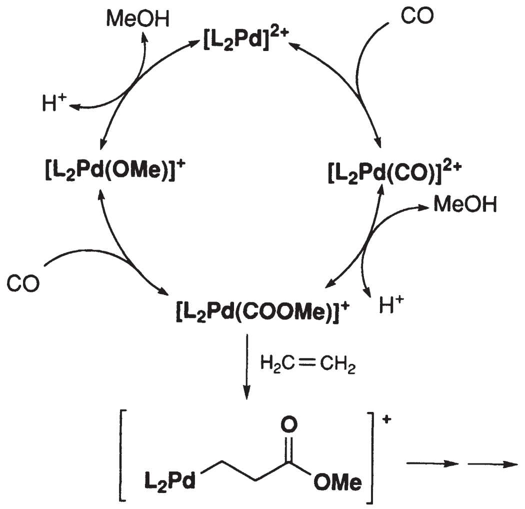

3
diester
n ≥ 1


4
diketone
n ≥ 0

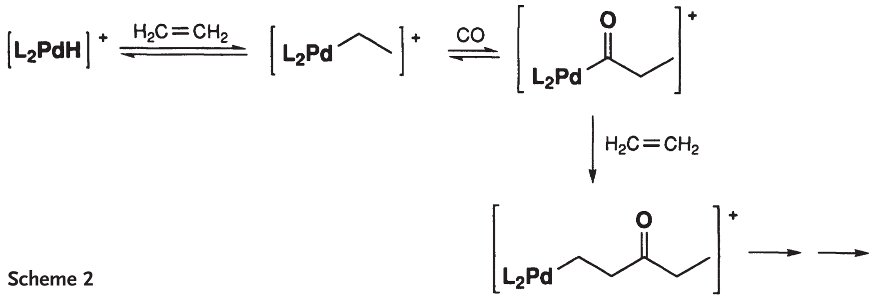
At low temperatures (below ~85 °C), the majority of the product molecules are keto-esters, with only small but balancing quantities of diesters and diketones. At higher temperatures, the same product molecules are produced in a **2**/**3**/**4** ratio close to 2 : 1 : 1. These observations have been explained [13] by assuming two initiation and two termination mechanisms for polyketone formation.

One initiation pathway produces ester end-groups. It starts with a palladium–carbomethoxy species, which can be formed either by CO insertion in a palladium methoxide or by direct attack of methanol on coordinated CO (Scheme 1).

Alternatively, a polymer chain can start by insertion of ethylene in a palladium hydride (vide infra), producing a ketone end-group. Ethylene insertion in palladium hydride and CO insertion in the resulting ethyl complex are both rapid and reversible; it is thought that the second ethylene insertion (in the Pd–acyl) is irreversible and "traps" the acyl complex to start the chain (Scheme 2).

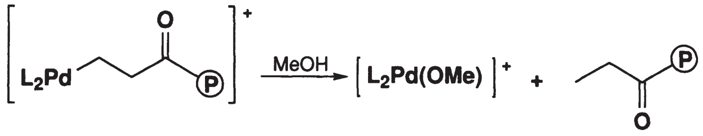


Scheme 1



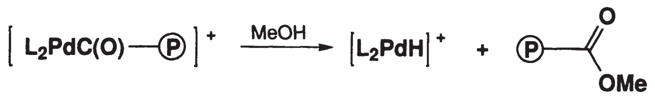
Scheme 2

For ethylene/CO copolymerization, two relevant termination mechanisms have been proposed. One mechanism, protonolysis of the palladium–alkyl bond, produces a saturated ketone end-group and a palladium methoxide [Eq. (6)]. The latter can again be converted to a palladium carbomethoxide initiator by CO insertion into the palladium–methoxide bond.



(6)

A second mechanism, the alcoholysis of the palladium–acyl bond, gives an ester end-group and a palladium hydride species [Eq. (7)], which is again an initiator for the next polymer chain.



$$[L_2PdC(O)—Ⓟ]^+ \xrightarrow{MeOH} [L_2PdH]^+ + Ⓟ—C(=O)OMe \qquad (7)$$

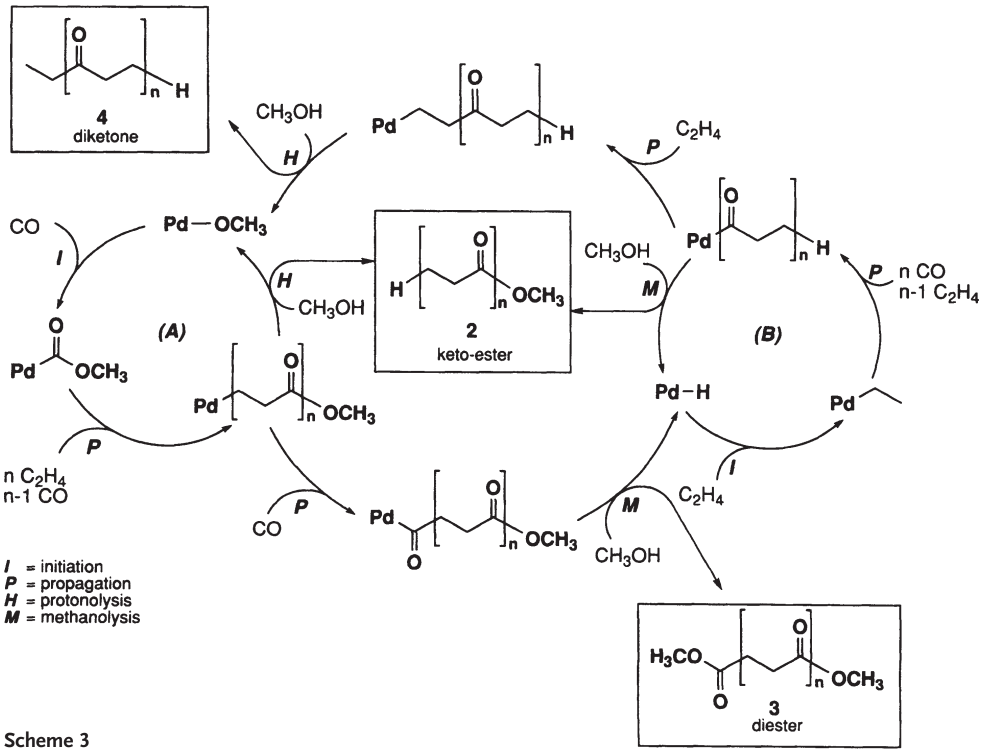
Scheme 3 summarizes the formation of the three possible polymeric products of **2**, **3**, and **4** by the two initiation–propagation cycles (*A*) and (*B*). Both cycles produce keto-ester molecules, but the cycles are connected by two "cross"-termination steps to give diester and diketone products.

The formation of substantial amounts of **3** and **4** at the higher temperatures demonstrates that transfer between the cycles is rapid and that both cycles contribute with comparable rates [23].

Copolymers with predominantly ketone end-groups (i.e., **4**) can be produced either by admitting water to the polymerization or by adding some hydrogen [13]. In aprotic solvents diketones can be produced exclusively. This indicates that palladium hydrides, generated via the water-gas shift reaction [Eq. (8)], or by heterolytic hydrogen splitting [Eq. (9)], are indeed efficient initiators and it also shows that protonolysis and/or hydrogenolysis of palladium alky Is can be an efficient termination mechanism.

$$[L_2Pd]^{2+} + H_2O + CO \rightarrow [L_2PdH]^{+} + H^{+} + CO_2 \qquad (8)$$

$$[L_2Pd]^{2+} + H_2 \rightarrow [L_2PdH]^{+} + H^{+} \qquad (9)$$

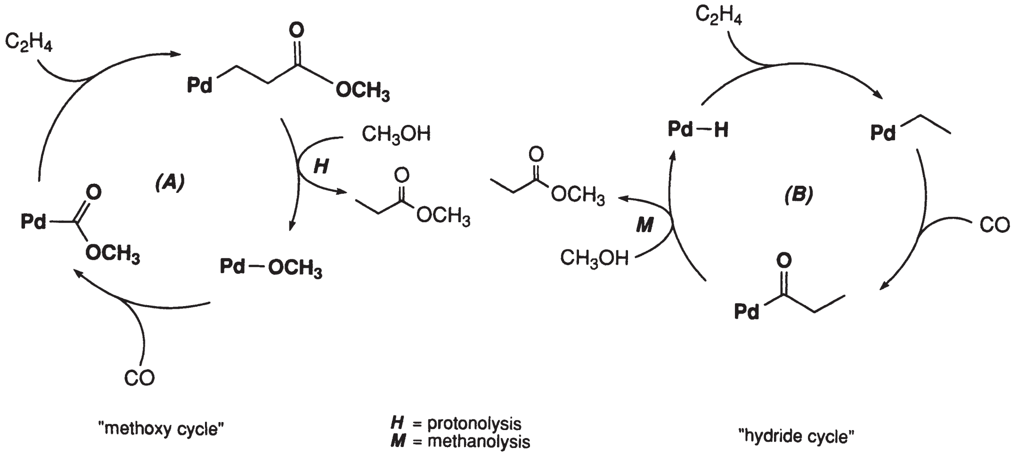


Scheme 3

b) The Role of Bidentate Ligands

Under conditions of polyketone catalysis, cationic palladium(II) catalysts modified with excess of *monodentate* phosphine and Brønsted acids of weakly coordinating anions selectively give methyl propionate with high rates [Eq. (1)]. Methyl propionate formation can be considered as a combination of polyketone initiation and termination steps without intervening propagation steps. Again, there are two possible catalytic cycles ((*A*) and (*B*), Scheme 4). There is no a priori argument to decide which cycle is actually responsible for methyl propionate formation. The absence of the cycle-transfer products diethyl ketone and dimethyl succinate suggests that only one cycle is operative, but it is also possible that both cycles operate in isolation.

The most obvious difference between monodentate and bidentate ligands is that the latter are always *cis* coordinated, whereas the former can also coordinate in a *trans* fashion. If bidentate ligands are used, the starting or growing polymer chain and the "empty" fourth coordination site are always *cis* to each other, which is the most favorable position for insertion reactions. Therefore, olefin insertion in the palladium–acyl is a probable reaction in *bidentate* phosphine complexes. If *monodentate* phosphines are used, both palladium–alkyl and palladium–acyl species prefer a *trans* orientation of the two phosphine ligands, which avoids the unfavorable situation of a Pd–P bond *trans* to a Pd–C bond. At the same time, *cis*/*trans* isomerization is expected to be rapid because of the presence of excess ligand [24]. It is further expected that both the insertion of ethylene in Pd–H and CO insertion in Pd–alkyl can only occur when the phosphine ligands are *cis* to each other. Immediately after insertion, *cis*/*trans* isomerization is likely to occur which places the "chain" and the fourth coordination site *trans* and thus opposes further monomer insertions. Therefore, the palladium–acyl can rapidly terminate by alcoholysis of the Pd–acyl bond to give methyl propionate.



Scheme 4 Two possible mechanisms for methyl propionate formation.

c) The Role of the Anions

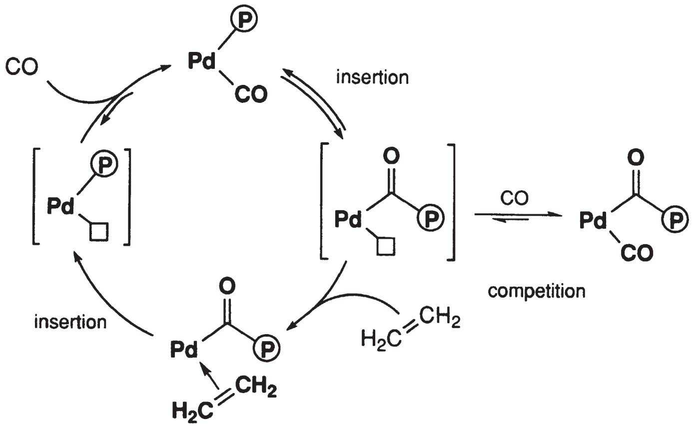
Apart from the requirement of *cis*-chelating neutral ligands (L_2), the high-activity catalyst complexes, L_2PdX_2, also require weakly or noncoordinating anions (X^-) [10, 13].

The higher reactivity of catalyst systems formed with such anions is thought to stem at least partly from the easier access of the substrate molecules to the coordination sites at the metal center. Nevertheless, it is suggested that the anionic ligands are actively involved in the catalytic cycle. Their presence in the proximity of the cationic palladium center, forming more or less strongly associated cation–anion pairs, can have a profound effect on the catalysis at that center. A contributing factor may be that less strongly coordinating anions, because of their easier dissociation from the ion-pair, generate a more electrophilic palladium center. The lower electron density on the palladium center may cause a lower binding energy with the comonomers because of less back-donation from metal to ligand. The intermediate palladium species which are involved in the catalytic cycles would therefore be less stable, with the result that, for instance, carbon monoxide, occupying vacant coordination sites at the palladium center, can be displaced by the olefin, and vice versa. At the same time (migratory) transformations between the various intermediate complexes would require lower activation energies and so proceed at a higher rate.

Coordination of the anions to the cationic palladium center may strongly depend on the polarity of the reaction medium. Solvation of the ion-pair by protic solvent molecules, such as methanol, is expected to facilitate cation–anion dissociation and therefore render the ijietal center more electrophilic and more easily accessible for substrate molecules. In relatively apolar solvents, close-contact ion-pairs are generally expected to exist. Anion displacement by substrate molecules may then require the use of noncoordinating anions, such as certain tetraaryl borates [19], with a relatively strong affinity for interaction with the solvent molecules. This will lead to a reduced barrier for displacement of these anions by monomer molecules.

d) Alternation Phenomena

Chain propagation of CO/ethylene copolymerization proceeds by a strictly alternating insertion of CO and olefin monomers in the growing chain. It is safe to assume that *double CO* insertion does not occur for thermodynamic reasons [1c]. However, the complete absence of double ethylene insertions is remarkable because ethylene insertion in a Pd–alkyl species must be exothermic by about 20 kcal mol^{-1} (84 kJ mol^{-1}). The observation of strict alternation is the more surprising since the same palladium catalysts also efficiently dimerize ethylene to butenes [25]. The perfect alternation is maintained even in the presence of very low concentrations of carbon monoxide. When starting a batch polymerization at a high ethylene/CO ratio, error-free copolymer is produced until all the CO is consumed; then the system starts forming butenes (with some catalyst systems at about twice the rate of copolymerization!).



Scheme 5 Competition between CO and ethene coordination in polyketone formation.

One reason for the perfect alternation is probably the stronger coordination of CO to palladium(II), compared with ethylene. Once a palladium–*alkyl* is formed, the stronger CO coordination ensures that the next monomer to insert will usually be a CO molecule (assuming similar insertion barriers). Of course, CO also coordinates more strongly to a palladium–*acyl* but since the CO insertion is thermodynamically unfavorable, there the system will "wait" for an ethylene molecule to displace CO, to coordinate and insert (Scheme 5).

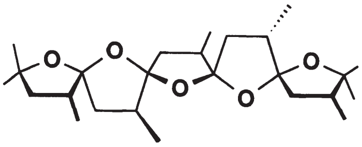
Chain propagation involves alternating *reversible* carbon monoxide insertion in Pd–alkyl species and *irreversible* insertion of the olefin in the resulting Pd–acyl intermediates. The overall exothermicity of the polymerization is caused predominantly by the olefin insertion step. Internal coordination of the chain-end's carbonyl group of the intermediate Pd–alkyl species, together with CO/olefin competition, prevents double olefin insertion, and thermodynamics prevent double CO insertions. The architecture of the copolymer thus assists in its own formation, achieving a perfect chemoselectivity to alternating polyketone.

A more detailed description of mechanistic aspects has been given in a previous article [26].

2.4.4.6.3
Scope of Olefin/CO Copolymerization

One of the unique further features of the catalysts is their ability to catalyze *also* the alternating co- or terpolymerization of higher olefins (both simple aliphatic and heteroatom-functionalized olefins) with carbon monoxide [27–32].

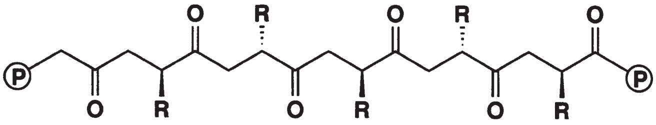
Chemoselectivity of Copolymerization (e.g., perfect alternation) with these olefins is governed by similar factors to those discussed for ethylene/CO Copolymerization, although some differences are noteworthy. Whereas β-H elimination does not take place to a significant extent with ethylene/CO Copolymerization, this termination pathway can play a significant role in Copolymerization with higher olefins. Another difference is that, under certain circumstances and with certain ligands, the polymers can be formed in a polyspiroketal structure (**5**), isomeric with polyketones [33, 34].



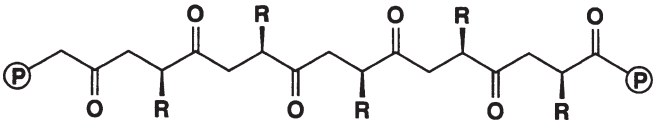
5 polyspiroketal

Apart from chemoselectivity, regio- and stereoselectivity of olefin insertion are also important factors to consider with higher olefin/CO copolymers.

By a suitable choice of ligands (L_2) and anions (X^-) it appears possible to control the regioselectivity of olefin insertion in intermediate Pd–acyl species (1,2- vs. 2,1-insertion) to give polymers with olefin enchainments via CO, varying from regioirregular to completely regioregular (for example, exclusively head-to-tail enchainment). The stereochemistry of olefin insertion can also be controlled to give atactic, isotactic, or syndiotactic olefin/CO copolymers (structures **6** and **7**) [36]. Stereoregularity can be achieved by a chain-end control mechanism [15, 36, 37] or by enantiomorphic site control [16, 28].



6 isotactic



7 syndiotactic

In contrast to polyolefins such as polypropene, polyketones possess true stereogenic centers along the polymer backbone. Therefore, polyketones present a unique opportunity to use simple monomers in combination with chiral, enantiomerically pure palladium catalysts to prepare highly isotactic, optically active polymers (or oligomeric compounds) with main-chain chirality.

2.4.4.6.4
Conclusions

The synthesis of alternating olefin/CO copolymers, discussed here, presents a new chapter in the history of olefin polymerization. Moreover, it constitutes an example of transition metal-catalyzed carbonylation with potentially almost perfect control over selectivity. The cationic palladium(II) complex catalysts derive their ability to activate the nucleophilic substrate molecules from the electrophilic nature of the palladium (d^8) center. The *cis* arrangement of the neutral chelate ligand around the metal center in a square-planar configuration ensures that the polymer's chain-end and incoming monomers will also be in the *cis* configuration required for chain propagation. The electronic and steric properties of both the ligand and polymer chain-end together determine the mode of olefin coordination at the fourth coordination site, which in turn will determine the mode and ease of (higher) olefin insertion during chain propagation. It is likely that the interaction between the polar polymer chain-end and the electrophilic palladium center will play a crucial role not only in achieving the alternating mode of chain propagation (chemo-selectivity), but also in obtaining a high regio- and stereoselectivity for higher olefin insertion in intermediate palladium–acyls.

Although the basic principles of polyketone formation are now reasonably well understood, further studies, both of polymerization characteristics and of the elementary steps underlying polyketone catalysis, will be needed to exploit fully the potential of these selective polymerizations.

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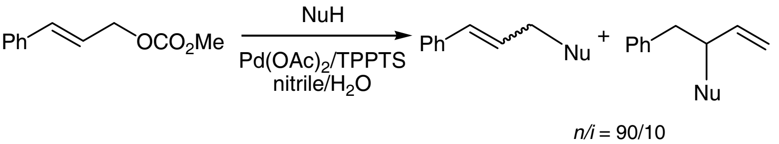
2.4.5
Allylic Substitution Reactions

Denis Sinou

Palladium-catalyzed allylic substitution, the so-called Tsuji–Trost reaction, is now a well-used methodology in synthetic organic chemistry, allowing the chemo-, regio-, and stereoselective formation of carbon–carbon bonds as well as carbon–heteroatom bonds under very mild conditions [1–3]. Although it was shown in the late 1980s that palladium(0)-catalyzed reaction of sodium azide with various allyl esters [4] or 1,3-diene monoepoxides [5] occurred in aqueous tetrahydrofuran, leading to allylic azides in quite good yields, the first example of palladium(0)-catalyzed alkylation in a two-phase water/organic solvent system using a palladium complex associated with TPPTS appeared in the literature as early as 1991 [6].

The water-soluble palladium(0) complex was generated in situ generally from $Pd(OAc)_2$ in association with a water-soluble ligand such as TPPTS [6–8], a nitrile being used as the co-solvent. Allylic carbonates such as cinnamyl carbonate reacted with various carbonucleophiles in this two-phase system, giving substitution products in moderate to high yields [Eq. (1)] [6, 9–11]. Since the reaction occurred in neutral medium, only traces of base being generated in the catalytic cycle, the allylic carbonates are stable to hydrolysis. It was noted that the selectivity in the formation of mono- and diallylated compounds was very sensitive to the nature of the carbonucleophile and its pK_a; the acyclic carbonucleophiles such as ethyl acetoacetate, acetylacetone, dimethyl malonate, dicyanomethane, and bis(phenylsulfone)methane gave predominantly the monoallylated product, when the cyclic carbonucleophiles such as tetronic acid, dimedone, and barbituric acid gave predominantly the diallylated product.



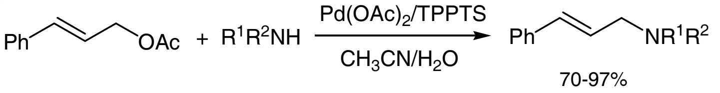
(1)

R: $CH_3COCH_2CO_2C_2H_5$, $CH_3COCH_2COCH_3$, $NO_2CH_2CO_2C_2H_5$

A detailed investigation using (*E*)-2-hexenyl methyl carbonate as the π-allyl precursor and ethyl acetoacetate as the nucleophile showed that the regioselectivity of the reaction is independent of the $Pd(OAc)_2$/TPPTS ratio, the reaction temperature, the water/nitrile ratio, or the nature of the nitrile [9]. However, the catalytic activity is deeply affected by these parameters, and the highest activity was obtained for a $Pd(OAc)_2$/TPPTS ratio of 9 : 1 in acetonitrile/water as the solvent mixture.

Alkylation of allylic acetates or vinyl epoxide occurred also under these conditions, NEt_3 or preferably 1,8-diazabicyclo[5.4.0]undec-7-ene (dbu) being used as the base in the former case.

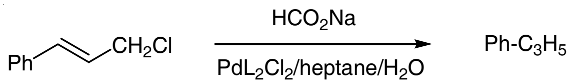
The alkylation reaction in a two-phase system was also extended to various heteronucleophiles [11]. Secondary amines (morpholine, benzylmethylamine, etc.) as well as primary amines (*n*-butylamine, 2,2-diethylpropargylamine, cyclohexylamine, α-methylbenzylamine, etc.) react for example with (*E*)-cinnamyl acetate to give only the monoallylated product in quite good yields [Eq. (2)]. The water-soluble nucleophiles sodium azide and sodium *p*-toluene sulfinate react also under these conditions, giving the corresponding allyl azide and allyl *p*-toluene sulfone in 92 and 95% yield, respectively.



(2)

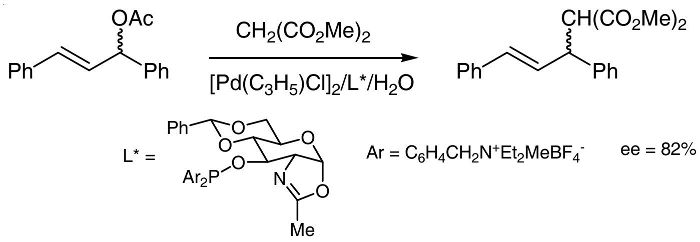
The use of benzonitrile or butyronitrile as the organic solvent allows an easy recycling of the catalyst, without any decrease in the yields [11].

Allyl chlorides and acetates are reduced to the corresponding alkenes in a two-phase system heptane/water in the presence of water-soluble palladium complexes containing ligands such as polyether phosphines, TPPMS, or carboxylic phosphines in the presence of HCO_2Na [Eq. (3)] [12]. The most active catalyst is $PdCl_2L_2$ with L being a polyether phosphine; a mixture of nonenes are obtained in 82% yield, $PdCl_2(P\text{-}n\text{-}Bu_3)_2$ giving lower yields under these conditions.



(3)

Asymmetric allylic substitution of 1,3-diphenyl-2-propenyl acetate in water or in an aqueous/organic biphasic medium has been performed in the presence of the complex obtained from $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and a chiral amphiphilic phosphinite-oxazoline derived from natural D-glucosamine, enantioselectivity up to 85% *ee* being obtained [13]; recycling of the catalyst is possible [Eq. (4)].



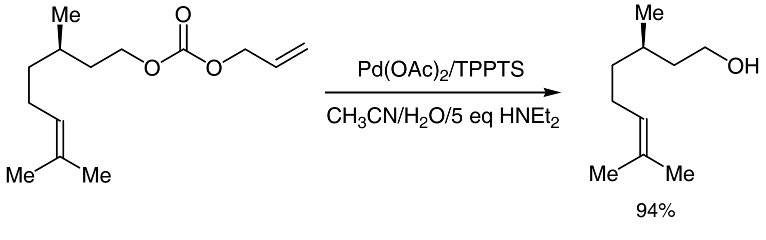
(4)

It has been observed that the rate of palladium-catalyzed allylic alkylation in water is drastically enhanced when the reaction is performed in the presence of surfactant [14]. Enantioselectivity up to 92% is obtained in the reaction of dimethyl malonate with 1,3-diphenyl-2-propenyl acetate when a chiral ligand such as Binap is used in the presence of cetyltrimethylammonium hydrogen sulfate [15, 16].

Water-soluble polymer-bound Pd(0)–phosphine catalyst has also been efficiently used in aqueous or mixed aqueous/organic media, the catalyst being recycled by solvent or thermal preparation methods [17]. Amphiphilic resin-supported palladium–phosphine complexes show high catalytic activity in allylic substitution reactions of various allylic acetates with different nucleophiles in aqueous media [18, 19]. Enantiomeric excess up to 98% is obtained using amphiphilic resin-supported MOP ligand or resin-supported P,N-chelating palladium complexes, the catalyst being recyclable [20, 21]. The catalyst could be recovered by simple filtration and re-used without any loss of activity and enantioselectivity.

A supported aqueous phase system (SAPC; see Section 2.6) has also been developed for allylic substitution. Alkylation of (*E*)-cinnamyl ethyl carbonate by ethyl acetoacetate or morpholine occurs in acetonitrile or benzonitrile using Pd(OAc)$_2$–TPPTS supported on mesoporous or nonporous silica; no leaching of the catalyst has been observed, allowing proper recycling of the catalyst [22–26]. Polyhydroxylated supports such as cellulose and chitosan have also been used successfully in this approach [27–29].

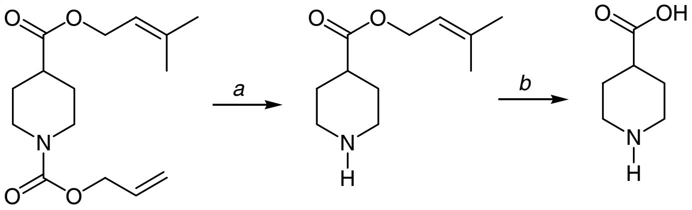
One of the most interesting applications of this palladium-catalyzed alkylation reaction in an aqueous biphasic system was the selective deprotection of amines and alcohols protected by the allyloxycarbonyl group (Alloc). Whereas a variety of nucleophilic species, such as carbonucleophiles, amines, thiols, carboxylates, and hydride donors, have been used in a homogeneous organic medium for intercepting the intermediate π-allyl complexes, Genêt et al. used the aqueous palladium catalyst obtained from Pd(OAc)$_2$ and TPPTS for the catalytic allyl transfer, diethylamine being the allyl scavenger [30–33]. Either nitrile/water or diethyl ether/water is equally suitable for the removal of the alloc moiety from nitrogen or oxygen, the reaction proceeding under very mild conditions with a very high chemoselectivity compared to the usual deprotection techniques. For example, deprotection of alloc-protected primary alcohols, such as (*R*)-citronellol, occurs in a few minutes upon exposure to Pd(OAc)$_2$–TPPTS in CH$_3$CN/H$_2$O, diethylamine being used in a 2–2.5-fold excess [Eq. (5)] [30, 31]. Under these conditions, *t*-butyldiphenyl ether or ester functions are stable. The deprotection of secondary alcohols such as menthol proceeds smoothly.



(5)

When the *N*-alloc protecting group of primary amines such as benzylamine is cleaved rapidly under these standard conditions in quantitative yields, the use of a 40-fold excess of diethylamine as the π-allyl scavenger or a five-fold excess of diethylamine in a butyronitrile/water system is necessary for the quantitative deprotection of alloc derivatives of secondary amines.

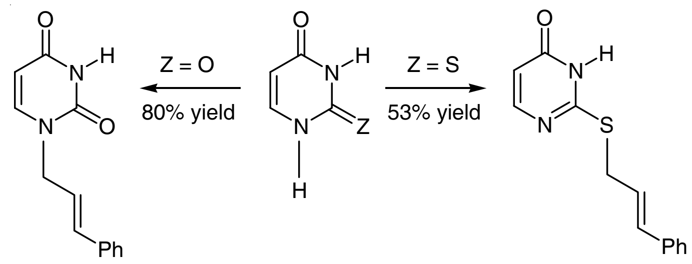
Deprotection of allyl groups from carboxylic allyl esters is also possible using these conditions [31, 33]. The conditions can be finely adjusted to allow selective differential deprotection of similar protective groups. In a homogeneous CH_3CN/H_2O medium, the facility of cleavage of the allyl group follows the order allyl > cinnamyl > dimethylallyl. However, under biphasic conditions (C_3H_7CN/H_2O), the allyl group of phenylacetic acid allyl ester is still cleaved at room temperature, giving phenylacetic acid in quite good yields, whereas the cinnamyl and the dimethylallyl esters remain intact even after three days of 25 °C. This procedure can also be used for the selective cleavage of allyloxycarbamate in the presence of substituted allyl carboxylate [Eq. (6)]. The allyloxycarbamate is selectively and quantitatively cleaved under homogeneous conditions, in the presence of 1% of palladium complex; treatment of the resulting monodeprotected product with a higher amount of catalyst (5 mol%) gives the free amino acid. Conversely, selective cleavage of an allyloxycarbonate could be performed in the presence of an allylcarbamate using successively C_3H_7CN and CH_3CN as the nitrile.



(6)

The use of the water-soluble sodium azide as the allyl scavenger allows the cleavage of allyloxycarbonyl-protected alcohols to occur under essentially neutral conditions [34]. It has been shown that the phosphines $(t\text{-Bu-}p\text{-}C_6H_4)_nP(C_6H_4\text{-}m\text{-}SO_3Na)_{3-n}$ ($n = 1, 2$) are more efficient than TPPTS in the deprotection of long alkyl chain alcohols [35].

The use of water or of a two-phase water/organic solvent system as the reaction medium could also change drastically the selectivity of a given reaction. This dramatic enhancement of selectivity was effectively observed in the allylation of uracils and thiouracils [36, 37]. Whereas the reaction of uracil with (*E*)-cinnamyl acetate in tetrahydrofuran in the presence of $Pd(PPh_3)_4$ gives a complex mixture of mono- and diallylated products, performing the reaction in CH_3CN/H_2O with $Pd(OAc)_2$–TPPTS as the catalyst leads to allylation only at N-1 in quite good yield [Eq. (7)]. In the case of thiouracil, performing the reaction in CH_3CN/H_2O with $Pd(OAc)_2$–TPPTS as the catalyst gave a unique product of monoallylation at sulfur, whereas the use of dioxane as the solvent in the presence of $Pd(PPh_3)_4$ gave a complex mixture of products resulting from allylation at N-1, N-3, and sulfur.



(7)

(*E*) Ph-CH=CH-CH_2OAc, cat Pd$(OAc)_2$/TPPTS, dbu, CH_3CN/H_2O

In conclusion, although the first aim of the use of a water-soluble palladium catalyst in allylic alkylation in a two-phase system was the recycling of the catalyst, this methodology finds quite interesting applications in the deprotection of amines, alcohols, and acids, as well as in the selective alkylation of uracils and thiouracils. More recently the effective use of supported aqueous-phase catalysis, as well as asymmetric alkylation in water in the presence of surfactants or amphiphilic resin-supported phosphines, opens new applications and developments for the future.

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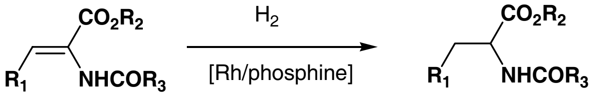
2.4.6
Asymmetric Synthesis

Denis Sinou

Since the mid-1980s there have been very important advances in asymmetric organometallic catalysis, enantioselectivities higher than 95% being obtained currently in reactions such as hydrogenation, isomerization, epoxidation, hydroxylation, or allylic substitution [1]. Although water-soluble catalysts have been known and used since the 1970s, it is only recently that this methodology has been extended to the preparation of chiral compounds from prochiral ones.

The enantioselective hydrogenation of some α-amino acid precursors **1** [Eq. (1)] in water or in an aqueous/organic two-phase system has been thoroughly investigated using rhodium or ruthenium complexes associated with chiral water-soluble ligands **3–13**. Some of the most interesting results are summarized in Table 1.



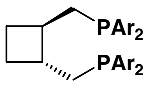
1 **2**

(1)

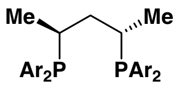
e.g.
a: $R_1 = C_6H_5$, $R_2 = H$, $R_3 = CH_3$; **b**: $R_1 = C_6H_5$, $R_2 = R_3 = CH_3$; **c**: $R_1 = R_3 = C_6H_5$, $R_2 = H$;
d: $R_1 = R_3 = C_6H_5$, $R_2 = CH_3$; **e**: $R_1 = 3\text{-MeO-4-AcO-}C_6H_3$, $R_2 = H$, $R_3 = CH_3$

Table 1 Asymmetric reduction of some α-amino acid precursors **1** at 25 °C in the presence of rhodium complexes containing ionized ligands **3**–**5** and 7–**9**.

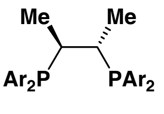
Precursor 1	*Ligand*	*Solvent*	p_{H_2} *[MPa]*	*Product*	
				ee [%] (Config.)	*Ref.*
1a	(*S*,*S*)-**3**	H_2O/AcOEt (1 : 1)	0.1	34 (*S*)	[3]
1a	(*S*,*S*)-**4**	H_2O/AcOEt (1 : 1)	1.5	65 (*R*)	[3]
1a	(*S*,*S*)-**5**	H_2O/AcOEt (1 : 2)	1.0	87 (*R*)	[3]
1a	(*R*,*R*)-**7a**	H_2O	1.4	25 (*S*)	[6]
1a	(*R*,*R*)-**7b**	H_2O	1.4	34 (*S*)	[6]
1a	(*S*,*S*)-**8a**	H_2O	1.4	67 (*R*)	[6]
1a	(*S*,*S*)-**8b**	H_2O	1.4	71 (*R*)	[6]
1a	(*S*,*S*)-**9a**	H_2O	1.4	94 (*R*)	[6]
1a	(*S*,*S*)-**9b**	H_2O	1.4	90 (*R*)	[6]
1b	(*S*,*S*)-**3**	H_2O/AcOEt (1 : 1)	0.1	20 (*S*)	[3]
1b	(*S*,*S*)-**4**	H_2O/AcOEt (1 : 1)	1.5	45 (*R*)	[3]
1b	(*S*,*S*)-**5**	H_2O/AcOEt (1 : 1)	1.0	81 (*S*)	[3]
1b	(*R*,*R*)-**7a**	H_2O	1.4	8 (*S*)	[3]
1b	(*R*,*R*)-**7b**	H_2O/EtOAc/C_6H_6 (2 : 1 : 1)	1.4	25 (*S*)	[6]
1b	(*S*,*S*)-**8a**	H_2O/EtOAc/C_6H_6 (2 : 1 : 1)	1.4	45 (*R*)	[6]
1b	(*S*,*S*)-**8b**	H_2O/EtOAc/C_6H_6 (2 : 1 : 1)	1.4	50 (*R*)	[6]
1b	(*S*,*S*)-**9a**	H_2O/EtOAc/C_6H_6 (2 : 1 : 1)	1.4	77 (*R*)	[6]
1b	(*S*,*S*)-**9b**	H_2O/EtOAc/C_6H_6 (2 : 1 : 1)	1.4	74 (*R*)	[6]
1c	(*S*,*S*)-**3**	H_2O/EtOAc (1 : 2)	0.1	13 (*S*)	[3]
1c	(*S*,*S*)-**4**	H_2O/EtOAc (1 : 1)	1.5	44 (*R*)	[3]
1c	(*S*,*S*)-**5**	H_2O/EtOAc (1 : 2)	1.0	86 (*R*)	[3]
1d	(*R*,*R*)-**7a**	H_2O/EtOAc/C_6H_6 (2 : 1 : 1)	1.4	9 (*S*)	[6]
1d	(*R*,*R*)-**7b**	H_2O/EtOAc/C_6H_6 (2 : 1 : 1)	1.4	11 (*S*)	[6]
1d	(*S*,*S*)-**8a**	H_2O/EtOAc/C_6H_6 (2 : 1 : 1)	1.4	54 (*R*)	[6]
1d	(*S*,*S*)-**8b**	H_2O/EtOAc/C_6H_6 (2 : 1 : 1)	1.4	67 (*R*)	[6]
1d	(*S*,*S*)-**9a**	H_2O/EtOAc/C_6H_6 (2 : 1 : 1)	1.4	65 (*R*)	[6]
1d	(*S*,*S*)-**9b**	H_2O/EtOAc/C_6H_6 (2 : 1 : 1)	1.4	58 (*R*)	[6]
1g	(*S*,*S*)-**3**	H_2O/EtOAc (1 : 2)	0.1	37 (*S*)	[3]
1g	(*S*,*S*)-**4**	H_2O/EtOAc (1 : 1)	1.0	58 (*R*)	[3]
1e	(*S*,*S*)-**5**	H_2O/EtOAc (1 : 2)	1.0	88 (*R*)	[3]
1e	(*R*,*R*)-**7a**	H_2O	1.4	42 (*S*)	[6]
1e	(*R*,*R*)-**7b**	H_2O	1.4	67 (*S*)	[6]
1e	(*S*,*S*)-**8a**	H_2O	1.4	76 (*R*)	[6]
1e	(*S*,*S*)-**8b**	H_2O	1.4	79 (*R*)	[6]
1e	(*S*,*S*)-**9a**	H_2O	1.4	93 (*R*)	[6]
1e	(*S*,*S*)-**9b**	H_2O	1.4	88 (*R*)	[6]



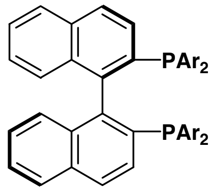
(S,S)-CBD **3**



(S,S)-BDPP **4**

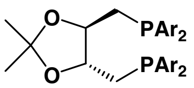


(S,S)-CHIRAPHOS **5**

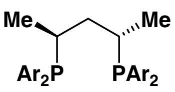


(R)-BINAP **6**

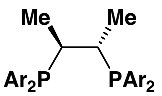
Ar = 3-NaO_3S-$C_6H_4^-$



(R,R)-**7**

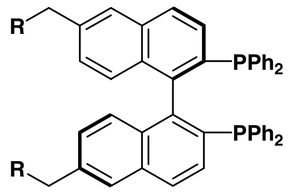


(S,S)-**8**



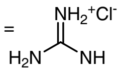
(S,S)-**9**

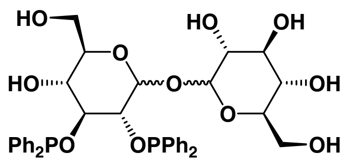
a Ar = C_6H_4-4-$NMe_3^+BF_4^-$; **b** Ar = C_6H_4-4-$NHMe_2^+BF_4^-$



(R)- diamo-BINAP **10** R = $NH_3^+Br^-$

(R)- digm-BINAP **11** R =

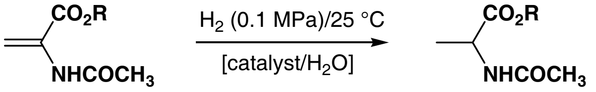




12 α,α
13 β,β

The most investigated chiral ligands were the sulfonated phosphines **3**–**5** [2, 3] and those possessing a quaternary ammonium function (**7**–**9**) [4–8]. Rhodium complexes of water-soluble 1,2-diphosphines, such as sulfonated or aminoquaternized ammonium CHIRAPHOS **5** and **9**, reduced unsaturated α-amino acid precursors in water or in a two-phase system with high enantioselectivities (*ee* = 65–96%), close to the values obtained in organic media (Table 1). Conversely, rhodium complexes of water-soluble 1,4-diphosphines **3** and **7**, derived from CBD or DIOP, and 1,3-diphosphines **4** and **8**, derived from BDPP, gave lower enantioselectivities in aqueous phase than the non-water-insoluble analogues in organic solvents (8–34% *ee* for **3** and **7**, and 40–71% *ee* for **4** and **8**, respectively). Later, Hanson and co-workers [9] prepared a surface-active tetrasulfonated chiral diphosphine derived from BDPP which showed similar selectivity but improved reactivity compared to the unmodified BDPP in the reduction of **1b** (with *ee* up to 69%).

Rhodium and ruthenium complexes associated with water-soluble BINAP **6** gave enantioselectivities up to 88% in the reduction of α-acetamidoacrylic acid and its methyl ester [10, 11], quite close to the values obtained in organic solvents [Eq. (2)]; it is to be noted in these cases that the direction of enantioselection was the opposite using the rhodium or the ruthenium catalyst, as in organic solvents.

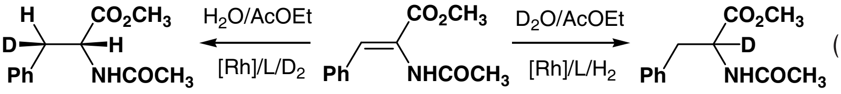


(2)

R = H cat [Rh]/*(R)*-**6** ee 70% (*S*); cat [Ru]/(*R*)-**6** ee 68.5% (*R*)
R = CH_3 cat [Rh]/*(R)*-**6** ee 69.5% (*S*); cat [Ru]/(*R*)-**6** ee 82% (*R*)

Carbohydrate-based bisphosphinites **12** and **13** derived from α,α- and β,β-trehalose associated with rhodium complexes gave enantioselectivities up to 88% in the reduction of **1** in water or in a two-phase H_2O/AcOEt system [12–14]; this enantioselectivity was improved to 98% *ee* when the reaction was carried out in H_2O/AcOEt/CH_3OH.

The lower enantioselectivity observed in water for the reduction of amino acid precursors using water-soluble diphosphines in asssociation with rhodium complexes was attributed to solvent effects and to the reaction kinetics in the two solvents [15]. When the reaction was carried out in alcohol/water solvent mixtures, an increase in water content induced a decrease in enantioselectivity. In a systematic study on the influence of various solvents on the enantioselectivity in the reduction of dehydroamino acids, a linear relationship was found between log (%S/%R) and the solvophobicity parameter S_P of various solvents, log (%S/%R) decreasing with increasing S_P. However, another possibility could be the presence of a different mechanism than the usual one, occuring via a monohydride species. Effectively, although the biphasic hydrogenation of α-amino acid precursors was shown to be a truly homogeneous process [16], it was also shown that water not only was a solvent, but also had a chemical effect on the reduction [17–19]. Hydrogenation of α-acetamidocinnamic acid methyl ester in AcOEt/D_2O in the presence of a rhodium complex associated with a sulfonated ligand such as TPPTS occurred with a 75% regiospecific monodeuteration at the position α to the acetamido and the ester functions, the amount of deuterium incorporation depending on the ligand used [Eq. (3)]. When the reduction was performed under a deuterium atmosphere in the presence of water, hydrogen incorporation occurred at the same position, the overall reaction being a *cis* addition of HD.



1b

(3)

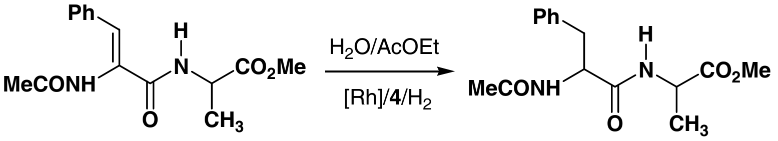
It is to be noted that under these conditions the reaction rates are generally lower than in a homogeneous organic phase. However, one of the important points is that these catalytic solutions can be readily recycled, without loss of enantioselectivity, as shown in Table 2. This recycling was performed with little rhodium loss (< 0.1%) in a two-phase system.

Dehydropeptides **14** were also reduced in a two-phase system using [Rh(COD)Cl]$_2$ associated with ligands **3** and **4** [Eq. (4)] [20]; the diastereomeric excess (*de*) of the dipeptide **15** obtained was strongly influenced by the absolute configuration of the

Table 2 Catalyst recycling in the asymmetric hydrogenation of α-amino acid precursors **1** at 25 °C using a rhodium catalyst.

Precursor 1	*Ligand*	*Solvent*	p_{H_2} *[MPa]*	*Cycle*	*Product*	
					ee [%] (Config.)	*Ref.*
1b	(*S*,*S*)-**3**	H_2O/AcOEt (1 : 1)	0.1	1	34 (*S*)	[3]
				2	37 (*S*)	
1c	(*S*,*S*)-**3**	H_2O/AcOEt (1 : 1)	0.1	1	20 (*S*)	[3]
				2	23 (*S*)	
1c	(*S*,*S*)-**5**	H_2O/AcOEt (1 : 1)	1.0	1	82 (*R*)	[3]
				2	88 (*R*)	
				3	87 (*R*)	
1c	(*S*,*S*)-**9a**	H_2O/AcOEt/C_6H_6) (2 : 1 : 1)	1.4	1	75 (*R*)	[6]
				2	77 (*R*)	
				3	77 (*R*)	
1c	**12**	H_2O/AcOEt (1 : 1)	0.5	1	68 (*S*)	[11]
				2	66 (*S*)	
1c	**13**	H_2O/AcOEt (1 : 1)	0.5	1	87 (*S*)	[11]
				2	85 (*S*)	

unsaturated substrate. For example, reduction of Ac-Δ-Ph-(*S*)-Ala-OCH_3 using [Rh]-**4** gave a *de* as high as 72% in favor of the (*R*,*S*) diastereoisomer, while a *de* of 6% was obtained in the reduction of Ac-Δ-Ph-(*R*)-Ala-OCH_3 in favour of the (*R*,*R*) diastereoisomer.



14 **15**

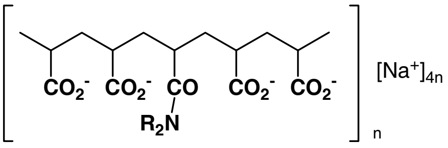
(4)

(R) ⟶ *de* 53/47 *(RR)/(RS)*

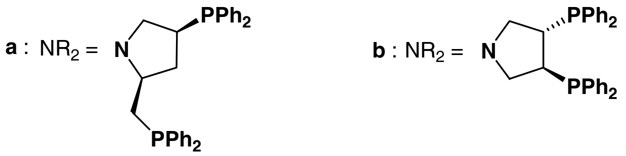
(S) ⟶ *de* 86/14 *(SR)/(SS)*

Rhodium complexes of water-soluble polymer ligands **16a**,**b** (see also Chapter 7) were also quite efficient in the reduction of α-acetamidocinnamic acid and its methyl ester; enantioselectivities up to 89% *ee* being obtained using water and EtOAc/H_2O (1 : 1) as the solvents [21].

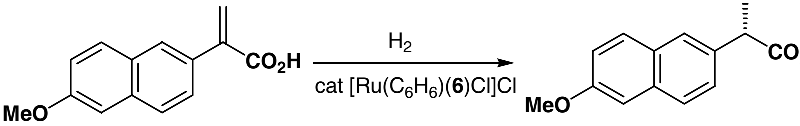
Reduction of unsaturated acid **17** in a two-phase AcOEt/H_2O system using the ruthenium complex associated with ligand **6** allowed the preparation of naproxen (**18**) in 81% *ee*, *ee* values in the range 78–83% being obtained over several recycles of the catalytic solution [Eq. (5)] [22]. The analogous supported aqueous-phase catalyst (SAPC) was also prepared and used in this reduction, an enantioselectivity



16

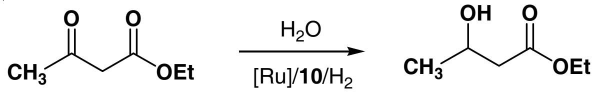


up to 70% being obtained in ethyl acetate saturated with water; the use of ethylene glycol instead of water as the hydrophilic phase gave *ee* values up to 96%.



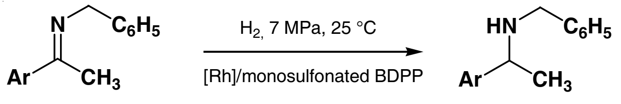
17 **18** (5)

The hydrogenation of various β-keto esters was also performed in water in the presence of ruthenium complexes associated with ligands **10** and **11** [23, 24], affording the corresponding hydroxy ester with enantioselectivities up to 94% [Eq. (6)]. The *ee* values remained unchanged in the first three recycles.



19 **20** (6)

Sinou [25] and de Vries [26, 27] reported the influence of the degree of sulfonation of chiral BDPP on the enantioselectivity in the reduction of prochiral imines. The rhodium complex of monosulfonated BDPP gave *ee* values up to 94% in the reduction of imines **21** in a two-phase AcOEt/H_2O system [Eq. (7)], when the tetrasulfonated or disulfonated BDPP gave 34% and 2% *ee* only, respectiveley, in the reduction of the benzylimine of acetophenone.



21 **22** (7)

Enantioselectivities up to 43% *ee* were obtained in the hydroxycarboxylation of vinylarenes in the presence of $Pd(OAc)_2$ and tetrasulfonated CBD **3** or BDPP **4**, recycling of the catalyst being possible with no loss in activity and enantioselectivity [28].

Asymmetric palladium-catalyzed alkylation of various allylic acetates occurred in water or in an aqueous/organic biphasic medium, using as ligands phosphines derived from carbohydrates [29], amphiphilic resin-supported MOP and P,N-chelating ligands [30, 31], or BINAP in the presence of surfactants [32]; enantioselectivities up to 85%, 98%, and 92% have been obtained in the alkylation of 1,3-diphenyl-2-propenyl acetate, respectively.

Rhodium-catalyzed asymmetric addition of aryl borates to cycloalkenones occurred with a high level of enantioselectivity in dioxane (*ee* up to 99%) using BINAP as the ligand when 1 equiv of water was added [33]. The benefit of water was also observed in the asymmetric cyclopropanation of styrene with diazoacetates using chiral bis(hydroxymethyldihydrooxazolyl)pyridineruthenium catalyst (*ee* up to 97%); in this latter case, the utilization of a H_2O/toluene medium allowed recycling of the catalyst [34]. Finally, Kobayashi and co-workers carried out catalyzed asymmetric aldol reactions in aqueous media using a catalyst obtained by mixing $Cu(OTf)_2$ $Pb(OTf)_2$, or $Ln(OTf)_2$, and a chiral bisoxazoline or crown-ether [35–37]; very high chemical yields, as well as diastereo- and enantioselectivities (up to 85% *ee*), have been obtained.

In conclusion, asymmetric catalysis, and particularly asymmetric hydrogenation, occurred in water or in a two-phase system in moderate to high enantioselectivities, allowing a very easy recycling of the catalyst without loss of enantioselectivity. Different techniques have been used in order to solubilize the catalyst and the products in the aqueous phase. It is obvious that in the future this technique will be extended to other asymmetric organometallic-catalyzed reactions.

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2.4.7
Biological Conversions

Peter J. Quinn

2.4.7.1
Introduction

Water is the universal solvent in biology. In the order of 80% of the gross weight of living organisms consists of water. The catalysts responsible for mediating the biochemical reactions that create and sustain life depend on an aqueous environment to preserve their stability and catalytic functions. Moreover, their activity is limited to reaction conditions of temperature, pressure, pH, etc., which are compatible with survival of the living organism.

Many biological catalysts, or to give them their correct name, enzymes, often acquire their catalytic functions under these stringent reaction conditions by incorporating transition metals into their catalytic site. The metals are coordinated to ligands, which are constituents of the polypeptide chain, and participate in the formation of transition-state complexes with substrates in the performance of biochemical reactions. While Nature can provide a rich diversity of organometallic catalysts that require an aqueous solvent, it is a challenge to the chemist to duplicate these enzymatic reactions so that they can be exploited and adapted to industrial-scale processes.

2.4.7.2
Biochemical Substrates

Lipids which constitute structural components of living cells and represent a store of metabolic energy contain unsaturated bonds. Chemical modification of these unsaturated fatty acids in living organisms have greatly increased our knowledge of the role of these constituents in biological membranes. Their presence in food, however, presents problems with storage, and catalytic hydrogenation in processing of fats and oils to prevent spoilage and development of off-flavors is a common practice. Such processing, nevertheless, results in the creation of *trans* isomers of fatty acids which are known to present a health risk. Improved practices are actively being sought to meet regulations framed to reduce or eliminate *trans* fatty acids in processed oils.

2.4.7.3
Hydrogenation using Water-Soluble Catalysts

Hydrogenation of unsaturated phospholipids dispersed in aqueous systems using a water-soluble homogeneous catalyst was first reported by Madden and Quinn [1]. The catalyst was a sulfonated derivative of Wilkinson's catalyst which did not appear to affect the structure of bilayers with respect to their permeability barrier properties [2]. The catalyst was found to hydrogenate oil-in-water emulsions and two-phase oil–water systems without the need for organic co-solvents [3]. The reaction rate could be increased significantly by screening the electrostatic charge on the sulfonate groups with inorganic cations added to the aqueous phase. This allowed the catalyst to penetrate into the substrate at the interface; partition of the catalyst from the aqueous into the lipid phase could not be detected.

The reactivity of water-soluble palladium catalyst, $\mathrm{Pd(QS)_2}$ (palladium di(sodium) alizarine monosulfonate) has been examined in multilamellar dispersions of unsaturated phospholipids [4]. With substrates of dioleoylphosphatidylcholine there is a transient appearance of *trans* ω9 but no *cis* double bonds were observed when the *trans* ω9 derivative of phosphatidylcholine was used as substrate.

2.4.7.4
Hydrogenation of Biological Membranes

The presence of unsaturated lipids in biological membranes confers a fluid character on the structure and this is integral to its function. Evidence for this has been established by homogeneous catalytic hydrogenation of these lipids in membrane preparations [5, 6] and living cells [7]. Furthermore, the topology of lipids in the membranes of complex organisms or in subcellular membrane preparations has been probed by determining access to hydrogenation catalysts. Water-soluble catalyst complexes, for example, are not readily permeable to membranes, and when added to suspensions of cells or closed vescular structures their action has been shown to be largely restricted to the outer monolayer, at least at short time intervals after commencement of the reaction [8].

An important question as to how cells regulate the fluidity of their membranes by adjusting the proportion of unsaturated lipids has also been addressed by homogeneous hydrogenation methods. This strategy has been used in the unicellular green alga, *Daniella salina*, to define pathways of biosynthesis of unsaturated membrane lipids and the process of redistribution from the site of biosynthesis to the different subcellular membranes [9]. Similar studies have been reported in the regulation of desaturase enzymes in microsomal membranes isolated from yeast [10] and potato tubers [11].

2.4.7.5
Conclusions

The chemical modification of membranes containing unsaturated hydrocarbon substituents has been shown to be a useful tool in the study of the role of these lipids in membrane structure and stability. Homogeneous catalytic hydrogenation of biological membranes in isolated organelles or living cells has developed rapidly over the past few years with the introduction of more active catalytic complexes, especially under conditions of hydrogenation more compatible with living organisms. Advances in targeting catalysts to specific membranes and localizing action to specific membrane sites are likely to be important in future developments.

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2.4.8
Other Examples

2.4.8.1
Lanthanides in Aqueous-Phase Catalysis

Shu Kobayashi

2.4.8.1.1
Introduction

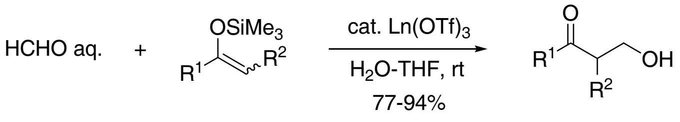
Lewis acid-catalyzed reactions have been of great interest in organic synthesis because of their unique reactivities, selectivities, and the mild conditions used [1].Lewis acid-promoted reactions must be carried out under strictly anhydrous conditions despite the general recongnition of the utility of aqueous reactions [2]. The presence of even a small amount of water stops the reaction, because most Lewis acids immediately react with water rather than the substrates and decompose or deactivate; this fact has restricted the use of Lewis acids in organic synthesis.

On the other hand, lanthanide compounds (including scandium and yttrium compounds) were recently found to be stable Lewis acids in water, and many useful aqueous reactions using lanthanide compounds as catalysts have been reported. Lanthanides have larger radii and specific coordination numbers than typical transition metals. They have been expected to act as strong Lewis acids because of their hard character, and to have strong affinity toward carbonyl oxygens [3]. Among these compounds, lanthanide trifluoromethanesulfonates (lanthanide triflates, $Ln(OTf)_3$) were expected to be some of the strongest Lewis acids because of the strongly electron-withdrawing trifluoromethanesulfonyl group. Their hydrolysis was postulated to be slow on the basis of their hydration energies and hydrolysis constants [4]. In fact, while most metal triflates are prepared under strictly anhydrous conditions, lanthanide triflates were reported to be prepared in an aqueous solution [5, 6]. After the finding that lanthanide triflates are stable and act as Lewis acids in water [7], many synthetic reactions using these triflates as catalysts have been developed [8]. This section surveys use of these lanthanides in carbon–carbon bond-forming reactions in aqueous solutions.

2.4.8.1.2
Aldol Reactions

Formaldehyde is a versatile reagent [9]. It has some disadvantages, however, because it must be generated before use from solid polymer paraformaldehyde by way of thermal depolymerization and it self-polymerizes easily [10]. On the other hand, commercial formaldehyde solution, which is an aqueous solution containing 37% formaldehyde and 8–10% methanol, is cheap, easy to handle, and stable even at room temperature [11, 12].

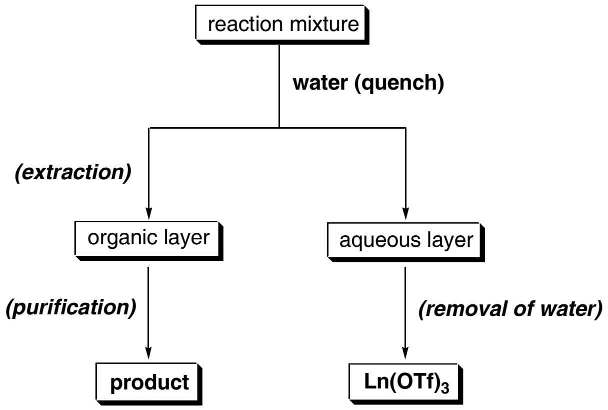
It was found that the hydroxymethylation of silyl enol ethers with commercial formaldehyde solution proceeded smoothly by using lanthanide triflates as Lewis acid catalysts [7, 13]. The reactions were first carried out in commercial formaldehyde solution–THF media. The amount of the catalyst was examined by taking the reaction of the silyl enol ether derived from propiophenone with commercial formaldehyde solution as a model, and the reaction was found to be catalyzed even by 1 mol% ytterbium triflate ($Yb(OTf)_3$) [Eq. (1)].



(1)

Ln = Sc, Y, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu

Lanthanide triflates are effective for the activation of aldehydes other than formaldehyde [13–15]. The aldol reaction of silyl enol ethers with aldehydes proceeds smoothly to afford the aldol adducts in high yields in the presence of a catalytic amount of scandium triflate ($Sc(OTf)_3$), ytterbium triflate ($Yb(OTf)_3$), gadolinium triflate ($Gd(OTf)_3$), lutetium triflate ($Lu(OTf)_3$), etc. in aqueous media (water–THF). Diastereoselectivities are generally good to moderate. One feature in the present reaction is that water-soluble aldehydes, for instance, acetaldehyde, acrolein, and chloroacetaldehyde, can react with silyl enol ethers to afford the corresponding cross-aldol adducts in high yields. Some of these aldehydes are supplied commercially as water solutions and are appropriate for direct use. Phenylglyoxal monohydrate also works well. It is known that water often interferes with the aldol reactions of metal enolates with aldehydes and that in the cases where such water-soluble aldehydes are employed, some troublesome purifications including dehydration are necessary. Furthermore, salicylaldehyde and 2-pyridinecarboxaldehyde can be successfully employed.



Scheme 1 Recovery of the catalyst.

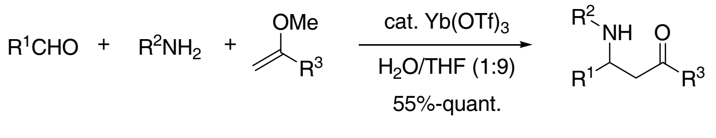
Lanthanide triflates are more soluble in water than in organic solvents such as dichloromethane. Very interestingly, almost 100% of lanthanide triflate is quite easily recovered from the aqueous layer after the reaction is completed and it can be re-used. The reactions are usually quenched with water and the products are extracted with an organic solvent (for example, dichloromethane). Lanthanide triflates are in the aqueous layer and only removal of water gives the catalyst which can be used in the next reaction (Scheme 1). It is noteworthy that lanthanide triflates are expected to solve some severe environmental problems induced by mineral acid- or Lewis acid-promoted reactions in industrial chemistry [16].

The aldol reactions of silyl enol ethers with aldehydes also proceed smoothly in water–ethanol–toluene [17].

2.4.8.1.3
Mannich-Type Reactions

The Mannich and related reactions provide one of the most fundamental and useful methods for the synthesis of β-amino ketones. Although the classical protocols include some severe side reactions, new modifications using preformed iminium salts and imines have been developed [18].

Mannich-type reactions between aldehydes, amines, and vinyl ethers proceed smoothly using $Ln(OTf)_3$ in aqueous media [19]. The procedure is very simple: in the presence of 10 mol% of $Yb(OTf)_3$, an aldehyde, an amine, and a vinyl ether are combined in a solution of THF–water (9 : 1) at room temperature to afford a β-amino ketone [Eq. (2)]. Commercially available formaldehyde– and chloroacetaldehyde–water solutions are used directly and the corresponding β-amino ketones are obtained in good yields. Phenylglyoxal monohydrate, methyl glyoxylate, an aliphatic aldehyde, and an α,β-unsaturated ketone also work well to give the corresponding β-amino esters in high yields. Other lanthanide triflates can also be used; in the reaction of phenylglyoxalmonohydrate, *p*-chloroaniline, and 2-methoxypropene, 90% ($Sm(OTf)_3$), 94% ($Tm(OTf)_3$), and 91% ($Sc(OTf)_3$) yields are obtained. In some Mannich reactions with preformed iminium salts and imines, it is known that yields are often low because of the instability of the imines derived from these aldehydes or troublesome treatments are known to be required for their use [20]. The present method provides a useful route for the synthesis of β-amino ketones.



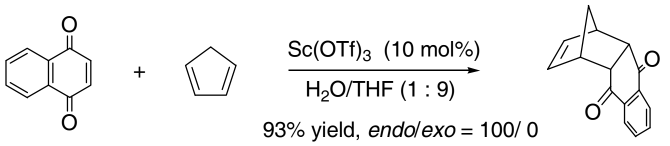
(2)

A possible mechanism of the present reaction is accompanied by imine formation, and successive addition of a vinyl ether proceeds smoothly in aqueous solution. Use of lanthanide triflates, water-tolerant Lewis acids, is of key importance and essential in this reaction.

2.4.8.1.4
Diels–Alder Reactions

Although many Diels–Alder reactions have been carried out at higher reaction temperatures without catalysts, heat-sensitive compounds in complex and multistep syntheses cannot be employed. While Lewis acid catalysts allow the reactions to proceed at room temperature or below with satisfactory yields in organic solvents, they are often accompanied by diene polymerization and excess amounts of the catalyst are often needed to catalyze carbonyl-containing dienophiles [21].

It was found that the Diels–Alder reaction of naphthoquinone with cyclopentadiene proceeded in the presence of a catalytic amount of a lanthanide triflate in H_2O–THF (1 : 9) at room temperature to give the corresponding adduct in 93% yield (*endo*/*exo* = 100 : 0) [Eq. (3)] [22].

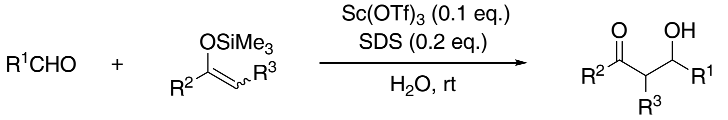


(3)

2.4.8.1.5
Micellar Systems

Aldol Reactions

Recently, it has been found that scandium triflate ($Sc(OTf)_3$)-catalyzed aldol reactions of silyl enol ethers with aldehydes could be successfully carried out in micellar systems [23]. While the reactions proceeded sluggishly in pure water (without organic solvents), remarkable enhancement of the reactivity was observed in the presence of a small amount of a surfactant [see Eq. (4)].

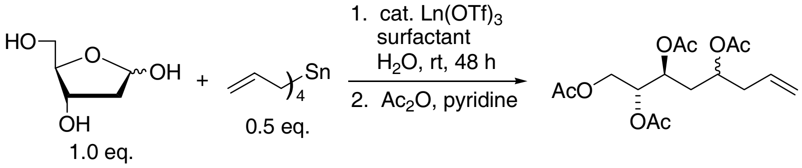


(4)

Lewis acid catalysis in micellar systems was first found in the model reaction of the silyl enol ether of propiophenone with benzaldehyde. While the reaction proceeded sluggishly in the presence of 0.2 equiv $Yb(OTf)_3$ in water, remarkable enhancement of the reactivity was observed when the reaction was carried out in the presence of 0.2 equiv $Yb(OTf)_3$ in an aqueous solution of sodium dodecyl sulfate (SDS, 0.2 equiv, 35 mM), and the corresponding aldol adduct was obtained in 50% yield. In the absence of the Lewis acid and the surfactant (water-promoted conditions) [11], only 20% yield of the aldol adduct was isolated after 48 h, while a 33% yield of the aldol adduct was obtained after 48 h in the absence of the Lewis acid in an aqueous solution of SDS. The amounts of the surfactant also influenced the reactivity, and the yield was improved when $Sc(OTf)_3$ was used as a Lewis acid catalyst. Judging from the critical micelle concentration, micelles would be formed in these reactions, and it is noteworthy that the Lewis acid-catalyzed reactions proceeded smoothly in micellar systems [24]. Although several organic reactions in micelles were reported, there was no report on Lewis acid catalysis in micelles. Since the amount of the surfactant used in the present case was small, the aldol reaction would *not* proceed *only in micelles*. It was also found that the surfactants influenced the yield, and that Triton X-100 was effective in the aldol reaction (but required a long reaction time), while only a trace amount of the adduct was detected when using cetyltrimethylammonium bromide (CTAB) as a surfactant.

Allylations of Aldehydes

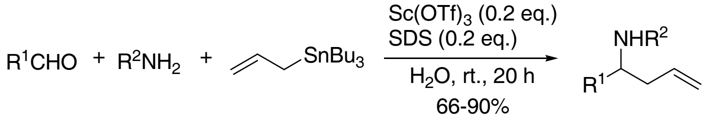
It was also found that the allylation reactions of aldehydes with tetraallyltin proceeded smoothly in micellar systems using $Sc(OTf)_3$ as a catalyst [25]. Utilities of organometallic reagents are now well recognized in organic synthesis, and a variety of organometallics have been developed to achieve unique reactivities as well as selectivities [26]. In general, however, most organometallic reagents are hygroscopic, and therefore they are deactivated or decomposed in the presence of even a small amount of water, which sometimes limits their use in organic synthesis. On the other hand, the allylation reaction of 2-deoxyribose (an unprotected sugar) was found to proceed smoothly in water under the influence of 0.1 equiv of $Sc(OTf)_3$ and 0.2 equiv of SDS (sodium dodecyl sulfate) by using tetraallyltin (0.5 equiv) as an allylating reagent [Eq. (5)] [27]. Not only aromatic but also aliphatic and α,β-unsaturated aldehydes reacted with tetraallyltin to afford the corresponding allylated adducts in high yields. Under the present reaction conditions, salicylaldehyde and 2-pyridinecarboxaldehyde reacted with tetraallyltin to afford the homoallylic alcohols in good yields. Other unprotected sugars than 2-deoxyribose also reacted directly to give the adducts, which are intermediates for the synthesis of higher sugars [28], in high yields.



(5)

Three-Component Reactions of Aldehydes, Amines, and Allyltributylstannane

The reaction of imines with allyltributylstannane provides a useful route for the synthesis of homoallylic amines [29]. The reaction is generally carried out in the presence of a Lewis acid in organic solvents under strictly anhydrous conditions [30], because most imines, Lewis acids, and the organotin reagents used are hygroscopic and easily decompose in the presence of even a small amount of water [31]. Dispite the utility of aqueous reactions, it was believed that the above reaction would remain difficult to perform in water because of the use of water-sensitive imines, Lewis acids, and organotin reagents. It was found that three-component reactions of aldehydes, amines, and allyltributylstannane proceed smoothly in micellar systems using $Sc(OTf)_3$ as a Lewis acid catalyst [32] [Eq. (6)]. The reaction of benzaldehyde, aniline, and allyltributylstannane was chosen as a model, and several reaction conditions were examined. While the reaction proceeded sluggishly in the presence of $Sc(OTf)_3$ without SDS or in the presence of SDS without $Sc(OTf)_3$, a 77% yield of the desired homoallylic amine was obtained when $Sc(OTf)_3$ and SDS were both present. It was suggested that an imine formed from the aldehyde and the amine rapidly reacted with allyltributylstannane to afford the desired adduct. The effect of the amount of $Sc(OTf)_3$ and SDS was also examined.



(6)

The present three-component reactions of aldeheydes, amines, and allyltributylstannane proceeded smoothly in water without using any organic solvents in the presence of a small amount of $Sc(OTf)_3$ and SDS, to afford the corresponding homoallylic amines in high yields. Not only aromatic aldehydes but also aliphatic, unsaturated, and heterocyclic aldehydes worked well [29, 34, 35].

2.4.8.1.6
Asymmetric Catalysis in Aqueous Media

Catalytic asymmetric aldol reactions have emerged as one of the most powerful carbon–carbon bond-forming processes affording synthetically useful, optically active β-hydroxy carbonyl compounds [36]. Among them, chiral Lewis acid-catalyzed reactions of aldehydes with silyl enol ethers are one of the most promising methods. Although several successful examples have been developed since 1990 [37], most of the reactions have to be conducted at low reaction temperatures (e.g., –78 °C) in aprotic anhydrous solvents such as dry dichloromethane, toluene, and propionitrile.

Although lanthanide triflates are the first metal salts which were found to catalyze aldol reactions of aldehydes with silyl enol ethers efficiently in aqueous media, it has been difficult to realize asymmetric versions of lanthanide triflate-catalyzed reactions in such media. Recently, the first example of this type of reaction using chiral bis-pyridino-18-crown-6 (1) has been developed [38]. In the reaction of benzaldehyde with silyl enol ethers in water–ethanol (1 : 9), the cation size of lanthanide triflates strongly affected the diastereo- and enantioselectivities of the aldol adduct. For the larger cations such as La, Ce, Pr, and Nd, both diastereo- and enantioselectivities were high, while the smaller cations such as Sc and Yb showed no enantioselection.

A study on the reaction profile of the asymmetric aldol reaction catalyzed by $Pr(OTf)_3$ with **1** revealed that this crown ether-type chiral ligand did not significantly reduce the activity of the metal triflates. This retention of the activity even in the presence of the crown ether containing oxygen and nitrogen atoms is a key to realizing the asymmetric induction in this asymmetric aldol reaction in aqueous media. The X-ray structure of $[Pr(NO_3)_2 \cdot \mathbf{1}]_3[Pr(NO_3)_6]$ shows that the Pr(III) cation is located in the center of the crown ring. The use of a chiral multidentate ligand such as the crown ether is a versatile concept for catalytic asymmetric reactions in aqueous media.

2.4.8.1.7
Conclusions

Lanthanide triflates ($Ln(OTf)_3$) are stable Lewis acids in water and are successfully used in several carbon–carbon bond-forming reactions in aqueous solutions. The reactions proceeded smoothly in the presence of a catalytic amount of the triflate under mild conditions. Moreover, the catalysts can be recovered after the reactions are completed, and can be re-used. Lewis acid catalysis in micellar systems will lead to clean and environmentally friendly processes, and it will become a more important topic in the future. Finally, catalytic asymmetric aldol reactions in aqueous media have been attained using a $Ln(OTf)_3$–chiral crown ether complex as a catalyst.

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2.4.8.2
Dehalogenation

Mario Bressan

A large number of halogenated organics have been produced commercially in the past few decades and used for a variety of purposes. The quest for environmentally friendly technology in general has developed into a substantial drive to get away from chlorocarbons and halogenated materials altogether, due to the generic deleteriousness associated with them. Dehalogenation treatments of the mess created as a result of past expediency are important issues [1], because of the persistence in groundwater of halogenated compounds: indeed, all of the persistent organic pollutants (POPs) recommended by UN Environment Program to be phased out of production and use are chlorinated organics. Serious problems are still associated with the combustion of chlorinated organics, since they are characterized by a high degree of chemical inertness and thermal stability. Catalytic treatments in situ can be effective remediation systems, although a careful identification of degradative products is necessary.

The ubiquitous presence of methane monooxygenase (MMO) and cytochrome P450 (CyP450) enzymatic systems indicates that they may be of principal importance for the oxidative degradation of halo-organics. In many instances, however, current techniques of bioremediation of contaminated groundwaters involving entire microorganisms are inadequate, because of pollutant concentrations, nutrient limitations, and the lack of membrane permeability for halo-organics (which, coupled with absence of suitable extracellular enzymes, is the accepted basis for a molecule being recalcitrant [2]). MMO is capable of oxidizing a variety of haloalkenes at rates comparable to those of other substrates for the enzyme, the competitive inhibitor tetrachloroethylene being the only substrate not turned over [3]. The rates observed are two orders of magnitude faster than those reported for whole-cell oxidations by nonmethanotrophs and up to ten times faster than comparable oxidations catalyzed by CyP450 containing mixed-function oxidase systems [4].

Compounds with high halogen substitution (i.e., with carbon atoms in high formal oxidation states) are expected to be resistant to the aerobic degradation and more susceptible to the reductive one. Reductive dehalogenation refers specifically to the reaction in which two electrons and a proton act as substrates along with the halogenated compound to yield a reduced product and the corresponding halide [Eq. (1)].

$$RX + 2\,e^- + H^+ \rightarrow RH + X^- \tag{1}$$

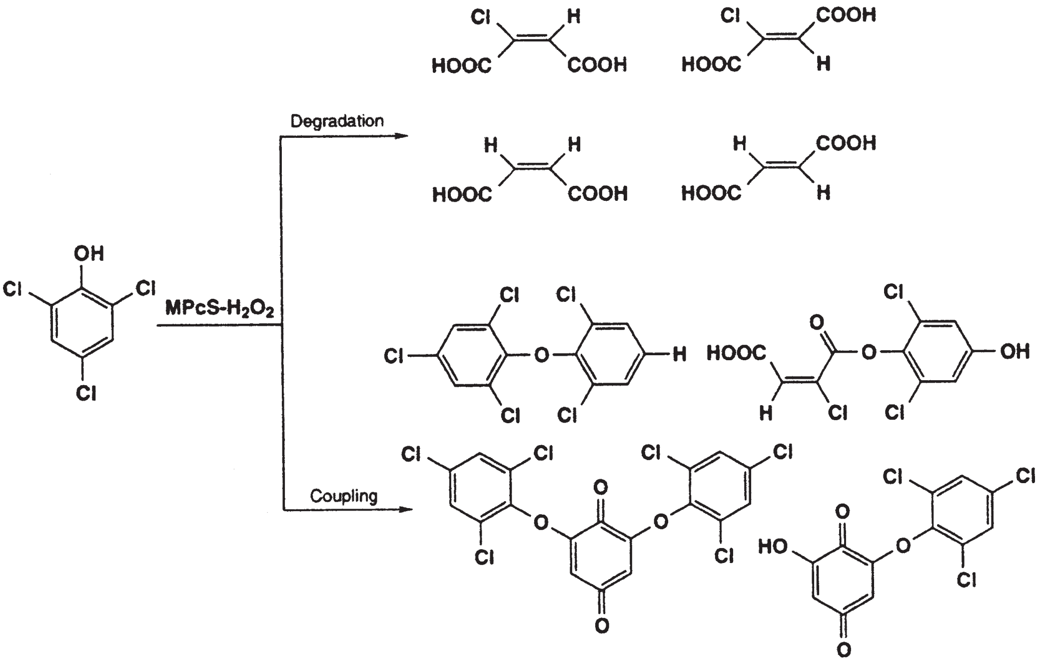
CyP450 and other reduced Fe-porphyrins are reported to mediate reductive dehalogenation of haloalkanes and -alkenes [5], and of the aliphatic portion of DDT [6]. Products similar to anaerobic bacteria or CyP450 treatments were obtained by depositing stable ordered film of myoglobin (Mb) and a surfactant on electrodes:

a highly reduced form of Mb was produced, which was successfully used to catalyze reduction of trichloroacetic acid and polyhaloethylenes 87]. Lindane dechlorination is effected by Fe-containing hemin and hematin, by Co-containing protoporphyrin, or by various cobalamins [8]. Vitamin B_{12} was also shown to reductively dechlorinate pentachlorphenol and trichlorophenoxyacetic acid [9]; cobalamins have also been used in the reductive dechlorination of CCl_4, polychlorinated ethanes, polychlorobenzenes, and PCBs [10]. Reductive dehalogenation of chlorinated aliphatic hydrocarbons and Freons was reported to occur with participation of coenzyme F430, a Ni-porphyrinoid present in anaerobic bacteria [11].

Transition metal complexes, in particular metal porphyrins, corrins, and phthalocyanines, have been studied as potential remediation catalysts in homogeneous abiotic aqueous systems. Cationic water-soluble Fe-, Co- and Ni-porphyrins with various functional groups in *meso* positions, suitable for immobilization, have been tested as catalysts for reductive dehalogenation of CCl_4 with dithiothreitol: $CHCl_3$, CH_2Cl_2, and CO were found to be breakdown products [12]. Ni(I) octaethylisobacteriochlorin has been used as a model of the F430 factor for the reduction and coupling of alkyl halogenides [13]. Photoreductive dehalogenation of aqueous $CHBr_3$ was mediated by CoPcS (PcS = tetrasulfophthalocyanine anion) adsorbed on the positively charged titania surface [14]. Nonspecific biomimetic macrocycles, CoTMPyP (TMPyP = tetrakis(*N*-methyl-4-pyridin)porphyrin cation) and CoPcS, were used as homogeneous and mineral-supported catalysts and were able to reductively dechlorinate CCl_4 in water, even at high concentrations that would inhibit microbial activity [15]. The C–X bond in aliphatic or benzyl halides can be transformed into a C–H bond in a transfer hydrodehalogenation reaction with formate as hydrogen donor and water-soluble Ru catalysts, $RuCl_2$(TPPMS) (TPPMS = *m*-sulfophenyldiphenylphosphine anion) or $Ru(H_2O)_3(PTA)_3(tos)_2$ (PTA = 1,3,5-triaza-7-phosphaadamantane) [16].

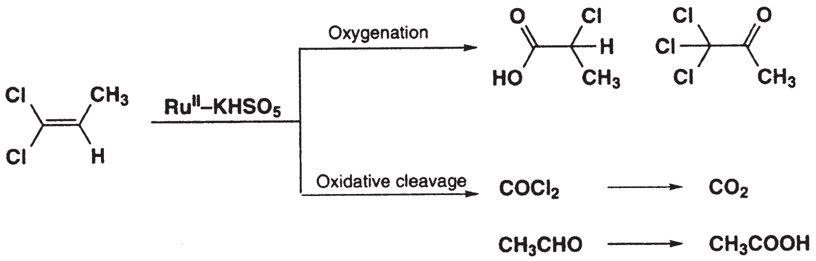
The oldest catalytic oxidative system for dehalogenation is Fenton's reagent: the hydroxyl radical is one of the few chemical species capable of attacking refractory halo-organic compounds, but the scope of the reaction in terms of effective substrate oxidation versus H_2O_2 dismutation is often limited by sensitivity to pH and a narrow H_2O_2/Fe^{2+} ratio [17]. Various water-soluble iron or manganese sulfophenylporphyrins catalyzed with exceedingly high activity (up to 20 cycles per second) the oxidative dechlorination of trichlorophenol (TCP) with $KHSO_5$ in aqueous acetonitrile [18]. The more easily accessible MnPcS or FePcS catalysts behaved equally in water in the presence of H_2O_2 also, with rates in excess of 0.1 cycles per second: products of dechlorination (up to two chloride ions were released per TCP molecule), of aromatic ring cleavage, and of oxidative coupling have been detected (Scheme 1) [19]. The catalysts, which have also been successfully tested for the dechlorination of chloroanilines [20], maintained their activities when immobilized on cationic resins.

RuO_4 was shown to oxidize PCBs in water [21]. Water-soluble Ru complexes, such as $[Ru(H_2O)_2(dmso)_4]^{2+}$, were effective catalysts for the $KHSO_5$ oxidation of a number of polychlorobenzenes and polychlorophenols, mainly converted into HCl and CO_2 [22]. Replacement of the dmso-“solvated” ruthenium by RuPcS resulted



Scheme 1 Oxidation of TCP by MPcS catalysts (M = Mn, Fe) and hydrogen peroxide.

in a definite improvement in the reaction, which could be performed with H_2O_2: oxidation of chlorophenols led to the complete disappearance of the substrates within minutes, with almost quantitative (80%) evolution of inorganic chlorine and massive (50%) formation of carbon dioxide [23]. RuPcS is also able to degrade α-chlorinated olefins to HCl and the appropriate carboxylic acid and/or CO_2, with turnover rates in excess of 1 s^{-1} (Scheme 2) [24].



Scheme 2 Oxidation of 1,1′-dichloropropene by Ru(II) catalysts and monopersulfate.

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2.4.8.3
Various Other Reactions

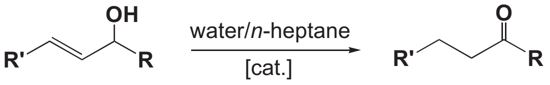
Fritz E. Kühn, Ana M. Santos, and Wolfgang A. Herrmann

2.4.8.3.1
Isomerizations

Recently, the nickel-catalyzed isomerization of geraniol and prenol has been investigated in homogeneous and two-phase systems. The best results with respect to activity and selectivity have been obtained in homogeneous systems with a bis(cycloocta-1,5-diene) nickel(0)/1,4-bis(diphenylphosphanyl)butane/trifluoroacetic acid combination. Catalyst deactivation occurs in the course of the reaction owing to coordination of the aldehyde group formed to the nickel species or as a result of protonolysis of hydrido- or (π-allyl)nickel complexes [1].

Isomerization of allylic and homoallylic alcohols is also catalyzed by the zwitterionic Rh(I) complex (sulphos)Rh(COD), with sulphos = $[O_3S(C_6H_4)CH_2C(CH_2PPh_2)_3]^-$, in water/*n*-octane to give the corresponding aldehyde or ketone in high yield and chemoselectivity. A π-allyl metal hydride mechanism was proposed on the basis of various independent experiments in both homogeneous and biphasic systems [2a]. Additionally, a water-soluble rhodium bisphosphine complex was used for the aqueous-phase isomerization of selected allylic alcohols. For the isomerization of cinnamyl alcohol, the catalyst was recycled with slight loss of activity and the optimum phosphine/rodium ratio was found to be 6 : 1 [2b].

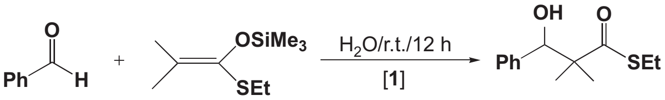
The isomerization of allylic alcohols, being a process of current industrial interest in the geraniol chemistry [3], was furthermore used as a liquid/liquid test reaction for high-throughput screening (HTS) of polyphasic fluid reactions. Nowadays high-throughput synthesis methodologies, such as combinatorial techniques, are applied to the discovery of pharmaceuticals, catalysts, and a multitude of other new materials [4]. The effectiveness of this approach has been demonstrated for restricted libraries in the case of catalysis in a single liquid phase. HTS in one phase is assumed to be unproblematic as long as the reactions are not too fast compared with the micromixing rates. However, numerous reactions of interest, e.g., hydrogenation, carbonylation, and hydroformylation, operate in gas/liquid or gas/liquid/liquid systems [5]. Inadequate control of phase and catalyst presentation, a result of nonoptimized agitation, may dramatically affect the estimation of selectivity and reactivity. Therefore a major challenge is to develop special reactors for rapid catalyst screening that would ensure good mass and heat transport in a small volume. The liquid/liquid test reaction, based on the isomerization of allylic alcohols [Eq. (1)] was performed with various Rh-, Ru-, Pd-, and Ni-based catalyst systems in aqueous/*n*-heptane reaction mixtures with a residence time of 100 s at 80 °C. The best results with respect to conversion have been achieved with $RhCl_3$ and $RuCl_3$/TPPTS catalyst systems [6].



(1)

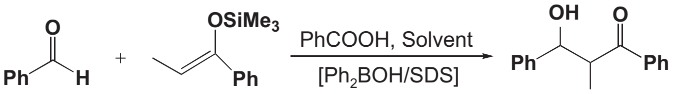
2.4.8.3.2
Aldolizations

As already exemplified in many other cases throughout this book, the main driving force for performing aldolizations in water is the reduction or even exclusion of any harmful organic solvents [7]. Several useful synthetic reactions in an aqueous medium need the presence of an organic co-solvent [8] (see also Section 2.2.3.3). Nevertheless many of these reactions proceed sluggishly in pure water, probably because most of the organic reagents are not completely dissolved. To overcome this problem Lewis acid–surfactant combined catalysts (LASCs) have been developed. In the presence of a catalytic amount of an LASC, organic materials rapidly form a dispersed colloidal system in water and several organic reactions proceed smoothly without the use of organic solvents. In order to solve the problems associated with catalyst recovery, polymer-supported Lewis acid catalysts (**1**) have been developed, which show high activity in water and can be easily recovered and re-used. Among the reactions performed with these polymer-supported catalysts is the aldolization reaction given in Eq. (2), promoted by a scandium-based catalyst (see also Chapter 7). Yields of 98% have been reached by the reaction of benzaldehyde with 1-ethylthio-1-trimethylsiloxy-2-methylpropene at room temperature in water in the presence of 3.2 mol% of catalyst [9a].



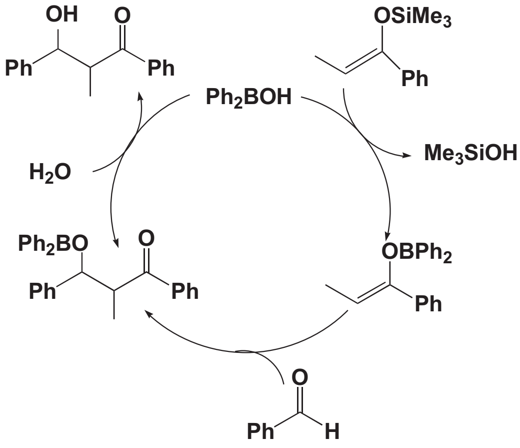
(2)

Diphenylboronic acid (Ph_2BOH), which is soluble in water, is an effective catalyst for the Mukaiyama aldol reaction in the presence of dodecyl sulfate (SDS) as surfactant. Yields of 93% with *syn/anti* ratios of 94 : 6 have been reached according to Eq. (3).The proposed mechanism of this reaction is shown in Scheme 1 [9b].



(3)

Furthermore, lead(II) and lanthanide(III) complexes were synthesized, which worked well as chiral Lewis acids in aqueous media. Until then, chiral crown ether-based Lewis acids had not been used successfully in catalytic asymmetric reactions. The asymmetric aldol reactions, however, proceed smoothly at –10 to 0 °C in water–alcohol solutions while retaining high levels of diastereo- and enantioselectivity. In most previously established catalytic asymmetric aldol reactions the use of aprotic anhydrous solvents and reaction temperatures of –78 °C were necessary. In the asymmetric aldol reaction using rare earth metal triflates $M(OTf)_3$ and chiral bispyridino-18-crown-6, slight changes in the ionic diameter of the metal cations greatly affect the diastereo- and enantioselectivities of the products. The substituents at the 4-position of the pyridine rings of the crown ether influence the binding ability of the crown ether with the M cations. The binding ability of the crown ether



Scheme 1 Mukayama aldol reaction.

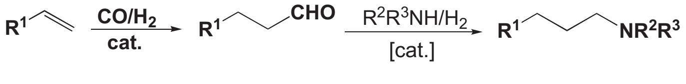
with the M cation, however, is important for achieving high selectivities in the asymmetric aldol reactions. Water plays an essential role for the good yield and selectivities. Several aldehyde and silyl enol ethers derived from ketones and thioesters can be applied [10].

Additionally, organocatalytic cross-aldol reactions catalyzed by cyclic secondary amines in aqueous media provide a direct route to a variety of aldols, including carbohydrate derivatives and may warrant consideration as a prebiotic route to sugars [11a].

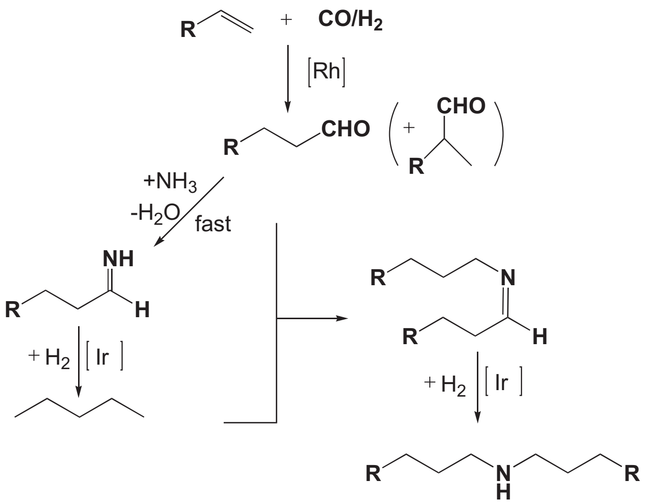
Dichloroindium hydride, generated by transmetallation between tributyltin hydride and indium trichloride, predominantly reduces unsaturated ketones (enones) with 1,4-selectivity in the presence of aldehydes. Under anhydrous conditions, the successive aldol reaction between the resulting enolates and the remaining aldehydes proceeds with high *anti* selectivity. The stereochemistry, however, is reversed to be *syn*-selective by the use of water and methanol as an additive and solvent, respectively [11b].

2.4.8.3.3
Hydroaminomethylation and Amination

Aliphatic amines are among the most important bulk and fine chemicals in the chemical and pharmaceutical industry [12]. Hydroaminomethylation of olefins to amines presents an atom-economic, efficient and elegant synthetic pathway toward this class of compounds. In hydroaminomethylation a reaction sequence of hydroformylation of an olefin to an aldehyde with subsequent reductive amination proceeds in a domino reaction [Eq. (4)] [13].



(4)

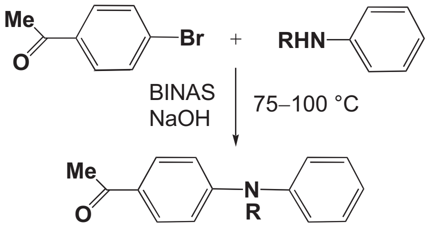


Scheme 2 Selective hydroaminomethylation of alkenes catalyzed by a new Rh/Ir system.

Recently, the highly selective hydroamination of olefins with ammonia to form linear primary and secondary aliphatic amines with a new Rh/Ir catalytic system ([{Rh(cod)Cl}$_2$, [{Ir(cod)Cl}$_2$], aqueous TPPTS solution) has been described (Scheme 2) [14]. The method is of particular importance for the production of industrially relevant, low molecular weight amines.

New methodologies have been reported in recent years for the amination of aromatic halides and triflates according to Eq. (5) with amines to yield aromatic amines of the type ArNRR′ [15]. In contrast to the homogeneous reaction conditions (1–5 mol% Pd(0) catalyst and 1.4 equiv *tert*–butoxide in PhMe at 80–100 °C), by using a two-phase protocol, the separation of products (and unreacted starting material) from the catalyst and subsequent reapplication of the catalyst in further reactions is made facile [16]. The use of the sixfold sulfonated ligand BINAS-6 permits the Pd(0)-catalyzed amination of aromatic halides in water containing single- or two-phase systems [17]. NaOH is used instead of the expensive NaOBu^t as the base. Further advantages are the facile catalyst/product separation and the reusability of the water-soluble Pd(0)/BINAS-6 catalyst. Yields higher than 90% have been reached according to Eq. (6).

$$\mathrm{ArX} + \mathrm{HNRR}^1 \xrightarrow[\mathrm{[Pd^0L\,/\,NaOBu}^t]]{\text{Toluene, 80–100 °C}} \mathrm{ArNRR}^1 \qquad (5)$$

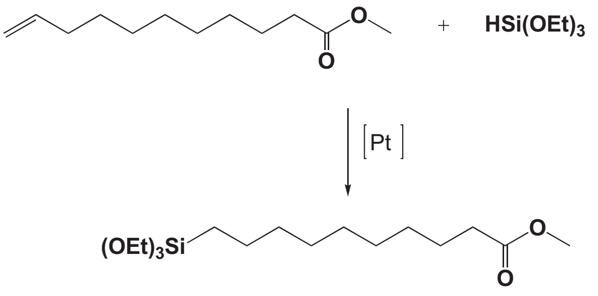


(6)

2.4.8.3.4
Hydrosilylation Reactions

The hydrosilylation of 1-alkenes can be carried out with catalysts of subgroup VIII. Platinum compounds, e.g., the Speier catalyst ($H_2PtCl_6 \cdot H_2O$) and the Karstedt solution, a complex compound of $H_2PtCl_6 \cdot (H_2O)_6$ and vinyl-substituted disiloxanes, are well known and very active catalysts [18]. Several other catalytic systems, e.g., $Pt(cod)_2$, leading to the formation of platinum colloids, have been examined [19]. More recently, hydrosilylation with the Speier catalyst has been examined both under single- and two-phase conditions. The hydrosilylation reaction was thereby optimized for the possibility of technical realization [20].

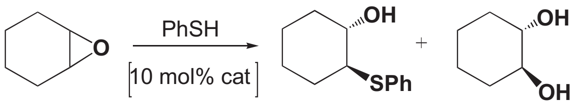
Different Pt(IV), Pt(II), and Pt(0) catalysts were screened for the hydrosilylation of fatty acid esters [Eq. (7)] containing terminal as well as internal double bonds. The reaction of terminally unsaturated fatty acid esters proceeds smoothly with short reaction times for nearly all the catalysts examined, whereas the Pt(IV) species, and Pt(II) or Pt(0) species with labile ligands, are sufficiently active in the reaction of internally unsaturated compounds. For methyl linoleate, a conjugation of the two internal double bonds before the hydrosilylation was observed. The reaction can be carried out without solvents as well as in solvent systems, allowing catalyst recycling and re-use. In these systems, however, hydrogenation and double bond isomerization are found as side reactions [21].



(7)

2.4.8.3.5
Thiolysis

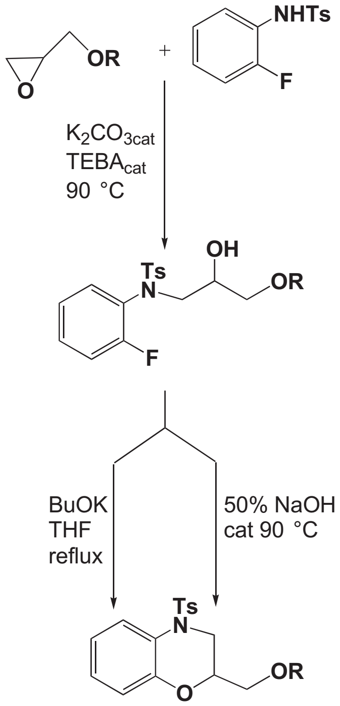
Ring opening of 1,2-epoxides with thiol-derived nucleophiles is a well established route to β-hydroxy sulfides that has been applied for the preparation of allylic alcohols, cyclic sulfides, and thioketones, and of important intermediates for the synthesis of natural products and compounds of biological and pharmacological interest [22]. The thiolysis of 1,2-epoxides is usually performed fundamentally in two ways: by using thiolates under basic conditions or thiols in the presence of a variety of activating agents [23]. The Lewis acid catalyzed thiolysis of epoxides in aqueous medium has been investigated recently [24]. The pH dependence of the thiolysis of 1,2-epoxides with thiophenol in water and the influence of a Lewis acid catalyst was examined. $InCl_3$ showed a very high efficiency in catalyzing this process at pH 4. The regioselectivity of the nucleophilic attack is markedly influenced on going from pH 9 to pH 4. A one-pot procedure in water alone, to prepare *trans*-2-(phenylsulfinyl)cyclohexan-1-ol, was reported starting from epoxycyclohexane, via thiolysis and oxidation with TBHP (*tert*-butyl hydroperoxide). An example of the thiolysis of epoxycyclohexane by thiophenol in water is shown in Eq. (8).



(8)

2.4.8.3.6
Synthesis of Heterocycles

Easy and efficient access routes to heterocyclic complexes are of significant interest in organic chemistry and its application in synthesis both in the laboratory and industry. During the recent years several novel routes toward such compounds in aqueous media have been described. 2-Substituted 3,4-dihydro-2*H*-1,4-benzoxazines have been prepared in excellent yields and short reaction times through the cyclization of hydroxysulfonamides in water under phase-transfer catalysis conditions (Scheme 3) [25].



Scheme 3 Cyclization of hydroxysulfonamides in water under phase-transfer conditions.

Reactions of 6-amino-1,3-dimethyluracil with substituted α-ketoalkynes using homogeneous nickel catalysts in aqueous alkaline media afford substituted 2,4-dioxopyrido[2,3-*d*]pyrimidine derivatives in quantitative yields under very mild conditions. A mechanism has been proposed for the reaction involving the nucleophilic attack by a Ni(0) anion, formed in situ of the triple bond of the substrate [26].

Additionally, the efficient synthesis of substituted phenylalanine-type amino acids using a rhodium-catalyzed, conjugate addition of arylboronic acids has been described. The reactions are run in water and use a low loading (0.5 mol%) of the rhodium catalyst [27].

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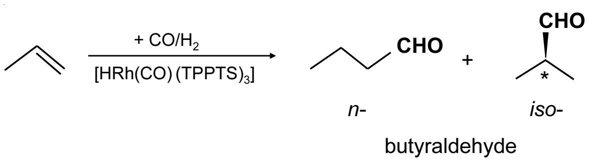
2.5
Commercial Applications

2.5.1
Oxo Synthesis (Hydroformylation)

Boy Cornils

Commercially, the aqueous-phase concept was firstly applied in Ruhrchemie/Rhône-Poulenc's (RCH/RP) process (for the fundamentals, see Section 2.4.1.1). In several units the RCH/RP process has been converting propene to *n*-butyraldehyde and isobutyraldehyde (or butenes to valeraldehydes) since 1984 in the presence of $HRh(CO)(TPPTS)_3$ (with TPPTS = *m*-trisulfonated triphenylphosphine or tris-(sodium-*m*-sulfonatophenyl)phosphine as water-soluble ligand) according to Eq. (1). The output of the units mentioned is approximately 890 000 tpy, which corresponds to roughly 13% of the world's total production.



(1)

This has to be considered against a background of an enormous growth in production capacity of aldehydes that has taken place since 1993. Worlwide oxo capacity in 1993 exceeded 6 MM tpy and increased within five years to more than 9.2 MM tpy [1]. With a share of 75%, C_4 products manufactured from propene have by far the pole position. With a share of only 3%, ethylene hydroformylation is of minor importance. Alkenes with medium chain lengths (diisobutene, tripropene, etc.) make up 17% of the total production capacity. Only 5% are used for the hydroformylation of alkenes with > 12 carbon atoms and thus for detergent alcohols. About 45% of the total C_4 capacity (or about 52% of the *n*-butyraldehyde capacity) is used for the production of 2-ethylhexanol (2-EH), the major plasticizer alcohol for PVC (dioctyl phthalate, DOP). Approximately 70% of the total hydroformylation capacity (converting light alkenes such as ethylene, propene, and butenes) is based on the low-pressure oxo processes (LPOs) using phosphine-modified rhodium catalysts. The various processes for the hydroformylation of propene with their catalysts (Rh, Co) are depicted in Table 1.

The process is described in detail in Section 2.4.1.1.3, and the development in Section 2.4.1.1.1. One of the units is depicted on the front cover of this book. Characteristic of RCH/RP's process is how the problem of catalyst deactivation, catalyst recycle, and catalyst removal/work-up has been solved [3].

As has been mentioned earlier, the part of the aqueous catalyst solution which leaves the oxo reactor accompanying (but not dissolved in) the reaction products

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Table 1 Capacities for C_4 products by various processes (excluding 2-EH).

Process	*Central atom of catalyst*	*Ligand*	*Capacity [× 1000 t]*	*[%]*
Union Carbide	Rh	TPP[a)]	3040	46
BASF	Rh	TPP[a)]	900	14
RCH/RP (Celanese)	Rh	TPPTS[b)]	890	13
Mitsubishi	Rh	TPP[a)]	680	10
Eastman	Rh	TPP[a)]	610	9
Neftekhim	Co	–	425	7
Shell	Co	Spec. P[d)]	75	1
Unknown[c)]			230	–
Total			6850	100

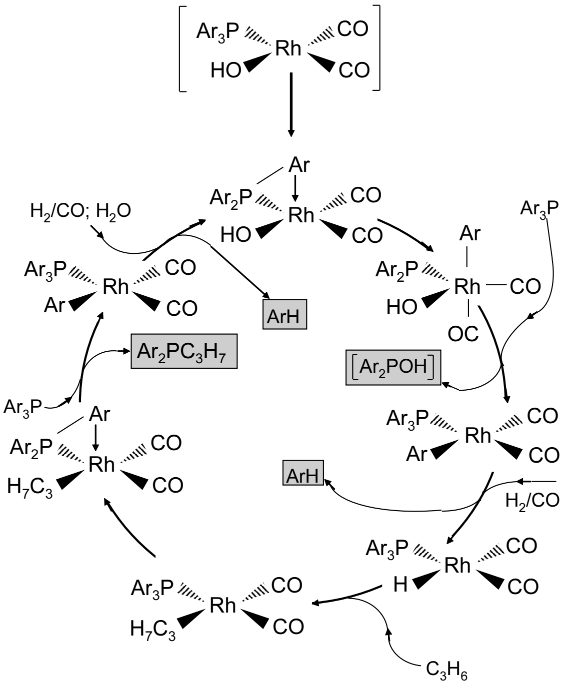
a) Triphenylphosphine.
b) Triphenylphosphine trisulfonate.
c) Not attributable.
d) Special phosphine [2].

passes a phase separator (decanter **2** in Section 2.4.1.1.1, Figure 3) which is a characteristic part of the plant shown on the front cover. In this decanter, which ensures spontaneous phase separation, the crude aldehyde formed by hydroformylation according to Eq. (1) is freed from gases and separated into mutually insoluble phases. The catalyst solution, supplemented by an amount of water equivalent to the water content of the crude aldehyde, is recirculated to the reactor. During its active life, the Rh catalyst is mainly situated in the oxo reactor, it is not moved (only part of it flows in a short circuit around the reactor), and no aliquots are withdrawn as in other processes. For this reason, rhodium losses are low – in the range of parts per billion (ppb) – and thus this provides the background for the high economy [4].

Like every technically used and therefore "real" catalyst, the complex HRh(CO)-$(TPPTS)_3$ and the excess ligand TPPTS undergo a degree of decomposition that determines the catalyst's lifetime as measured in years. The catalyst deactivation mechanism is known in detail and depicted in Scheme 1 [5].

The hydroxo complex $(HO)Rh(CO)_2TPPTS$ starts the deactivation cycle as shown in the Scheme 1 [5] (for graphical simplification, Ar_3P is TPPTS and Ar_2P is bis[*m*-sulfophenyl]phosphine) [6]. The various steps will not be discussed here. Other decomposition products such as the reductively eliminated bis(*m*-sulfophenyl)phosphinous acid Ar_2POH (cf. Scheme 1) and the phospine oxides $Ar_2P(OH)(=O)$ and $Ar_2P(=O)(CH[OH]C_3H_7)$ have been identified.

According to Figure 1, the intermittent addition of excess ligands extends the catalyst's lifetime in a sawtooth curve. This addition of ligand compensates for the system-immanent formation of deactivating substances which are brought into the system by the feedstocks. Filters, guard beds, or special precautions to avoid larger sulfur or oxygen inputs and their concentrations are not necessary. Additionally, other activity-lowering oxo poisons may be separated with the organic product phase of the decanter and are thus continuously removed at the very point of their formation from the system: any accumulation of activity-decreasing poisons in the



Scheme 1 Deactivation mechanism.

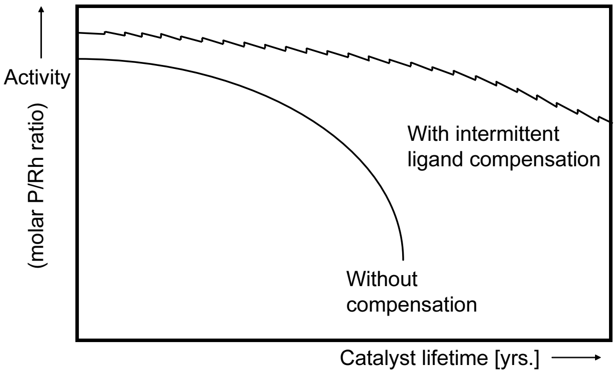


Figure 1 The effect of excess ligand on the catalyst's lifetime.

catalyst solution is prevented. It might be worth mentioning that the Ruhrchemie plant has been supplied over longer periods with syngas manufactured from coal by the TCGP (Texaco coal gasification process) [7].

Catalyst deactivation includes (among other reactions) the formation of inactive Rh species, ligand decomposition, or P–C cleavage by direct oxidative insertion of the rhodium metal for formation of PDSPP (propyl-di[*m*-sulfophenyl]phosphine) acting as strong electron donor reducing the amount of active Rh catalyst.

It turned out to be beneficial to control the P(III)/Rh ratio and the CO partial pressure very carefully.

Catalyst solutions after years of use typically contain 20 mg L^{-1} iron and 0.7 mg L^{-1} of nickel, thus showing no remarkable corrosivity. The Rh content of crude aldehyde is in the ppb range; this corresponds to “real” losses of less than 10^{-9} g kg^{-1} *n*-butyraldehyde, totalling 5 kg rhodium over a 20-year period and production of five million metric tons of *n*-butyraldehyde.

The recovery of rhodium from spent catalyst solutions proceeds according to the expertise and the rules of the rare metals producer; the technical know-how includes trade secrets. Because of its relatively low value, TPPTS is not recovered. This may be changed if higher-valued ligands, co-ligands, co-solvents, modifier, surfactant promoters, etc., are necessary for hydroformylation of long-chain alkenes. There are small-scale processes employing aqueous-phase catalysis which use “exotic” ligands such as bi-, tri-, or multidentate phosphines where the situation demands drastic measures such as ligand recovery.

The “real” oxo precatalyst $[HRh(CO)(TPPTS)_3]$ is easily made in the oxo reactor by reaction of suitable Rh salts (e.g., rhodium acetate or rhodium 2-ethylhexanoate) with TPPTS without any additional preformation step. After formation of the active species and adjustment of the whole system with water up to the desired P/Rh ratio (ensuring the stability of the catalyst and the desired n/i ratio), the reaction starts.

In total, RCH/RP’s process – although neither company still exists: Ruhrchemie went its way through Hoechat AG and Celanese to the present owner Blackstone and the joint venture European Oxo; Rhône-Poulenc became a part of the late Aventis SA and now Sanofi – is still the only oxo version of the fifth-generation hydroformylation processes.

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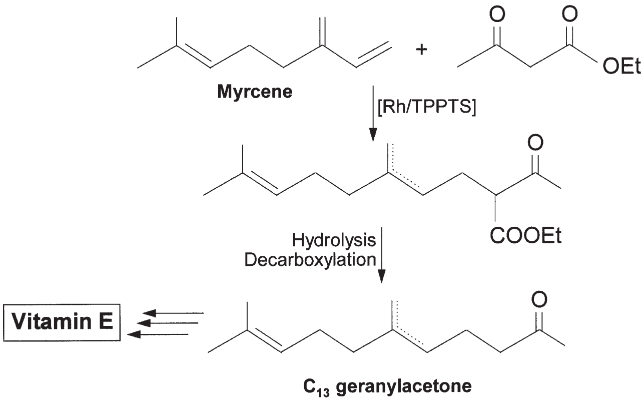
2.5.2
Other Reactions

Boy Cornils

Accompanying Ruhrchemie/Rhône-Poulenc's industrial realization of the aqueous biphasic hydroformylation reaction (cf. Sections 2.4.1.1.3 and 2.5.1) and Kuraray's hydrodimerization process (see Section 2.4.4.2), there are some other minor processes for the production of fine chemicals.

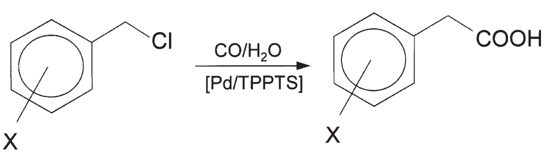
Rhodia runs a process for the manufacture of geranylacetone by Rh/TPPTS-catalyzed addition of ethyl acetoacetate to myrcene, a building block for vitamin E (Scheme 1) [1, 2a].



Scheme 1 Rhodia's process for manufacture of geranylacetone.

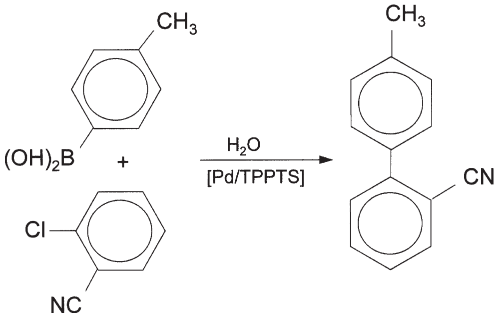
The process uses TPPTS from Ruhrchemie's production unit. Interestingly, in commercial operation supported aqueous-phase catalysis operation is more effective than the nonsupported catalyst version [2b]. Moreover, TPPTS-modified Ru or Pd catalysts have been proposed for the homogeneous catalyzed hydrogenation step for converting unsaturated into saturated ketones. It is not known how many of these proposals have been realized industrially [3].

Industrial significance has also been acquired by the aqueous biphasic Pd-catalyzed carbonylation of benzyl chloride to phenylacetic acid [Eq. (1)]. Once more, TPPTS is the ligand of choice [4].



(1)

Mention may be made of the Suzuki coupling of aryl halides and arylboronic acids. In earlier days, TPPMS could be used to convert the brominated or iodinated aromatics; nowadays, cheaper chlorinated aromatics and catalysts based on Pd/TPPTS are used in an aqueous procedure on a commercial scale [Eq. (2)] [5].



(2)

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2.6
Supported Aqueous-Phase Catalysis as the Alternative Method

Henri Delmas, Ulises Jáuregui-Haza, and Anne-Marie Wilhelm

2.6.1
Introduction

As seen in the preceding sections, many attempts have been done to heterogenize the homogeneous catalysts. In general, the immobilized systems never approach the necessary combined activity/selectivity performance levels and tend not to retain the metal complex, causing its leaching to the organic phase. In general, the drawback of all these immobilization methods is that they are not applicable for liquid-phase reactants/products that are miscible with the nonvolatile solvent phase [1]. Only biphasic catalysis, involving water-soluble ligands to maintain the catalytic complex in the aqueous phase, is successfully used in industry [2–4]. But the low solubility of higher olefins in the aqueous catalytic phase represents a serious problem in extending this outstanding technology to a broader variety of substrates (see Section 2.4.1.1) [2, 3, 5]. Several attempts to increase reaction rates with heavy substrates have been investigated: increasing olefin solubility in the aqueous phase using co-solvents, increasing interfacial area and mass transfer via phase tensioactive agents, or trying to locate the catalyst complex at the liquid–liquid interface with amphiphilic ligands or convenient hydrophylic–hydrophobic ligand mixtures. All these techniques would involve significant catalyst leaching, and probably for this reason none of them is known to be used in commercial plants.

The alternative could arise from development of an elegant immobilization method designed specifically to convert liquid-phase reactants: the supported aqueous-phase catalysis (SAPC) [6]. SAPC is a special case of the supported liquid-phase catalysis whose development began according to proposals by Moravec [7] and Rony [8, 9]. SAPC is very promising due to its high capacity in conversion and selectivity, its better stability, and also the very easy recovery of the catalyst from the organic phase. Comprehensive reviews of SAPC are available [1, 10–12].

2.6.2
SAPC: the Concept and Main Applications

SAPC consists in adsorbing on the surface of an hydrophilic solid a thin film of water containing the catalyst precursor. The catalyst should present hydrophilic ligands allowing its dissolution in the water film and thus its anchorage on the support. The hydrophilicity of the ligands and the support creates interaction energies sufficient to maintain the immobilization [1]. The metal atom is oriented toward the organic phase, with the catalytic reaction taking place efficiently at the aqueous–organic interface. The concept of SAPC has been expanded to other hydrophilic liquids such as ethylene glycol and glycerol [13].

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It has been proven that SAPC can perform a broad spectrum of reactions such as hydroformylation, hydrogenation, and oxidation, for the synthesis of bulk and fine chemicals, pharmaceuticals, and their intermediates. Table 1 summarizes some of the reported applications of SAPC. Although rhodium complexes are the most extensively used in SAPC, the complexes of ruthenium, platinum, palladium, cobalt, molybdenum, and copper have also been employed (Table 1).

Due to interfacial reactions, one of the main advantages of SAPC upon biphasic catalysis is that the solubility of the olefins in the catalytic aqueous-phase does not limit the performance of the supported aqueous phase catalysts (SAPCs); the turnover frequencies (TOFs) are roughly independent of olefin carbon number [17]. This has been shown to be true also for carbon numbers as high as 17 [15].

Table 1 Main applications of SAPC.

Reaction	***Metal***	***Ligand***	***Substrate***	***Ref.***
Hydroformylation	Rh	TPPTS	Alkenes	[1, 6, 14–33]
		TPPTS	α,β-Unsaturated esters	[34, 35]
		TPPTS	Monoterpenes	[36, 37]
		HexDPPDS	Alkenes	[20]
		Xantphos	Alkenes	[24]
		PAA–PNH	Alkenes	[38]
		Norbos	Alkenes	[39]
		PEI–PNH	Alkenes	[38]
	Co	TPPTS	Alkenes	[40, 41]
		TPrPTS	Alkenes	[20]
	Pt	TPPTS	Alkenes	[42]
	Pt/Sn	TPPTS	Alkenes	[20, 42]
		TBeTS	Alkenes	[20]
		TEtPTS	Alkenes	[20]
		TPrPTS	Alkenes	[20]
		(S,S)-BDPP	Styrene	[20]
Hydrogenation	Rh	(S,S)-BDPP	Alkenes	[20]
		chiraphos	Alkenes	[20]
	Ru	TPPTS	α,β-Unsaturated aldehydes	[43]
		BINAP	Alkenes	[44]
Oxidation	Pd/Cu		Alkenes	[45]
	Mo		Alkenes	[46]
Allylic substitution	Pd	TPPTS	Allyl acetates	[47–49]
Indolization	Rh	TPPTS	Azobenzene	[50]
Asymmetric reactions		BINAP		[51]
Alkoxycarbonylation	Pd	TPPTS	Alkenes	[52]

Concerning the position of the double bond, from the data presented by Arhancet et al. [16] it was clear that the activity of SAPC for the hydroformylation of internal olefins is of approximately the same order of magnitude as for the hydroformylation of terminal olefins. However, the rate of isomerization for the internal olefins is higher than for external ones (e.g., heptene). In the same study, the interesting fact is that the hydroformylation of higher external linear alkenes and dienes gives similar results, although the hydroformylation of dienes takes place sequentially, beginning with the external double bond. A different result was obtained when the role of monoterpenes (linear or monocyclic) in the reactivity of linalool, limonene, and geraniol undergoing hydroformylation by SAPC was investigated [36]. The efficiency of SAPC to achieve hydroformylation of linalool, geraniol and limonene depends strongly on the location of the double bond and of some properties of SAP catalysts, as pore size and hydration ratio. The low reactivity and the lower conversion levels of geraniol and limonene, as compared with linalool, were explained in terms of double bond polarization and of steric hindrance and configuration.

2.6.3
The Supports and the Preparation of the SAP Catalysts

Different inorganic materials have been used as supports in SAPC: glass beads of controlled pore size [6, 14–17, 24, 39–42, 44, 45, 53]; porous [11, 15, 18, 19, 21, 23, 28–32, 35, 36, 38, 39, 43, 48, 49] and nonporous [28, 33, 48] silica nanoparticles; synthetic phosphate [27]; carbon [39], and alumina [15, 39]. It was shown that glass beads, silica, and synthetic phosphate gave the best performance. All these supports have a high specific surface with an average diameter of the pores, in the case of porous supports, between 60 and 345 Å. The use of chitosan as a natural polymeric support of SAP catalysts for the synthesis of fine chemicals has been reported recently [54].

Several methods have been used for preparing the SAP catalysts. According to the preparation procedure, the methods can be classified into two groups: (a) indirect methods, when the support is first impregnated with the hydrosoluble catalytic complex, then dried and rehydrated before use [6, 14, 15, 17, 41, 42, 49]; (b) direct methods, when the support, catalytic complex, and water are mixed at the same time in the reaction system [15, 21, 29]. In general, the best conversions in the hydroformylation of alkenes by SAPC have been obtained by indirect preparation. However, the direct methods being of much easier implementation than the indirect ones, they are most widely used.

2.6.4
Main Factors Influencing the Efficiency of SAPC

Many typical parameters usually investigated in biphasic catalysis, such as temperature, pressure, the excess of water-soluble ligand, and the nature of the reactants and the catalyst, have roughly similar effects on SAPC.

As seen before, a major difference with respect to biphasic catalysis is the low dependence on substrate solubility in the catalytic aqueous phase as the SAPC reaction occurs at the interface. SAPC is strongly dependent on the water content of the solid support. Two types of water content effects have been reported: usually SAPC is efficient over a very restricted hydration range where activity exhibits a clear peak, while only recently a large plateau was observed in a higher hydration range.

Most often a very narrow optimum range of support hydration yielding the best conversion has been found [14–17, 48]. Drastically decreased activity observed at higher or lower water loadings was not due to metal loss through leaching [6, 14–17, 20, 28, 35, 51]. This typical effect of the hydration ratio of the support has been related to three different environments [14]. First, at a very low water content, the catalytic complex is strongly adsorbed to the surface, as evidenced by the lack of mobility seen in the solid-state NMR spectra for the adsorbed complex. The lack of mobility may be responsible for the low catalytic activity observed at low water contents. Furthermore, at low water content the catalysts are very stable. Secondly, at intermediate water contents the catalytic activity reaches a maximum while the complex stability is still enhanced. Thirdly, at high water loading the SAP materials lose both activity and stability and approach the behavior of the unsupported catalyst; this may correspond to a flooded catalyst.

It is clear that this high sensitivity would constitute a serious drawback of the SAPC concept, as crucial measurement and control of the water content would be very difficult during continuous operation or multiple catalyst re-use. Nevertheless, conditions where SAPC is equally efficient over a much wider hydration range have been reported recently [28, 33, 36, 37]. The influence of the hydration rate on the support was studied extensively for the hydroformylation of 1-octene and linalool on several porous silica supports [28, 36, 37]. Data for 1-octene are shown in Figure 1, where the degree of hydration is the ratio of the water content to that corresponding to complete pore filling. Two very different behavior were observed, depending on the support pore characteristics. For S200 and S60, the silica supports with larger

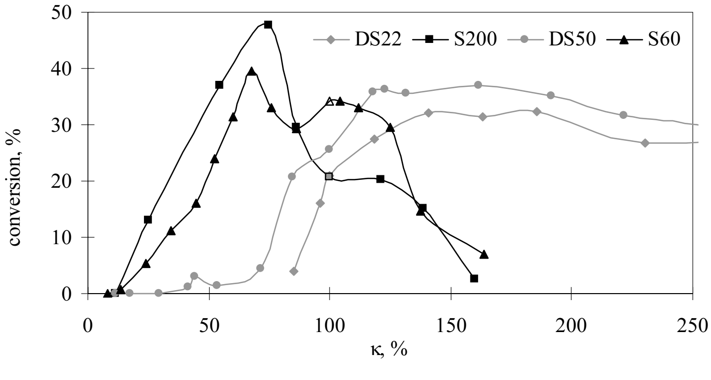

Figure 1 Effect of the degree of hydration (water volume/pore volume) on conversion for various supports [55].

pores, an optimum degree of hydration corresponding to incomplete pore filling was found, while for DS22 and DS50 the large range of approximately constant conversion corresponds to a significant excess of water. The same results were reported for linalool [36, 37]. In both cases, decreased conversion and leaching of rhodium through aqueous droplets were observed when the amount of water was further increased. The same behavior was found during the hydroformylation of 1-hexene with aqueous phosphine–Rh complexes supported on non-porous fumed-silica nanoparticles [33]. A positive effect on the reaction performance was observed for the particle size and surface area of the nanoparticles.

The influence of the hydration ratio and the physico-chemical properties of five supports in the hydroformylation of 1-octene was also studied [28]. The results confirm that the size of the pores and the amounts of water were found to be the determining factors contributing to SAPC efficiency.

Most authors have found the excess of water-soluble ligands to have limited effects on both activity and selectivity for linear/branched aldehydes, whether the optimum hydration ratio zone was narrow or wide. The ratio of linear aldehydes (about 80%) is lower than that observed in biphasic aqueous catalysis.

The main limitation for the use of SAPC is due to the limited stability and reusability of the support–catalytic complex matrix. There are two approaches to solving this problem. The first is the use of more stable ligands. Wan and Davis [44] reported the use of the complex Ru–BINAP in the selective hydrogenation of 2-(6′-methoxy-2′-naphthyl)acrylic acid. After seven cycles the conversion and selectivity remain stable. The xantphos-based complexes of rhodium used in the hydroformylation of olefins have been used successfully as selective and recyclable catalysts [11, 24]. The second option is the addition of basic alkali metal salts such as Na_2CO_3, K_2CO_3, and NaH_2PO_4, which depressed the oxidation of TPPTS [33].

2.6.5
Perspectives and Challenges

Despite promising results, SAPC has not yet been used for large commercial production. The new possibility of efficient SAPC over a wide range of support hydration [27, 28, 33] has technological importance since it significantly improves flexibility by avoiding a strict control of the hydration ratio. Therefore, this modification may open the way to apply SAPC on a commercial scale.

The main technical advantage of SAPC with respect to the usual biphasic catalysis is the much faster reaction rate with poorly water-soluble substrates which may have direct access to the catalyst. Such performances are obtained in relatively mild reaction conditions (temperatures up to 393 K and pressures up to 2 MPa) and with less catalyst loss in the organic phase than in any other boosted aqueous phase catalysis. Nevertheless, one of the most critical points for a SAPC process to be economically successful remains the difficulty in extending widely the reusability of the support–catalytic complex matrix. This difficult catalyst recycling has been attributed to the loss of water from cycle to cycle and to the degradability of the hydrosoluble ligands. Useful data on catalyst leaching and SAPC decreasing efficiency after a large number of re-uses are absent in the open literature. As water content control appears less critical with convenient support, the major improvements should come from more stable water-soluble ligands [11, 24, 51] (e.g., not oxidized like TPPTS) and with even better interaction with the hydrophilic support.

Concerning the fields of application, SAPC has prospects of being used either in the basic chemical industry and petrochemistry, or in fine and pharmaceutical chemistry, in biotechnology, and in the food industry; in these last two it may be associated with enzymatic processes. In basic chemistry and petrochemistry the main target is clearly the hydroformylation of higher olefins. In this case, if catalyst losses are economically acceptable, the best way to improve plant productivity would be to use SAPC in continuous fixed-bed reactors such as the usual trickle-bed reactors. Such operation allows both much higher catalyst support loading, up to 60%, and better reaction performance than slurry reactors, due to plug flow. Based on recently reported data on a TOF of about 500 h^{-1} and, due to a higher water content, a rhodium concentration up to 20 $\mu mol\ g^{-1}\ SiO_2$, a fixed-bed reactor could produce aldehydes higher than C_6 in very attractive conditions, at up to 0.5 $t\ h^{-1}\ m^{-3}$.

Nevertheless major possibilities for using SAPC in the short term can be foreseen in fine and pharmaceutical chemistry, e.g., for the selective hydrogenation of α,β-unsaturated aldehydes such as retinal [43] and to the production of the commercially anti-inflammatory agent naproxen [44].

The hydroformylation of α,β-unsaturated esters by SAPC has also been investigated [34]. Several 2-formylpropanoate esters, which are widely used as intermediates in the synthesis of pharmaceuticals like rifamycin and vitamin E, were obtained using the water-soluble complexes. There are huge prospects for SAPC in the hydroformylation reaction for obtaining molecules having a broad-spectrum therapeutic activity.

The synthesis of many pharmaceutical agents and complex molecules from natural sources is strongly dependent on the availability of intermediates suitable for further structural change. In this context, the hydroformylation by SAPC, especially when catalyzed by rhodium carbonyl complexes, which ensure higher chemo- and regioselectivity with respect to other metal derivatives under comparable reaction conditions, offers a concrete possibility of obtaining a wide variety of molecules endowed with therapeutic activity. As an example, the hydroformylations of styrene and related vinylaromatics to yield 2-arylpropanoic acids (anti-inflammatory and analgesic agents) [54] can be accomplished by SAPC. Recently a new process using a SAP Pd catalyst for the preparation of saturated carboxylic acids by alkoxycarbonylation of olefins was patented [52].

Using the techniques developed to synthesize the organometallic-based SAP catalysts, several enzyme-based SAP catalyst, using porous glass beads and the enzymes polyphenol oxidase and horseradish peroxidase have been studied [53]. These SAP catalysts were active in the reaction of phenol with O_2 or H_2O_2, respectively. Thus, porous enzyme-based SAP catalysts can be synthesized.

2.6.6
Conclusion

Supported aqueous-phase catalysis brings a clear opportunity to overcome the two main limitations of biphasic catalysis for liquid substrates: poor activity and/or significant catalyst losses. SAPC provides relatively high turnover frequencies due to a large interfacial area where the metal is available even for highly hydrophobic substrates. In addition, metal losses are reduced by convenient selection of hydrophilic supports and water-soluble ligands, but the outstanding preservation of Rh in gaseous propene hydroformylation on a water-soluble catalyst is far from being matched again.

As recently reported, the efficiency of SAPC over a much wider hydration range will facilitate its use in industry. Two major commercial applications of SAPC are expected: first, many fine chemicals and pharmaceuticals could be produced in better conditions due to high enantioselectivity; and secondly, hydroformylation of liquid olefins in continuous fixed-bed reactors under mild conditions with relatively high productivity and selectivity is possible.

Nevertheless, the question of costly catalyst losses is not yet perfectly clarified and constitutes the main limitation for the development of SAPC-based processes.

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2.7

The Way Ahead: What Should be Done in the Future?

Boy Cornils and Wolfgang A. Herrmann

As a result of the assessment of all the known techniques regarding multiphase homogeneous catalyses, the aqueous-phase operation is clearly ahead of the other possibilities (cf. Chapter 8). This is mainly due to the attractiveness of the principle as well as to the state-of-the-art attained: the process makes it possible to utilize fully the inherent advantages of homogeneous catalysis. A major aspect of this technology is the tailoring of the organometallic complexes as catalysts (which is nowadays becoming increasingly important for industrial applications) for new reactions, and for new products. The avoidance of selectivity- and yield-reducing operations (such as thermal stress caused by chemical catalyst removal or distillation) to separate products and catalysts makes it possible to use sensitive reactants and/or to obtain sensitive reaction products from homogeneous catalysis. Figure 2 of Section 2.1 demonstrates the advantages of the aqueous-phase technique over the conventional ones, taking the hydroformylation reaction as the prominent example: the aqueous-phase methodology avoids extensive technical equipment except for the column just behind the reactor – a tremendous cost-saving effect.

It is true that only those technologies that use the separation of products and catalysts with organic/organic or organic/water solvent couples are operative to a larger extent. Beyond that, the aqueous biphasic variety is the only one with a convincing "green" touch – more satisfying than just reading about an "even greener ionic liquid" [2], "toward greener chemistry" [1], the "greening" of reactions [3], "green chemistry gets greener" [4], or "clean solutions for chemical synthesis" [5]. On the other hand there are reasonable doubts about "ionic liquids are not always green" [6] and "you think your process is green – how do you know?" [7a]. And things can hardly get any worse: there are serious publications about the "noninnocent nature" of various ionic liquids and "undesirable transformations" yielding corrosive and/or toxic degradation products [7b]. This all has to be seen a realistic background of, on the one hand, the Ruhrchemie/Rhône-Poulenc process being the only realization of a biphasic process which provides data about its "Life Cycle Assessment" (LCA), "Failure Mode, Effects, and Criticality Analysis" (FMECA), "Fault Tree Analysis" (FA), and "Maintainability Analysis" (MA) [8]. On the other hand it is true that the RCH/RP process has been developed with the aim of better catalyst activity, handling, selectivity, and efficiency, improved process economics, reduction of by-products, etc.; i.e., it takes as a basis catalyst design, process intensification, and the principles of sustainable development – but it does not work under the label "green"!

And it is obvious that only the aqueous biphase technology has a far-ranging claim for wider applicability as far as substrates and the tuning of appropriate catalyst systems (consisting of central atoms *and* ligands) are concerned. Yet it is difficult to believe that the very special Shell approach of an organic/organic separation will be extended to other syntheses.

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Aqueous, two-phase catalysis is used industrially in a number of processes for the production of bulk-scale chemicals such as *n*-butyraldehyde (in amounts up to 800 000 tpy; in total since the start of the new technology, 5 MM tons) to a series of fine chemicals such as precursor compounds of fragrances or vitamins. Here, the possibility of the spontaneous separation of the aqueous catalyst phase complies in a fortunate way with the usual mode of operation of fine chemicals manufacture: the work in discontinuously operated stirred-tank reactors, the decanting of the reaction mixture from the first run, and the use of the catalyst phase for a subsequent run. Taking a broad view, solution of chemical engineering questions will be a task for the future: from basic problems (where does the reaction between the catalyst, in aqueous solution, and the substrates and reaction products, based in the organic phase, take place?) through to specific questions concerning various aspects of the technology, such as reaction control, alternative concepts of catalyst recycling and work-up, reactor design, use of mixtures of solvents with mixture gaps, combinations with ultrasonic and microwave reactors, and so on. The experiences gained so far with the inclusion of membrane techniques in aqueous-phase processes may give the decisive impetus for their further development which will be necessary for the use of other multiphase operations (e.g., polymer-supported homogeneous catalysts) which will be described in Chapter 7.

Quite another part of work will be the extension of the scope of the reactants. Due to the decrease solubilities of the starting alkenes and products in water with an increasing number of carbon atoms, the bulk-scale technology (of hydroformylation) has so far been restricted to the use of alkenes from propene up to pentenes. The further development of ligands will be one of the fields of activity. For today's exotic ligands such as carbohydrates and dextrins, proteins, porphyrins, paracyclophanes, calix[*n*]arenes, supramolecular compounds (dendrimers, etc.), or templates, once more the use of membrane separation techniques has to be evaluated. Temperature-regulated or thermomorphic variants have to be checked as well as the work on microemulsions or micellar systems. In any case, a look at the bulk-scale operation and its cost situation prohibits most of the proposals discussed. The same is true for advanced or even highly sophisticated ligand developments: it is known that so far none of the so-called "second generation ligands" has paid off its costs. On the whole, on closer inspection, any additional effort increases the costs – it may be an additional process step, an extra or expensive auxiliary (such as co-solvents, co-catalysts, counterions, surfactants, promoter ligands, or other additives), bimetallic or bifunctional catalyst systems, or supplementary amounts of reactant to move or to separate. In the handbook *Aqueous-Phase Organometallic Catalysis* [9], all these lines of development are discussed in detail.

In terms of "green syntheses", the community expects ongoing intensive research work with aqueous biphasic operations. One of the reasons is that water is the only "green solvent" being used industrially. Aspiring users of the others, such as supercritical carbon dioxide or ionic liquids, suffer from lack of experience, and with *all* the other biphasic variants they have to cope with the problem that the demanding catalyst systems need to be tolerated by the second phase – mostly as far as the extremely complicated and costly ligands are concerned.

Additionally, various papers dealing with "effective" (but extremely costly) perfluoro compounds as ligands or with liquids which are hampered by insufficient stability ("which are not always green" – in fact the contrary of a green solvent!) read like fairy tales. They ought to be regarded with scepticism.

The field is in flux. As a consequence of the increases scientific study of aqueous biphasic homogeneous catalysis, an increasing number of commercial applications may be expected in the future. Here one should mention one-pot and tandem reactions which combine the aqueous-phase hydroformylation with subsequent steps such as cyclotrimerization, Michael or Mannich additions, or aldolizations. Another example might be catalyzed reactions in water which use the extremely high enthalpy of the O–H bond. This value (436 kcal mol^{-1}) predestines water as an excellent solvent for carrying out free–radical reactions because in order for a radical to abstract a hydrogen atom from water, the bond enthalpy of the bond formed between a new heteroatom and hydrogen must be greater than that of the O–H bond. Several other processes are the subject of detailed surveys and reviews. Further methodological progress will comprise both the improvement of the technology and extension of the respective reaction to other applications.

The investigation of "hybrid" processes comprising the combination of the aqueous with other biphasic options such as those described in Chapters 3–7 (preferably for hydroformylation reactions) may be included – but will enhance the overall costs. The same is true for other hybrid applications such as SAPC (**s**upported **a**queous-**p**hase **c**atalysis) or SOMC (**s**urface **o**rgano**m**etallic **c**hemistry). The serious drawback of these special variants originates from the notorious "leaching" of the catalyst, concerning the (usually expensive) transition metal as central atom of the catalyst complex, the ligand (which, as a tailor-made compound to meet special demands, may be even more expensive), or both. By following this, no real progress can be expected. Ligands which imply phase-separating properties, such as the "thermoregulating ligands" developed by Jin t al. and as described by Ishihara and Yamamoto in Chapter 4, Section 4.2.6, may be worth developing. PEG has some disadvantages, but the basic idea of bringing in different behavior of the operative phases as part of the properties of the ligand is tempting! Only this (or a similar development) will extend the horizons of the aqueous biphasic technology to higher boiling and less soluble substrates. But once more: in this respect, the whole (commercially inclined) community agrees that additional additives would be too expensive to handle, to remove, and to recycle (not to mention their costs).

From the standpoint of solvents and their environmental friendliness and nontoxicity one can image a hybrid process comprising an "inverted aqueous biphasic catalysis" where the catalyst is immobilized in the organic phase and the polar substrates and products reside in the aqueous phase [10] – but there is no indication for serious industrial research work.

Further methodological progress will comprise both the improvement of the technology and the extension of the respective reactions to other applications. Reaction engineering may be improved by other and new reactor concepts, as demonstrated by the Oxeno researchers [11]. Also, a new understanding of the micro-events is demanded with regard to phase boundaries (or the interfacial processes) and their reciprocal solubility and dissolution of gases, fractional holdups of different phases (holdup is the volume fraction occupied by the flowing phase besides the catalyst phase), mass and heat transfer, overall and intrinsic reaction rates, and the coupled influence of mass transfer with chemical reaction. This understanding will justify the preceding research.

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3
Organic–Organic Biphasic Catalysis

Dieter Vogt (Ed.)

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3.1
Introduction

Dieter Vogt

Many attempts have been made to combine the advantageous features of homogeneous and heterogeneous catalysis. In general, these methods can be combined in two categories as heterogenization and immobilization of molecular catalysts. These involve the deposition of metal complexes on solid carriers or anchoring them onto the outer or inner surface of the support. The heterogenized metal complex catalysts so far have been found unacceptable for large-scale applications because of poor performance or stability. A more successful technique of catalyst immobilization is the separation of the reactants (products) and the catalyst(s) by immiscible liquid phases. This is the concept of biphasic catalysis of which several variants have been developed during recent years (see Chapter 1).

Biphasic systems are built up of (at least) two solvents with limited mutual solubility. Depending on which solvents are chosen, biphasic systems can be divided into six categories:

- In *aqueous–organic* biphasic systems one of the solvents is water and the other is a solvent immiscible with water. The substrate/product mixture may also constitute the organic phase with no added solvent.
- In *organic–organic* biphasic systems both solvents are organic compounds with limited mutual solubility.
- In *fluorous* biphasic systems one of the solvents is a highly fluorinated organic compound and the other the usual organic solvent.
- Using *ionic* liquid biphasic systems means that melts of specially designed, low melting salts are used as one of the liquid phases in combination with an aqueous phase or an immiscible organic solvent.
- Solvents under *supercritical* conditions use the peculiar properties of the supercritical state and its phase behavior.
- Last but not least, catalysis with polymer-bound, water-soluble ligands has been recommended.

All six variations have been introduced in Chapter 1 and the following sections.

In this chapter only the second category will be discussed: organic–organic biphasic systems. However, the distinction between the first two categories is not always clear. In some cases water is added to an organic–organic biphasic system to improve the performance of the system. In that case, depending on the reaction and the amount of water added, the system will be discussed as well. There are also transitions between ionic liquids and water or fluorous solvents, between water and $scCO_2$, or between water-soluble polymers and organic solvents.

Besides the above-mentioned classification into six categories, depending on the solvents chosen, biphasic systems have been classified into up to 12 categories, depending on how and at which moment in the process product(s) and catalyst(s)

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are being separated [1, 2]. Finally, the effect of temperature on solvent mixtures has to be mentioned. Even the simplest biphasic catalytic system contains at least five components: two solvents, a reactant, a product, and the catalyst. It is therefore not a big surprise that the mutual solubility may vary in a complex way with temperature. Certain biphasic (or multiphasic) systems show a sharp phase transition into a homogeneous phase when the temperature is raised. If the resulting homogeneous liquid phase dissolves both the substrate(s) and the catalyst, then a genuine homogeneous catalytic reaction takes place (without limitation of mass transfer at the liquid–liquid phase boundary). After the reaction is completed, the temperature is lowered and two immiscible liquid phases are obtained again, leading to easy separation of catalyst and product(s). Section 3 of this chapter will be devoted to examples of such systems; another proposal is described in Chapter 2.3.5.

It is noteworthy that the only example of a large-scale industrial process based on organic–organic two-phase catalysis so far, the Shell higher olefin process, SHOP, was at the same time the first example of a two-phase homogeneous catalytic process applied in industry [1, 3]. Then, after the introduction of the successful example of aqueous–organic biphasic catalysis by Kuntz [4, 5] and the development of the Ruhrchemie/Rhône-Poulenc process [6], the organic–organic systems lost interest. It is only very recently that academic groups became interested again in this concept. One reason might be the fact that many more empirical data and much more knowledge are required for a thorough description of such a process. The description of the phase behavior with the corresponding phase diagrams considering all the components of the system is a particular prerequisite. On the other hand, the reaction engineering aspects of liquid–liquid reactions seem to have been well examined [7–12].

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3.2
State-of-the-Art and Typical Reactions

3.2.1
Organic–Organic Biphasic Catalysis on a Laboratory Scale

Dieter Vogt

3.2.1.1
Hydrogenation

The hydrogenation of different double bonds has often been performed in biphasic systems. Hydrogenations in the homogeneous phase has often been performed with the Wilkinson [$(Ph_3P)_3RhCl$] catalyst. By modification of the ligands a catalyst suitable for biphasic catalysis can be obtained. Da Rosa et al. [13] described a biphasic system containing poly(ethylene oxide) (PEO), *n*-heptane and either dichloromethane (CH_2Cl_2) or methanol. This liquid biphasic system was tested in the hydrogenation of 1-hexene. As catalyst, Wilkinson's catalyst was used, as well as the cationic rhodium complex [Rh(cod)(dppe)]PF_6. The catalyst was used in a ternary mixture of PEO, *n*-heptane, and CH_2Cl_2. This polymer solution shows phase separation of the UCST (upper critical solution temperature) type. For PEO solutions in CH_2Cl_2 the phase separation temperature ranges from –80 °C to –40 °C for PEO 3350 concentrations between 1 and 60% (w/w). Therefore, by cooling the reaction system with N_2, it was possible to selectively separate the catalyst and the reaction products. Owing to large density differences, this biphasic system was kinetically stable for a longer time, even close to room temperature, allowing easy separation of the liquid phases.

This procedure resulted in an efficient and selective substrate conversion and it was established by spectrophotometry that there was no catalyst leaching to the apolar phase. However, a marked decrease in the catalytic activity was observed after the third cycle. This was probably caused by a continuous loss of free triphenylphosphine ligand present in equilibrium with the rhodium complex, ultimately generating inactive species. To overcome this problem the cationic rhodium complex [Rh(cod)(dppe)]PF_6 was tested. In the ternary mixture containing CH_2Cl_2 this complex showed poor catalytic activity. Using methanol instead clearly increased the activity. This effect of increased activity in methanol is well known for rhodium complexes.

The cationic rhodium complex was used in a homogeneous system of methanol, PEO, and 1-hexene, resulting in a conversion of 54 ± 5% and a selectivity of 90 ± 10% after 2.5 h. Under biphasic conditions, i.e., a system composed of 14 mL methanol, 3.6 g PEO, and 14 mL *n*-heptane, 0.0335 mmol of rhodium complex, 8.01 mmol of 1-hexene, and a hydrogen pressure of 1 MPa, the cationic rhodium complex was tested as well: five runs were conducted with complete conversion of 1-hexene to *n*-hexane and without loss of catalytic activity or selectivity. However, considering

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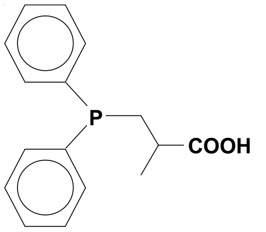
the fact that the solvent system has to be cooled to a very low temperature for separation, the energy costs of such a system will prevent a larger-scale application.

Other ligands for the biphasic hydrogenation (and hydroformylation) were investigated by Mieczyńska et al. [14]. The rhodium complexes were formed from the precursor [Rh(acac)$(CO)_2$] and the (water-soluble) phosphine ligand. The phosphine ligands PH and PNS, **1** and **2**, were tested in the hydrogenation reactions of 1-hexene, toluene, *o*-xylene, and cyclohexene. However, only 1-hexene showed considerable conversion by each rhodium complex in a 1-hexene/water mixture. The yield of *n*-hexane for the ligands PNS and PH was determined to be 67% and 42% respectively after 4 h. For the system [Rh(acac)$(CO)_2$/PNS] different co-solvents were added to water in order to improve the yield of hydrogenation. The solvent systems thus investigated are given in Table 1. The resulting biphasic system was composed of 1.5 mL 1-hexene, 1.0 mL Water, and 0.5 mL co-solvent at a rhodium concentration of $5 \cdot 10^{-3}$ M, a hydrogen pressure of 1 MPa, and a temperature of 80 °C. The reaction time varied between 1.5 and 4 h for the different co-solvents. Only for the co-solvents ethanol (83%), diglyme (80%), tetraglyme (73%), and ethylene glycol (75%) was an increase in the yield of *n*-hexane (after 3 h) determined. However, in case of the ethers more isomerization reaction also took place (2-hexene). It was therefore concluded that a mixture of water–ethanol is the best choice for the hydrogenation of 1-hexene.



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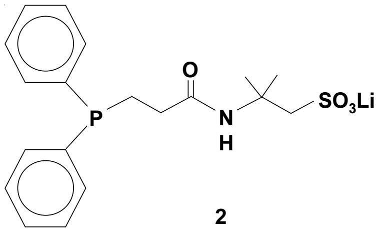

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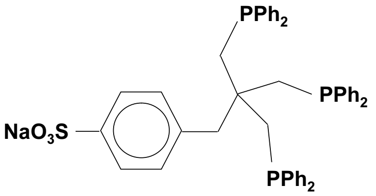
Bianchini et al. [15] reported a sulfonated ligand for use in hydrogenation reactions. They synthesized the complex [Rh(sulphos)(cod)] (where sulphos is structure **3**), which was tested in the biphasic hydrogenation of styrene. Styrene was dissolved in a 1 : 1 (v/v) mixture of methanol and *n*-heptane in the presence of

Table 1 Solvent systems tested according to Mieczyńska et al. [14].

	Solvent system	*Ratio [v/v/v]*
1	Water–ethanol/1-hexene	2 : 1 : 3
2	Water–diglyme/1-hexene	2 : 1 : 3
3	Water–tetraglyme/1-hexene	2 : 1 : 3
4	Water–ethylene glycol/1-hexene	2 : 1 : 3
5	Water–poly(ethylene glycol)/1-hexene	2 : 1 : 3
6	Water–THF/1-hexene	2 : 1 : 3
7	Water–decamethylene glycol/1-hexene	2 : 1 : 3
8	Water–crown ether/1-hexene	2 : 1 : 3

[Rh(sulphos)(cod)] (1 : 500 catalyst/substrate ratio). The hydrogen pressure was 3 MPa, and the temperature was 65 °C. After 3 h a conversion of more than 90% was obtained and complete disappearance of styrene occurred after a further 2 h of reaction. After cooling the reaction mixture to room temperature, separation of the two phases did not give complete organic product separation, whereas the rhodium catalyst remained in the alcohol phase. Simple addition of water resulted in complete elimination of ethylbenzene (and residual styrene) from the alcohol phase. Remarkable, the catalytic activity of [Rh(sulphos(cod)] in the biphasic system is the same as in pure methanol, indicating that at the reaction temperature a homogeneous phase is formed.



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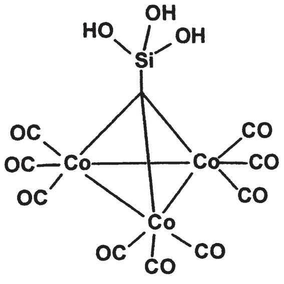
These examples demonstrate that research has not passed the proof-of-principle state so far. Future work on biphasic (organic–organic) hydrogenation has to address more realistic substrates. The conditions have to be defined under which biphasic hydrogenation could compete with homogeneous systems.

3.2.1.2
Hydroformylation

There are only a very few reports dealing with the organic–organic biphasic hydroformylation, although aqueous–organic biphasic hydroformylation is harder for water-insoluble (i.e., higher) olefins.

One suitable polar phase for hydroformylation is poly(ethylene glycol) (PEG), in which higher olefins are somewhat more soluble than in water. Ritter et al. [16] described the hydroformylation of 1-hexene catalyzed by two PEG-substituted cobalt clusters: [tris(tricarbonylcobalto)methylidyne]silanetriol and a derivative of it (**4** and **5**). The reaction was performed in toluene in the case of catalyst **4** or in PEG for catalyst **5**. An equal quantity of 1-hexene with respect to PEG was added to the mixture. The autoclave was pressurized with CO/H_2 (1 : 1) to 7 MPa, heated to 120 °C and stirred for 8 h. After the reaction, phase separation took place, which could be promoted by the addition of pentane. Both catalysts resulted in high yields (> 90% based on 1-hexene), but the reaction produced a rather low n/i ratio of 0.75. As usual, the regioselectivity could be enhanced by the addition of phosphines. For each catalyst no formation of alcohols occurred, which makes these catalysts interesting for further investigation, since formation of alcohols is characteristic of cobalt-catalyzed hydroformylation. Although the catalyst could be separated from the product mixture, the recycled catalyst showed a decrease in activity and selectivity.



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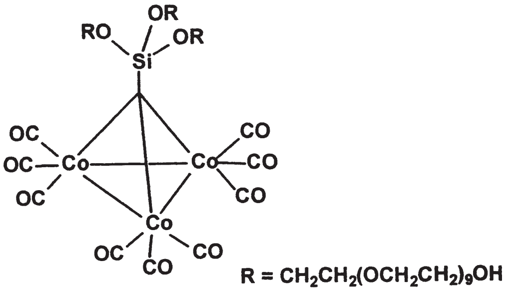

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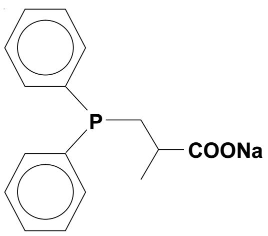
Bianchini et al. [15] described the use of the rhodium catalyst [Rh(sulphos(cod)] (**3**) for the hydroformylation of 1-hexene. The catalyst was dissolved in a 1 : 1 (v/v) mixture of methanol–isooctane to which 1-hexene was added (1 : 100 catalyst/substrate ratio). The CO pressure and the H_2 pressure were both 1.5 MPa and the temperature was set to 80 °C. At this temperature the biphasic system had become a homogeneous phase. Cooling the system to room temperature resulted in phase separation. Water was added as a co-solvent, resulting in a 1 : 1 : 1 (v/v/v) mixture of water–methanol/isooctane. This hydroformylation in the absence of water gave aldehydes (heptanal, 2-methylhexanal, and 2-ethylpentanal) and alcohols (1-heptanol, 2-methylhexanol, and 2-ethylpentanol) in an overall ratio of only 22 : 78. The total conversion of 1-hexene into aldehydes and alcohols was 76%. If the reaction time was prolonged, eventually only alcohols were formed. The formation of alcohols is rather remarkable, since rhodium catalysts normally produce aldehydes only.

In the presence of water during hydroformylation only heptanal and 2-methylhexanal in an overall yield of 54% (based on the aldehyde) were formed. Only traces of the aldehyde remained in the water–methanol phase after cooling to room temperature. The rhodium complex was completely recovered in the water–methanol phase, as was established by ^{31}P NMR spectroscopy and atomic absorption spectrophotometry.

Mieczyńska et al. [14] used the rhodium complexes $[HRh(CO)(L)_3]$ of ligands PNa (**6**) and PNS (**2**) as catalysts for the hydroformylation of 1-hexene. In the case of the PNa ligand, hydroformylation was performed in a water–ethanol/toluene (7 : 5 : 5, v/v/v) solvent system. The catalyst/substrate ratio was 1 : 800 at a pressure of 2 MPa CO/H_2 (1 : 1) and a temperature of 80 °C. The yield of aldehydes after



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2.5 h was 94%, with an *n*/*i* ratio of 2.4. In comparison to the homogeneous hydroformylation in toluene the yield increased considerably (from 26% to 94%) whereas the *n*/*i* ratio did not change (2.4 in both cases). For the PNS ligand, different water–ethanol/toluene mixtures and water–ethanol/1-hexene mixtures were examined.

For the first solvent mixture it was found that the total yield of aldehydes increased more than proportionally with the amount of ethanol in the polar phase. For a ratio of 2 : 11 : 2 (v/v/v) of water/ethanol/toluene the total yield of aldehydes of 86% was obtained with an *n*/*i* ratio of 2.9. For the system water–ethanol/1-hexene similar results were obtained. For a ratio of 11 : 15 : 4 (v/v/v) the total yield of aldehydes was 93% with an *n*/*i* ratio of 3.0. Replacement of ethanol by methanol or isopropanol gave almost identical results. However, when pure ethanol was used as the polar phase a total yield of only 77% was obtained. This might be caused by the lower solubility of the catalyst in ethanol, compared with that in water–ethanol mixtures.

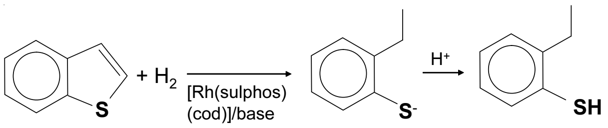
The stability of the $[HRh(CO)(PNS)_3]$ catalyst was investigated as well and it was found that during the nine following catalytic cycles the catalytic activity demonstrated by the yield of aldehydes remained practically constant.

The results discussed above show that hydroformylation in organic–organic solvent systems is basically possible. However, much more detailed studies are needed to determine whether it is economically feasible. Aspects such as catalyst deactivation during recycling, reaction time, (undesired) formation of alcohols, and continuous operation should be considered.

3.2.1.3
Hydrogenolysis

Hydroprocessing of fossil fuel feedstocks for the removal of sulfur, nitrogen, and residual metals is a large-scale refinery process. Sulfur in fossil materials is found in various compounds, such as thiols, sulfides, disulfides, thiophenes, benzothiophenes, and dibenzothiophenes. The removal of sulfur from these fossil materials is commonly referred to as hydrodesulfurization (HDS), which is important in order to reduce the amount of sulfur introduced into the atmosphere since this contributes to acid rain. Secondly, the poisoning of catalysts in downstream processing has to be reduced.

HDS catalysts generally consist of (heterogeneous) Mo or W sulfides on alumina supports. However, Bianchini et al. described a two-step procedure for HDS of thiophenes by the hydrogenolysis of thiols, followed by the desulfurization of the thiols by applying their zwitterionic rhodium(I) complex, [Rh(sulphos((cod)] (see previous section) [17]. This complex is soluble in polar solvents, such as methanol and methanol–water mixtures, but not in hydrocarbons. Benzo[*b*]thiophene was chosen as substrate since it is one of the most difficult thiophene derivatives to degrade. Under the mild reaction conditions of the two-step process, the benzene rings of the (di)benzothiophenes were not affected. In the absence of a base, the double bond of benzo[*b*]thiophene was hydrogenated, while in the presence of a base (NaOH) 2-ethylthiophenolate was the major product (Scheme 1).



Scheme 1 Hydrogenolysis of benzo[*b*]thiophene.

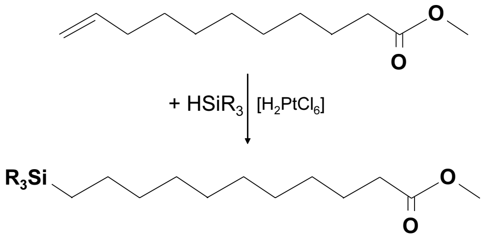
Hydrogenolysis of benzo[*b*]thiophene was performed in 20 mL of solvent mixture (methanol/*n*-heptane or methanol–water/*n*-heptane) with 180 mg of NaOH present. The catalyst/substrate ratio was 1 : 100, at an H_2 pressure of 3 MPa, and 160 °C for 5 h. After the reaction, hydrochloric acid was added to obtain 2-ethylthiophenol. Both biphasic systems gave good yields of 2-ethylthiophenol (95% for methanol/*n*-heptane and 89% for methanol–water/*n*-heptane). These results were similar to those obtained in the monophasic systems of methanol (93%) and methanol–water (84%). In both biphasic systems, all the 2-ethylthiophenol is found in the polar phase as sodium 2-ethylthiophenolate, leaving the hydrocarbon phase almost completely desulfurized.

The hydrogenolysis to *thiols* can be carried out effectively in a biphasic system, with the catalyst exclusively soluble in the polar phase, thus enabling easy catalyst recycling. However, to introduce this biphasic technique to industrial hydrodesulfurization, much research has to be carried out to design catalysts that are suitable for biphasic catalysis and that contain inexpensive metals (cobalt, ruthenium). Furthermore the catalysts have to tolerate the great thermal and chemical stress of the reaction conditions.

3.2.1.4
Hydrosilylation

One of the most important methods to synthesize organic silicon compounds is the addition of hydrosilanes to double bonds. Production of plasticizers, adhesives, and cosmetic formulation compounds are examples of industrial hydrosilylation products. The most widely used catalyst is hexachloroplatinic acid, H_2PtCl_6 (Speier's catalyst). The method described by Behr et al. [18–20] uses a biphasic liquid–liquid system under mild conditions at ambient pressure and short reaction times.

Hydrosilylation of methyl undec-10-enoate with various silanes has been carried out on a laboratory scale [Eq. (1)]. In a typical experiment 10.0 mmol of methyl undec-10-enoate and 10.0 mmol of the silane were dissolved in 8 mL of cyclohexane,



(1)

the apolar solvent. The catalyst H_2PtCl_6 (0.10 mmol) was dissolved in 8 mL of propylene carbonate. The solutions were warmed to 40 °C and combined under intensive stirring. Phase separation was allowed to take place after 2 h. The product was isolated by distillation and analyzed by NMR spectroscopy. The catalyst was recycled without any purification.

Triethoxysilane gave the best results with an excellent selectivity (> 99%) and a good reactivity (77% conversion of fatty acid ester). Alkyl- and arylsilanes gave poor yields, while chlorosilanes attained moderate yields and selectivity. The catalyst activity and selectivity was maintained during five recycle runs. Based on these results thermomorphic solvent systems were developed, which will be described in Section 3.2.3.

In the future, other solvent systems than cyclohexane/propylene carbonate should be investigated to optimize this biphasic hydrosilylation.

3.2.1.5
Oxidation

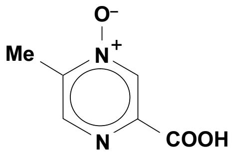
The direct oxidation of benzene to phenol is of great interest. The selectivity of this reaction is often poor, due to the higher reactivity of phenol towards further oxidation. As a result, over-oxidized byproducts usually occur, such as catechol, hydroquinone, benzoquinone, and tars. Bianchi et al. described a biphasic system using hydrogen peroxide as the oxidant for the selective oxidation of benzene to phenol. $FeSO_4$ was used in the absence of additional ligands, with trifluoroacetic acid as a co-catalyst [21]. The effect of different organic solvents on the selectivity was investigated using water–co-solvent/benzene (45 : 45 : 10, v/v/v) as the reaction medium. The results for different co-solvents are given in Table 2.

Acetonitrile gave the best selectivity, nearly twice as high as for water (21% versus 38% based on H_2O_2) and less over-oxidation to byproducts (2% versus 1% based on H_2O_2). The reason for the increased selectivity is a better solubility of benzene in the resulting polar phase, and phenol is largely extracted into the organic phase. Reducing the contact between phenol, which is soluble in the polar phase, and the catalyst, the biphasic system minimizes over-oxidation.

Table 2 Effect of the solvent system on the oxidation of benzene.

Co-solvent	*Fraction of H_2O_2 oxidizing benzene to phenol [%]*	*Fraction of H_2O_2 oxidizing benzene to double-oxygenated products [%]*
H_2O	21	2
MeCN	38	1
EtCN	6	1
tert-BuOH	17	1
Acetone	10	1
Dioxane	7	20
DMF	1	33
n-Octane	3	1

A series of bidentate N⌒N, N⌒O, and O⌒O ligands for iron were tested. 5-Carboxy-2-methylpyrazine-*N*-oxide (**7**) proved to give the most selective catalyst (78% based on H_2O_2).



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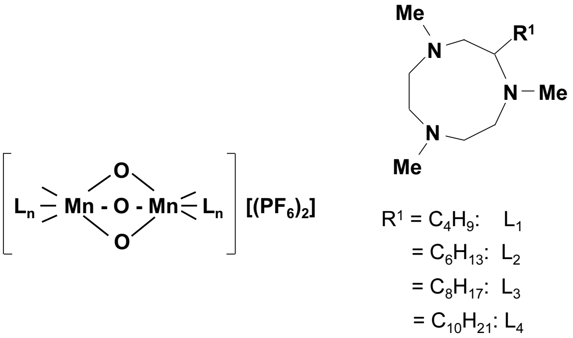
The influence of different acid co-catalysts was pronounced. Trifluoroacetic acid gave the best results, increasing the selectivity from 68% in the absence of co-catalyst to 78% based on H_2O_2. Under optimized reaction conditions at a benzene conversion of 8.6%, a selectivity of 97% (based on benzene) and 88% (based on H_2O_2) was obtained. These results are superior to any other iron-based catalyst system reported so far. The recycling of the catalyst in the biphasic system is also easier than in a homogeneous system.

Koek et al. described the biphasic epoxidation of styrene and 1-dodecene using the complex $[\mathrm{Mn}^{\mathrm{IV}}_2(\mu\text{-O})_3(\mathrm{L}_n)_2]^{2+}$ (**8**). These manganese complexes of cyclo-1,4,7-triazanonane ligands were used with hydrogen peroxide as the oxidant [22]. The catalyst was dissolved in 1.0 mL of dichloromethane, then 1.0 mL of the substrate solution, and 1.0 mL of a 30% aqueous hydrogen peroxide solution were mixed. While stirring, 0.3 mL of methanol was added to allow mixing of the hydrogen peroxide with the dichloromethane. The two phases were mixed and epoxidation was allowed to take place for 16 h. The yields for styrene epoxidation increased from 9% (L_1) to 19% (L_4). 1-Dodecene showed only very little conversion, probably due to low solubility.



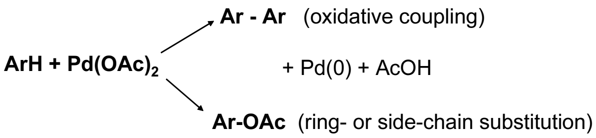
$R^1 = C_4H_9$: L_1
$= C_6H_{13}$: L_2
$= C_8H_{17}$: L_3
$= C_{10}H_{21}$: L_4

8

3.2.1.6
C–C Bond-Forming Reactions

3.2.1.6.1
Oxidative Coupling versus Hydroxylation

Oxidation of arenes by Pd(II), which is typically carried out in acetic acid solution, leads to oxidative coupling and ring or side chain substitution, depicted in Scheme 2.



Scheme 2 Oxidative coupling and ring or side chain substitution.

Analogously to the Wacker-type oxidations, the reaction can be made catalytic by reoxidizing the Pd(0) with oxygen. As redox co-catalyst, a hetero-polyacid of formula $H_{3+n}[PMo_{12-n}V_nO_{40}]$ (HPA-*n*, $n > 1$) can be used. It is known that strong acids favor coupling, while basic additives favor substitution. The oxidative coupling of arenes proceeds by the following sequence [Eqs. (2)–(4)].

$$2\,\mathrm{ArH} + \mathrm{Pd(II)} \rightarrow \mathrm{Ar{-}Ar} + \mathrm{Pd(0)} + 2\,\mathrm{H}^+ \tag{2}$$

$$\mathrm{Pd(0)} + \mathrm{HPA}\text{-}n + 2\,\mathrm{H}^+ \rightarrow \mathrm{Pd(II)} + \mathrm{H_2[HPA}\text{-}n] \tag{3}$$

$$\mathrm{H_2[HPA}\text{-}n] + \tfrac{1}{2}\,\mathrm{O_2} \rightarrow \mathrm{HPA}\text{-}n + \mathrm{H_2O} \tag{4}$$

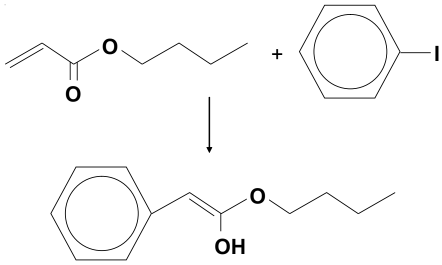
Burton et al. studied the oxidation of arenes (benzene and toluene) with O_2 catalyzed by $Pd(OAc)_2$ and HPA-*n* in a biphasic system [23]. The system consisted of an arene phase and a catalyst phase in aqueous acetic acid. Reactions were carried out at 100 °C at an oxygen pressure of 0.5 MPa for about 2 h. The catalyst phase (5.0 mL) consisted of 0.010 M $Pd(OAc)_2$ and 0.050 M HPA-2, dissolved in aqueous acetic acid. About 3 mL benzene or toluene was used as the arene phase. The formation of a Pd-black slurry in the arene phase made phase separation difficult. The reaction products were separated by extraction with water and diethyl ether, the latter containing the products. Addition of water up to 20–30 vol.% increased the conversion of arenes as well as the selectivity to biaryls substantially. Further increases had a negative effect. The explanation for this result can be found on the basis of the mechanism of electrophilic aromatic substitution by Pd(II), which is the rate-determining step. Adding water to acetic acid accelerates the process, but at higher water content the solubility of arenes decreases, causing a lower conversion. Another advantage of the increase in the water fraction is the large increase in the biphenyl/terphenyl ratio, which can be explained by the decreasing solubility of biphenyl. The most important advantage, however, was the increased selectivity for the oxidation of benzene to phenol obtained by increasing the amount of water.

The selectivity to phenol reached 64%, at 6% conversion in a polar phase of AcOH/H_2O (30 : 70, v/v).

3.2.1.6.2
Heck Reaction

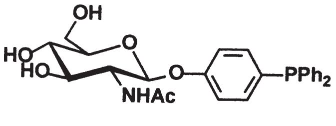
Heck vinylation of aryl halides is one of the most widely used methods for carbon–carbon bond formation. Bhanage et al. described a method for a Heck reaction of iodobenzene in a biphasic system of ethylene glycol/toluene. Several metal–TPPTS complexes were tested [24].

The toluene phase contained the reactants and products and the ethylene glycol phase the metal complex and KOAc. The reaction takes place in the ethylene glycol phase and at the interface [Eq. (5)]. In a typical experiment, 0.1 mmol of catalyst was dissolved in 10 mL of ethylene glycol, mixed with a solution of 10 mmol of iodobenzene and 10 mmol of butyl acrylate in 10 mL of toluene. These two phases were then mixed at 140 °C along with 10 mmol KOAc for several hours. Yields of > 99% at 100% selectivity were obtained for the *trans* compound.



(5)

Another biphasic Heck reaction was described by Beller et al. [25]. The medium consisted of xylene and ethylene glycol. The catalyst was a palladium complex with a carbohydrate-substituted triphenylphosphine (**9** and **10**). Aryl bromide (15 mmol), styrene (22.5 mmol), and NaOAc (16.5 mmol) were suspended in 10 mL of xylene and 10 mL of ethylene glycol. The catalyst precursor ($(Pd(OAc)_2)$) and ligand (Pd/ligand ratio 1 : 3) were added and the mixture was heated to 130 °C for 20 h. Both ligands A and B showed better results than the TPPTS ligand (cf. Section 2.2.3.2) in the case of activated aryl bromides (for instance, *p*-nitrobromobenzene). However, for deactivated aryl bromides (for instance, 2-bromo-6-methoxynaphthalene) TPPTS proved to generate a more stable and thus more productive catalyst system.



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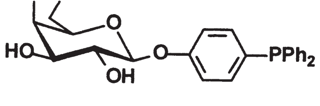

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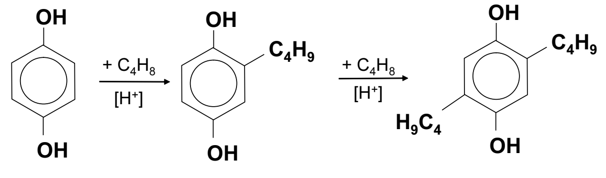
3.2.1.6.3
Suzuki Coupling

Due to the growing importance of asymmetrically substituted biaryl derivates used as drug intermediates, the Suzuki coupling reaction is increasingly important. Mostly, however, large amounts of catalyst are used and the catalyst recycling is often hindered by precipitation of palladium black.

Although the Suzuki reaction often occurs in biphasic mixtures, very few examples are known using catalyst systems soluble in polar phases. Beller et al. used the carbohydrate-substituted triphenylphosphine ligands described in Section 3.2.1.6.2, rendering the catalyst soluble in the polar phase [25]. Two different biphasic mixtures were investigated: ethanol–water/toluene (2 : 1 : 3 and ethanol–water/di-*n*-butyl ether (2 : 1 : 3). Phenylboronic acid (15 mmol), aryl bromide (13.5 mmol), and $N_2CO_3 \cdot 10\ H_2O$ (40.5 mmol) were dissolved in 36 mL of the biphasic mixture being investigated and preheated to 60 °C. The catalyst precursor ($Pd(OAc)_2$) and the ligand were added to the mixture and refluxed for 2 h at 78 °C. For the solvent mixture ethanol–water/toluene better conversions were obtained than for ethanol–water/di-*n*-butyl ether. In general yields higher than 50% were obtained, while the TONs ranged between 550 and 9000. In comparison with the TPPTS ligand, the carbohydrate-substituted phosphines performed better or at least equally well.

3.2.1.6.4
Alkylation of Hydroquinone with Isobutene

Timofeeva et al. [26] described the acid-catalyzed alkylation of hydroquinone with isobutene (Scheme 3). Traditionally, the alkylation of hydroquinone with isobutene is carried out in the presence of strong acids such as H_2SO_4, H_3PO_4, sulfonic acid resin, etc. Timofeeva et al. investigated tungsten hetero-polyacids (HPAs) in a biphasic system as alternative catalysts for the alkylation of hydroquinone. The apolar phase consisted of toluene and the polar phase was the liquid HPA dioxane etherate $HPA \cdot 39\ C_4H_8O_2 \cdot 26\ H_2O$. The alkylation was performed in a glass reaction vessel equipped with a stirrer and a reflux condenser. The reactor was charged with 20 mL of toluene and 3–9 mL of HPA etherate and heated to 75–95 °C. Hydroquinone (5 g) was added under intensive stirring and isobutene was fed at a rate of 15 mL min^{-1}. After the reaction, the alkylated product (upper phase) was separated and the solvent was distilled to afford a crystalline residue. The residue was dried in vacuum at 80 °C for 2 h. The most efficient catalyst was found to be



Scheme 3 Alkylation of hydroquinone with isobutene.

the etherate ($PW_{12} \cdot 39\,C_4H_8O_2 \cdot 26\,H_2O$ ($PW_{12} = H_3PW_{12}O_{40}$). Under optimal conditions (85 °C, hydroquinone/isobutene ratio of 0.7) a 71% yield of monoalkylated hydroquinone was obtained at 90% conversion of hydroquinone.

Raising the temperature resulted in a decreased yield, due to side reactions (double alkylation of hydroquinone and isobutene oligomerization). Since the catalyst was present in the etherate phase and the reactants and products in the toluene phase, the catalyst could be easily recovered and re-used. The recycled catalyst retained the initial activity and selectivity.

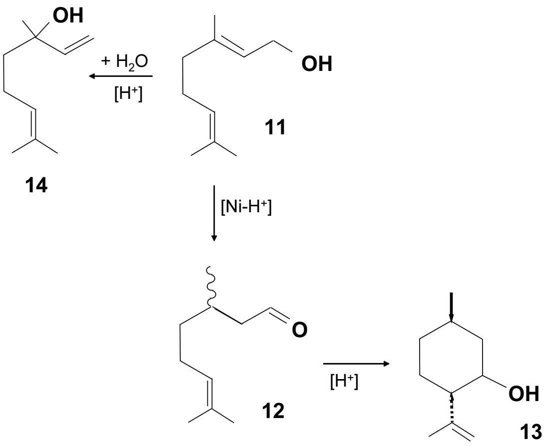
In comparison to H_2SO_4 and H_3PO_4, PW_{12} is about twice as efficient based on an equal molar amount of catalyst, and about 100 times more efficient based on an equal number of protons.

3.2.1.7
Isomerization

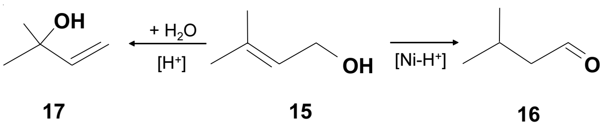
Bricout et al. [27] described the nickel-catalyzed isomerization of geraniol and prenol in homogeneous and biphasic systems. The catalyst was $Ni(dppe)_2$ with trifluoroacetic acid as a Brønsted acidic co-catalyst.

The isomerization of geraniol (**11**) into citronellal (**12**) is illustrated in Scheme 4, together with unwanted side reactions that occur.

The isomerization of prenol (**15**) into isovaleraldehyde (**16**) is depicted in Scheme 5, as well as an unwanted side reaction.



Scheme 4 Isomerization of geraniol (**11**) into citronellal (**12**) and reaction side products (**13** and **14**).



Scheme 5 Isomerization of prenol (15) into isovaleraldehyde (16) and reaction side product (17).

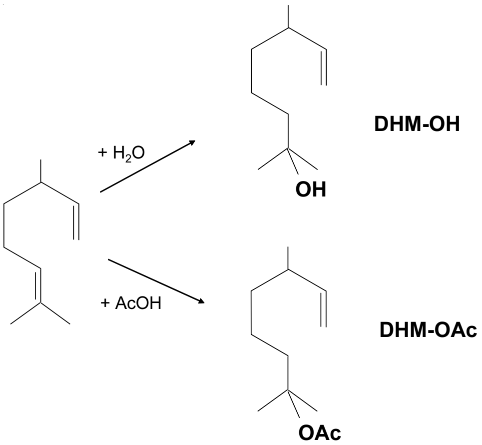
Two biphasic solvent systems were investigated: a water/toluene mixture (2 : 1, v/v) and a water–dimethylformamide/toluene mixture (1 : 1 : 1, v/v/v). The isomerization reaction was carried out at 110 °C for 16 h, with a catalyst/substrate ratio of 1 : 700. For the isomerization of geraniol, in the case of the water/toluene solvent system, a yield of only 3% citronellal was obtained with a selectivity of only 5%. However, side product **14** was obtained with a selectivity of 95%. Adding dimethylformamide to the water/toluene mixture resulted in a yield of 14% citronellal with a selectivity of 74%. Side product **13** was obtained with a selectivity of 11% and side product **14** with 15% selectivity. Reducing the reaction time to 2 h gave a yield of 13% citronellal, but with a higher selectivity of 86%.

Dimethylformamide reduces the polarity of the aqueous phase and consequently suppresses undesirable side reactions. As dimethylformamide is crucial for an effective working catalyst, this system is considered to be organic–organic biphasic and not aqueous–organic biphasic. In the case of prenol isomerization similar yields were obtained for the water–dimethylformamide/toluene solvent system, but with a lower selectivity.

In all biphasic reactions a rapid color change of the polar phase from orange to pale green was observed, indicating irreversible catalyst decomposition. Future research on catalytic isomerization should focus on increased stability of the catalyst.

3.2.1.8
Hydration and Acetoxylation

Acid-catalyzed hydration and acetoxylation of terpenes are important synthetic routes to terpenols and terpene esters that are used in perfumery and flavoring compositions. Such perfume ingredients as dihydromyrcenol (DHM-OH) and dihydromyrcenyl acetate (DHM-OAc) are prepared by the hydration and acetoxylation of dihydromyrcene (DHM) (Scheme 6).



Scheme 6 Manufacture of DHM, DHM-OH, and DHM-OAc.

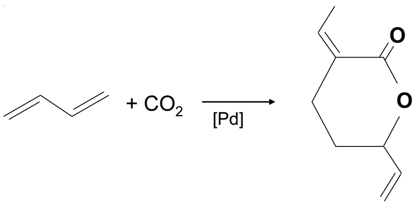
This process is complicated by acid-catalyzed isomerization and cyclization of DHM. In order to overcome this problem, Kozhevnikov et al. [28] used the biphasic hydration and acetoxylation in the presence of hetero-polyacids (HPAs) of the Keggin series: $H_3PW_{12}O_{40}$ (= PW_{12}) and $H_3PMo_{12}O_{40}$ (PMo_{12}). HPAs are highly soluble in water and polar organic solvents, such as lower alcohols, ketones, carboxylic acids, etc., but only scarcely soluble in hydrocarbons. The biphasic combined acetoxylation and hydration was performed in a DHM/AcOH–water solvent system. DHM (1.5–4.0 g) was mixed with 8.0 g of a 50–70 wt.% HPA solution in AcOH–water (1 : 1 or 77 : 23, v/v) at 20–30 °C under vigorous stirring for 1–5 h. The upper product phase was separated. A 90% selectivity could be obtained at 21% DHM conversion, when a 77 : 23 (v/v) AcOH–water mixture containing 68 wt.% PW_{12} was used. About 10% of DHM was converted to DHM isomers. The molar ratio DHM-OH/DHM-OAc in the product phase is 80 : 20 – 70 : 30, changing to 96 : 4 – 85 : 5 after work-up.

The PW_{12} catalyst was practically entirely retained in the polar phase, enabling easy and clean catalyst recycling. The catalyst recycling behavior, when tested, showed constant conversion and selectivity during six runs. No decomposition of the PW_{12} took place, as was seen from ^{31}P NMR spectroscopy. PMo_{12} showed a high activity but low selectivity in converting DHM. The quick reduction of PMo_{12} made catalyst separation from the product phase difficult. The Keggin-type HPA, $H_3PW_{12}O_{40}$ (PW_{12}), is thus an excellent catalyst for the hydration and acetoxylation of DHM. The HPA shows a much higher catalytic activity than conventional acid catalysts such as H_2SO_4 and Amberlyst-15 (ion-exchange resin). Because of the high selectivity and efficient recycling of the catalyst without loss of activity, application of the system seems feasible.

3.2.2
Biphasic Catalysis on a Miniplant Scale

Arno Behr

In this section one example of catalysis on a miniplant scale is described. Although the reaction itself is homogeneous, the catalyst separation is done by extraction, making the whole system biphasic. The reaction carried out is the palladium-catalyzed telomerization of 1,3-butadiene and CO_2 to a δ-lactone [Eq. (6)] described by Behr et al. [29, 30]. A possible side product in this reaction is the γ-lactone.



(6)

The reaction is homogeneously catalyzed by a system formed in situ from $Pd(acac)_2$ and tricyclohexylphosphine in acetonitrile. During a batch experiment at 90 °C and 4 MPa, 48% conversion of butadiene could be reached with 95% selectivity to the lactone. The reaction mixture was separated by flash evaporation into a vapor phase consisting only of CO_2, 1,3-butadiene plus acetonitrile and a liquid phase consisting of more than 95% δ-lactone (and side products). The vapor phase, after condensation, was recycled to the reactor, which allowed a closed loop for solvent and nonconverted feedstocks.

The liquid phase was separated by extraction with 1,2,4-butanetriol into a raffinate phase containing the catalyst and an extract phase containing the δ-lactone. The raffinate stream was recycled to the reactor. The extract phase was separated by distillation into a δ-lactone stream and a 1,2,4-butanetriol stream. The bottom stream consisted of 95 wt.% δ-lactone and 5 wt.% 1,2,4-butanetriol. The top stream consisted of 98 wt.% 1,2,4-butanetriol and 2 wt.% δ-lactone (and some catalyst), and was recycled to the extraction unit.

This process was realized in a continuous miniplant for 24 h of operation. The acetonitrile and the unreacted substrates were recycled from the flash evaporator to the reactor. No accumulation of side products was observed; their amount after the continuous experiment was as high as after the batch experiment. Raising the temperature from 100 °C to 160 °C resulted in the isomerization of the δ-lactone to γ-lactones and in the oxidation of the ligand. Therefore it was concluded that the several separation steps should be performed below 100 °C to avoid isomerization and catalyst deactivation. In further investigations, efforts should be made to close the remaining recycle lops.

3.2.3
Thermomorphic Solvent Systems

Arno Behr

The liquid/liquid two-phase technique is limited to processes where the organic reactants are sufficiently dissolved in the polar catalyst phase. If the mass transport between the two phases is scarce, the reaction must be operated in a single homogeneous phase. Behr developed a new concept using “thermomorphic solvent systems” [29–31]. This concept allows a single-phase reaction process combined with an easy catalyst/product separation by the two-phase technique. These new solvent systems consist of a polar solvent **s1** and a nonpolar solvent **s2**, which have to be immiscible. The third, semi-polar, solvent **s3** must be miscible with both **s1** and **s2** and acts as a solubilizer. The miscibility of such ternary solvent mixtures is strongly dependent on the temperature (Figure 1). In the new concept of thermomorphic solvent systems a catalytic reaction is performed at the temperature **T1** in a single-phase homogeneous system, after which a partition into two phases takes place by cooling to temperature **T2**.

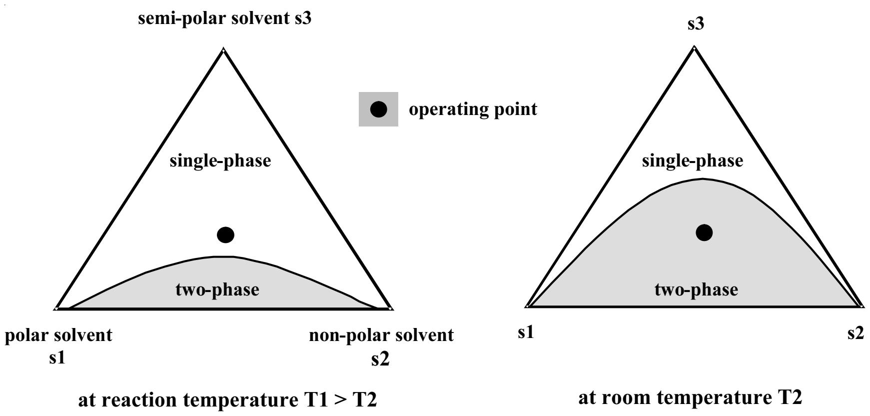
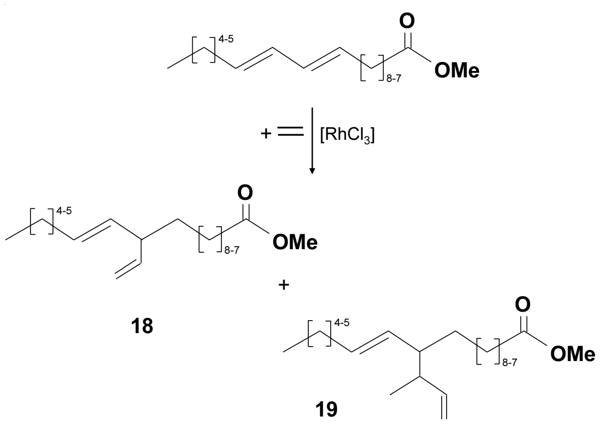


Figure 1 Temperature-dependent miscibility gap of ternary solvent mixtures.

The new recycling concept has been applied to the following model reactions:

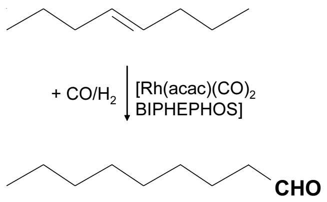
- The rhodium-catalyzed co-oligomerization of double unsaturated fatty substances with ethylene was studied in different thermomorphic solvent systems [Eq. (7)] [32]. Using a biphasic system this reaction gives about 40% of products **18** and **19**. Performing the conversion in a system consisting of propene carbonate (**s1**), SFAME (**s2**) (SFAME = sunflower fatty acid methyl ester, which contains 60.5% CML), and dioxane (**s3**), the yield increases to up to 95%. This combination of solvents allows a single-phase process at the reaction temperature and therewith a high catalytic activity without mass-transfer limitation. According to the new concept, product and catalyst are easy to separate. The catalyst can be recycled several times with only small decrease of the product yield.



(7)

Furthermore temperature-dependent solvent systems containing poly(ethylene glycol) 1000 (PEG 1000) as a polar component were applied to the above-mentioned reaction. High conversion of methyl linoleate and high selectivity of co-oligomers were obtained. By using the novel PEG 1000-based temperature-dependent solvent systems, an easy separation of product and catalyst phase can be achieved. In addition, the effect of ligands on the catalyst recycling was investigated.

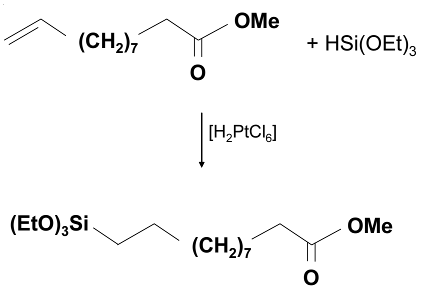
- The consecutive isomerization–hydroformylation reaction of *trans*-4-octene yields high conversion and high selectivity of *n*-nonanal in the polar solvent propene carbonate [Eq. (8)] [33].



(8)

The catalyst phase can be recovered with the subsequent extraction of the product by the nonpolar solvent dodecane. Thermomorphic solvent systems based on the two solvents with different semipolar components as solubilizer were investigated and used in the hydroformylation mentioned. With this new recycling concept the product phase and the catalyst phase can be separated directly after the conversion without any additional extraction step.

- The hydrosilylation of methyl 10-undecenoate with triethoxysilane catalyzed by anhydrous H_2PtCl_6 was studied in the thermomorphic solvent system propene carbonate (**s1**)/cyclohexane (**s2**)/toluene (**s3**) [Eq. (9)] [18].



(9)

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The conversion finishes after 15 s and gives 80% of product **20** at 80 °C under single-phase conditions. Cooling brings about a partition of the ternary solvent mixture. The nonpolar phase (cyclohexane) contains the product, the polar phase (propene carbonate) the catalyst.

3.3
Economical Applications (SHOP Process)

Dieter Vogt

3.3.1
Introduction

The Shell higher-alkene process was undoubtedly the first commercial catalytic process taking benefit from two-phase (but nonaqueous) liquid/liquid technology. In this special case two immiscible organic phases are used to separate the catalyst from the products formed, with the more or less pure products forming the upper phase.

The basis for this nickel-catalyzed oligomerization of ethene goes back to Ziegler and his school at the Max Planck Institute of Mülheim. There the so-called “nickel effect” [35, 36] was found, and Wilke and co-workers learned how to control the selectivity of nickel-catalyzed reactions by use of ligands. Keim introduced $\widehat{\mathrm{P\,O}}$ chelate ligands and on this basis carried out the basic research for the oligomerization process at the Shell research company at Emeryville [37–46]. The whole process was developed in a collaboration between Shell Development, USA, and the Royal Shell Laboratories at Amsterdam in the Netherlands [47–56]. The SHOP is not only a process for ethene oligomerization, but a very efficient and flexible combination of three reactions: oligomerization, isomerization, and metathesis. It was designed to meet the market needs for linear α-alkenes for detergents [57].

The first commercial plant was built at Geismar, LA, USA, in 1977. The development of this plant and that at Stanlow (UK) is summarized in Table 3, together with other oligomerization capacities based on other technology [58].

Table 3 Linear α-alkene capacities via ethene oligomerization.

Technology	***Company***	***Location***	***Capacity [10^3 tpy]***		
			Initial (year)	***Expansion (year)***	***Present total***[a]
Ziegler-type	Chevron	Cedar Bayout, TX	125 (1966)	125 (1990)	250
	Ethyl	Pasadena, TX	400 (1971)	55 (1989)	472
	Ethyl	Feluy, Belgium	200 (1992)		200
	Chemopetrol	Czech Republic	120 (1992)		120
	Mitsubishi Kasei Corp.	Kurashiki, Okayama Pref., Japan	50		50
SHOP	Shell	Geismar, LA	200 (1977)	320 (2002) 390 (1989)	910
	Shell	Stanlow, UK	170 (1982)	100 (1989)	270
Zr	Idemitsu Petrochemicals	Ichihara, Chiba Pref., Japan	50 (1989)		50

a) In 1992.

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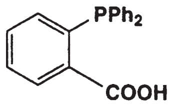
The two operational SHOP sites today have a total capacity of nearly 1 million tons of α-alkenes per year. This is about one-half of the total amount made by oligomerization. Today linear α-alkenes are produced mainly by ethene oligomerization because of the high product quality and the good availability of ethene. The wide application and increasing need for short-chain α-alkenes as co-monomers for polymers cause the linear alkene market to continue growing.

3.3.2
Process Description

The oligomerization is carried out in a polar solvent in which the nickel catalyst is dissolved but the nonpolar products, the α-alkenes, are almost insoluble. Preferred solvents are alkanediols, especially 1,4-butanediol (1,4-BD). This use of a biphasic organic liquid/liquid system is one of the key features of the process. The nickel catalyst is prepared in situ from a nickel salt, e.g., $NiCl_2 \cdot 6\,H_2O$, by reduction with sodium borohydride in 1,4-BD in the presence of an alkali hydroxide, ethene, and a chelating $\overset{\frown}{P\;O}$ ligand such as *o*-diphenylphosphinobenzoic acid (**21**) [45, 54]. Suitable ligands are the general type of diorganophosphino acid derivatives (**22**).



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The nickel concentration in the catalyst system is in the range 0.001–0.005 mol% (approx. 10–50 ppm). The oligomerization is carried out in a series of reactors at temperatures of 80–140 °C and pressures of 7–14 MPa. The rate of the reaction is controlled by the rate of catalyst addition [53]. A high partial pressure of ethene is required to obtain good reaction rates and high product linearity [45]. The linear α-alkenes produced are obtained in a Schulz–Flory-type distribution with up to 99% linearity and 96–98% terminal alkenes over the whole range from C_4 to C_{30+} (cf. Table 4) [57].

The shape of the Schulz–Flory distribution and the chain length of the α-alkenes are controlled by the geometric chain-growth factor *K*, defined as $K = n(C_{n+2})/n(C_n)$ (Figure 2).

Table 4 Comparison of product qualities of technical C_6–C_{18} α-alkenes [59].

Product	*Wax-cracking*	*Quality (wt.% α-alkene)*		
		Chevron	*Ethyl*	*SHOP*
α-Alkenes	83–89	91–97	63–98	96–98
Branched alkenes	3–12	2–8	2–29	1–3
Paraffins	1–2	1.4	0.1–0.8	0.1
Dienes	3–6	–	–	–
Monoalkenes	92–95	99	> 99	99.9

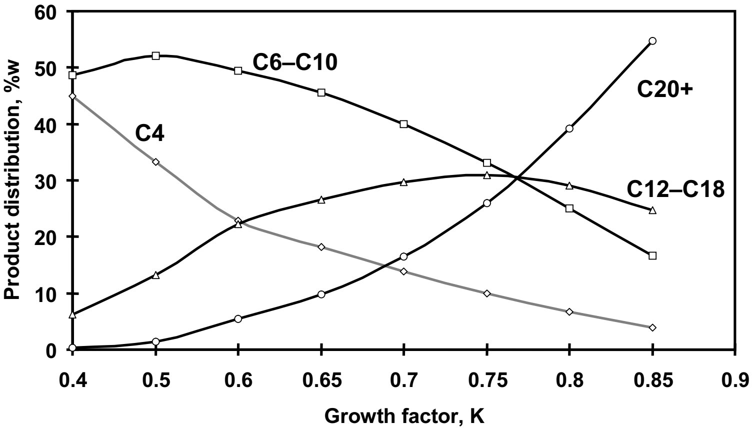


Figure 2 Schulz–Flory product distribution dependence on the chain-growth factor *K*.

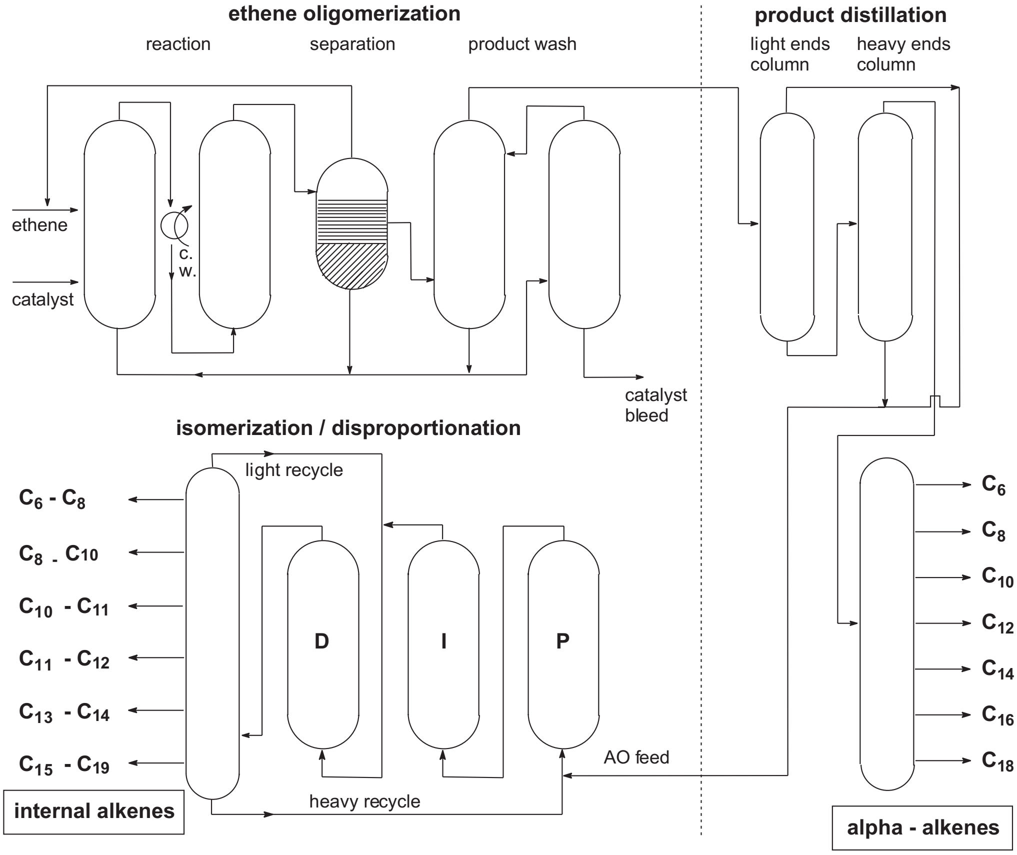


Figure 3 Flow scheme of the Shell higher-alkene process (SHOP).
P = purification; I = isomerization; D = disproportionation; AO = α-alkene; c.w. = cooling water.

For the economy of the whole process it is very important that the *K* factor can easily be adjusted by varying the catalyst composition. Usually the value is between 0.75 and 0.80. The heat of the reaction is removed by water-cooled heat exchangers between the reactors (Figure 3). In a high-pressure separator the insoluble products and the catalyst solution as well as unreacted ethene are separated.

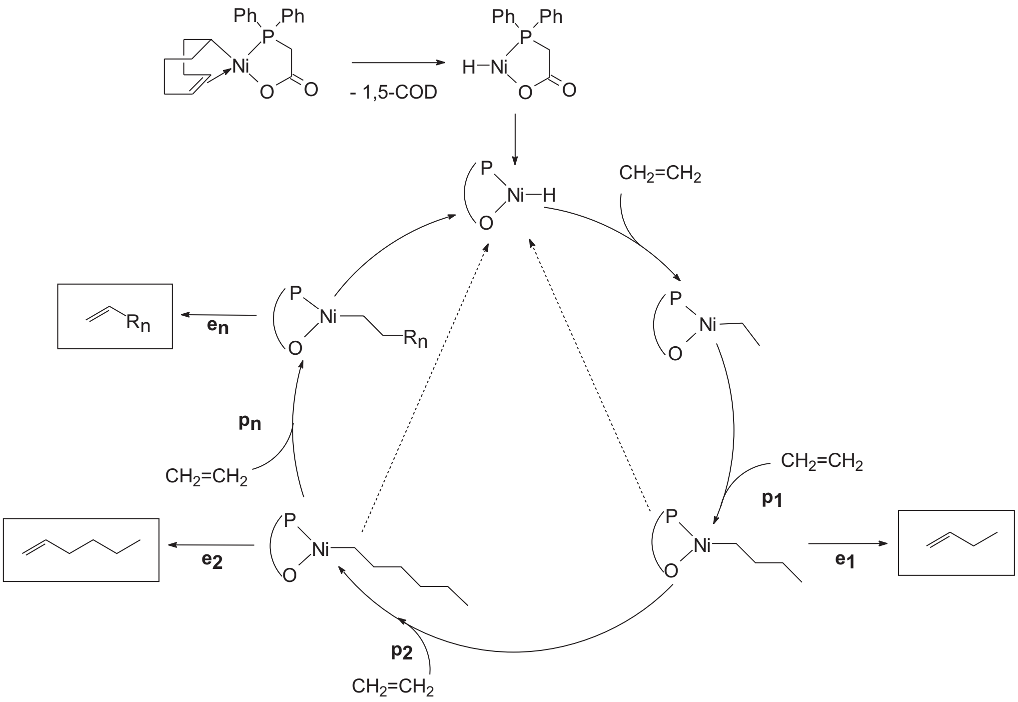
The catalyst solution is fed back into the oligomerization reactor. Washing of the oligomers by fresh solvent in a second separator removes traces of the catalyst. This improves product quality and the catalyst utilization [60]. Traces of remaining catalyst in the product can lead to the formation of insoluble polyethene during upstream processing, resulting in fouling of process equipment [61].

The formation of insoluble polyethene causes problems also in other parts of the process. During catalyst preparation this can be avoided by adding the preformed, stable nickel complex and the chelate ligand separately to the oligomerization reactor. By this simple change, the catalyst utilization is enhanced markedly, resulting in a significant reduction of nickel salt and borohydride consumption [62–64]. So one major problem is the complete separation of the catalyst. Many attempts have been made to improve this [53]. One approach was using methanol/water solvent mixtures together with sulfonated ligands [65–71]. In the course of this it was shown that the catalyst is not deteriorated by water [72], which might lead to new approaches in the future.

Completely different liquid/liquid two-phase applications for oligomerization of ethene have been reported. Chauvin used ionic liquids as solvents for oligomerization catalysts [73] (cf. Chapter 5). Another approach is the use of perfluorinated solvents together with catalysts bearing perfluorinated ligands (Chapter 4) [74, 75].

Further processing of the product α-alkenes involves separation into the desired product fractions in a series of distillation columns. First the lower C_4–C_{10} α-alkenes are stripped off. In a heavy-ends column the C_{20+} α-alkenes are removed from the desired C_{12}–C_{20} α-alkenes. Finally the middle-range products meeting the market needs are separated into the desired cuts and blends. The very high flexibility of the "SHOP" results from the following steps. The C_4–C_{10} and the C_{20+} fractions are combined to be isomerized to internal linear alkenes and then subjected to a metathesis reaction. Both steps require about 80–140 °C and 0.3–2 MPa. Isomerization is accomplished by a typical isomerization catalyst such as Na/K on Al_2O_3 or a MgO catalyst in the liquid phase [76], where about 90% of the α-alkenes are converted to internal alkenes. Metathesis of the lower and higher internal alkenes gives a mixture of alkenes with odd and even carbon chain lengths. The mixture comprises about 11–15% of the desired C_{11}–C_{14} linear internal alkenes, which are separated by distillation. The undesired fractions can be recycled, feeding the light alkenes directly back to metathesis while the higher-boiling fractions are again subjected to isomerization. Because of the high proportion of short-chain alkenes in the metathesis feed, the double bonds in the end product are shifted toward the chain ends. Altogether the different possibilities of shifting products to the desired chain length and double-bond position makes the SHOP the most elegant and flexible process operating today. It is furthermore one of the larger applications of homogeneous catalysis.

The mechanism of the nickel-chelate complex-catalyzed oligomerization has been investigated in detail by Keim and co-workers [77–86]. Based on these results, the mechanism shown in Scheme 7 was postulated.



Scheme 7 Postulated mechanism for ethene oligomerization via a $\widehat{PO}$-stabilized nickel hydride species: p_1, p_2 ... p_n = propagation steps; e_1, e_2 ... e_n = elimination steps.

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3.4
Conclusions and Outlook

Dieter Vogt

Biphasic catalysis in general is an attractive technique, combining the advantages of homogeneous and heterogeneous catalysis. Common organic solvents are available in bulk quantities for an acceptable price, giving organic–organic biphasic catalysis an advantage over ionic liquids and fluorous biphasic catalysis.

However, when comparing organic–organic biphasic systems with other categories of biphasic catalysis, there are some difficulties to overcome. There are not that many combinations of immiscible organic solvents for which the catalyst is exclusively soluble in one of the phases. This leads in most cases to application of at least ternary mixtures, which makes a much more thorough study of the phase behavior necessary. However, possibilities given by modern parallel and automated experimentation techniques and their consequent application should help to overcome these hurdles. Academic research on several catalytic transformations has outlined the potential of organic–organic biphasic catalysis. As the substrates and products, as well as the catalyst, will influence the phase compositions and miscibility ranges of such systems, it has to be expected that each catalytic process will require individual optimization for maximum performance.

The success of the SHOP has shown that the difficulties can be overcome, leading to very efficient catalyst recycling.

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4
Fluorous Catalysis

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4.1
Introduction

István T. Horváth

Homogeneous catalysts can be designed at the molecular level to achieve high product selectivity at an economically favorable reaction rate (cf. Chapter 1). The development of facile separation of the homogeneous catalysts from the products is crucial for their industrial applications. Theoretically three types of separation methods can be used for homogeneous catalytic reactions performed in the liquid phase. If the catalyst is a gaseous molecule, it could dissolve in the liquid phase under pressure during reaction and simple depressurization could result in its complete removal from the product. One could imagine a similar system in which a soluble catalyst precursor is activated or turned on by a gaseous molecule under pressure and deactivated or turned off by depressurization after the product formed. The second and most popular approach involves the use of liquid–liquid biphasic systems, in which one of the phases contains the dissolved catalyst and the other the products. Since the formation of a liquid–liquid biphase system is due to the sufficiently different intermolecular forces of two liquids, the selection of a catalyst phase depends primarily on the solvent properties of the product phase at high conversion levels. For example, if the product is apolar the catalyst phase should be polar; and vice versa, if the product is polar the catalyst phase should be apolar. The success of any biphasic system depends on whether the catalyst could be designed to dissolve preferentially in the catalyst phase. Perhaps the most important rule for such design is that the catalyst has to be catalyst phase like, since it has been known for centuries that *similia similibus solvunture*, or “like dissolves like”. The third approach is based on solid–liquid separation. If the product has no or limited solubility in the liquid reaction mixture, it could be continuously removed by precipitation or crystallization. Alternatively, a solid catalyst can be dissolved in the reaction medium at a higher temperature and later separated from the product by lowering the temperature again. It should be noted that the latter approach could also operate in the opposite manner, when a solid catalyst precursor can be dissolved in the reaction medium at a lower temperature and separated from the product by increasing the temperature.

Perfluorinated alkanes, dialkyl ethers, and trialkylamines are unusual because of their nonpolar nature and low intermolecular forces. Their miscibility even with common organic solvents such as toluene, THF, acetone, and alcohols is low at room temperature; thus these materials could form *fluorous biphase systems* [1, 2]. The term *fluorous* was introduced [3, 4], as the analogue to the term *aqueous*, to emphasize the fact that one of the phases of a biphase system is richer in fluorocarbons than the other. Fluorous biphase systems can be used in catalytic chemical transformations by immobilizing catalysts in the fluorous phase. A fluorous catalyst system consists of a fluorous phase containing a preferentially fluorous-soluble catalyst and a second product phase, which may be any organic or inorganic solvent with limited solubility in the fluorous phase (Scheme 1).

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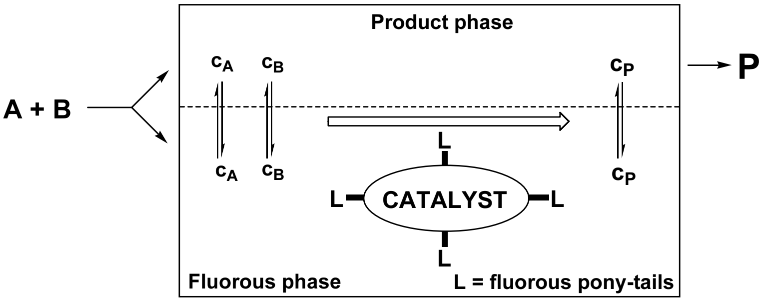


Scheme 1 The fluorous biphase concept for the catalytic conversion of substrates **A** and **B** to product **P**. The attachment of appropriate fluorous ponytails **L** to a homogeneous catalyst ensures that the fluorous catalyst remains in the fluorous phase.

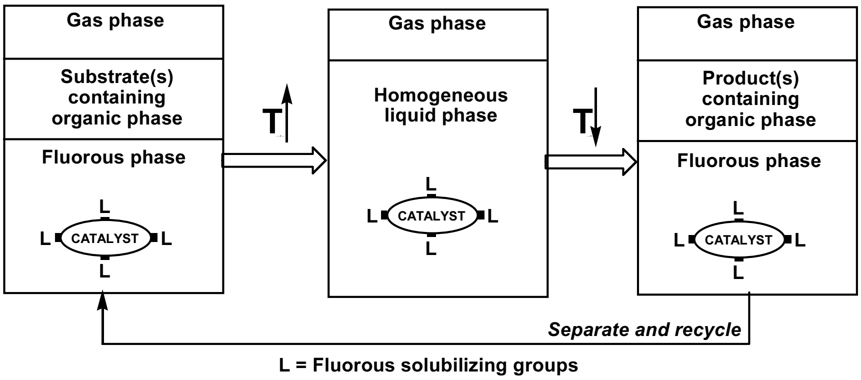
Conventional homogeneous catalysts can be made fluorous-soluble by incorporating fluorocarbon moieties to their structure in appropriate size and number. The most effective fluorocarbon moieties are linear or branched perfluoroalkyl chains with high carbon numbers that may contain other heteroatoms (the "fluorous ponytails"). It should be emphasized that *perfluoroaryl* groups do offer dipole–dipole interactions [5], making perfluoroaryl-containing catalysts soluble in common organic solvents and therefore less compatible with fluorous biphase systems.

The most effective fluorous solvents are perfluorinated alkanes, perfluorinated dialkyl ethers, and perfluorinated trialkylamines. Their remarkable chemical inertness, thermal stability, and nonflammability coupled with their unusual physical properties make them particularly attarctive for catalyst immobilization. Furthermore, these materials are practically nontoxic by oral ingestion, inhalation, or intraperitoneal injection [6]. Although their thermal degradation can produce toxic decomposition products, such decomposition generally begins only at very high temperatures well above the thermal stability limits of most homogeneous catalysts.

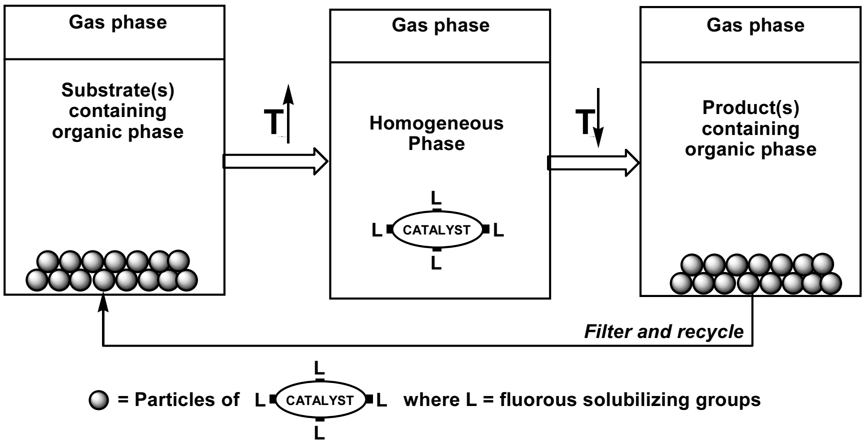
A fluorous biphase reaction could proceed either in the fluorous phase or at the interface of the two phases, depending on the solubilities of the substrates in the fluorous phase. When the solubilities of the substrates in the fluorous phase are very low, the chemical reaction may still occur at the interface or appropriate phase-transfer agents may be added to facilitate the reaction. It should be emphasized that a fluorous biphase system might become a one-phase system by increasing the temperature [3]. Thus, a fluorous catalyst could combine the advantages of one-phase catalysis with biphasic product separation by running the reaction at higher temperatures and separating the products at lower temperatures (Scheme 2).

Alternatively, the temperature-dependent solubilities of *solid* fluorous catalysts in liquid substrates or in conventional solvents containing the substrates could eliminate the need for fluorous solvents (Scheme 3) [7, 8].

Because of the well-known electron-withdrawing properties of the fluorine atom, the attachment of fluorous ponytails to conventional catalysts could change



Scheme 2 The temperature-dependent fluorous-liquid/liquid biphase concept.



Scheme 3 The temperature-dependent fluorous-solid/liquid biphase concept.

significantly their electronic properties and consequently their reactivity. Insertion of insulating groups before the fluorous ponytail may be necessary to decrease the strong electron-withdrawing effects, an important consideration if catalyst reactivity is desired to approximate to that observed for the unmodified species in hydrocarbon solvents. For example, the first theoretical calculations have shown that the electronic properties of the fluorous phosphines $P[(CH_2)_x(CF_2)_yCF_3]_3$ ($x = 0$, $y = 2$ or 4 and $x = 0–5$, $y = 2$) can be tuned by varying the number of methylene groups between the phosphorus atom and the perfluoroalkyl moiety [9] (Table 4). It was later shown that the electron-withdrawing effect of even five methylene units was observable according to the variation in ν_{CO} values of *trans*-$[IrCl(CO)L_2]$ complexes [10]. It appears that between eight and ten methylene groups would be needed to insulate effectively the lone pair of the phosphorus atom from the perfluoroalkyl moiety [11].

Table 1 Electronic properties of fluorous phosphines.[a)]

Phosphines	***P***		***Protonation energy [eV]***	***P–H [Å]***	***∢ HPL [°]***
	Mulliken population [q]	***Lone pair level [eV]***			
$P[CF_2CF_3]_3$	0.83	–11.7	–6.5	1.189	85.9
$P[CF_2CF_2CF_2CF_3]_3$	0.83	–11.7	–6.4	1.192	85.4
$P[CH_2CF_2CF_3]_3$	0.62	–10.6	–7.7	1.205	86.3
$P[(CH_2)_2CF_2CF_3]_3$	0.48	–9.9	–8.3	1.218	92.3
$P[(CH_2)_3CF_2CF_3]_3$	0.40	–9.5	–8.6	1.225	91.8
$P[(CH_2)_4CF_2CF_3]_3$	0.38	–9.3	–8.8	1.226	92.0
$P[(CH_2)_5CF_2CF_3]_3$	0.36	–9.2	–8.9	1.228	91.8
$P[CH_2CH_2CH_2CH_3]_3$	0.33	–8.7	–9.3	1.230	91.7

a) The calculations were performed using the UniChem version of MNDO93 and employed the PM3 parameter set. Full geometry optimizations were performed.

Fluorous catalysts are best suited for converting apolar substrates to products of higher polarity, as the partition coefficients of the substrates and products will be higher and lower, respectively, in the fluorous phase. The net results are no or little solubility limitation on the substrates and easy separation of the products. Furthermore, as the conversion level increases, the amount of polar products increases, further enhancing separation. One of the most important advantages of the fluorous biphase catalyst concept is that many well-established hydrocarbon-soluble catalysts could be converted to fluorous-soluble. In general, fluorous catalysts have similar structures and spectroscopic properties to the parent compounds. The major difference arises from the presence of the fluorous ponytails, which provide a fluorous blanket around the hydrocarbon domain of the catalyst. If the electron-withdrawing effect of the fluorous ponytails on the ligands is not mitigated by insulating groups, the reactivity of the organometallic catalysts could be significantly different. Accordingly, most fluorous analogues of hydrocarbon-soluble catalysts have been prepared by incorporating insulating groups and shown to have comparable catalytic performance with the additional benefit of facile catalyst recycling.

Fluorous catalysis is now a well-established area and provides a complementary approach to aqueous and ionic biphase catalysis [12]. Since each catalytic chemical reaction could have its own *perfectly* designed catalyst (the chemzyme), the possibility to select from biphase systems ranging from fluorous to aqueous systems provides a powerful portfolio for catalyst designers.

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4.2
State-of-the-Art and Typical Reactions

4.2.1
Carbon–Carbon Bond-Forming Reactions

Siegfried Schneider, Carl Christoph Tzschucke, and Willi Bannwarth

Metal-catalyzed cross-coupling reactions are among the most prominent reaction types in synthetic organic chemistry [1]. The search for new chemical entities in medicinal chemistry requires the synthesis of growing numbers of compounds in shorter periods of time. To meet this demand, not only parallel synthesis formats need to be employed, but also the simplification of work-up procedures becomes increasingly important. In catalytic processes this can be accompanied by the recovery and re-use of the catalyst. Several concepts have recently been developed to simplify work-up procedures and to avoid time-consuming purification steps like column chromatography or distillation [2, 3]. They comprise in essence the use of polymer-supported catalysts (see Chapter 7) [4], the use of molten salts (or ionic liquids) as reaction media (see Chapter 5) [5, 6], reactions in $scCO_2$ or water (see Chapters 2 and 6) [7, 8], and the use of fluorous biphasic systems (FBS – see Scheme 1 in Section 4.1) [9–14]. In the FBS concept, fluorous ligands mediate the solubility of the pertinent catalyst in fluorous solvents and the reaction is carried out in a two-phase mixture consisting of a fluorous and an organic solvent. Such two-phase systems often become homogeneous at elevated temperatures (see Scheme 2 in Section 4.1). Lowering the temperature after reaction leads to the re-formation of the two phases. The organic phase contains the product and the fluorous phase the catalyst to be re-used.

Palladium-catalyzed cross-coupling reactions often require relatively large amounts of catalysts which have to be removed from the reaction product. Fluorous palladium complexes offer a solution to this problem, since they are soluble in fluorous solvents and can be readily separated from the organic product by liquid–liquid extractions.

Betzemeier and Knochel performed cross-couplings of aryl iodides with arylzinc bromides in a toluene/1-bromoperfluorooctane mixture in the presence of a Pd catalyst derived from fluorous phosphine **1a** and $Pd_2(dba)_3$ (Scheme 1) [15]. The reaction yielded the desired coupling products in excellent yields (87–99%). By using 1.5 mol% of catalyst it was possible to re-use the catalyst up to four times, yielding biphenyl derivative **2**. This cross-coupling reaction could be extended to benzyl- and alkenylzinc bromides forming **3** (76%) and **4** (92%).

The first Heck reaction in fluorous solvents was described by Pozzi et al. with either $Pd_2(dba)_3$ or $Pd(OAc)_2$ as palladium source and the fluorous phosphines **1a**–**1c** as the ligands [16]. Reactions between iodobenzene and methyl acrylate were conducted with 0.5 mol% of catalyst in an acetonitrile/D-100 (mainly *n*-perfluorooctane) mixture. The expected products were formed quantitatively and good

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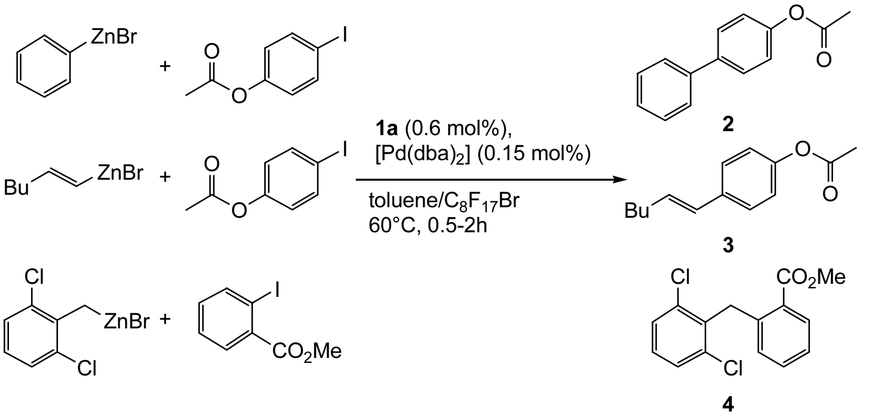
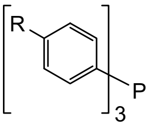


Scheme 1 Cross-coupling of aryl iodides with arylzinc bromides.

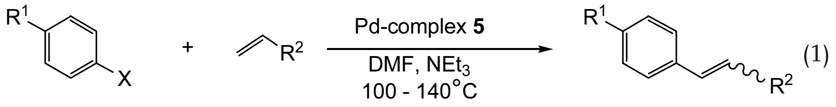
selectivity (88–93%) was observed. Recycling of the catalyst was possible, but resulted in lower conversions of the iodobenzene in the second and third runs, respectively.

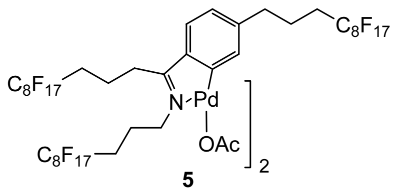


1a: R = C_6F_{13}
1b: R = $OCH_2C_7F_{15}$
1c: R = $O(CH_2)_2OCH_2CF_2[OCF(CF_3)CF_2)_p(OCF_2)_qOCF_3$
with p = 3.38 und q = 0.11

Rocaboy and Gladysz prepared a fluorous Schiff base, which was converted to palladacycle **5**. This represents a phosphane-free Pd catalyst which exhibits thermomorphic behaviour [Eq. (1)] [17]. Reactions were performed under homogeneous conditions (DMF, 100–140 °C) without fluorous solvents using (0.68–1.83) · 10^{-6} mol% of palladacycle. After work-up the Heck coupling products were obtained in 49–100% yield. Recycling experiments were done with 0.02 mol% of **5**, using $C_8F_{17}Br$ as a "carrier" which forms a biphasic mixture with DMF. After phase separation and removal of $C_8F_{17}Br$, the catalyst was charged with fresh starting materials and DMF. The results revealed a gradual loss of conversion and yield. The authors assumed that either loss of activity is due to limited stabililty of the catalyst, or that the catalyst is stable but the recycling is not as efficient as anticipated. Reaction rate and transmission electron microscopy indicated the presence of soluble Pd nanoparticles as active catalyst.

Stabilized Pd nanoparticles of compounds featuring perfluorinated chains **6–10** were described by Moreno-Mañas et al. [18, 19]. The Pd nanoparticles were obtained by the reduction of $PdCl_2$ with methanol in the presence of **6–10**, respectively. The presence of such nanoparticles was confirmed by transmission electron microscopy. Due to the stabilization by the perfluorinated ligand, the palladium colloids are soluble in perfluorinated solvents. Pd nanoparticles stabilized by 1,5-bis(4,4′-bis(perfluorooctyl)phenyl)-1,4-pentadien-3-one (**6**) were active in Heck and Suzuki couplings [18].





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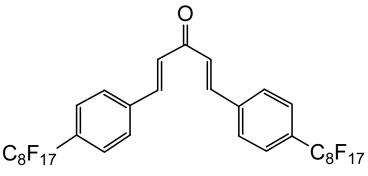

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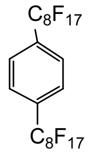

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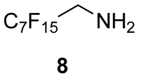

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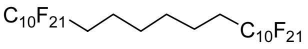

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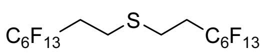

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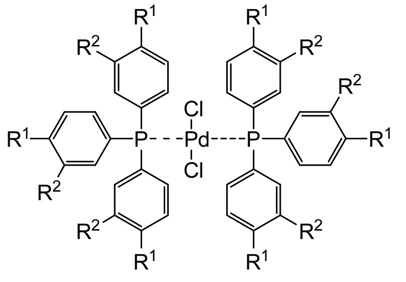
Schneider and Bannwarth have developed fluorous triphenylphosphine-modified palladium complexes (**11a–11c**) for Stille couplings in DMF/perfluoromethylcyclohexane (1 : 1) using 1 equiv of LiCl as additive at 80 °C for 3–24 h [Eq. (2)] [20].

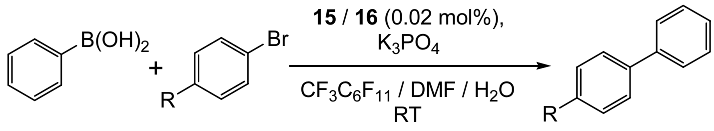
$$\text{R–Br} + \text{Ar–Sn}(n\text{-Bu})_3 \xrightarrow[\text{2.) KF}]{\substack{\text{1.) 1.5 mol\% Pd-catalyst (\textbf{11a-c}),} \\ \text{DMF/CF}_3\text{C}_6\text{F}_{11}\text{, LiCl,} \\ \text{80°C, 3 - 24h}}} \underset{\substack{\textbf{12} \\ [39 - 98\%]}}{\text{R–Ar}} + \text{F–Sn}(n\text{-Bu})_3 \quad (2)$$



11a: $R^1 = C_8F_{17}$, $R^2 = H$
11b: $R^1 = H$, $R^2 = C_8F_{17}$
11c: $R^1 = C_2H_4C_8F_{17}$, $R^2 = H$
11d: $R^1 = H$, $R^2 = C_2H_4C_8F_{17}$

From the organic phase the C–C coupling products (**12**) were obtained in good yields, while the fluorous phase containing the catalyst was used as such for the next cycle. The catalysts could be used up to six times without significant decrease in yield.

Schneider and Bannwarth applied the same fluorous bis(triphenylphosphane)-palladium dichloride complexes **11a–11d** as catalyst precursors in Suzuki reactions [21] as well. The reactions took place in a H_2O/DMF/PFMCH triphasic mixture with 1.5 mol% of Pd complex. It could be demonstrated that perfluoro-tagged complexes **11a–11d** are highly effective precatalysts for Suzuki couplings under FBS conditions with either electron-rich or electron-deficient bromoarenes and arylboronic acids. The catalysts could be recycled and re-used after phase separation up to six times without a significant decrease in coupling yields. It could be shown in one example that the amount of catalyst could be reduced from 1.5 mol% to 0.1 mol% still resulting in a high yield (> 86%) in the first run but considerable loss of activity in repetitive cycles. Rocaboy and Gladysz prepared perfluoro-tagged dialkyl sulfides ($R^F(CH_2)_n)_2S$ (n = 2–16) which are soluble in most fluorous and organic solvents with a $CF_3C_6F_{11}$/toluene partition coefficient of 98.7 : 1.3 for **13** and 96.6 : 3.4 for **14** at 24 °C [Eq. (3)] [22].



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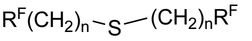
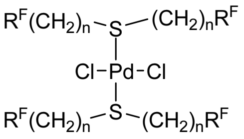


$R^F = C_8F_{17}$

n=2 **13**

n=3 **14**



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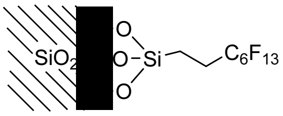
Reaction of **13** or **14** with Na_2PdCl_4 gave Pd complexes **15** and **16** respectively, which are soluble in only a limited range of fluorinated solvents at room temperature. With **15** and **16** as catalyst they were able to achieve turnover numbers of 4500–5000 in Suzuki couplings of aryl bromides and phenylboronic acid in $CF_3C_6F_{11}$/DMF/H_2O in the presence of K_3PO_4. Under fluorous recycling conditions, decreased activities of the catalysts were observed. For this loss of activity the following reasons could be responsible: (a) inefficient recycling of the perfluoro-tagged catalyst; (b) gradual deactivation of the catalyst; (c) slow generation of an active, nonrecyclable heterogeneous catalyst from a homogeneous precursor and recycling of the remaining precursor; (d) generation of a heterogeneous catalyst which is not stable but can be efficiently recycled. The appearance of palladium black in recycling experiments and recent reports on heterogeneous or metallic palladium species lead the authors to favor possibilities (c) and (d) [18, 19, 23, 24].

Bannwarth and co-workers have recently developed new protocols for the separation and recycling of perfluoro-tagged catalysts without the need for fluorous solvents [25]. They have employed Pd complexes **11c**, **11d**, and **17**, immobilized by adsorption on fluorous reversed-phase silica gels (FRPSG) **18** and **19**, and demonstrated the application to Suzuki couplings in organic solvents. Coarse-grained silica of 100–300 μm particle size was used with loadings between 0.1 and 100 mg complex per g FRPSG. The coupling of *p*-nitrobromobenzene and phenylboronic acid was carried out using 10 mg Pd complex per g FRPSG with 0.1 mol% palladium. Complete conversions were obtained and recycling was possible by filtration or decantation without a significant decrease of activity. With 0.001 mol% of catalyst, a TON of 131 000 was observed. ICP-MS measurements indicated a leaching of 1.9% of catalyst when adsorbed to FRPSG **18** and 1.6% when adsorbed to FRPSG **19**, respectively. Suzuki couplings with catalyst **11c** on support **18** were performed with different substrates giving high yields for electron-deficient aryl bromides and for aryl iodides. Markert and Bannwarth employed the Pd complexes **11c**, **11d**, and **17** as catalyst precursors for the coupling of bromoarenes with alkynes [Eq. (4)] [26]. The reactions were carried out in a mixture of DMF and perfluorodimethylcyclohexane (PFMCH) with 2 mol% of **11c**, **11d**, or **17** and 5 mol% of CuI as co-catalyst in the presence of 2 equiv of Bu_2NH. After the reaction the phases were separated at 0 °C and the fluorous phase containing the catalyst was washed several times with DMF and was re-used as such for the next run. As known for Sonogashira couplings, electron-deficient bromoarenes proved to be good substrates, whereas the coupling of donor-substituted bromoarene resulted in lower yields. Recycling and re-use of the catalyst was possible in most cases but no influence on product yield dependent on the position of the perfluoro tag in the phosphane or the nature of the spacer group was observed.

Perfluoro-tagged Pd complexes **11c**, **11d**, and **17** adsorbed on FRPSG **18** or **19** (2 mol%) were also used for Sonogashira couplings of phenyl acetylene and



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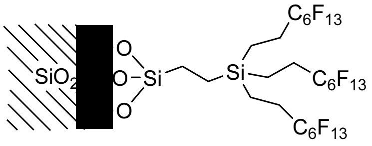

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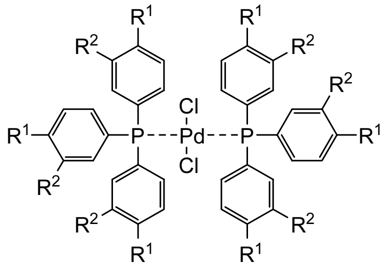
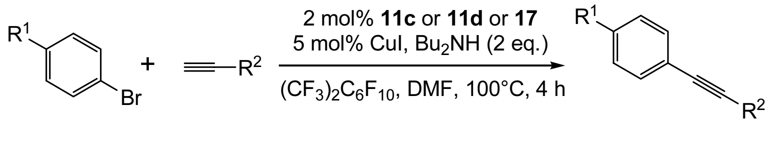


11c: $R^1 = C_2H_4C_8F_{17}$, $R^2 = H$
11d: $R^1 = H$, $R^2 = C_2H_4C_8F_{17}$
17: $R^1 = OCH_2C_7F_{15}$, $R^2 = H$



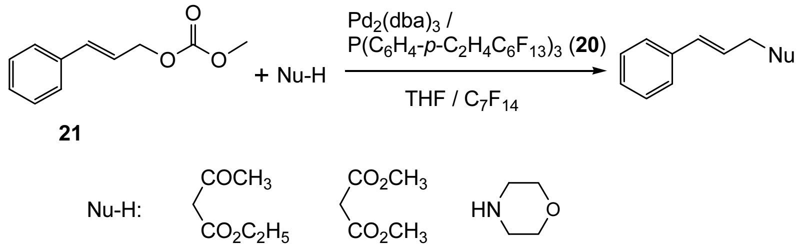
(4)

$R^1 = NO_2$; COMe; CO_2Et, OMe

R^2 = TIPS; Ph; CMe_2OH

p-nitrobromobenzene, without the need for fluorous solvents similar to those in the protocol outlined for Suzuki couplings [25]. High yields were obtained for three successive experiments.

Leitner and co-workers described Pd-catalyzed nucleophilic substitutions of allylic substrates with different nucleophiles [27]. They used $Pd_2(dba)_3$ as the palladium source and phosphane **20** as perfluoro-tagged ligand [Eq. (5)]. Reaction between cinnamyl methyl carbonate (**21**) and various nucleophiles (Nu–H) were performed in a THF/C_7F_{14} biphasic mixture. A decrease in conversion was observed only after the ninth run (with 5 mol% Pd complex). By reducing the amount of Pd complex to 1 mol%, five quantitative recyclings were possible. The standard protocol was also applied to the condensation of dimethyl malonate with allyl methyl carbonate, (2-vinyl)butyl carbonate, and cyclohex-2-enyl carbonate. In each case two recyclings were performed without any decrease in conversion.



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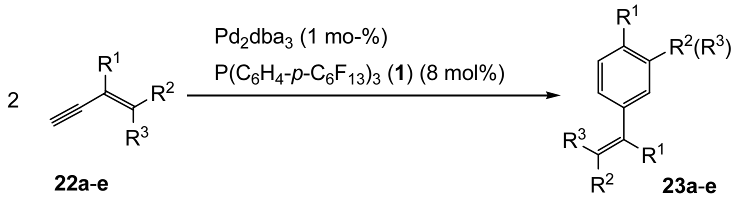
(5)

Cyclodimerizations of conjugated enynes **22a**–**22e** in the presence of perfluoro-tagged Pd catalyst were reported by Saito et al. [Eq. (6)] [28]. Reactions of enynes **22a**–**22e** were carried out in toluene/hexane/perfluorodecalin with 1 mol% of $Pd_2(dba)_3$ as palladium source and 8 mol% of perfluoro-tagged phosphane **1** giving the desired products (**23a**–**23e**) in moderate to good yield (43–78%). Recovery of the perfluoro-tagged catalyst was possible up to four times. However, IPC atomic emission analysis of the fluorous phase indicated that the concentration of the palladium species decreased significantly.



22a-e **23a-e**

(6)

22a: R^1 =H; R^2 = H; R^3 = CO_2Et

22b: R^1 = H; R^2 = H; R^3 = $CO_2n\text{-}C_8H_{17}$

22c: R^1 = $n\text{-}C_6H_{13}$; R^2 = H; R^3 = CO_2Et

22d: R^1 = H; R^2 = $CO_2n\text{-}C_8H_{17}$; R^3 = H

22e: R^1 = $n\text{-}C_6H_{13}$; R^2 = CO_2Et; R^3 = H

23a: 78% (76, 81, 79, 13)

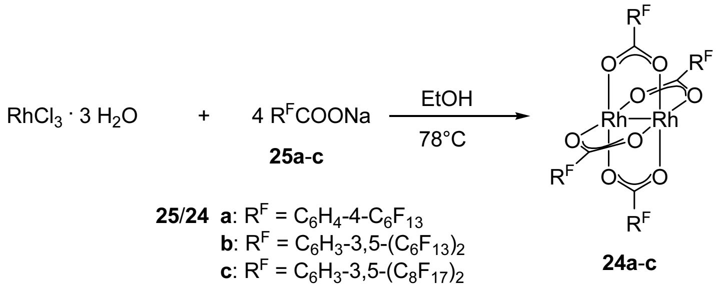
23b: 76% (71, 78, 74, 81, 71, 41)

23c: 74%

23d: 43%

23e: 53%

Endres and Maas prepared dimeric rhodium(II) carboxylate complexes **24a**–**24c** from the sodium salts **25a**–**25c** and rhodium(III) chloride hydrate in ethanol [Eq. (7)] [29, 30].



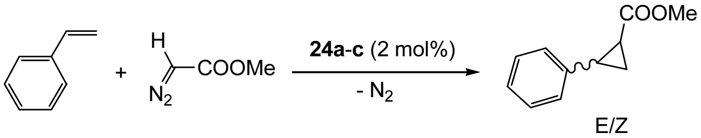
25a-c

25/24 **a**: $R^F = C_6H_4\text{-}4\text{-}C_6F_{13}$
b: $R^F = C_6H_3\text{-}3,5\text{-}(C_6F_{13})_2$
c: $R^F = C_6H_3\text{-}3,5\text{-}(C_8F_{17})_2$

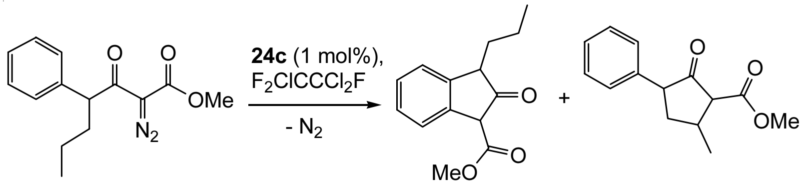
24a-c

(7)

Complexes **24a**–**24c** were applied to cyclopropanations of styrenes with methyl diazoacetate [Eq. (1), Scheme 4.2-12]. Reactions were performed in CH_2Cl_2 with **24a** or in the fluorous/organic hybrid solvent FC-113 (CCl_2F–$CClF_2$) with **24b**–**24c**. Recovery of the catalyst was achieved by extraction into PFMCH (with **24a**) or by replacement of FC-113 with PFMCH/CH_2Cl_2 (with **24b**–**24c**) and phase separation, respectively. Yields remained high over four cycles with **24a** or five cycles with **24b**–**24c**, respectively. Nevertheless, a total loss of 38–56% after five cycles, as shown by gravimetric determination, was observed. The authors attributed this to a partial destruction of the complex. Intramolecular carbenoid C–H insertions of a-diazo-β-keto ester **26** [Eq. (9)] were catalyzed by **24c** with good selectivity for **27a** and good yields [30]. By extraction with PFMCH/CH_2Cl_2, 96% of the catalyst could be recycled.



(8)

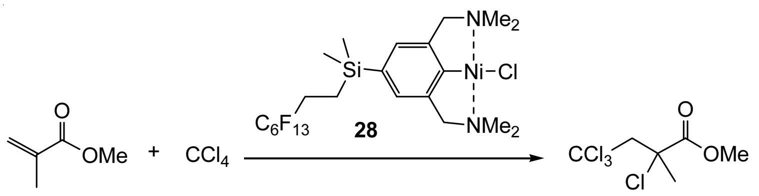


(9)

26 **27a** **27b**

The addition reaction of CCl_4 to methyl methacrylate in DCM was catalyzed by perfluoro-tagged nickel compound **28** as described by van Koten et al. [Eq. (10)] [31]. Unfortunately, **28** did not have an improved affinity for fluorous solvents, which prevented its efficient recycling.

The Friedel–Crafts acylation of arenes with acetic anhydride was efficiently catalyzed by ytterbium tris(perfluoroalkanesulfonyl)methides **29a**–**29c** [32]. It was demonstrated that catalyst **29c** could be recovered in 96% yield by extraction of the reaction mixture with hot perfluoromethyldecalin and could be re-used in a second run.



(10)

$Yb[C(SO_2R^{F1})_2(SO_2R^{F2})]_3$

29a: $R^{F1} = R^{F2} = C_4F_9$
29b: $R^{F1} = R^{F2} = C_6F_{13}$
29c: $R^{F1} = C_6F_{13}$; $R^{F2} = C_8F_{17}$

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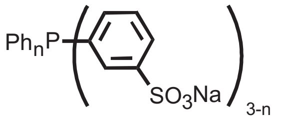
4.2.2
Hydroformylation and Hydrogenation Catalyzed by Perfluoroalkylated Phosphine–Metal Complexes

Eric G. Hope and Alison M. Stuart

4.2.2.1
Hydroformylation

The hydroformylation of alkenes has been extensively investigated and was exploited commercially for the first time in the 1940s using cobalt-carbonyl catalysts [1]; see Chapter 2. Enhanced hydrogenation of aldehydes to give alcohols coupled with improved selectivity to the linear (*n*-) product has been accomplished by the introduction of phosphine ligands [2] and these technologies are still in use today for the hydroformylation of long-chain alkenes. In the hydroformylation of propene, where the volatile butanal product can be readily distilled directly from the reactor, more selective rhodium-triphenylphosphine catalysts operating under milder reaction conditions have replaced the cobalt-based catalysts in continuous processes operating at 3.5 million tonnes per annum [3]. However, the thermal instability of these rhodium catalysts has precluded their widespread adoption and has led to the evaluation of a number of alternative approaches including fluorous chemistry. In fact, Horváth and Rábai highlighted the potential for fluorous technologies for the hydroformylation of long-chain alkenes in their original disclosure on the fluorous biphase [4].

The relative instability of the rhodium-based catalysts has already been overcome, and the technique exploited commercially, in the Ruhrchemie-Rhône Poulenc hydroformylation of propene, where the sodium salt of a sulfonated triphenylphosphine ligand **1** is used to solubilize the rhodium catalyst in the aqueous phase [5]; see Section 2.5.1. However, this approach cannot be extended to the hydroformylation of longer-chain alkenes because of their very low aqueous solubility, leading to commercially prohibitive low reaction rates. A potential solution to this problem was reported in 1998 in which the sulfonated triphenylphosphine ligand was replaced with triphenylphosphine functionalized with a single, very long, poly(ethylene glycol) ponytail **2** [6] (cf. Section 2.3.5). Here, although the rhodium–phosphine catalyst is exclusively soluble in water at room temperature, on heating the ponytail undergoes a phase transition rendering the catalyst preferentially soluble in the organic phase. Consequently, the catalyst acts on the substrate under classical homogeneous conditions but, on cooling, reversal of the phase transition returns the catalyst to the aqueous phase, allowing the product to be separated by a simple decantation.



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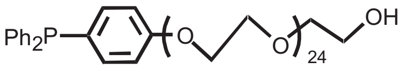

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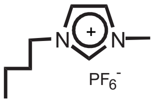
Ionic liquids, such as 1-butyl-3-methylimidazolium hexafluorophosphate (**3**), are salts that (a) are liquid at room temperature, (b) have extremely low vapor pressures, (c) can be tuned to dissolve organic compounds, and (d) can dissolve ionic catalysts or, in specific examples, the liquid may act as a catalyst as well as the solvent. Consequently, there has been considerable interest in their potential application as alternative solvents for organic synthesis and catalysis (cf. Chapter 5). In initial work on the rhodium-catalyzed hydroformylation of 1-pentene, using the sulfonated phosphine ligand **1** to solubilize the catalyst in the ionic liquid, conversions were disappointingly low [7]. More recently, two groups have reported highly active and regioselective rhodium-catalyzed hydroformylation of 1-octene with Xantphos-type ligands in ionic liquids, {**4**, *n*/*i* 21 : 1 and < 0.07% rhodium leaching [8]; **5**, *n*/*i* 49 : 1 and < 5 ppb rhodium loss [9]}, where separation of the 1-nonanal product can be achieved again by a simple decantation.



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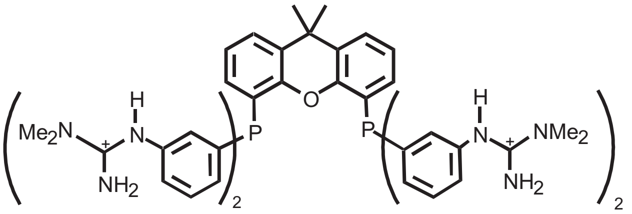

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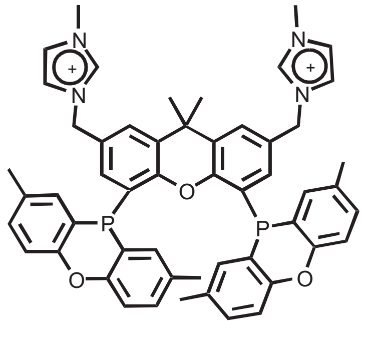
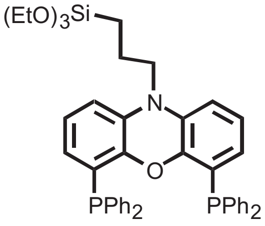


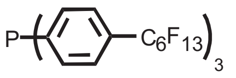
5

Rhodium catalysts for hydroformylation supported on both insoluble (for example, inorganic oxides or polymers) and soluble materials (for example, dendrimers) have been reported. Work on insoluble solid supports has been dogged by loss of activity and high levels of catalyst leaching as a consequence of bonds breaking between the catalyst and support during catalysis (cf. Chapter 7). However, acceptable catalyst leaching (< 100 ppb rhodium) coupled with reasonable activity and excellent regioselectivity (n/i 40 : 1) has been demonstrated for a sol–gel solution incorporating a triethoxysilyl-functionalized Xantphos-type ligand **6** [10]. Dendrimers are large treelike soluble molecules with a globular shape making them suitable for ultrafiltration in which the solvent and reaction product(s) pass through while the dendrimer is retained. Rhodium for hydroformylation can be supported on the "surface" of the dendrimer functionalized with phosphines, and such a system shows enhanced regioselectivity but loss of activity on recycling [11].



6

Most metal-containing complexes, particularly rhodium-based hydroformylation catalysts incorporating aryl–phosphine ligands, are virtually insoluble in apolar $scCO_2$. Solubility can be enhanced by the incorporation of the perfluoroalkyl groups characteristic of fluorous chemistry and reaction rates and regioselectivities for the hydroformylation of long-chain alkenes, comparable to those observed under fluorous biphase conditions, have been reported using derivatized rhodium catalysts [12, 13]. In two reports, significantly enhanced rates of reaction have been reported in $scCO_2$ in comparison to those in toluene for the rhodium-catalyzed hydroformylation of acrylic esters using the perfluoroalkylated phosphine **7** [14], or a fluoropolymer ligand [15]. However, although there has been considerable interest in $scCO_2$ as an environmentally friendly solvent for homogeneous catalysis [16, 17], for which removal of the solvent just requires decompression back to the gaseous phase, this does not *per se* overcome the principal issue for homogeneous catalysis outlined above: that is, the separation of product from catalyst (see Chapter 6). In theory, since solubility in supercritical fluids is pressure-dependent, with careful control of the catalyst/substrate/product system it should be feasible to accomplish the desired separation, and this has been achieved with moderate success (< 170 ppb rhodium leaching) in the hydroformylation of 1-octene using the perfluoroalkylated triphenylphosphine **8** [12]. Alternative approaches to the catalyst/product separation problem have combined $scCO_2$ with a supported catalyst (for example **6** [18]) and $scCO_2$ with an ionic liquid [19], both of which are potentially very powerful systems, but in both cases the reaction rates are relatively low.



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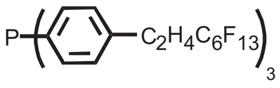

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In the earliest reports of the application of perfluorocarbon solvents and perfluoroalkylated ligands/metal catalysts, Horváth and Rábai outlined the hydroformylation of 1-octene in a toluene/$CF_3C_6F_{11}$ (PP2) two-phase system at 100 °C under 1 MPa CO/H_2 (1 : 1) using a catalyst generated in situ from $[Rh(CO)_2(acac)]$ and $P(C_2H_4C_6F_{13})_3$ (**9**) which gave an 85% conversion to aldehydes with an *n*/*i* ratio of 2.9 [4, 20]. In the following full paper [21], an in-depth analysis of hydroformylation under fluorous biphase conditions generated a series of important conclusions. Here, the hydroformylation of 1-decene and ethylene were investigated with the same rhodium catalyst (generated in situ) under both batch and semi-continuous conditions at 100 °C and 1.1 MPa CO/H_2 (1 : 1) in a 50/50 vol% toluene/PP2 biphase. The long-term stability of this catalyst under these conditions is significantly greater than that for the catalyst based on triphenylphosphine, the regioselectivity is similar, but the catalytic activity is an order of magnitude lower. The reaction, as expected, is first order in both rhodium and alkene and is inhibited by excess phosphine, whereas the regioselectivity increases with phosphine concentration such that the best *n*/*i* ratio (7.84) is obtained at a P/Rh ratio of approximately 100 : 1 ([ligand] = 0.3 mol dm^{-3}). The semi-continuous experiments were highly successful with total turnovers of up to 35 000 during nine cycles with only 1.18 ppm (4.2%) loss of rhodium per mole of product(s), which arises from the low solubility of the catalyst in the organic phase.

$$P(C_2H_4C_6F_{13})_3$$

9

It is well established that triarylphosphines give much better regioselectivity than trialkylphosphines in rhodium-catalyzed hydroformylation reactions [3, 22], so rhodium catalysts based upon **7** have been evaluated [23, 24]. Initial screening of the hydroformylation of 1-hexene in a toluene/1,3-$(CF_3)_2C_6F_{10}$ (PP3) two-phase system at 70 °C under 20 MPa CO/H_2 (1 : 1) using a catalyst generated in situ from $[Rh(CO)_2(acac)]$ and **7** (1 : 3) gave a 98% conversion to aldehydes with an *n*/*i* ratio of 3.8. Visual inspection of the solvent system under 2 MPa syngas indicated that the alkene starting materials were miscible with the fluorous solvent at the reaction temperature while the more polar aldehyde products were immiscible, and this work led to an evaluation of the perfluoralkylated rhodium hydroformylation catalyst in the absence of the second organic phase. Here, thorough investigation of the hydroformylation of 1-octene in PP2 between 70 and 90 °C under 2 MPa CO/H_2 (1 : 1) using the same rhodium catalyst with metal/ligand ratios of 1 : 3 and 1 : 10 gave 95–98% conversions with *n*/*i* ratios of 3.0–6.3. Crucially, rhodium leaching levels, detected at the best regioselectivity (*n*/*i* 6.3; conditions rhodium/phosphine 1 : 10; 70 °C), were excellent (80 ppb), indicating that the omission of toluene from the solvent system had enabled the development with excellent retention of rhodium,

Table 1 Rhodium catalyzed hydroformylation of 1-octene.[a)]

System	*Ligand*	*Pressure [MPa]*	*T [°C]*	*TOF [h^{-1}]*	*Rate [mol dm^{-3} h^{-1}]*	*n : i*	*Rh loss [mg (mg product^{-1}]*	*Ref.*
Homogeneous[b)]	PPh_3	1.5	95	770	2.0	8.8 : 1	n.a.	[3]
Aqueous biphase[b)]	**1**	5.0	120	400	1.1	19 : 1	< 0.005	[5]
Aqueous biphase	**2**	5.0	100	182	0.5	n.r.	n.r.	[6]
Ionic liquids	**4**	3.0	100	50	n.r.	21 : 1	< 0.07% [c)]	[8]
Ionic liquids	**5**	4.6	100	318	1.2	49 : 1	< 0.005	[9]
Supported catalyst	**6**	5.0	80	287	0.19	40 : 1	< 0.1	[10]
$scCO_2$	**8**	20.0	65	430	14.2	5.5 : 1	< 0.17	[12]
Supported/$scCO_2$	**6**	17.0	90	160	n.r.	33 : 1	< 1.2	[18]
Fluorous biphase	**9**	1.0	100	837	0.1	4.5 : 1	0.12	[21]
Fluorous biphase	**7**	2.0	70	4400	8.8	6.3 : 1	0.08	[24]

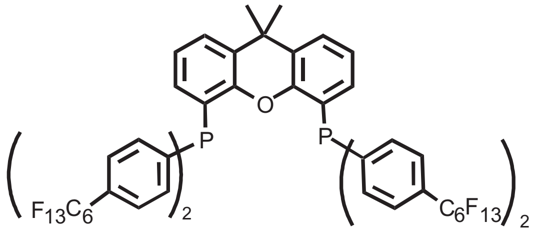
a) n.a. = not applicable; n.r. = not reported.

b) Propene as substrate.

c) Reported as % of catalyst loading.

while both the high reaction rate and good regioselectivity required for commercial application are maintained.

Table 1 summarizes the key catalytic data for these hydroformylation reactions under fluorous biphase conditions alongside data for representative examples from the alternative solvent systems outlined above. In general, the results are comparable; in some cases there are better regioselectivities, in others better reaction rates, in yet others better catalyst retention. In attempts to improve regioselectivity and catalyst retention under fluorous biphase conditions, we and others have been investigating perfluoroalkylated bidentate ligands based upon Xantphos, for example, **10** [25] and BIPHEPHOS [26, 27]. Unfortunately, the introduction of perfluoroalkyl units onto biphenol has, to date, prevented the synthesis of fluorous BIPHEPHOS-type bisphosphite ligands, while **10** with only four perfluoroalkyl groups, although it is active in the rhodium-catalyzed hydroformylation of 1-octene (*n*/*i* 16 : 1), is not soluble in fluorous solvents and attempts to increase the number



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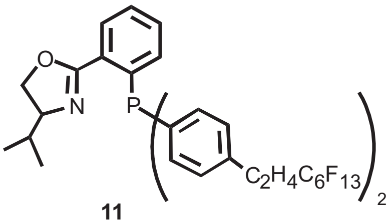
of perfluoroalkyl substituents have not yet been successful. These latest results appear to suggest that the future development of fluorous chemistry in hydroformylation probably rests with simpler, monodentate, ligand systems.

4.2.2.2
Hydrogenation

The hydrogenation of unsaturated organic compounds represents one of the most environmentally benign processes, in that it produces virtually no waste. Since heterogeneous catalysts (for example, Raney nickel, palladium on carbon) are highly effective, homogeneous hydrogenation catalysts will only find application when other factors (for example, substrate incompatibility, enantioselectivity, transfer hydrogenation to avoid the need to use gaseous hydrogen) are important [28]. An industrial example is the rhodium-catalyzed homogeneous enantioselective hydrogenation of dehydroamino acids in the synthesis of L-dopa [29]. In these cases, as for the homogeneous hydroformylation catalysts outlined above, product/catalyst separation is a major issue that has led to the synthesis and evaluation of homogeneous catalysts in a variety of alternative solvents such as water [30–32], ionic liquids [7, 33, 34], and supercritical carbon dioxide [16, 17, 35–39] (see Chapters 2 to 6).

In contrast with the research into hydroformylation under FBS conditions that has been directed toward a commercially important process, publications on hydrogenation under FBS conditions have been focused upon the physical and chemical consequences of using perfluoroalkylated phosphine ligands and fluorous solvents and the ability to recover and recycle the metal catalyst. Horváth et al. [40], using the analogue of Wilkinson's catalyst, [$RhClL_3$], where L = $P(C_2H_4C_6F_{13})_3$ (**9**), studied the hydrogenation of a series of alkenes (2-cyclohexen-1-one, 1-dodecene, cyclododecene, and 4-bromostyrene) in a toluene/PP2 biphase under 0.1 MPa. H_2 at 45 °C affording the hydrogen addition products in 87–98% yields. Although the catalyst activity is significantly poorer than those for conventional homogeneous catalysts, recovery and re-use of the catalyst were illustrated by recharging the fluorous phase with second and third aliquots of substrate and obtaining comparable conversions; however, some catalyst decomposition was also observed. It is well known that alkylphosphines give much less effective analogues of Wilkinson's catalyst than arylphosphines, and perfluoroalkylated arylphosphines have been evaluated by other groups. A soluble fluoropolymer-supported alkyldiphenylphosphine is active for the hydrogenation of 1-octene and cyclohexene in a THF/perfluorooctane biphase under 0.2 MPa. H_2 at 25 °C, where re-use seven times shows no loss in activity although rhodium leaching levels have not been measured [41]. Using styrene as a substrate, the catalytic activities of the analogues of Wilkinson's catalyst containing perfluoroalkylated phosphines, for example, **7**, with those of their protio-parents in toluene/hexane : PP3 or fluorobenzene : PP3 biphases under 0.1 MPa. H_2 have been compared at 63.5 or 75 °C respectively, where just the introduction of the fluorous phase had a significant impact upon the rates of reaction, but < 1 ppm rhodium leaching was observed [42]. In line with well-established trends, the incorporation of the electron-withdrawing perfluoroalkyl groups caused a reduction in rate relative to those for the protio-parents; this effect is most pronounced for the trialkylphosphine with the C_2H_4 spacer unit, indicating that it is a poorer electronic insulator than the C_6H_4 group. The most promising results were obtained for a $C_6H_4OCH_2$ spacer group although, even with this unit, complete electronic insulation of the phosphorus atom was not possible. The most effective insulation is reported in a direct comparison of the aryl–silyl spacer ligand (**12**; TOF 870 h^{-1}) with Wilkinson's catalyst (TOF 960 h^{-1}) in the hydrogenation of 1-octene in α,α,α-trifluorotoluene under 0.1 MPa. H_2 at 80 °C [43]. In PP2 (using **12**, 1-octene at 80 °C) the TOF drops to 177 h^{-1}, but on cooling to 0 °C a biphase forms that allows separation of the octane product, and the catalyst phase can be recycled nine times with just 3 ppm (0.12%) rhodium leaching per cycle. The reactivity appears to increase during the subsequent cycles, although this can be ascribed to loss of the perfluorocarbon solvent (ca. 12% per cycle) during phase separation and the nonzero miscibility of PP2 with the product phase. The best catalyst retention (> 99.92%) has been reported following hydrogenation of 1-octyne under 0.1 MPa. H_2 at 40 °C with the cationic [Rh(COD)(13)][BF_4] in an FC-75/hexane biphase, where the chelating bidentate phosphine ligand **13** has 12 fluorous ponytails [44].



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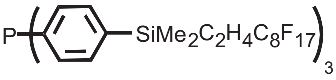

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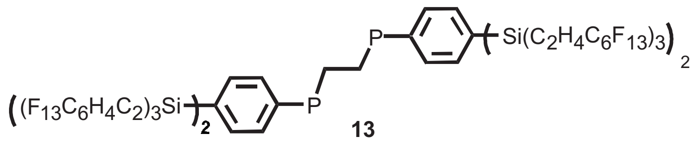

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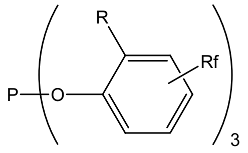
4.2.3
Hydroformylation Catalyzed by Fluorous Triarylphosphite–Metal Complexes

Eric Monflier, André Mortreux, and Yves Castanet

Fluorous biphasic catalysis is a particularly elegant concept for the recycling of homogeneous catalysts as the catalyst and product phases are generally well separated at room temperature and can become homogeneous at higher temperatures [1–3]. Obviously, this behavior allows the combination of the activity and selectivity of homogeneous catalysts with the simplicity of product isolation. The hydroformylation of olefins in a fluorous phase was first reported by Horváth and Rábai in 1994 [1, 4] and discussed in Section 4.2.2.1. Since this pioneering work, the attention of research groups has been focused on the synthesis of new fluorinated ligands showing a better affinity for the fluorous phase and a better *l*/*b* (*n*/*i*) ratio. With the aim of keeping the high selectivities and activities observed in classical organic solvents, three classes of ligands have been rapidly developed for hydroformylation under fluorous biphasic conditions: triarylphosphines [5] and triarylphosphites [6–10] bearing one or two perfluoroalkyl group per aromatic ring and more recently, chiral phosphine-phosphite ligands with fluorous ponytails [11].

The behavior of rhodium catalysts generated in situ from fluorous phosphites **1–10** and Rh(acac)(CO)$_2$ has been investigated.

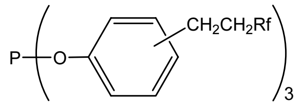


1a R=H, Rf=2-C_6F_{13} [8]
1b R=H, Rf=2-C_8F_{17} [9]

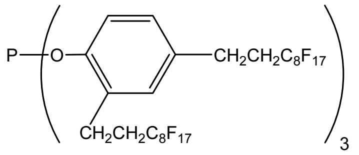
2a R=H, Rf=3-C_6F_{13} [8]
2b R=H, Rf=3-C_8F_{17} [9]

3a R=H, Rf=4-C_6F_{13} [7, 8]
3b R=H, Rf=4-C_8F_{17} [9]

4 R=CH_3, Rf=2-C_6F_{13} [9]



7 Rf=2-C_8F_{17} [13]
8 Rf=4-C_8F_{17} [13]



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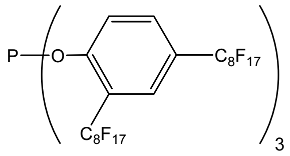

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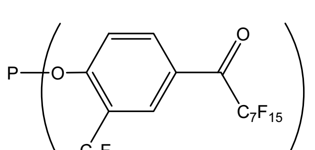
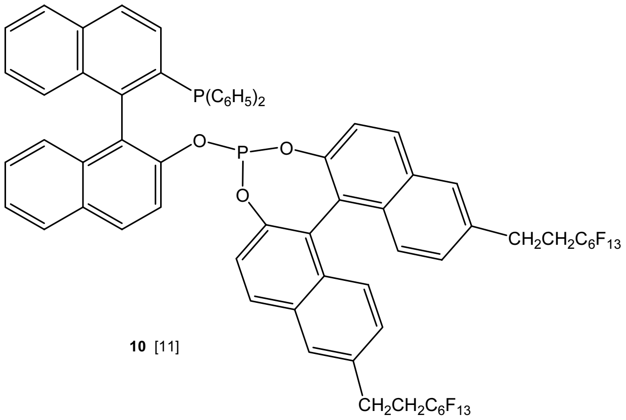


6 [10]



10 [11]

Phosphites **1–6** induce high activity in hydroformylation of terminal alkenes in comparison with the classical ligands PPh_3 and $P(OPh)_3$ (Table 1). Nevertheless, considerable differences in activity and selectivity exist according to the nature, the position, and the number of substituents on the aromatic ring of the phosphite. For instance, bulky *ortho*-substituted phosphites lead to catalytic systems that are much more active than those resulting from their *meta* or *para* counterparts. However, these *ortho*-phosphites give lower *l*/*b* ratios. Indeed, the *l*/*b* ratios are between 2 and 3, i.e., greatly inferior to those observed with the *meta* and *para* phosphites (ca. **5–8**) and slightly inferior or similar to those obtained with ligands PPh_3 or $P(OPh)_3$.

Classically, the reactivity decreases with the size of the substrate and, more unexpectedly, the *l*/*b* ratio and aldehyde selectivity vary in the same way. Interestingly, internal alkenes are also hydroformylated with significant activity with these catalytic

Table 1 Hydroformylation of higher alkenes under fluorous biphasic conditions with phosphites **1**–**6**.

Conditions	*Substrate*	*Ligand*	*TOF*[a)] *[h^{-1}]*	*l/b*	*Aldehyde selectivity [%]*	*Ref.*
A	1-hexene	PPh_3	900	2.7	93.1	[12]
B	1-hexene	$P(OPh)_3$	1700	2.9	92	[12]
B	1-hexene	**1a**	4200	0.9	99.2	[12]
B	1-hexene	**2a**	1300	5.2	96.1	[12]
B	1-hexene	**3a**	2650	8.4	85.4	[12]
B	2-nonene	**3a**	880	–	75.1	[12]
C	1-octene	**3a**	15600	6.3	83.9	[12]
D	1-decene	**1b**	10000	2.3	71	[6]
D	1-decene	**2b**	6300	5.8	80	[6]
D	1-decene	**3b**	3500	5.3	85	[6]
D	1-decene	**4**	7100	2.9	80	[6]
D	1-decene	**5**	7900	2.4	46	[6]
D	1-decene	**6**	6200	2.6	39	[6]
D	1-octene	**2b**	6900	6.3	87	[6]
E	2-octene	**2b**	1400	–	75	[6]
E	4-octene	**2b**	800	–	76	[6]

Conditions:

(A) A solution of $[Rh(acac)(CO)_2]$ (10.0 mmol dm^{-3}), ligand (30 mmol dm^{-3}), 1-hexene (8 mmol, 1 cm^3), toluene (4 cm^3) at 70 °C, 2 MPa CO/H_2 (1 : 1) for 1 h.

(B) A solution of $[Rh(acac)(CO)_2]$ (10.0 mmol dm^{-3}), ligand (30 mmol dm^{-3}), 1-hexene (8 mmol, 1 cm^3) in a mixture of perfluoro-1,3-dimethylcyclohexane (2 cm^3) and toluene (2 cm^3) at 70 °C, 2 MPa CO/H_2 (1 : 1) for 1 h.

(C) A solution of $[Rh(acac)(CO)_2]$ (2.0 mmol dm^{-3}), ligand (6 mmol dm^{-3}), 1-octene (1 cm^3) in perfluoro-1,3-dimethylcyclohexane (4 cm^3) at 80 °C, 2 MPa CO/H_2 (1 : 1) for 1 h.

(D) $[Rh(acac)(CO)_2]$ (10 mg, 0.039 mmol), ligand (0.194 mmol), alkene (77.4 mmol), 1H-perfluorooctane (15 cm^3), undecane (internal standard for GC analysis, 1.21 g), 80 °C, 4 MPa CO/H_2 (1 : 1).

(E) As conditions D except $C_8F_{17}H$ (10 cm^3), toluene (10 cm^3).

a) TOF = initial turnover frequency: moles of alkene converted per mole Rh per hour.

systems. Another interesting feature of the process is that better reaction rates and *l*/*b* ratios are obtained when the reaction is carried out in the absence of organic solvent.

Phosphites with spacer group (**7**–**9**) showed little difference from phosphites **1**–**6** (see Table 2). Indeed, the *ortho*-substituted phosphites **7** and **9** differ from the *para*-substituted **8** by much higher activities (TOF > 10 000 vs. 3900 h^{-1} respectively), by a lower *l*/*b* ratio (2 vs. 3.5), and by a lower aldehyde selectivity. The main difference lies in the fact that the *l*/*b* ratio for the *para*-substituted phosphite **8** is much lower than those obtained with phosphites **2** and **3** and close to the one obtained with $P(OPh)_3$.

Experiments made with different fluorous solvents proved that the nature of the fluorous phase has practically no effect on the *l*/*b* ratio and on the aldehyde selectivity. On the other hand, this factor greatly influences the activity, since the TOF dropped from 3900 h^{-1} when using 1*H*-perfluorooctane to 3800, 2500, and 2300 h^{-1} with perfluoromethylcyclohexane (PFMC), perfluoromethyldecalin (PFMD) and perfluoroperhydrophenanthrene (PFPP) respectively. These observations are explained by the fact that at the reaction temperature (80 °C), PFMD and PFPP are not totally miscible with 1-decene, in contrast with the 1-decene–$C_8F_{17}H$ and 1-decene–PFMC couple [13].

Other heavy terminal olefins behave similarly to 1-decene (Table 2), giving, for example, with phosphite **8**, an *l*/*b* ratio of about 3.0 and an aldehyde selectivity of 95%, but the activity drops markedly going from 1-decene to 1-dodecene, presumably again due to their partial solubility with the fluorous solvent $C_8F_{17}H$.

Table 2 Hydroformylation of higher alkenes under fluorous biphasic conditions with a fluorous phosphites with spacer group [13].

Phosphite	*Substrate*	*Solvent*	*Time*[a] *[min]*	*TOF*[b] *[h^{-1}]*	*l/b*	*Aldehyde selectivity [%]*
7	1-decene	$C_8F_{17}H$	15	10000	2.0	85
8	1-decene	$C_8F_{17}H$	30	3900	3.5	95
9	1-decene	$C_8F_{17}H$	12	11000	2.0	85
8	1-decene	$C_8F_{17}H$/Tol.	60	3500	3.0	98
8	1-decene	PFMC	60	3800	3.0	98
8	1-decene	PFMD	90	2500	3.3	95
8	1-decene	PFPP	90	2300	3.6	95
8	1-octene	$C_8F_{17}H$/Tol.	60	3600	3.0	95
8	1-dodecene	$C_8F_{17}H$/Tol.	60	2600	3.0	94
8	2-decene	$C_8F_{17}H$/Tol.	90	1200	–	82
8	4-decene	$C_8F_{17}H$/Tol.	150	440	–	77
8	cyclohexene	$C_8F_{17}H$/Tol.	–	45	–	100

Conditions:
[Rh(acac(CO)$_2$)] (10 mg, 0.039 mmol), phosphite (0.194 mmol), alkene (77.4 mmol), solvent (15 cm^3: pure fluorous solvent or 10 cm^3 $C_8F_{17}H$ and 10 cm^3 toluene), undecane (1.21 g), 80 °C, 4 MPa CO/H_2 (1 : 1).

a) Time required to reach 100% conversion.

b) TOF = initial turnover frequency: moles of alkene converted per mole Rh per hour.

The asymmetric hydroformylation of styrene catalyzed by the (*S*,*R*)-**10**/Rh complex was briefly investigated in various fluorous solvents with or without toluene. The nature of the solvent has no significant effect on the catalytic activity of the catalyst. While the regioselectivity was slightly higher than that observed in organic solvent (*l*/*b* ratio: 94 : 6 vs. 88 : 12), the enantioselectivity was lower (87 vs. 94%) and an apparent racemization was observed in the course of the reaction [11].

The results obtained with *ortho*-substituted phosphites differ from those of *meta* or *para* counterparts by a remarkably higher initial rate under the same conditions. At the same time, they lead to a more modest *l*/*b* ratio and aldehyde selectivity. This difference is probably related to the fact that with the former bulky phosphites, only one phosphite coordinates to the Rh center to give the active species $HRhL_f(CO)_3$ (L_f = fluorous phosphite) [14]. In contrast with the latter phosphites which are less sterically demanding, two phosphites are bonded to rhodium $[HRhL_{f2}(CO)_2]$ as in the classical triphenylphosphine-modified catalyst. Complex $HRhL_f(CO)_3$ is more prone to CO dissociation than $HRhL_{f2}(CO)_2$, resulting in a much higher reaction rate. Due to the large space available with the $HRhL_f(CO)_3$ system in comparison with $HRhL_{f2}(CO)_2$, the reactions giving the branched aldehyde as well the β-H elimination proceed with relative ease, resulting in modest linearity and aldehyde selectivity.

An other important finding is the high *l*/*b* ratio observed with *meta*- and *para*-phosphites **2** and **3**. Electron-withdrawing groups attached to the aryl rings of these phosphites afford less basic ligands. Consequently, the electron density on complex $HRhL_{f2}(CO)_2$ decreases, which promotes the olefin insertion on its terminal carbon, giving a linear alkylrhodium intermediate leading to the linear aldehyde. On the other hand, a decrease in the electronic density on the metal also favors the CO dissociation and hence the formation of low-coordination alkylrhodium species, which induce easier β-H elimination and thus olefin isomerization [15].

In the case of phosphites **5** and **6**, the combination of the steric and electron withdrawing effects greatly promotes the β-H elimination, leading to a very low aldehyde selectivity.

Investigations into the recovery and re-use of the catalytic system have been made with phosphites **1b**, **2b**, and **6** on the one hand and with phosphites **7**, **8**, and **9** on the other hand. Figure 1 shows the evolution of the conversion for four reaction cycles with phosphites **1b**, **2b** and **6**. With each phosphite, the activity decreased after each re-use but whereas the decrease was moderate in the case of *ortho*-substituted phosphites **1b** and **6**, in the case of **2b** the activity fell dramatically after the second cycle and practically no activity was observed during the fourth run. Concomitantly, the *l*/*b* ratio and the aldehyde selectivity decreased after the first run with phosphite **2b** while they remained practically unchanged with **1b** and **6**.

In the case of phosphites with a spacer group (Figure 2), the activity was maintained or even slightly increased (with phosphite **8**) during the three first cycles. On the other hand, the conversion dropped dramatically during the course of the fourth cycle with *ortho*-substituted phosphite **7**. This decrease in activity that was more important than expected according to the high partition coefficient of the phosphites, and the variation of the *l*/*b* ratio observed during the recovery

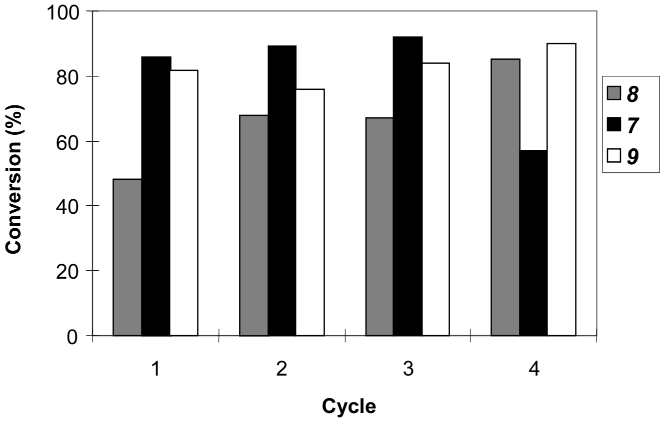


Figure 1 Hydroformylation of styrene: conversion after each of first four cycles with catalyst ligands **1b**, **2b**, and **6**.

experiments, have been interpreted by considering that the phosphites are not stable in the reaction medium. Different modes of decomposition could be envisaged for the fluorous phosphites. The main ones include hydrolysis by water produced by aldehyde condensation, nucleophilic attack on aldehyde, and oxidative cyclization with aldehydes [16, 17]. Aldol condensation of aldehydes could give traces of water that could react with phosphite but no evidence of formation of the expected aldol products was found by GC-MS [12]. To estimate the extent of the other modes of decomposition, the stability of various fluorous phosphites has been studied under hydroformylation reaction conditions. A sample of each phosphite was heated in a mixture of 1-decene/$C_8F_{17}H$ (1 : 1, v/v) or in mixture of 1-decene/undecanal/$C_8F_{17}H$ (1 : 1 : 1, v/v/v). ^{31}P NMR analyses of the fluorous phase after 1 h showed that in the absence of aldehyde, all phosphites remained unchanged. In contrast, in the

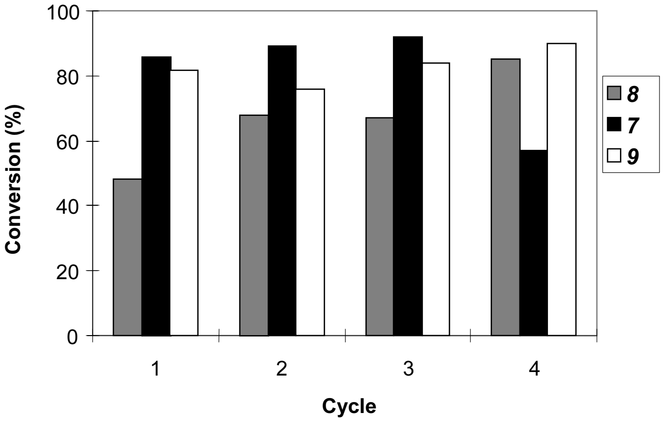


Figure 2 Hydroformylation of styrene: conversion after each of first four cycles with catalyst ligands **7**, **8**, and **9**.

presence of undecanal, a large proportion of the *para*- and *meta*-substituted phosphites **2b** and **8** were converted into oxidation products (30% and 50% of decomposition, respectively) whereas bulky *ortho*-substituted phosphites **1b**, **7**, and **9** appeared more stable (3%, 20%, and 20% of decomposition, respectively) [13]. The decrease in the ligand concentration due to the attack of the phosphites by aldehydes explains the change in *l*/*b* ratios and the aldehyde selectivity observed with some phosphites. Nevertheless, due to the good stability in particular of phosphites **1b** and **6**, other parameters can be taken into account to explain the decrease in activity observed with these ligands [6, 13].

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4.2.4
Fluorous Nitrogen Ligands

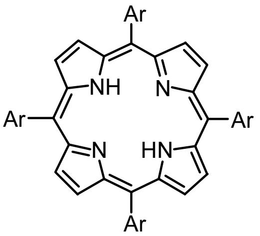
4.2.4.1
For Oxidation Reactions

Gianluca Pozzi and Silvio Quici

Selective oxidation reactions catalyzed by transition metal complexes of organic ligands under homogeneous conditions have been the subject of intensive investigations [1] including the titanium-mediated asymmetric epoxidation of allylic alcohols [2]. Nevertheless, two major issues still prevent a widespread application of most of these homogeneous catalytic systems: (a) considerable synthetic efforts are often required for the preparation of suitable organic ligands and (b) the corresponding catalytically active complexes suffer from limited stability in the oxidative environment. Immobilization on organic polymers or inorganic supports represents the most obvious and explored strategy for increasing the lifetime of homogeneous oxidation catalysts and possibly recycling them after reaction completion [3]. In addition, water-soluble organometallic oxidation catalysts have been tested under aqueous–organic biphasic conditions [4, 5], and evidence for some positive effects related to the use of alternative reaction media such as ionic liquids [6], supercritical CO_2, or CO_2-expanded solvents [7] has been presented recently (cf. Chapters 2–6).

Fluorous biphasic (FB) techniques are particularly suited to oxidation reactions, where the substrates are converted to products of greater polarity, in that these are very easily expelled from the fluorous phase [8]. This fact, together with the thermal and chemical inertness of perfluorocarbons and the possible improvement of the catalyst stability due to its confinement in the fluorous phase, made catalytic oxidation reactions one of the first and most appealing targets of fluorous chemistry [9]. In this short review, complementary to the contribution of Vincent et al. (see Section 4.6), attempts at using the FB approach in the case of oxidation reactions catalyzed by metal complexes of bi- and polydentate nitrogen ligands will be highlighted, with emphasis on the epoxidation of alkenes, the aerobic oxidation of alcohols to carbonyl compounds, and the oxidation of organic sulfides to sulfoxides and/or sulfones.

Metal complexes of fluorous tetraarylporphyrins (**1**–**5**) have been used as catalysts in the epoxidation of alkenes under FB [9] or more traditional conditions [10], depending on their affinity for perfluorocarbons. Free base porphyrins 1–**5** were readily metallated with transition metal cations under standard conditions normally employed for their nonfluorous counterparts. In particular, porphyrins **1**–**4** were metalated with $Mn(OAc)_2 \cdot 4\,H_2O$ in boiling DMF to give their respective Mn(III) complexes **Mn-1**–**Mn-4** [10], whereas the perfluorocarbon-soluble porphyrin **5** was similarly converted into the cobalt(II) complex **Co-5** by treatment with $Co(OAc)_2 \cdot 4\,H_2O$ [9].



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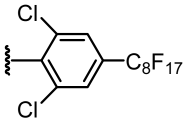

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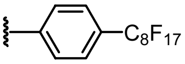

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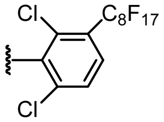

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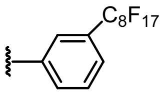

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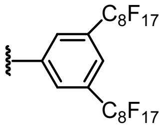


Complexes **Mn-1**–**Mn-4** (< 60% F) were investigated under aqueous–organic biphasic conditions by using NaOCl or 30% H_2O_2 as oxygen donors [10]. Cyclooctene and 1-dodecene were used as models of reactive and poorly reactive alkenes, respectively, whereas the robust complex {Mn(III)-[5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin]} chloride (**Mn-6**) was used as reference catalyst (Table 1). Computational studies, taking into account electronic effects, indicated that the introduction of R_F substituents on the *meso*-phenyl rings should improve the ligand

Table 1 Catalytic epoxidation of alkenes by aqueous NaOCl at pH = 10.[a)]

Entry	*Catalyst*	*Substrate*	*Time [h]*	*Yield [%]*	*Selectivity*[b)] *[%]*
1	**Mn-6**	Cyclooctene[c)]	3	80	88
2	**Mn-1**	Cyclooctene[c)]	1	8	95
3	**Mn-2**	Cyclooctene[c)]	1	5	95
4	**Mn-3**	Cyclooctene[c)]	3	35	67
5	**Mn-4**	cyclooctene[c)]	3	90	92
6	**Mn-6**	1-Dodecene	4	33	69
7	**Mn-6**	1-Decene	3	54	80
8	**Mn-6**	Hexadec-1-ene	3	18	45
9	**Mn-4**	1-Dodecene	3	67	96
10	**Mn-4**	1-Decene	3	65	86
11	**Mn-4**	Hexadec-1-ene	3	63	70
12	**Mn-4**	2-Methylundec-1-ene	3	41	41
13	**Mn-4**	1-Methylcyclohexene	4	15	23
14	**Mn-4**	Norbornene	4	60	60

a) Reaction conditions: $T = 0$ °C; solvent = CH_2Cl_2; molar ratio alkene/oxidant/catalyst = 1 : 2 : 0.001.
b) Selectivity = (moles of epoxide)/(moles of substrate converted).
c) Solvent = AcOEt.

stability under oxidizing conditions [11]. The experimental results did not confirm this hypothesis: **Mn-1**–**Mn-4** underwent extensive decomposition and only poor yields in epoxide were obtained. Apparently, factors not considered in computational studies, such as solvation effects and the steric protection provided by the bulky chlorine atoms in the 2,6-positions of the *meso*-aryl rings, prevailed in determining the catalytic activity. Nevertheless, the introduction of R_F substituents coupled with steric protection had a definite positive effect on the course of the epoxidation of terminal alkenes catalyzed by **Mn-4** which gave consistently higher epoxide yields than the reference catalyst **Mn-6**. This effect was particularly marked in reactions carried out in CH_2Cl_2 as the solvent and using aqueous NaOCl as the oxygen donor [10].

The perfluorocarbon-soluble complex **Co-5** (65% F) proved to be an efficient catalyst for the FB epoxidation of alkenes by molecular oxygen and 2-methylpropanal as reducing agent (Table 2) [9]. Reactions were carried out at room temperature under O_2 at atmospheric pressure, by adding a solution of the catalyst in perfluorohexane to a solution of the substrate in CH_3CN containing an excess of 2-methylpropanal and vigorously stirring the resulting biphasic mixture. The epoxide yields varied from 95% for cyclic substrates to 52% for terminal alkenes and the fluorous phase containing the catalyst could be easily separated and re-used at least three times in the case of the oxidation of cyclooctene. Rather interestingly, the FB approach allowed the use of a much higher substrate/catalyst ratio (1000 : 1) than that reported for the oxidation of (other) alkenes with O_2/aldehyde catalyzed by cobalt complexes of standard tetraarylporphyrins (20 : 1) [12]. Moreover, epoxide yields were higher than those obtained in reactions catalyzed by **Mn-4** under optimized aqueous–organic conditions, except for 1-dodecene (entry 2, Table 2, vs. entry 10, Table 1).

Tetraaza-macrocycle **7** was developed as an alternative to the synthetic demanding porphyrin ligands [13]. At the same time, the triaza-macrocycle **8** bearing three R_F substituents was introduced independently by Fish and co-workers [14]. Metal complexes of these ligands provided new FB catalysts for the oxidative functionalization of hydrocarbons in the presence of *t*-BuOOH and O_2. In particular, oxidation of cyclohexene afforded mixtures of 2-cyclohexen-1-one and 2-cyclohexen-1-ol.

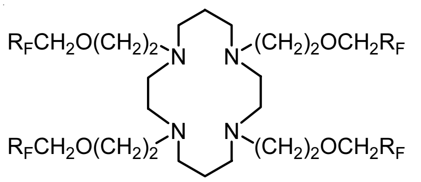
Table 2 FB catalytic epoxidation of alkenes with O_2/2-methylpropanal catalyzed by **Co-5**.[a)]

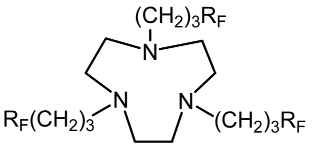
Substrate	*Time [h]*	*Yield [%]*	*Selectivity[b)] [%]*
Cyclooctene	3	95	88
1-Dodecene[c)]	14	52	87
2-Methylundec-1-ene	5	72	90
1-Methylcyclohexene	4	95	95
Norbornene	5	90	95

a) In CH_3CN/perfluorooctane 1 : 1 v/v. Reaction conditions: $T = 25$ °C; molar ratio alkene/aldehyde/catalyst = 1 : 2 : 0.001.

b) Selectivity = (moles of epoxide)/(moles of substrate converted).

c) Using 3-methylbutanal instead of 2-methylpropanal.





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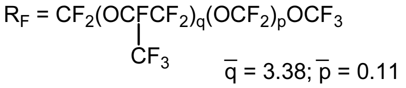
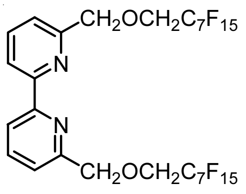


$$R_F = CF_2(OC\underset{CF_3}{F}CF_2)_q(OCF_2)_pOCF_3 \qquad \bar{q} = 3.38;\ \bar{p} = 0.11$$

8 $R_F = CF_2(CF_2)_6CF_3$

Perfluoroalkylated bipyridines **9–11** are readily soluble in some organic solvents, for instance CH_2Cl_2, and were tested in the ruthenium-catalyzed epoxidation of *trans*-stilbene with $NaIO_4$ under aqueous–organic biphasic conditions [15], as previously described for 2,2′-bipyridine [16]. In the presence of this ligand, oxidative cleavage of the carbon–carbon double bond strongly affected epoxidation yields at room temperature. The use of fluorous bipyridines **9–11** reduced the incidence of the side reaction and *trans*-stilbene epoxide was obtained in good yields (70–87%) [15]. Since the fluorous affinity of the ruthenium catalysts generated in situ from **9–11** was found to be higher than that of the free ligands, *trans*-stilbene epoxidation was also studied in an aqueous/organic/fluorous triphasic system at 0 °C. Higher epoxide yields (92–96%) were obtained and the fluorous phase could be re-used without addition of $RuCl_3$ for at least three further runs before the epoxide yields decreased significantly.



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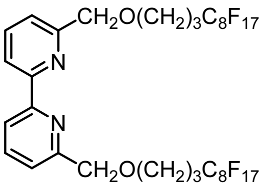

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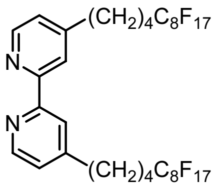

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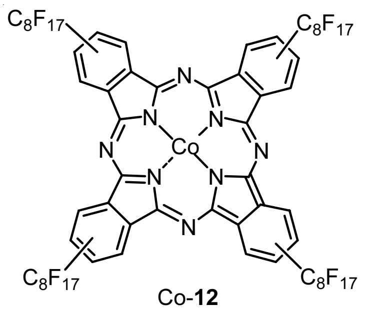
Primary and benzylic alcohols were smoothly oxidized to the corresponding aldehydes by O_2 in the presence of catalytic amounts of 2,2,6,6-tetramethylpiperidin-1-oxyl radical (TEMPO, 3.5%) and a Cu(I) complex (2%) generated in situ from $CuBr \cdot Me_2S$ and bipyridine **11** [17]. Reactions were carried out at 90 °C in a biphasic $C_8F_{17}Br/C_6H_5Cl$ system affording analytically pure aldehydes in 73–96% isolated yield. The recyclability of the catalyst was demonstrated in the case of the oxidation of 4-nitrobenzyl alcohol to give 4-nitrobenzaldehyde: the fluorous phase was re-used eight times with a slight decrease in aldehyde yield (from 93% to 86%) and no apparent decrease in reaction rate. Secondary alcohols also underwent oxidation to the corresponding ketones under fluorous biphasic conditions [17, 18]. Reaction rates and yields were comparable to those observed with primary alcohols in the case of benzylic, allylic, and cyclic substrates, but in general secondary alcohols were less easily oxidized and higher amounts of TEMPO (up to 10%) were required in order to achieve fast reactions. Sterically hindered secondary alcohols were particularly hard to oxidize and incomplete conversions were observed even using 10% TEMPO. This allowed the selective oxidation of the less sterically hindered isomer in *cis–trans* mixtures of 2-, 3- and 4-substituted cyclohexanols and the easy separation of the unreacted isomer by column chromatography [18].

The first example of FB oxidation of sulfides dates back to 1995: dibenzothiophene and diphenyl sulfide gave the corresponding sulfones in low yields (1.4% and 10%, respectively) upon treatment with O_2 at 100 °C in the presence of a not fully characterized perfluorocarbon-soluble iron–phthalocyanine [19]. Following this earlier report, Co(II)–tetraarylporphyrin **Co-5** and Co(II)–phthalocyanine **Co-12** (cf. Structure) were tested as catalysts for the FB oxidation of methyl phenyl sulfide and *para*-substituted aryl methyl sulfides with O_2 and a sacrificial aldehyde (Table 3) [20].



Co-**12**

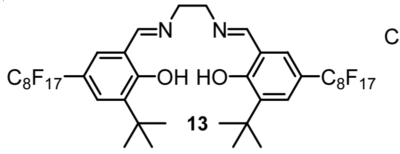
Turnover numbers comparable to those obtained in similar FB oxidations catalyzed by nickel complexes of fluorinated 1,3-diketones were observed [21]. Sulfoxides were usually obtained in good yields (50–100%) and selectivities (> 90%) together with variable amounts of sulfones. The latter were the major products both in the oxidation of *p*-nitrophenyl methyl sulfide and *p*-methoxyphenyl methyl sulfide catalyzed by **Co-5**. The absence of any definite relationship between the electronic properties of the *para* substituents and selectivity ruled out the hypothesis of a heterolytic reaction mechanism involving the formation of high-valent oxometal species. Moreover, the addition of a free-radical scavenger was found to inhibit the oxidation process, thus suggesting that acyl and peroxyacyl radicals generated by the action of the cobalt complexes on the sacrificial aldehyde were the true oxidizing agents. As a consequence of the peculiar reaction environment, both **Co-5** and **Co-12** were progressively bleached and the effectiveness of their recycling was limited.

Formation of high-valent oxometal species from (salen)metal complexes and iodosylbenzene (PhIO) and the mechanism of the oxygen transfer from these species to alkyl aryl sulfides have been investigated in detail [22]. Fluorous salen ligands **13** and **14** were synthesized and the corresponding (salen)manganese(III) complexes **Mn-13** and **Mn-14** were evaluated in the oxidation of alkyl aryl sulfides with PhIO under homogeneous and FB conditions, respectively [23].

Table 3 Catalytic oxidation of aryl methyl sulfides with O_2/2,2-dimethylpropanal under FB conditions.[a)]

Catalyst	*Substrate*	*Conversion [%]*	*Selectivity*	
			Sulfoxide [%]	*Sulfone [%]*
Co-5	$PhSCH_3$	82	90	10
Co-5	*p*-$CH_3OPhSCH_3$	100	0	100
Co-5	*p*-CH_3PhSCH_3	100	94	6
Co-5	*p*-$ClPhSCH_3$	67	100	0
Co-5	*p*-$FPhSCH_3$	100	95	5
Co-5	*p*-NO_2PhSCH_3	100	10	90
Co-12	$PhSCH_3$	68	100	0
Co-12	*p*-$CH_3OPhSCH_3$	59	100	0
Co-12	*p*-CH_3PhSCH_3	40	100	0
Co-12	*p*-$ClPhSCH_3$	58	100	0
Co-12	*p*-$FPhSCH_3$	49	100	0
Co-12	*p*-NO_2PhSCH_3	100	15	85

a) In CH_2Cl_2/perfluorooctane (1 : 1 v/v).
Reaction conditions: $T = 20$ °C; $t = 4$ h; molar ratio sulfide/aldehyde/catalyst = 1 : 1 : 0.001.



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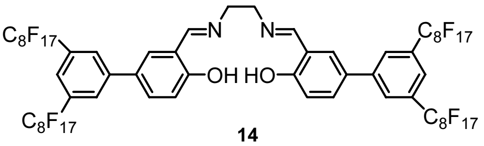

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Both complexes were able to catalyze the oxidation of *p*-substituted methyl phenyl sulfides at a substrate/catalyst molar ratio of 100, with good sulfoxide selectivities (≥ 90%). It should be noted that FB reactions catalyzed by **Mn-14** consistently afforded higher sulfoxide yields than homogeneous reactions catalyzed by **Mn-13** (Table 4). Moreover, three consecutive recyclings of the fluorous layer were performed with no appreciable loss of catalytic activity and selectivity.

Table 4 Catalytic oxidation of aryl methyl sulfides with PhIO catalyzed by achiral (salen)manganese(III) complexes.[a)]

Catalyst	*Substrate*	*Conversion [%]*	*Selectivity*	
			Sulfoxide [%]	*Sulfone [%]*
Mn-13[b)]	$PhSCH_3$	70	91	9
Mn-13[b)]	*p*-$BrPhSCH_3$	59	91	9
Mn-13[b)]	*p*-NO_2PhSCH_3	64	88	12
Mn-14[c)]	$PhSCH_3$	95	95	5
Mn-14[c)]	*p*-$BrPhSCH_3$	87	96	4
Mn-14[c)]	*p*-NO_2PhSCH_3	100	95	5

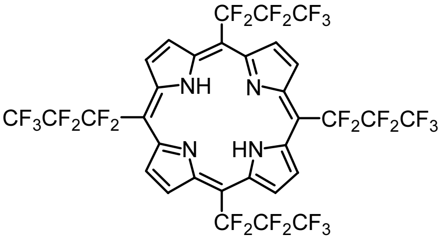
a) Reaction conditions: $T = 25$ °C; $t = 5$ h; molar ratio sulfide/oxidant/catalyst = 1 : 1 : 0.01.

b) Homogeneous conditions (CH_2Cl_2/CH_3CN 1 : 1 v/v).

c) FB conditions (CH_3CN/perfluorooctane 1 : 1 v/v).

Oxidation of unsaturated compounds with singlet oxygen ($^1O_2$) has been extensively studied because of its considerable synthetic interest [24]. Dye-sensitized photooxidation of triplet oxygen is a practical method for generation of the labile $^1O_2$ reagent on the laboratory scale. However, the presence of the dye and/or of its decomposition derivatives in the final reaction mixture can complicate the purification of the desired organic products. Another point to be considered is the choice of solvent, which must readily dissolve O_2, ensure a relatively long lifetime for the generated $^1O_2$, and be inert to this reagent. Perfluorocarbons fulfill all these requirements and have been used as alternative medium for the photooxidation of alkenes to give hydroperoxides, in the presence of tetraphenylporphyrin (TPPo) dissolved in pyridine as a sensitizer [25]. The biphasic mixture was irradiated while maintaining a constant supply of O_2. After reaction completion the two layers were separated to give an organic phase containing the hydroperoxide (plus TPPo and its decomposition products) and a fluorous phase free from organic compounds.

The issues of sensitizer degradation and purification of the oxidation products were taken into account by DiMagno et al., who used the electron-deficient fluorous porphyrin **15** (5,10,15,20-tetrakis(heptafluoropropyl)porphyrin) as a sensitizer in the photooxidation of cyclohexene and allylic alcohols in CH_3CN/perfluorohexanes [26].



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In a CCl_4 solution, porphyrin **15** showed increased chemical stability toward $^1O_2$ and hydroperoxides with respect to TPPo. However, physical segregation into the fluorous phase was found to be the most important factor in reducing the incidence of degradation processes. In addition, the FB approach ensured the easy separation of the hydroperoxides from **15** at the end of the reaction. The fluorous layer containing the sensitizer (57–94% of the starting material-depending on reaction conditions) could be re-used without further treatments.

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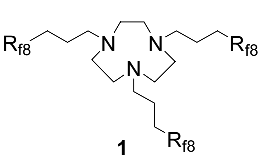
4.2.4.2

Synthesis of Fluorous Nitrogen Ligands and Applications, Including Atom-Transfer Radical Reactions

Jean-Marc Vincent, Dominique Lastécouères, María Contel, Mariano Laguna, and Richard H. Fish

Since the seminal paper in 1994 by Horváth and Rábai that introduced the fluorous biphasic catalysis concept (FBC) [1], numerous examples of this methodology for many classical organic reactions have been demonstrated [1, 2]. Unlike the more classical aqueous/hydrocarbon biphasic systems, water-sensitive reactants can also be employed, with the solubility of organic substrates being higher in the perfluorocarbons than in water; therefore, more favorable reaction kinetics could be expected. Moreover, because of the unique thermomorphic properties of the perfluorocarbon solvents, it is possible under FBC reaction conditions, by judiciously choosing the solvent system, to obtain a homogeneous monophasic solution when elevating the temperature of the reaction mixture, while re-formation of the biphasic system occurs at room temperature. In 1996, we initiated an FBC program at the Lawrence Berkeley National Laboratory with the objective of developing new catalytic systems for alkane/alkene oxidation chemistry. Thus, the FBC process appeared as a very attractive procedure for alkane and alkene functionalization reactions, not only for the ability to recycle the catalyst, but also because of the chemical inertness of the fluorocarbon solvents, and their unique characteristic of solubilizing O_2 in large concentrations.

Nitrogen-containing ligands are widely used in coordination chemistry, particularly in the field of oxidation catalysis [3]. Relatively simple synthetic procedures are available to introduce the fluoro ponytails, making these ligands valuable targets for the development of fluorous catalysis with transition metal complexes. Representative examples of fluorous nitrogen ligands that have been prepared and, for most of them, applied to fluorous catalysis chemistry, are **1–10**.



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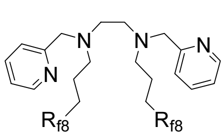

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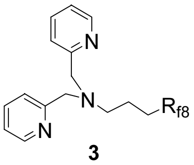

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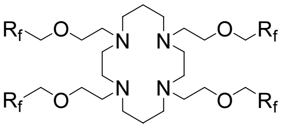

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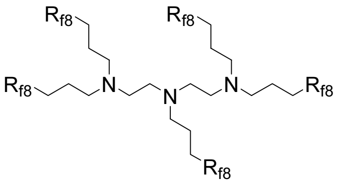

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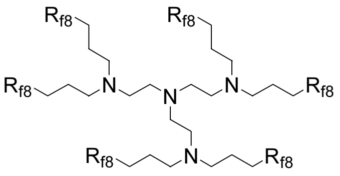

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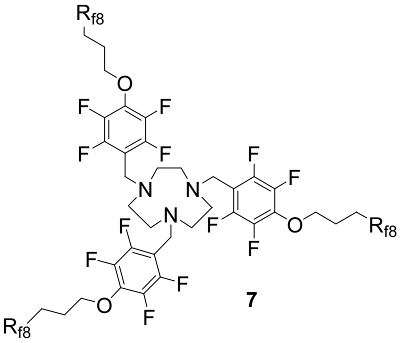

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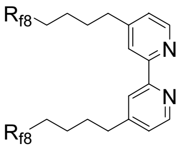

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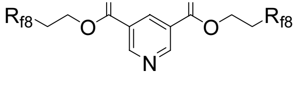

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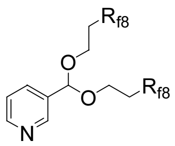

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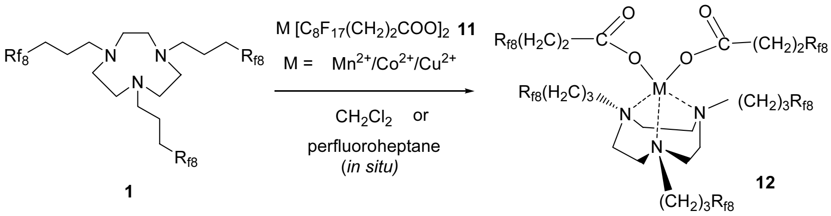
One of the most successful synthetic strategies used to obtain fluorous nitrogen ligands was the direct alkylation of secondary amines (R_2NH) with perfluoroalkyl iodide derivatives, such as $R_{f8}(CH_2)_3I$ ($R_{f8} = C_8F_{17}$) [4, 5]. The three-methylene spacer was necessary, not only to insulate the nitrogen ligating atom from the strong electron-withdrawing effect of the perfluoroalkyl chain, but also to avoid a facile elimination reaction of HI that predominantly occurs during the alkylation step when a two-methylene spacer is used. Ligands **1**, **2**, and **3** were synthesized in fair to good yields (50, 60, and 40%, respectively) by reaction of the corresponding secondary amines with $R_{f8}(CH_2)_3I$ in DMSO/K_2CO_3 at 90 °C [4, 5]. Interestingly, amongst the three ligands mentioned, the 1,4,7-triazacyclononane (TACN) derivative **1** with a fluorine content of 64.2%, was the only ligand found to be soluble in perfluorocarbons at room temperature. Furthermore, tosylate derivatives have also been shown to be effective alkylating agents. The fluorous peralkylated cyclam **4** was obtained in 60% yield by refluxing $R_fCH_2O(CH_2)_2OTs$ in CH_3CN/Na_2CO_3 for 24 h [6]. The tosylate, $R_{f8}(CH_2)_3OTs$, was recently used in our group in Bordeaux for the preparation of the fluorous, peralkylated polyamino ligands **5** and **6** [7]. The alkylations were conducted by refluxing a CH_3CN/K_2CO_3 solution of the diethylenetriamine or tris(aminoethyl)amine with the tosylate (1.1 equiv/amine group) for 48 h; the ligands **5** and **6** were obtained in 65 and 55% yields, respectively. Interestingly, it has been shown that by using $R_{f8}(CH_2)_3I$, instead of the corresponding tosylate, one can not only increase the yield of **5** from 65 to 79%, but also isolate the ligand as a powder rather than an oil. Moreover, an aromatic nucleophilic substitution on the *N*-pentafluorophenyl TACN derivatives was used for the preparation of the fluorous TACN **7** [5]. This reaction proceeds efficiently (yield 80%) by reaction of $R_{f8}(CH_2)_3OH$ in a 50% mixture of NaOH/trifluorotoluene at 85 °C in the presence of a phase-transfer agent. Rather surprisingly, this ligand with three fluoro ponytails and a fluorine content of 58.6% was found to be insoluble in perfluorocarbons at room temperature.

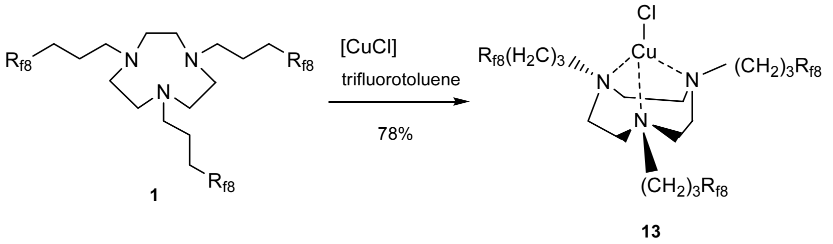
Bipyridines are another important class of nitrogen ligands in coordination chemistry and transition metal catalysis. The fluorous bipyridine ligand **8** was conveniently prepared in 40% yield by reacting the dianion, obtained from 4,4′-dimethyl-2,2′-bipyridine, with $R_{f8}(CH_2)_3I$ at low temperature (78 °C) [8a]. Recent studies in Zaragoza/Berkeley provided full synthetic details and spectroscopic characterization of ligand **8** [8b]. The fluorous pyridine ligand **9** was synthesized in 26% yield by reaction of the pyridin-3,5-diacyl chloride with the alcohol $R_{f8}(CH_2)_2OH$, while the pyridine ligand **10** was prepared in 94% yield from pyridine-3-carbaldehyde and $R_{f8}(CH_2)_2OH$ in the presence of CF_3SO_3H [9].

Above, the parameters necessary to solubilize important nitrogen ligands in fluorocarbon media have been established. In a concomitant manner, important metal complexes that are needed as precatalysts for many classical catalytic reactions require special attention with regard to fluorocarbon solubility, simply because of the polar and/or ionic nature of these complexes. Thus, we found in our experience that, in many cases, the counteranion also needed fluoro ponytails to ensure fluorocarbon solubility, even if the metal ion was coordinated to a fluorous-soluble ligand such as **1**. Therefore, we [4, 5], and Pozzi et al. [6], have addressed this critical aspect by using fluoro-ponytailed carboxylate ligands as counterions for the metal ions of interest [4, 5]. When fluorous metal carboxylates, such as complexes **11** [Eq. (1)], were reacted with fluorous-soluble ligand **1**, either in situ (Mn^{2+} and Co^{2+} complexes in perfluoroheptane) [4, 5], or via isolation and characterization (Cu^{2+} complex, CH_2Cl_2) [8b], to provide precatalysts **12** for alkene, alkane, and alcohol FBC oxidation, the complexes formed were fully fluorocarbon-soluble [Eq. (1)].



(1)

In another example, the reaction of a Cu(I) complex, [CuCl], with ligand R_{f8}-TACN **1**, provided a fully fluorocarbon-soluble complex **13** (fully characterized) [8b], without appended fluoroponytails on the Cu(I) metal ion [Eq. (2)], isolated from trifluoromethylbenzene. This appears to be a general phenomenon with Cu(I) complexes and fluorous ligands, and apparently is predicated on their hydrophobic properties that engender their solubility in hydrophobic solvents, such as fluorocarbons.

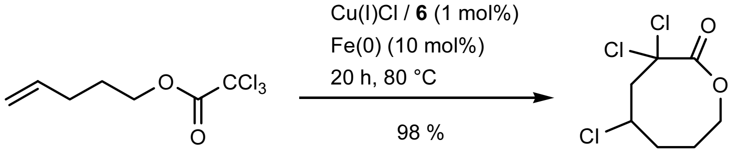


(2)

In 1997, we demonstrated unequivocally, possibly for the first time, that indeed this novel FBC approach for separation of the R_f-Mn^{2+} and Co^{2+} precatalysts from the substrates was viable for oxidation of alkanes and alkenes in the presence of the necessary oxidants, TBHP and O_2 gas [4], soon thereafter Pozzi et al. also verified this FBC oxidation chemistry [6]. The R_f-TACN complexes **12** (eq 1) were found to be particularly effective for allylic oxidation of alkenes; the Cu^{2+} analogue [Eq. (1)] and the Cu(I) complex **13** [Eq. (2)] gave comparable results [8b]. We also provided clear evidence that these FBC oxidation reactions occurred via classical autoxidation mechanisms [4, 5]. The limited scope of the substrates studied also showed that allylic oxidation, for example, cyclohexene to cylohexenol and cyclohexenone, was more favorable than alkane functionalization with cyclohexane as the substrate, based on thermodynamic grounds.

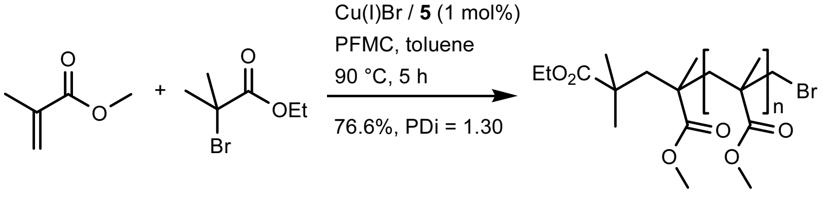
The selective oxidation of alcohols to ketones or aldehydes is a very important transformation in organic chemistry. Using the bipyridine ligand **8** (2 mol%), CuBr · Me_2S (2 mol%), and TEMPO (3.5–10 mol%) under O_2 (0.1 MPa) in biphasic perfluorooctyl bromide/chlorobenzene at 90 °C, various primary and secondary alcohols (aromatic and aliphatic) were oxidized to the corresponding aldehydes and ketones in good to excellent yields [10, 11]. The stability of the catalyst was found to be excellent, with no observed decrease in yield and reaction rate during the oxidation of 4-nitrobenzyl alcohol to the corresponding aldehyde, after eight reaction cycles. Further, the fluorous biphase system consisting of $Pd(OAc)_2$ (5 mol%)/10 (20 mol%), in perfluorodecalin/toluene, under O_2 (0.1 MPa) at 80 °C, was another effective catalytic process for the oxidation of primary and secondary alcohols (aliphatic and aromatic) to aldehydes and ketones [9]. Recycling efficiency was also excellent, the yield of isolated acetophenone after five cycles still being 74%, compared to 98% for the first run. The Zaragoza/Berkeley groups have recently studied the mechanism of the FBC oxidation of 4-nitrobenzyl alcohol to 4-nitrobenzaldehyde at 90 °C (single-phase) with precatalyst R_f-TACN-R_f-Cu^{2+} **12** [Eq. (2)], TEMPO, and O_2, by using EPR techniques [8b]. The EPR spectra clearly defined a Cu(II) to Cu(I) redox reaction, and the role of TEMPO and O_2 in this selective conversion to aldehyde from alcohol. Precatalyst R_f-TACN-R_f-Cu^{2+} [Eq. (2)] was solubilized in perfluoroheptane, and then chlorobenzene, TEMPO, and 4-nitrobenzyl alcohol were added to the reaction mixture. The reaction started at 90 °C in the presence of O_2, and after 30 min, followed by cooling to room temperature, an aliquot was removed from the perfluoroheptane phase and immediately frozen at 77 K in an EPR tube. The EPR spectrum shows a narrow central signal at about $g = 2.006$ that can be associated with the TEMPO radical. This was further demonstrated by measuring this radical in perfluoroheptane at 77 K, together with a Cu(II) signal, with $g_{||} = 2.26(1)$ and $g_{\perp} = 2.06(1)$, $A_{||} = 520(5)$ MHz and $A_{\perp} < 50$ MHz. The behavior of the different signals was in accordance with a mechanism proposed by Semmelhack et al. [12]. After 4 h, a 65% yield of aldehyde had been obtained; however, by leaving the reaction for longer periods of time, a ~100% yield of aldehyde was formed, concomitantly with a full recovery of the initial R_f-Cu(II) complex.

Atom-transfer radical addition (ATRA) is a particularly useful radical process for the preparation of lactones and lactams through metal-catalyzed cyclization of unsaturated trichloro esters or amides [13]. One of the most efficient catalysts for both ATRA and atom-transfer-radical polymerization (ATRP) reactions is the copper(I)/pentamethyldiethylenetriamine complex [14]. The fluorous polyamino ligands **5** or **6**, associated with copper(I) chloride (1 mol%) and iron powder (10 mol%) catalyzed the intramolecular cyclization of the pent-4-enyl trichloroacetate in almost quantitative yields under FBC conditions [Eq. (3)] [7]. By using a ternary solvent system (perfluoroheptane/trifluorotoluene/1,2-dichloroethane), the reaction was carried out under homogeneous conditions at 80 °C, while phase separation occurred at room temperature enabling facile recycling of the catalyst and recovery of the substrate, with only 1–2% of the copper(I) leaching into the organic phase. Ensuring that no oxygen was introduced during the recycling procedure, the yield of lactone, after the fourth run, was still 91%, making the Cu(I)Cl/**5** and Cu(I)Cl/**6** complexes highly efficient and recoverable catalysts for atom-transfer radical reactions.



(3)

ATRP is a transition metal-mediated living radical polymerization of vinyl monomers that is closely related to ATRA, enabling the synthesis of well-defined and complex macromolecular architectures. The major limitation of ATRP is that the polymer is usually contaminated by the colored transition metal catalyst, therefore requiring purification steps such as column chromatography or precipitation of the polymer. Catalysts grafted onto insoluble supports have been developed to lower the copper content of the final product and for recycling [15]. However, heterogeneous supported catalysts are less efficient than their homogeneous analogues, leading to broader polydispersity (PDi = 1.4–1.5) and lower initiator efficiency. Lower polydispersity and higher recycling efficiency were observed using copper(I) catalysts immobilized on polyethylene-*block*-poly(ethylene glycol), a polymer soluble in toluene above 70 °C but insoluble at room temperature [16]. Using the catalytic system, CuBr/**5**, and ethyl 2-bromoisobutyrate as the polymerization initiator, Haddleton and co-workers have shown that living radical polymerization of methyl methacrylate can be carried out very efficiently under FBC conditions [Eq. (4)] [17]. Interestingly, PMMA was also obtained as a colorless solid after separation of the upper hydrocarbon phase and removal of the volatiles. The catalyst was recycled twice with similar results in terms of kinetics and polydispersity, making this FBC system very attractive for further applications.



(4)

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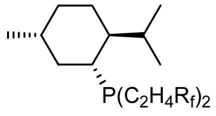
4.2.5
Enantioselective Catalysis

4.2.5.1
Under Biphasic Conditions

Denis Sinou

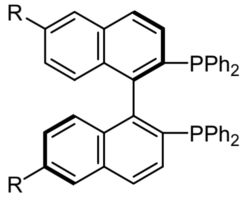
Since the mid-1980s there have been very important advances in asymmetric synthesis via the use of a soluble chiral organometallic catalyst [1]. Although homogeneous organometallic catalysts have many advantages over their heterogeneous counterparts (higher activities and selectivities, mild reaction conditions), one of the major problems is the separation of the products from the soluble catalyst, which is generally a costly and toxic transition metal; this is particularly important for industrial applications. A possible solution to this problem is the heterogenization of the chiral homogeneous catalyst on an inorganic or organic support [2] (see Chapter 7). Another approach is the use of a liquid–liquid two-phase system, the chiral catalyst being immobilized in one phase, the reactants and the products of the reaction being in the other phase. Aqueous–organic systems have been successfully applied [3], and other two-phase systems such as ionic liquids [4] or perfluorohydrocarbons [5] in combination with an organic phase have also been proposed. This section will focus on enantioselective catalysis performed under biphasic conditions, one phase being a fluorous solvent. Catalytic reactions performed in fluorous biphasic systems can effectively show several advantages over classical homogeneous systems or even two-phase systems. One of them is the easy product separation by simple work-up techniques of liquid–liquid extraction, due to the low miscibility of fluorous solvents with common organic solvents, and so the recycling of the catalyst. Moreover, warming the mixture renders the organic and fluorous phases miscible, allowing the reaction to occur under homogeneous conditions [5], and so solving the problems of mass transfer between the two phases. Some examples performed in homogeneous systems, followed by separation of the fluorous catalyst or ligand via extraction with a fluorous solvent, will also be presented, although separation of organic and fluorous compounds by solid-phase extraction with fluorous silica gel is excluded.

The catalytic asymmetric reduction of unsaturated compounds is now a well used methodology in organic synthesis. Enantioselectivities higher than 95% have been obtained using molecular hydrogen from hydrogen donors in the presence of various chiral organometallic complexes [1]. If the asymmetric hydrogenation has been successfully extended to the two-phase water–organic solvent system using water-soluble catalysts [3], the observed enantioselectivities are generally lower than those obtained in the usual homogeneous systems. As phosphorus-based ligands have been extensively used in catalytic hydrogenation, many efforts have been devoted to the synthesis of their fluorous analogues. Klose and Gladysz [6] described the synthesis of the chiral ligand **1** derived from menthol, without any application in catalysis. More recently, a fluorous analogue of BINAP, **2a**, was synthesized by Hope's group [7] and used as a ligand of ruthenium in the asymmetric hydrogenation of dimethyl itaconate; although enantioselectivity up to 95% *ee* was obtained, quite similar to that observed using the original Ru–BINAP complex, recycling of the catalyst was not possible.



$R_f = C_6F_{13}$ or C_8F_{17}

1

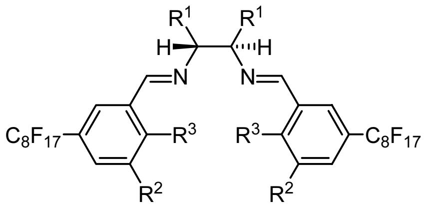


2

a : R = $C_2H_4C_6F_{13}$; **b** : R = $Si(C_2H_4C_6F_{13})_3$

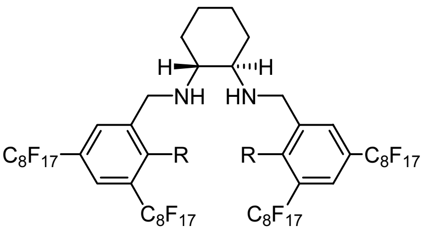
Asymmetric transfer hydrogenation of ketones in the presence of soluble transition metal catalysts has been developed [8–10], enantioselectivities up to 99% *ee* being obtained using a ruthenium catalyst bearing mono-*N*-tosylated diphenylethylenediamine as a ligand. Iridium complexes associated with fluorous chiral diimines **3a**–**3c** or diamines **4a**–**4b** have also been shown to be effective catalysts in hydrogen-transfer reduction of ketones [11, 12].

Enantioselectivities up to 56% *ee* were obtained using $[Ir(COD)Cl]_2$ associated with fluorous diimines **3a**–**3c** at 70 °C in the reduction of acetophenone with isopropanol as the hydride source in the presence of Galden D-100 (mainly *n*-perfluorooctane, b.p. 102 °C) as the fluorous solvent. The hydrogen-transfer reduction was extended to other ketones, enantioselectivity of 60% *ee* being obtained



3

a : R^1,R^1 = -$(CH_2)_4$- , R^2 = C_8F_{17} , R^3 = OH
b : R^1 = C_6H_5 , R^2 = *t*-Bu , R^3 = OH
c : R^1,R^1 = -$(CH_2)_4$- , R^2 = C_8F_{17} , R^3 = H

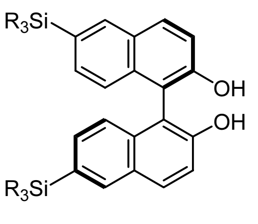


4

a : R = OH ; **b** : R = H

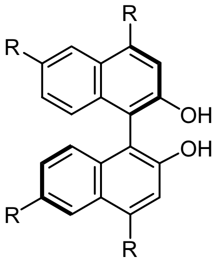
for ethyl phenyl ketone, for example. However, recycling of the catalyst gave lower activity and enantioselectivity, iridium leaching being very high. In order to circumvent the problem of the recycling of the fluorous catalyst, the chiral fluorous diamines **4a**–**4b**, obtained by reduction of **3a** and **3c**, were used as ligands of $[Ir(COD)Cl]_2$ in the reduction of acetophenone in the two-phase isopropanol/Galden D-100 system. While ligand **4a** gave low enantioselectivity (23% *ee*) and a very high iridium leaching (51%) in the organic phase, ligand **4b** gave enantioselectivity up to 69, 79, 59, and 58% *ee* for the first, second, third, and fourth cycle, respectively, the iridium leaching being pretty low (less than 4%).

The asymmetric 1,2-addition of diethylzinc to aromatic aldehydes catalyzed by a BINOL–Ti complex occurs with enantioselectivity up to 97% *ee* [13, 14]. Different groups reported the enantioselective carbon–carbon bond formation in a fluorous biphasic system using a titanium–fluorous-BINOL complex. Various chiral fluorous-BINOL ligands **5**, **6**, and **7**, bearing two $-Si(C_2H_4C_6F_{13})_3$ or $-Si(C_2H_4C_8F_{17})_3$ chains [15–17], four C_4F_9 or C_8F_{13} chains [18, 19], or two $-C_2H_4C_6F_{13}$ or $-C_2H_4C_8F_{17}$ chains [20], respectively, have been used in this reaction.



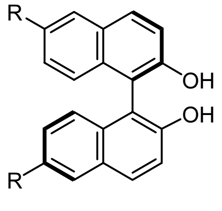
***(R)*-5**

a : R = $C_2H_4C_6F_{13}$
b : R = $C_2H_4C_8F_{17}$



***(R)*-6**

a : R = C_4F_9
b : R = C_8F_{17}



***(R)*-7**

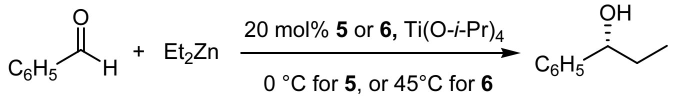
a : R = $C_2H_4C_6F_{13}$
b : R = $C_2H_4C_8F_{17}$

Takeuchi and collaborators reported the condensation of benzaldehyde with Et_2Zn at 0 °C in the presence of the complex prepared in situ by mixing $Ti(O\text{-}i\text{-}Pr)_4$ and fluorous BINOL **5** [15–17]. When the reaction was performed in a toluene/hexane/

Table 1 Condensation of benzaldehyde [Eq. (1)].

Ligand	*Solvent*	*Yield [%] (cycle)*	*ee [%] (cycle)*	*Recovery of ligand [%] (cycle)*
5a	Toluene/hexane/FC-72 (3 : 3 : 5)	81 (1), 89 (2), 87 (3), 87 (4), 87 (5)	83 (1), 82 (2), 82 (3), 81 (4), 80 (5)	10 (1), 12 (2), 12 (3), 11 (4), 10 (5)
5a	Toluene/FC-72 (3 : 5)	85 (1), 85 (2), 80 (3)	78 (1), 78 (2), 77 (3)	< 1 (1), < 1 (2), < 1 (3)
5b	Toluene/hexane/FC-72 (1 : 1 : 2)	82 (1), 82 (2), 77 (3)	79 (1), 78 (2), 78 (3)	1 (1), 1 (2), 1 (3)
6a	$C_{11}F_{20}$/hexane (1 : 0.7)	98 (1), 99 (2), 99 (3), 95 (4), 76 (5)	41 (1), 53 (2), 31 (3), 15 (4), 7 (5)	
6b	$C_{11}F_{20}$/hexane (1 : 0 : 7)	69 (1), 80 (2), 79 (3), 76 (4), 80 (5), 79 (6), 80 (7), 79 (8), 79 (9)	54 (1), 57 (2), 58 (3), 55 (4), 60 (5), 58 (6), 57 (7), 56 (8), 55 (9)	

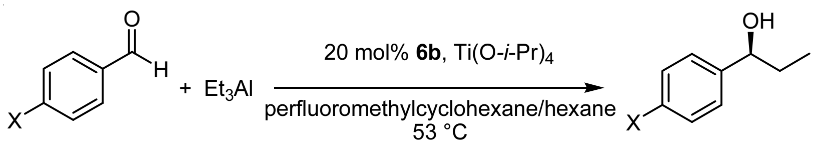
FC-72 system, the enantioselectivity of the obtained alcohol was 80% *ee*, quite similar to that obtained using nonfluorous titanium–BINOL, and remained constant through five consecutive runs, the chemical yield being 80–89%. However, about 10% of the fluorous BINOL was recovered from the organic phase after acidic work-up of the reaction mixture. Since the partial solubilization of the fluorous catalyst in the organic phase was due to the presence of hexane, the use of the fluorous biphasic toluene/FC-72 system gave enantioselectivities up to 78% *ee* (85% yield) and 79% *ee* (82% yield) using ligand **5a** and **5b**, respectively; the enantioselectivity was constant during three consecutive runs, as well as the chemical yields, the leaching of ligand in the organic phase being negligible (less than 1%).



(1)

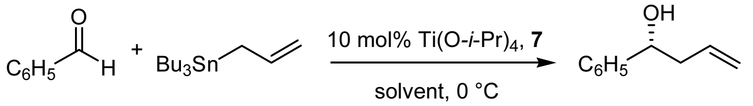
The condensation of Et_2Zn with other aromatic aldehydes in the presence of ligand **5a** or **5b** gave the corresponding alcohols with high enantioselectivity (76–85%) and chemical yields (73–97%). A similar approach was devised by Chan et al. [18, 19], who condensed Et_2Zn with benzaldehyde at 45 °C using the fluorous biphasic system hexane/perfluoromethyldecalin (or $C_{11}F_{20}$) in the presence of the catalyst obtained by mixing Ti(O-*i*-Pr)$_4$ and fluorous BINOL **6** [Eq. (1), Table 1]. When the ligand **6a** was used, the corresponding alcohol was obtained with 98% conversion and 41% *ee*; however, the enantioselectivity of the reaction decreased slowly with the reaction runs, and was lost after six runs. Fortunately, when ligand **6b**, which contains 32 fluorocarbons, was used, the enantiomeric excess of the product (55–60% *ee*) as well as the chemical yields (76–80%) were maintained constant after nine reaction runs. The lower enantioselectivity observed using **6** as the ligand instead of **5** (55–60% *ee* vs. 78–79% *ee*) is probably due to the reaction temperature; in the last case, the critical temperature was 45 °C, lower chemical yield and enantioselectivity being obtained at lower temperature due to the heterogenization of the catalytic system. Similar enantioselectivities as well as chemical yields were obtained in the condensation of Et_2Zn with other aromatic aldehydes in the presence of these ligands **6**, the enantioselectivities remaining constant over three consecutives runs (51–54% *ee* for 4-chlorobenzaldehyde, and 37–40% *ee* for 4-methoxybenzaldehyde).

Chan et al. [19] used ligand **6b** in association with Ti(O-*i*Pr)$_4$ in the condensation of aromatic aldehydes with Et_3Al in the biphasic hexane-perfluoro(methyldecalin) system at 53 °C [Eq. (2)]. Enantioselectivities in the range 76–88% *ee* and chemical yields of 77–82% were obtained during six consecutive runs when fresh titanium was added. When the reaction was extended to the electron-deficient 4-chlorobenzaldehyde, the yield was the same (59–88% for three runs) and the enantioselectivity a little lower (63–79% *ee* for three runs); for the electron-rich 4-methoxybenzaldehyde, only 10% of product was obtained with an enantioselectivity of 38%.



(2)

Zhao and collaborators [20] performed the the condensation of allyltributyltin with benzaldehyde in the presence of the catalyst Ti(O-*i*Pr)$_4$/BINOL **7** in various fluorous biphasic systems [Eq. (3)]. The highest enantioselectivities, up to 90% *ee*, were obtained using the hexane/FC-72 system, the yield being 85%. The ligand was recovered by continuous liquid–liquid extraction and could be re-used in further experiments. The reaction was extended to other aromatic aldehydes; however, only substrates with strong withdrawing groups showed good yields and enantioselectivities, while aldehydes bearing halides or electron-donating groups gave rather poor yields and enantioselectivities.

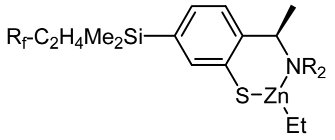


(3)

van Koten et al. [21] synthesized fluorous chiral ethylzinc arene thiolates **8a–8c**. These organometallic complexes are active in the 1,2-addition of diethylzinc to benzaldehyde in hexane, the activity and enantioselectivity being even better than that of the nonfluorous catalyst. Moreover, further experiments showed that they are also active in a two-phase perfluoromethylcyclohexane/hexane medium. The catalyst could be recycled, although a drop in enantioselectivity was observed after two runs: enantioselectivities of up to 92, 92, 76, and 43% *ee* were obtained using ligand **8c** for four consecutive runs [Eq. (4)].

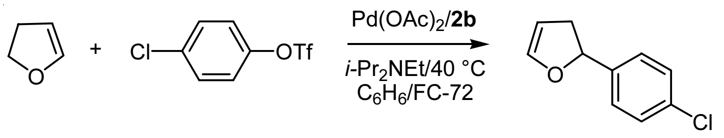
Among the organometallic catalysts used for alkylation and coupling reactions, palladium has a predominant role. Palladium catalysts are used effectively in a

$$C_6H_5\text{-}CHO + Et_2Zn \xrightarrow[C_7F_{14}/\text{hexane (1:1), 15 h, 25 °C}]{2.5\text{ mol\% }\mathbf{8}} C_6H_5\text{-}CHOH\text{-}C_2H_5 \qquad (4)$$



8a : $R_f = C_6F_{13}$, R = Me
8b : $R_f = C_{10}F_{21}$, R = Me
8c : $R_f = C_{10}F_{21}$, R = $-(CH_2)_4-$

large number of useful transformations in organic chemistry [22]. Surprisingly, there are few examples of applications of chiral palladium complexes in the literature. Nakamura et al. [23] carried out the Heck reaction between 2,3-dihydrofuran and 4-chlorophenyl triflate in the presence of $Pd(OAc)_2$ associated with ligand **2b** in the two-phase benzene/FC-72 system [Eq. (5)]; enantioselectivity up to 93% was obtained, the yield being 39%. Unfortunately, recycling of the catalyst was not possible, due probably to its inactivation by ligand oxidation.

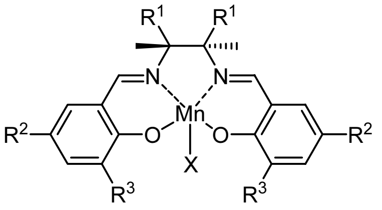


(5)

ee 93%

Palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate with carbonucleophiles occurred using fluorous bisoxazolines as the ligands in benzotrifluoride or CH_2Cl_2 as the solvent with *ee* up to 95% [24]; although recycling of the catalyst was not possible, extraction of the ligand allowed the recycling of the later with the same enantioselectivity.

Pozzi's group has shown that asymmetric epoxidation of prochiral alkenes occurred under fluorous biphasic conditions using various chiral fluorous (salen)-manganese complexes **9** [25, 26]. The chiral (salen)manganese complexes **9a** and **9b**, bearing fluorous alkyl substituents in the 3,3′ and 5,5′ positions in the ligand, were used in the epoxidation of indene in the two-phase CH_2Cl_2/D-100 system in the dark at 20 °C under atmospheric pressure of oxygen in the presence of pivalaldehyde, giving the corresponding epoxide with 83 and 77% yield, and 92 and 90% *ee*, respectively. Recycling of the catalyst was possible without loss of the enantioselectivity: *ee* values up to 89 and 92% were obtained, respectively, in a second run. However, very low enantioselectivities were achieved in the epoxidation of other alkenes, such as dihydronaphthalene and benzosuberene, whose structures are very closed to indene, whatever the oxidant used. More recently, chiral fluorous second-generation Mn(salen) complexes **9c** and **9d** were prepared [27, 28]. These complexes took into account the fact that the low *ee* values observed were probably due to the low steric hindrance ensured by the fluorous substituents at the 3,3′ and 5,5′ positions, as well as their electronic effects. These catalysts were successfully used in the asymmetric epoxidation of dihydronaphthalene system at 100 °C in



9

a : R^1,R^1 = $-CH_2)_4^-$, $R^2 = R^3 = C_8F_{17}$, X = Cl
b : $R^1 = C_6H_5$, $R^2 = R^3 = C_8F_{17}$, X = Cl
c : R^1,R^1 = $-CH_2)_4^-$, $R^2 = R^3 = C_6H_2$-2,3,4-tri$(OC_2H_4C_8F_{17})_3$, X = $OCOC_7F_{15}$
d : R^1,R^1 = $-CH_2)_4^-$, $R^2 = C_6H_2$-2,3,4-tri$(OC_2H_4C_8F_{17})_3$, R^3 = *t*-Bu, X = $OCOC_7F_{15}$

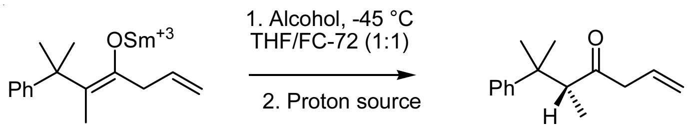
CH_3CN/perfluorooctane in the presence of PhIO/PNO (pyridine *N*-oxide) as the oxidant. For example, in the case of **9d**, the highest yield was obtained above 40 °C (76% yield), although the *ee* increased with increasing temperature, the highest value (50% *ee*) being obtained at 100 °C.

The epoxidation reaction using complexes **9c** and **9d** as the catalysts was extended to other alkenes: benzosuberene, 1-methylindene, 1-methylcyclohexene, and triphenylethylene, affording the corresponding epoxides in 68–98% yields, and 50–92% enantioselectivities, very close to the values obtained by Regen and Jan [29] using a Mn(salen) supported on a gel-type resin. The fluorous catalysts could be recycled efficiently, the same activities and enantioselectivities being maintained for three consecutive runs. The lower activity generally observed for the fourth run was mainly due to the oxidative decomposition of the catalyst.

It should be noted that the corresponding Co(salen) complexes have also been used in the hydrolytic kinetic resolution of terminal epoxides, enantioselectivies up to 99% being obtained; however these complexes were never used in a two-phase system [30].

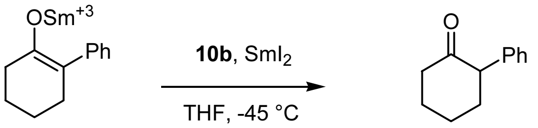
The catalytic enantioselective protonation of a samarium enolate using a C_2-symmetric chiral diol as the catalyst and trityl alcohol as the proton source afforded the corresponding ketone with *ee* up to 93% [31]. The use of (*S*)-2-bis-[(perfluorohexyl)ethyl-2-methoxy-1-phenylethanol (Rfh_2-MPE) and $(C_6F_{13}C_2H_4)_3OH$ (or Rf_3COH) in a biphasic THF/FC-72 system (3 : 4) at –45 °C gave the ketone in 59% yield and 60% *ee*, although the use of **10a** as the chiral proton source increased the enantioselectivity to 89% *ee* [Eqs. (6)–(8)] [32]. This enantioselective protonation was extended to a samarium enolate derived from cyclohexanone in THF using fluorous alcohol **10b** as the proton source [15]; enantioselectivities of up to 89% have been obtained. The fluoro alcohol was recovered quantitatively by a simple extraction with FC-72 and re-used in five consecutive runs without loss of enantioselectivity.

Fache et al. used fluorous cinchona derivatives in asymmetric Diels–Alder reactions in $CHCl_3/C_6F_{14}$ (1 : 1); low enantioselectivity (13%) was obtained [33]. Moreover, due to the low fluorine content of the catalyst (45 wt.% F), the reaction probably occurred in the nonfluorous phase.



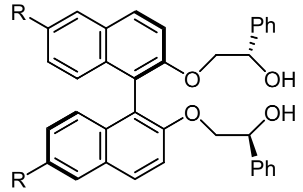
(6)

Rfh_2-MPE 59 % (60 % *ee*)
10a 55 % (89 % *ee*)



(7)

10a : 70 % (87% *ee*)
10b : 73-82 % (81-89% *ee*)



10a : R = H
10b : R = $Si(C_2H_4C_6F_{13})_3$

(8)

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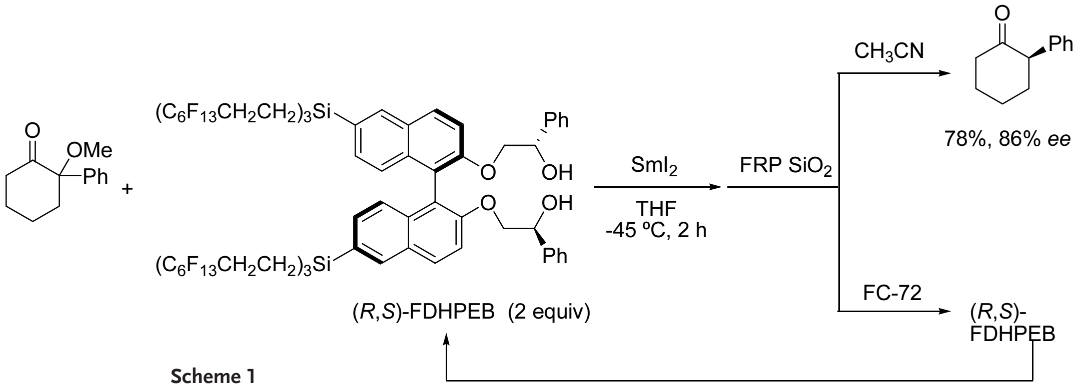
4.2.5.2
Under Non-biphasic Conditions

Seiji Takeuchi and Yutaka Nakamura

Chiral ligands that contain more than 60 wt.% of fluorine atoms are usually fluorous enough to ensure immobilization of the catalysts in a fluorous phase. However, when the fluorous contents of the ligands are much lower than 60%, the solubilities of the ligands and/or catalysts in fluorous solvents decrease significantly. In such cases, asymmetric reactions cannot be carried out in organic and fluorous biphasic conditions but are conducted in common organic solvents or amphiphilic solvents such as benzotrifluoride (BTF). The products and the ligands and/or catalysts are separated from the products for re-use by fluorous liquid–liquid extraction or solid-phase extraction with a fluorous reverse-phase (FRP) silica gel column [1], depending upon the partition coefficients of the ligands or catalysts. Another option for such ligands is to carry out the reactions in supercritical carbon dioxide ($scCO_2$). The catalysts are recycled successfully by separating the products by the $scCO_2$ extraction method.

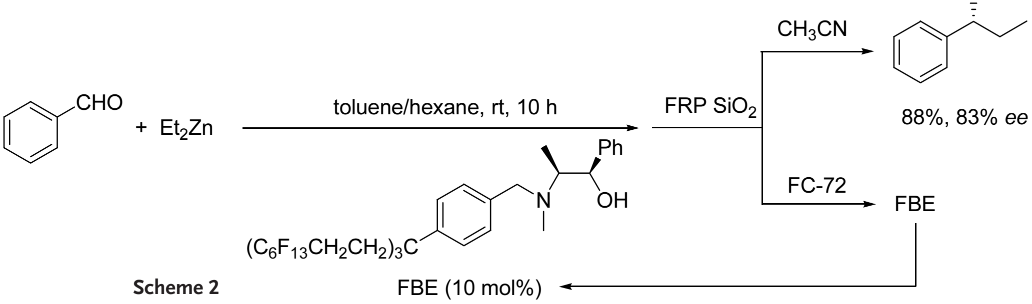
Takeuchi, Curran, and co-workers synthesized a fluorous chiral diol, (*R*)-2,2′-bis[(*S*)-2-hydroxy-2-phenylethoxy]-6,6′-bis[tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)silyl]-1,1′-binaphthyl ((*R*,*S*)-FDHPEB) (F content = 56%, partition coefficient: benzene/FC-72 = 1 : 32, THF/FC-72 = 19 : 1) and applied it to a SmI_2-mediated enantioselective protonation of 2-methoxy-2-phenylcyclohexanone [2]. The reaction was carried out under the same reaction conditions as those of the original nonfluorous reaction [3]. In the original reaction, the product was separated from the nonfluorous chiral proton source (2 equiv realtive to the substrate) with preparative TLC to give the product in 70% chemical yield and 87% *ee*. In the fluorous version, the product and the fluorous chiral proton source were separated by FC-72 extraction (six times) and more simply by fluorous solid-phase extraction with an FRP silica gel column.



Scheme 1

The recovered (*R*,*S*)-FDHPEB was used for the next reaction and the reaction was repeated five times. The average chemical yield and enantioselectivity were 78% and 86% *ee*, respectively (Scheme 1). The recovery of (*R*,*S*)-FDHPEB was quantitative in each run and the recovered (*R*,*S*)-FDHPEB after the fifth reaction showed the same ^{1}H NMR spectrum as that of the pure compound. When the crude product was analyzed by HPLC with CD and UV detectors, the enantioselectivity was found to reach 95% *ee*. The enantiomeric excess was reduced to 87% *ee* owing to partial racemization during purification of the crude product by a preparative TLC. Quick separation of the product from (*R*,*S*)-FDHPEB by FRP silica gel revealed these facts.

Nakamura and co-workers reported an enantioselective addition of diethylzinc to benzaldehyde using a fluorous chiral β-amino alcohol, (1*R*,2*S*)-*N*-[4-tris-(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)silyl]benzylephedrine (FBE) (F content = 56%, partition coefficient: CH_3CN/FC-72 = 12 : 88, toluene/FC-72 = 41 : 59), as a catalyst. The reaction was carried out in toluene by using Et_2Zn in hexane at room temperature [4]. The product was separated from the catalyst by FRP silica gel column and the recovered chiral catalyst was used for the next reaction. The reaction was repeated 10 times and the average chemical yield and enantioselectivity were 88% and 83% *ee*, respectively (Scheme 2). The recovery of the chiral catalyst was almost quantitative in each run and the enantioselectivity and chemical yield did not change significantly throughout the experiments. For an alternative system,

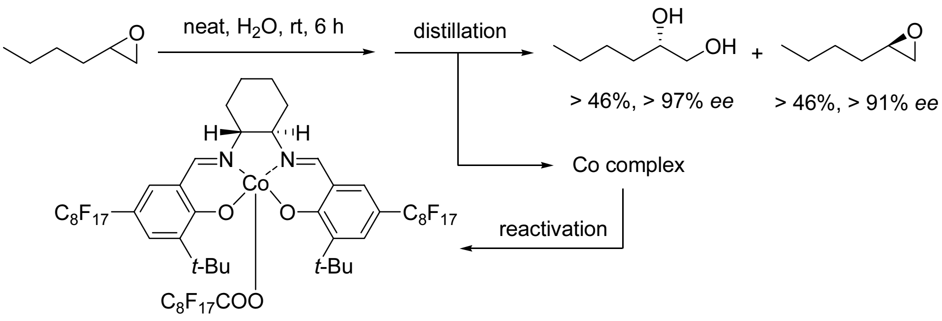


Scheme 2

Soai and co-workers reported that *N*-benzylephedrine, the original source of the fluorous catalyst, and the corresponding polymer-supported compound substituted at the *para* position of benzyl gave the product in 92% *ee* and 89% *ee*, respectively [5]. They recovered another polymer-supported ephedrine catalyst and used it again without any loss in catalytic activity and enantioselectivity (the catalyst being used twice).

In the two reactions described above, the chiral fluorous ligands were recovered quantitatively by FRP silica gel and re-used repeatedly for the reactions. Since no significant drop was observed in chemical yield, enantioselectivity, and recovery throughout the experiments, the reactions can be repeated any number of times until the chiral ligands have been consumed by mechanical losses.

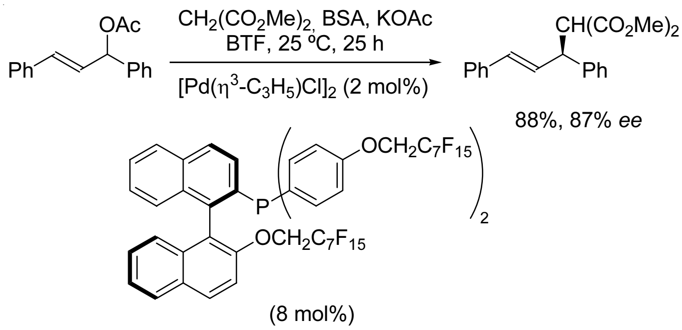
Pozzi et al. used their fluorous chiral salen compounds for the ligands of cobalt(III) complexes in a catalytic hydrolytic kinetic resolution of terminal epoxides [6]. Among them, (1*R*,2*R*)-[*N*,*N*′-bis(3,3′-di-*tert*-butyl-5,5′-diheptadecafluorooctylsalicyliden)-1,2-cyclo-hexanediamine]cobalt(III) (F content = 49%) was most effective for the reaction in the presence of counterion $C_8F_{17}COO^-$. The complex was soluble in neat 1-hexene oxide as well as in common organic solvents such as CH_2Cl_2 and toluene but insoluble in perfluorocarbons at room temperature. Therefore, the reactions were carried out at room temperature without addition of any co-solvent with substoichiometric amount of H_2O under aerobic conditions. In the case of 1-hexene oxide, 1,2-hexanediol and unreacted 1-hexene oxide were isolated by fractional distillation in 47% and 51% chemical yields, respectively, and in enantioselectivities higher than 99% *ee* (in the original nonfluorous reaction, 98% *ee* for the both products at 50% conversion [7]). The nonvolatile residue obtained after the distillation was taken up in toluene and treated with $C_8F_{17}COOH$ in air. The recovered and reactivated catalyst was used for the next reaction and the reaction was repeated four times. Activity of the recovered catalyst was somewhat decreased at the fourth reaction, although the chemical yield and enantioselectivity of the diol were still higher than 46% and 97% *ee*, respectively (Scheme 3). Next, they tried to recycle the catalyst by using fluorous separation methods, liquid–liquid extraction, and solid-phase extraction. *n*-Perfluorooctane, BTF, and CH_3CN were used for the liquid–liquid extraction and the recovered catalyst resulted in 99% *ee* for 1,2-hexanediol although the reaction time was four times longer than the first one. The catalyst



Scheme 3

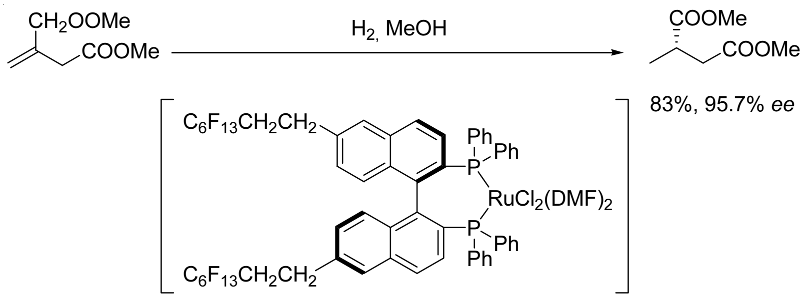
recovered by FRP silica gel provided the product in 99% *ee* but the reaction rate was reduced to one-eighth of the first one.

Pozzi, Sinou, and co-workers prepared a fluorous chiral phosphine, (*R*)-2-{bis[4-(1*H*,1*H*-perfluorooctyloxy)phenyl]phosphino}-2′-(1*H*,1*H*-perfluorooctyloxy)-1,1′-binaphthyl (F content = 52%, partition coefficient: *n*-perfluorooctane/toluene = 0.23, *n*-perfluorooctane/CH_3OH = 7.42) and used for a chiral ligand of palladium complex in an asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate [8]. The reaction was carried out at room temperature in BTF or toluene and gave the corresponding product in 99% and 88% chemical yields and 81% *ee* and 87% *ee*, respectively after the nonfluorous MOP complex gave the product in 95% yield and 99% *ee* in toluene at 0 °C [9]) [Eq. (1)]. When toluene was used as a solvent, the simple extraction of the reaction mixture with *n*-perfluorooctane (twice) allowed the complete removal of the ligand and of the palladium complex. However, the recovered palladium complex did not have catalytic activity for the reaction.



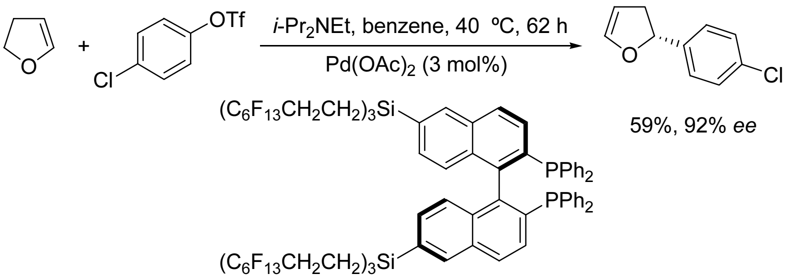
(1)

Stuart and co-workers reported the first synthesis of a “light” fluorous BINAP, (*R*)-6,6′-bis(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (F content = 38%), and its application to a Ru complex catalyzed asymmetric hydrogenation of dimethyl itaconate [Eq. (2)] [10]. The reaction was carried out at ambient temperature under the same reaction conditions as those reported by Noyori [11]. The chemical yield (83%) and enantioselectivity (95.7% *ee*) were similar to those reported (88% and 95.4% *ee*, respectively). However, there was no description of the recovery of the catalyst or ligand.



(2)

Nakamura and co-workers synthesized a heavily fluorinated chiral BINAP, (*R*)-6,6′- bis[tris(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)silyl]-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl ((*R*)- F_{13}BINAP) (F content = 54%, partition coefficient: benzene/FC-72 = 26 : 74, CH_3CN/FC-72 = 2 : 98) and applied it to an asymmetric Heck reaction [12]. The reaction between 2,3-dihydrofuran and 4-chlorophenyl triflate was carried out under the same conditions as those of original nonfluorous reaction by using F_{13}BINAP in BTF or benzene to provide the corresponding product, 2-(4-chlorophenyl)-2,3-dihydrofuran, in 59% chemical yield or in 90% *ee* and 92% *ee*, respectively (71% chemical yield and 91% *ee* in the original reaction in benzene [13]) [Eq. (3)]. The reaction rate was about one-third of that in the original reaction. The products and the fluorous chiral ligand were separated by FRP silica gel and about 70% of the chiral ligand was recovered. However, the compound recovered was F_{13}BINAPO and could not be re-used for the next reaction.



(*R*)-F_{13}BINAP (6 mol%)

(3)

The examples on fluorous chiral phosphine ligands described above indicate that finding a chiral phosphine ligand effective for recycling it by fluorous techniques is still an important challenge.

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4.2.6
Liquid/Solid Catalyst-Recycling Method without Fluorous Solvents

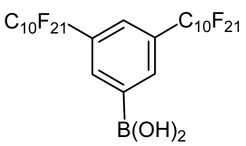
Kazuaki Ishihara and Hisashi Yamamoto

Fluorous biphasic catalysis has emerged since the late 1990s as an attractive alternative to traditional catalysis methods [1]. Fluorous techniques take advantage of the temperature-dependent miscibility of organic and perfluorocarbon solvents to provide easier isolation of products and recovery of a fluorinated catalyst. The large-scale use of fluorous solvents, however, has drawbacks: cost, and concern over environmental persistence.

The fluorous biphasic technique involves dissolving a catalyst with long fluorinated alkyl chains in a perfluorocarbon. The reactants are added to an organic solvent that is immiscible with the perfluorocarbon at room temperature, forming a second phase. On heating, the two phases mix and the reaction occurs; on cooling, the fluorinated and organic layers separate. The organic phase can be removed and the product isolated, while the fluorinated catalyst–solvent phase can be re-used.

In 2001, it has been independently reported [2, 3] that the fluorous solvent can be skipped by designing fluorinated catalysts that themselves have a temperature-dependent phase miscibility – that is, solubility – in ordinary organic solvents.

A direct amide condensation catalyst, 3,5-bis(perfluorodecyl)-phenylboronic acid (**1**) has been developed, which can be recovered without using any fluorous solvents [2]. Arylboronic acids bearing electron-withdrawing substituents on the aryl group behave as water-, acid-, and base-tolerant thermally stable Lewis acids and can be easily handled in air. 3,5-Bis(trifluoromethyl)phenylboronic acid (**2**) and 3,4,5-trifluorophenylboronic acid (**3**) are highly effective catalysts for the amide condensation of amines (1 equiv) and carboxylic acids (1 equiv) [4]. To the best of our knowledge, this is the first example of a catalytic and direct amide condensation which does not require excess amounts of substrates. Most of the above homogeneous catalytic reactions require relatively large quantities of arylboronic acid catalysts (1–20 mol%), and trace amounts of the catalysts must be removed from the reaction products. This hampers the application of this methodology to large-scale syntheses. Therefore, we have designed phenylboronic acids **1** and **4** bearing perfluorinated ponytails based on the direct coupling of fluoroalkyl iodides with halobenzenes. Their fluorous boronic acids can be easily recovered by the fluorous biphasic technique [2].



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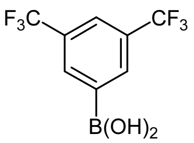

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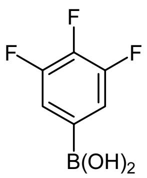

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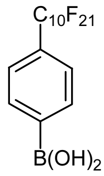


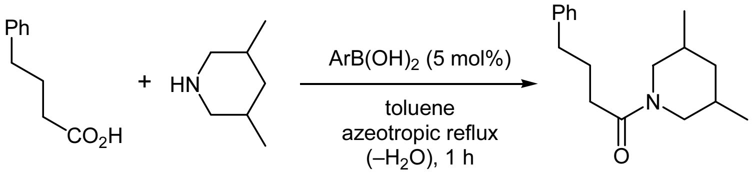
4

Table 1 Catalytic activities and recovery of arylboronic acid for the direct amide condensation.

$ArB(OH)_2$	*Yield of amide [%]*[a]	*Recovery of $ArB(OH)_2$ [%]*[b]
2	59	0
3	60	0
4	39	57
1	47 (95)[c]	> 99
$PhB(OH)_2$	23	0
–[d]	< 2	–

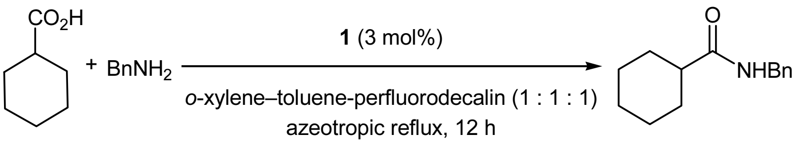
a) Isolated yield.
b) Extraction with perfluoromethylcyclohexane.
c) Yield after heating at azeotropic reflux for 15 h is indicated in parentheses.
d) No catalyst was added.

The catalytic activity of arylboronic acids **1**–**4** (5 mol%), which promote the model reaction of 4-phenylbutyric acid (1 equiv) with 3,5-dimethylpiperidine (1 equiv) in toluene at azeotropic reflux with removal of water (4 Å molecular sieves in a Soxhlet thimble) for 1 h, and their recoverability by extraction with perfluoromethylcyclohexane, are shown in Eq. (1) and Table 1.



(1)

As expected, **1** is more active than **4**, and is recovered in quantitative yield by extraction with perfluoromethylcyclohexane. Although **2** and **3** are more active than **4**, they cannot be recovered by extraction with any fluorous solvents. The amide condensation proceeds cleanly in the presence of 5 mol% of **1**; the desirable amide has been obtained in 95% yield by azeotropic reflux for 15 h. In addition, the corresponding *N*-benzylamide has been obtained in quantitative yield by heating 4-phenylbutyric acid with benzylamine in the presence of 2 mol% of **1** under azeotropic reflux conditions for 4 h. Based on these results, the re-use of **1** has been examined for the direct amide condensation reaction of cyclohexanecarboxylic acid and benzylamine in a 1 : 1 : 1 mixture of *o*-xylene, toluene, and perfluorodecalin under azeotropic reflux conditions with removal of water for 12 h [Eq. (2) and Table 2] [5]. After the reaction has been completed, the homogeneous solution is cooled to ambient temperature to be separated in the biphase mode of *o*-xylene–toluene/perfluorodecalin. The corresponding amide is obtained in quantitative yield from the organic phase. Catalyst **1** can be completely recovered from the fluorous phase and re-used in the recyclable fluorous immobilized phase.



(2)

Table 2 Recovery and re-use of **1** in the recyclable fluorous immobilized phase.[a)]

Cycle[a)]	*1*	*2*	*3*	*4*	*5*[c)]
Conversion [%][b)]	> 99 (99)	> 99	> 99	> 99 (98)	> 99 (99)

a) Reaction conditions: *o*-xylene (2.5 mL), toluene (2.5 mL), and perfluorodecalin (2.5 mL). After the reaction, a solution of the amide in the upper phase was decanted and **1** in the lower phase was recycled successively.

b) Values in parenthesis refer to the isolated yields.

c) Catalyst **1** was recovered in 98% yield from the perfluorodecalin phase.

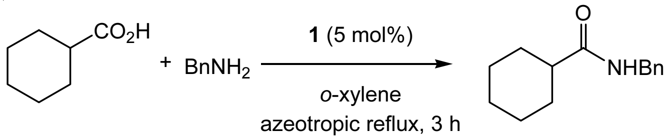
Table 3 Re-use of catalyst **1** for amide condensation of cyclohexanecarboxylic acid with benzylamine.[a)]

Use of 1[b)]	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Conversion [%]	> 99	> 99	> 99	> 99	99	> 99	> 99	> 99	> 99	> 99

a) Reaction conditions: **1** (0.05 mmol), cyclohexanecarboxylic acid (1 mmol), benzylamine (81 mmol), xylene (5 mL). After the reaction, the solution was decanted and the residual catalyst **1** was re-used without isolation (see Scheme 1).

b) Recovered catalyst **1** was used successively (Use 2, 3, 4, ...).

Catalyst **1** is insoluble in toluene and *o*-xylene at room temperature even in the presence of carboxylic acids, amines, and amides. However, the amide condensation catalyzed by **1** proceeds homogeneously under reflux conditions. To demonstrate this advantage of **1** with respect to solubility, we have attempted to re-use **1** (5 mol%) 10 times for the condensation of cyclohexanecarboxylic acid with benzylamine [Eq. (3) and Table 3] [6].

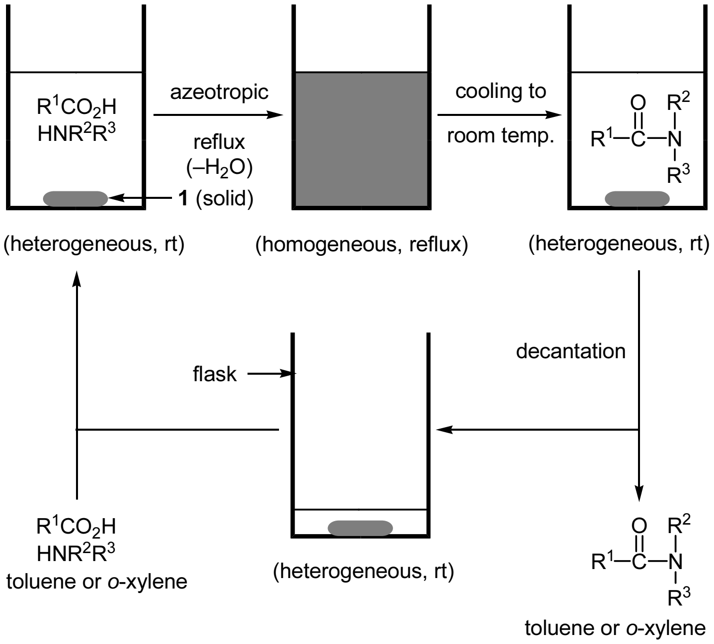


(3)

Total (10 times): 96% isolated yield

After the reaction mixture has been heated at reflux with removal of water for 3 h, it is allowed to stand at ambient temperature for 1 h to precipitate **1** (Scheme 1). The liquid phase of the resultant mixture is decanted and the residual solid catalyst **1** is re-used without isolation. No loss of activity has been observed for the recovered catalyst, and 26% of **1** remains in the flask in the tenth reaction. This means that 88% of **1** has been retained in each cycle. The total isolated yield of the amide which is obtained in 10 reactions is 96%. Moreover, pure compound **1** can be recovered in 97% yield as a white solid from the above reaction mixture by filtration and washing with toluene [6].

Gladysz's group has also reported the temperature-dependent solubility of the solid phosphine catalyst **5** in octane [3]. Between 20–80 and 20–100 °C, **5** exhibits ca. 60- and 150-fold increases of solubility in octane. Although octane is one of the best organic solvents for dissolving nonpolar fluorous compounds, little **5** can be detected at 0 °C by GC (0.31 mM) or ^{31}P NMR. At 20 °C, millimolar concentration

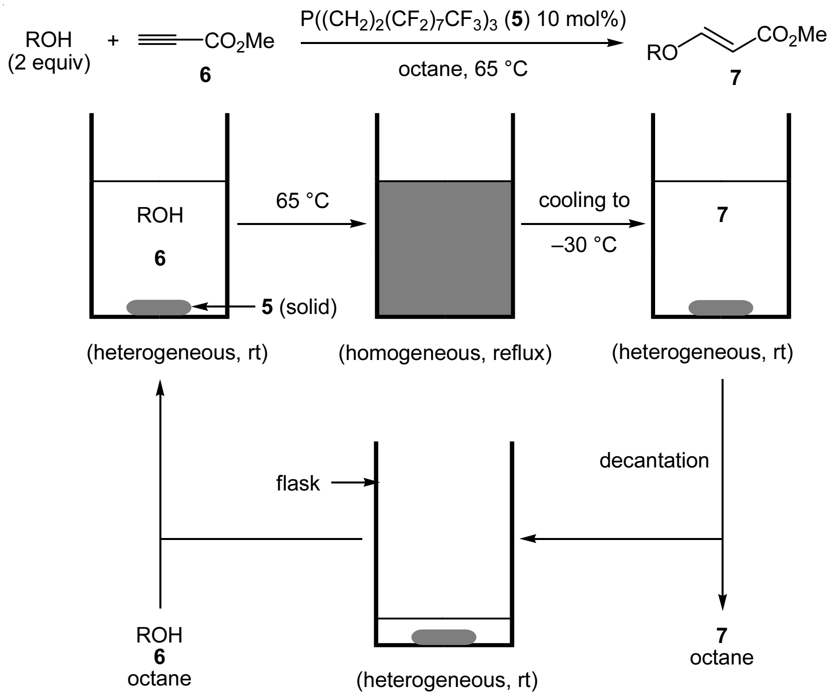


Scheme 1 Recovery of **1** by decantation and its re-use without isolation.

levels are present (1.13 mM, GC; 0.97 mM, NMR). A distinct jump in solubility has been observed near the melting point (19.6 mM, 50 °C), followed by continued increases (63.4 mM, 80 °C; 157 mM, 100 °C). Such a dramatic solubility/temperature dependence suggests an obvious catalyst method. The method has been tested by carrying out a series of additions of alcohols to methyl propiolate (**6**) in octane. Catalyst 5 (10 mol%), benzyl alcohol (2 equiv), and **6** are combined in octane (65 mM in **6**). The sample is kept at 65 °C (8 h) and cooled to –30 °C (arbitrary temperature of a convenient freezer). The precipitated catalyst (in some cases orange-colored) is isolated by decantation. GC analysis of the supernatant indicates an 82% yield of **7**. The recovered catalyst has been used for four further cycles without deterioration in yield, as summarized in Scheme 2.

In a further refinement, Gladysz's group has shown that the above reaction of benzyl alcohol with **6** can be made even greener by not using a solvent at all [3]. Raising the temperature of a mixture of the neat reactants and solid catalyst above the catalyst's melting point of 47 °C yields the addition product. The solid catalyst can be recovered at room temperature and is recyclable with yields consistently above 95%.

We have developed a fluorous super-Brønsted acid catalyst, 4-(1*H*,1*H*-perfluorotetradecanoxy)-2,3,5,6-tetrafluorophenylbis(trifluoromethanesulfonyl)methane (**8**), which can be recycled by applying liquid/solid phase separation without fluorous solvents [8] and an organic-solvent-swellable resin-bound super-Brønsted acid, polystyrene-bound tetrafluorophenylbis(trifluoromethanesulfonyl)methane (**9**) [9].



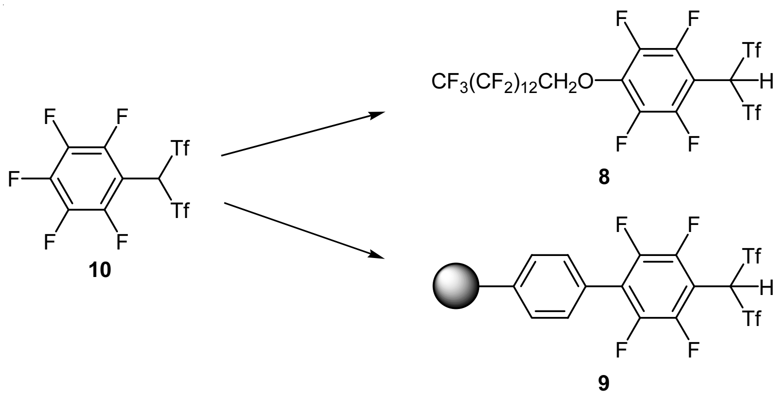
The addition of $PhCH_2OH$ to **6**:

Cycle	1	2	3	4	5
Yield [%]	82	82	80	81	75

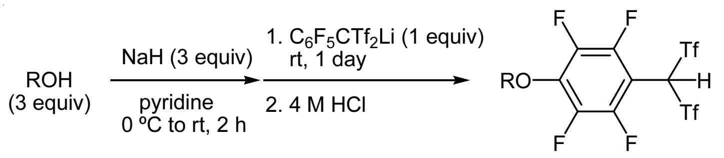
Scheme 2 Recovery of **5** by decantation and its re-use without isolation.

These super-Brønsted acids can be synthesized by using the *para*-substitution reaction of pentafluorophenylbis(trifluoromethanesulfonyl)methane (**10**) with nucleophiles such as sodium alkoxide and alkyllithium as a key step (Scheme 3).

Pentafluorophenylbis(trifluoromethanesulfonyl)methane **10** (47 wt.% F) is soluble in most organic and fluorous solvents. However, it is possible to achieve high fluorous-phase affinity for 4-alkoxy-2,3,5,6-tetrafluorophenylbis(trifluoromethane-sulfonyl)methane by appending "a fluorous ponytail", $OCH_2(CF_2)_nCF_3$ group, to the *para* position of **10** via the nucleophilic *para* substitution reaction. In preliminary experiments, the preparation of 4-hexanoxy- and 4-trifluoroethanoxy-2,3,5,6-tetrafluorophenylbis(trifluoromethanesulfonyl)methane, **11** and **12**, has been examined by reacting a lithium salt of **10** with the corresponding sodium alkoxide in pyridine at room temperature [Eq. (1)] [9]. As expected, **11** and **12** have been obtained in respective yields of 83% and 93%. Fluorous Brønsted acid **13** (59 wt.% F) has been also prepared in 97% yield from a lithium salt of **10** and sodium 1*H*,1*H*-perfluorodecanoxide.



Scheme 3 Preparation of **8** and **9** from **10** via nucleophilic *para*-subsutitution reaction.

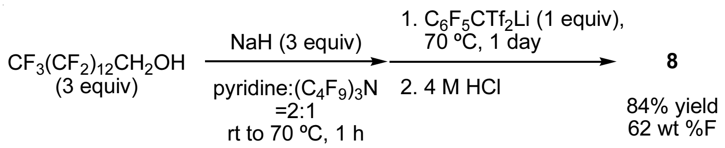


(4)

11 (R: n-C_6H_{13}): 83% yield
12 (R: CF_3CH_2): 93% yield, 47% wt% F
13 (R: $CF_3(CF_2)_8CH_2$): 97% yield, 59 wt% F

Their pK_a values in glacial acetic acid have been measured by the ^{1}H NMR method of Schantl et al. (Table 4) [8, 10]. The Brønsted acidity of **11** is less than that of concentrated H_2SO_4, while **12** is a superacid like **10**.

To obtain a higher fluorinated Brønsted acid, **3d** (62 wt.% F) has been prepared in 84% yield by heating a lithium salt of **1** and sodium 1*H*,1*H*-perfluorotetradecanoxide in a 2 : 1 mixed solvent of pyridine and perfluorotributylamine at 70 °C [Eq. (5)]. Perfluorotributylamine has been added to partially dissolve sodium 1*H*,1*H*-perfluorotetradecanoxide.



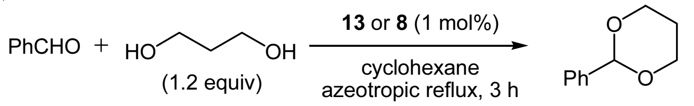
$$\underset{(3\ \text{equiv})}{CF_3(CF_2)_{12}CH_2OH} \xrightarrow[\substack{\text{pyridine}:(C_4F_9)_3N\\ =2:1\\ \text{rt to 70 °C, 1 h}}]{\text{NaH (3 equiv)}} \xrightarrow[\text{2. 4 M HCl}]{\substack{\text{1. } C_6F_5CTf_2Li \text{ (1 equiv),}\\ \text{70 °C, 1 day}}} \underset{\substack{84\%\ \text{yield}\\ 62\ \text{wt \%F}}}{\mathbf{8}} \qquad (5)$$

Table 4 Brønsted acidities of arylbis(trifluoromethanesulfonyl)methane.

	11	*Conc. H_2SO_4*	12	1
^{1}H NMR (ppm)[a)]	6.19	–	6.23	6.21[b)]
pK_a in AcOH	11	7.5[b)] (7.0)[c)]	6.6	1.5[b)]

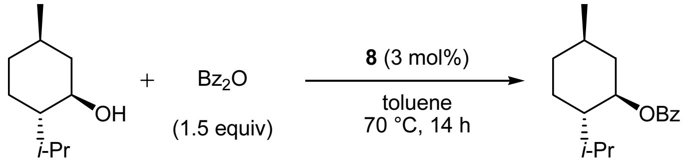
a) ^{1}H NMR chemical shift observed for an acidic proton of $ArCHTf_2$ in $CDCl_3$ is indicated.
b) Reference [8a].
c) Reference [10].

The acetalization of benzaldehyde with 1,3-propanediol has been examined in the presence of 1 mol% of a fluorous super-Brønsted acid, **13** or **8**, at azeotropic reflux in cyclohexane with the removal of water for 3 h [Eq. (6)]. Both solid acids are soluble in cyclohexane under reflux conditions, and promote the reaction well to give the desired acetal in good yields. Post-reaction, **13** has been recovered in 96% yield by precipitation at room temperature. However, **13** can not be recovered in the same manner. Besides this acetalization, **8** is also effective as a fluorous catalyst for the acylation of *l*-menthol with benzoic anhydride [Eq. (7)] and esterification of 3-phenylpropionic acid in methanol [Eq. (8)] [11].



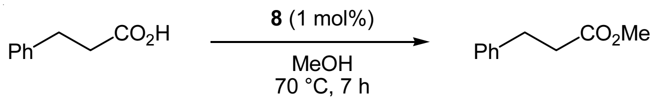
(6)

The use of **13**: Acetal: 74% yield; recovery of **13**: failed
The use of **8**: Acetal: 86% yield; recovery of **8**: 96%



(7)

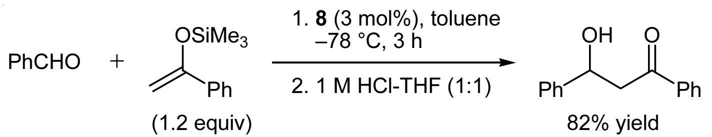
> 99% yield; recovery of **8**: 70%



(8)

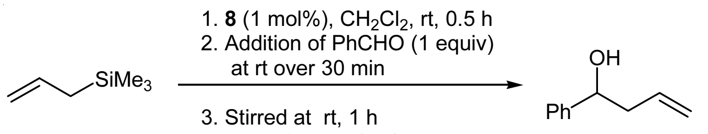
> 99% yield; recovery of **8**: 68%

Fluorous solid catalyst **8** is highly effective for the Mukaiyama aldol reaction [Eq. (9)] and Sakurai–Hosomi allylation reaction [Eq. (10)]. These reactions have been performed at –78 °C and room temperature, respectively, under heterogeneous conditions. Post-reaction, **8** has been recovered in high yield by decanting the liquids at room temperature.



(9)

82% yield
Recovery of **8**: 92%

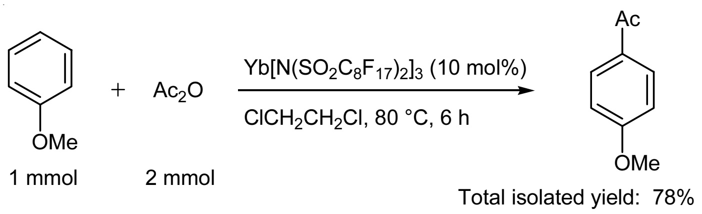


(10)

84% yield
Recovery of **8**: 97%

Pentafluorophenylbis(trifluoromethanesulfonyl)methane **10** offers a great advantage over other analogous super-Brønsted acids such as tris(trifluoromethanesulfonyl)methane, trifluoromethanesulfonimide, and trifluoromethanesulfonic acid from the perspective of synthetic modification. Barrett's [12] and Mikami's groups [13] have independently reported metal tris(perfluoroalkanesulfonyl)methides as fluorous Lewis acids. Similarly, it may be possible to design pentafluorophenylbis(perfluoroalkanesulfonyl)methanes. However, it is synthetically more concise and practical to append 1*H*,1*H*-perfluoroalkoxy groups to **10** by a *para*-substitution reaction. In addition, solid acids **8** and **9** are more active catalysts than perfluoresinsulfonic acids such as Nafion® [8].

Mikami's group has also demonstrated the advantage of the fluorous super-Lewis acids such as lanthanide tris(perfluorooctanesulfonyl)methide and perfluorooctanesulfonimide complexes with respect to temperature-dependent solubility [13b]. For example, these complexes can be re-used for the Friedel–Crafts acylation reaction without fluorous solvents [Eq. (11)]. After the reaction mixture of anisole has been heated with acetic anhydride in 1,2-dichloroethane in the presence of ytterbium perfluorooctanesulfonimide (10 mol%) at 80 °C for 6 h, the mixture is allowed to stand at –20 °C for 30 min to precipitate the ytterbium complex. The liquid phase is decanted and the residual lanthanide complex is re-used without isolation. No loss of activity is observed for the catalyst recovered. The total isolated yield of the product, which is combined from the three runs, is 78%.



(11)

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4.3
Concluding Remarks

István T. Horváth

As has been demonstrated in Chapter 4, fluorous catalysts are well suited for converting apolar substrates to products of higher polarity, as the partition coefficients of the substrates and products will be higher and lower, respectively, in the fluorous phase. The net results are little or no solubility limitation on the substrates and easy separation of the products. Furthermore, as the conversion level increases, the amount of polar products increases, further enhancing separation. One of the most important advantages of the fluorous biphase catalyst concept is that many well-established hydrocarbon-soluble catalysts could be converted to fluorous-soluble. In general, fluorous catalysts have similar structures and spectroscopic properties as the parent compounds.

The major difference arise from the presence of the fluorous ponytails, which provide a fluorous blanket around the hydrocarbon domain of the catalyst. If the electron-withdrawing effect of the fluorous ponytails on the ligands is not mitigated by insulating groups, the reactivity of the organometallic catalyst could be significantly different. Accordingly, most fluorous analogues of hydrocarbon-soluble catalysts have been prepared by incorporating insulating groups and have been shown to have comparable catalytic performance with the additional benefit of facile catalyst recycling.

Fluorous catalysis is now a well-established area and provides a complementary approach to aqueous- or ionic-biphase catalysis and the other possibilities of multiphase homogeneous catalysis (not to mention combinations of the different processes). Since each catalytic chemical reaction could have its own perfectly designed catalyst (e.g., a chemzyme), the possibility of selecting from biphase systems ranging from fluorous to aqueous systems provides a powerful portfolio for catalyst designers.

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5
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5.1
General Introduction[1]

Yves Chauvin

Ionic liquids (with melting point near or under room temperature) are becoming a major research topic because of their specific physical and chemical properties. They cover a large range of composition for both cations and anions with more or less charge delocalization (softness/hardness). These have often been reviewed [1]. Ionic liquids are useful as electrolytes in batteries and in inorganic and organic electrochemistry, in fuel and solar cells, for the synthesis of various materials, as a medium in liquid/liquid extraction, and in biphasic organic or enzymatic synthesis and catalysis. Ionic liquids are by far the most complex solvents with the possibility of all types of interactions with organic reactants, with catalysts, and, of course, with transition states between the reactions. Thus, a single quantitative scale of polarity cannot be established at present [2]. In spite of the foreseeable complexity, every chemist would like to be the first to describe a given organic reaction in ionic liquids. This is all the easier as various ionic liquids can as easily be purchased as any common organic solvents [3], but often with no information concerning nature, or level of impurities (for an exception see for example Ref. [4]).

However, the choice of ionic liquids for an industrial reaction raises a series of specific problems.

- *The solubility of ionic liquids in the reaction products* is an important factor. The simplest way to recycle a catalyst is by decantation of organic products from the ionic phase. But one should be sure that the solubility of the ionic liquid in the organic phase is very low, or practically nil. In fact it could be difficult to recover the part of the ionic liquid that is dissolved in the organic products, and yet trace amounts of ionic liquids in the reaction products could be at the origin of undesirable impurities. In this way, reactions of aliphatic hydrocarbons (oligomerization, paraffinic alkylation, isomerization, metathesis, hydrogenation and so on) are particularly favorable mainly when “hard” anions are used. Increasing the lipophilic character of the cation in order to increase the solubility of reactants could have a detrimental effect on the solubility of the solvent in the reaction products. In other cases, to ensure a good phase separation the use of organic solvents or supercritical carbon dioxide [5] has been envisaged but this makes the process scheme more complex and more energy-consuming. Special membranes have been proposed for the separation of organic compounds from ionic liquids [6]. This approach can be considered only for chemicals of sufficiently high value added. Distillation of organic products in the presence of ionic liquid is the last solution but its applicability is limited to sufficiently highly volatile products and to thermally stable catalysts and solvents. Moreover, a partial

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[1] Acronyms for the ligands mentioned in this chapter are listed at the end of this introduction.

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solubility of the reaction products in the ionic phase is less important, as the part of the dissolved products then being recycled with the ionic liquid and catalyst would be without any important detrimental effect.

- *Immobilization of homogeneous transition metal catalysts* in ionic liquids is another important factor. This can be achieved in three ways:
  - *Using ionic complexes.* It seems that this is the best way to immobilize transition metal complexes. Good results were obtained in dimerization of olefins catalyzed by $[RNiL_n]^+[AlCl_4]^-$ [7], hydrogenation of olefins catalyzed by $[Rh(norbornadiene)(PPh_3)_2]^+[PF_6]^-$ [8], in metathesis with $[RuCl(=C=C=CPh_2)(PCy_3)(p\text{-cymene})]^+[PF_6]^-$ [9], silylformylation of alkynes catalyzed by $[Rh(cod)]^+[BPh_4]^-$ [10], oligomerization of ethylene with $[(allyl)NiDPPM\text{-}O]^+[SbF_6]^-$ [11], arene hydrogenation catalyzed by $[Ru(\eta^6\text{-}p\text{-cymene})_2(\eta^2\text{-TRIPHOS})Cl]^+[PF_6]^-$ [12], and oxidation of alcohols catalyzed by $[RuO_4]^-[NPr_4]^+$ [13]. However, in some cases cationic complexes could exist in equilibrium with molecular species. For example, disproportionation of a $[(\pi\text{-allyl})NiCl]_2$ complex in a hydrocarbon solvent (hc) in the presence of water into ionic Ni^{2+} and a molecular Ni complex has been described [Eq. (1)].

$$[(\pi\text{-allyl})NiCl]_2 \rightarrow NiCl_{2\,aq} + Ni(\pi\text{-allyl})_{2\,\mathrm{hc}} \qquad (1)$$

    Although not yet studied, this could happen in the presence of ionic liquids too. Thus such a reaction could be responsible for the slow deactivation of the catalyst in the dimerization of olefins, as a small proportion of the Ni is found in the hydrocarbon phase (Difasol process; see Section 5.5.1) [14].
  - *Using ionic ligands.* The principle of immobilization of a molecular complex in a polar phase by means of a polar ligand has been introduced (among others such as Keim) by Kuntz [15] with the synthesis of sodium salt of the triphenylphosphine tri-*m*-sulfonate, which is able to dissolve transition complexes in water. This was at the origin of many publications and of several industrial processes, the main one of which being the Ruhrchemie/Rhône-Poulenc hydroformylation of propene catalyzed by rhodium (see Section 2.5.1). The same approach has been used for catalysis in ionic liquids. However, as will be discussed later, the nature of the ionic bond could be crucial. Whatever the ionic ligand, deactivation can occur by displacement of the ligand with a reactant. This may favor the extraction of the metal into the organic phase (op) while the ligand remains into the ionic phase (il) [Eq. (2)]. Here L = ionic ligand; the reactants are, e.g., carbon monoxide; M(reactants) = molecular complex.

$$M(L)_n + \text{reactants} \rightarrow M(\text{reactants})_{\mathrm{op}} + n\ L_{\mathrm{il}} \qquad (2)$$

    To prevent such a reaction, a large excess of the ligand is often used with, as a consequence, a detrimental effect on the reaction rate. On the other hand one can be sure of the stability of the ligand (no defunctionalization reaction in the operating conditions).

  - *Using the two preceding approaches simultaneously* (ionic complexes/ionic ligands). This could be considered to improve immobilization.
  - *Possible reaction of quaternary cations, especially imidazolium, with transition metal complexes.* Thus oxidative addition of 2H-imidazolium salts to Pt(0), Pd(0), and Ni(0) was found to occur readily, forming M(II) complexes [16].

- *Exchange of heteroelements with anions.* For reactants – and ligands – containing heteroelements (oxygen, nitrogen, halogens, phosphorus), one should ensure that no exchange takes place between the heteroelement and the anions, or elements of the anions present in the ionic liquid, even at a low level. If such an exchange occur, modification of reactants and of the physical and chemical properties of the solvent will be progressively observed and reaction performances may be altered.

- *Introduction of trace amounts of impurities.* This has to be avoided in reaction products. The impurities can come either from the catalyst, the solvent, or the reactants, as may be the case in classical homogeneous catalysis. For example, small amounts of chorinated or fluorinated organic compounds often have a detrimental effect on the properties of many chemicals. It is well known that trace amounts of water or hydroxylic compounds can decompose anions such as BF_4^-, PF_6^-, $AlCl_4^-$, forming halogenated acids which can react with reactants or products. Thus, reactants have to be purified, as is currently done for heterogeneous catalysts often with very high efficiency. Some transition metal complexes are known to decompose CF_3–C bonds and even C–F bonds. Generally speaking, it would be better to choose a solvent that does not contain any heteroatoms differing from those already present in the reactants, a condition which is rarely fulfilled but which should be thoroughly investigated.

- *Toxicity.* The toxicity of ionic liquids is important in the case where the products are at the disposal of the general public. For example, it is out of the question to use toxic ionic liquids (e.g., based on AsF_6^-!) as electrolytes in batteries for mobile phones or other electronic devices. On the contrary, the chemical industry currently manages enormous quantities of gaseous, highly toxic chemicals such as carbon monoxide, chlorine, phosgene, cyanide hydride, fluorine, hydrofluoric acid, etc. Such reactants are at present essential for the production of many customer-based polymers, e.g., CDs, plastic coverings in hospitals (of course, the chemical industry makes tireless efforts to find substitutes for these compounds). In this way ionic liquids with no vapor presure do not set a real problem. It is only necessary to foresee recyclability, disposal, or destruction of the used ionic liquids. Thus a “green solvent” could be not really “green” without real detrimental effects, but they bring some advantages such as yields, regio- or stereoselectivities of the reaction, catalyst consumption, etc.

- *Cost.* The cost of ionic liquids has to be taken into consideration. If completely insoluble in the reaction products and/or stable enough during separation, they can be considered as a simple investment. Thus, in the Difasol process [14] it has been demonstrated that 1-butyl-3-methylimidazolium chloride/$AlCl_3$ liquid has been used in a pilot plant for more than six months (more than 5000 hours) without any loss. In this case the solvent has practically no impact on the operating costs; but this could be not a general case, and experiments have to be conducted for each set of circumstances.

- *Physical properties.* Melting point, glass transition, surface tension, viscosity, and density are also among the parameters to take into account. These parameters can influence the choice of stirring and decantation devices for biphasic and ionic liquids/organic systems. Although the anion has a dominant effect on physical properties, modulation of cations can improve some specific properties.

Therefore, the selection of an ionic solvent for a given reaction is based on general knowledge but has to be the subject of specific experiments.

Another important question is: where does the reaction take place? It is important not only from a fundamental but from an also practical point of view. Surprisingly this is not so evident.

Thus it has been demonstrated that typically “hard” anions such as NO_3^-, Cl^-, and SO_4^{2-} associated with Sr^{2+} complexed by crown ethers are only partly, if at all, extracted from 1-octanol into 1-methyl-3-pentylimidazolium bis[(trifluoromethyl)-sulfonyl]amide ionic liquid [17]. As a consequence, ligands containing a $-SO_3^-Na^+$ “hard” moiety or similar “hard” anions could be not really soluble in a “soft” ionic liquid and could form a secondary phase (microdomains).

In a medium half made up of cations, π-cation interactions with unsaturated molecules, e.g., aromatic, olefinic, acetylenic, and other compounds, probably play a very important role, not yet evaluated, in organic reactions. This type of interaction has been underestimated and has mainly been studied in the case of aqueous media in biological structures. The binding energy of π-cation interactions (from 10 to 40 kcal mol^{-1}) has been reviewed by Dougherty [18]. At present, it is not known if free molecules or π-bonded ones (if present) are reacting in ionic liquids. Recently [19] it has been shown that the π-cation interaction of the aromatic group of a ligand derived from the family of *o*-hydroxybenzyliminodiacetic acid has a strong effect on the structure of the coordination complex of Fe(III). Thus, by analogy, aromatic moieties of, for example, phosphine or phosphite ligands are also probably not indifferent toward cations and can impose a preferred geometry on a complex. More, the existence of a π-anion interaction between C_6F_5 moieties and a BF_4^- anion was suggested [20]. On the other hand, ionic liquids may have the ability to incorporate within their lattices organic molecules of suitable size by physical emprisonment (clathrates) with no chemical bonding.

Yet unlike molecular solvents, ionic liquids have an ordered structure similar to that of the solid state. This has been dicussed by Hardacre [21] and others. Although there is no segregation between cations and anions (ion pairs), imidazolium cations adopt a parallel orientation with three repetitions of this pattern [22]. This complicates the solubility scheme of reactants and catalysts.

In conclusion, the coordination environment in ionic liquids could not be the same as in molecular solvents. Considerable work has to be done to clarify this point. The concept of "green chemistry" is general and is not limited to the utilization of a specific solvent. Chemical specifications are obviously the most important parameter of a product. Yield and selectivity are important in order to minimize the byproducts, mainly the toxic ones. The cost of reactants is an essential part of the final cost. Energy consumption (cooling, distillation) has to be taken into consideration. Clearly ionic liquids are not a panacea for the majority of chemical processes. However, they can bring advantages, for example, decreasing the volume of reactors, saving catalyst, or improving selectivities. Other aspects concern the use for which they were originally designed, as electrolytes for electrochemical reduction or oxidation of transition metals, thus generating or regenerating active species.

Acronyms

$[(CF_3SO_2)_2N]^-$ $[NTf_2]^-$	bis(triflyl)imide anion
$[AMIM]^+$	1-amyl-3-methylimidazolium cation
$[BIM]^+$	1-butylimidazolium cation (from the reaction of butylimidazole with a strong Brønsted acid)
$[BMIM][BF_4]$	1-butyl-3-methylimidazolium tetrafluoroborate
[BMIM][Cl]	1-butyl-3-methylimidazolium chloride
$[BMMIM]^+$	1,2-dimethyl-3-butylimidazolium cation
$[BMPY]^+$	*N,N'*-methylbutylpyrrolidinium cation
$[BP]^+$	*N*-butylpyridinium cation
$[DEIM]^+$	1-decyl-3-ethylimidazolium cation
$[DMIM]^+$	1-decyl-3-methylimidazolium cation
$[EEIM]^+$	1-ethyl-3-ethylimidazolium cation
$[EMIM]^+$	1-ethyl-3-methylimidazolium cation
$[EMMIM]^+$	1,2-dimethyl-3-ethylimidazolium cation
$[HEIM]^+$	1-hexyl-3-ethylimidazolium cation
$[HMIM]^+$	1-hexyl-3-methylimidazolium cation
$[HpMIM]^+$	1-heptyl-3-methylimidazolium cation
$[MIM]^+$	1-methylimidazolium cation
$[MMIM]^+$	1-methyl-3-methylimidazolium cation
$[NMIM]^+$	1-nonyl-3-methylimidazolium cation
$[OMIM]^+$	1-octyl-3-methylimidazolium cation
$[OTf]^-$	trifluoromethanesulfonate anion
$[OTs]^-$	tosylate anion
$[PEIM]^+$	1-propyl-3-ethylimidazolium cation
$[RMIM]^+$	1-alkyl-3-methylimidazolium cation

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5.2
State-of-the-Art

5.2.1
Homogeneous Catalysis in Ionic Liquids

5.2.1.1
Ionic Liquids: Opportunities for Catalytic Reactions

Hélène Olivier-Bourbigou and Christophe Vallée

5.2.1.1.1
Introduction

Homogeneously catalyzed processes such as hydroformylation, oligomerization, hydrogenation, metathesis, or hydrocyanation still contribute greatly to the inventory of bulk chemicals. Besides these applications, homogeneous catalysis also contributes to high-value fine chemicals manufacture. Homogeneous catalysis very often makes progress through the design and development of novel, sometimes sophisticated and costly, tailor-made ligands and of new ligand/metal/solvent combinations. As well as the ligand, the solvent acts as a key ingredient in the catalytic system. Its interaction with the active species may impact on the catalyst stability, activity, and selectivity. But despite the advantages of using a solvent, one of the challenges of homogeneous catalysis is to solve the problem of separating the solvent and the catalyst (including the ligand) from the products and of recycling the solvent/catalyst couple.

A great number of papers deal with the immobilization of homogeneous catalysts on supports such as solid inorganic supports, soluble polymers, or liquid supports. There is of course no general – universal – solution. The best solution will depend upon the type of reaction and catalyst, and the existence and nature of byproducts or side reactions. Very often, the nature of the active catalyst and its resting state remain uncertain. Then, the rational design of recoverable catalyst is difficult. However, a very promising technology is multiphasic (biphasic) catalysis. It can combine some advantages of homogeneous and of heterogeneous catalysis. For example, the catalyst can be tailor-made for a special purpose, and it often operates in a liquid phase under mild reaction conditions with the possibility of separating it and recycling it with the solvent from the reaction products. However, the selection of the solvent is often difficult and governs the development and expansion of this concept.

Ionic liquids offer new opportunities for development of a biphasic (multiphasic) approach. The ionic liquids known today are based on many different combinations of organic cations and inorganic or organic anions. They have the advantages over conventional solvents of being liquid over a large range of temperatures and of having a nonvolatile character. This latter property has probably been one of the driving forces of their development as alternative environment-friendly solvents,

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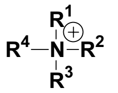
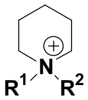
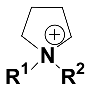
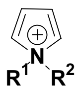
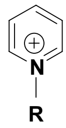
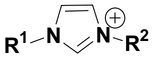
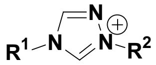
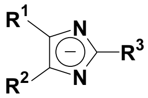
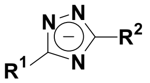
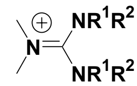
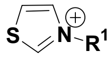
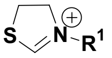
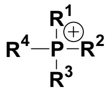
but the use of ionic liquids (ILs) may present other benefits. Even if imidazolium salts are by far the most widely employed ILs, there is now a broad range of cations and anions and of their combinations. Most of them have already been described in recent reviews; some examples are given in Table 1 [1–6].

Table 1 Examples of cations and anions.

Cations	***Anions***
Tetraalkylammonium, piperidinium [7]  	*Halogenated anions* HF_2^- BF_4^-, PF_6^-, $PF_3(C_2F_5)_3^-$, SbF_6^-, $Sb_2F_{11}^-$, $CF_3SO_3^-$, $CF_3CO_2^-$, $N(SO_2CF_3)_2^-$, $N(SO_2CF_3)(COCF_3)^-$, $N(CF_3)_2^-$
Pyrrolidinium [8], pyrrolinium [9]  	*Non-halogenated anions* $N(CN)_2^-$, $N(SO_2CH_3)_2^-$ SCN^- SO_4^{2-}, RSO_4^- [14] (sulfate and alkylsulfate) PO_4^{3-}, $R_2PO_4^-$ (phosphate and alkylphosphate) $CH_3CO_2^-$ (acetate) $CH_3SO_3^-$ (sulfonate and alkylsulfonate)
Pyridinium, imidazolium (including chiral imidazolium and protic imidazolium)  	
1,2,4-Triazolium [10] 	*Heterocyclic anions* imidazolate, triazolate [15]  
Tetraalkyldimethylguanidinium [11] 	$B(Ar)_4^-$ [16] bis(oxalato)borates (BOB^-) [17] closo-$(CB_{11}H_{12})^-$ carborane anion [18] benzoate [19] lactate, salicylate [20]
Thiazolium, thiazolinium (including chiral thiazolinium) [12]  	
Tetraalkylphosphonium [13] 	*Polynuclear and/or organometallic anions* $AlCl_4^-$, $Al_2Cl_7^-$, $Al_3Cl_{10}^-$ $FeCl_4^-$, $Fe_2Cl_7^-$ SbF_6^-, $Sb_2F_{11}^-$ $Co(CO)_4^-$ [21], $AuCl_4^-$ [22] $GaCl_4^-$, $SnCl_3^-$, $ZnCl_3^-$, $CuCl_3^-$

5.2.1.1.2
Ionic Liquids: Non-Innocent Solvents

Most of these ILs are now commercially available, which contributes to the development of their applications. The most commonly used ILs are probably those with BF_4^- or PF_6^- anions. For example, [BMIM][PF_6] has often been used as a solvent for catalytic reactions for a combination of reasons including its ease of preparation and purification, its hydrophobicity, and the possibility of separating a large range of reaction products by decantation without addition of an extractant solvent. But despite the widespread use of these salts, the PF_6^- anion, and to a lesser extent the BF_4^- anion, are known to decompose. In the presence of water, they give HF and phosphoric acid [23]. It has to be underlined here that the hydrolysis reaction of the PF_6^- anion may be acid-catalyzed. Consequently, the synthetic procedure used to prepare the [BMIM][PF_6] salt may have an influence on its overall stability. The preparation procedure consisting of the reaction of [BMIM][Cl] with $NaPF_6$ in acetone may be preferred over that using HPF_6. The possible presence of the remaining acidic protons may explain some observed solvent effects [24].

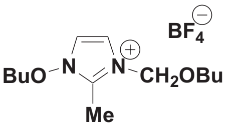
Alternative anions, more stable toward hydrolysis, have been introduced in which, for example, the fluorine is bonded to carbon as in the NTf_2^-, $CF_3SO_3^-$, or $CF_3CO_2^-$ anions. It has now become apparent that the bis(trifluoromethanesulfonyl)amide anion NTf_2^- gives ILs with substantially lower melting points and higher fluidity due to weak van der Waals interactions, even with tetraalkylammonium cations. These NTf_2^--based ionic liquids have the additional advantage of being extremely stable, both thermally and electrochemically. However, despite all their advantages, the NTf_2^--based ILs may have some limitations when used in catalysis. It has been demonstrated that the NTf_2^- anion may behave as a competitive ligand toward electrophilic metals dissolved through direct metal–nitrogen or metal–oxygen bonds [25]. The consequence is that such ligands create a novel environment around the metal, which modifies their chemical and electrochemical properties. Another limitation is that for the same cation, the NTf_2^- ionic liquids are generally the most hydrophobic ones [26], which may render difficult the separation and/or extraction of organic products. As an example, aldehydes such as heptanal are completely miscible in [BMIM][NTf_2] although they are only partially soluble in [BMIM][PF_6].

Interestingly, the [EMIM][$N(SO_2CH_3)_2$] ionic liquid is a low-melting salt completely miscible with water. However, the hydrogen bonding within the salt results in an increase in viscosity and a decrease in thermal stability compared to the NTf_2^- analogue [27].

Other nonhalogenated anions, such as tosylate, sulfate, alkylsulfate, sulfonate, borate, lactate, or salicylate, have been developed more recently and their physicochemical properties have been described. ILs with triazolate anions can serve as both solvent and basic catalyst for the isomerization of isocyanate [15].

Concerning *cations,* the most popular ILs contain a 1,3-dialkylimidazolium cation. However, liquids are also described in the literature in which a functional feature, such as $(CH_2)_xOR$ [20], CH_2CH_2SR [28], CH_2CH_2CN [29], $CH_2CH_2C(O)CH_3$, or $(CH_2)_3NHCONHR$, is incorporated instead of the alkyl chain on the nitrogen atom

(**1**–**5** are examples). Particular properties of these ILs can be achieved. These "task-specific ionic liquids" can be used as both catalyst solvent and ligand. Another example is given by the presence of a fluorous appendage upon the imidazolium cation [30]; this perfluoroalkyl chain on the nitrogen alters the capacity of conventional ILs to hold traces of water. Although these species are not really liquid at room temperature (melting point in the range 60–150 °C), they may exhibit interesting properties in the development of two-phase ILs/fluorous reaction systems. As opposed to other ILs, they exhibit high miscibility with apolar compounds such as alkenes and are similar to fluorous solvents in their behavior with organic solvents. They have been used as solvents for the homogeneous hydrosilylation of 1-octene catalyzed by a fluorous version of the Wilkinson catalyst (cf. Chapter 4) [31].



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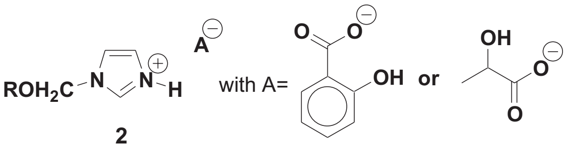

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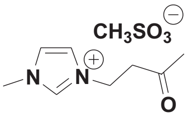

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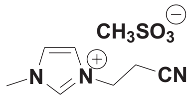

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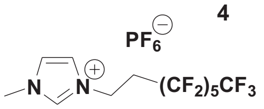

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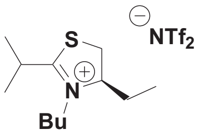
ILs containing a chiral cation or a chiral anion have been reported and are thought to play an important role for asymmetric synthesis or for chiral separation (**6**–**9**) [32–37]. A chiral IL based on 1-((–)-menthoxycarbonylmethylene)-3-methylimidazolium) hexafluorophosphate has been applied in stereospecific free-radical polymerization of vinyl monomers. The asymmetric environment of chiral ILs is believed to have some effect on the stereostructure of polymers [38].



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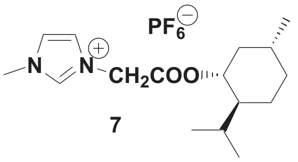

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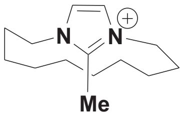

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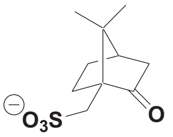

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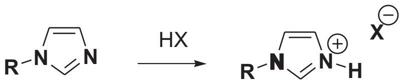
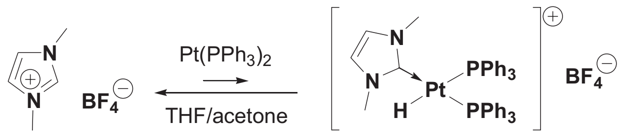
Protic ILs are easily accessible by direct, halogen-free, reaction of strong Brønsted acids with *N*-alkylimidazole [Eq. (1)]. These ionic liquids have in general higher melting points than the dialkylimidazolium analogues, but they may be liquid under the reaction conditions (< 110 °C). They may act as both catalyst solvent and catalyst precursor activator for reactions such as dimerization of methyl acrylate catalyzed by Pd and Rh complexes or ring-closing metathesis catalyzed by Ru complexes [39]. These protic imidazolium-based salts have been used as starting materials for the straightforward introduction of keto or cyano functionality in the imidazolium cation [29] (see the task-specific ionic liquids **1–5**).



(1)

If ILs are to be used in metal-catalyzed reactions, imidazolium-based salts may be critical due to the possible formation and involvement of heterocyclic imidazolylidene carbenes [Eqs. (2)–(4)]. The direct formation of carbene–metal complexes from imidazolium ILs has already been demonstrated for palladium-catalyzed C–C reactions [40, 41]. Different pathways for the formation of metal carbenes from imidazolium salts are possible either by direct oxidative addition of imidazolium to the metal center in a low oxidative state [Eq. (2)] or by deprotonation of the imidazolium cation in presence of a base [Eq. (3)]. It is worth mentioning here that deprotonation can also occur on the 4-position of the imidazolium [Eq. (4)]. The in-situ formation of a metal carbene can have a beneficial effect on catalytic performances in stabilizing the metal–catalyst complex (it can avoid formation of palladium black, for example). However, given the remarkable stability of this imidazolylidene-metal bond with respect to dissociation, the formation of such a complex may also lead to deactivation of the catalyst. This is probably what happens in the telomerization of butadiene with methanol catalyzed by palladium–phosphine complexes in [BMIM]-based ILs [42]. The substitution of the acidic hydrogen in the 2-position of the imidazolium by a methyl group or the use of pyridinium-based salts makes it possible to overcome this problem. Phosphonium-based ILs can also bring advantages in this case.



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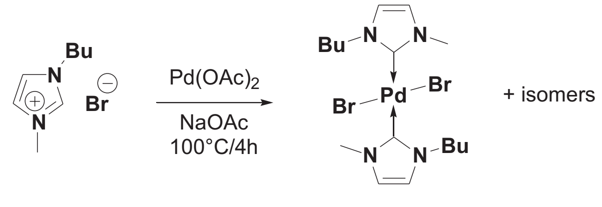

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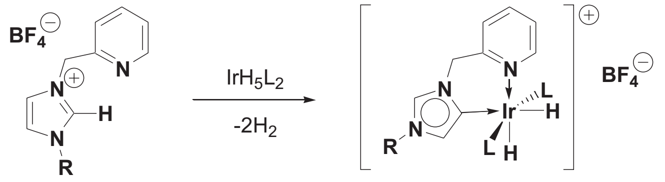


(4)

The guidelines for the development of novel ionic liquids when used as solvents for catalysis are dependent on the reaction studied. But there is no "universal" or "ideal" IL.

5.2.1.1.3
How to Choose Ionic Liquids

Conventional organic solvents can be placed roughly in one of the following four categories [43], even if more refined versions of this scheme are available: (a) apolar aprotic (e.g., cyclohexane); (b) weakly polar aprotic (e.g., diethyl ether); (c) dipolar aprotic (e.g., acetonitrile, dimethylformamide); (d) protic (e.g., water).

Where are ionic liquids in this classification? Except for nonpolar groups, we can say that with a proper choice of the anion and the cation, ionic liquids could fit into any of these categories. If we consider the large number of possible anion–cation combinations (see Table 1), the selection of the IL is far from being obvious and a series of problems have to be overcome before development of industrial processes (cf. Section 5.1). Some of the properties have to be known when ILs are used for catalysis.

The Importance of the Purity of Ionic Liquids

While their nonvolatile character is a major advantage over conventional solvents, it is a limitation due to the impossibility of purifying ILs by distillation. Purification can then be a significant challenge.

Traces of halide impurities (Cl^-, F^-, or even other anionic impurities) are often present in ionic liquids, notably when they are obtained by an anion exchange reaction. Most of the time, this presence of halides greatly influences the course of the catalytic reaction. For example, a detrimental effect of chlorides was observed for hydrogenation or Michael addition [44, 45], while a beneficial effect was reported for the Heck reaction [46]. It is therefore necessary to measure carefully the amount of halide impurity in ILs, and this amount can be quantified by high-performance ionic chromatography [47]. This precaution is especially important for colored commercial ionic liquids, which are likely to contain a significant amount of halide impurity as well as of other anions.

All ILs, either hydrophobic or hydrophilic, are hygroscopic and quickly absorb a significant quantity of water when exposed to air. Their properties, such as viscosity, solubility, polarity, conductivity, and electrochemical characteristics [48] (see Section 5.2.1.2), are significantly dependent on the concentration of water. "Wet" ionic liquids cannot be considered as homogeneous solvents but rather as "nanostructured" with polar and nonpolar regions. As a consequence, the reaction performances may also be altered in the presence of water. Water may interact with specific and localized C(sp^2)–H protons of the imidazolium capable of establishing hydrogen bonds. The degree of imidazolium ring stacking may then be disturbed and the organization of the IL changed [49]. For the same cation, such as [BMIM], the amount of absorbed water depends on the nature of the anion. The anion may act as a hydrogen bond acceptor. In conclusion, the presence of traces of water may change the structure of "pure" ILs based on the imidazolium cation.

Impurities present in ILs may have an impact not only on physico-chemical properties of the liquid but also on catalytic performances when the liquid is used as a solvent. In order to obtain reproducible results, a great amount of attention has to be dedicated to a precise characterization of ILs and in particular to the degree of purity.

Solvent Properties

The *polarity* of the solvents is often thought to be influential in selectivity and activity of catalytic processes. The polarity of ILs is difficult to measure. Hydrogen-bond properties have often been described as playing an important role in the structure and properties of these solvents. The polarity of ionic liquids has been measured using solvatochromic dyes [50, 51] (see also Section 5.2.1.2). It is often assumed that the polarity of ionic liquids is much lower than that of water and closer to that of ethanol. However, their ability to undergo multiple solvation interactions with many molecules places them among the most complex solvents [52].

If one of their key and unique characteristics is that their physical properties are tunable, it is still very difficult to predict and establish relationship between the physico-chemical properties of the ILs (packing, nature of interaction of ionic and hydrogen bonding, etc.) and their chemical structure [53]. A quantitative structure–property relationship (QSPR) method has been used to relate *melting point* to cation structure [54]. The influence of the nature of the cation has been clearly illustrated. For example, a decrease in cation symmetry contributes to poorer packing and thus lowers the melting point. However, the anion also appears to exhibit a major influence [55, 56]. The QSPR method has also been proven useful for predicting infinite-dilution coefficients of organic solutes in ILs [57].

What is the structure of neat ionic liquids? Even though the structure of liquids, such as water, has been studied for many years, the study of room-temperature ionic liquids is still in its infancy [58]. *Purified* [BMIM][PF_6], probably the most studied IL, has been shown to be purely monophasic, with no aggregates, but to have a local structure [47]. Imidazolium groups are positioned in pairs with a plane-to-plane separation of 4.5 Å. The structure of ILs is also characterized by a degree of anion–cation association. Thus, in [EMIM][NTf_2] and [BP][NTf_2], the self-diffusion coefficients of the anions and the cations measured by pulsed-gradient spin–echo NMR are superior to the diffusion coefficients deduced from the molar conductivity, which demonstrates the existence of ion pairs which cannot contribute to the ionic conduction [53].

Different PF_6^- or NTf_2^- imidazolium-based ionic liquids have been used as solvents and electrolytes for several typical electrochemistry reactions. Although the structure of molecular solvents and ILs are expected to be quite different, the main result is that the use of ionic liquids does not modify the nature of the mechanisms investigated using conventional organic media. An effect of the structure of ILs can nevertheless be observed in the case of bimolecular reactions (e.g., oxidative electrodimerization), as kinetic rate constants are lower in ionic liquids than in conventional polar solvents. This phenomenon cannot be simply attributed to the high viscosity of ILs but may be explained by a specific solvation of the reactants due to a high degree of ion association in ILs [59].

ILs have to fit the reaction and the catalytic system (metal center and ligand) and vice versa. In some cases, new ionic liquids can be created that are constituted of the same heteroatoms as those present in the reactants.

5.2.1.1.4
Advantages and Limitations of Using Ionic Liquids in Catalysis

The range of homogeneous reactions that has been transposed into ILs is probably wider than into $scCO_2$ or perfluorinated solvents due to the great versatility of ILs. Most of these reactions are performed on a bench scale. Up to now, just a few examples of pilot-scale (or commercial) applications of ILs have been described (see Section 5.3).

The potential benefits of using ionic liquids in catalysis may be numerous. Some of these advantages are listed in Table 2. In many cases, the focus is put on the possibility of recycling the catalyst with no loss of activity/selectivity and minimum loss of catalyst. This is all the more important when high-cost ligands and metals are used. An example is enantioselective catalytic hydrogenation applied to the production of pharmaceutical intermediates. The expensive catalyst has to be recycled without deterioration of its performances (activity and enantioselectivity) and the organic products have to be separated free from trace amounts of metal contaminants [60, 61].

In several other applications, ILs have proven to be an effective means for immobilization of catalysts (oligomerization, hydroformylation, metathesis). However some important issues remain to be addressed for their use on an industrial scale (Table 3). The immobilization of the catalyst and the separation of reaction products are among the points that have to be considered carefully.

Due to their unique set of physico-chemical properties (solvation, polarity, structure), one would expect more from ILs than the possibility of recycling catalysts. For some applications, ILs have been proved to be more than “physical” solvents and to act as activators of the pre-catalyst. The highly active species, generally unstable, can be generated in situ in the ILs from air-stable, easy to handle, transition-metal precursors. An example is the oligomerization of olefins catalyzed by the cationic Ni(II) organometallic complex. The acidic alkylchloroaluminate activates the Ni(II) salt precursor and generates the Ni–carbon or Ni–hydrogen cationic active species.

Table 2 Some physico-chemical properties of ionic liquids and their beneficial impacts on catalysis.

Properties	***Benefits for catalysis***
Very low vapor pressure Nonflammable	May offer "environmental" advantages over traditional organic solvents easy to contain and to handle possibility of separation of reaction products by distillation
Low melting point Reasonable thermal stability	Large working liquid range of temperature
High heat conductivity (higher than water)	Facilitates the management of large reactors. Permits a very rapid dispersal of the heat of the reaction.
Good ionic conductivity wide electrochemical window	Can be combined with electrochemical processes Can be combined with microwave irradiation
May be nonprotic	May be used with organometallic compounds
May be protic	May be used as both acidic catalyst and solvent
Adjustable coordination properties	Ionic liquids have the potential to be polar yet weakly coordinating toward transition metal complexes; they may enhance reaction rates involving cationic electrophilic intermediates When they contain coordinating anions (e.g., Cl^-) they may stabilize anionic transition metal intermediates (e.g., Pd Heck coupling catalysts)
Can exhibit Lewis acidity (e.g., chloroaluminates)	May act as both co-catalyst (catalyst activator) and solvent Catalytic species can be generated in situ in the ionic liquid (e.g., Ziegler–Natta systems)
Adjustable miscibility with organic compounds (may be hydrophobic or hydrophilic)	Unique ability to dissolve polar substrates in a nonaqueous environment (potential for biocatalysis; see Section 5.2.2.5) Good solvents for multiphasic catalysis May provide a solution to product separation from catalyst/solvent May influence reaction selectivity by selective extraction of reaction intermediates
High affinity for ionic intermediates	Ionic metal–catalysts can be immobilized without modification
Complementary properties with $scCO_2$	$scCO_2$ can be used for product extractions and/or in combination with ionic liquids
Imidazolium cation can be functionalized	Possibility of using the ionic liquid as both solvent and ligand Possibility of introducing a chirality on the cation Possible combinatorial ionic–liquid development [29]
Large number of potentially available cation–anion combinations	Can be used in high-throughput combinatorial chemistry

Table 3 Some limitations on the use of ionic liquids for catalysis.

Ionic liquid characteristic	*Limitations*
Very low vapor pressure	Purification may be a challenge; purification methods must be optimized Ionic liquid impurities must be controlled, determined and quantified; these impurities may significantly affect ionic liquid properties The removal of ionic liquids from reaction products may be difficult
"Polar solvent"	Isolation of polar nonvolatile products may be problematic
High viscosity	Solute diffusion, stirring, and pumping for large-scale process are affected
Gas solubility may be low	Critical effect on reaction rate and conversion
Stability	Stability toward hydrolysis (e.g., PF_6^-, BF_4^-, or $MeSO_4^-$) and thermal stability (e.g., $CF_3CO_2^-$) has to be carefully considered IL lifetimes under reaction conditions have to be studied; TGA measurements may overestimate thermal stability
Very complex solvent	Difficult to make the good ionic liquid choice for a given reaction
Toxicity	Very few data available
Disposal	No published guidelines Methods have to be adapted to the ionic liquids

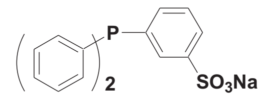
The palladium-catalyzed coupling reaction of olefins with aryl halides (Heck reaction) is probably among the most powerful methods for the synthesis of arylated olefins. The scope and limitations of this reaction have been reviewed [62]. It is usually performed in polar solvents such as acetonitrile or dimethyl sulfoxide, in combination with a base and a Pd(II) pre-catalyst that may or may not be associated with a phosphorus ligand. It is known that quaternary ammonium or phosphonium salts increase the speed of the reaction and limit catalyst deactivation. Thus, ILs appear obviously as good solvents for this reaction. The first example of a Pd-coupling reaction in ionic liquids was reported in 1996 [63]. Since then, it has been one of the most active areas of research in ILs. It has been reported that [BMIM][BF_4] can influence the regioselectivity of the coupling of 1-bromonaphthalene to butyl vinyl ether [64]. Imidazolium-based ionic liquids can also act as both solvent and precursor of imidazolylidene ligands that stabilize palladium catalysts. Molten tetrabutylammonium bromide associated with tetrabutylammonium acetate (base) were also proven to be interesting solvents for arylation of butyl methacrylate and α-methylstyrene [65]. The ionic liquid/base system play different roles: it stabilizes the Pd nanoparticles and it controls the coupling regioselectivity (favoring terminal olefin).

ILs, when used as solvents, offer the possibility of combining catalysis with various other processes. Owing to their inherent conductivity, they are promising solvents for electrosynthesis. They avoid the addition of a supporting electrolyte and may provide nonprotic solvents with a large electrochemical window. Their high viscosity may limit ion mobility, but this drawback can be overcome by the addition of a co-solvent or by heating the solution. An example is given by the electroreductive C–C homocoupling of an aryl halide catalyzed by nickel complexes [59]. The preliminary results show that electrochemistry and homogeneous catalysis can be combined advantageously with the use of ILs. Another interesting example of combining electrochemistry and nonaqueous and polar solvents is the electroassisted oxidation activation of oxygen by the Jacobsen catalyst in [BMI][PF_6] [66].

Ionic liquids can also be advantageously used as solvents or co-solvents in conjunction with microwave irradiation for catalytic reactions [67]. Small amounts of ILs are sufficient to reduce the heating time of nonpolar solvents such as toluene or cyclohexane under microwave conditions. In recent literature there are many examples in which microwaves and ionic liquids are associated to accelerate catalytic reactions (Heck [68], metathesis [69]). More recently, ILs have been used in sonochemical accelerations of Heck and Suzuki cross-coupling reactions [70, 71]. Ionic liquids may be interesting due to their low vapor pressure. However, they can decompose under ultrasonic conditions [72].

5.2.1.1.5
Immobilization of the Metal Catalyst in the Solvent Phase

Another challenge of multiphasic catalysis is the immobilization of metal–catalyst in the solvent phase. How can one prevent leaching of the metal into the organic phase? The solubility and stabilization of the different active intermediates in ILs depend on the nature of these intermediates (charged or neutral) and on the difference in polarity between the IL and the reaction products. The immobilization of the catalytic system is made all the more complicated where several active intermediates may be involved in the catalytic cycle and where the reaction products can be composed of a mixture of compounds with different polarity. If the active intermediates are charged species (anionic or cationic), they can be retained in the ILs without the addition of specially designed ligands. This may be an advantage over other nonpolar solvents used in multiphasic systems that often need ligands to solubilize charged complexes. Different examples of immobilization of cationic or anionic catalysts in ionic liquids are already described in the literature and are presented in the course of the chapter (e.g., dimerization, hydrogenation, metathesis, oxidation). If the active catalyst is an uncharged complex (e.g., for hydroformylation), leaching of the metal into the organic phase can be limited by incorporating a function on the ligand. This function is often chosen because of its high affinity for the ILs. It can be anionic [73], cationic [74], or polar [75] (**10**–**14**). The nature of the counterion associated with the ionic ligand may also play a major role in the catalyst recyclability and stability. The efficiency of cationic ligands has been demonstrated for Rh-catalyzed olefin hydroformylation. The phenoxaphosphino-modified ligand (**13**) plays a dual role: it leads to high linear aldehyde selectivity and it makes possible the retention of the Rh catalyst in the [BMIM][PF_6] ionic liquid (< 5 ppb; Rh leaching is under the ICP detection limit) [76].



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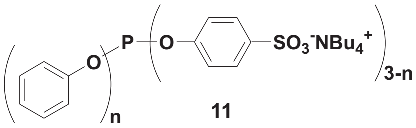

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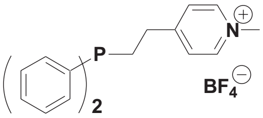

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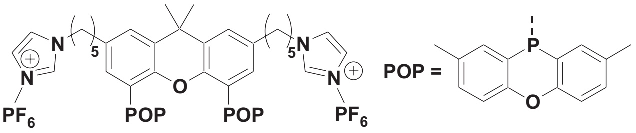

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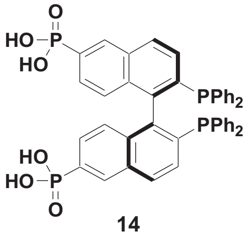

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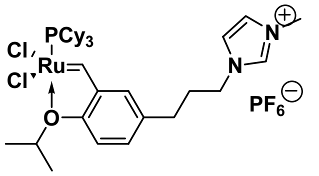
Another example is given by the Hoveyda-type modified ruthenium complexes (**15**, **16**). The strategy to immobilize the Ru catalyst in the ionic liquid is the same as that developed with various polymeric or inorganic supports. A designer ionic tag (imidazolium moiety) is incorporated on the isopropoxybenzylidene ligand. These catalysts can be recycled and re-used several times for the ring-closing metathesis of various dienes and stored several months in [BMIM][PF_6] without significant loss of its activity and selectivity [77, 78]. But this raises the question of where the catalytic reaction occurs. In the case of a metathesis reaction, the benzylidene ligand reacts with the carbon–carbon double bond and should be transformed into the methylene–Ru uncharged active catalyst. Even if the mechanism of the reaction in the presence of ILs is not really demonstrated, it can be assumed that the reaction occurs in the organic layer or at the interphase.



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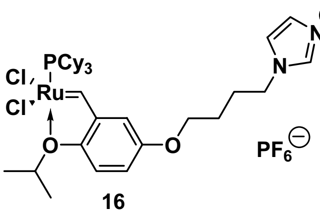

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Another recently developed approach that combines the advantages of ILs with those of heterogeneous catalysis is to anchor ILs, through covalent bonding, on an inorganic high-surface solid. This concept was first applied to perform acid-catalyzed reactions (cf. Section 5.2.2.4). It has been successfully expanded to Rh-catalyzed hydrogenation and hydroformylation reactions. In that case the homogeneous rhodium catalyst is dissolved in the excess of ionic liquid phase at the surface of the solid. Enhanced activity and selectivity are described in comparison to that of a biphasic system [79]. The increased activity has been attributed to an increase in the concentration of active species at the interface of the IL and the organic layer. But to reduce the loss of metal in the organic phase and the depletion of the IL phase, the aldehyde concentration in the product mixture has to be kept below 50%. In addition, an excess of phosphine ligand relative to Rh metal has to be used to minimize Rh leaching.

ILs can also be immobilized by impregnation of an inorganic support. This is a direct transposition of the Supported Aqueous-Phase Catalysis (SAPC) concept to ionic liquids (see Section 2.6). Supported Ionic Liquid Phase (SILP) catalysts containing Rh-biphosphine ligands were applied to perform continuous-flow gas-phase hydroformylation of propene in [BMIM][PF_6] or [BMIM][RSO_4] (R=octyl).

Some examples in the literature explore the use of ILs as soluble supports: a new type of hydrolytic ionic liquid based on fructose was developed and used for Diels–Alder and transesterification reactions [80–82]. The advantages are the tunable miscibility and the high loading capacity compared to other soluble supports such as PEG.

5.2.1.1.6
Separation of the Catalyst/Solvent from the Reaction Products

When ILs are used in catalytic processes, reaction products, byproducts and residual reactants need to be separated from the solvent and the catalyst, which are recycled and re-used. The product solubility can be difficult to predict because distribution of products can depend on reactant conversion, residence time, and operating conditions. Consecutive reactions can provide byproducts with different polarities or functionalities. The existence of these byproducts can modify the partitioning of the desired product in the organic effluent/ionic liquid system (see also Section 5.2.1.3).

In some cases, liquid/liquid extraction may afford the opportunity to separate selectively some products or intermediates. In general ILs can be compared to dipolar aprotic solvents or short-chain alcohols. The solubility of organic substrates depends on both the nature of the cation (i.e., the length of the alkyl chain on the imidazolium moiety, the existence of H-bonding with the proton on the 2-position) and on the anion type. ILs tend to be immiscible with nonpolar solvents (i.e., hydrocarbons, diethyl ether) and these solvents are often used to extract the products at the end of the reaction (for organic synthesis). Unsaturated hydrocarbons are generally much more soluble than saturated ones: for example, aromatic hydrocarbons are remarkably soluble in ionic liquids even if they are rarely completely soluble. Liquid clathrate phases are formed. These phases contain nonstoichiometric but reproducible compositions. The existence of strong interactions between the π-system of the aromatic hydrocarbon and the imidazolium cation has been demonstrated [83]. These data are probably to be considered when looking at the separation of reaction products from ILs.

Different techniques of separation can be envisioned depending on the solubility of the product mixture in the ionic liquid phase.

- The products separate during the reaction, forming a biphasic liquid/liquid system: decantation may be an option. This type of separation has been applied in reactions that produce apolar products such as hydrocarbons. Examples are given with olefin oligomerization, metathesis, or hydrogenation. The tunable dissolving power of ILs may provide opportunities to couple biphasic reaction and selective separation. The primary products separate as they are formed before subsequent reactions to unwanted byproducts can take place (see Section 5.2.2.1).
- The products are partially or totally miscible in the IL. This may be the case for polar products such as aldehydes or alcohols. Distillation can be envisioned but is limited to volatile products. In addition, it uses energy and may decompose the catalytic species. Products can be separated during or after the reaction by adding a solvent that is poorly miscible with the ionic liquid. In olefin hydroformylation, the unconverted olefin can be recycled to optimize product extraction. This scheme presents the advantage of avoiding contamination of products by an additional organic solvent.
  The addition of water to hydrophobic ionic liquids can result in the formation of a triphasic system consisting of the ionic liquid + catalyst/water/organic product. The aqueous phase eventually contains the inorganic salt formed during the reaction. This approach has been applied in Pd-catalyzed cross-coupling reactions [84]. The products can also separate after the reaction by "perturbation" (of a "latent" biphasic system). This can be realized by tuning the temperature to crystallize the ionic liquid. But the refrigeration cost may be problematic, and some ILs may remain in the product.

5.2.1.1.7

Ionic Liquids and scCO$_2$

In all cases, mutual solubility, i.e., the solubility of ILs in reaction products and the solubility of products in ILs, may render the separation process more complex. Contamination of the extract phase with the IL, and sometimes with catalyst losses, is an important consideration in a process. This represents a downstream separation problem and treatment to extract IL that is partially soluble in the phase product.

As an alternative, the use of supercritical CO$_2$ to remove target species from ILs has been proposed and the feasibility of this concept has been demonstrated for continuous-flow catalytic processes (see hydroformylation [cf. Chapter 5.2.2.2] or hydrogenation [cf. Chapter 5.2.2.3] and enzymatic catalysis [cf. Chapter 5.2.2.5]) [85–87]. ILs and scCO$_2$ can be considered as complementary solvents [88] (Table 4). While ionic liquids can be compared to polar organic solvents, scCO$_2$ possesses the characteristics of nonpolar solvents with a high volatility. Carbon dioxide can be considered as an "antisolvent" to remove traces of ILs from organic and aqueous solutions. For example, [BMIM][PF$_6$] and methanol are completely miscible in ambient conditions. However, if a pressure of CO$_2$ is placed upon this mixture, a second liquid phase is formed which is rich in methanol [89]. A significant amount

Table 4 Complementary properties of ionic liquids and $scCO_2$.

Ionic liquids	***$scCO_2$***
Considered as polar solvent, low gas solubility	Nonpolar, good solubility with gas
Nonvolatile	High volatility
Low diffusivity and moderate or high surface tension	High diffusivity, low surface tension
Good affinity for charged transition metal complexes	Weak solubility of transition metal complexes Special ligand required (e.g., with fluorous ponytails)
Product extraction may be complex cross-contamination possible	Ease of separation of reaction products, recoverability
Reactor design may be quite simple	Relatively high cost of equipment for producing and handling $scCO_2$
May be costly, limited data concerning toxicity	Low cost, nontoxic

of CO_2 dissolves in ILs but ionic liquids do not dissolve in CO_2 (below detection limit). In the presence of $scCO_2$, the viscosity of IL solutions is reduced. This can facilitate mass-transfer processes and $scCO_2$ can be used in combination with ILs during catalytic reactions. In this case, given the significant solubility of CO_2 in ILs, the physico-chemical properties of the solvent will be changed and one can expect differences in reaction performances. $scCO_2$ can also be added after the reaction. But the choice of the extraction method will probably affect the outcome of the reaction. A wide variety of organic products can be extracted using $scCO_2$ [90], but in general products having a higher affinity for CO_2 (poorly polar solutes) are more easily removed. The main disadvantage of using $scCO_2$ is relatively high-pressure operation.

Other separation techniques have been proposed, such as membrane separation, adsorption, chromatography, pervaporation [91], and the use of chelating agents (but essentially for extraction of metal ions).

While biphasic or multiphasic systems facilitate homogeneous catalyst separation and recovery, they introduce kinetic barriers and can make the resulting process more complex. The low concentration of gas in ILs could lead to mass-transfer problems [92]. As an example, the solubility of hydrogen, most commonly used in hydrogenation and hydroformylation reactions, has been determined in 11 different ionic liquids using high-pressure ^1H NMR spectroscopy. It is much lower than for organic solvents and in the same range as for water [92, 93].

In general, ILs have a higher viscosity than many organic solvents and that may reduce the rate of diffusion of the reactants to the surface of the catalyst. For some reactions, higher activity may be obtained with IL-free catalysts.

5.2.1.1.8
Conclusion

Ionic liquids are now commercially available, which makes their broader application easier. The range of chemistry demonstrated in ILs is wider than in fluorous solvents and supercritical CO_2. Most of reactions are bench-scale. Some applications have been developed on a pilot scale and the specific benefits of using ILs are underlined.

There is a growing variety of cation–anion combinations leading to ILs, and novel salts, with specific properties, are still emerging. Among the more than 20 reactions investigated, there is a strong focus on C–C bond formation, hydrogenation (including enantioselective hydrogenation), hydroformylation, oligomerization, and the use of ILs as both solvents and catalysts for acidic reactions. Biocatalysis is also emerging as a new area in ILs. Some of these reactions are described in the following sections.

Is there evidence of really new chemistry? It is often more the demonstration of known chemistry using an improved technology, better use of catalyst and the possibility of recycling it. However, in some cases, new selectivities/activities have been observed.

Very often, some issues remain to be addressed, such as mechanistic studies, kinetics, and the location of the reaction. The level of knowledge concerning the physico-chemical properties of ILs has been raised in recent years but is still to be improved.

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5.2.1.2
Fundamentals

Tom Welton

5.2.1.2.1
Ionic Liquids: A New Class of Solvents

In the mid-1990s you would have been very unlikely to find a synthetic chemist considering whether an ionic liquid (IL) might be the best possible solvent in which to try a catalytic reaction. At that time there were very few chemists who had even heard of them. They may have remembered from their undergraduate days that metals are often extracted from their ores electrochemically in molten salt baths operating at high temperatures, but it is likely that this would be the full extent of their knowledge. Today, I would be very surprised to find that the same chemist was not well aware of the existence of ILs and that they could possibly be a useful addition to the range of solvents that they might use. So how has this change come about in such a short time?

Much of this interest is centered on the possible use of ILs as “green” alternatives to volatile organic solvents. This claim rests on the fact that ILs are practically nonvolatile under ambient conditions. Hence, the exposure risk to ILs is much lower than it is for a volatile solvent, thus removing one of the most important, and costly to control, vectors for their absorption by the body, particularly important for workers in the chemical industry. The nonvolatility also leads to ILs being nonflammable at ambient, and considerably higher, temperatures [1]. However, there are many potential solvents in existence that meet these criteria but have not been the subject of over 600 research papers in 2003 alone. So, why are ILs of such intense interest?

It seems that ILs have really sparked the collective imagination of the chemical community. The possibility that using this new type of liquid may lead to significant differences in the reactivities of solute species is very exciting. Added to this, in the early 1990s the liberation of those studying ILs from the constraints imposed by working with highly corrosive, moisture-sensitive chloroaluminate(III) systems occurred. These had been investigated for their possible electrochemical applications since their discovery in 1951 [2], but in 1992 the first of the air- and moisture-stable ILs, [EMIM][BF_4], was announced [3]. More recently, the ability to buy ILs in a range of qualities from a variety of suppliers has lowered the activation barrier to their use by nonspecialists still further.

Before embarking upon the main part of this section it is necessary to define the terms that will be used. When pure, ILs are liquids composed entirely of ions. Generally, they are defined as liquid at temperatures below 100 °C; however, *ambient-temperature* ILs are liquid at and below room temperature.

5.2.1.2.2
Physico-chemical Properties of ILs

In selecting a solvent for catalysis, both physical properties, such as melting points and viscosities, and chemical properties need to be considered. There have been several review articles covering these data in recent years [4].

Liquid Ranges

The existence of a useful liquid range is a prerequisite for a material being used as a solvent. Since ILs are nonvolatile they do not have a boiling point. For that reason their upper limits are generated by their decomposition (see below). The lower limits are provided by their melting or glass transition temperatures.

Melting Points

The accurate prediction of the melting points of salts remains an elusive aim. Lattice energies are relatively easy to calculate, but as shown in Table 1 they are poor predictors of melting points, even for the simplest salts. The principal reason for this is that the structure of the liquid form, which plays no part in determining the lattice energy of the salt, is as important in determining its melting point as the solid-state structure and can introduce a number of complications.

An attempt has been made to use the quantitative structure–property relationship (QSPR) method to correlate and predict the melting points of organic salts based on the quaternary ammonium cation [5]. Moderate correlations were found for a set of 75 tetraalkylammonium bromides (see Figure 1), and for a set of 34 (*n*-hydroxyalkyl)trialkylammonium bromides. Descriptors used in the correlations were analyzed to determine which structural features led to lower melting points (e.g., asymmetry in the ions – see below). However, this technique cannot, as yet, extend to the prediction of melting points for salts that are either chemically or topologically dissimilar to those used in defining the QSPR.

As shown below, there are a number of factors that all together lead to the melting point of a salt. For different materials each factor contributes to a different degree. Further to this, many of the materials that form ILs are glass-forming. This means that the change of state can happen at different temperatures when heating or

Table 1 The melting points and lattice energies of some simple salts.

Salt	*Melting point [°C]*	*Lattice energy [kJ mol^{-1}]*
NaCl	801	–778
NaBr	747	–741
NaI	660	–690
LiCl	614	–845
AgBr	432	–890
CsI	621	–602

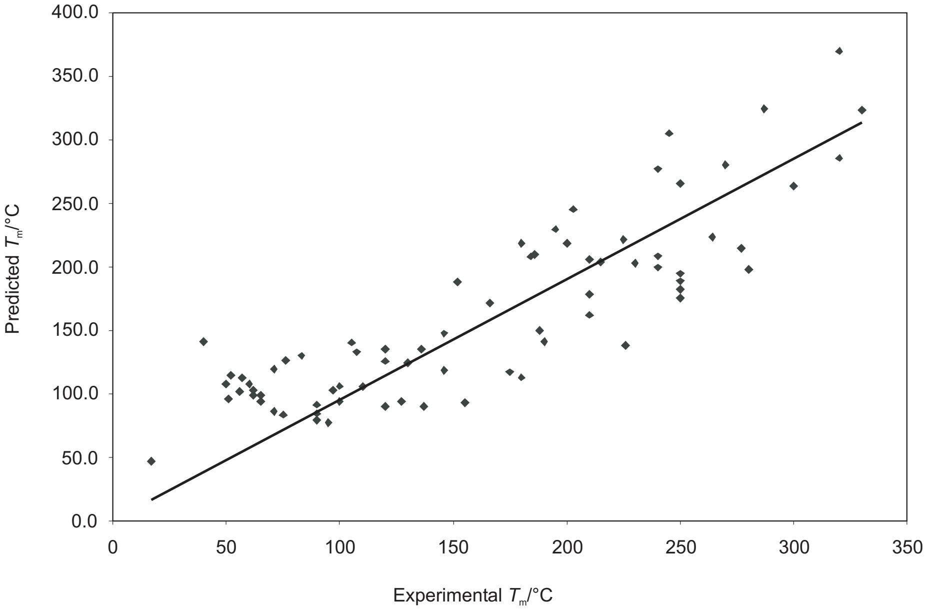


Figure 1 Predicted (QSPR) vs. experimental melting points for a series of tetraalkylammonium bromide salts ($R^2 = 0.775$).

cooling and, in the latter case, are usually dependent on the cooling rate. Therefore, it is unsurprising that melting points are difficult to predict. However, there are some generalizations that can be made.

In order to reduce the melting of a salt it is necessary to reduce the attraction of the ions for each other. The principal attraction of ions for each other comes from Coulombic forces [see Eq. (1) where q_i is the charge on the particle i, ε_r is the relative permittivity of the medium and r is the separation of the charges]. Hence, it is rare to find an IL with multiply-charged ions.

$$\text{force} = \frac{q_1\, q_2}{4\,\pi\,\varepsilon_r\, r^2} \tag{1}$$

By increasing the charge separation one can reduce the Coulombic attraction of the ions for each other. Table 2 shows the changing melting points of some tetraalkylammonium salts [6].

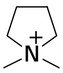
Generally, as the ion gets larger the melting point of the salt gets lower. However, other effects also have a role to play and it can be seen that the masses, polarizabilities, etc., of the ions can be more important than their size; for example, $[Bu_4N][BF_4]$ has a much lower melting point than $[Bu_4N][PF_6]$.

Another way of reducing the melting point of a salt is to delocalize the charge over several atoms. For instance 1,3-dimethylimdazolium bis(trifluoromethyl)imide (**1**), in which the cation has an aromatic ring, has a melting point of 22 °C, while the 1,1-dimethylpyrrolidinium salt (**2**), in which the ring is not aromatic, has a melting point of 105 °C [7].

Table 2 The melting points of some tetraalkylammonium chlorides.

Salt	*Melting point [°C]*
$[Et_4N]Cl$	> 300 (dec)
$[Pr_4N]Cl$	240–242
$[Pe_4N]Cl$	~195
$[He_4N]Cl$	111–113
$[Oct_4N]Cl$	50–54
$[Dodec_4N]Cl$	82–84
$[Bu_4N]Br$	103–104
$[Bu_4N]I$	145–148
$[Bu_4N][Br_3]$	74–76
$[Bu_4N][I_3]$	69–71
$[Bu_4N][BF_4]$	155–161
$[Bu_4N][PF_6]$	246
$[Bu_4N][BPh_4]$	235–237

1



2

The ability of the ions to approach each other closely and, hence, the melting point of a salt can also be reduced by disrupting the structure of the crystal and preventing efficient crystal packing. This can be achieved by breaking the symmetry of the ions. Again the 1,3-dialkylimidazolium bis(trifluoromethyl)imide salts provide some good examples (Table 3) [7], with the melting point of $[EMIM][NTf_2]$ being lower than that of the bulkier $[EEIM][NTf_2]$.

It is also possible to reduce the melting point of a salt by manipulating the chemical properties if the ions. On going from $[EMIM][CH_3CO_2]$ to $[EMIM][CF_3CO_2]$ (Table 4)

Table 3 The melting points of some 1,3-dialkylimidazolium bis(trifluoromethyl)imide salts [7].

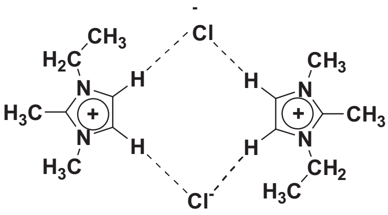
Cation	*Melting point [°C]*
$[MMIM]^+$	22
$[EMIM]^+$	–3
$[EEIM]^+$	14
$[BMIM]^+$	–4

Table 4 The melting points of some 1,3-dialkylmethylimidazolium and trialkylmethylimidazolium salts [7].

IL	*Melting point [°C]*
$[EMIM][CH_3CO_2]$	45
$[EMIM][CF_3CO_2]$	–14
$[EMIM][CF_3SO_3]$	–9
$[EMMIM][CF_3SO_3]$	109
$[EMM^5IM][CF_3SO_3]$	6

the electronegative fluorine atoms remove electron density from the acetate group, making the ion less basic and less attractive to the cation, partly due to the weakening of the cation–anion hydrogen bond. This reduces the melting point by over 50 °C.

However, the blocking of hydrogen bonding does not always have the expected result. One might expect that the methylation of an $[EMIM]^+$ cation at the 2-position of the imidazolium ring would lead to a lower melting point for salts of the $[EMMIM]^+$ ion. In fact, quite the reverse is seen (Table 4) and it leads to an increase in the melting point of over 100 °C. It is not clear why such a dramatic increase in melting point should occur with this substitution, especially when methylation at the 5-position of the ring leads to only a 15 °C increase in the melting point. In both of these cases a hydrogen bond donor position is blocked, the stronger one being at the 2-position of the ring, and the addition of an electron-donating substituent to the cation would be expected to reduce the hydrogen bond donor character of the remaining sites further. Although some additional mass has been added to the cation, it would not be expected to make a difference of this amount. The crystal structures of [EMMIM]Cl and $[EMMIM]_2[MCl_4]$ (M=Co or Ni) are known and show that cyclic structures bridged by hydrogen bonds are formed (**3**) [8]. One possible explanation for the high melting point of these $[EMMIM]^+$ salts is that this formation is particularly difficult to break apart.



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The interplay of these various effects is very well demonstrated in a study of the thermal behavior of 45 different salts prepared by the reaction of five different substituted imidazoles and nine different Brønsted acids [9]. The study shows particularly well that predictions based on any one of the parameters that can affect melting points alone will often fail.

The final way in which the melting point of a salt can be reduced is by mixing it with another salt. This technique has been used for many years to reduce the melting points of high temperature molten salts [10]. For instance, sodium is produced on the industrial scale in the Down's cell from $NaCl–CaCl_2–BaCl_3$ mixtures, giving an operating temperature 200 °C below the melting point of pure NaCl.

The phase diagram for $[EMIM]Cl–AlCl_3$ is probably the most well recognized of any nonaqueous IL and is reproduced in Figure 2 [11]. The local maximum at the 50 mol% $AlCl_3$ composition (7 °C) represents the compound formation point of $[EMIM][AlCl_4]$. The phase diagram can then be considered in two parts. The compositions with less than 50 mol% $AlCl_3$ (so-called basic compositions) contain mixtures of [EMIM]Cl and $[EMIM][AlCl_4]$. The deviation from ideal mixing is not

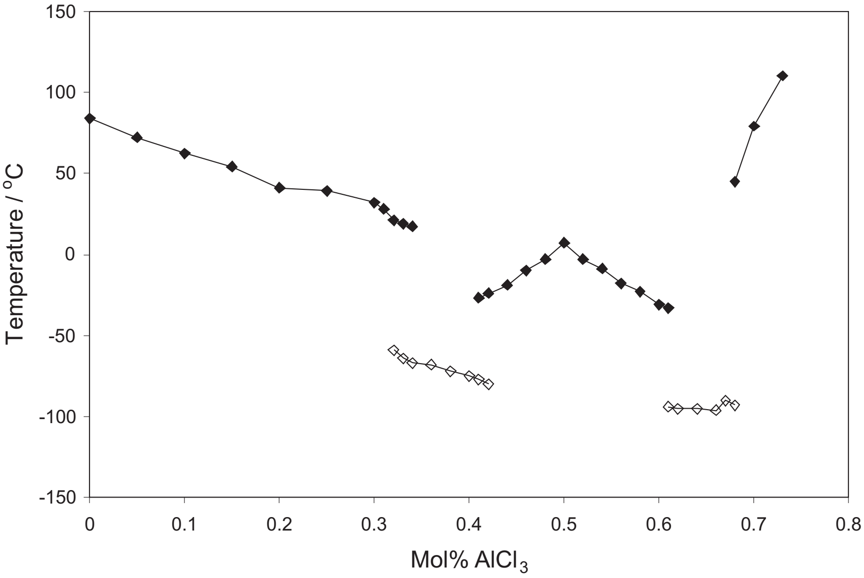


Figure 2 The phase diagram for [EMIM]Cl–$AlCl_3$ [11].

very pronounced at low concentrations of $AlCl_3$ and becomes more important close to the neutral composition. In addition to this, compositions with between 36 and 40 mol% $AlCl_3$ fail to crystallize and only give glass transitions, leading to the liquid being maintained at temperatures as low as –75 °C.

At compositions with more than 50 mol% $AlCl_3$ (acidic compositions) the situation is more complex. Here, as well as the expected $[AlCl_4]^-$ and $[Al_2Cl_7]^-$, heavier chloroaluminate(III) ions, such as $[Al_3Cl_{10}]^-$, can be found. The phase diagram for the acidic compositions again shows significant deviation from ideal mixing and a range of compositions from 61 to 68 mol% $AlCl_3$ which fail to crystallize and glass transform at very low temperatures (~90 °C). This “W” formation is common in phase diagrams of the ternary ILs.

Decomposition Temperatures

For molecular solvents the upper operating temperature is usually defined by its boiling point. ILs, however, have no vapor pressure and do not boil. All known ILs decompose at temperatures much lower than those at which they might evaporate as ion pairs, in the way that simple salts do. Hence, the upper operating limit of an IL is caused by its thermal decomposition. One consequence of this is the loss of the ability to control a reaction’s temperature by using the simple reflux technique.

Of course, decomposition is a chemical phenomenon and depends on the nature of the ions that compose the IL. Angell et al. [9, 12] have investigated the decomposition behavior of various binary ILs that can be formed by the proton transfer that occurs between neat Brønsted acids and bases [Eq. (2)].

$$B + AH \rightleftharpoons [BH]^+ + A^- \qquad (2)$$

They found that the temperature at which the total vapor pressure reaches 1 atm, or 0.1 kPa (boiling), can be predicted by the difference in the pK_a values, in dilute aqueous solution, of the acid and base (ΔpK_a). The larger the difference in pK_a the higher the boiling temperature. The differential thermal analysis scan reproduced in the paper showed that, under the conditions used, the onset of boiling was over a small temperature range and can be used as an estimation of the upper limit of the useful liquid range of the IL.

The decomposition pathway for these IL is the reverse of their formation and the regeneration of the molecular acid and base, which are volatile materials. That is, ΔpK_a is acting as a good indicator of the degree of proton transfer for the pure materials and therefore the amount of molecular material in the mixture. Water is a polar solvent that can act as both a hydrogen bond acid and base. Many ionic liquids match this behavior (see below) and this may explain why the aqueous pK_a values give such good predictions. This is the only report that, to the author's knowledge, provides a method for the prediction of decomposition temperatures for ILs. When ΔpK_a was above 10, the boiling point elevation was so high (> 300 °C) that other decomposition pathways became important.

At these elevated temperatures or when facile proton transfer is not available as a route for decomposition, other reactions assume importance. For the ILs reported to date, thermal decomposition is associated with the cation, the principal reaction proposed being a simple nucleophilic substitution to give volatile products [Eq. (3)].

$$X^- + [R_4N]^+ \rightarrow RX + R_3N \qquad (3)$$

Therefore, most studies have identified the nucleophilicity of the anion of the IL as a key determinant of the decomposition temperature (cf. Table 5 [1, 13–16]. Of the currently commonly used anions, $[NTf_2]^-$ gives rise to the most stable IL. If good thermal stability is required then halide ions, which are good nucleophiles, should be avoided. The addition of water, which can act as a nucleophile, has been shown to reduce the decomposition temperature of a number of ILs [14].

It has been shown that the thermal stability of a series of 1-alkyl-3-methylimidazolium-based ILs increases as the length of the alkyl chain increases [16].

Table 5 The decomposition temperatures of some $[BMIM]^+$ IL [14].

Anion	*Melting point [°C]*
Cl^-	254
I^-	265
$[BF_4]^-$	403
$[PF_6]^-$	349
$[NTf_2]^-$ (dry)	439
$[NTf_2]^-$ (wet)	394

Methylation at the 2-position of the imidazolium ring also results in an increase in the stability of imidazolium-based ILs [13]. This is probably best explained by the addition of an electron-donating substituent leading to a reduction in the electrophilicity of the α-carbons of the alkyl chains.

Some caution must be used when relying on the literature in this area. It has been demonstrated that slow decomposition can occur at temperatures considerably below the decomposition onset temperatures found in thermograms recorded at conventional heating rates [1]. Measurement of the isothermal decomposition rate for [BMMIM][PF_6] showed that although a decomposition temperature of 420 °C had been noted, significant mass loss (15% h^{-1}) occurred at 300 °C and there was noticeable mass loss as low as 200 °C. Of course, if the IL is to be used for extended periods of time, or repeatedly, then this could prove to be crucial in determining appropriate operating temperatures and/or selection of the IL.

Nucleophiles may be used as one of the reagents for a reaction. In this situation it is possible that the reagent may lead to the decomposition of the IL. This has been noted in studies of fluorination reactions [17]. In this paper the decomposition products of [BMIM][PF_6] included both 1-fluorobutane and 1-butene, showing that both substitution and elimination reactions were occurring [Eq. (4)].

$$2\,[\mathrm{BMIM}]^+ + 2\,\mathrm{F}^- \rightarrow \mathrm{C_4H_9F} + \mathrm{C_2H_5CH{=}CH_2} + 2\,\mathrm{MEIM} \tag{4}$$

Scientists working for the US Air Force have prepared “highly energetic” ILs [18]. 4-Amino-1,2,4-triazolium, 1,2,4-triazolium, and 1,2,3-triazolium cations were combined with nitrate, perchlorate, and dinitramide anions to give nine different ILs. The onset of thermal decomposition was a function of both the cation and the anion and is most likely the consequence of proton transfer from the cation to the anion, to generate molecular species. The ILs were also tested for impact stability. Interestingly, as the anion was changed the thermal stability varied in the order $[N(NO_2)_2]^- > [NO_3]^- > [ClO_4]^-$, reflecting the basicity of the ions [12], whereas the impact stability varied in the order $[NO_3]^- > [ClO_4]^- > [N(NO_2)_2]^-$, reflecting the oxidizing ability of the ions.

Selection of Ions

As stated, it is not yet possible to predict the liquid range of any given combination of cation and anion. However, if one wishes to prepare an IL with a particular cation or anion, because it has a specific chemical property of interest, some advice on the selection of the counterion can be given. Generally, $[N(CN)_2]^-$ and $[NTf_2]^-$ appear to give ILs with relatively low melting points for any given cation. $[N(CN)_2]^-$ is more nucleophilic than $[NTf_2]^-$, so if the upper liquid range is important then the $[NTf_2]^-$ ion is probably the best place to start. Similarly, if the anion is fixed, $[BMIM]^+$ cations give relatively low melting points for any given anion.

5.2.1.2.3
Viscosities

As well as having a useful liquid range an IL that is going to be used as a solvent for catalysis should also be of moderate viscosity. Low-viscosity liquids help to reduce mass-transfer problems and, of course, make stirring easier. Ionic liquids have a reputation for being highly viscous. While it is true that all of those prepared to date have higher viscosities than most commonly used organic solvents, they are generally not so high as to make them difficult to engineer. For example, acetone at 25 °C has a viscosity of 0.32 cP, whereas [BMIM][CF_3SO_3] has a viscosity of 90 cP [7], which is similar to that of olive oil (84 cP at 20 °C) [19]. To date all published studies of the viscosities of ILs have assumed that they are Newtonian fluids, i.e., their viscosity is independent of shear rate, like common molecular solvents. However, this has not been investigated in detail, particularly at temperatures where the liquid is in a supercooled or near-glass condition.

One feature of ILs that is mainly the result of their high viscosities is the time that it takes for many solid materials to dissolve. It is common to find that materials that are perfectly soluble in an IL in terms of saturation concentration will require stirring, often for several days, to reach that concentration. This can lead to a belief that the material is not soluble in the IL and can also be very inconvenient. This problem is often addressed by heating the mixture until the material dissolves, or by first dissolving it in a volatile solvent that mixes well with the IL (e.g., dichloromethane) then adding the solution to the IL and removing the volatile solvent in vacuo. If this latter technique is used, one must ensure that the volatile solvent does not interfere with the reaction being conducted.

In order for a liquid to flow, its component molecules or ions must be able to move relative to each other. Intermolecular or interionic interactions restrict this motion and cause the viscosity of the liquid, its resistance to flow, to increase. These frictional forces are the same forces that were considered when understanding the melting points of the IL, i.e., Coulombic attraction, dipole interactions, hydrogen bonding, etc. As with melting points, no single interaction dominates the viscosity of the IL; it arises from combinations of all of them [7, 9, 14, 20]. The consensus is that the viscosities of ILs are determined largely by a complex combination of van der Waals interactions, hydrogen bonding, and ion size. For example, when the cation was 1-ethylimidazolium {$[EIM]^+$} it was found that the viscosity of a range of ILs varied such that $[BF_4]^- < [NTf_2]^- < [CF_3SO_3]^- < [ClO_4]^- < [PF_6]^-$ [9]. If the Coulombic interactions and hydrogen bonding were dominant then the viscosities of $[BF_4]^-$ and $[PF_6]^-$ would be reversed, but $[PF_6]^-$ is larger and has greater potential for dispersion interactions. If size were the only important factor, $[EIM][NTf_2]^-$ would be the most viscous, rather than one of the least. It was noted that the room-temperature viscosities were related to the glass transition temperatures, with those having the lowest glass transition temperature having the highest room-temperature viscosity. When the anion was kept constant and various $[NTf_2]^-$-based ILs were investigated the same complex behavior was seen, including the relationship with the glass transition temperature. It is easier to make predictions if only small changes are being made in the ILs. For instance, it has been shown that lengthening the alkyl chain for a series of $[RMIM]^+$ ILs leads to an increase in viscosity [14].

The complexity of this behavior makes it difficult to predict the viscosity of any new IL. However, some general statements can be made. As a rule of thumb, but no more, $[N(CN)_2]^-$- and $[NTf_2]^-$-based ILs appear to be the ions that will give relatively low viscosities for any given cation, and $[EMIM]^+$ cations give relatively low viscosities for any given anion.

It is well known that the viscosity of a liquid decreases upon heating. This would usually be expected to fit to an Arrhenius type of behavior. That is, the natural logarithm of the viscosity should vary in a linear manner with temperature. All of the ILs for which the temperature dependence of the viscosity has been studied deviate from this behavior [7, 9, 11, 14, 20]. Rather, they fit a Vogel–Tammann–Fulcher interpretation where the viscosity of the IL at any given temperature is better related to a material-specific temperature such as the difference between the temperature of the study and the glass transition temperature of the IL.

The viscosities of ILs have been shown to be highly sensitive to small amounts of other solvents [14, 21]. Given that it is commonly expected that ILs will be used in biphasic conditions or that molecular solvents will be used in extraction processes, this is a very important observation. A study of the effect of a range of different co-solvents, from water to toluene, showed that the viscosity reduction of $[BMIM][BF_4]$ was a colligative property, independent of the chemical nature of the co-solvent and only dependent on the concentration (mol mol^{-1}, Figure 3) [21].

This has important implications for the engineering of reactions in ILs. In a reaction where the overall sum of the concentrations of all the solutes is not changing (e.g., a substitution reaction with no precipitation of products) then there should be no change in the viscosity of the solution during the reaction. However, when the reaction is such that the overall sum of the concentrations of all the solutes is changing (e.g., addition or elimination, or when a product is precipitated) then the viscosity of the solution would be expected to change during the reaction.

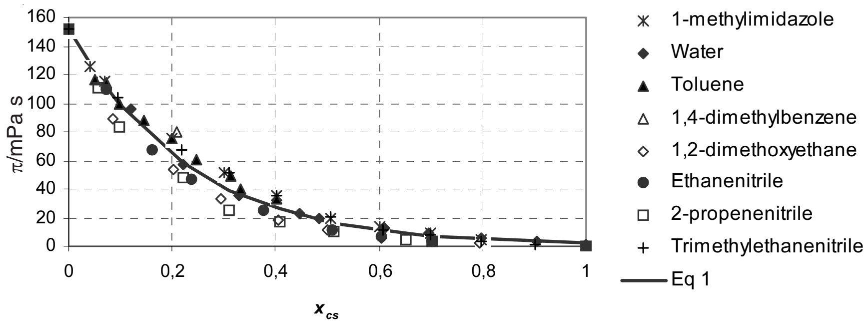
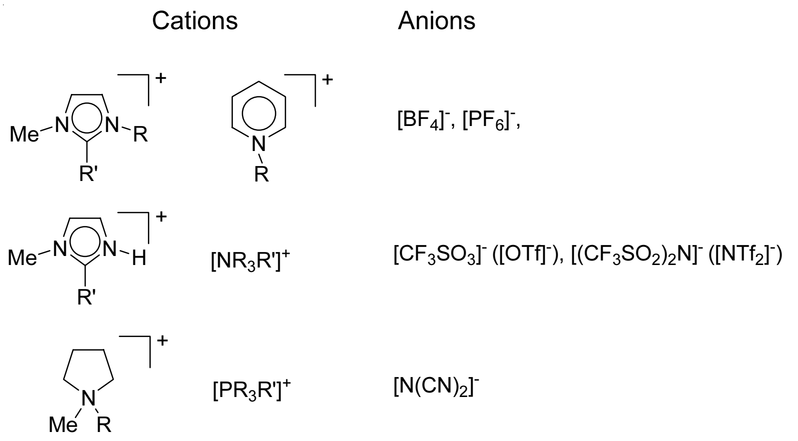


Figure 3 The effect of adding a co-solvent to $[BMIM][BF_4]$ [21].

5.2.1.2.4
Commonly Used ILs

Although there is an ever-growing list of ILs, a relatively small number of cations and anions get used often (**4**–**6**). It is on the basis that they give room-temperature liquids with reasonable viscosities (i.e., there is no difficulty in stirring with standard magnetic stirrers) and that they are available at a realistic cost that they are chosen. The 1,3-dialkylimidazolium salts remain the most intensively investigated, with the 1-alkylimidazolium salts becoming more common. Typically, the anions are inorganic and include $[PF_6]^-$, $[BF_4]^-$, $[CF_3SO_3]^-$ and $[(CF_3SO_2)_2N]^-$, although, more recently, organic anions (e.g., $[RCO_2]^-$) have also been introduced.



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5.2.1.1.5
Solubilities

When using a solvent in catalysis it is important to understand its mixing behavior with potential solutes or other solvents that may be used with it in biphasic reaction systems. For example, it has been shown that the rate (TOF) of the rhodium-catalyzed hydroformylation of 1-hexene in a range of ILs is generally well correlated with the solubility of the 1-hexene [22]. If, as in this example, a particular material is of great interest, its miscibility with the solvent should be studied in detail. However, it is also useful to be able to gain some capacity to predict how a wide range of different materials will interact with the solvent. Both approaches have been used with ILs.

Water/Ionic Liquids

The miscibility of ILs with water has attracted a great deal of attention; this is partly because water is ubiquitously present, but also because its behavior in ILs is particularly interesting and controllable. All ILs described to date are hygroscopic.

Some will mix with water in all compositions and are called hydrophilic, whereas others eventually saturate and then form two layers with the water and are called hydrophobic [9, 14, 21]. This behavior is principally controlled by the anion, which can form hydrogen bonds to the water [23]. Consequently, ILs with good hydrogen bond base (see below) anions, such as $[OTf]^-$, form strong hydrogen bonds to water (~16 kJ mol^{-1} in [BMIM][OTf]) and are hydrophilic, whereas those with weak hydrogen bond base anions, such as $[NTf_2]^-$, form weaker hydrogen bonds to water (~10.5 kJ mol^{-1} in $[BMIM][NTf_2]$) and are hydrophobic. For any given anion, the solubility of water decreases as the degree of alkylation of the cation increases [24]. This has a very interesting set of consequences for the $[BF_4]^-$-based ILs. $[EMIM][BF_4]$ is miscible with water in all compositions over its entire liquid range, $[BMIM][BF_4]$ separates from water below 4 °C and $[OMIM][BF_4]$ forms two layers with water at room temperature. This behavior has been exploited to provide a temperature-controlled reversible IL/water two phase–single phase protocol for hydrogenation catalysis [25]. The mixture of solvents, reagents, and catalyst is a single homogeneous phase at the temperature of the reaction, but on cooling to room temperature the water-soluble substrate separates into the aqueous layer that has formed above the $[OMIM][BF_4]$, which contains the IL-soluble $[Rh(\eta^4\text{-}C_7H_8)(PPh_3)_2][BF4]$ catalyst. The solubility of water in ILs can also be manipulated by adding short-chain alcohols to biphasic systems to increase mixing [26], or adding salts to separate otherwise water-miscible ILs [27].

Electrochemical studies suggest that water can form nanoscale droplets in ILs [28]. IR spectra suggest that this is so for IL with highly basic anions such as $[CF_3CO_2]^-$, but that in other ILs the water is well dispersed [23].

A potentially quick and easy method for the determination of the solubility of ILs in water using electrospray mass spectrometry has recently been reported [29]. The method determines the concentration of an IL in solution by using the cation and anion of another IL as internal standards.

CO_2/ILs

Ionic liquids form biphasic mixtures with supercritical CO_2 ($scCO_2$), with the IL showing very low solubility in the CO_2 layer, but the CO_2 having significant solubility in the IL [30]. It is widely hoped that this will be developed into a "green" biphasic reaction system, in which the catalyst is trapped in the IL layer and the reagent and products can be added and removed in the CO_2 layer [31]. This system also offers the possibility of reducing mass-transfer constraints, by the $scCO_2$ increasing reagent solubility in the IL phase at the same time as reducing its viscosity. However, it has been noted that the presence of other solutes can lead to the IL becoming significantly soluble in the $scCO_2$ phase, which could limit the use of this technique [32]. Polar compounds such as ethanol and acetone, in which the IL is soluble, had a greater effect than nonpolar compounds in which it is not soluble.

The solubility of CO_2 in ILs can be manipulated by changing both the cation and anion [33]. The solubility of the CO_2 increases as the anion is changed from $[PF_6]^-$ to $[N(Tf)_2]^-$ and as the cation is substituted with a fluoroalkyl chain. The affinity of highly fluorinated compounds for CO_2 is well established and has been used to make CO_2-soluble catalysts with highly fluorinated phosphine ligands (see Chapter 4). It is this affinity that is being exploited here.

Other Gases

The solubilities of a range of different gases (carbon dioxide, ethylene, ethane, methane, argon, oxygen, carbon monoxide, hydrogen, and nitrogen) in 1-butyl-3-methylimidazolium hexafluorophosphate have been measured [34]. Carbon dioxide had much the highest solubility at all gas pressures used, but showed a nonlinear increase in solubility with pressure, indicating that a pressure-independent solubility limit was being approached. The next most soluble gases were ethylene and ethane, which did show linear increases in solubility with pressure. Argon, oxygen, and methane had solubilities in the $[BMIM][PF_6]$ that were much lower than found in many molecular solvents. Carbon monoxide, hydrogen, and nitrogen all had solubilities below the detection limit of the apparatus used. The low solubility of the dipolar CO in comparison to the high solubility of CO_2 is, at first glance, surprising. However, molecular dynamics simulations have attributed the high solubility of CO_2 to its high *quadrupole* moment [35].

The low solubility of gases that are reagents in many reactions (hydrogenations, hydroformylations, oxidations) raises some concern that there may be mass-transfer limitations for processes involving their use in ILs. This has been specifically investigated for the hydrogenation of benzene to cyclohexane in a range of ILs [36], where no correlation between H_2 solubility and the reaction rate was found. Evidence from the asymmetric hydrogenation of 2-phenylacrylic acid and 2-(6-methoxy-2-naphthyl)acrylic acid in $[BMIM][BF_4]$ using the chiral catalyst $[RuCl_2–(S)\text{-}BINAP]_2 \cdot NEt_3$ revealed that the enantioselectivity was independent of the hydrogen pressure [37]. Since the enentioselectivities of these hydrogenations are known to be positively dependent on the availability of H_2 to the catalyst and hence on the hydrogen concentration in the solution [38], this suggests that at the hydrogen pressures used (3.5–10 MPa) the hydrogen concentration in the solution was maintained at the saturation concentration in the IL and that H_2 transfer into the IL was fast in comparison to hydrogen uptake by the substrate. Hence, it is possible that, for the relatively slow arene hydrogenations, the rate of uptake of the H_2 is sufficiently fast for it not to affect the overall rate of the reaction. However, the faster hydrogenation of α-acetamidocinnamic acid with $[Rh(COD)(EtDUPHOS)][CF_3SO_3]$ in $[BMIM][BF_4]$ or $[BMIM][PF_6]$ did show that it was indeed the saturation concentration of H_2 in the different ILs at a given pressure that controlled both the activity and the selectivity of the catalyst rather than the H_2 pressure (0.5–10 MPa) in the reaction vessel itself [39].

Hydrocarbons

In many biphasic systems with ILs the second phase will be a hydrocarbon. The solubility of $[BMIM][PF_6]$ in aromatic hydrocarbons (benzene, toluene, ethylbenzene, *o*-xylene, *m*-xylene, *p*-xylene), in *n*-alkanes (pentane, hexane, heptane, octane), and in cyclohydrocarbons (cyclopentane, cyclohexane) has been measured [40]. In aromatic hydrocarbons it decreases with an increase in the hydrocarbon's molecular weight, and there is little difference in the solubility in the three different xylenes. However, [BMIM][PF_6] is significantly more soluble in the aromatic hydrocarbons than in the alkanes. The reason for this has been addressed in a theoretical paper [35]. Molecular dynamics simulations of solutions of benzene in dimethylimidazolium chloride and dimethylimidazolium hexafluorophosphate showed that the local electrostatic IL–benzene interactions that are possible because of the presence of the aromatic π-system could almost entirely explain these solubility differences.

5.2.1.2.6
Polarity

In order to predict the likely solubilities (and other properties) of compounds that have not been tested and to compare ILs to other solvents it is necessary to have some measure of how they interact with solute species. Polarity is the sum of all possible (nonspecific and specific) intermolecular interactions between the solute and the solvent, excluding such interactions leading to definite chemical changes (reactions) of the solute. In ILs any ion–ion, dipole–ion, dipole–dipole, and dipole–induced-dipole interactions, dispersion interactions, hydrogen bonding, and/or π-interactions may be important. The contribution of each in any given solution is dependent upon both the solvent and the solute, each with its own particular characteristics. So it is not possible to measure the properties of ILs in isolation and some other answer to the problem is required.

Given the complexities that can arise from so many different interactions acting together, it is unsurprising that a single physical parameter such as dielectric constant is incapable of adequately modeling the solvent–solute interactions. Various empirical polarity scales have been developed in an attempt to give some approximation to all or some of these interactions [41]. A number of them have been used with different ILs. All of these have their advantages and disadvantages and no single approach can be thought of as exclusively "right".

Chromatographic Measurements

Abraham's solubility model is based on solvation occurring by first generating a cavity in the solvent and then incorporating the solute into that space [42]. By working with GC, and therefore gaseous solutes, the self-association of the solute can be ignored. The form of the model used to investigate IL properties is according to Eq. (5), where K_L is the solute gas–liquid partition coefficient, r is the tendency of the solvent to interact through π- and n-electron pairs (Lewis basicity), s is the contribution from dipole–dipole and dipole–induced-dipole interactions (in molecular solvents), a is the hydrogen bond basicity of the solvent, and b is its hydrogen bond acidity; l expresses how well the solvent will separate members of a homologous series and has contributions from solvent cavity formation and dispersion interactions.

$$\log K_L = c + r\,R_2 + s\,\pi_2{}^H + a\,\alpha_2{}^H + b\,\beta_2{}^H + l\log L^{16} \qquad (5)$$

Poole and his co-workers have used GC measurements and the Abraham solubility model to describe the solvation properties of 38 different organic salts, some of which meet our definition as ILs [43]. Another group of 17 ILs have been studied by Armstrong et al. [44]. Differences in the detail of the measurements mean that it is not possible to make direct comparisons between the two studies, but general trends can be seen.

In both studies the salts had large *s* values, which is usually interpreted as having large dipole–dipole and dipole–induced-dipole interactions. However, this is a value to which one would expect a significant Coulombic contribution. This is probably important in making this value generally high. However, the ILs are not all the same and *s* does vary for the different salts in both studies. Unfortunately, it is not possible to pick out any simple trend.

In both studies it was found that ILs were strong hydrogen bond bases with the basicity being derived from the anion. Fluorinating the anion leads to a reduction in its basicity as electrons are drawn toward the highly electronegative fluorine atoms. The hydrogen bond basicity of the IL generally followed, as one would expect, the Brønsted acidity of the anions.

None of the ILs in either study was found to be a strong hydrogen bond acid. Some of those in the Armstrong study do show some degree of hydrogen bond acidity [44]. However, no cations that would be expected to be very strong hydrogen bond donors, such as $[R_3NH]^+$, were included in the studies. It is interesting to note that although this property must reside with the cation of the IL, the value for the IL as a whole was found to be highly dependent on the selection of the anion.

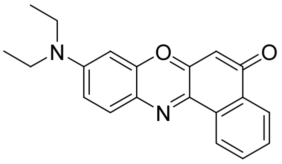
In both studies the ability of the ILs to separate members of a homologous series, which is usually associated with cavity formation and dispersion interactions and, therefore, nonpolar solvents, was unusually high in comparison to nonionic polar solvents. Increasing the alkylation of the cation increased this ability, and so it is open to synthetic manipulation.

Absorption Spectra

The term "solvatochromism" was introduced in 1922 by Hantzshlater [45] to explain the influence of the solvent on electronic absorption spectra. In 1951 Brooker et al. [46] suggested that the solvatochromic effect induced by a solvent on certain probes that have a strong absorption in the UV/Vis could be used as a visual indicator of the solvent polarity. One of the main reasons that spectroscopic measurements are such a popular method to obtain empirical polarity parameters is the simplicity of the experiment. Electronic absorption spectroscopy is a readily available tool that requires little specialist skill to operate. Hence, several of these scales have been used with ILs.

Nile Red

The first solvatochromic dye to be used with a number of IL was Nile red (7) [47]. The ILs used were composed of $[RMIM]^+$ with $[NO_2]^-$, $[NO_3]^-$, $[BF_4]^-$, $[PF_6]^-$, and $[NTf_2]^-$ ions. Although the values of the energy of the electronic transition, E_{NR}, did not vary greatly and fell in the same region as those for short-chain alcohols, there were some differences between the ILs. In molecular solvents the E_{NR} value has been shown to be little affected by hydrogen bonding effects, has been correlated with the Kamlett–Taft π^* scale (see below), and is thought to be dominated by dipolarity and polarizability effects [48]. What is actually being measured is the difference in energy between the ground and excited states and how this is affected by the immediate chemical environment generated by the solvent. Therefore, one would expect a significant contribution from the ion$_{\text{solvent}}$–dipole$_{\text{solute}}$ interactions possible in ILs. This is probably why the values for all of the ILs are high. However, it is clearly not enough to make them in any way “super-polar”.



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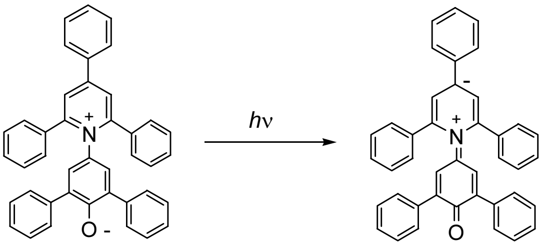
The polarity of the IL was shown generally to decrease with increasing size of the anion. The increased polarizability of the $[NTf_2]^-$ anion led to a slight increase in the polarity of [BMIM][NTf$_2$] in comparison to [BMIM][PF$_6$].

Reichardt’s E_T^N Scale

The longest-wavelength absorption band of Reichardt’s dye (2,4,6-triphenylpyridinium-*N*-4-(2,6-diphenylphenoxide) betaine [Eq. (6)] shows one of the largest solvatochromic shifts known (375 nm between diphenyl ether and water) [49]. It changes to higher energy with increasing solvent polarity. The energy scale is then normalized to the values for TMS and water to give the E_T^N scale of solvent polarity. This is probably the most commonly used empirical polarity scale and it is the scale that has been applied to the greatest number of ILs (Table 6) [50–54].



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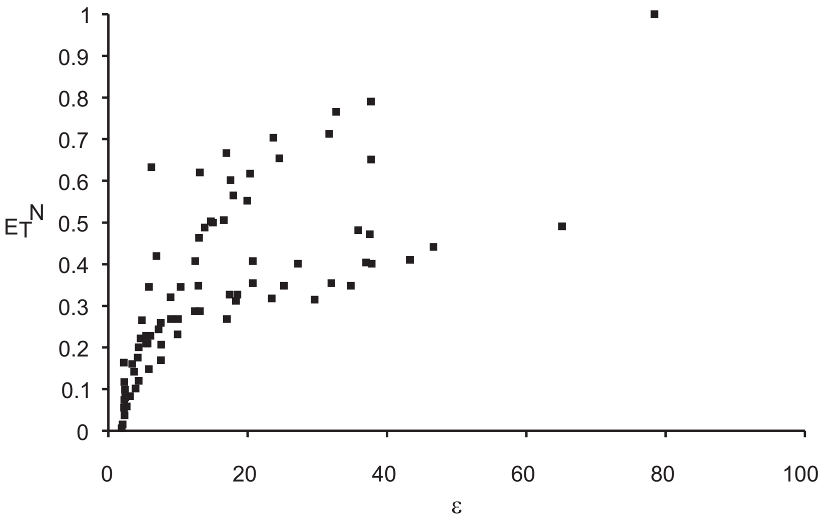


Figure 4 The E_T^N values of a selection of molecular solvents (ε = dielectric constant) [41].

Again the E_T^N value can be attributed to differences in the stabilization of the more polar ground state and the less polar excited state.

It can register effects arising from the solvent dipolarity, hydrogen bonding, and Lewis acidity, with the greatest contribution coming from the hydrogen bond donor property of the solvent [55]. This can be seen in Figure 4, which shows how E_T^N varies with dielectric constant for 75 molecular solvents.

As the solvents become more polar the difference between those that can act as good hydrogen bond donors and aprotic solvents of similar dielectric constant becomes more pronounced. This arises because the phenoxide oxygen of the ground state of the dye acts as a good hydrogen bond acceptor.

It can be seen (Table 6) that the E_T^N values for the ILs are dominated by the identity of the cation. For instance, values for monoalkylammonium nitrates and thiocyanates are ca. 0.95–1.01, whereas the tetraalkylammonium salts have values ca. 0.42–0.46. The 1,3-substituted imidazolium salts lie between these two extremes, with values of ca. 0.64–0.67 (similar to those of polar hydrogen bond donor solvents such as alcohols). The E_T^N value for [HO(CH$_2$)$_2$MIM][NTf$_2$] is much higher (0.93), which is similar to the values for the N–H hydrogen bond donors. This can be attributed to the bearing of an alcohol functionality on one of its alkyl chains. [CH$_3$O(CH$_2$)$_2$MIM][NTf$_2$] also has a higher than expected E_T^N value. This probably arises from the electron-withdrawing effect of the oxygen atom of [CH$_3$O(CH$_2$)$_2$MIM]$^+$ increasing the acidity of the neighboring protons, rather than from the ether link itself, which is basic.

The [BMMIM]$^+$ salts have lower E_T^N values than the equivalent [BMIM]$^+$ salts, showing the role of the 2-position of the ring in determining the hydrogen bond donor properties of these cations.

Although the hydrogen bond donor component of the ionic liquid is the cation, ionic liquids with the same cation but different anions do have different E_T^N values.

Table 6 Solvent polarity measurements of some ILs.

Compound	E_T^N	π^*	α	β	***Ref.***
$[Pr_2NH_2][SCN]$	1.006	1.16	0.97	0.39	[53]
[*sec*-$BuNH_3$][SCN]	1.006	1.28	0.91		[53]
Water	1.000	1.09	1.17	0.47	[53]
$[EtNH_3][NO_3]$	0.954	1.24	0.85	0.46	[52]
$[HO(CH_2)_2MIM][Tf_2N]$	0.929				[53]
$[BuNH_3][SCN]$	0.948	1.23	0.92		[53]
$[PrNH_3][NO_3]$	0.923	1.17	0.88	0.52	[53]
$[Bu_3NH][NO_3]$	0.802	0.97	0.84		[52]
$[CH_3O(CH_2)_2MIM][Tf_2N]$	0.722				[54]
$[BMIM][SbF_6]$	0.673	1.04	0.64	0.15	[50]
$[BMIM][BF_4]$	0.673				[54]
	0.670	1.05	0.63	0.38	
[BMIM][TfO]	0.667				[50]
	0.656	1.01	0.63	0.46	
$[BMIM][PF_6]$	0.667				[54]
	0.669	1.03	0.63	0.21	
Ethanol	0.654	0.54	0.75	0.75	[50]
$[BMIM][Tf_2N]$	0.642				[54]
	0.644	0.98	0.62	0.24	
$[EtNH_3]Cl$	0.636				[50]
$[OMIM][PF_6]$	0.633				[54]
$[OMIM][NTf_2]$	0.630				[53]
$[Pr_4N][CHES]$[a]	0.62	1.08	0.34	0.80	[50]
$[BMIM][CF_3CO_2]$	0.620				[50]
$[Bu_4N][CHES]$[a]	0.62	1.01	0.34	0.98	[53]
$[Pe_4N][CHES]$[a]	0.58	1.00	0.15	0.91	[50]
$[Bu_4N][BES]$[a]	0.53	1.07	0.14	0.81	[53]
$[BMMIM][BF_4]$	0.576	1.08	0.40	0.36	[53]
$[BMMIM][NTf_2]$	0.525				[53]
	0.541	1.01	0.38	0.24	
$[Bu_4N][MOPSO]$[a]	0.49	1.07	0.03	0.74	[54]
$[BMPY][Tf_2N]$	0.544	0.95	0.43	0.25	[50]
$[OMMIM][BF_4]$	0.543				[54]
$[OMMIM][Tf_2N]$	0.525				[53]
Acetonitrile	0.460	0.75	0.19	0.31	[54]
Diethylether	0.117	0.27	0.00	0.47	[50]
Cyclohexane	0.009	0.00	0.00	0.00	[50]

a) CHES, 2-(cyclohexylamino)ethanesulfonate; BES, 2-{bis(2-hydroxoethyl)amino}ethanesulfonate; MOPSO, 2-hydroxo-4-morpholinepropanesulfonate.

However, the difference in the values for $[Et_4N]Cl$ and $[Et_4N][NO_3]$ is only 0.006, whereas the difference between those for $[EtNH_3]Cl$ and $[EtNH_3][NO_3]$ is 0.318. Hence, it is clear that the magnitude of the effect of changing the anion depends on the nature of the cation. ILs with strong hydrogen bond donor cations can have their hydrogen bond acidity moderated more by the use of hydrogen bond acceptor anions than those that are poor hydrogen bond acids in the first place.

It has been proposed that this behavior is the result of a competition between the anion and the Reichardt's dye solute for the proton [54]. So, the E_T^N values of the ILs are controlled by the ability of the liquid to act as a hydrogen bond donor (cation effect) moderated by its hydrogen bond acceptor ability (anion effect). This can be explained by considering the following equilibria. The cation can hydrogen-bond to the anion of the IL [Eq. (7)], and the cation can hydrogen-bond to the solute, in this case Reichardt's dye [Eq. (8)].

$$[\text{bmim}]^+ + \text{A}^- \rightleftharpoons [\text{bmim}]\ldots\text{A} \qquad K'_{\text{eqm}} = \frac{[[\text{bmim}]\ldots\text{A}]}{[[\text{bmim}]^+][\text{A}^-]} \tag{7}$$

$$[\text{bmim}]^+ + \text{solute} \rightleftharpoons [\text{bmim}]\ldots\text{solute} \qquad K''_{\text{eqm}} = \frac{[[\text{bmim}]\ldots\text{solute}]}{[[\text{bmim}]^+][\text{solute}]} \tag{8}$$

It can be easily shown that the value of K'' is inversely proportional to the value of K' and that K' is dependent on both the cation and the anion of the IL. Hence, it is entirely consistent with this model that the difference made by changing the anion should depend on the hydrogen bond acidity of the cation. A recent molecular dynamics study has confirmed this interpretation [56]. This study also suggests that nonspecific interactions between the dye molecule and the ionic liquid are entirely local in nature and dependent on the nature of the first solvation shell of the solute.

Kamlet–Taft Parameters

In spite of its success as a solvent polarity scale the E_T^N scale remains a single-parameter scale. The Kamlet and Taft system [57] gives complementary scales of hydrogen bond acidity (α), hydrogen bond basicity (β) and dipolarity/polarizability effects (π^*). This more sophisticated treatment holds the potential for greater insight into the solvent behavior of the IL. However, it must be stressed that these are not fundamental physical properties and the values can change according to the selection of dye sets or by the precise method used to calculate the values. Different investigators have used different dye sets for their measurements and care should be taken when comparing the results of different studies. However, the dye sets have been carefully chosen so that general trends within any one set are paralleled in the others. It is in this light that the following should be considered.

All of the π^* values (0.97–1.28, Table 6) for the ILs are high in comparison with most molecular solvents. The π^* value results from the ability of the IL to induce a dipole in the solute and so will incorporate the Coulombic interactions from the ions as well as dipole–dipole and polarizability effects. It is unlikely, therefore, that it will ever be possible to make an IL with a low π^* value. Although differences between the ILs are small, both the cation and the anion can affect the value.

The values for quaternary ammonium salts are lower than those for the monoalkylammonium salts. This probably arises from the ability of the charge center on the cation to approach the solute more closely for the monoalkylammonium salts.

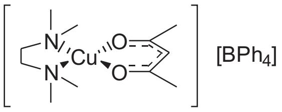
The π^* value for [BMPY][NTf$_2$] is lower than that that for [BMIM][NTf$_2$], suggesting that the decrease in Coulombic interactions caused by delocalizing the charge around the imidazolium ring is more than compensated for by the increased polarizability of the delocalized system. However, these differences are minor and there is little synthetic flexibility. If you want a nonpolar solvent, do not use an ionic liquid.

The difference in the hydrogen bond acidities and basicities is far more marked. There is a genuine synthetic flexibility in these two parameters. The α value is largely determined by the availability of hydrogen bond donor sites on the cation. Values range from ca. 0.9 for the monoalkylammonium salts, ca. 0.6 for the [BMIM]$^+$ salts, and 0.4 for the [BMMIM]$^+$ and [BMPY]$^+$ salts, and are lowest for the simple tetraalkylammonium salts. As with the E_T^N scale there appears to be a secondary anion effect [see Eqs. (7) and (8)]. It appears that more basic anions give lower values of α with a common cation.

There is, again, a great deal of synthetic flexibility in the β value. These have been shown to depend upon the gas-phase acidity of the conjugate acid of the anion [54]. Hence, Poole's sulfonates show very high values, whereas the anions used in conjunction with the [BMIM]$^+$ cations show only moderate hydrogen bond basicity.

The Complex [Cu(acac)(tmen)][BPh$_4$]

In catalysis the solvent can interact with the active site of the catalyst so as to slow, or sometimes even stop, the reaction. This solvent poisoning is commonplace and it is often one of the key determinants of the selection of the solvent for a reaction. The wavelength λ_{Cu} of the lowest-energy d → d band of the square planar cation of (acetylacetonato)(*N,N,N′,N′*-tetramethylethylenediamine)copper(II) tetraphenylborate {[Cu(acac)(tmen)][BPh$_4$]} is thought to be a good guide to the solvent's ability to coordinate to a soft metal center. It correlates well with both solvent donor numbers [58] and the β values described above. Not surprisingly, this value is dominated by the nature of the anion of the IL, since the cations cannot coordinate to the [Cu(acac)(tmen)]$^+$ complex probe.



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That any great difference between these ILs with "noncoordinating" anions is seen at all requires comment. Clearly, in the IL these anions do coordinate the metal center. Indeed, what else could they do? In an IL there are no molecules available to separate the [Cu(acac)(tmen)]$^+$ and the anions of the IL and close contact between the cations and anions is the only possibility. Since λ_{Cu} gives a measure of the ability of the anion to coordinate to a soft metal center, it is expected to poison a catalyst center (particularly if cationic) to some degree. This idea has been used to explain the reactivity of nickel catalysts in the biphasic oligomerization reactions in $[PF_6]^-$ ILs [59].

Comparison of Different Polarity Scales

In order to make rigorous comparisons between the different solvent polarity scales and how they report the behavior of ILs, there needs to be sufficient overlap in the ILs used in the studies. Further to this, it is well known that these empirical polarity parameters are easily affected by impurities, so it is best to have common samples. So far, only one study that has used common samples has been made into how the same ILs are described by different polarity scales [44, 54].

λ_{Cu} was shown to agree well with the Kamlet–Taft parameter β, as it does for molecular solvents. This has important consequences for the idea of solvent design. Since β is correlated with gas-phase acidities of the conjugate acid of the anion and λ_{Cu} has been found to be an important influence in the rates of catalytic reactions, it is possible to design an IL with some idea of its likely effect on a catalytic reaction. This is the first time that a real possibility of designing the solvent for a reaction has arisen and it could prove to be a very powerful tool in the future.

The Welton and Armstrong groups (see above) used both multiple solvation interactions, based on GC measurements, and the Kamlet–Taft approach to characterize a range of ILs. Eight of the ILs used were from the same samples for both studies and so can be directly compared. The nonspecific interactions are not directly comparable for the two methods, because they are made up of different contributions, but the hydrogen bonding effects might be expected to give similar results in both experiments.

The hydrogen bond basicities of the ILs follow the same trend in both studies, are controlled by the anion, and are moderate in value. Comparisons of hydrogen bond acidity are, however, not so clear-cut. In the solvation study the ILs' hydrogen bond acidity was found to be dominated by the hydrogen bond *basicity* of the anions, with a much lesser contribution from the hydrogen bond acidity of the cation. Low and even negative values were found for the hydrogen bond acidity function. The only ILs to display significant hydrogen bond donor ability where those of the $[NTf_2]^-$ ion. In contrast, the Kamlet–Taft study has strongly emphasized the role of the hydrogen bond acidity of the cation. A plot (Figure 5) of the two functions, α from the Kamlet–Taft study and *b* from the solvation study, reveals a complex relationship.

It can be seen, for the $[NTf_2]^-$ IL, that the hydrogen bond acidity does indeed vary with cation, with $[BMIM]^+$ being the most acidic followed by $[BMPY]^+$ and finally $[BMMIM]^+$ in both studies. However, changing to more basic anions leads to a dramatic drop in the acidity measurements in the solvation study, whereas it has only a limited effect in the Kamlet–Taft experiment. That is, the solvation measurement is anion-dominated, whereas the Kamlet–Taft measurement is cation-dominated.

The intimate relationship that exists between solute and solvent is such that the nature of the solute strongly influences which solvent properties will be expressed.

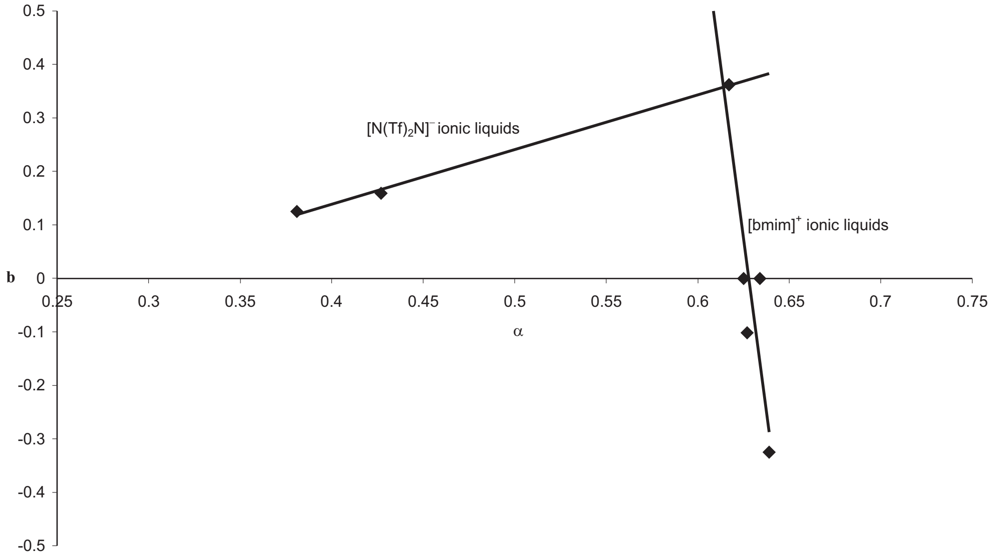

Figure 5 Comparison of the hydrogen bond donor *b* vs. α functions for the ILs.

Indeed this is the basis of the Abraham solvation approach. In that study the set of probes was deliberately selected to provide a broad range of interactions, whereas Reichardt's dye has a strongly hydrogen bond accepting phenoxide oxygen, which is anionic and will strongly and exclusively interact with the cation of the IL [56] and emphasize its role.

In summary, the Kamlet–Taft study reveals the interactions of which the ILs are capable in the presence of a strongly and specifically interacting solute and how they are influenced by the nature of the two competing ions, whereas the solvation study reveals the value when the nature of any particular solute has been deliberately downplayed by averaging over many solutes and how that is influenced by the nature of the ions.

5.2.1.2.7
General Conclusions

More and more physical data on ILs and their properties are being collected. For some measurements there are even multiple values. But there is a need for the reproducibility of data to be tested in several laboratories as well as an ever-growing list of ILs on which to collect data. At this early stage it is possible to draw some tentative general conclusions.

- All ILs are not the same; different combinations of anions and cations lead to solvents with different properties.
- Many physical properties are affected by the presence of even trace amounts of other materials. The lack of rigorous and generally applied purification procedures makes direct comparison of the results of different studies difficult at present.

- IL are generally glass-transforming materials whose useful liquid ranges are bounded by their glass transition temperatures at the lower end and their decomposition temperatures at the higher end.
- The viscosity of an IL at any given temperature is related to how far above the glass transition temperature it is.
- IL are all polar materials that can, depending on the selection of ions, act as hydrogen bond acids and/or hydrogen bond bases.

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5.2.1.3
Separation and Catalyst Recycling Techniques

Christian P. Mehnert

Since the mid-1990s, ionic liquids (ILs) have gained importance as alternative solvent systems for catalyst applications. Although the early catalysis applications date back more than 30 years [1], there has been a growing interest in the use of these tunable ionic phases as potential solvent replacements. The ideal operability for catalysis is given when the IL is able to dissolve the active species and display partial miscibility with the substrate. An additional requirement is that the resulting products should have limited solubility in the IL, which allows for their removal via simple decantation while the catalyst remains unaffected. This general separation approach has been used for the majority of catalyst investigations and has been summarized in several reviews [2].

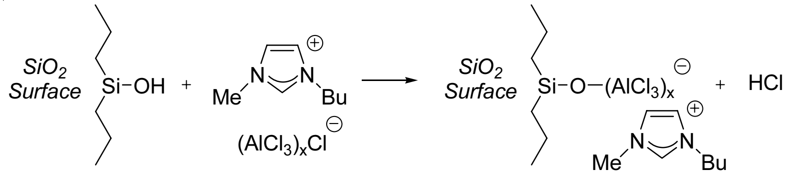
An alternative approach to decantation is distillation [3]. Although this separation method is facilitated by the low volatility of the IL, it can be limited by high volatility and/or thermal instability of the product. In addition, potential instabilities of the catalyst or the IL system may limit the success of this approach.

The shortcomings described are only partially responsible for the development of novel separation methodologies for IL systems. The other driver of this research is the dominance of heterogeneous catalyst systems in commercial chemical processes. This preference for heterogeneous catalyst systems is motivated by the advantages of easy separation and fixedbed reactors. Furthermore, the use of a biphasic reaction system would require a large amount of IL, which is costly and raises potential toxicological concerns (see Section 5.4).

One approach to IL separations involved their immobilization onto solid supports, which had the added benefit of minimizing the required quantity of IL. An early example of this methodology involved a molten-salt Wacker catalyst [4] containing palladium chloride/copper chloride dissolved in a eutectic mixture, supported on the surface of a porous silica gel material. Although the melting point of this supported molten salt (423 K) is slightly higher than for room-temperature ILs, the potential of such supported ionic systems was recognized and led to their further exploration.

Following the logic of this approach, a variety of Lewis-acidic IL systems were immobilized on solid supports and investigated for various catalysis applications. In most cases, the solid support material was impregnated with a preformed IL phase which was also the catalytically active species. For example, a supported chloroaluminate-based IL acted as the catalyst for the alkylation reactions of 2-butene [5] and benzene [6].

Work on similar supported Lewis-acidic catalysts was further extended to a variety of Friedel–Crafts alkylation [7] and acylation [8] reactions (see Section 5.2.2.4). In these investigations the catalysts are simply prepared by the addition of a liquid to a solid support. A typical catalyst preparation [9] involves treating a previously dried support with a chloroaluminate ionic liquid (e.g., 1.5 mol of $AlCl_3$ to 1 mol [BMIM]Cl) until the appearance changes from a dry to a wet powder [see Eq. (1)]. This method is also referred to as "incipient wetness" treatment. After the mixture is stirred for an extended period of time, the excess IL is removed via Soxhlet extraction.



(1)

The resulting ionic liquid is immobilized on the surface via its chloroaluminate-based anion. The confinement of the IL to the surface is due to the formation of covalent bonds between the aluminum atoms and the surface OH groups. Extensive surface science analysis and comparison studies with $AlCl_3$ bound on silica gel supported the covalent immobilization of the IL phase [10]. The accessibility and concentration of the surface OH groups proved to be convenient levers for controlling the amount of immobilized IL. Different concentrations of ILs could also be achieved by using different supports (see Figure 1). As expected, the low surface area and the lack of surface OH groups in ZrO_2 and TiO_2 led to a reduced loading after the extraction. Although most of the supported ionic liquid materials retained respectable surface areas, X-ray diffraction analysis of the crystalline materials, such as β-zeolite, showed the partial destruction of the structure. This pore damage is caused by the formation of hydrochloric acid during bond formation between the chloroaluminum-based IL and the surface OH groups.

These types of supported chloroaluminate-based, Lewis-acidic ILs were tested for the alkylation reaction of benzene with dodecene. In these investigations the supported catalysts showed improved activity and selectivity as compared to the

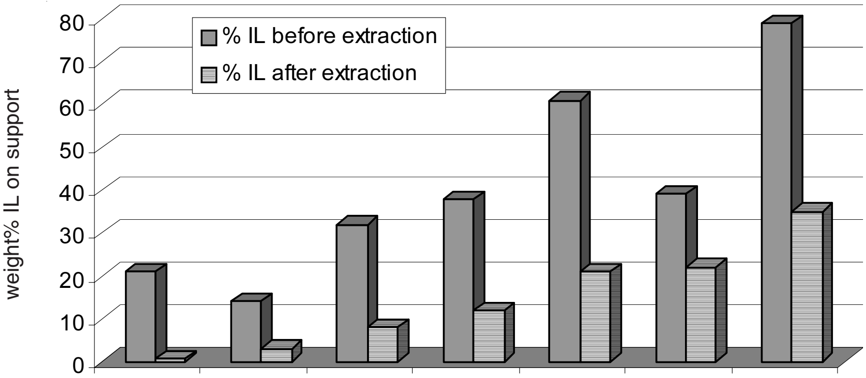


Figure 1 Immobilization of chloroaluminate ILs via impregnation onto different support materials [7a].

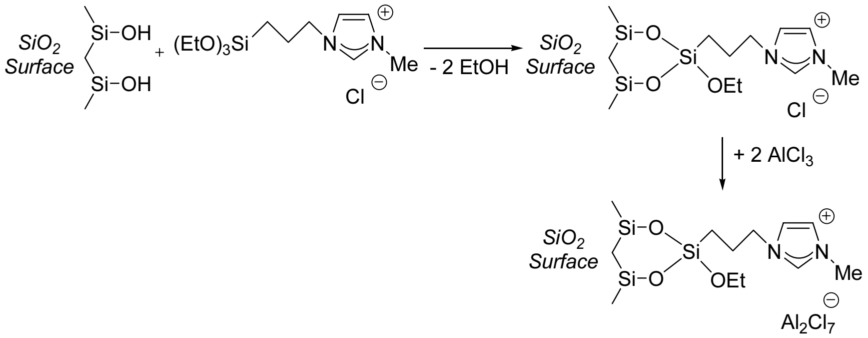
Table 1 Dodecene conversion and selectivity for the alkylation of benzene [7a].[a)]

Catalyst	*T [°C]*	*Benzene/ C_{12}= ratio [mol mol^{-1}]*	*C_{12}= conversion [%]*	*C_{12}= isomers [%]*	*Selectivity mono-alkylated*	*Selectivity heavier products*
AL-IL, pure	80	10 : 1	4.5	86.7	13.3	0
MCM-41, pure	80	10 : 1	0.1	100.0	0	0
FK700/$AlCl_3$	80	10 : 1	15.7	80.2	19.8	0
FK700/Al-IL	80	10 : 1	99.4	0	99.7	0.3
T350/Al-IL	80	10 : 1	99.9	0.1	99.8	0.1
T350/Al-IL	40	10 : 1	81.0	0	100.0	0
T350/Al-IL	80	5 : 1	62.4	13.1	86.0	1.0
T350/Al-IL	80	1 : 1	82.7	16.1	82.5	1.4
FK700/Al-IL, filtered, 2nd run	80	10 : 1	2.2	100.0	0	0
FK700/Al-IL, filtered, 2nd run	80	10 : 1	79.9	0	99.5	0.5
T350/Al-IL, washed, 2nd run	80	10 : 1	47.2	92.7	92.7	0.4
H-β, pure	80	10 : 1	56.8	39.0	39.0	2.1

a) Conditions: batch reactor, reaction time 30 min, 6 wt.% catalyst.

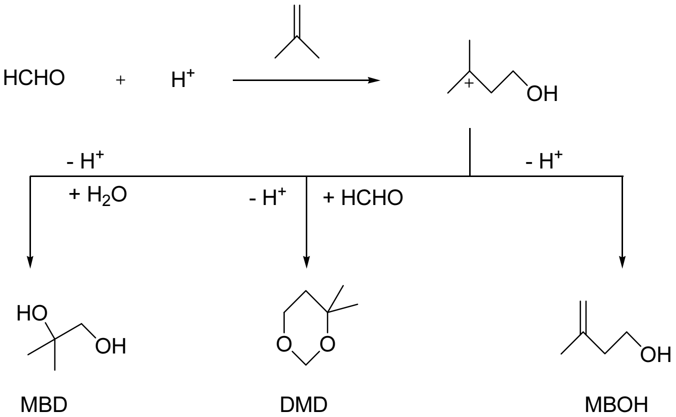
free IL (see Table 1). In general, the distribution of the monoalkylated products was close to that of reactions catalyzed with pure $AlCl_3$ or pure chloroaluminate ILs. As catalyst lifetime is an important feature for heterogeneous catalysis, these materials were also tested for their durability. Leaching studies carried out by ICP analysis showed only a negligible loss of the active species. Despite this minimal leaching, the reduced catalyst activity which was observed in consecutive runs was attributed to the presence of moisture and the possible adsorption of reactants onto the catalyst surface. It is believed that a side reaction such as the oligomerization of the olefin can cause the blockage of the active species and therefore suppresses the alkylation reaction.

As mentioned above, one major drawback of the “incipient wetness” method for the immobilization of chloroaluminum-based ILs is the formation of hydrochloric acid, which destroys the pore structure of certain support materials [10]. To avoid this problem, an alternative immobilization route was devised which focused on the confinement of the cation [11]. In this approach, instead of adding the preformed IL to the solid support, an organic halide which contained the cation of the IL was grafted onto the support. In the following step the aluminum halide was introduced which generated a highly acidic ionic complex on the surface of the support (see Scheme 1). The resulting catalysts, which were investigated for the alkylation of benzene with different olefins, exhibited excellent activities and selectivities.



Scheme 1 Immobilization of chloroaluminate-based IL by grafting of imidazolium chloride followed by the addition of $AlCl_3$ [11].

A similar immobilization approach was also applied for the preparation of an acidic tin catalyst [12]. Here, the new catalyst was synthesized by anchoring the active $SnCl_4$ catalyst on silica that was previously functionalized with an organic quaternary ammonium chloride species. Analogously to the formation of the chloroaluminate-based ILs, the addition of tetraalkylammonium halides to $SnCl_4$ leads to the formation of the pentacoordinated anionic tin species. Such complexes of general formula $[NR_4][SnCl_5]$ have the characteristics of an IL and can be used as effective Friedel–Crafts catalysts. The resulting catalysts were investigated for the condensation reaction of alkenes with formaldehyde for the production of unsaturated alcohols (see Scheme 2). Various silica-based catalysts were tested in the selective synthesis of 3-methyl-3-buten-1-ol (MBOH) (see Table 2). The catalysts that were immobilized on silica functionalized with the organic quaternary ammonium species showed the highest selectivity for MBOH (88–93%). Leaching studies confirmed full retention of the catalyst on the support and subsequent reactions with the same catalyst did not show any significant drop in activity.



Scheme 2 Prins condensation of isobutene with formaldehyde. MBD = 3-methylbutane-1,3-diol, DMD = 4,4-dimethyl-1,3-dioxane, MBOH = 3-methyl-3-buten-1-ol [12].

Table 2 Condensation of isobutene and formaldehyde to give 3-methyl-3-buten-1-ol (MBOH) over silica-based catalysts and with catalyst recycling [12].[a)]

Entry	*Catalyst*	*$SnCl_4$ loading [mmol g^{-1} support]*	*Conversion of formaldehyde [%]*	*MBOH selectivity [%]*	*MBOH yield [%]*
1	SIL-$TPA^+SnCl_5^-$ [b)]	0.32	64.1	88.1	56.4
2	SIL-$TPA^+SnCl_5^-$ [c)]	0.32	57.0	79.8	45.5
3	Silica/$SnCl_4$	0.95	77.9	63.2	49.2
4	SIL-$NR_4^+SnCl_5^-$ [d)]	0.78	64.6	92.8	59.9
5	recycle 1 [e)]	0.78	63.3	91.1	57.6
6	recycle 2	–	61.9	91.0	56.3
7	SIL-$NR_4^+SnCl_5^-$ [f)]	0.78	100	76.1	76.1
8	SIL-$Py^+SnCl_5^-$ [g)]	0.48	66.3	91.9	60.9
9	SIL-$Py^+SnCl_5^-$ [f)]	0.48	97.8	82.6	80.7

a) 56 g isobutene, 3 g paraformaldehyde, catalyst containing 4 mmol of $SnCl_4$, and 40 g of chloroform were introduced into the reactor and stirred for 2 h at 60 °C.
b) Tetrapropylammonium chloride functionalized silica complex.
c) Direct immobilization of complex on silica.
d) Catalyst prepared by method 1.
e) Recycling of SIL-$NR_4^+SnCl_5^-$ after exhaustive washing with dichloromethane.
f) Reaction continued for 3.5 h.
g) Pyridinium chloride functionalized silica complex.

In an interesting approach, a support material containing a cationic group such as an imidazolium chloride derivative was prepared via sol–gel synthesis methods [13]. Here, the complex 1-(triethoxysilylpropyl)-3-methylimidazolium chloride was added to a mixture of a silicon source (tetraethyl orthosilicate) and a template (dodecylamine). After the hydrothermal synthesis and the extraction of the template, the metal halide was introduced, leading to the formation of the ionic complex. Although the resulting complex was covalently attached to the walls of the support, it is likely that the anion existed as a number of different aluminum chloride species bound to the surface. Catalysts prepared using this method have been investigated for Friedel–Crafts alkylation reactions of benzene. The activities and selectivities of these complexes were reduced in comparison to materials prepared by the grafting of an organic halide followed by the introduction of the metal halide.

Yet another approach which can be used to immobilize ILs involves treatment of a solid with a substantial amount of IL (5–50 wt.%). In contrast to the earlier studies, the ILs used here were non-acidic and did not undergo reactions with the support. This approach resulted in the formation of multiple layers of free IL on the carrier which could then act as an inert reaction phase to dissolve various homogeneous catalysts [14]. Although the resulting material was a solid, the active species was dissolved in the IL phase and acted like a homogeneous catalyst (see Figure 2).

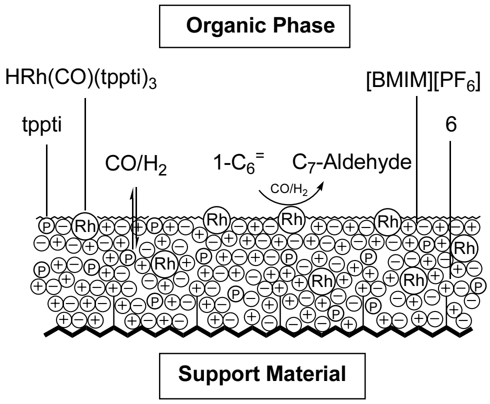
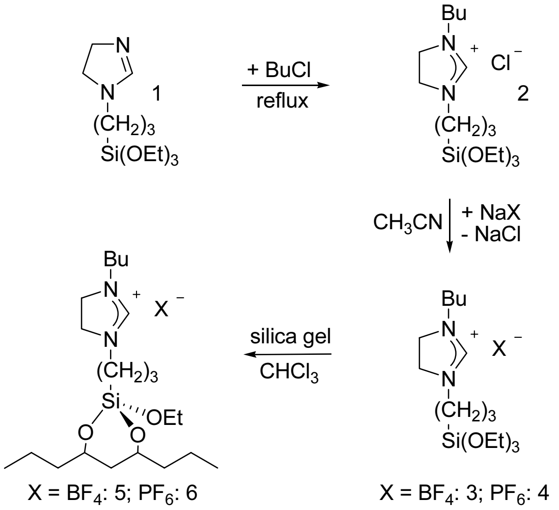


Figure 2 The concept of supported IL catalysis used in the hydroformylation of 1-hexene to form *n*,*i*-heptanal [14].

This concept of supported IL catalysis (SILC) combines the advantages of IL phases with those of heterogeneous support materials and is similar in nature to the elegant studies of supported aqueous-phase catalysis [15]. In addition, this methodology overcomes one of the shortcomings of supported aqueous-phase catalysis (see Section 2.6), namely the depletion of the aqueous layer. This improvement is due to the low volatility of the ILs. To enhance the interaction between the free IL and the surface, a modified support material with a monolayer of covalently attached IL fragments can be used (see Scheme 3).

For the preparation of such a modified silica gel, the complex *N*-3-(3-triethoxysilylpropyl)-4,5-dihydroimidazole **1** is reacted with 1-chlorobutane to give the complex 1-butyl-3-(3-triethoxysilylpropyl)-4,5-dihydroimidazolium chloride **2**.



Scheme 3 Anchoring of IL fragments for enhanced interaction between surface and free IL [14].

The resulting compound is further treated with either $NaBF_4$ or $NaPF_6$ to form the corresponding anchor complexes **3** and **4**. To immobilize **3** and **4** pretreated silica gel is refluxed with a chloroform solution, giving the modified support materials **5** and **6**, respectively. These modified supported materials were then used for the preparation of "heterogeneous" hydroformylation catalysts. In the catalyst preparation a solution of the precursor $Rh(CO)_2(acac)$ (acac = acetylacetonate) was either treated with the ligand tri(*m*-sulfonyl)triphenylphosphine trisodium salt (tppts) or tri(*m*-sulfonyl)triphenyl phosphine tris(1-butyl-3-methylimidazolium) salt (tppti) (Rh/P ratio of 1 : 10). The ligand tppti dissolved in both ionic media, $[BMIM][BF_4]$ and $[BMIM][PF_6]$, while the ligand tppts exhibited solubility only in $[BMIM][BF_4]$. The resulting solutions were combined with the IL phases and added to the corresponding support materials. After the solvent was removed the catalysts were obtained as free-flowing powders.

In the hydroformylation reaction 1-hexene reacted with syngas (CO/H_2 ratio of 1 : 1) to produce *n,i*-heptanal (see Table 3 and Section 5.2.2.2). A comparison between the supported IL catalyst and the biphasic IL reaction showed that the supported system exhibited a slightly enhanced activity with comparable selectivity (*n*/*i* ratio). The supported system containing the IL $[BMIM][BF_4]$ produced *n,i*-heptanal with a TOF of 65 min^{-1}, while the biphasic IL system showed a value of 23 min^{-1}. This improved activity was attributed to a higher concentration of the active rhodium species at the interface due to the generally larger interface area of the solid support as compared to the biphasic system. If the reaction was conducted without a ligand, the rhodium species leached from the IL layer and formed an active hydroformylation catalyst in the organic phase. This species is responsible for the conversion of the olefin. For further comparison, the aqueous biphasic reaction and the conventional homogeneous catalyst in toluene were investigated under similar reaction conditions. As expected the aqueous system was significantly less active due to the low solubility of the olefin in the aqueous phase. With respect to the homogeneous catalyst system a TOF of 400 min^{-1} was recorded. Although the homogeneous system is clearly favored due to its higher activity, the supported IL system is attractive on the basis of its convenient product separation.

The potential of SILC has been further investigated for hydrogenation reactions [16]. In this study the complex $[Rh(NBD)(PPh_3)_2]PF_6$ (NBD = norbornadiene, PPh_3 = triphenylphosphine) was investigated in IL and organic media and was then compared to the supported catalyst system. The catalytic studies were conducted in a Robinson–Mahoney reactor under varying reaction conditions using different olefins. The catalyst evaluation revealed enhanced activity for the supported IL system in comparison to both the homogeneous and the biphasic reaction systems. For example, the homogeneous base case with 1-hexene as a substrate showed a k_h of 0.4 min^{-1} at a reaction temperature of 50 °C, while the supported IL catalyst achieved a k_h of 11.2 min^{-1} for the same reaction at 30 °C. The enhanced activity of the rhodium complex in an IL phase had been observed previously and may be explained by the absence of any coordinating solvent [17]. In an acetone solution under hydrogen pressure the complex exhibited coordination of two solvent molecules to the metal center. In theory, if the catalysis is carried out in an IL

Table 3 Evaluation of the hydroformylation reaction of 1-hexene to form *n*,*i*-heptanal using supported IL catalysis (silc), biphasic catalysis, and homogeneous catalysis [14].

Entry	*Condition*[a)]*/Ligand*	*Solvent*	*Time [min]*	*Yield [%]*	*n/i*	*TOF*[b)] *[min^{-1}]*
1	silc/tppti	[BMIM][BF_4]	300	33	2.4	65
2	silc/tppts	[BMIM][BF_4]	240	40	2.4	56
3	silc/tppti	[BMIM][PF_6]	270	46	2.4	60
4	silc/no ligand	[BMIM][PF_6]	180	85	0.4	190
5	biphasic/tppti	[BMIM][BF_4]	230	58	2.2	23
6	biphasic/tppti	[BMIM][PF_6]	180	70	2.5	22
7	biphasic/tppts	H_2O	360	11	23	2.4
8	homog./PPh_3	toluene	120	95	2.6	400

a) Reaction conditions: All runs were conducted at 100 °C with a Rh/P ratio of 1 : 10, silc runs were evaluated in a 70mL autoclave at 1500 psi and biphasic and homogeneous catalyst systems were evaluated in a 300 mL autoclave at 600 psi.

b) TOF is defined as mol(aldehyde) per mol(rhodium) per minute (full reaction time).

medium, there should be no coordinating species present, leading to easy accessibility of the metal center and higher reactivity. In addition to the higher activity, the supported IL catalysts also showed excellent long-term stability. The same catalyst was re-used for 18 batch runs without any significant loss of activity. The level of the rhodium in the medium remained below the detection limit and the isolated organic phases did not exhibit any further reactivity, which additionally verified full retention of the active species.

In a continuing effort to explore the potential of supported ILs these systems have also been extended to continuous gas-phase reactions [18]. Rhodium catalyst precursor and biphosphine ligand systems such as sulfoxanthpos were supported in the presence of [BMIM][PF_6] and [BMIM][*n*-octylsulfate] on silicas and tested for the hydroformylation of propene. As expected, the supported rhodium sulfoxantphos catalyst proved to be more regioselective than the catalysts without ligands. Furthermore, the performance of the catalysts tested was strongly influenced by the catalyst composition. Low activities and low selectivities were obtained for catalysts with low ligand/rhodium ratios. It is believed that under such reaction conditions most of the active rhodium species are ligand-free complexes. In contrast, the catalyst with a high ligand/rhodium ratio of 10 : 1 and 20 : 1 showed a higher selectivity, giving a n/i ratio of up to 23.7. Furthermore, the increased IL loading led to a decrease in activity, which indicates that the catalysts are operating under mass-transfer limitations.

Further experimentation focusing on continuous reactions using a variety of monodentate phosphine ligands has also been carried out for the hydroformylation of propene and 1-octene [19]. The rhodium precursor, together with either of the ligand systems bis(m-phenylguanidinium)phenylphosphine or NORBOS, was immobilized in a multiple layer of IL on the surface of the silica gel. The catalysts were active in the continuous gas- and liquid-phase hydroformylation of propene and 1-octene, exhibiting TOFs of up to 88 h^{-1}. Despite the respectable activities, the selectivity for the *n*-aldehyde was reduced to only 74% (n/i ratio 2.8), which emphasizes the advantages of multidentate phosphine ligands for the production of highly linear aldehydes.

In a more specialized approach, IL phases have been immobilized in membrane materials. Although the primary driver of this work was the use of these materials as electrochemical devices, they have also been investigated for catalytic applications [20]. Membrane materials composed of air-stable, room-temperature ILs and poly(vinylidene fluoride)–hexafluoropropene copolymers were prepared with the incorporation of the active catalyst species in the form of palladium on activated carbon. Optical imaging revealed that the prepared membranes contained a high dispersion of the palladium catalyst particles. Studies on the materials included evaluating their gas permeability and their catalytic activity for the hydrogenation reaction of propene.

Another example of a hydrogenation study using supported IL membranes involved the incorporation of a homogeneous catalyst into the porous framework of the membrane [21]. A series of different imidazolium-based ILs with perfluoroanions were treated with the complex $[Rh(NBD)(PPh_3)_2]PF_6$ and loaded into poly(vinylidene fluoride) filter membranes. During the investigation, the olefin was maintained at atmospheric pressure on the feed side of the membrane, while hydrogen at the same pressure was swept over the permeate side and sent through a sampling loop for product analysis. Hydrogenation of the olefin to the corresponding alkane took place as the olefin diffused through the IL region of the composite membrane structure. A detailed analysis of reaction rates was carried out and showed that the maximum rates for the propene hydrogenation to propane in different ILs followed the order $[EMIM][NTf_2] > [EMIM][OTf] > [EMIM][BF_4] > [BMIM][PF_6]$. The rates for the propene hydrogenation reactions using the supported IL membranes compare favorably to the rates determined for the hydrogenation of 1-pentene in the liquid–liquid biphasic catalysis reaction using the identical rhodium catalyst [17].

In addition to hydrogenation catalysis, supported IL membranes were also studied for their use as oligomerization catalysts. Such membranes were prepared by loading porous polyethersulfone support membranes with chloroaluminate-based ILs with and without a nickel dimerization catalyst [22]. Although both catalyst types converted ethylene with high activity, the nickel-containing membrane exhibited the higher selectivity for butene production.

Apart from catalysis, supported IL membranes have also been investigated for a variety of separation applications [23], which ranged from the separation of isomeric amines [24] to the enzyme-facilitated transport of (*S*)-ibuprofen through a supported liquid membrane [25]. The latter study demonstrated the selective separation of the (*S*)-enantiomer from the racemic mixture (see Figure 3). The concept was that by employing certain enzymes, such as lipase, it would be possible to catalyze the hydrolysis or the esterification of ibuprofen enantioselectively. In this investigation

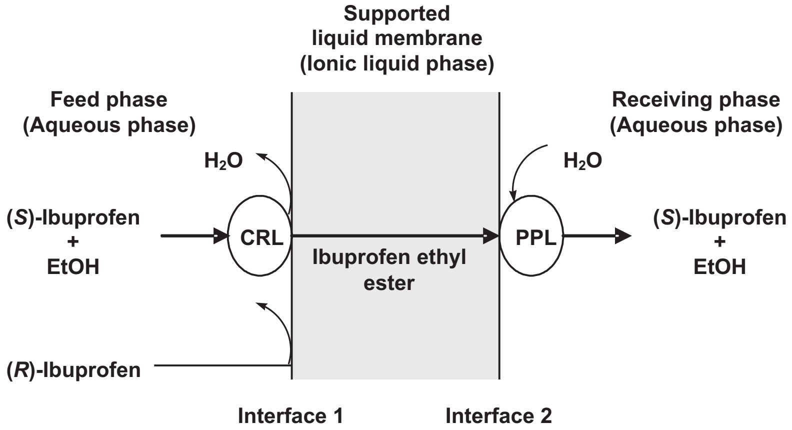


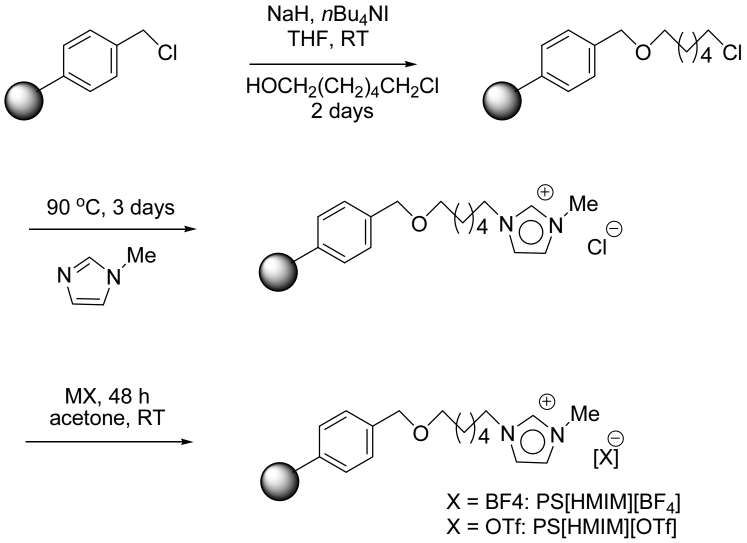
Figure 3 Schematic diagram of enantioselective transport of (S)-ibuprofen through a lipase-facilitated supported liquid membrane based on an IL [25b].

lipase from *Candida rugosa* facilitated the selective esterification in the feed phase while lipase from *Porcine pancrea* was responsible for the hydrolysis of the ester. The ibuprofen ester formed dissolved in the supported IL membrane and diffused across to the receiving phase, where it was hydrolyzed.

Other potential carriers, such as polymeric materials, have also been explored for ILs in catalytic applications [26]. In one preparation, a transition metal catalyst and the IL were impregnated into a polymeric material such as poly(diallyldimethylammonium chloride). In this system, the polymeric phase simultaneously heterogenizes the catalyst and the IL. The resulting material was active for a selection of liquid-phase hydrogenation reactions. For example, the substrates 2-cyclohexen-1-one and 1,3-cyclooctadiene were hydrogenated with Wilkinson's catalyst $RhCl(PPh_3)_3$ in a polymer-supported $[BMIM][PF_6]$ matrix. In all evaluations the polymer-supported IL catalysts showed higher activities than the unsupported IL system. The improved behavior of the polymeric system was ascribed to improved mass transfer between the IL phase and the substrates. Furthermore, analysis of the products did not show any metal content and confirmed the full retention of the catalyst on the polymeric support.

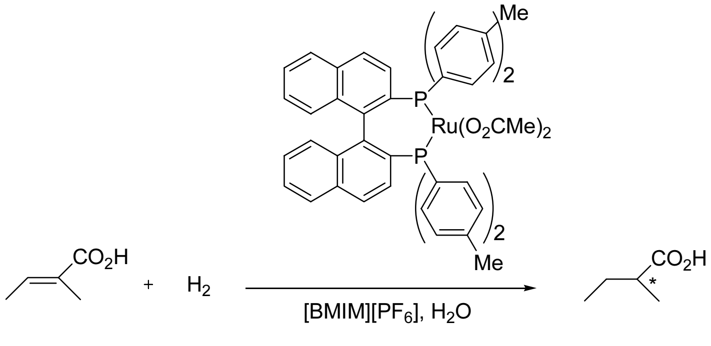
In a different approach a polymer-supported IL was prepared through the covalent anchoring of an imidazolium salt to a polystyrene resin [27]. In this multi-step synthesis a Merrifield peptide resin was modified with 1-*n*-hexyl-3-methylimidazolium cations (see Scheme 4) and investigated for nucleophilic substitution reactions including fluorinations. These novel materials together with alkali metal fluorides proved to be highly efficient catalysts, which converted various haloalkanes and sulfonylalkanes to their corresponding fluorinated products. Furthermore, the polymer-supported systems showed a much higher activity than when the catalysis was carried out in free ILs.

Although elegant separation approaches such as aqueous/organic [28] and fluorous/organic [29] biphasic systems have been investigated for catalysis,



Scheme 4 Preparation of polymer-supported imidazolium salts PS[HMIM][BF_4] and PS[HMIM][OTf] with PS = polymer support [27].

supercritical carbon dioxide ($scCO_2$) in conjunction with IL phases may also offer an interesting alternative [30]. The potential of combining ILs with $scCO_2$ for chemical separations was initially suggested in the early miscibility studies of CO_2 in ILs [31]. Two studies later appeared simultaneously investigating such $scCO_2$/IL biphasic catalysis systems. While the work of one investigation [32] focused on the hydrogenation of 1-decene using Wilkinson's catalyst $RhCl(PPh_3)_3$, the other study [33] evaluated asymmetric hydrogenation reactions. In the latter investigation the wet IL [BMIM][PF_6] was used as the reaction medium for the catalyst $Ru(O_2CMe)_2$-((*R*)-tolBINAP) in the asymmetric hydrogenation of tiglic acid to give 2-methylbutanoic acid with high enantioselectivity and conversion [Eq. (2)]. The resulting product was extracted with $scCO_2$, giving a clean separation of product and catalyst. The catalyst/IL solution was then re-used repeatedly without any significant loss of enantioselectivity or conversion.



(2)

In a further example using $scCO_2$ as the extracting solvent, methyl acrylate was dimerized to dimethyl dihydromuconate derivatives [34]. This novel approach could open an alternative route for the manufacture of adipic acid. In this palladium-catalyzed reaction using the IL [BMIM][BF_4], the catalyst showed a higher activity than under the conventional monophasic reaction conditions.

The biphasic $scCO_2$/IL separation concept was further extended to the hydroformylation of an alkene in a continuous-flow system [35]. The active rhodium complex was immobilized in the IL [BMIM][PF_6] with the help of the modified phosphine [1-propyl-3-methylimidazolium]$_2$[PhP($C_6H_4SO_3$-3)$_2$] and investigated for the hydroformylation of 1-octene. In this continuous-flow process the substrate, gases, and products were transported in and out of the reactor dissolved in $scCO_2$. The catalyst system exhibited a constant rate of more than 20 h^{-1} with a rhodium metal content of less than 1 ppm in the collected product.

In a different example, the nickel-catalyzed hydrovinylation reaction was investigated in a variety of different IL phases [36]. In this reaction styrene reacted with ethylene to yield 3-phenyl-1-butene with the in-situ activation of the catalyst. The effectiveness of the activation however, depended significantly on the nature of the IL's anion. A comparison of different ILs revealed a decrease in activity in the order BARF > Al[OC(CF_3)Ph]$_4$ > NTf_2 > BF_4 (BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate). Although the nickel catalyst showed a high activity in the IL [EMIM][BARF], the corresponding products showed a high degree of isomerization and oligomerization. The testing of different ILs under varying reaction conditions led to the identification of [EMIM][NTf_2] as the IL of choice. It is interesting to note that the recycle study showed a significant loss of catalyst activity when operated in a batchwise manner. It was believed that the deactivation results from an instability of the active species in the absence of substrate, which could be avoided by operating the reaction in a continuous-flow reactor. The corresponding lifetime study in a continuous system showed a remarkably stable catalyst which only experienced a slight drop in enantioselectivity over a long reaction period.

Apart form being an excellent solvent, $scCO_2$ can also be used as a very effective reagent [37] (see Chapter 6). In the preparation of propene carbonate, carbon dioxide was used together with propene oxide as starting materials. The related study was carried out in the IL [OMIM][BF_4] and the TOF values obtained for the production of propene carbonate were 77 times higher than any values reported in the literature for this particular reaction.

In an effort to find a sustainable method for the introduction of oxygen into a molecule, $scCO_2$/IL systems have been studied for epoxidation reactions [38]. The related investigation described the epoxidation of electron-deficient olefins, in particular vitamin K_3 and its analogues, with aqueous basic solutions of hydrogen peroxide in a variety of ILs. The resulting yields ranged between 80% and 99% with almost quantitative extraction of the epoxide from the reaction medium using $scCO_2$.

The combination of ILs and $scCO_2$ as a reaction medium has also attracted the attention of the biocatalysis community. In an interesting study the new concept of continuous biphasic biocatalysis was described. A homogeneous enzyme solution was immobilized in one liquid phase and the substrates and products resided largely in the supercritical phase [39]. In these investigations the enzyme *Candida antarctica* lipase B was dissolved in the IL [EMIM][NTf_2] or [BMIM][NTf_2] and studied for transesterification reactions. Both the synthesis of butyl butyrate from vinyl butyrate and butan-1-ol, and the kinetic resolution of *rac*-1-phenylethanol by transesterification with vinyl propionate, were selected as test reactions. Following the same concept another study focused on the lipase-catalyzed transesterification of secondary alcohols [40]. The results of both investigations showed high activity, enantioselectivity, and excellent stability. Moreover, the protective effect of the IL against the thermal and solution denaturation of the enzyme was clearly observed.

In summary, the recent advances in separation and recycle procedures for ILs have shown a tremendous potential and will help to accelerate their introduction into commercial processes. Continuing research in the area of catalysis and separations will demonstrate that ILs have the ability to rival or even surpass conventional solvent systems.

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5.2.2
Selected Examples

5.2.2.1
Oligomerization

Hélène Olivier-Bourbigou

5.2.2.1.1
Introduction

Hydrocarbon cracking processes, such as steam cracking or catalytic cracking, and Fisher–Tropsch synthesis produce significant amounts of light olefins (C_2 to C_5 fractions). Dimerization, co-dimerization, or polymerization reactions are widely used on an industrial scale either to provide chemicals of high value or to upgrade byproduct olefinic streams [1].

Acidic catalysts, either liquid or solid, can be used for butene or propene cationic oligomerization (see also Section 5.2.2.4). However, these cationic processes are poorly selective and afford mainly branched olefins. Better selectivities can be achieved by use of transition metal complexes. The possibility of tailor-making the ligand variation around the metal center offers a broad spectrum of reactivities and diversified selectivities. Industrial olefin oligomerization processes catalyzed by coordination complexes (Ti, Zr, Ni, or Cr) are generally performed in homogeneous systems [2]. The active organometallic catalyst is dissolved in the reaction medium and operates in a liquid phase. When it is possible, homogeneous processes are carried out without any solvent to avoid solvent recycling procedures and potential product cross-contamination. Homogeneous catalysts are often neutralized at the output of the reactor and are not recycled. But costly catalysts may need to be recycled to make industrial processes more economically viable. The Shell Higher Olefin Process (SHOP) was the first industrial catalytic process to benefit from two-phase liquid–liquid technology [3]. The P–O chelate Ni complex operates in butanediol, in which the α-olefins produced by ethylene oligomerization are only partially soluble (cf. Chapter 3).

The majority of oligomerization-active catalysts involves organometallic species, most often metal–alkyl complexes, which are considered to be prone to hydrolysis. Moreover, the coordination sites of the complexes can be blocked by the solvent. Nonprotic weakly coordinating solvents should therefore be preferred. In regard to these requirements, ILs provide good alternative solvents.

5.2.2.1.2
Oligomerization in Chloroaluminate Ionic Liquids

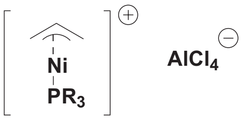
The Role of Chloroaluminate Ionic Liquids

In 1990, Wilkes [4] reported that Cp_2TiCl_2 (Cp = cyclopentadienyl) associated with Et_xAlCl_{3-x} catalyzes the polymerization of ethylene in acidic chloroaluminate ([EMI][Cl]/$AlCl_3$, where the molar ratio of $AlCl_3$ to imidazolium chloride is greater than 1). Analogous zirconium or hafnium complexes display no activity. The lack of activity of Zr and Hf complexes may be ascribed to the complexation of the $AlCl_4^-$ anion with the metal center resulting in a strong M–Cl–Al bond precluding formation of the M–R active catalyst [Eq. (1)]. The M–Cl bond strength was shown to increase in strength according to the order Ti–Cl < Zr–Cl < Hf–Cl. The coordination of $AlCl_4^-$ on titanium is weak enough to allow its alkylation with the alkylaluminum derivative and to form the suspected $Cp_2TiR(AlCl_4)$ active species. This example demonstrates the importance of the solvation properties of the anion.

$$Cp_2MCl_2 + Al_2Cl_7^- \rightleftharpoons Cp_2MCl(AlCl_4) + AlCl_4^- \qquad (1)$$

Many nickel-based systems catalyze the dimerization of olefins. In 1966, Wilke [5] demonstrated that the well-defined cationic η^3-allylnickel complex (**1**) catalyzes the regioselective dimerization of propene in organic chlorinated solvent. The $AlCl_4^-$

anion is sufficiently weakly coordinating toward the nickel electrophilic metal center and does not inhibit its reactivity.



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This type of cationic nickel complex can be generated directly in acidic chloroaluminate starting from an air-stable nickel(II) salt and in the presence of an alkylaluminum derivative [6]. When an alkylaluminum derivative such as $EtAlCl_2$ is added in acidic chloroaluminates $[BMIM][Cl]/AlCl_3$, mixed alkylchloroaluminate anions are formed, as characterized by Raman spectroscopy [Eq. (2)] [7]. The resulting IL plays the dual role of solvent and nickel activator (or co-catalyst). As shown in Scheme 1, in basic chloroaluminates, the Ni(II) salt is solvated by strongly coordinating chloride anions to afford an anionic inactive nickel chloride complex.

$$AlCl_4^- + EtAlCl_2 \rightleftharpoons EtAl_2Cl_6^- \qquad (2)$$

Another important motivation to perform olefin oligomerization in acidic chloroaluminate is that oligomers and ILs are very weakly miscible. The reaction system is then biphasic and the product mixture can be easily separated as a less dense second phase by decantation without the need to add a co-solvent. Consequently, secondary consecutive reactions of the primary reaction products can be minimized because they are extracted in the organic upper phase and are less prone to further reaction with monomer to give higher oligomers. Selectivity toward dimers is consequently higher than in one-phase homogeneous systems (Table 1).

The nature of the anion associated with the cationic nickel catalyst greatly influences the activity of the system. The more basic the anion, the less active is the catalyst. For example, in $[BMIM][Cl]/EtAlCl_2$ (1 : 1.2) ILs, dimerization of propene with $NiCl_2 \cdot 2\,L$ as the precatalyst is slower than in $[BMIM][Cl]/AlCl_3/EtAlCl_2$ (1 : 1.2 : 0.11) mixture. In addition, in $[BMIM][Cl]/EtAlCl_2$, deactivation of the catalyst is observed. This deactivation is ascribed to a change in the nature of the anion present in the IL in the presence of a hydrocarbon layer. Indeed, the $Et_2Al_2Cl_5^-$ polynuclear aluminum species disproportionates according to Eq. (3).

In basic chloroaluminate:

$NiX_2 + 2\,Cl^- \rightleftharpoons NiX_2Cl_2^{2-}$ (inactive complex)

In acidic alkylchloroaluminate:

$NiCl_2 + Et_2Al_2Cl_5^- \rightleftharpoons [Ni\text{–}Et]^+\ EtAlCl_3]^- + AlCl_4^-$ (active catalyst)

Scheme 1 Activation of nickel precatalyst in chloroaluminates.

Table 1 Dimerization of butenes[a] in homogeneous and biphasic systems: comparison of dimer selectivity.

Catalytic system	***NiX_2 + $EtAlCl_2$***	***NiX_2***
Solvent	No[b]	[BMIM][Cl]/$AlCl_3$/$EtAlCl_2$[c]
Butene conversion [wt.%]	70	70
C_8 selectivity [wt.%]	85	93

a) Feed containing 60% butenes (the remainder being butane and isobutane).
b) Reaction is performed in the liquid phase using products and unconverted butenes as solvent.
c) Solvent and co-catalyst.

After extraction, the IL is essentially composed of $AlCl_4^-$ anions, which do not activate nickel.

$$Et_2Al_2Cl_5^- \rightleftharpoons AlCl_4^- + Et_2AlCl \qquad (3)$$

It has been shown [8] that, for the same global aluminum molar fraction, the global acidity of a [BMIM][Cl]/$EtAlCl_2$+$AlCl_3$ mixture was higher than that of a [BMIM][Cl]/$EtAlCl_2$ mixture. The activity of the nickel system is dependent upon this Lewis acidity. An accurate adjustment of the $EtAlCl_2$/$AlCl_3$ ratio is required to optimize the efficiency of the catalytic system.

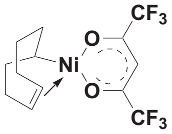
The Effect of Ligands

Propene and Butene Oligomerization

The dimerization of propene with a nickel catalyst precursor that does not contain any phosphine ligand usually gives oligomers with uncontrolled regioselectivity (typically a mixture of dimethylbutenes, methylpentenes, and hexenes). The addition of bulky basic phosphines such as triisopropylphosphine can drive the reaction to high selectivity in 2,3-dimethylbutenes (1-DMB and 2-DMB). 2,3-Dimethylbutenes are highly valuable products used as starting materials for the synthesis of fine chemicals. Regioselective propene dimerization can be performed in acidic chloroaluminates. The phosphine effect can be maintained, providing a proper adjustment of the IL acidity [9].

In the case of Ni-catalyzed oligomerization of butenes in acidic chloroaluminates, it has been shown that octene distribution (typically 39% dimethylhexenes, 56% methylheptenes, and 6% octenes) is independent of the addition of phosphine ligand. In addition 1-butene and 2-butene lead to the same product mixture due to very fast isomerization of 1-butene to the thermodynamic butene composition.

Square-planar Ni(II) with *O,O′*-chelating ligands (**2**) have been described as affording good linear octene selectivity in one homogeneous phase using toluene as the solvent. Using this same Ni complex, butene dimerization can be performed in a continuous-flow reactor using slightly acidic chloroaluminate ILs as the solvent, giving up to 52% linear octene selectivity [10, 11]. No alkylaluminum is necessary to activate the Ni complex, which already contains a Ni–carbon active bond. However, the slightly acidic chloroaluminate salt ([BMIM][Cl]/$AlCl_3$ with 0.43 : 0.53 molar ratio) has to be buffered with an additional organic base, such as *N*-methylpyrrole, to prevent the formation of oligomers by acidic cationic side reactions.



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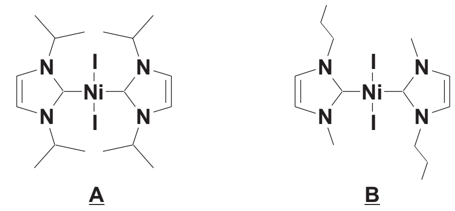
Heterocyclic imidazolylidene carbenes proved to be very interesting ligands of transition metal complexes. Their electronic properties have very often been compared to those of basic phosphines. They are indeed good σ-donors but weak π-acceptors. A number of carbene complexes have been involved in catalytic reactions such as metathesis (Ru) or C–C coupling (Pd, Ni). They can be generated easily by deprotonation of an imidazolium salt in the presence of an organic base.

Ni(II) diisopropylimidazolylidenes (**3**) have been involved in catalytic oligomerization of olefins (butene or propene) [12, 13]. In homogeneous one-phase reaction, using toluene as the solvent and dichloroethylaluminum as the activator, the Ni–carbene complex **3A** presents very low activity toward 1-butene. Slow decomposition to Ni(0) is observed. It has been demonstrated that reductive elimination can occur resulting in the formation of 1,3-diisopropylimidazolium or 1,3-diisopropyl-2-alkylimidazolium salts. When the reaction is performed at room temperature in buffered acidic chloroaluminate [BMIM][Cl]/$AlCl_3$/*N*-methylpyrrole ILs (0.45 : 0.55 : 0.1 molar ratio), high TOFs are obtained (higher than with $NiCl_2 \cdot 2\ PCy_3$). Unfortunately, the distribution of isomeric octenes was not significantly affected by the presence of the carbene ligand. It is worth mentioning that, in a similar way, the presence of the PCy_3 ligand does not modify the octene distribution. Dimerization of propene with the carbene–Ni complex **3B** results in good activity, but there is no ligand effect on the branching of hexene isomers.

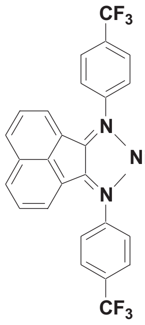


3

Ethylene Dimerization and Oligomerization

High-purity linear α-olefins (LAOs) are mainly produced by ethylene-catalyzed oligomerization. Depending on their chain length, these olefins can be used in different applications, for example, in polymers (LLDPE), plasticizers, lubricants, or detergents [14]. The main interest in LAO use is currently focused on C_4–C_{10} cuts that are used as co-monomers in high- and low-density polyethylene production. Oligomer distribution (C_4, C_6, C_8 ...) can vary over a wide range depending on the metal-surrounding ligands.

Recently, nickel complexes based on "hard" nitrogen ligands such as α-aryldiimines (**4**–**7**) or oxygen donors have been successfully applied for ethylene oligomerization and polymerization in conventional organic solvents. Using chloroaluminates ([BMIM][Cl]/$AlCl_3$) as the solvent, and methylaluminoxane (MAO) as the nickel activator, much more active systems are obtained (Table 2) [15]. The catalytic structure has a substantial effect on the product chain length distribution. Unhindered diimine complex (complex **4**) leads to high selectivity in C_4–C_8 (Table 2, entries 1 and 5). Sterically encumbered substitution patterns (e.g., complex **5**) reduce the chain-transfer rate, yielding polyethylene as the major product (entries 4 and 7) [16]. However, in chloroaluminate the isomerizing activity of the Ni system is enhanced and internal olefins are obtained as the major linear oligomer components.



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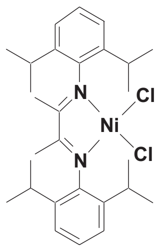
(L1-$NiCl_2$)



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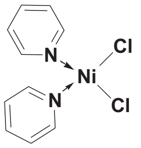
(L2-$NiCl_2$)



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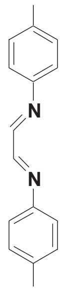
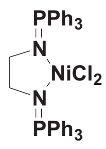
(L3-$NiCl_2$)



7
(L4)

Ni–diiminophosphorane complexes (**8**–**11**) also proved to be highly active under mild reaction conditions [17]. But a dramatic evolution of oligomer distribution is observed upon recycling the IL containing catalyst. α-Olefin selectivity decreases and higher oligomers (C_6–C_{12}) are formed. This can be ascribed to the displacement of the ligand from the Ni coordination sphere by the potential Lewis-acidic aluminum species present in the IL [Eq. (4)].



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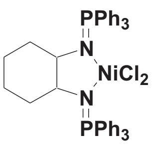

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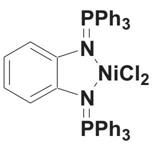

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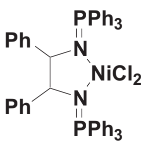

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$$\mathrm{LNiH^+ + Al_2Cl_7^- \rightleftharpoons AlCl_3 \cdot L + [Ni{-}H]^+\, AlCl_4^-} \tag{4}$$

Table 2 Ethylene oligomerization in biphasic chloroluminate systems and in homogeneous organic solvents.

Entry	*Catalyst*	*Solvent*	*TOF*[b] · 10^{-3}	*Selectivity [wt.%]*					α-*Olefin*[e] *[wt.%]*
				C_4	C_6	C_8	C_{10}	*PE*[f]	
1	**4**/MAO	Toluene[c]	17	27	23	17	12	0	80
2	**4**/MAO	Chlorobenzene[c]	23	56	31	8	5	0	66
3	**6**/MAO	Toluene[c]	2.5	97	3	0	0	0	30
4	**5**/MAO	Toluene[c]	18	27	2	0	0	72	33
5	**4**/MAO	BMIC/AlCl$_3$[d]	41	64	30	4	1	0	41
6	**6**/MAO	BMIC/AlCl$_3$[d]	68	66	31	3	0	0	27
7	**5**/MAO	BMIC/AlCl$_3$[d]	25	41	2	0	0	57	26

a) Reaction conditions: for entries **1**–**4**, P = 2.5 MPa, T = 40 °C, time = 30 min, Ni: 0.009 mmol; for enties **5**–**7**, T = 25 °C (except entry **6**, when T = 40 °C), time = 30 min, Ni: 0.02 mmol; MAO in toluene, Al/Ni = 200 : 1.

b) TOF units: g of ethylene consumed/g Ni h^{-1}.

c) Homogeneous reaction: 50 mL solvent.

d) Biphasic reaction: 1-butyl-3-methylimidazolium chloride/AlCl$_3$ (1 : 1 molar ratio), 8 mL.

e) Wt.% of 1-butene in C_4 fraction; remainder is 2-butene.

f) Polyethylene.

Sasol reported the use of a chromium-based catalyst (Cr salt, 2,5-dimethylpyrrole ligand) for the trimerization of ethylene into 1-hexene (P = 5 MPa, T = 115 °C) [18, 19]. According to Sasol, the IL of choice is 1-ethyl-2,3-dimethylimidazolium chloride/AlEt$_3$ containing an excess of AlEt$_3$. When compared to typical homogeneous catalytic systems, the activity and yield in 1-hexene are lower.

Despite all the advantages of using acidic chloroaluminates as catalyst solvents, high degrees of isomerization of α-olefins to internal olefins are often observed in these solvents and a competition for Lewis-basic ligands between soft transition metal centers such as Ni-H$^+$ and hard acid AlCl$_3$ may exist which results in loss of ligand effect. This is the reason why olefin oligomerization in nonacidic ILs based on weakly coordinating anions has been developed.

5.2.2.1.3
Oligomerization in Non-chloroaluminate Ionic Liquids

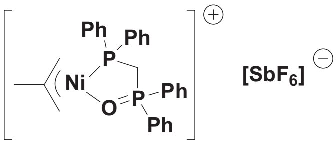
The cationic Ni complex **2** catalyzes the oligomerization of ethylene with higher activity in [BMIM][PF$_6$] IL than in dichloromethane, despite the lower solubility of ethylene in the IL than in the organic solvent (Table 3) [20, 21]. The good selectivity for α-olefins proves that the ligand remains coordinated to the Ni metal center. Interestingly, the oligomer distribution (C_4, C_6, C_8, etc.) is shorter in biphasic [BMIM][PF$_6$] system (α = mol C_{10}/mol C_8 = 0.16) than in the homogeneous dichloromethane one (α = 0.48). Because of their weak coordination ability toward the electrophilic Ni catalyst, non-chloroaluminate ILs are shown here to be interesting solvents for ethylene oligomerization. However, complex **12** is extremely

Table 3 Solubility of ethylene in different solvents.

Solvent	*Solubility [g(ethylene)/10 mL solvent]*
CH_2Cl_2	6.51
[BMIM][PF_6]	1.10
[HMIM][PF_6]	1.25
[OMIM][PF_6]	1.83

$T = 25$ °C, $P_{\text{ethylene}} = 5$ MPa.

sensitive to water. The known hygroscopicity of ILs and the absence of an Ni activator or proton scavenger such as an alkylaluminum derivative may be a limitation to the development of such systems.



12

Ni active catalysts can be generated directly in ILs by reaction of nickel(0) (such as Ni(COD)$_2$, where COD = 1,5-cyclooctadiene) with a Brønsted acid such as H(Et$_2$O)$_2$BArF (denoted as HBArF in Table 4 with BArF = B[3,5-(CF_3)$_2$$C_6H_3$]$_4$), in

Table 4 Ethylene oligomerization in biphasic non-chloroluminate[a)] systems and in toluene.

Entry	*Catalyst*	*Solvent*	*Time [min]*	*TOF*[d)]	*Selectivity [wt.%]*				*α-Olefin [wt.%]*[f)]
					C_4	*C_6*	*C_8*	*C_{10}*	
1	Ni(COD)$_2$/HBArF	toluene[b)]	110	170	98	2	0	0	
2	Ni(COD)$_2$/HBArF	[BMIM][NTf_2]	40	4000	60	35	5	0	33
4	Ni(COD)$_2$/HBArF	[BMPy]]NTf_2][c)]	30	1400	61	33	5	1	37
6	Ni(COD)$_2$/HBArF	[BMIM][PF_6]	130	500	94	6	0	0	34
7	Ni(COD)$_2$/HBArF[g)]	[BMIM][SbF_6]	100	12000	64	29	5	2	34
8	Ni(COD)$_2$/HBArF/**L1**	[BMIM][NTf_2]	60	2200	57	15	9	7	45
9[e)]	Ni(COD)$_2$/HBArF/**L1**	[BMIM][SbF_6]	28	2000	28	23	17	5	60
10	Ni(COD)$_2$/HBArF/**L2**	[BMIM][NTf_2]	20	2500	3	97% polyethylene			
11	Ni(COD)$_2$/HBArF/**L4**	[BMIM][SbF_6]	20	1500	80	13	4	2	60

a) Reaction conditions: $P = 2.8$ MPa, $T = 25$ °C, Ni: 0.1 mmol; biphasic system with 5 mL IL and 5 mL toluene.
b) Ni: 0.2 mmol, toluene 10 mL.
c) [BMPy]: butylmethylpyrrolidinium.
d) TOF: g of ethylene consumed/g Ni h^{-1}.
e) Ni: 0.05 mmol. HBArF: 0.05 mmol. **L1**: 0.05 mmol.
f) Wt.% of 1-butene in C_4 fraction; remainder is 2-butene.
g) Catalyst phase has been recycled 3 times with no change in reaction performances.

the absence of Al co-catalyst. In the absence of ligand, the reaction activity is much higher in ILs than in toluene [15]. The nature of the anion of the IL plays a crucial role (Table 4). While no activity is observed in triflate-based salts, high TOFs can be obtained by using [BMIM][SbF_6] or [BMIM][NTf_2] ILs. The polarity and coordination properties of the IL, which are likely to be anion- and cation-dependent, are probably one of the factors that contribute to affect the Ni catalyst activity. For a highly active system, the nature of the IL does not seem to affect the product distribution. Butenes are obtained as the major products. But as for chloroaluminate, the 1-butene selectivity is low. In order to control this selectivity, diimine ligands (see **4–7**) have been added to the catalytic system. Variation of the nickel structure has a significant effect on the product selectivity. Polyethylene is the major product when the diimine has sterically bulky *ortho*-aryl substituents (e.g., the **L2** ligand, **5**). When diimine is lacking aryl substituents (e.g., the **L4** and **L1** ligands, **4** and **7**), mainly C_4–C_8 oligomers are produced. In [BMIM][SbF_6], with **L4** (Table 4, entry 11), high butene selectivity is obtained with 60% of 1-butene.

5.2.2.1.4
Conclusion

Due to the sensitivity to proton or coordinating solvents of most dimerization or oligomerization transition-metal catalysts, ILs proved to be very promising alternative solvents to water, or to protic or polar coordinating organic conventional solvents. Chloroaluminates have been widely studied and applied as both solvents and co-catalysts for biphasic Ni-catalyzed olefin dimerization. Electrophilic cationic nickel catalysts are stabilized in the ionic phase without the need for specially designed ligands. Apolar oligomers, which are very poorly miscible in the catalyst phase, can be easily separated given their lower density compared to that of the ILs. Non-chloroaluminate ILs are also interesting solvents because of the versatility of their solvation properties.

Besides the chemistry, the design of the reactor also plays an important role in reaction performances. In biphasic systems, the reactor volume may be much smaller than in homogeneous systems, which may have some benefits in the industrial process [22].

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5.2.2.2
Hydroformylation

Lionel Magna

5.2.2.2.1
Introduction

The hydroformylation reaction was discovered in 1938 by Otto Roelen in the Ruhrchemie laboratories at Oberhausen (Germany) [1, 2]. Since that day, hydroformylation has become a widely studied and interesting reaction for both academic and industrial researchers. This reaction consists formally in the transformation of olefins under carbon monoxide and hydrogen pressure leading to linear and branched aldehydes as primary products (see Section 2.4.1.1). The interest of such a reaction resides in the formation from an olefin of a new carbon–carbon bond with the introduction of a carbonyl function which can be easily transformed into different products of industrial interest like detergents, plasticizers, and pharmaceutical products. The overall production capacity of oxo products was estimated to be around 10 million tons per year in 2001 and this production is still increasing.

It is generally accepted that the different industrial oxo processes can be divided in three main generations [3]:

- The *first-generation process* is based on the use of cobalt carbonyl complexes (BASF, Ruhrchemie, ICI, Exxon). The reaction conditions are drastic. The pressure required for the stabilization of active species ranges from 20 to 35 MPa and the temperature has to be around 150–180 °C to obtain acceptable yields. The main difference between those processes resides in their catalyst recycling technique: BASF and Ruhrchemie have chosen to oxidize the cobalt (with oxygen in acidic solution or by hydrothermal treatment) while Exxon (in what was known earlier as the Kuhlmann process) transforms the cobalt catalyst to $[Na][Co(CO)_4]$ in an aqueous basic solution and then extracts this salt for regeneration of $HCoCO_4$ in acidic solution. At the beginning of the 1960s, Shell developed a process associating a phosphine ligand with a cobalt catalyst precursor which forms a stable complex and allows less drastic reaction conditions, the pressure being inferior to 10 MPa. The separation of the catalyst remains possible by distillation of the reaction products.
- The *second-generation process* corresponds to the use of the more active rhodium catalysts (Celanese Corporation, Union Carbide, BASF, Mitsubishi). These processes are performed under mild reaction conditions and generate many fewer byproducts. The selectivity for linear aldehydes is also increased. Thanks to the use of phosphine ligands, the thermal stability of the catalyst is increased and the recycling can be performed by distillation with moderate rhodium losses.
- Finally, *the third generation,* in which a liquid–liquid biphasic system is used, corresponds to the development of the Ruhrchemie/Rhône-Poulenc process. Olefins of the organic phase are converted by a rhodium complex maintained in an aqueous phase by adjunction of an hydrosoluble phosphine, the sodium salt of the *meta*-sulfonated triphenylphosphine [Na][TPPTS]. The separation of aldehydes from the catalytic phase is then performed by a simple decantation.

For the different hydroformylation processes described above, the catalyst separation and recycling remain a constant preoccupation. This point is particularly crucial when a very expensive metal is used as catalyst (rhodium). The recycling is either operated by chemical transformation or by direct distillation, depending on the catalyst and its stability. In that way, the development of the aqueous biphasic process can be considered as an important breakthrough [4–6]. The separation is operated by decantation, which simplifies the process scheme and limits the risks of catalyst decomposition during distillation. Even if the oxo Ruhrchemie/Rhône-Poulenc process presents undeniable advantages, this process remains limited to short-chain olefins (C_2–C_5) because of the low solubility of higher olefins in water which renders the reaction rates too low for viable processes [7].

In order to overcome this limitation, the elegant concept of biphasic catalysis for hydroformylation reaction was further extended to media other than water [8]. The identity of this ideal second phase is far from obvious as very few solvents present chemical and physical properties in accordance with the hydroformylation requirements. Without giving a complete list, one can cite perfluorinated solvents [9] (see Chapter 4), supercritical fluids [10] (see Chapter 6), and nonaqueous ILs [11]. At the moment, ILs, because of very particular properties [12], represent the most promising solvents to substitute for water in the biphasic hydroformylation of olefins.

5.2.2.2.2
General Considerations for the Use of Ionic Liquids in Hydroformylation

ILs exhibit many properties that could, a priori, satisfy the requirements for the hydroformylation reaction. First, they have essentially no vapor pressure. This point considerably limits the problem of VOCs (volatile organic compounds) observed with conventional organic solvents. Furthermore, as they do not evaporate, a good sequestration of the IL in the process can be envisioned. This property is also an interesting means to facilitate the separation of products from the IL if a distillation is used. In that case the catalyst is solubilized and stabilized in the IL while the products are evaporated and separated in the distillation column. The thermal stability of ILs is also of great interest [13]. Some of them (e.g., [EMIM][NTf$_2$]) are described as stable up to 400 °C, which gives a wide range of use for this class of solvents [14, 15]. The very hard conditions sometimes necessary for hydroformylation can be envisioned with ILs, these conditions being impossible with water.

ILs also present good and tunable solubility with olefins. As described above for organic/water biphasic hydroformylation systems, the partial solubility of olefins in the phase containing the catalyst is essential to obtain a viable biphasic process. For comparison, Figure 1 represents the solubility of different olefins in [BMIM][BF$_4$] and water [16]. One can observe that the solubility of 1-hexene is 100 times higher in [BMIM][BF$_4$] than in water. Beyond an increased olefin solubility, ILs offer the opportunity to modulate this solubility by varying their composition. The nature of the cation and the anion greatly influences the olefin solubility, as described in Figure 2 for 1-hexene [16, 17].

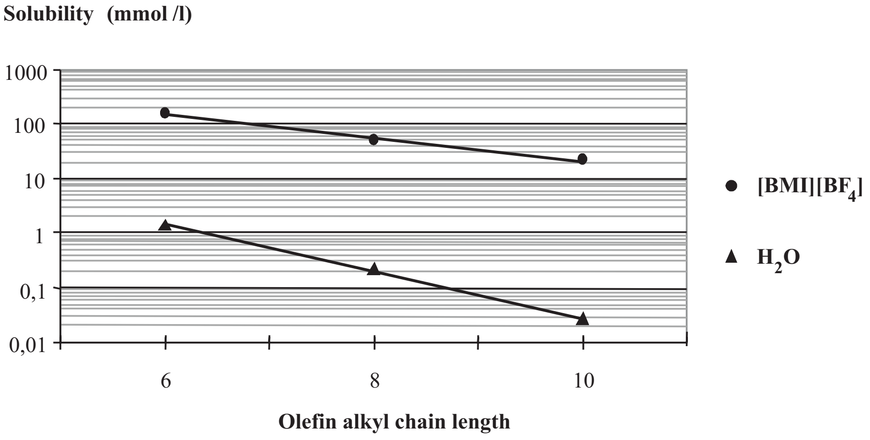


Figure 1 Olefin solubility in water and [BMIM][BF$_4$].

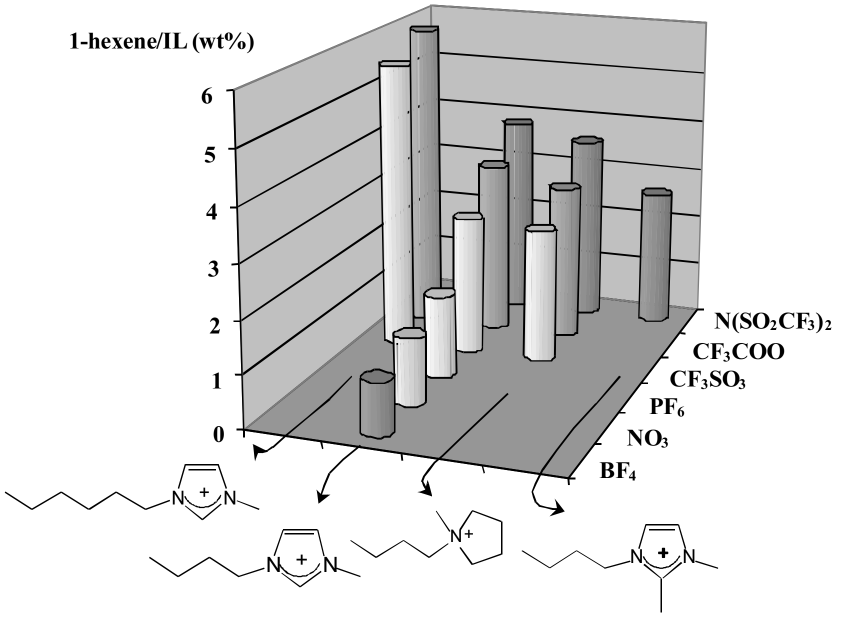


Figure 2 Solubility of 1-hexene in different ionic liquids.

Last but not least, ILs are able to act as solvents for inorganic and organometallic species without undesirable interactions with the metal center. This property is an incredible advantage of ILs with respect to other media. These solvents are indeed considered as noncoordinating, or more carefully, weakly coordinating media (depending on the anion) [18]. Interactions between the solvent and the catalyst can be controlled and modulated following the specificities of the system. The weak coordinating power of the IL anion will limit the competition between the solvent and the ligand for the coordination to the metal center. Some recent discussions seem to qualify this property and care must be taken with any generalization to all IL classes.

Despite these advantages, the transposition of hydroformylation in a biphasic system using ionic liquids as the catalytic phase remains a big challenge. First, one must keep in mind that the generally accepted active species in the hydroformylation mechanism is a neutral complex (e.g., $[HRh(CO)L_3]$ for a rhodium catalyst) [3, 19]. The immobilization of this complex in an ionic media is far from obvious. Partitioning of this species between the organic and the IL phase is highly probable but, as for aqueous biphasic systems, good immobilization of the catalyst can be achieved by a correct design of the ligand. Furthermore, in an ideal biphasic system the reaction products must have very limited solubility in the catalytic phase for a perfect decantation and recycling [7]. If, for oligomerization or other transformations using apolar reagents and products, this problem remains limited, the situation can be completely different for hydroformylation. In this latter case, the polarity of aldehydes can bring some trouble. A perfect separation between hydroformylation

Table 1 Qualitative solubility of *n*-heptanal in common ILs.[a)]

Ionic liquids	***Total amount of n-heptanal***[b)]		
(2 mL)	***1 mL***	***2 mL***	***6 mL***
[BMIM][PF_6]	p.m	p.m	p.m
[BMIM][BF_4]	p.m	p.m	p.m
[BMIM][NTf_2]	m.	m.	m.
[BMIM][CF_3CO_2]	m.	m.	m.
[BMIM][CF_3SO_3]	m.	m.	m.

a) Experiments are performed in a double-walled glass reactor regulated at 30 °C.
IL is first introduced into the reactor, followed by *n*-heptanal.
The magnetic stirring bar is run for 15 min and stopped for another period of 15 min before the observation of miscibility.

b) p.m.: partially miscible (biphasic system remains); m.: totally miscible (single-phase system).

products and IL is often difficult to obtain (Table 1). This problem is often circumvented by the use of an apolar co-solvent (heptane), which unfortunately reintroduces the problem of VOCs and makes the process scheme more energy-consuming. The search for ILs with good solubility for olefins and limited solubility for aldehydes is of particular interest. The final and ideal solution would be the identification of a perfect "ionic liquid/metal/ligand" threesome.

Another important parameter which must be considered in the case of hydroformylation, is the solubility of gaseous substrates (CO and H_2) in the phase containing the catalyst. Measurements of Henry's constants for CO and H_2 in common ionic liquids indicate a very poor solubility of these gases [20]. For the correct design of the reactor and process scheme, this point has to be seriously considered as it can yield to mass-transport limitation.

Even if very few toxicity data are available, it is generally accepted that ILs are nontoxic (see Section 5.4). Nevertheless, this point must be further checked by more detailed studies. For complete investigations of the toxicity, one would consider all the possible decomposition pathways of ILs. The main known ILs present perfluorinated anions. Their decomposition potentially forms HF, a particularly toxic and corrosive compound. This was demonstrated for PF_6^--based ILs [21] but it certainly occurs for other halogenated anions. This will have consequences for both the stability of the catalyst [22] and the material design of the process. For this purpose, many research groups tend to develop ILs based on nonperfluorinated anions [23]. Furthermore, even if many ILs are now commercially available, they remain difficult to prepare with a high purity level. Scale-up could be a problem in certain cases. The research for cheaper anions is also of crucial interest for the generalization of this technology to larger-scale applications than laboratories.

5.2.2.2.3
Hydroformylation in Ionic Liquids

As a consequence of classical homogeneous hydroformylation systems, the study of this reaction in ILs has essentially been developed around rhodium as catalyst. Only a few exceptions deal with the use of other metals such as platinum, cobalt, or ruthenium.

Ionic Liquids as Solvents and Co-catalysts

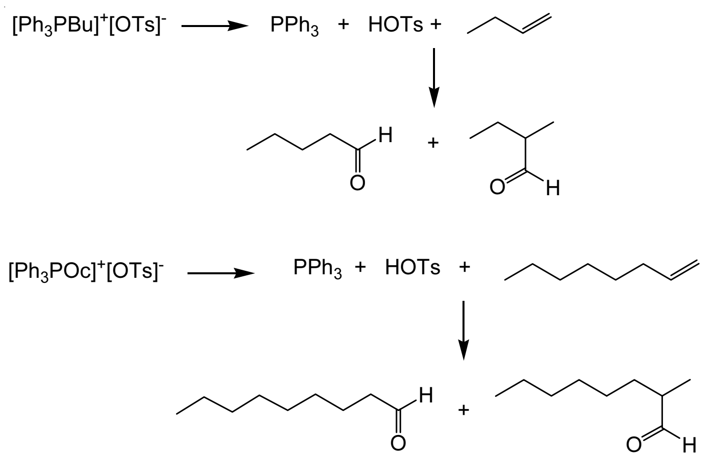
The first report on the use of ILs, or at that time "molten salts" for hydroformylation of olefins was by Parshall in 1972 [24]. The relatively low-melting tetraalkylammonium salts of the $SnCl_3^-$ anion were used as convenient solvents for several homogeneous platinum-catalyzed reactions. The tetraethylammonium salts of the trichlorostannate anion melts (around 78 °C) to give a clear, colorless liquid. In this medium, up to 7% of the $[PtCl_2]$ catalyst precursor can be dissolved. Under very hard conditions (90 °C, 40 MPa of H_2/CO in a 1 : 10 ratio), the system described can hydroformylate ethylene to give 65% combined yield of oxo products. The author comments that "The great similarity in activity between a solution of $PtCl_2$ in a molten trichlorostannate salt and that observed with preformed $SnCl_3^-$ complexes ($[(C_2H_5)_4][Pt(SnCl_3)_5]$) suggests that the catalytic species may be similar or identical in the two systems." The anionic platinum species was even isolated by extraction of a concentrated solution of $PtCl_2$ in $[(C_2H_5)_4N][SnCl_3]$. In order to study in more detail the preliminary work of Parshall, the Wasserscheid group has investigated the use of platinum catalysts ($[(PPh_3)_2PtCl_2]$) in association with chlorostannate melts for the hydroformylation of functionalized (methyl-3-pentenoate) and nonfunctionalized alkenes (1-octene) [25]. Because of their high melting point, chlorostannate ILs described by Parshall caused some restrictions for reaction parameters and processing conditions. Consequently, room-temperature liquid chlorostannate salts described by Ling and Koura were used for this work [26]. As for chloroaluminate salts, those ILs can be considered as slightly Lewis-acidic media. They were prepared by mixing [BMIM][Cl] or 1-butyl-4-methylpyridinium chloride with $SnCl_2$ in a molar ratio of 1 : 1.04. Both compositions were liquid at room temperature. The moderate Lewis-acidity of these ILs allows the activation of the Pt catalyst combined with tolerance for the functional groups. Reaction rates observed for both reactions studied were comparable or even better than those obtained in CH_2Cl_2. As an example, 1-octene was hydroformylated at 9 MPa and 120 °C with a reaction rate as high as 126 h^{-1}. The n/i ratio is very high (up to 24) but a large amount of hydrogenated product (*n*-octane) was formed (up to 41.7%). This last effect is common for both olefins studied. The authors postulate that under reaction conditions the hydrogen of the syngas has a higher solubility in the chlorostannate IL than carbon monoxide. This point was not checked experimentally but seems to correlate well with the results observed. Another interest of this system resides in the efficiency of the catalyst immobilization. Indeed, for hydroformylation of 1-octene, no leaching of the platinum catalyst in the organic phase was detected, giving one more argument for the ionic character of the active species. In these first two examples, it is important to note that the IL has a crucial role in the generation of the active species. The chemical interaction between the anion of the IL and the catalyst precursor favors the stability, the activity, and the immobilization of the catalyst.

Ionic Liquids as Stabilizing Agents for Ionic Catalysts

More than one decade after Parshall's work, Knifton demonstrated the crucial role played by the addition of quaternary phosphonium salts in the hydroformylation of internal olefins catalyzed by ruthenium "melt" [27]. In the system described, the anionic ruthenium cluster $[HRu_3(CO)_{11}]^-$ generated in situ from $[RuO_2]$, $[Ru(OAc)_2]$, or $[Ru(acac)_3]$ is the predominant metal carbonyl species in the reactant solutions. This anionic species seems to be particularly stabilized by the quaternary phosphonium salt matrix, even under low-pressure and high-temperature conditions. The author assumes that "improvement in product alcohol regioselectivity by using this salt likely has its roots in the ion pair interactions with the $[HRu_3(CO)_{11}]^-$ cluster anion". Both the desired alcohol and aldehyde product fractions can be readily isolated from the crude product by fractional distillation and the residual "melt" catalyst can be recycled without loss of activity [28].

Ionic Liquids as Stabilizing Agents for Neutral Catalysts

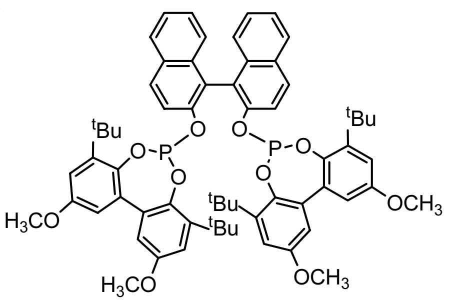
Because of their relatively high melting points, phosphonium salts were not the most widely studied IL class for hydroformylation reactions. Nevertheless, the remarkable solvent effect of these ILs was pointed out for the hydroformylation of 1-hexene [29]. Four different tetraalkylphosphonium tosylate salts with melting points between 70 and 117 °C were used as solvents, with $[Rh_2(OAc)_4]$ as catalyst precursor associated or not with PPh_3. The results demonstrated that without added phosphine different conversion ranges can be obtained with n/i ratios varying from 2.5 : 1 to 1 : 4. In contrast, addition of an excess of PPh_3 yields very similar results for all the phosphonium salts used. The authors postulated that for all the phosphonium solvents used, the presence of PPh_3 leads logically to $[HRh(CO)(PPh_3)_3]$ as the catalytic species. At the end of the run, the catalytic phase is cooled to room temperature. It can then be easily recovered by simple decantation and recycled with fresh 1-hexene. In all the cases described, no significant leaching of the rhodium catalyst was detected, indicating that it remains within the structure of the solid solvent. Recycling of the solvent has been operated several times and has given reproducible results. Nevertheless, it is important to note that the choice of the alkyl substituents in the phosphonium cation is not inert in terms of chemical reactivity. In the case of $[Ph_3PBu][OTs]$ and $[Ph_3POc][OTs]$, the authors observed in the reaction mixture the formation of the corresponding C_5 and C_9 aldehydes respectively. These products derive from the elimination of the alkyl moiety to form the corresponding alkene (and then aldehyde) by the analogous Hoffmann eliminations in ammonium salts (Scheme 1). One can then imagine that the



Scheme 1 Side reactions of phosphonium salts during hydroformylation.

subsequent alkylphosphine generated in situ can act as a rhodium ligand and influence the course of the reaction. This result points out that ILs derived from phosphonium salts are not always inert solvents for this reaction.

The study of methyl-3-pentenoate hydroformylation with platinum complexes in acidic chlorostannate ILs was later completed by the use of neutral ([BMIM][PF_6]) IL with rhodium as catalyst [30]. In this work, the great potential of neutral ILs as solvents for homogeneous catalyst recycling, even in cases where the reaction mixture is monophasic, was demonstrated. The particularity of the system studied resides in the homogeneous single phase observed during and at the end of the transformation. The recycling of the catalyst is then performed by distillation under reduced pressure at 110 °C. The possibility of recycling the catalyst results from the IL's nonvolatile nature. Furthermore, the catalyst, depending on the added ligand, is stabilized by the IL during this operation of intense thermal stress. With PPh_3 the catalyst activity decreases to almost zero after four cycles, whereas with 2,2′-bis[((2,2′-bis(4-methoxy-6-t-butyl)phenoxy)phosphino)oxy]-1,1′-binaphthyl (**1**) the catalyst remains active after ten runs (with noticeable deactivation, however).



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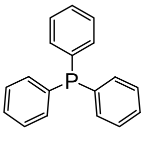
The authors consider this method as a very general way to recycle homogeneous catalysts from monophasic reaction mixtures [31]. In addition to a technical advantage for recycling the catalyst, the IL has a significant effect on the catalyst's activity when phosphite or phosphine is used as ligand. Indeed, if we can consider that the regioselectivity is ligand-controlled and quite independent of the solvent used, the activities are almost twice as high when an IL is used instead of a common organic solvent like toluene.

Charged Ligands for Hydroformylation in Ionic Liquids

Despite the independent work of Parshall [24] and Knifton [27], one may ascribe the real start of the use of ILs for two-phase hydroformylation to the work of Chauvin's group at IFP in 1995 [11] (see Section 5.1). Two-phase 1-pentene hydroformylation was achieved by using $[Rh(CO)_2(acac)]$ as a catalyst precursor. Preliminary experiments using a $[Rh(CO)_2(acac)]/PPh_3$ neutral system showed high catalytic activity in the $[BMIM][PF_6]$ salt (TOF = 333 h^{-1}). Unfortunately, important leaching of the catalyst to the organic phase was observed. One can assume that the active species in the IL phase ($[HRh(CO)_2(PPh_3)_2]$) is the same molecular one as in the homogeneous phase, the retention of this uncharged catalytic species being limited in the IL. Immobilization of the catalyst in the IL with charged ligands gave better results later. The sodium salt of the monosulfonated-triphenylphosphine [Na][TPP*MS*] (**3**) and the sodium salt of the trisulfonated triphenylphosphine [Na][TPP*TS*] (**4**) are two examples of these charged ligands. The decrease in the catalytic activity (59 h^{-1} with TPPMS instead of 333 h^{-1} with PPh_3) was compensated in a way by the complete avoidance of catalyst leaching.



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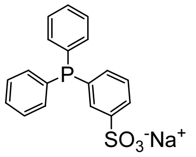

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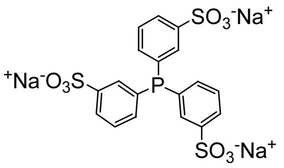
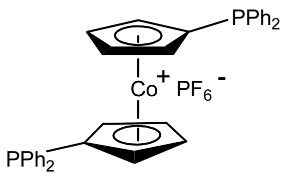


4

Much work was then developed around the functionalization of the ligand for a better immobilization of the catalyst in the IL phase. The first study was described by Saltzer et al. in 2000 [32]. The authors used electron-poor phosphine-substituted cobaltocenium salts as ligands for the biphasic hydroformylation of 1-octene (**5** and **6**).

In the ligand series synthesized, 1,1′-bis(diphenylphosphino)cobaltocenium hexafluorophosphate (**5**) proved to be particularly suitable. In $[BMIM][PF_6]$, high catalyst activity (810 h^{-1}), high selectivity for aldehydes (94%) and for the *n*-product ($n/i = 16.2$), and above all no detectable catalyst leaching were demonstrated. The analogous cobaltocenium (**6**), in which an alkyl bridge was placed between the cyclopentadienyl and the phosphorus atom, yields much less positive effects (e.g., TOF = 66 h^{-1}). This result can be explained by the electronic influence of the central



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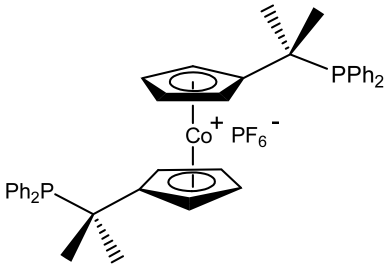
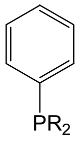


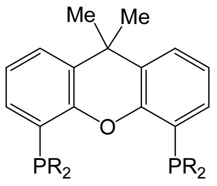
6

cobalt atom on the phosphorus atom which becomes considerably weaker in **6** than in **5**. Catalytic performances of **6** become more comparable with the almost isoelectronic diphenylphosphinoethane (dppe).

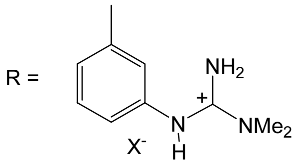
For a better solubility of the catalyst in the ionic liquid phase, guanidinium-modified mono- and diphosphine ligands were synthesized [33]. Originally developed for their pronounced solubility in water [34, 35], ligand **7** appeared to be particularly suitable for application in ILs. Comparison of this ligand to other classical neutral (PPh_3) or ionic monophosphines ([Na][TPPTS]) demonstrates higher overall activity and higher regioselectivity for 1-octene hydroformylation in [BMIM][PF_6]. The best results were obtained for the guanidinium-modified diphosphine ligands with a xanthene backbone (**8**). It is indeed well known that diphosphine ligands with large natural P-metal-P bite angles form highly regioselective catalysts [36]. Functionalization of these bidentate structures with guanidinium moieties yields an efficient catalyst which can be recycled in ten consecutive runs with an overall TOF of 3500 mol 1-octene per mol Rh catalyst. In good agreement with the recycling efficiency, the rhodium leaching into the organic phase was found to be very low (< 0.007% – detection limit). As expected with a xanthene backbone ligand, very good selectivity for the linear aldehyde was obtained (96–98.5%). The *n*/*i* ratio was stabilized around 20 (depending on the recycling experiment).



7 X = PF_6



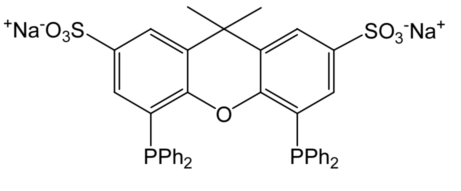
8 X = I



The characteristics of the xantphos-type ligands in terms of activity and selectivity were later exploited by Dupont et al. [37]. For a better solubility in ILs, sulfonated groups were grafted onto the xanthene backbone (**9**). Because of the poor natural solubility of this ligand in ILs, catalyst formation was achieved by mixing the ligand with [$Rh(CO)_2$(acac)] in a mixture of [BMIM][PF_6] and methanol. After evaporation of the methanol under vacuum, a yellow homogeneous IL phase was obtained.

Under optimized reaction conditions (1.5 MPa, 100 °C), it appears that the chemoselectivity and *n*/*i* ratio in the hydroformylation of 1-octene are very dependent on the nature of the IL. The best results were obtained using pure [BMIM][PF_6]. Lack of organization and local nano-inhomogeneity of impure systems (IL/water or toluene) were evoked to explain the less interesting results obtained with [BMIM][BF_4] or mixtures of [BMIM][PF_6] with H_2O. The authors assumed that the local nano-inhomogeneity in the IL "dramatically changes the partial miscibility of the alkenes, syngas and distribution products in the ionic catalytic phase". A complementary study on the use of the sulfonated xantphos ligand in [BMIM][PF_6] was recently published [38]. High-pressure infrared experiments were conducted in the presence of [$HRh(CO)_2$(sulfoxantphos)] in [BMIM][PF_6]. Similar *ee* (bis-equatorial) and *ea* (equatorial–apical) catalytic species, as observed in organic solvents [39], were detected in the IL. The coordination mode of the bidentate ligand to the metal is in good accordance with the *n*/*i* ratio obtained in the IL. The high-pressure ^{31}P NMR spectra were also recorded in [BMIM][PF_6], indicating that the ligand is mainly coordinated to the rhodium in a bis-equatorial fashion. Once again this result is consistent with those observed in organic solvents [40]. Nevertheless, contrary to the situation in organic solvent, the partial hydrogen pressure has just a marginal influence on the catalytic activity. This was explained by the limited solubility of hydrogen in [BMIM][PF_6], which is assumed to be much lower than that of carbon monoxide [41].

van Leeuwen, who was one of the originators of the xantphos-type ligand for homogeneous hydroformylation [42, 43], described a more specifically designed ligand structure for application in ILs [44]. In order to obtain a catalytic system that combines a high activity, a high selectivity, and a good retention, a novel cationic phenoxaphosphino-modified xantphos-type ligand (**10**) was developed. Ligands based on this structure proved to be very active and selective for 1-octene hydroformylation in conventional solvents such as toluene. Transposition of these ligands to biphasic ILs was realized in [BMIM][PF_6]. The choice of this IL was directed by both availability and easy synthesis of the salts but also by a good correspondence with the anion of the charged ligand. The catalyst precursor [$Rh(CO)_2$(acac)] and 4 equiv. of the ligand were first dissolved in CH_3CN/[BMIM][PF_6] before acetonitrile was removed in vacuum. The IL catalytic phase appears as a red homogeneous solution. Hydroformylation of 1-octene was then carried out at 100 °C and 1.7 MPa CO/H_2 (1 : 1). As expected, the selectivity for aldehydes and the linear to branched ratio were very high (respectively, 90.3% and *n*/*i* up to 49). Nevertheless, relatively low reaction rates were obtained. This result was explained by the formation of dimeric rhodium species. The equilibrium between the dimeric form and the active hydride rhodium species was shifted by modification of the reaction conditions. Experiments carried out in a large excess of H_2 ($P_{H2} = 4.0$ MPa, $P_{CO} = 0.6$ MPa) led to a considerable increase in reaction rates. From an average of 100 h^{-1} (depending on the cycle) with an equimolar CO/H_2 ratio, it reached 318 h^{-1} under the new conditions. Recycling experiments and ICP analysis of the organic phase demonstrated that no detectable phosphorus (< 100 ppb) or rhodium (< 5 ppb) was leached from the IL.



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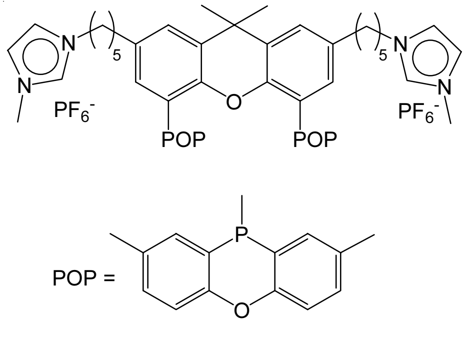
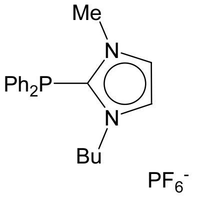


10

Following the general concept developed by Manassen, "like dissolves like" or *"similia similibus solventur"*, other functionalization moieties recalling the structure of the ILs based on the imidazolium cation were studied [45]. The 2-imidazolium phosphine **11** and para-phenyl-2-imidazolylphosphine **12** are two examples of this interesting approach.



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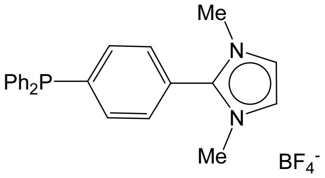

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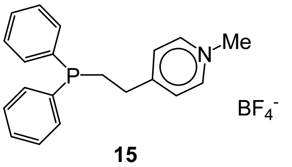
Rhodium-catalyzed hydroformylation of 1-octene was realized by mixing $[Rh(CO)_2(acac)]$ in situ with 2 equiv. of the ligand in $[BMIM][PF_6]$. Under reactions conditions (3 MPa, 100 °C), higher TOF values ($552\ h^{-1}$) were obtained with ligand **11** whereas with the phosphine **12** TOF decreases considerably ($51\ h^{-1}$). The close proximity of the positive charge to the phosphorus atom seems to enhance the catalytic activity greatly. Once again, with both ionic imidazolium ligands used in this study, no catalyst leaching was detected in the organic phase. As the use of imidazolium-functionalized ligands appeared to be of particular relevance, the same group later described general pathways for the synthesis of this type of ligand [46].

For this purpose they used 1-vinylimidazole as a versatile building block for the synthesis of cationic phosphines potentially attractive for hydroformylation in ILs.

Phosphorus ligand/IL systems were also developed by the Olivier-Bourbigou's group in 2001 [47, 48]. Phosphines with guanidinium (**13** and **14**) or pyridinium moieties (**15**) and phosphites with sulfonated groups (**16**) were synthesized. In this study, the crucial role of the anion associated with the ionic ligand was demonstrated. When monosubstituted guanidinium triphenylphosphines **13** and **14** are used in [BMIM][BF_4], similar results were obtained in terms of both reaction rates and selectivity. However, the best catalyst retention was obtained for **13** when the anion of the ionic *ligand* was the same than the anion of the ionic *liquid*. In another series of experiments, specially designed phosphites were applied. Phosphites are indeed well-known ligands for rhodium hydroformylation but their instability often prevents their use in classical water biphasic systems. In ILs this prejudice is refuted. The reaction using phosphite ligand **16** in [BMIM][PF_6] yields comparable reaction rates but higher selectivity toward linear aldehydes (n/i = 12.6) than ligands **13** and **14**. Recycling of the catalytic phase was even possible, giving one more argument for the potential of IL as solvents for catalytic reactions using particularly sensitive compounds. In parallel with the search for "ideal" ionic ligand structures, a wide range of ILs based on imidazolium and pyrrolidinium cations associated with weakly coordinating anions ($CF_3SO_3^-$, BF_4^-, PF_6^-, $CF_3CO_2^-$, NTf_2^-, etc.) were tested. Using the sodium salt of the monosulfonated triphenylphosphine (TPPMS) as a model, a great influence of the IL with respect to activity was highlighted. A direct correlation between the observed reaction rate and the measured solubility of 1-hexene in the IL was evidenced. The selectivity in aldehydes as the n/i ratio was not affected by changing the nature of the ILs.



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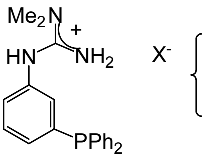
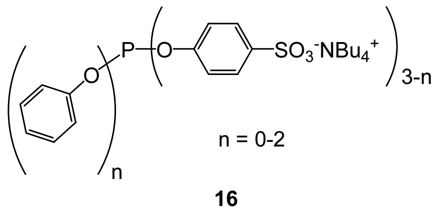


X = BF_4 **13**
X = PF_6 **14**



16

Ionic Liquid–ScCO$_2$ Fluid Hydroformylation Systems

Besides the now "classical" homogeneous organic–IL biphasic system, another original approach consists in the use of supercritical fluid–IL mixtures. In this strategy, the catalyst is first dissolved in an IL while the alkene, CO, and H_2 dissolved in $scCO_2$ are transported into the reactor, which simultaneously acts as a transport vector for aldehyde products. Decompression of the fluid mixture downstream yields products which are free from both reaction solvent and catalyst. Chapter 6 provides further details of this technology. This approach was applied to hydroformylation for the first time by the Cole-Hamilton group in 2001 [22]. In this work, hydroformylation of olefins in [BMIM][PF_6] was realized in both batch and continuous mode using [$Rh_2(OAc)_4$] as a catalyst precursor. The results observed were very dependent on the ligand used. With triphenylphosphite, the selectivity for aldehydes was increased in a significant manner in IL–$scCO_2$ systems compared to classical pure IL systems. Unfortunately, after several repetitive uses of the same catalyst, selectivity and activity drop considerably. This phenomenon was ascribed to the formation of HF from [BMIM][PF_6] and water and the consecutive degradation of the $P(OPh)_3$ into $P(OPh)_nF_{3n}$ ($n = 1–2$). Less water-sensitive phosphines were then used, suppressing to a large extent the degradation of the ligand. Because of the particularly low solubility of the classical [Na][TPPTS] in [BMIM][PF_6], the [BMIM][TPPMS] ligand was developed. This system applied to the 1-octene hydroformylation yielded very good results in terms of activity and selectivity. As evidence of the interest of the system, no rhodium was detected in the isolated organic phase (< 0.003% – detection limit). A series of nine runs were realized with no catalyst leaching. From the ninth run, phosphine oxide and neutral rhodium both soluble in $scCO_2$ are formed leading to significant catalyst leaching. Oxidation of the ionic phosphine was attributed to air contamination due to the frequent opening of the reactor. A continuous laboratory process was then developed on the same catalytic system. In these conditions, the catalyst was proven to be stable (activity, selectivity, and leaching) at least over a period of 30 h. This work was recently completed with additional results on the use of ILs other than [BMIM][PF_6] and olefins of relatively low volatility such as 1-dodecene [49]. Optimization of reaction conditions has demonstrated that the $scCO_2$–ionic liquid system could be operated continuously for several weeks without any visible sign of catalyst degradation.

Supported Ionic Liquid Hydroformylation Systems (SILCs)

Immobilization of ILs on a solid support is the direct transposition of the well-documented supported aqueous-phase catalysis (SAPC; see Section 2.6). For ILs this strategy can be of particular interest if we consider that the IL-phase remains liquid during reaction and is easy to maintain on the support due to its negligible volatility. Furthermore, because of the ease of separation and the possibility of using a fixed-bed reactor, a solid catalyst can be highly industrially advantageous for the production of aldehydes.

This concept was first applied for hydroformylation in 2002 by Mehnert at ExxonMobil [50]. This work involves a surface of a support material (silica gel) that is modified with a monolayer of covalently anchored fragments of 1-*n*-butyl-3-[3-(triethoxysilanyl)propyl]imidazolium. Treatment of this surface with additional IL results in the formation of a multiple layer of free ionic liquid which serves as the reaction phase in which the homogeneous catalyst is dissolved. As for classical biphasic systems using ILs, specially designed ligand must be added to limit the amount of catalyst leached in the organic phase. In this investigation, [Na][TPPTS] and [BMIM][TPPTS] were used in a first series of experiments. The preparation of the catalytic material was achieved by successive impregnation steps. Once the chemically grafted imidazolium layer was obtained, a solution containing [BMIM][BF_4] or [BMIM][PF_6], the rhodium catalyst precursor, and the ligand were added. After the solvent was removed, slightly yellow-colored free-flowing powder was obtained. Batch 1-hexene hydroformylation experiments were performed at 10 MPa and 100 °C to produce linear and branched aldehydes. For the different supported IL systems studied, increased reaction rates were observed with respect to the corresponding IL biphasic system. The authors assumed that "the improved activity might be attributed to a higher concentration of the active rhodium species at the interface and the generally larger interface area of the solid support in comparison to the biphasic system". Because of partial solubility of [BMIM][BF_4] in aldehydes, the concentration of oxo products in the reaction mixture has to be controlled below 50%. This limits the depletion of the IL in the organic phase and the subsequent rhodium leaching, which when measured was similar to that in supported and biphasic IL systems.

Similar results were recently published for the continuous-flow gas-phase hydroformylation of propene [51]. This time, the supported system was prepared by direct impregnation of an unmodified silica gel with methanol solution containing [$Rh(CO)_2$(acac)], the ligand, and the IL. The sulfonated xantphos used in this investigation must be added in large excess (10–20 equiv. per Rh) to afford the expected selectivity for the linear aldehyde ($n/i = 16.9$). The performance of the optimized catalytic support remains stable up to 5 h before a decrease in activity and selectivity was observed. This work was also completed using other ligands derived from the series developed in classical biphasic IL systems, and applied to the continuous hydroformylation of propene and 1-octene [52].

Ionic Liquid as Ligand

The use of ILs as both solvents and ligands is a very special and original approach which was not extensively developed. To the best of my knowledge only one example was reported in a patent by Bahrmann from Ruhrchemie in 1998 [53]. In this patent, the use of a "non aqueous ionic ligand liquid" of general formula $[Q]^{+}_{a}[A]^{a-}$ is described. The anion of the IL corresponds to the well-known $TPPTS^{-}$ phosphorus ligand while the cation corresponds to the protonated 1-amino-3-(di-*n*-octyl)aminopropane. This ionic liquid ligand was synthesized by mixing [Na][TPPTS] with 1-amino-3-(di-*n*-octyl)aminopropane in toluene and subsequent addition of sulfuric acid. Extraction of the hydrogensulfate with water yielded the final product. At the final stage, an excess of 0.45 equiv. of the sodium salt of the trisulfonated triphenylphosphine was present in the nonaqueous IL. In the catalytic experiments described, only [Rh(2-ethylhexanoate)] and cyclohexane (co-solvent) were added to this composition to perform the hydroformylation of 1-hexene [54]. The reaction was carried out at a temperature of 125 °C and a pressure of 2.5 MPa. Under these conditions, conversion after 45 min was 97% and the ratio of *n*-heptanal to 2-methylhexanal was 66 : 34. This catalyst was used repeatedly under the same conditions for 16 runs. Only small variations of the conversion and n/i ratio were observed with a rhodium loss which decreased steadily on multiple recirculation.

In this review, the use of *N*-heterocyclic carbene complexes derived from imidazolium salts as a part of the different strategies involving ionic liquids has not been considered. Nevertheless, it can be important to take into account this reactivity, especially when 1,3-dialkylimidazolium ILs are involved. For more details about this aspect and applications in hydroformylation, one can refer to Herrmann's recent review [55] and the later publication of Poyatos et al. in 2003 [56].

5.2.2.2.4
Conclusions

Since the first report on the use of ionic liquids for hydroformylation reactions, the attempts to improve catalytic systems in these media have reached a high level of performance. Successful systems with high reaction rates, selectivity, and catalysts retention efficiency have been reported. At the moment, those systems are able to overcome most of the limitations of the classical aqueous two-phase system. Thanks to intensive research on these media, ILs are now considered as conventional solvents like the classical known organic solvents. To illustrate this fact, one can see that in the patents literature ILs are increasingly mentioned in the list of potential solvents claimed for the application.

Since 2002, the range of technologies and strategies using ILs in hydroformylation has increased. Combination of ILs with supercritical carbon dioxide or supported ionic liquids (SILPs) widens the scope of investigations in a very interesting manner. Even if much work remains to be done before an industrial hydroformylation process using ILs becomes feasible, one can be optimistic that the real infatuation with ILs, and the constant accumulation of knowledge about them, will increase the prospects of their industrial development.

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5.2.2.3
Hydrogenation

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5.2.2.3.1
Introduction

The catalytic reduction of unsaturated bonds in the presence of a hydrogen source, usually molecular hydrogen, is one of the most important chemical processes for synthesis of fine and bulk chemicals. Various innovative hydrogenation catalysts were developed during the 20th century; of particular importance are the homogeneous catalysts, which provide high activity, selectivity, and, if required, enantioselectivity, features which are difficult to achieve with heterogeneous catalysts [1]. As with most homogeneous catalysts, product separation and catalyst stability tend to be less easy than with heterogeneous catalysts, and this is why ILs (ILs) are being investigated as immobilization and also stabilization solvents for homogeneous (or soluble nanoparticle) catalysts. The availability of several very good ionic transition metal hydrogenation catalysts [2], which can be dissolved in ILs without any modification, is perhaps partly responsible for the more rapid advances in IL immobilized hydrogenation catalysts over other types of catalysts. In fact, ionic catalysts were the first catalysts to be evaluated in ILs in hydrogenation reactions [3]. Since this initial study, a wide range of transition metal catalysts, based on rhodium, ruthenium, palladium, platinum, and iridium as well as other metals, have been used to hydrogenate various substrates including alkenes, alkynes, arenes, carbonyls, CO_2, and polymers. In general, the results obtained so far are very promising. Many of the catalysts can be recovered simply by phase separation and then used for further catalytic cycles. Some catalysts that are prone to deactivation are even found to be stabilized in ILs. Importantly, higher catalyst activities and chemo-, regio-, and enantioselectivities are observed in ILs than in conventional molecular solvents. Furthermore, some new methods have been introduced into catalytic hydrogenation reactions in ILs to enhance performance: for example, the separation of hydrogenated products using supercritical (or dense-phase) carbon dioxide, supporting ILs on solid supports, and the implementation of functionalized ILs, and these will be discussed in more detail below. Mechanistic studies, hydrogen transfer under photochemical conditions, and the solubility of hydrogen in ILs have also helped to probe the basic properties of ILs that lend themselves to hydrogenation catalysis, and such basic studies will inevitably help direct future research in the field.

5.2.2.3.2
Gas Solubilities in Molecular and Ionic Solvents

The solubility and thermodynamic properties of various gases in $[BMIM][PF_6]$ has been determined using a gravimetric microbalance [4]. Essentially, the solubility of CO_2 (particularly relevant as a carbon source) was very high, with reasonable solubilities observed for ethylene, ethane, and methane and low solubilities for oxygen, carbon monoxide, and hydrogen (H_2 could not be detected). Subsequently, Henry coefficient solubility constants of hydrogen in $[BMIM][BF_4]$ and $[BMIM][PF_6]$

Table 1 Solubility of H_2 in water, organic solvents, and ILs at 0.101 MPa.

Solvent	***Henry's constant, k^H [Mpa]***[d]	***10^3 [H_2] [M]***
Water[a]	$6.8 \cdot 10^3$	0.81
Methanol[a]	$6.6 \cdot 10^2$	3.75
Ethanol[a]	$5.9 \cdot 10^2$	2.98
Toluene[a]	$2.69 \cdot 10^2$	3.50
Benzene[a]	$4.47 \cdot 10^2$ ($4.39 \cdot 10^2$)	2.54 (2.57)
Cyclohexane[a]	$2.57 \cdot 10^2$ ($2.55 \cdot 10^2$)	3.63 (3.66)
$[BMIM][BF_4]$[a]	$5.8 \cdot 10^2$ ($1.63 \cdot 10^2$)	0.86[c] (3.0)
$[BMIM][PF_6]$[a], [b]	$6.6 \cdot 10^2$ ($5.38 \cdot 10^2$)	0.73[c] (0.88)
$[BMIM][NT_{f2}]$[b]	$4.5 \cdot 10^2$	0.77[c]
$[BMMIM][NTf_2]$[b]	$3.8 \cdot 10^2$	0.86[c]
$[BPy][NTf_2]$[b]	$3.9 \cdot 10^2$	0.89[c]
$[BMPy][NTf_2]$[b]	$3.7 \cdot 10^2$	0.90[c]
$[BMIM][SbF_6]$[b]	$4.9 \cdot 10^2$	0.93[c]
$[BMIM][CF_3CO_2]$[b]	$4.9 \cdot 10^2$	0.98[c]
$[HMIM][BF_4]$[b]	$5.7 \cdot 10^2$	0.79[c]
$[OMIM][BF_4]$[b]	$6.4 \cdot 10^2$	0.62[c]
$[BMIM][OTf]$[b]	$4.6 \cdot 10^2$	0.97[c]
$[P(C_6H_{13})_3(C_{14}H_{29})][PF_3(C_2F_5)_3]$[b]	$0.7 \cdot 10^2$	1.84[c]

a) 293 K.
b) 298 K.
c) Calculated from the solubility under 10.1 MPa, supposing that it changes linearly with the partial pressure.
d) $k_H = PH_2/XH_2$, where the partial pressure of hydrogen is expressed in MPa.

of 1.65 · 10^2 and 5.43 · 10^2 MPa, respectively, were determined using an electronic flow mass controller [5]. The range of ILs studied was increased to 11 (including those of the previous studies), this time using high-pressure ^{1}H NMR spectroscopy to determine the solubility, which is an excellent method when only a small amount of IL sample is available [6]. The data from this latter study are listed in Table 1 and comparisons with molecular solvents show that the solubility of hydrogen in ILs is low in general, similar to that in water.

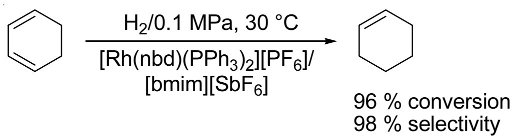
In $[P(C_6H_{13})_3(C_{14}H_{29})][PF_3(C_2F_5)_3]$ the solubility of hydrogen is significantly higher than in the other ILs, and while it is not possible to find any trends from the limited data available, it is not unreasonable to assume that ILs will be discovered in which even higher hydrogen solubilities can be achieved. These studies were particularly helpful as there was a general misconception in the literature that hydrogen solubility in ILs was higher than in molecular solvents, largely based on increased reaction rates observed. From a catalytic study conducted in the same 11 ILs that are used for the hydrogen solubility determinations it has been proposed that mass transfer of hydrogen into ILs is high and hydrogen availability is unlikely to be rate limiting for most processes.

5.2.2.3.3
Detailed Examples

Most of the numerous reviews on catalyzed reactions in ILs [7] include hydrogenation reactions. A relatively comprehensive book also contains many basic data on the physical properties of ILs [8]. In this section we have arranged hydrogenation reactions according to the transition metal used in the catalyst.

Hydrogenation by Rhodium Catalysts

Rhodium is widely used to catalyze hydrogenation reactions in heterogeneous [9], homogeneous [10], and aqueous–organic biphasic processes [11]. In 1995 Chauvin and co-workers reported the first examples of hydrogenation catalysis carried in ILs [12]. In order to overcome the problems associated with aqueous–organic systems, i.e., poor substrate solubility in water leading to low reaction rates and the coordinating nature of water, Chauvin used imidazolium-based ILs with noncoordinating anions such as $[BF_4]^-$, $[PF_6]^-$, and $[SbF_6]^-$ for the two-phase hydrogenation of 1-pentene with Osborn's complex, $[Rh(nbd)(PPh_3)_2][PF_6]$ (nbd = norbornadiene). The TOF was five times higher in the ILs than in acetone and the ionic solutions containing the catalyst can be re-used with less than 0.02% rhodium loss detected. This study demonstrated that without any ligand modification, the catalyst could be *immobilized* because of its ionic character. Importantly, it was also shown that ILs could have a marked influence on the selectivity of reactions [see Eq. (1)]. For example, the hydrogenation of cyclohexadiene to cyclohexene was achieved with 98% selectivity and 96% conversion in $[BMIM][SbF_6]$. The selectivity was ascribed to the fact that the cyclohexadiene substrate was five times more soluble than cyclohexene in $[BMIM][SbF_6]$.

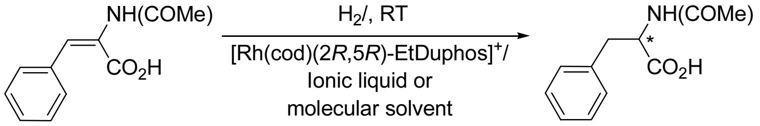


(1)

Subsequently, de Souza, Dupont and co-workers used Wilkinson's catalyst, $RhCl(PPh_3)_3$, to reduce cyclohexene in $[BMIM]–AlCl_3$ (mole fraction 0.45), $[BMIM][BF_4]$ and $[BMIM][PF_6]$ [13]. More recently, the structure of $RhCl(PPh_3)_3$ dissolved in chloroaluminate IL in the presence of hydrogen has been probed spectroscopically [14]. The ionic catalyst $[Rh(cod)_2][BF_4]$ (cod = 1,5-cyclooctadiene) was also used as a catalyst in $[BMIM][BF_4]$. Slightly higher activity was observed in the ILs than in molecular solvents.

Hydrogenation of the low molecular weight polymers polybutadiene (PBD), nitrile–butadiene rubber (NBR) and styrene–butadiene rubber (SBR), using a water-soluble analogue of Wilkinson's catalyst, $RhCl(tppts)_3$ (tppts = triphenylphosphine trisulfonated salt), has been carried out in $[BMIM][BF_4]$–toluene [15]. A small amount of water is added to increase the solubility of the catalyst, which increases the conversion. Addition of NaCl to the IL in the hydrogenation of PBD resulted, not surprisingly, in the catalytic activity decreasing.

A number of asymmetric hydrogenations using chiral rhodium catalysts have been conducted in ILs. The first example comprised the hydrogenation of α-acetamidocinnamic acid using the asymmetric and ionic catalyst $[Rh(cod)\{(–)\text{-diop}\}]PF_6$ [(–)-diop = (–)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane] in $[BMIM][SbF_6]$. The reactions proceeds with an enantiomeric excess (*ee*) of 64% [3]. The related catalyst $[Rh(cod)(2R,5R)\text{-EtDuphos}][CF_3SO_3]$ [(*2R,5R*)-EtDuphos = (–)-1,2-bis((2*R*,5*R*)-2,5-diethylphospholano)benzene] has been used to effect the enantioselective hydrogenation of (*Z*)-a-acetamidocinnamic acid hydrogenation [see Eq. (2)] [64]. The solubility of hydrogen in the solvent was shown to have a critical effect on both the conversion and the *ee*, with increasing hydrogen concentrations leading to increased conversions and *ee* values. Thus, when propanol was used as a comparison, higher conversions and *ee* values were obtained at lower hydrogen pressures, since hydrogen is considerably more soluble in the molecular solvent.

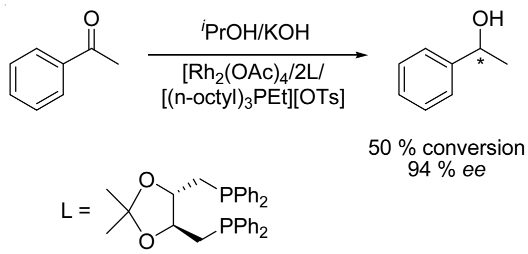


(2)

$[BMIM][PF_6]$, H_2/0.5 MPa, 7% conversion, 66% *ee*;
$[BMIM][PF_6]$, H_2/5 MPa, 26% conversion, 81% *ee*;
^{i}PrOH, H_2/0.5 MPa, 99% conversion, 94% *ee*.

The chiral complex $[Rh(cod)(2R,5R)\text{-MeDuphos}][CF_3SO_3]$ [(*2R,5R*)-MeDuphos = (–)-1,2-bis((2*R*,5*R*)-2,5-dimethylphospholano)benzene], immobilized in $[MIM][PF_6]$, has been used in the asymmetric hydrogenation of enamides [16]. Methyl α-acetamidocinnamate is hydrogenated with a conversion of 83% and *ee* of 96%. However, the conversion decreases to 83% in the second catalytic cycle, although the *ee* is essentially unaffected. With subsequent re-uses the conversion continues to decline steadily, suggesting that although the catalyst is naturally charged it can still leach into the organic phase (^{i}PrOH), or decompose slowly.

A rhodacarborane catalyst precursor containing what is termed a suicide alkene ligand, i.e., $[\mathit{closo}\text{-}1,3\text{-}\{\mu\text{-}(\eta\text{-}3\text{-}CH_2{=}CHCH_2CH_2)\}\text{-}3\text{-}H\text{-}3\text{-}PPh_3\text{-}3,1,2\text{-}RhC_2B_9H_{10}]$, together with the chiral co-ligand (*R*)-binap, has been used to catalyze the reduction of ketones to alcohols under hydrogenation conditions [17]. The catalyst was immobilized in [OMIM][BF_4], [BMIM][PF_6], and an IL containing a 1-carbadodecaborate anion, [BPy][$CB_{10}H_{12}$]. In the hydrogenation of acetophenone and ethyl benzoylformate to their corresponding alcohols, quantitative conversion and high *ee* values (> 97%) were obtained in the ILs, while only moderate conversion and enantioselectivity was observed in THF. The catalyst and co-catalyst could be recycled following the removal of the reaction product under high vacuum. Fresh ketone was then added and a second cycle was carried out without catalytic deactivation or loss of selectivity. Hydrogen-transfer reactions which employ ^{i}PrOH and KOH in place of H_2 are more commonly used to reduce ketones to alcohols and rhodium catalysts combined with phosphonium tosylate-based salts, none of which are liquid at room temperature, have been used in such reactions [18]. Two different chiral ligands, (1*S*,2*R*)-*cis*-aminoindanol and (–)-diop, were combined with rhodium acetate for the transfer hydrogenation of acetophenone, with only the latter giving rise to any enantioselectivity, although the conversion is low. The most effective combination evaluated is illustrated in Eq. (3).



(3)

A temperature-controlled reversible IL–water partitioning system has been used for the hydrogenation of 2-butyne-1,4-diol [19]. The IL [OMIM][BF_4] was selected as it forms two phases with water at low temperatures, but at about 80 °C it forms a homogeneous system with water. Using the hydrophobic and ionic catalyst $[Rh(nbd)(PPh_3)_2][BF_4]$, 2-butyne-1,4-diol was hydrogenated under 6 MPa hydrogen at 80 °C to give a mixture of the corresponding alkene and alkane. After reaction, the system was cooled to room temperature and two phases formed enabling facile separation of the product without catalyst contamination. The IL–catalyst system could be re-used several times without depreciation in activity. It is worth pointing out that 2-butyne-1,4-diol is an easy substrate to hydrogenate and, for example, has been hydrogenated in supercritical CO_2 with the stainless steel reactor serving as the catalyst [20]. However, the reaction in [OMIM][BF_4] illustrates the potential of

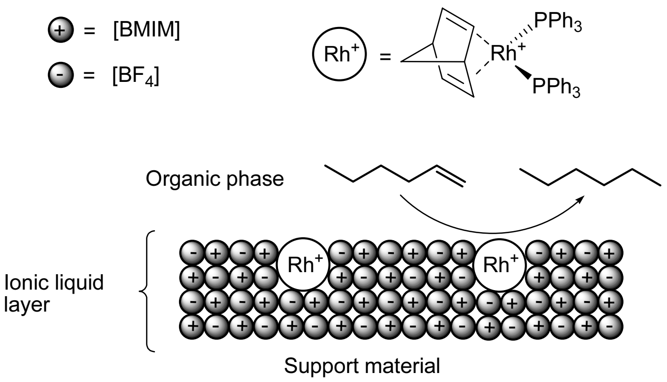


Figure 1 Confined IL phase containing the rhodium catalyst on the surface of a silica gel support material.

eliminating organic solvents completely from reactions involving water-soluble substrates. A similar technique has been used in the hydrodimerization of butadiene [21].

The concept of supported IL catalysis depicted in Figure 1 has recently been introduced [22]. Preparation of the supported IL catalyst involved dissolving $[Rh(nbd)(PPh_3)_2][PF_6]$ in a mixture of $[BMIM][PF_6]$ and acetone, followed by addition of silica gel. The acetone was removed under vacuum, leaving the catalyst in which the IL and rhodium catalyst were immobilized on the silica support. The catalyst was used in a Robinson–Mahoney reactor to hydrogenate 1-hexene, cyclohexene and 2,3-dimethyl-2-butene. Moderate to excellent yields could be obtained and 18 batch runs without significant loss of activity were achieved. Compared with liquid–liquid biphasic catalysis the amount of IL required was drastically reduced.

Immobilization of catalysts in ILs using polymeric solid supports has been demonstrated using a simple technique that involves mixing the transition metal catalyst and IL with poly(diallyldimethylammonium chloride) [23]. When Wilkinson's catalyst and $[BMIM][PF_6]$ were used, a material (termed a supported IL phase or SILP) was isolated, in which the catalyst was not leached. The system was evaluated in the hydrogenation of 2-cyclohexen-1-one and 1,3-cyclooctadiene and compared to homogeneous and "conventional" biphasic systems. For the conversion of 1,3-cyclohexadiene the SILP system was the most effective of the three systems in terms of TOF, selectivity to cyclooctene, and re-use. Using a slightly different strategy, a ROMP gel consisting of a polymerized IL and Wilkinson's catalyst has been prepared, but it was found to be inactive in hydrogenation reactions [24].

Soluble transition metal nanoparticles have attracted increasing attention in recent years and their preparation, structural characterization, and application in alternative solvents are under intense scrutiny [25]. While it is likely that a number of the molecular hydrogenation catalysts are actually precursors to nanoparticle catalysts, because of the reducing environment generated under high pressures of hydrogen, several studies comprising the application of deliberately prepared nanoparticle catalysts in ILs have been reported. Hydrated rhodium(III) chloride, $RhCl_3 \cdot 3\,H_2O$,

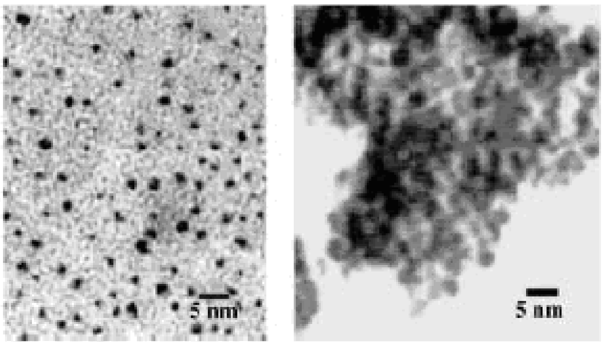


Figure 2 TEM micrograph of rhodium nanoparticles, isolated before (left) and after (right) catalysis. (Reproduced from [26] with permission from John Wiley & Sons Inc.).

can be reduced in dry [BMIM][PF_6] using hydrogen to form $[Rh(0)]_n$ nanoparticles with a mean diameter of 2.3 nm (see Figure 2) [26]. These nanoparticles can be redispersed in ILs or acetone, or used under solvent-free conditions for biphasic, homogeneous, or heterogeneous hydrogenation of arenes under mild conditions. However, the nanoparticles recovered after catalysis showed significant agglomeration into large particles which results in a reduction in catalytic activity. Various methods have been used to stabilize nanoparticle catalysts in ILs and these will be discussed below.

Hydrogenation by Ruthenium Catalysts

Hydrogenation reactions involving ruthenium-based catalysts immobilized in ILs are amongst the most widely studied. The complex $RuCl_2(PPh_3)_3$ immobilized in [BMIM][BF_4] has been used to catalyze the hydrogenation of 1-hexene, cyclohexene, and 1,3-butadiene [27]. Quantitative conversion and, for butadiene, high selectivity for the partial reduction product 1-butene, could be obtained. The IL [BMIM][$ZnCl_3$] was also used as an immobilization solvent for $RuCl_2(PPh_3)_3$ in the hydrogenation of 1-hexene [28]. The IL is a solid at room temperature, but the reaction is conducted at elevated temperatures, and once the reaction is complete the system is cooled and the ionic solution solidifies, which facilitates product separation. Using $scCO_2$ combined with [BMIM][PF_6], 1-decene may be hydrogenated in the presence of $RuCl_2(PPh_3)_3$ [29]. However, in this case, little advantage is observed compared to when *n*-hexane is used to extract the product, except that volatile organic solvents are eliminated from the process. The ruthenium–carbonyl cluster anion $[Ru_6C(CO)_{16}]^{2-}$ was used as a catalyst precursor for the hydrogenation of 1-hexene, 1-octene, styrene, cyclohexene, 1,3-cyclohexadiene, 1,4-cyclohexadiene, and 1,5-cyclooctadiene in [BMIM][BF_4] [30]. For styrene, catalytic activity was essentially the same, irrespective of whether the reaction was conducted in the IL or in molecular solvents. For the diene substrates, however, partial reduction was observed which could not be achieved in molecular solvents. The nature of the active catalyst was probed using a previously reported mass spectrometry method [31] and high pressure in-situ

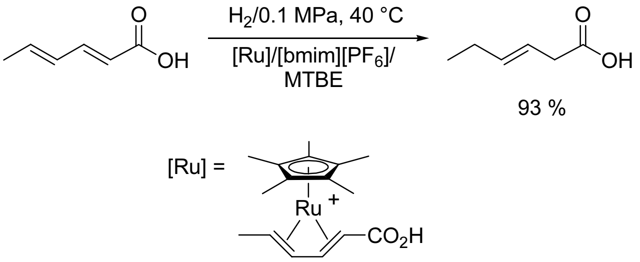
NMR studies. Combined with mercury poisoning experiments, it was concluded that the active catalyst species were nanoparticles or colloids, although other techniques such as TEM were not used to confirm the hypothesis.

Acrylonitrile–butadiene rubber (NBR) may be reduced in [BMIM][BF_4] using the catalyst $RuHCl(CO)(PCy_3)_2$ [32]; the saturated product is a very useful engineering polymer with applications in oil seals, timing belts, and hoses [33]. An enhanced reaction rate has been observed. The same reaction was reported in a range of halide-free IL mixtures based on dialkylimidazolium cations and the tetrafluoroborate anion [34].

Hydrogenation of arene substrates has been conducted using ruthenium catalysts immobilized in ILs. The dicationic cluster catalyst $[H_4Ru_4(\eta^6\text{-}C_6H_6)_4][BF_4]_2$, originally used to hydrogenate arenes in aqueous–organic biphasic processes [35], was found to be active in ILs for the hydrogenation of benzene, toluene, and cumene in [BMIM][BF_4] [36]. Similar or slightly higher TOFs were obtained when the catalyst was immobilized in the IL. Subsequently, it was shown that the purity of the IL has a significant impact on the activity of the catalyst [37]. The contaminant in the IL which was found to affect catalytic activity was, not unexpectedly, chloride. The effect of chloride on the physical properties of ILs has been well documented [38] and chloride is also a good nucleophile well known to deactivate catalysts by blocking reactive coordination sites. In chloride-free [BMIM][BF_4] the hydrogenation of benzene to cyclohexane gave a TOF of 406 mol mol^{-1} h^{-1}, which decreased to 364 mol mol^{-1} h^{-1} in the same IL containing 0.2 mol kg^{-1} of chloride. In water, a turnover frequency of 352 mol mol^{-1} h^{-1} was observed and the higher activity in [BMIM][BF_4] than in water is probably due to the higher solubility of the benzene substrate in the IL phase. In addition to this study in which the activity of $[H_4Ru_4(\eta^6\text{-}C_6H_6)_4][BF_4]_2$ was compared in water, [BMIM][BF_4], and [BMIM][BF_4] containing chloride, the cluster was immobilized in the 11 ILs for which the hydrogen concentration is known (see Table 1) to establish whether hydrogen solubility affects reaction rate [6]. To within the experimental error, there is essentially no difference between the rate of catalyzed reaction in any of the ILs, except $[P(C_6H_{13})_3(C_{14}H_{29})][PF_3(C_2F_5)_3]$, where the TOF and hydrogen solubility are the highest. Therefore, there may be some benefits to discovering ILs which dissolve high concentrations of hydrogen. However, since the solubility of hydrogen in the substrate, and consequently the mixture, is higher than in the neat IL, the hydrogen solubility in the neat IL seems to have less influence on the reaction rate.

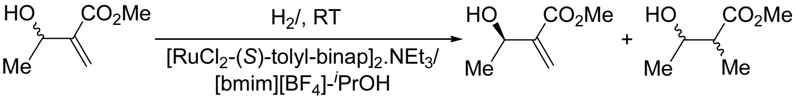
Other ruthenium catalysts that have been used for the hydrogenation of arenes include the water-soluble and IL soluble complex $Ru(\eta^6\text{-}C_{10}H_{14})(pta)Cl_2$ (pta = 1,3,5-triaza-7-phosphaadamantane) [37]. Comparisons were made between the catalytic activity in water and tetrafluoroborate ILs including ones contaminated with chloride, and again, in the chloride-free ILs catalytic activity is highest. The related ruthenium catalyst, $[Ru(\eta^6\text{-}p\text{-cymene})(\eta^2\text{-triphos})Cl][PF_6]$ [triphos = 1,1,1-tris(diphenylphosphinomethyl)ethane] has also been shown to hydrogenate arene substrates [39]. The activity of the catalyst was compared in [BMIM][BF_4] and dichloromethane and was found to be considerably more active in the IL. For example, in the hydrogenation of benzene to cyclohexane the TOF is 477 mol mol^{-1} h^{-1} when the reaction is immobilized in [BMIM][BF_4], but only 242 mol mol^{-1} h^{-1} when the reaction is carried out homogeneously in dichloromethane. The catalyst is less active for the hydrogenation of alkenes, and as such, has been used for the regioselective hydrogenation of allylbenzene to ethylbenzene. This unusual selectivity has been attributed to the free phosphine arm, which is believed to coordinate reversibly to the ruthenium center, thus facilitating hydrogenation of coordinated arene rings.

The hydrogenation of sorbic acid to *cis*- and *trans*-3-hexenoic acid using the ionic ruthenium complex [$Ru(C_5Me_5)(MeCH{=}CH{-}CH{=}CHCO_2H)$][$CF_3SO_3$] as the catalyst has been conducted in [BMIM][PF_6]-methyl *tert*-butyl ether (MTBE) [40]. The formation of *cis*-3-hexenoic acid can be achieved with selectivity up to 93% [Eq. (4)].



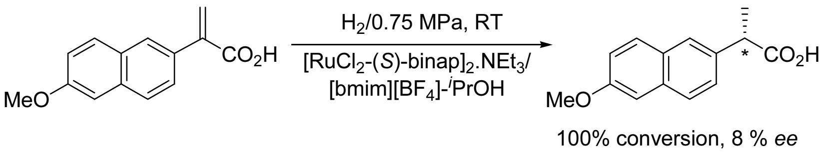
(4)

The asymmetric ruthenium catalyst [$RuCl_2$–(*S*)-tolyl-binap$]_2$ · NEt_3 ((*S*)-tolyl-binap = dichloro[(*S*)-(–)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl]) has been used in [BMIM][BF_4]–^{i}PrOH to catalyze the hydrogenation of (±)-methyl-2-hydroxy-2-methylenebutanoate [see Eq. (5)] [64]. The effect of hydrogen pressure was evaluated in this study and it was found that the highest *ee* of 98% was obtained at 4 MPa, although the yield of the product was quite low.



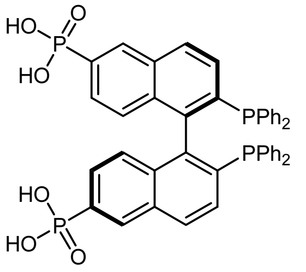
(5)

The related ruthenium catalyst [$RuCl_2$-(*S*)-binap$]_2$·NEt_3 [(*S*)-binap = (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl] immobilized in [BMIM][BF_4] has also been used to for the hydrogenation of 2-arylacrylic acids under biphasic conditions [64]. Specifically, 2-phenylacrylic acid and 2-(6-methoxy-2-naphthyl)acrylic acid were investigated, the product from the latter being the important anti-inflammatory and analgesic drug (*S*)-Naproxen. A co-solvent is used in these reactions, usually ^{i}PrOH, but also MeOH. Quantitative conversion of 2-phenylacrylic acid to 2-phenylpropionic acid can be obtained in [BMIM][BF_4]– ^{i}PrOH even after eight re-uses, but the *ee* varies as the reaction mixture is recycled and re-used. The highest *ee* of 86% is actually observed when MeOH is used as the co-solvent, but the reaction is homogeneous and isolation of the product is more difficult than from the biphasic system, where separation of the product is simplified by decantation at the end of the reaction. It is worth noting that while quantitative conversion was obtained over a number of batches, a reaction time of 20 h was used. It is possible that these data indicate that the catalyst was not leached from the IL phase; however, if the reaction is actually complete in a few hours, then significant catalyst loss might be taking place with the conversion remaining unchanged. The hydrogenation of 2-(6-methoxy-2-naphthyl)acrylic acid to (*S*)-Naproxen [Eq. (6)] was achieved in quantitative yield in 80% *ee*.



(6)

In order to overcome catalyst loss in ILs, two derivatives of binap with polar phosphonic acids groups in the 4,4′- and 6,6′-positions have been prepared (see **1** and **2**) and evaluated using ruthenium-derivatized complexes [41]. The catalysts were evaluated in methanol, [BMIM][BF_4]–MeOH, [BMIM][PF_6]–MeOH, and [BMIM][NTf_2]–MeOH for the hydrogenation of some β-keto esters. Quantitative conversion was obtained and in some cases higher *ee* values were observed in IL–methanol systems than those achieved in methanol alone. The catalytic system can be recycled after product extraction and used for four runs with minimal loss of activity and enantioselectivity, but despite the presence of the polar groups on the ligand, after four runs both the conversions and the *ee* values decrease gradually.



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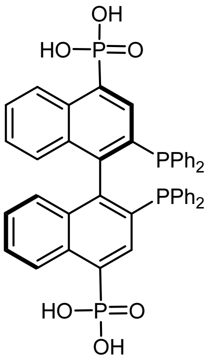
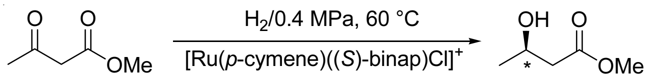


2

2,2′-bis(diphenylphosphino)-1,1′-binaphthyl-4,4′-bis(phosphonic acid)
2,2′-bis(diphenylphosphino)-1,1′-binaphthyl-6,6′-bis(phosphonic acid)

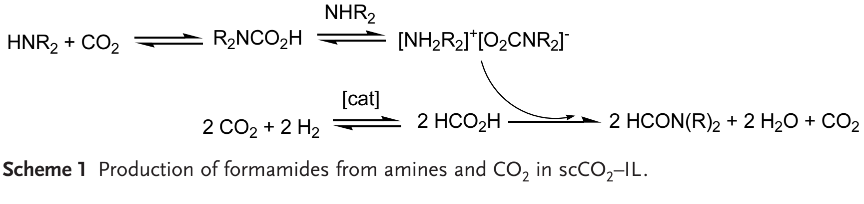
The supported IL polymer approach described above has also been used to immobilize the ionic asymmetric catalyst [Ru(*p*-cymene)((*S*)-binap)Cl]Cl [23]. The SILP catalyst was compared to [Ru(*p*-cymene)((*S*)-binap)Cl]Cl immobilized in [BMIM][PF_6] and used under homogeneous conditions in molecular solvents for the hydrogenation of methyl acetoacetate [Eq. (7)]. The SILP catalyst compared well to the IL biphasic system, but was inferior to the homogeneous reactions, but no loss in activity was observed upon re-use.



(7)

Supercritical carbon dioxide ($scCO_2$), also used as a solvent for catalysis [42] including asymmetric hydrogenations [43], has been combined with ILs for the asymmetric hydrogenation of tiglic acid employing $Ru(O_2CMe)_2$((*R*)-tol-BINAP) as the catalyst [44]. The reaction was conducted in [BMIM][PF_6] with added water, and the 2-methylbutanoic acid product was subsequently extracted with $scCO_2$. High enantioselectivity (85–91%) together with a conversion remaining as high as 97% on the fifth cycle, was observed. The enantioselective hydrogenation of atropic and tiglic acids using $Ru(O_2CMe)_2$((*R*)-tolBINAP) as the catalyst has been studied in MeOH, supercritical CO_2, ionic liquids, and CO_2-expanded ILs [45]. The study showed that the solubility of hydrogen plays an important role (hydrogen is an anti-solvent in CO_2, decreasing the solubility of other solutes) affecting the catalytic performance. The hydrogenation of atropic acid, which requires high solubility and rate of mass transfer of hydrogen, yielded high *ee* values in methanol, CO_2-expanded methanol, and $scCO_2$ (≥ 90%), in which a high hydrogen concentration can be obtained. Poor results were observed in ILs and IL-CO_2 or co-solvent mixtures where the H_2 solubility is lower. In contrast, the hydrogenation of tiglic acid only requires low H_2 concentration for high enantioselectivity, and higher *ee* values were observed in ILs and CO_2-expanded ILs systems compared to methanol. The ILs evaluated were [BMIM][PF_6], [BMIM][BF_4], [BMPy][BF_4], [DMPIM][NTf_2], and [EMIM][OTs], the latter giving the highest *ee* of 95%. From this study it is clear that the choice of IL used, and whether an IL is used at all, for a hydrogenation reaction will depend to a great extent on the substrate.

The hydrogenation of CO_2 to formic acid has been conducted in [BMIM][PF_6] and [BMIM][NTf_2] ILs containing 1 M $NaHCO_3$ [46]. Three different catalysts were evaluated, these being $RuCl_2(PPh_3)_4$, $RuCl_2(PCy_3)_4$, and [RuCl(dppe)$_2$][PF_6]. The highest initial TOF was obtained using $RuCl_2(PPh_3)_4$ dissolved in [BMIM][NTf_2]. If the hydrogenation of CO_2 is conducted in a $scCO_2$–IL system in the presence of dialkylamines using the catalyst $RuCl_2(dppe)_2$ (dppe = $Ph_2PCH_2CH_2PPh_2$), then formamides can be prepared in a single step (see Scheme 1) [88]. The conversion of 100% which was observed in [BMIM][PF_6] is considerably higher than when the reaction was carried out in $scCO_2$ alone.

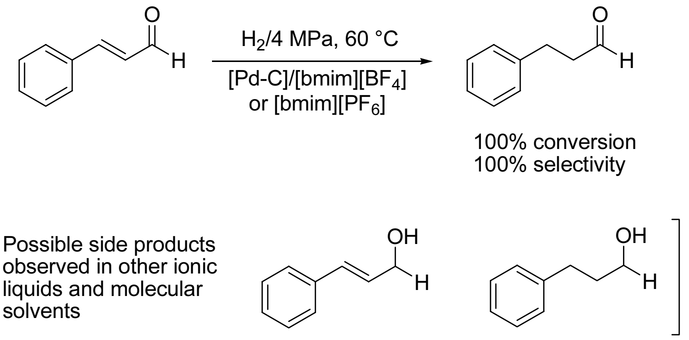


Scheme 1 Production of formamides from amines and CO_2 in $scCO_2$–IL.

Hydrogenation by Palladium and Platinum Catalysts

Palladium and platinum are widely employed in hydrogenation catalysis, often showing excellent activity in regioselective reactions [47]. Unlike other transition metal hydrogenation catalysts immobilized in ILs, which are usually used in the form of molecular species, the palladium and platinum catalysts used in ILs are generally heterogeneous. The only example of a molecular catalyst comprises palladium(II) acetylacetonate immobilized in [BMIM][BF_4] or [BMIM][PF_6], which has been used to catalyze the partial reduction of a series of diene substrates including 1,3-butadiene, 1,3- and 1,4-cyclohexadiene, and 1,5-cyclooctadiene as well as others [48]. Highly selective hydrogenation of dienes to monoenes was achieved (selectivity up to 100%) and the high selectivity was attributed to the formation of thermodynamically favored η^3-allyl Pd intermediates and also to the higher solubility of the dienes in the ionic phase compared to the monoenes. The catalytic system can be recycled up to 15 times in the case of 1,3-butadiene by simple phase separation and addition of fresh substrate.

The selective reduction of either the C=C or the C=O bond of α,β-unsaturated aldehydes is a very important reaction [49]. The reduction of the C=C bond in cinnamaldehyde and citral has been catalyzed by 10% palladium on activated carbon in a range of ILs, although in some cases other products are also obtained [see Eq. (8)] [50]. Much higher selectivity toward the product of C=C bond reduction was achieved in ILs than in organic solvents. By tuning the reaction conditions such as temperature and H_2 pressure, and using the appropriate IL, 100% conversion and 100% selectivity may be acheived. Of the 12 different ILs screened, 100% conversion and 100% selectivity could be obtained for the production of hydrocinnamaldehyde from cinnamaldehyde in [BMIM][BF_4] and [BMIM][PF_6]. With citral, 100% selectivity toward the C=C bond was obtained in several ILs, but conversions were quite low. However, 99% conversion and 99% selectivity were achieved in [BMIM][BF_4] and [EMIM][NTf_2]. Extraction of the product by diethyl ether at the end of the reaction enables facile catalyst recycling without the need for filtration.



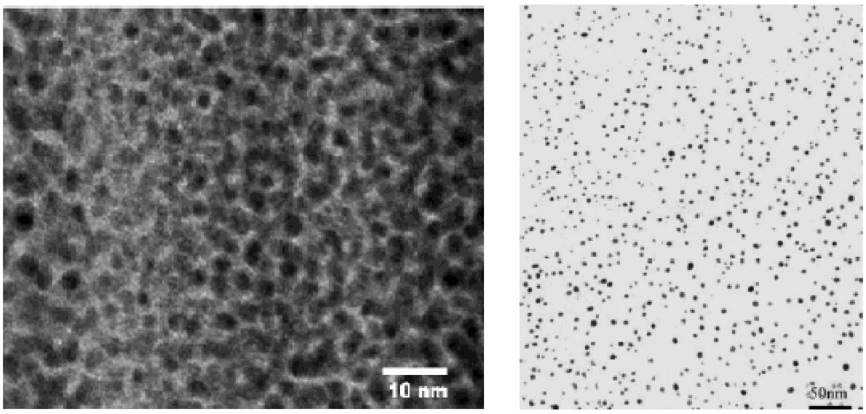
(8)

Activated carbon containing 10% palladium has also been used to catalyze transfer hydrogenations of various organic substrates with nitro, alkene, and alkyne groups

[51]. Formic acid and its ammonium salt have been used as the hydrogen source in place of molecular hydrogen and microwave dielectric heating was used. Nitro groups and C=C bonds were hydrogenated selectively in substrates also containing C=O or C=N bonds. Similar or better yields than in organic solvents and clean product/catalyst separation and extraction were observed. However, a 40% loss of catalytic activity was observed after five cycles, although addition of more catalyst restored the activity.

Palladium on activated carbon has been immobilized in a gas-permeable IL-polymer gel membrane and used to catalyze the hydrogenation of propene to propane [52]. The membrane was prepared by mixing [BMIM][PF_6] with the catalysts and poly(vinylidene fluoride)–hexafluoropropylene copolymer in 4-methylpentan-2-one, followed by heating and evaporation of the 4-methylpentan-2-one. The resulting membrane was placed in a membrane reactor and used to hydrogenate propene to propane with conversions of up to 70%.

Palladium and platinum nanoparticles have also proven to be effective catalysts for hydrogenation reactions conducted in ILs. The platinum(0) compound $Pt_2(dba)_3$ (dba = bis-dibenzylidene acetone) was decomposed in [BMIM][PF_6] under hydrogen to form nanoparticles [53]. Transmission electron microscopy indicated the diameter of the particles was in the range 2.0–2.5 nm (Figure 3a). A detailed examination of the nanoparticles showed that they interact with the [BMIM][PF_6] IL. The nanoparticles were collected by centrifugation and redispersed in acetone or IL, or used under solvent-free conditions and evaluated as catalysts for the hydrogenation of alkenes and arenes. Impressively, benzene could be hydrogenated to cyclohexane under 0.4 MPa hydrogen although the TOF was not high (11 h^{-1} in [BMIM][PF_6] and 28 h^{-1} under solvent-free conditions). The nanoparticles were compared with the classic Adam's catalyst (PtO_2) under identical conditions: the Pt(0) nanoparticules showed higher catalytic activity and superior recyclability.



(a) (b)

Figure 3 TEM of (a) Pt(0) in [BMIM][PF_6] and (b) Pd(0) after hydrogenation of cyclohexene (reproduced from [53]).

Palladium nanoparticles stabilized by phenanthroline have been used to hydrogenate alkenes in [BMIM][PF_6] [54]. $Pd(CH_3CO_2)_2$ was used as a catalyst precursor which was reduced in situ to form the palladium nanoparticles in the IL in the presence of the phenanthroline ligand. The TEM showed that the size of the palladium nanoparticles was in the range of 2–5 nm (Figure 3b). High hydrogenation activity, stability, and recyclability of the nanoparticles was achieved in [BMIM][PF_6].

Hydrogenation by Other Transition Metal Catalysts

A number of hydrogenation catalysts based on other transition metals have been used in ILs. The highly successful water-soluble catalyst $K_3Co(CN)_5$ [55] was evaluated in [BMIM][BF_4] [86]. The catalyst is known to selectively reduce conjugated dienes [56] and in the IL [BMIM][BF_4] 1,3-butadiene could be converted to 1-butene with 100% conversion and 100% selectivity at 20 °C. As the temperature is increased both the conversion and the selectivity decreased. The catalytic system was deactivated after one run and it is suggested that the [BMIM] salt of the cobalt catalyst, i.e., $[BMIM]_3[Co(CN)_5]$, is catalytically inactive. The inactivity of $[BMIM]_3[Co(CN)_5]$ was attributed to strong hydrogen bonding interaction between the $[BMIM]^+$ cation and the $[Co(CN)_5]^{3-}$ anion, blocking coordination of the diene to the metal center. The selective hydrogenation of 1,3-butadiene in the presence of $Co(acac)_2$, $Co(acac)_3$, $Fe(acac)_3$, and $Ni(acac)_2$ (acac = acetylacetonate) has also been accomplished in [BMIM][BF_4], [BMIM][OTf], and [BMIM][PF_6] [57]. In general, moderate conversion and high selectivity to the monoenes were obtained for all the catalyst precursors.

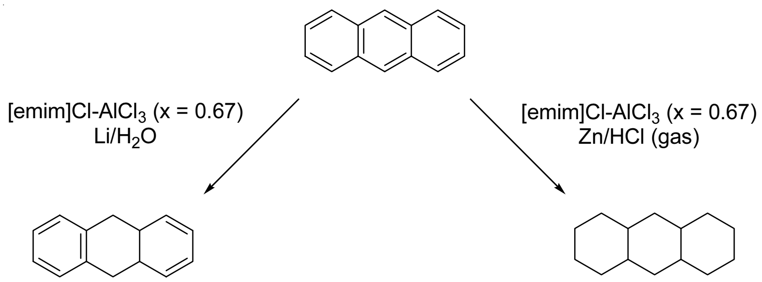
The osmium carbonyl cluster $[H_3Os_4(CO)_{12}]^-$ and the heteronuclear cluster $[HWOs_3(CO)_{14}]^-$ have been evaluated as catalysts in ILs for the hydrogenation of styrene [89]. Clusters have been extensively studied as hydrogenation catalysts [58] and recently the effect of solvent has been shown to be critical in directing the reaction mechanism [59]. Furthermore, there is a huge range of anionic clusters available and they are highly soluble in ionic liquids. Both clusters are considerably more active in [BMIM][BF_4] than in octane or methanol for the hydrogenation of styrene to ethylbenzene. High-pressure NMR spectroscopy was used to probe the nature of $[H_3Os_4(CO)_{12}]^-$ in ILs; it appears to be a homogeneous catalyst. The influence of ILs on the activity of $[H_3Os_4(CO)_{12}]^-$ was also studied and the highest reaction rates were observed in [OMPy][BF_4], (OMPy = 1-octyl-3-methylpyridinium cation), the only liquid in which the reaction system formed a single phase.

A study of 1-alkyne dimerization and hydrogenation catalyzed by $[Ir(H)_2(NCCH_3)_3(P^iPr_3)]^+$ has been reported [60]. The complex was reacted with $^tBuC{=}CH$ or $PhC{=}CH$ to form complexes with butadiene ligands. The resulting complexes were found to react with H_2 to afford the starting complex and alkenes, resulting from partial hydrogenation of the butadiene moieties. The hydrogenation reaction was compared in homogeneous and IL biphasic conditions and it would appear that the mechanism in both solvents is similar. Attempts to recycle the catalyst proved to be not very successful, with a progressive decrease in activity for each recycling step.

Iridium nanoparticles have been used in [BMIM][PF_6] to catalyze the hydrogenation of alkenes [61]. The Ir(0) nanoparticles were prepared from $[IrCl(cod)]_2$

(cod = 1,5-cyclooctadiene) by direct reduction in the [BMIM][PF_6] IL under 0.4 MPa of H_2. The nanoparticles were screened against a range of alkenes and were shown to have high activity; moreover, the nanoparticle–IL system could be easily recycled. Iridium nanoparticles have also been used to catalyze the hydrogenation of arenes in ILs and were found to be more active than rhodium nanoparticles generated in the same way [85].

The acidic chloroaluminate IL [EMIM]Cl-$AlCl_3$ ($x = 0.67$), combined with electropositive metals (Al, Zn, and Li) and a proton source, has been applied to the stereoselective hydrogenation of aromatic compounds [62]. Anthracene, pyrene, and 9,10-dimethylanthracene were partially or completely hydrogenated, and the selectivity appears to be a function of the proton source. It was found, for example, that anthracene could be converted to dihydroanthracene in [EMIM]Cl–$AlCl_3$ ($x = 0.67$) containing lithium and water, whereas in the presence of zinc and HCl gas complete hydrogenation was possible as shown in Scheme 2.



Scheme 2 The reduction of anthracene in chloroaluminate IL.

5.2.2.3.4
Concluding Remarks

The studies described in this section demonstrate that ILs can be used successfully as alternative solvents to immobilize transition metal hydrogenation catalysts. The application of ILs often allows facile recycling of the catalysts and it would also appear that the inert (noncoordinating) environment provided by many ILs helps to stabilize the catalyst and prevent decomposition/deactivation. Consequently, accelerated reaction rates and higher and increased turnover numbers can sometimes be achieved. Regioselective (or partial) hydrogenation is also often observed in ILs and this may be ascribed, at least in part, to the poorer solubility of many monoenes in ILs compared to their diene precursors, which helps to eliminate them from the vicinity of the catalyst. As yet, asymmetric induction has not been observed in chiral ILs, but this is in keeping with chiral solvents more generally.

Although hydrogenation reactions in ILs are still in many ways in their infancy, as are those in other alternative solvents such as fluorous phases and supercritical fluids, some comparisons can be made. Water has now been evaluated extensively as an immobilization solvent for biphasic hydrogenation reactions and while there are many excellent systems, water is limited by substrate solubility and the fact that many catalysts are unstable in it. Clearly, ILs overcome this limitation and in general the differences in polarity between a substrate and the related hydrogenated product result in a decrease in polarity, and hence a decrease in solubility in the IL and improved separation. There may be some cases, for example, the hydrogenation of certain functional groups, which do not lend themselves to ILs, and fluorous solvents might be better suited. Combining IL reactions with CO_2 extractions also seems very promising and an area for further investigations. Cost is sometimes cited as an inhibitory factor for employing ILs, but apart from continual reductions in cost, the fact that many catalysts do not require any modification to be used in ILs is also highly desirable.

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5.2.2.4
Acidic Catalysis

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5.2.2.4.1
Introduction

A large number of key industrial processes in oil refinery, petrochemistry, and chemistry are acid-catalyzed. Despite the large use of $AlCl_3$, there is an evident evolution to “greener” solid acid catalysts. The reasons for this evolution are a combination of economic and environmental factors. Indeed, the use of $AlCl_3$ results in a high level of waste catalyst streams, the inability to recycle used catalyst, and the economic impact of treatment of waste catalyst streams associated with a negative environmental image.

Ionic liquids (ILs) can offer the advantages of an improved recovery and recyclability combined with equivalent or superior reaction performances. They can be Brønsted and/or Lewis acids with solid-like nonvolatility and the potential activity of a liquid phase. In many cases, they have a dual role as catalysts and solvents, and present an increased ability to stabilize charged intermediates compared to organic solvents.

5.2.2.4.2
Use of Ionic Liquids in the Liquid Phase

One strategy to recover the Lewis (or Brønsted) acid is to operate in a biphasic system. The simplest way is to use the same Lewis acids as in homogeneous systems. Reactions catalyzed by $AlCl_3$ or $FeCl_3$ can be directly transferred in the corresponding acidic chloroaluminate or chloroferrate ILs. The Lewis acid can be “immobilized” in the IL solvent. Its acidity, and the strength and quantity of the active sites, depend on the composition of the ILs (see below). The success of chloroaluminates as liquid acid catalysts comes from the possibility of tuning their acidity by controlling the formulation (the ratio of [BMIM][Cl] to $AlCl_3$), their low freezing points and their wide liquid composition ranges.

Non-chloroaluminate ILs can also be used as solvents for Brønsted and/or Lewis acids. They offer interesting solvent properties. But in this case, the difficulty may be the solubilization and the stability of the acid in the IL in the presence of the upper phase.

Ionic Liquids Derived from Lewis Acids

Some Lewis acids, such as $AlCl_3$, $AlBr_3$, $GaCl_3$, SbF_5, $FeCl_3$, $ZnCl_2$, $SnCl_2$, etc., can associate with their corresponding anion to form polynuclear anionic species such as $Al_2Cl_7^-$ or $Al_3Cl_{10}^-$ $Ga_2Cl_7^-$, $Sb_2F_{11}^-$, $Fe_2Cl_7^-$, $Zn_2Cl_5^-$, $Zn_3Cl_7^-$, or $Sn_2Cl_5^-$. When associated with the dialkylimidazolium cation, these anions give ILs at low temperature. The acid–base properties of these ILs can be described by the equilibria in Eqs. (1)–(4). The equilibrium constant for Eq. (4) is in the order of 10^{-16} at ambient temperature, so that in melts containing a slight excess of $AlCl_3$, the Cl^- concentration is very small. Thus, $Al_2Cl_7^-$ anions are powerful Cl^- acceptors and are a source of high Lewis acidity. ILs containing polynuclear anions can therefore be referred to as acidic. They are a potential source of Lewis acid (e.g., $AlCl_3$). For example, in the presence of a base, the Eq. (5) can be driven to the right due to the formation of an $AlCl_3$-base adduct.

$$Cl^- + AlCl_3\ \text{(solid)} \rightleftharpoons AlCl_4^-\ \text{(liquid)} \qquad K = 1.6 \cdot 10^{19} \tag{1}$$

$$AlCl_3\ \text{(solid)} + AlCl_4^- \rightleftharpoons Al_2Cl_7^-\ \text{(liquid)} \qquad K = 1.6 \cdot 10^{3} \tag{2}$$

$$Al_2Cl_7^- + AlCl_3 \rightleftharpoons Al_3Cl_{10}^- \qquad K = 1 \cdot 10^{1} \tag{3}$$

$$2\ AlCl_4^- \rightleftharpoons Cl^- + Al_2Cl_7^- \qquad K = 1.0 \cdot 10^{-16} \tag{4}$$

$$Al_2Cl_7^- + \text{Base} \rightleftharpoons AlCl_3 \cdot \text{Base} + AlCl_4^- \tag{5}$$

The strength of the Lewis acidity of chloroaluminates can be increased by increasing the quantity of $AlCl_3$, which corresponds to an increase in the concentration, or molar fraction, of the $Al_2Cl_7^-$ and $Al_3Cl_{10}^-$ polynuclear anions. Of particular interest is the possible combination of Brønsted with Lewis (nonprotic) acidity. HX Brønsted acids ($X=Cl^-$ or Br^-) have been found to exhibit enhanced acidities in ILs in comparison with water. For example, when HCl is added under controlled pressure to acidic chloroaluminates, the IL functions as a Brønsted superacid (with estimated Hammett function ranging from –17 to –15) (Table 1). The Hammett acidities are increased in the ILs as a result of the formation of acids such as $[H–Cl–Cl(Al_2Cl_6)]^-$. This latter species has the ability to protonate weak bases such as aromatic hydrocarbons (e.g., toluene) [1]. More acidic systems can even be obtained by substituting the bromide anion for the chloride.

The acidity of chloroaluminate can be neutralized and buffered by addition of a base such as the chloride anion, introduced as MCl (M being an alkali metal) [Eq. (6)]. Buffered "neutral" chloroaluminates exhibit a "latent acidity". Surprisingly, the chloride anion could be displaced from the $AlCl_4^-$ anion, which does not react in

Table 1 Hammett acidity functions of selected superacids.

System	***Hammett acidity, H_0***
H_2SO_4	–11.9
HF	–11 to –14
$HClO_4$	–13
HSO_3F	–15.6
HSO_3CF_3	–14.6
HF–SbF_5	–21 to –28
[EMIM][Al_2Cl_7]/HCl	–15
[EMIM][Al_2Br_7]/HBr	–17

the presence of a base in unbuffered melts, to form an $AlCl_3$–base adduct [Eq. (7)]. This reaction is observed for weak bases such as acetylferrocene or pyrrole [2]. The driving force of the reaction is the precipitation of MCl. Consequently, differences in "latent acidity" can be obtained according to the nature of the alkali metal used to buffer the melt. In the case of the Li^+ ion, which precipitates chloride more strongly than Na^+, the Eq. (7) is further driven to the right, making the $AlCl_4^-$ ion more acidic [3]. The same effect of the buffering agent can be observed on the acidity of HCl in these media.

$$Al_2Cl_7^- + MCl \rightleftharpoons M^+ + 2\ AlCl_4^- \tag{6}$$

$$\text{Base} + AlCl_4^-\ Na^+ \rightleftharpoons AlCl_3 \cdot \text{Base} + NaCl(s) \tag{7}$$

In addition to acting as solvents, these ILs derived from Lewis acids can be used as acid catalysts. Many applications have been described in the literature [4, 5]. Particularly, hexafluoroantimonate-based ILs have been used successfully as catalysts for the HF hydrofluorination of saturated compounds with C–Cl bonds (see below).

Non-chloroaluminate Ionic Liquids

Acidic chloroaluminate ILs have been described as solvents and acid catalysts in many reactions. Some of them are described below. Despite their advantages, acidic chloroaluminates suffer from being extremely oxophilic, thus forming adducts with products containing oxygenated functions. Furthermore, as they react irreversibly with water forming HCl and aluminum hydroxides, accidental traces of water or other sources of protons can modify their acidity. Therefore, it may be difficult to control accurately the acidity of these media. For these reasons, non-chloroaluminates, air, and moisture-stable ILs have also been developed and used as solvents and even Brønsted acids for different reactions. It should be noted here that PF_6^--, BF_4^-- or SbF_6^--based ILs can be slowly hydrolyzed, resulting in the formation of HF. It cannot be excluded that the unique solvent properties of these ILs can originate from the presence of traces of HF.

Non-chloroaluminate Ionic Liquids as Solvents for Lewis Acids

Recently, considerable attention has been focused on the use of metal salts, such as lanthanide or scandium triflates, as water-tolerant, recyclable Lewis-acid catalysts for C–C bond formation [6, 7]. When reactions are conducted in water, several limitations have to be overcome. Even if these salts are described as compatible with water, they can undergo slow hydrolysis. Water can solvate the metal center and may compete with the reactants. It modifies its acidity and influences the catalytic performances. Moreover, the solubility problem of organic substrates in water has to be overcome. Most commonly, reaction products are extracted from water with organic solvents, since the Lewis acid remains in the aqueous phase and can be re-used.

Non-chloroaluminate ILs, which are in general poor nucleophiles, have proven to be attractive alternative media for Lewis acid catalyzed reactions. ILs may have a reaction rate accelerating effect, and they may improve selectivity and facilitate catalyst recovery. This is the case for scandium triflate catalyzed Diels–Alder cycloaddition [8, 9], three-component (aldehyde, aniline, triethylphosphite) synthesis of α-aminophosphonates [10], Claisen rearrangement and cyclization reactions [11], or Friedel–Crafts reactions [12, 13].

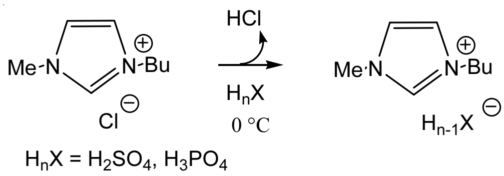
Non-chloroaluminate Ionic Liquids as Solvents for Protons

The acidity of protons is mainly determined by their solvation. Indeed, weakly solvated protons possess a higher chemical activity [14]. In solvents of low dielectric constant, dissociation of ion pairs involving protons should also be taken into account. Finally, the properties of protons depend on both the nature of the solvent and the nature and concentration of the acid. Air-stable non-chloroaluminate ILs are promising solvents because of their potential dissociating character and their low solvating properties. They have been used as solvents for catalytic amounts of protic acids. This application is exemplified by glycosidation reactions catalyzed by catalytic amounts of Brønsted acid dissolved in ILs containing the same anions as the acid [15]. Chemical yields were higher in ILs than in organic solvents.

Non-chloroaluminate Ionic Liquids as Dual Solvent—Brønsted Acids

Protic ILs can be synthesized easily either directly by reaction of Brønsted acids with organonitrogen bases or by reaction of [BMIM][Cl] with the Brønsted acid [Eqs. (8) and (9)]. These ILs have been used as catalysts–solvents for the alkylation of aromatic hydrocarbons with α-olefins [16].

It is interesting to note that low-melting salts can be obtained, in a similar way, by combining [EMIM][Cl] with HF. A new IL, [EMIM][F] · 2.3 HF, has been characterized which possesses some interesting properties such as chemical stability in air and inertness against borosilicate glassware in ambient conditions [17]. It is to be expected that this IL acts as a Brønsted acid. In the presence of an excess of BF_3, it acts as a fluorobase, forming [EMIM][BF_4]. The $B_2F_7^-$ anion is not formed.



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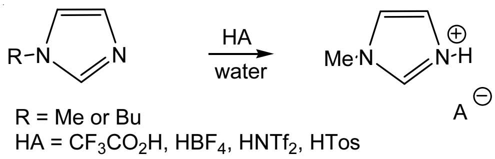
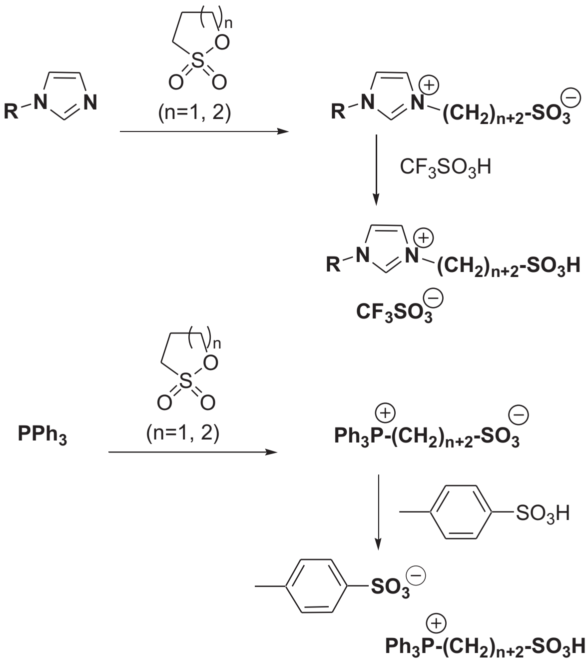


(9)

It is clear that these alkylimidazolium ILs containing nonprotic anions present a very low acidity. However, [MIM][BF_4] has been used successfully for esterification of a variety of carboxylic acids with common alcohols. Good yields and high selectivity for the esters are described. The esters are immiscible with the ILs while water is soluble in them, so that liquid esters can be separated by decanting [18]. Another example is the three-component (aldehyde, amine, ketone) Mannich reaction that provides β-aminocarbonyl compounds used in pharmaceutical and biological areas of chemistry. [MIM][CF_3CO_2] IL acts as both a solvent and a catalyst for the reaction, which simplifies the reaction procedure [19].



Scheme 1 Brønsted acid functionalized ionic liquids.

ILs have also been designed to be Brønsted acids by covalently tethering an alkanesulfonic acid group to the imidazolium or phosphonium cation of the IL. The synthetic approach consists in the synthesis of a zwitterion in a first step; then in a second step the zwitterion is acidified (Scheme 1) [20]. These salts are very viscous liquids. They can be used as both solvents and catalysts, or as functionalized Brønsted acids that can be immobilized in more classical ILs.

Determination of Acidity

Several methods of measuring acidity are known. In the case of ILs there are very few references dealing with the measurement of Brønsted or Lewis acidity, or with the acidity–activity relationship in comparison with conventional liquid and solid acids. Most of the work has been done on chloroaluminate ILs [21].

Recently, in a similar way to solid acids, the strength of Lewis and Brønsted acidity of different ILs derived from Lewis acids has been estimated by IR spectroscopy using pyridine and ethanenitrile as probe molecules. For a given molar fraction of the Lewis acid (0.67), it is demonstrated that the Lewis acidity of the corresponding [BMIM][Cl]/MCl_x ILs (M=Cu, Fe, Al, Zn) increases in the order $CuCl < FeCl_3 < ZnCl_2 < AlCl_3$. Brønsted sites are also present, as demonstrated by the formation and characterization of pyridinium ions [22].

The Brønsted acidity was also evaluated from the determination of the Hammett acidity functions, using UV–Vis spectroscopy. This method consists of evaluating the protonation extent of uncharged indicator bases (named I) in a solution, in terms of the measurable ratio $[I]/[IH^+]$. The chosen indicators belong to the same chemical family. Substituted dinitroanilines are the most common indicators. In a given solvent (named s), assumed to be dissociating, the Hammett function (H_0) is defined according to Eq. (10), where $pK(I)_{aq}$ is the pK_a value of the indicator referred to an aqueous solution, and $[IH^+]_s$ and $[I]_s$ are the molar concentrations of the protonated and unprotonated forms of the indicator, respectively, in the solvent s.

$$H_0 = pK(I)_{aq} + \log([I]_s/[IH^+]_s) \tag{10}$$

In ILs such as [BMIM][NTf_2] and [BMIM][BF_4], added Brønsted acids can reach acidity levels (measured as H_0) ranging from –3.35 to –7.00, depending on the nature of the IL and on the nature of the acid [23]. Strong $HNTf_2$ and HOTf acids exhibit similar acidity levels when dissolved at the same concentration in the same IL. It is observed in an aqueous medium that the leveling effect of the ionic solvent limits the acidity level which can be reached with strong acids. The linear H_0 correlation with the proton concentration has been verified. This demonstrates indirectly the dissociating character of [BMIM][NTf_2] and [BMIM][BF_4] ILs toward strong Brønsted acids. The addition of water decreases the acidity of the proton. Water behaves as a base, due to its more pronounced solvating character toward the proton than the IL. In [BMIM][BF_4] and [BMMIM][BF_4], the Brønsted acidity of $HNTf_2$ is higher than in [BMIM][NTf_2]. This suggests that the BF_4^- anion is less solvating toward H^+ than the NTf_2^- anion, leading to an increased acidity of the proton.

These acidic scales in room-temperature ILs could be further used as a predictive tool for studies of the acid-catalyzed reactions.

5.2.2.4.3
Use of Ionic Liquids in the Solid Phase

The concept of transferring liquid to solid catalysts was envisioned with acidic ILs. It is important to consider the support material and its properties, such as surface area, pore width, and thermal and chemical stability during the reaction. If properly chosen, the support may bring better dispersion and accessibility of the acidic active sites and an improvement in the separation of the reaction products. However, the main problem to be addressed for these supported catalysts is their instability, their regeneration, and the leaching of the active site under operational conditions.

Different ways to immobilize ILs are described, particularly for chloroaluminate-based ILs (see Section 5.2.1.3). Two preparation procedures can be envisioned. The simplest one is just an impregnation of the chloroaluminate IL to fill the pores of the dehydrated inorganic solid. The chloroaluminate anion is grafted on the surface by reaction with the surface hydroxyl group. This method may present some disadvantages, such as destruction of the structure of the support and the modification of the acidity of the Lewis acid.

ILs can also be anchored to the support through the imidazolium cation. The cation is first grafted on the support. The Lewis acid is added in a second step. As an example, IL has been anchored by reaction of a chloroaluminate of a 1-triethoxysilyl derivative of 3-methylimidazolium on the wall of silica MCM-41. Another approach is to anchor the cation on the support using a sol–gel method. The potential of these supported ILs has been investigated for aromatic hydrocarbon alkylation reactions (see below).

5.2.2.4.4
Selected Applications

Many examples of acid-mediated reactions are described using ILs. Some of them are described in recent reviews. The most important transformations that find applications in industrial chemistry, refinery, or petrochemistry are described below.

Friedel–Crafts Acylation

Aromatic ketones are important fine chemicals and/or intermediates for the preparation of fine chemicals such as phamaceuticals, insecticides, and other commercial products. The conventional method of forming aromatic ketones is the reaction of an aromatic compound with an acylating agent such as an acyl chloride or acid anhydride, in the presence of an acidic catalyst. In most cases, the catalyst is $AlCl_3$. However, the aromatic ketone can form a stable Lewis acid–base complex with $AlCl_3$. Thus, at least stoichiometric amounts of $AlCl_3$ are consumed with respect to the acylating agent. Furthermore, the products must be generally liberated by hydrolysis.

The first examples of catalytic aromatic acetylation in ILs have been performed in acidic chloroaluminates [24]. The most striking feature is the acetylation of naphthalene with acetyl chloride, which gives the thermodynamically unfavored 1-isomer with the highest reported selectivity. It is thought that in the IL the acylation agent is the free acetylium ion, which is smaller than the adduct with $AlCl_3$ [25]. However, the reaction still needs a high amount of catalyst.

The mechanism of the acetylation of benzene with acetyl chloride in the presence of acidic chloroaluminate has been investigated by in-situ IR spectroscopy. The results seem to indicate that the acetylium cation $[CH_3CO]^+[AlCl_4]^-$ is the key intermediate, in a similar way to the situation in traditional halogenated solvents [26].

Alternative catalysts are acidic ILs based on $FeCl_3$ and [BMIM][Cl] (2 : 1 molar ratio). Compared to [BMIM][Cl]/$AlCl_3$ (1 : 2 molar ratio), better conversion with similar selectivities were obtained (e.g., acetylation of mesitylene with acetyl chloride). One of the problems is the generation during the reaction of HCl which is not removed under the reaction conditions. If HCl contributes to an increase in the reaction rate, it also favors consecutive side reactions leading to formation of water, which deactivates the catalyst. Attempts to immobilize chloroferrate ILs on an inorganic support, such as silica, have been described but raise the problem of catalyst leaching [27].

The feasability of using metal triflates as Lewis catalysts for different aromatic acetylations in non-chloroaluminate ILs such as [BMIM][BF_4] has also been demonstrated. The faster rates were obtained with copper(II) triflate for the benzoylation of anisole but triflates are restricted to activated substrates [13].

Alkylation of Olefins with Isobutane

Gasoline specifications are changing toward cleaner-burning gasoline. Reduction in total aromatics, benzene, vapor pressure, olefins, and sulfur and limitations on the distillation endpoint affect the demand for all gasoline-blending components. In addition, due to the uncertainty concerning methyl *tert*-butyl ether (MTBE), the importance of alkylates has been elevated to that of an ideal gasoline-blending component, thanks to their high, nonaromatic, octane, and paraffinic nature. Alkylates are produced industrially by the reaction of isobutane with light olefins (butenes or a mixture of C_3–C_5 olefins) using liquid HF or sulfuric acid catalysts. While HF and sulfuric acid processes are used industrially, they suffer from some limitations (Table 2).

Alkylate quality is in general characterized by their RON (Research Octane Number) and their MON (Motor Octane Number), the amount of heavy ends and light ends resulting from side reactions such as cracking and polymerization. New catalysts are being considered for refining. The development of new solid catalysts would probably need a combination of innovative catalysts and reactor technology to overcome the problem of catalyst deactivation and regeneration. Despite many

Table 2 Limitations of butene–isobutane alkylation processes.

H_2SO_4	HF	Solid catalyst
Low catalyst productivity, high acid consumption (70–100 kg t^{-1} alkylate)	Safety problems in the case of acid release Environmental expense Public concerns	Feed pretreatment to remove sulfur impurities
Transport and disposal of spent catalyst on-site acid regeneration is expensive	High isobutane/olefin ratio	Fast catalyst deactivation
		No industrial demonstration

attempts to apply solid acid catalysts for the alkylation of isobutane with butene, no process operating on an industrial scale has been proven so far.

Aluminum chloride has been known for a long time to catalyze this reaction. However, its high acidity leads to low selectivity for alkylate. Acidic chloroaluminates proved to be interesting alternative catalysts and solvents [28] because it is possible to tune their Lewis acidity by adjusting their composition. The alkylation of ethylene or butene with isobutane has been performed in continuous-flow pilot plant operation at IFP. The feed, a mixture of olefin and isobutane, is pumped continuously into the well-stirred reactor, which contains the IL catalyst. In the case of ethylene, which is less reactive than butene, [pyridine, HCl]/$AlCl_3$ (1 : 2 molar ratio) IL proved to be the best candidate. The reaction can be run at room temperature and provides good quality alkylate (2,3-dimethylbutanes is the major product) over a period of 300 h (MON = 90–94; RON = 98–101).

When butenes are used instead of ethylene, a lower temperature and a fine tuning of the acidity of the IL are required to avoid cracking reactions and heavy byproduct formation. The continuous butene alkylation has been performed for more than 500 h with no loss of activity and stable selectivity (80–90% isooctanes are obtained containing more than 90% trimethylpentanes; MON = 90–95; RON = 95–98). A high level of mixing is essential for a high selectivity and then for a good quality alkylate. It has been shown that the addition of copper(I) chloride to the acidic chloroaluminate improves the reaction performances [29].

The IL can be impregnated on an inorganic support such as silica. Silica is first activated by calcination in dry air at 500 °C. Dry impregnation of acidic liquid chloroaluminate ([BMIM][Cl]/$AlCl_3$/CuCl) is then carried out. A feedstock containing 4.9% of 2-butene and 95.1% of isobutane is continuously pumped into a well-stirred reactor containing the solid catalyst over a period of 300 h. The effluent contains 98.5% of C_8 alkylate [30].

These applications are promising but efforts are still needed to compete with the existing effective processes based on hydrofluoric and sulfuric acids.

Friedel–Crafts Alkylation of Aromatic Hydrocarbons

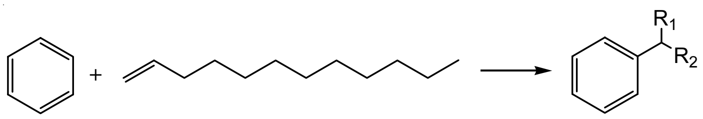
LAB Production

The alkylation of benzene with linear olefins (C_{10}–C_{14}) is largely used industrially to produce linear alkylbenzenes (LABs), precursors of alkylbenzenesulfonates which are employed as surfactants and detergent intermediates. LAB global demand is about 2.7 million metric tons per year. Traditional processes are catalyzed by acid catalysts such as $AlCl_3$ and mainly HF. The processes are designed to minimize skeletal isomerization of the linear olefins since high linearity is necessary to yield biodegradable products [31]. In order to improve the sustainability of these processes, various solid acids have been developed. The use of ILs is one of the possibilities to consider.

In that way, Akzo Nobel has developed an IL based on trimethylamine hydrochloride and aluminum chloride [Eq. (11)]. These ILs can be a cheaper alternative to imidazolium-based salts and can be applied in a similar manner. The preparation procedure of these media has been improved, in order to be applied on an industrial scale [32].

$$2\ AlCl_3 + (CH_3)_3NHCl \rightleftharpoons [(CH_3)_3NH]^+[Al_2Cl_7]^- \tag{11}$$

These ILs have been used as catalysts–solvents for the alkylation of benzene with 1-dodecene [33]. The reaction produces higher yields in 2-dodecylbenzene (46%/other monoalkylbenzene isomers) than the conventional HF process [Eq. (12)]. In addition the IL does not present the drawback of sludge byproduct formation as is the case with $AlCl_3$. One of the points of interest of operating the reaction in ILs is that alkylbenzenes are poorly miscible in ILs. The reaction proceeds in a biphasic mode, thus making catalyst recovery and recycling easier. In traditional processes, consecutive polyalkylation reactions may occur since the alkylated benzene hydrocarbons are more reactive than the nonalkylated starting material. In the biphasic IL mode, consecutive polyalkylation reactions are disfavored since the alkylated benzenes are less soluble in the catalytic phase than the nonalkylated benzenes.



(12)

$R_1 = CH_3$; $R_2 = (CH_2)_9CH_3$	2-phenyldodecane
$R_1 = CH_2\text{-}CH_3$; $R_2 = (CH_2)_8CH_3$	3-phenyldodecane
$R_1 = (CH_2)_2\text{-}CH_3$; $R_2 = (CH_2)_7CH_3$	4-phenyldodecane
$R_1 = (CH_2)_3\text{-}CH_3$; $R_2 = (CH_2)_6CH_3$	5-phenyldodecane
$R_1 = (CH_2)_4\text{-}CH_3$; $R_2 = (CH_2)_5CH_3$	6-phenyldodecane

This reaction has also been performed with chloroaluminates immobilized on different solid supports (silica, alumina, or zirconia) [34]. In general supported ILs show improved activity and selectivity for monoalkylated products (see Section

5.2.1.3) [35]. However, although H-Beta-zeolite affords predominantly the 2-dodecylbenzene isomer, the supported IL on the same zeolite gave similar isomer distribution to $AlCl_3$ or pure chloroaluminate IL.

As described previously, protic ionic liquids that are free of Lewis acidity, such as $[BMIM][HSO_4]/H_2SO_4$, have also been used as catalysts–solvents. Alkylation of benzene with 1-decene has been described. The difficulty is probably to adjust the acidity of the IL to have the right balance between olefin double bond isomerization and aromatic alkylation [16].

Ethylbenzene Production

Another important application of Friedel–Crafts alkylation of aromatic hydrocarbons includes the production of ethylbenzene via alkylation of benzene with ethylene. The industrial process is still dominated by the use of $AlCl_3$ red oil as the acid catalyst. The cost of production of ethylbenzene using zeolite technology is only marginally less. Nevertheless, environmental factors are enough to displace the $AlCl_3$ technology. However, the revamping of $AlCl_3$-based units with solid catalyst is costly and difficult to implement. So, recyclable forms of $AlCl_3$ catalyst may still be of interest for industry.

Different acidic dialkylimidazolium chloride/$AlCl_3$ (1 : 2 molar ratio) catalysts have been used and compared with the $AlCl_3$ red-oil system. The study indicated lower activity and selectivity to the monoalkylate product for the IL. Similar performances are obtained with amine-based chloroaluminates. The only advantage of ILs is the ease of recovery of the solvent–catalyst by gravity separation, which contrasts with the difficulty of separating red oil from the reaction products [36, 37].

Olefin Oligomerization and Polymerization

Short-chain olefin oligomerization can provide gasoline, middle distillate, or lubricant oils. Typical acids used to catalyze these reactions are now solid-type catalysts such as silica-supported phosphoric acids or zeolites.

Acidic chloroaluminates oligomerize linear olefins such as propene, butenes, or hexenes. The addition of proton scavenger, such as ethylaluminum dichloride may inhibit the cationic reaction, which suggests that it is initiated by protons. This ability to catalyze oligomerization of olefins was applied by BP Chemicals [38] for the transformation of butene-rich C_4 cuts such as Raffinate I (butadiene raffinate, rich in isobutene) or Raffinate II (isobutene raffinate) into polybutene. The polymer products form a separate layer that floats on the surface of the IL. Thus, further transformation of the olefinic end-group in the polymer (e.g., isomerization) can be minimized. Compared to $AlCl_3$ or BF_3 technology, the advantages of ILs are:

- The rate of polymerization is increased.
- A higher percentage of *n*-butene is incorporated in the polymer product.
- The polymer has a higher molecular weight even if higher temperatures are used.
- The separation of the reaction products from the catalyst phase is easier.

Further, unwanted reactions such as isomerization are minimized and the catalyst is not destroyed by quenching procedures.

In a similar way, isobutene is very quickly polymerized in acidic chloroaluminates to high molecular weight polyisobutene. The addition of alkylaluminum chloride does not stop the reaction [39].

The oligomerization of α-olefins such as 1-decene or 1-dodecene to prepare synthetic lubricating oil base stocks with low pour point and high viscosity index is of industrial interest. It is possible to oligomerize α-olefins to high-viscosity poly(α-olefin)s using acidic chloroaluminates [40]. The difficulty is to control the oligomer distribution. In general, ILs give a large amount of isomerization within a specific oligomer fraction. Recently, Chevron disclosed that it is possible to obtain oligomers with higher kinematic viscosity (31.6 cSt at 100 °C, viscosity index VI = 152) by performing the reaction with $Me_3NHCl/AlCl_3$ (1 : 2 molar ratio) in the absence of diluent organic solvent [41].

Paraffin Transformations

Paraffins with a high degree of branching are known to be useful blending components for motor gasoline due to their high octane number. Such paraffinic hydrocarbons can be produced by skeletal isomerization of normal paraffins. This reaction requires a strong Brønsted or Lewis catalyst. Acidic chloroaluminates may be strong enough acids to transform paraffins such as *n*-hexane at low temperature. The difficulty is to adjust the acidity of the system to favor isomerization over cracking. Solid $AlCl_3$ has often been described in combination with a copper(II) salt such as $CuCl_2$ or $CuSO_4$. In a similar way, different metal salts (e.g., $CuCl_2$) have been added to $[Me_3NH][Cl]/AlCl_3$ ILs in order to increase the yield of branched products under mild reaction conditions [42, 43].

Cracking of alkanes in acidic chloroaluminates (e.g., pyridine.HCl/$AlCl_3$) was also described to occur even at low temperature (below 90 °C) whereas conventional catalysts usually require high temperatures (300–1000 °C). The addition of a proton scavenger such as an alkylaluminum derivative (e.g., $EtAlCl_2$) or CaH_2 reduces the rate of cracking while the addition of protons (e.g., HCl gas) increases the reaction rate [44, 45].

Finally, the cracking of polyethylene (LLDPE or HDPE) can be catalyzed by acidic chloroaluminates in the presence of a proton source, affording gaseous alkanes and cyclic alkanes with no evidence for significant formation of aromatic compounds or olefins [46].

Carbonylation of saturated hydrocarbons to oxygenated hydrocarbons is difficult due to the high stability of C–H or C–C bonds. Superacids, which are generally corrosive and volatile, are often used. Imidazolium or pyridinium chloroaluminates have proven to be suitable catalysts [47]. Alkylaromatic compounds (e.g., toluene or xylene) can also react with carbon monoxide in the presence of an acidic chloroaluminate IL to form an alkyl aromatic aldehyde [48].

5.2.2.4.5
Conclusion

This introduction to acid-catalyzed reactions illustrates the wide range of reactions that can be performed in ILs. ILs derived from Lewis acids, such as chloroaluminates, chloroferrates, or fluoroantimonates, can be used as both solvents and catalysts for reactions usually catalyzed by the corresponding Lewis acid (e.g., $AlCl_3$, $FeCl_3$, SbF_5). They can be made superacidic by addition of a proton source which further extends their reactivity and range of applications. Compared to conventional liquid acids, they offer the additional benefit of being weakly miscible with hydrocarbon compounds which makes possible an easy product separation and catalyst recycling. This also often contributes in minimizing consecutive undesired side reactions often present in acidic catalysis. Non-Lewis-acidic ILs are also interesting solvents for Lewis or Brønsted acids and do not present the limitations of water.

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5.2.2.5
Biocatalysis

Jesper Brask, Christel T. Jørgensen, and Ole Kirk

5.2.2.5.1
Introduction

Enzymes have many potential advantages when used as catalysts for chemical synthesis. The unique properties offered by these biocatalysts are, first of all, their often outstanding chemo-, regio-, and, in particular, stereoselectivity. Furthermore, enzymes are highly efficient catalysts working under very mild conditions. However, enzymes do also have some drawbacks that may limit their potential use, such as ability to accept a limited substrate pool only, and a moderate operational stability. Ways of overcoming most of these potential limitations exist and they pose in most cases more of a perceived than a real problem. Well over 100 different biocatalytic processes have been implemented on an industrial scale [1]. A few processes are performed on a multi-thousand tonnes per year scale, such as the manufacturing of acrylamide using a nitrile hydratase, the thermolysin-catalyzed synthesis of the low-calorie sweetener aspartame, and the synthesis of β-lactam antibiotics using a penicillin acylase [2, 3]. The majority of the established processes are, however, performed on a much smaller scale (100 kg – 100 t per year). In most of these processes the unique enantioselectivity of the enzymes is utilized for the production of single-enantiomer intermediates used in the manufacture of drugs and agrochemicals [1, 2]. Accordingly, many examples exist of the successful industrial application of biocatalysis. Nevertheless, the area is still a very small niche within the chemical industry as such, and even though a significant growth is being experienced in the area [1] this will not change the picture dramatically on a short to medium term.

A new tool has recently been added to the area of biocatalysis as a variety of enzymes within the last few years have been shown to exhibit both stability and activity in ionic liquids (ILs). This section will give a short review of these findings and discuss what potential impact they can have on the area of biocatalysis in general.

5.2.2.5.2
Ionic Liquids and Enzymes

Solvent Properties of Ionic Liquids

As a new class of nonaqueous solvents, ILs offer the opportunity to replace traditional organic solvents. Various benefits have been claimed for ILs, first of all due to their lack of vapor pressure. This feature may eliminate many of the risks associated with the handling of traditional organic solvents and may, furthermore, enable an efficient re-use of the solvent in certain processes. Consequently, ILs have been claimed to be a potential "green" replacement for traditional organic solvents. Replacing traditional solvents with ILs may, indeed, offer some potential in certain processes, including biocatalytic ones. ILs would be of much more interest, however, if their use could offer additional advantages, primarily by enabling reactions that can otherwise not be performed in traditional nonaqueous solvents. One feature that could open up for new developments would be if ILs could offer a nonaqueous environment to substrates that are not, or are only very poorly, soluble in traditional organic solvents.

By nature ILs are polar compounds, a property that is easily studied with solvatochromic compounds such as Reichardt's dye [4]. On the normalized polarity scale (E_T^N) from 0.0 (tetramethylsilane, TMS) to 1.0 (water), most ILs can be found around 0.6–0.7. By comparison, E_T^N for ethanol is 0.654 [4]. In general, the polarity is largely controlled by the nature of the cation, whereas the ability of the ILs to participate in hydrogen bonding seems to depend on the anion. On the other hand, the miscibility of ILs with water seems unpredictable. A well-known example is [BMIM][BF_4] which is water-miscible, while [BMIM][PF_6] is not. Regarding biocatalysis, it has been pointed out that even trace amounts of ionic impurities can significantly affect the properties of the IL as well as the activity of added enzyme.

Kazlauskas and co-workers found a dramatically improved enzymatic performance in some tetrafluoroborate ILs after treatment with Na_2CO_3 [5]. The authors speculate that the effect could be due to precipitation of Ag_2CO_3 or neutralization of traces of acid, but can potentially also be explained by a more well-defined water content [6]. Traces of halide ions can also be a possible cause of poor enzymatic performance [7].

Recently, ILs that dissolve carbohydrates have received much attention. This is based on the fact that polysaccharides such as starch and cellulose constitute a renewable resource for the chemical industry, and that underivatized carbohydrates are insoluble in almost any solvent other than water. It has been found that cellulose can be dissolved in chloride containing ILs such as [BMIM]Cl (liquid at 65 °C) [8]. Solutions of 5–10% cellulose were easily prepared with microwave heating, and up to 25% cellulose was possible in anhydrous [BMIM]Cl [8]. However, Cl-based ILs are in general poorly compatible with enzymes (see also "Enzymatic stability and activity", below). This is illustrated by the findings of Rogers and co-workers that *Trichoderma reesei* cellulase is irreversibly inactivated by [BMIM]Cl [9]. Recently, MacFarlane and co-workers showed that ILs based on the dicyanamide (dca) anion are quite effective in dissolving mono-, oligo-, and even polysaccharides [10–12]. Quaternary ammonium, pyrrolidinium, and imidazolium dca salts have been prepared, most of which are low-viscosity liquids at room temperature, as well as being chemically and thermally inert. Whether these ILs are compatible with biocatalysts does, however, still remain to be investigated.

Modes of Operation

Roughly speaking, there are three modes of operating an enzymatic reaction with ILs: with the IL (1) as pure solvent, (2) as a co-solvent in aqueous buffer (requires water miscibility), and (3) as a co-solvent in a biphasic system [6, 13]. In the last case, the biphasic system could include supercritical carbon dioxide (no ILs dissolve in $scCO_2$ [14]). Hence, the enzyme is retained in the IL phase, whereas substrate and product can be extracted into $scCO_2$. A biphasic system of water and a IL that is not water-miscible could be advantageous for enzymes that require an aqueous system to work, if water does not interfere with the desired reaction [14]. Further, biphasic systems often have a built-in advantage of easy recycling of enzymes and/or ILs; however, if this is not enough, even three-phase systems can be constructed, consisting of water, IL, and organic solvent [6].

As ILs are nonvolatile, products can also be isolated be means of distillation. Alternatively, a reduced pressure can be applied to remove volatile products such as water or low alcohols, driving the reaction toward product formation. The latter technique was demonstrated by Itoh and co-workers, who continuously removed methanol from the transesterification of a methyl ester in [BMIM][PF_6] [15]. The reaction was catalyzed by the B-lipase from *Candida antarctica* (CaLB). Itoh's group also most recently identified [BMMIM][BF_4] (BMMIM = 1,2-dimethyl-3-butyl-imidazolium) to be an excellent solvent for setting up a lipase-recycling system using vinyl acetate as the acyl donor [16]. The lipase was used 10 times here without loss of reactivity and enantioselectivity.

Enzymatic Stability and Activity

Enzymes have been used for biocatalysis in organic solvents since the early 1980s, and in ILs since 2000 [17]. As biological catalysts, enzymes accelerate reactions but do not affect the equilibrium distribution. Hence, hydrolytic enzymes that, as an example, under normal circumstances in aqueous solutions hydrolyze esters and amides, will, when placed in water-free conditions, also catalyze the reverse reaction, the condensation of an acid with an alcohol or an amine, to give esters and amides, respectively. Further, under water-free conditions hydrolytic enzymes can accept alternative nucleophiles to catalyze reactions such as transesterifications. An important industrial example of this is the lipase-catalyzed transesterification of triglycerides to obtain fats with a desired melting point [18].

Often, the reactivity is found to be reduced in organic systems compared to that in aqueous buffer. This effect is thought to be the result of reduced structural flexibility of the enzyme. Many organic solvents lack the ability to participate in hydrogen bonding and also have a lower dielectric constant, leading to stronger intramolecular interactions, and so a more rigid enzyme. In an early report on biocatalysis in ILs, two of the authors of the present text compared the activity of lipases in [BMIM][PF_6] with the activity in the traditional organic solvents butanone, THF, and hexane [19]. The highest activity was found in hexane, whereas the activity in the IL was very similar to that in butanone or THF. In the same report, the hydrolytic activity in aqueous buffer of *Eschericia coli* β-galactosidase and the subtilisin protease Savinase^{TM} was compared to the activity in aqueous 50% [BMIM][PF_6], 50% ethanol, or 50% acetonitrile [19]. For both enzymes, the activity in the IL was found to be comparable with that in the traditional organic solvents, but lower than the activity in aqueous buffer (not surprisingly, considering the lower water activity). The most encouraging result was found for the protease in [BMIM][PF_6], in which it was twice as active as in acetonitrile, and only three times less active than in water.

Not all organic solvents are equally well tolerated by enzymes. Polar organic solvents such as DMF or DMSO often denature enzymes, whereas good enzymatic performance can be observed in hydrophobic solvents, in which the enzymes are suspended [6, 14, 20]. In certain cases the activity can even be improved by adding a small amount of water to an anhydrous suspension of enzyme in organic medium. Water can be seen here as a molecular lubricant that improves the flexibility of the enzyme. However, in other cases the addition of water may lead to the denaturation of the enzyme; in the organic medium it may be thermodynamically unstable, but kinetically stable due to the rigidity. After addition of water, the enzyme could both be thermodynamically unstable and have the kinetic drive needed to actually denature [20]. Results of enzyme inactivation have also been observed in ILs that dissolve enzymes. Erbeldinger and co-workers showed that [BMIM][PF_6] will dissolve 3.2 mg mL^{-1} of thermolysin, but that it will be inactive [17]. At higher enzyme concentrations a suspension was obtained that showed catalytic activity. Likewise, [BMIM][NO_3], [BMIM] lactate, and [EMIM][$EtSO_4$] have been observed to dissolve and cause a partly reversible deactivation of CaLB [21]. In general, it seems that ILs with large anions having the charge delocalized over many atoms are more compatible with enzymes than ILs with anions having a more defined charge. As such, ILs based on Cl^-, $[NO_3]^-$, $[OTf]^-$, $[CF_3CO_2]^-$, or $[CH_3CO_2]^-$ anions have been found to inactivate certain enzymes [7].

If the solvent does not in itself denature the enzyme, other factors could contribute to low or no reactivity. It has been found that enzymes in organic media have a "pH memory", meaning their catalytic activity depends on the pH of the aqueous environment to which they were last exposed [20]. Therefore, this medium should have the pH of the enzyme's activity maximum. Alternatively, organic acids or bases could be added to the organic solvent, but this is more difficult to control. Further, if the enzyme is lyophilized before being suspended in an organic medium, the lyophilization process itself could cause denaturation. This potential problem can be avoided by using immobilized enzymes, or freeze-drying with salts or structure-preserving lyoprotectants [22].

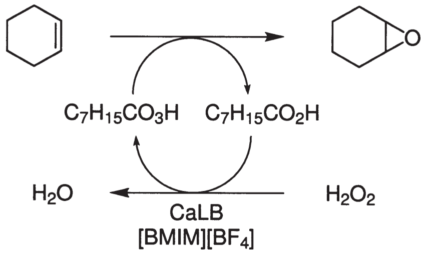
There are unexpected benefits too, in using an organic solvent. It is well documented that many enzymes show better thermal stability in an anhydrous medium than in an aqueous solution, probably due to the increased rigidity [14, 20]. Further, several groups have reported an even better enzyme stability in ILs than in traditional organic solvents [7]. Also, in certain cases remarkable increases or shifts in selectivity (for substrate, enantiomer, etc.) have been observed, in going from aqueous solution to organic solvents, or from one organic solvent to another [14, 20]. This can be the result of a different enzyme structure in the organic medium, but may in other cases be related to the properties of reaction substrates or products. Kazlauskas and co-workers showed an improved *O*-6 selectivity in CaLB-catalyzed acylation of D-glucose in ILs compared to organic solvents such as acetone or THF [5]. They speculated that the low selectivity in organic media giving diacylated products is related to the poor substrate solubility. As a suspension, most of the glucose is inaccessible to the enzyme, whereas the acylated product is much more soluble and hence available for further reaction.

5.2.2.5.3
Biocatalysis in Ionic Liquids

In recent years, the industrial use of biocatalysis has been reviewed several times [1–3, 23]. Also, since the first reports [17, 24] on biocatalysis in ILs appeared in 2000 this field has often been reviewed, recently for example by the groups of Sheldon [14, 21], Kragl [6], and Kazlauskas [7]. Comprehensive tables of the various enzymatic reactions attempted in ILs can be found in these excellent reviews (see, for example, Ref. [6]). Here only general trends will be outlined and illustrated by selected examples.

Lipases

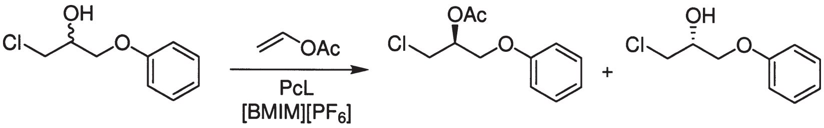
Lipases are known for their tolerance of hydrophobic media and are now widely used, also on an industrial scale [25], e.g., for enantioselective (de)acylations of alcohols and amines. Hence, it is not surprising that the most explored enzymes in ILs are lipases,



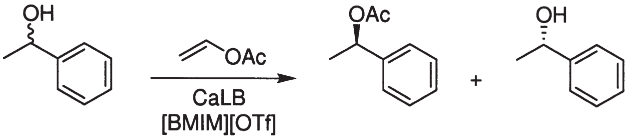
Scheme 1 Epoxidation of cyclohexene by peroxyoctanoic acid generated in situ by CaLB-catalyzed perhydrolysis [26, 27].

and examples have been mentioned already in this text. CaLB, especially, has proved to be very versatile, as it was first demonstrated by Sheldon and co-workers [26, 27]. They showed that the lipase could catalyze alcoholysis, ammoniolysis, and perhydrolysis in [BMIM][PF_6] and [BMIM][BF_4] at rates comparable to or higher than those observed in other organic solvents. The authors further utilized the peroxycarboxylic acid formed by perhydrolysis to epoxidize cyclohexane (Scheme 1). Using immobilized CaLB (Novozym 435^{TM}), an 83% yield was obtained in [BMIM][BF_4]. This type of coupled reaction had previously been investigated in hexane using a number of different lipases, carboxylic acids, and alkene substrates [28].

Since then, ILs have also been found to be suitable media for kinetic resolution of alcohols. Thus, Kim and co-workers showed enhanced enantioselectivities of both CaLB and *Pseudomonas cepacia* lipase (PcL) in the esterification of secondary alcohols in [EMIM][BF_4] and [BMIM][PF_6] compared to similar reactions in toluene and THF (> 99% *ee*) [29]. The more hydrophobic [BMIM][PF_6] appeared to give the best results, with up to 25 times the E value obtained in THF [Eq. (1)]. In several cases the enantioselectivity of the lipase in the IL reached a synthetically desirable level ($E > 400$), which was not obtained with either THF or toluene. In a systematic study, Kragl and co-workers compared the enantioselectivities of nine different lipases and two pig liver esterases in a wide range of ionic liquids and MTBE (methyl *tert*-butyl ether) [30]. The esterases did not maintain their activity in the ionic liquids but again CaLB showed excellent enantioselectivities in kinetic resolution of 1-phenylethanol by transesterification of vinyl acetate [Eq. (2)]. The lipases from *Pseudomonas* and *Alcaligenes* species offered an improved enantioselectivity in [BMIM][NTf_2] compared to MTBE, while for CaLB good results were also obtained in [BMIM][OTf] and [OMIM][PF_6]. In general, although these solvents only occasionally offer improved enantioselectivities, they allow resolutions in more polar solvents than previously possible. Furthermore, since no “best solvent for resolution” exists in biocatalysis in general, tailor-made ionic liquids may be designed that broaden the range of potential interesting reaction media.



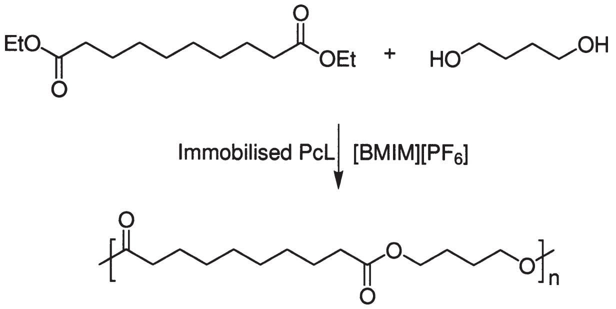
(1)



(2)

One of the more challenging tasks for a lipolytic enzyme within biocatalysis is the esterification of carbohydrates. Chemically prepared sugar ester detergents (for example, Span^{TM} and Tween^{TM}) are widely used as emulsifiers, but due to the rather sparing solubility of sugars in organic solvents the rate of lipase-mediated synthesis of such detergents is too low and the technique is therefore not competitive with chemical methods [18]. However, the use of ILs in carbohydrate ester synthesis is still rather unexplored. So far, CaLB has been shown to monoacetylate glucose in 99% yield in [MOEMIM][BF$_4$] (MOE = $CH_3OCH_2CH_2$–) [5]. Probably due to the poorer solubility the yield decreased drastically when maltose was used as the acceptor.

Lipase-catalyzed polyester synthesis has received considerable interest [31] due to the harsh conditions used in traditional chemical polymerization (> 200°C), and has also been subjected to reaction in ILs. Both CaLB and PcL lipases have been found to catalyze polyester synthesis in [BMIM][BF$_4$] and [BMIM][PF$_6$], but this approach does not seem to offer any advantages over state-of-the-art lipase-mediated polyester synthesis [32, 33] [Eq. (3)]. Still, the polydispersity index of the polymers formed in ILs were remarkably affected, giving values close to 1, which indicate a very narrow molecular weight range compared to material prepared by conventional polymerization processes [33].



(3)

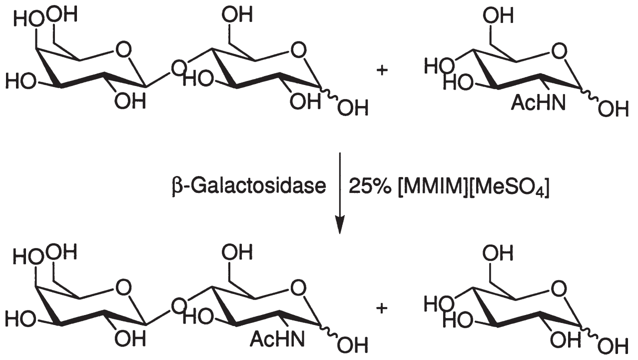
Other Enzymes

In the first report on (isolated) enzymatic catalysis in an IL, Erbeldinger and co-workers described the thermolysin-catalyzed synthesis of *Z*-aspartame in [BMIM][PF$_6$] [17]. By condensation of *Z*-Asp–OH and H–Phe–OMe, the sweetener could be prepared in 95% yield, which is similar to the yield that has been obtained in traditional organic solvents [Eq. (4)]. A 5% water content was found critical for the enzymatic activity. Moreover, removal of the water by vacuum resulted in easy isolation of the product by precipitation [17]. Further, in another application of a protease, Adlercreutz and co-workers used α-chymotrypsin to study transesterification of Ac–Phe–OEt with 1-butanol [34] [Eq. (5)]. They found that at low water activity (a_w), the catalytic activity was higher in [BMIM][NTf$_2$] than in traditional organic solvents such as ethyl acetate and MTBE, in which no activity was detected at $a_w = 0.11$.

$$\text{Z-Asp-OH} + \text{H-Phe-OMe} \xrightarrow[\text{[BMIM][PF}_6\text{]}]{\text{Thermolysin}} \text{Z-Asp-Phe-OMe} \tag{4}$$

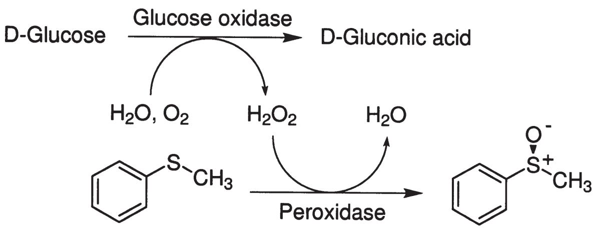
$$\text{Ac-Phe-OEt} + n\text{-BuOH} \xrightarrow[\text{[BMIM][NTf}_2\text{]}]{\alpha\text{-Chymotrypsin}} \text{Ac-Phe-OBu} \tag{5}$$

Kragl and co-workers recently reported the synthesis of a disaccharide by transglycosylation in 25% aqueous solution of [MMIM][MeSO$_4$] [13]. Using lactose as the donor for *Bacillus circulans* β-galactosidase, a galactose unit was transferred to *N*-acetylglucosamine to yield *N*-acetyllactosamine [Eq. (6)]. A higher concentration of the IL resulted in significantly lower enzymatic activity. When the reaction was performed in water, yields were limited to 30% due to enzymatic hydrolysis of the product. In the IL this hydrolysis is suppressed (due to lower water activity), giving a maximum yield of 58%. The reaction was performed in a stirred-tank reactor with retention of the β-galactosidase in an ultrafiltration membrane.



(6)

In redox reactions, isolated oxidative enzymes such as laccase C from *Trametes* and horseradish/soybean peroxidases (with mediators) have been shown to possess good catalytic activity in common ILs on syringaldizine and veratryl alcohol, respectively [35]. Recently, oxidase–peroxidase-catalyzed chemo- and stereoselective sulfoxidations of thioanisole and methyl-2-naphthyl sulfide have been successfully carried out with a system of *Coprinus cinereus* (CiP) peroxidase and *Aspergillus niger* glucose oxidase (GOD) in 10% water in [BMIM][PF$_6$] (Scheme 2). An enantiomeric

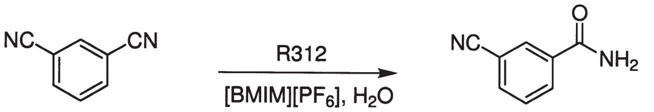


Scheme 2 Oxidation of sulfides [36]. A biphasic system with water and [BMIM][PF$_6$] was investigated.

excess *ee* of 92% was obtained for methyl-2-naphthyl sulfoxide. In general, yields and stereoselectivities were similar to those obtained in water, but isolation of the product sulfoxides was much facilitated by the ILs [36].

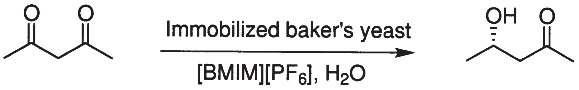
Whole-cell Systems

It has been demonstrated that yeast cells and other microorganisms are active in the presence of ILs [6, 37]. In the very first report on biocatalysis in ILs, Lye and co-workers showed that a toluene–water system has a more detrimental effect on the microorganism *Rhodococcus* R312 than a system of [BMIM][PF$_6$] and water, which is well tolerated [24]. Consequently, a better yield for the hydration of 1,3-dicyanobenzene [Eq. (7)] to 3-cyanobenzamide was obtained with the micro-organism in the two-phase IL/water system than in the toluene system.



(7)

Within biocatalysis, redox reactions especially are often carried out in biphasic systems using crude cell systems, as the recycling of expensive cofactors is vital. The organic phase, which holds the rather insoluble substrate (and products), can be replaced by a more harmless IL. By this means, baker's yeast was used by Howarth and co-workers for enantioselective reduction of ketones [37]. In a 10 : 1 mixture of [BMIM][PF$_6$] and water, reactions proceeded for a range of substrates giving yields and selectivities very comparable to those obtained by conventional methods [Eq. (8)].



(8)

5.2.2.5.4
Opportunities and Potential Problem Areas

As outlined above, a number of different biocatalysts have been demonstrated to be both active and stable in a variety of ILs. This opens up possibilities for a wide use of ILs as nonaqueous solvents in biocatalytic processes. Advantages of using ILs could be several. Of primary interest is the unique ability of ILs to dissolve polar substrates in a nonaqueous environment, thereby offering the opportunity to develop biocatalytic processes that convert important substrates such as carbohydrates, peptides, nucleotides, and other biochemical intermediates that are not, or only very sparingly, soluble in traditional organic solvents. Furthermore, ILs may also be directly substituted for traditional organic solvents in certain processes in which the ILs lack of vapor pressure may eliminate the risks associated with traditional organic solvents. The area of combining ILs and biocatalysts is still in its infancy, but it is receiving much attention in the scientific literature at present and the true opportunities of the combination will, therefore, be expected to be greatly clarified within the next few years.

Even though ILs may offer some unique opportunities to the development of new biocatalytic processes they also carry several inherent problems that may limit their use, especially in processes to be performed on an industrial scale. The lack of vapor pressure may be a potential advantage in certain applications, but it also poses a problem in many others. Thus, isolation of polar, nonvolatile products may be problematic and new technologies to enable it must be developed. The lack of volatility may also make it very difficult to remove ILs completely from the products. This may be a particular problem, as many ILs have unknown toxicological properties. Furthermore, the ILs described so far are highly expensive compared to traditional organic solvents. Therefore, a key to the industrial use of ILs will be the development of either dramatically less expensive ILs or of highly efficient methods for their recycling. Finally, most ILs described so far are rather viscous, a property that may cause great difficulties, especially when performing a process on a larger scale.

5.2.2.5.5
Conclusions and Perspectives

Ionic liquids may offer an attractive nonaqueous environment for biocatalysts to potentially open up for the development of new processes, in particular involving reactions with polar, complex substrates. However, many problems are also associated with ILs that may limit their use, at least on a larger industrial scale. It is, therefore, our prediction that biocatalytic processes performed in ILs will only become relevant from an industrial point of view when the use of ILs offers a true breakthrough opportunity in the manufacturing of potentially very valuable compounds, especially pharmaceutical ingredients, that cannot otherwise be synthesized. Identifying such opportunities is most likely to take significant time. That this is to be expected is indicated by the fact that, even though traditional chemical reactions performed in ILs have been an intensive focus area for a much longer time, the first industrial chemical process using an IL as solvent has only been described in 2003 [38]. In the laboratory, where economic considerations and process design are not so critical, biocatalysis in ILs may, however, become a very valuable tool in the synthesis of highly valuable research tools such as screening substrates and other compounds based on biomolecules such as carbohydrates and peptides.

As stated in Section 5.2.2.5.1, biocatalysis is still a very small niche area within the field of industrial organic synthesis in general. Even though the combination of ILs and biocatalysts may offer several exciting opportunities, we do not believe that this will change the overall position of biocatalysis significantly. Rather, the combination of ILs and biocatalysis will only become yet another niche area within the field of biocatalysis.

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5.2.2.6
Liquid-phase HF Fluorination

Philippe Bonnet

5.2.2.6.1
Introduction

In 1987, the Montreal protocol led to the phase down of the chlorofluorocarbons (CFCs) because of their ozone depletion potential. These products have been replaced in a first step by HCFCs (hydrochlorofluorocarbons), which still contain chlorine, and in a further step by HFCs (hydrofluorocarbons), which are completely chlorine-free products.

A number of chemical companies, such as ARKEMA (formerly ATOFINA), decided to face this huge challenge of CFC substitution. In the early 1990s, the first hydrofluorocarbon, 1,1,1,2-tetrafluoroethane (CF_3–CH_2F) or FORANE® F134a, was launched on the market as a substitute for CFC 12 (CCl_2F_2, dichloro difluoro methane) and was followed by others products like, for example, F143a (1,1,1-trifluoroethane, CF_3-CH_3) or F32 (difluoromethane, CH_2F_2).

All these products are used in the air-conditioning and refrigeration industry on their own, or blended. For example, F134a is used in mobile air conditioning (cars and trucks) and in refrigeration. It is also a component used to manufacture F407C, a blend also containing F125 (pentafluoroethane, CF_3–CF_2H) and F32, which is used, for example, in comfort and commercial air conditioning.

Basically, most of the chemical processes for HFC synthesis deal with HF as the fluorinating agent and proceed by chlorine/fluorine (Cl/F) halogen exchange or HF addition to a double bond, starting from chlorinated hydrocarbons. One of the competitive advantages of this business lies in the finding of the most accurate and the most economical process. In most of the cases, two main types of processes are in balance. The first is a liquid-phase process run under pressure, which requires soft conditions and can be catalyzed by Lewis acids. The second process, used when the Cl/F exchange requires more energy, is run in the gas phase. This last type of process involves a heterogeneous catalyst whose base element is chromium (Cr).

5.2.2.6.2
Context/Bibliographic Analysis

The liquid-phase fluorination processes can proceed in a noncatalytic way. This is the case for the exchange reaction by HF of the first Cl atom of 1,1,1-trichloroethane leading to 1,1-dichloro-2-fluoroethane [Eq. (1)] around 100 °C with HF as the reaction solvent [1].

$$CCl_3\text{–}CH_3 + HF \rightleftharpoons CCl_2F\text{–}CH_3 + HCl \qquad (1)$$

In most cases, however, the liquid-phase fluorination processes require a halogenated (Cl or F) Lewis-acid catalyst. For example, the first addition of HF on trichlorethylene followed by two subsequent Cl exchanges to reach the 1-chloro-2,2,2-trifluoroethane (F133a, which is an intermediate for F134a), are catalyzed by $SbCl_5$ [Eqs. (2) and (3)].

$$CCl_2{=}CHCl + HF \rightleftharpoons CCl_2F{-}CH_2Cl \tag{2}$$

$$CCl_2F{-}CH_2Cl + 2\ HF \rightleftharpoons CF_3{-}CH_2Cl + 2\ HCl \tag{3}$$

Generally speaking, liquid-phase fluorination catalysts are located in groups 4 (Ti [2], etc.), 5 (Nb, Ta [3], etc.), 6 (Mo, etc.), 14 (Sn [4], etc.) and 15 (Bi, As, Sb [5], etc.) columns of the Periodic Table of the chemical elements. Among all these compounds, $SbCl_5$ and more specifically the $Sb(V)Cl_xF_y$ entities which were first synthesized by Swarts in 1895 [6], are the most active catalysts. From a mechanistic point of view, $Sb(V)Cl_xF_y$ in the presence of HF form "superacidic" species such as $SbCl_xF_{y+1}^-\ H^+$. Cl/F exchange reaction can be concerted or can proceed via a carbocation followed by addition of F^- [7], while the addition of HF to a double bond could proceed via two types of attack, nucleophilic (F^-) or electrophilic (H^+) [8].

$SbCl_5$ is the most common liquid-phase fluorination catalyst and is used in nearly all liquid-phase fluorination processes. Therefore, improvements of such processes are made by the elimination/improvement of the drawbacks presented by $SbCl_5$:

- reduction from Sb(V) → Sb(III) (inactive species), leading to the industrial processes that co-feed Cl_2 in order to reoxidize Sb(III) or prevent Sb(V) from being reduced;
- formation of tars;
- corrosion with HF, which requires appropriately adapted material for reactor construction.

5.2.2.6.3
Super Acidic Ionic Liquids

Choice of the Anion

The most studied ionic liquids (ILs) in the literature are chloroaluminate-based ionic liquids. Chemical properties such as Lewis acidity depend on the nature of the anion, namely $Al_2Cl_7^-$. Considering the acidity parameter as the key point to design a liquid-phase fluorination catalyst, a new range of acidic ILs has been set up [9]. These ILs have been synthesized starting from halogenated metallic acids MX_n (with M = Ti, Nb, Ta, Sn, Sb and X = Cl and/or F), such as $Ta(V)Cl_xF_y$, $Nb(V)Cl_xF_y$, $Ti(IV)Cl_xF_y$, $Sn(IV)Cl_xF_y$, $Sb(V)Cl_xF_y$. Among these compounds, anions derived from $SbCl_xF_y$ ($x + y = 5$, $0 \leq x < 5$ and $0 < y \leq 5$) compounds turned out to be particularly interesting as Sb(V) compounds have been proven to be the most efficient catalysts for liquid-phase fluorination.

The Lewis-acidic nature of this new type of ionic liquids has been obtained, as for chloroaluminate-based ILs, by adjusting the ratio between the halogenated acid and the cation precursor to above 1.

Choice of the Cation

A suitable cation must be chosen according to the targeted application. For liquid-phase fluorination catalysis with HF as the fluorinating agent, this cation needs to be stable in the presence of HF.

Salts with carbenium ions and SbF_6^- as counteranion have already been described, such as magic methyl $CH_3^+\ SbF_6^-$. However, these super-electrophilic species can be involved in electrophilic additions to double bonds and carbenium cations, and are therefore not suitable for fluorination reactions.

Many ILs are prepared from a cation containing a heteroelement (N, P) such as tetralkylammonium, alkylpyridinium, dialkylimidazolium, or tetralkylphosphonium. A number of these cations have been extensively studied for Friedel–Crafts reactions and have shown a rather good stability [10]. Therefore, they represent good potential candidates.

Other cations with an O or S heteroelement are also very interesting candidates, thanks to the presence of a free pair of electrons. Indeed, their interest lies in the possibility of their protonation in superacidic medium giving a di-cation [11] which ends up with a different reactivity.

Therefore, a number of cations are suitable for liquid-phase fluorination, but in order to simplify the presentation, this article will mainly focus on imidazolium-based ILs.

5.2.2.6.4
Synthesis

The general method consists in the reaction between the desired number of equivalents of the halogenated acid per equivalent of a cation precursor at room temperature.

Focusing to the antimony compounds, the cation precursor can be a halogenated salt or a hexafluoroantimonate salt [12] (**2**):

$$Q^+X^- + n\ SbF_xCl_y\ (X = \text{halogen},\ x + y = 5,\ 0 \le x < 5 \text{ and } 0 < y \le 5) \qquad \mathbf{1}$$

$$Q^+SbF_6^- + (n - 1)\ SbF_xCl_y\ (x + y = 5,\ 0 \le x < 5 \text{ and } 0 < y \le 5) \qquad \mathbf{2}$$

This method is suitable for N-containing organic cations such as, for example, tetralkylammonium, alkylpyridinium, or dialkylimidazolium; for P-containing organic cations (e.g., tetralkylphosphonium for O-containing organic cation, such as trialkyl oxonium), or for S-containing organic cations, such as trialkylsulfonium.

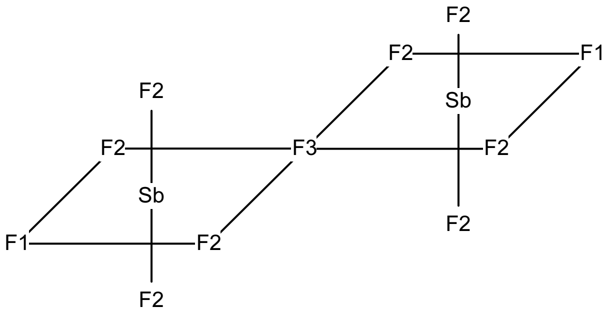
In the case of oxonium and sulfonium salts which are more sensitive to strong acidity, perfluorinated products can also be easily obtained by a solid–gas reaction. This reaction takes place between a solid perfluorinated salt ($Q^+BF_4^-$ or $Q^+PF_6^-$) and the desired number of SbF_5 in the vapor phase, with subsequent elimination of BF_3 or PF_5 [12].

5.2.2.6.5
Characterization of Superacidic Ionic Liquids Based on Sb

The compounds synthesized by the two methods described previously have been studied extensively by different spectroscopic techniques (Raman and ^{121}Sb,^{19}F NMR spectroscopies). This applies for dialkylimidazolium cations such as 1-butyl- or 1-ethyl-3-methylimidazolium ([BMIM] or [EMIM]).

$[BMIM]^+SbF_6^- + SbF_5$ (Compound S)

The comparison between the IR spectra of [BMIM][SbF_6] and compound **S** shows a new band for **S** at 491 cm^{-1} attributed to a μ-Sb–F–Sb bridge. However, no additional band is detectable on the Raman spectra, which means that this Sb–F–Sb bridge is linear. The ^{19}F NMR spectrum of **S** with SO_2ClF as solvent shows $Sb_2F_{11}^-$ and SbF_6^-. A peak (a singlet at –121.2 ppm) corresponding to SbF_6^- and three groups of peaks (a nonuplet at –92.5 ppm, $J_{F,F}$ = 62 Hz, a doublet of doublet at –115.8 ppm, $J_{F,F}$ = 102 Hz and a quintuplet at –138,1 ppm $J_{F,F}$ = 102 Hz) have been observed. These three groups of peaks correspond to three different F atoms present in a bimetallic dimer of two Sb atoms in hexagonal coordination sharing an F atom at one edge (Sb_2F_{11}) (see **3**).



3

The synthesis of **S** could be therefore described by the following equilibrium, which is similar to the one observed for the acid chloroaluminate IL [13].

$$Q^+SbF_6^- + SbF_5 \rightleftharpoons Q^+Sb_2F_{11}^- \qquad (4)$$

1 [EMIM]Cl + 1 or 2 SbF_xCl_y ($x + y = 5$, $0 \leq x < 5$ and $0 < y \leq 5$)

In this case, Cl atoms are involved in the reaction. Raman and ^{121}Sb,^{19}F NMR studies have proven that the 1 : 1 compound consists in a distribution of chlorofluoride anions involved in different equilibria [Eq. (5)]. Depending on the number of fluoride atoms available in the starting compound, equilibria are always driven to the formation of the most thermodynamically stable anion SbF_6^-.

$$2\ SbF_xCl_{y+1}^- \rightleftharpoons SbF_{x+1}Cl_y^- + SbF_{x-1}Cl_{y+2}^- \qquad (5)$$

For the 1 : 2 compound, the same equilibria are involved but uncharged species are also observed, leading to another redistribution of halogens in the compound which produces the most fluorinated anion possible [Eq. (6)].

$$[EMIM][SbF_xCl_{y+1}] + SbF_xCl_y \rightleftharpoons [EMIM][SbF_{x+1}Cl_y] + SbF_{x-1}Cl_y \qquad (6)$$

For example, the equilibrium for [EMIM]Cl + 2 SbF_5 proceeds according to the following Eq. (7).

$$[EMIM][SbF_5Cl] + SbF_5 \rightleftharpoons [EMIM][SbF_6] + SbF_4Cl \qquad (7)$$

In conclusion, reactions starting from hexafluoroantimonate or the chloride salt lead to the same compound and can be therefore described by Eqs. (8) and (9).

$$Q^+SbF_6^- + SbF_5 \rightleftharpoons Q^+Sb_2F_{11}^- \qquad (8)$$

$$Q^+Cl^- + (11 - x)\ HF + 2\ SbF_xCl_y \rightleftharpoons Q^+Sb_2F_{11}^- + (2\ y + 1)\ HCl \qquad (9)$$

5.2.2.6.6
Activity/Catalysis

Stoichiometric F/Cl Exchange

Cl/F exchange activity of such compounds has been investigated by testing them in stoichiometric Cl/F exchange with pentafluoroethane (CCl_3–$CHCl_2$) (see Table 1).

All ILs with the $Sb_2F_{11}^-$ anion (entries 2, 3, 4) show high activity in Cl–F exchange with little influence of the cation, while ILs with SbF_6^- anion are inactive (entry 5). However, $Sb_2F_{11}^-$ itself is not considered as a fluorinating agent. In the previous section, the presence of both $Sb_2F_{11}^-$ and SbF_6^- in ILs made from $Q^+SbF_6^-$ and SbF_5 has been justified by the existence of an equilibrium (10) (with a low K_1 constant), which therefore implies that SbF_5 would act as the real fluorinating agent.

$$Sb_2F_{11}^- \rightleftharpoons SbF_6^- + SbF_5 \qquad (10)$$

Table 1 Cl–F exchange activity of some ILs and SbF_5
(Q_1 = 1-butyl-3-methylimidazolium, Q_2 = trimethylsulfonium, Q_3 = trimethyloxonium, $CCl_3–CCl_2H$/ionic liquid = 1 : 1, $T = 60$ °C except for Q_3, when $T = 40$ °C).

Entry	*Reactant*	*Conversion [%]*	*Selectivity [%]*		
			($CFCl_2–CCl_2H$)	*($CF_2Cl–CCl_2H$)*	*($CF_3–CCl_2H$)*
1	SbF_5	100	3	60	37
2	$Q_1^+Sb_2F_{11}^-$	91	75	25	–
3	$Q_2^+Sb_2F_{11}^-$	95	63	37	–
4	$Q_3^+Sb_2F_{11}^-$	97	71	29	–
5	$Q_1^+SbF_6^-$	0	–	–	–

A previous study of Cl/F exchange activity between SbF_5 and chlorinated hydrocarbons such as CCl_3CH_2Cl [8] has shown that SbF_5 activity is ruled by equilibrium (11) (with a strong K_2 constant).

$$CCl_3CH_2Cl + SbF_5 \rightleftharpoons CFCl_2CH_2Cl + SbF_4Cl\ (K_2 > 1) \tag{11}$$

$Sb_2F_{11}^-$ activity is therefore ruled by the combination of equilibria (10) and (11) ($K_1 \cdot K_2 < K_2$), which explains the difference in activity observed between an IL with the $Sb_2F_{11}^-$ anion (entries 2, 3, 4) and SbF_5 itself (entry 1).

Catalytic F/Cl Exchange

This new range of ILs show a Lewis acidity and are able to realize Cl/F exchange. Figure 1 illustrates the average catalytic activity of the Sb(V)-based ionic liquids (IL on the graph) in batch conditions for liquid-phase fluorination with HF of dichloromethane to difluoromethane (F32) according to Eq. (12).

$$CH_2Cl_2 + 2\ HF \rightleftharpoons CH_2F_2 + 2\ HCl \tag{12}$$

For comparison, the activity of some typical liquid-phase fluorination catalysts ($TiCl_4$, $TaCl_5$, $SbCl_5$) are also plotted. The IL presents quite a good activity compared to typical catalysts such as $TiCl_4$ or $TaCl_5$ in the conditions cited above, but its activity is lower than that observed for $SbCl_5$.

However, interest in such ILs does not concern solely their activity but it includes their lower sensitivity to reduction of Sb(V) to Sb(III). Indeed, this reduction leads to inactive species and significant loss of yield due to necessary additional Cl_2 feed as an oxidant to prevent deactivation. Figure 2 compares the behavior of Q^+Cl^- + 2 SbF_5 with that of $SbCl_5$ in the absence of Cl_2 feed for the liquid-phase fluorination of trichloroethylene to 1-chloro-2,2,2-trifluoroethane [Eq. (13)].

$$CH_2{=}CHCl + 3\ HF \rightleftharpoons CF_3–CH_2Cl + 2\ HCl \tag{13}$$

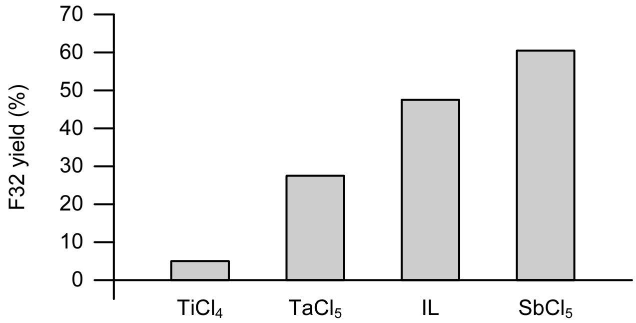


Figure 1 Liquid-phase fluorination of dichloromethane (F30), $T = 100$ °C, MR cat/F30 = 0.2, MR HF/F30 = 4, $P = 1$ MPa.

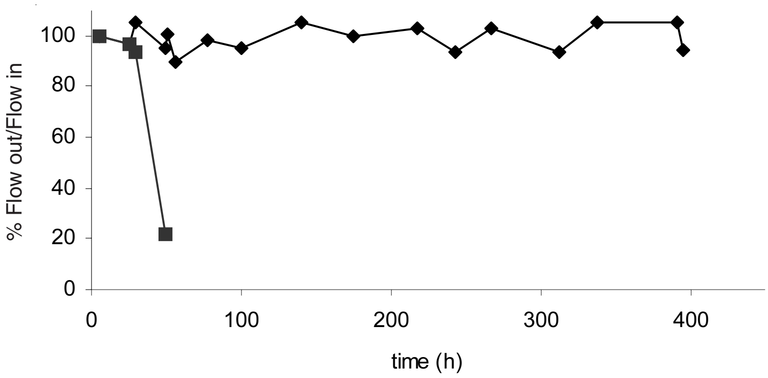


Figure 2 Liquid-phase fluorination of trichloroethylene (TCE), continuous run in the absence of Cl_2 feed (◆ $Q^+Cl^- + 2\ SbF_5$; ■ $SbCl_5$).

As expected, $SbCl_5$ shows a very fast deactivation after the Cl_2 feed stops, while the IL is able to run for more than 20 h without any deactivation, thus demonstrating the absence or at least the minimization of reduction of Sb(V) to Sb(III).

Finally, a specific Sb IL has been tested on a micropilot scale during at least 1000 h for the liquid-phase fluorination of trichloroethylene to 1,2-dichloro-2,2-difluoroethane (F132b) and 1-chloro-2,2,2-trifluoroethane (F133a). Selectivity to F132b and F133a has exceeded 99.5% without any noticeable deactivation after 1000 h.

In conclusion, all the data illustrate the potential of Sb(V)-based ionic liquids as catalysts to solve some of the main drawbacks raised by liquid-phase fluorination processes. In the future, they will probably be good candidates for the substitution of the current catalyst $SbCl_5$ in most of these processes.

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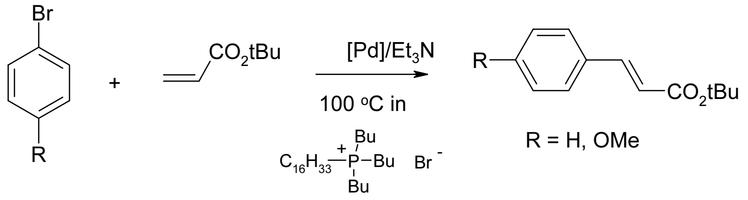
5.2.2.7
Application of Phosphonium Salts as Catalysts

James McNulty

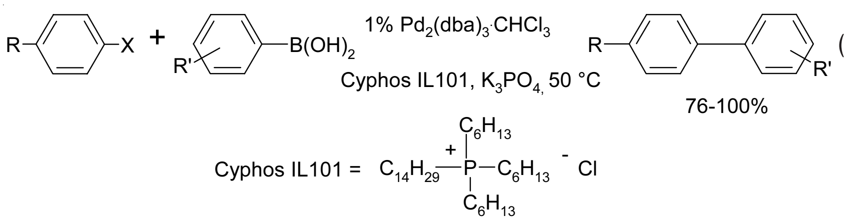
The use of nitrogen-based room-temperature ionic liquids (ILs) such as those based on simple ammonium, imidazolium, or pyridinium cores occupy center stage in the now voluminous literature pertaining to their use as reagents and solvents for a multitude of both catalytic and stoichiometric reactions [1–5]. This situation is no doubt due to the ready availability of quaternary nitrogen-based systems as well as the historical development of the field of molten salts [6]. Recently, the first multiton industrial process based on room-temperature IL technology involving a imidazolium salt as a hydrogen chloride scavenger was reported, representing a significant improvement in process chemistry [7] (cf. Section 5.3).

In contrast to this situation, few applications have been reported pertaining to the use of phosphonium salt ILs, several of which are now readily available in industrially relevant quantities [8].

One of the earliest reports on use of a phosphonium salt as an IL in such a process was that of Kaufmann and co-workers [9]. In this work, the use of tributyl(hexadecyl)phosphonium bromide as a recyclable medium for the palladium-mediated Heck coupling of aryl halides with acrylate esters was reported [9]. While these reactions proceeded without the use of an additive ligand, elevated temperatures (100 °C) were required and the process was most efficient only with more activated aryl halides [Eq. (1)]. More recently, the use of trihexyl(tetradecyl)-phosphonium chloride (Cyphos IL 101) has been reported as a useful medium for the Suzuki cross-coupling of aryl halides with boronic acid derivatives [Eq. (2)] [10]. In this process, a soluble palladium precursor such as $Pd_2(dba)_3$–$CHCl_3$ was dissolved in the phosphonium salt, forming a dark orange solution. This solution was stable in the absence of oxygen for an extended period of time and could be recycled after solvent extraction of the biaryl reaction products. Two advantages of this system are the milder conditions under which the Suzuki coupling takes place in comparison to imidazolium-based ILs and the reactivity of economical, readily available aryl chlorides. The Suzuki cross-coupling reaction requires ultrasonic irradiation in order to proceed at 30 °C in imidazolium-based ILs [11]. In addition, inactive palladium black is deposited during the reaction, resulting in lower yields of biaryl product even when reactive iodides and bromides are used, and more so with aryl chlorides. The use of imidazolium-type ILs in this manner is further compromised by the recent discovery that these solvents decompose when subjected to ultrasonic irradiation [12]. The purely thermal Suzuki coupling reaction does not proceed with aryl chlorides even at 110 C [13]. In contrast, the use of the phosphonium salt allows for very high conversion with all aryl bromides and iodides and electron-deficient chlorides at 50–70 °C. These results in conjunction with the recyclability of the palladium catalyst/IL indicate that the formation of a relatively stable and highly reactive palladium species occurs in this system. More recent work in our laboratories has shown that this same species is also very active in Heck coupling reactions [14]. While N-heterocyclic carbene complexes have been identified as being formed in situ when palladium species are dissolved in imidazolium-based ILs [5], the nature of the active palladium catalyst formed in the phosphonium salt cases remains uncertain. We are actively investigating the nature of the orange-coloured active catalyst that is generated in Cyphos IL 101 and are confident it will find application in other areas involving palladium catalysis.

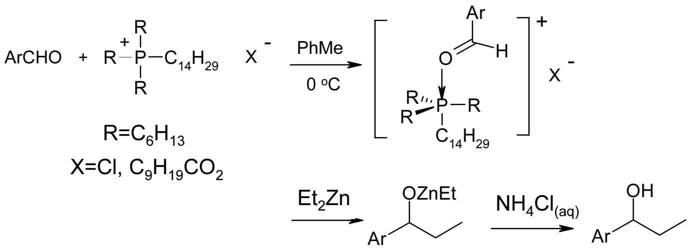


(1)



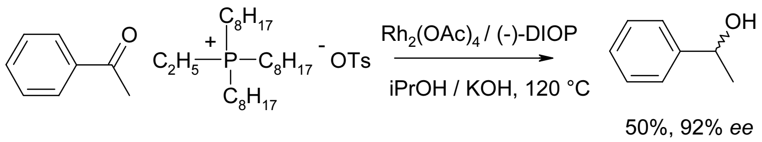
(2)

The above example illustrates how useful reactivity inherent in phosphonium salt ILs in comparison to nitrogen-based systems can be unraveled through reaction screening. We have engaged in a more systematic attempt to evaluate potential unique applications for phosphonium salt ILs. Our consideration of the nature and reactivity of phosphonium-based salts as catalysts or media for organic reactions, which differs or is not possible with nitrogen-based systems, led us to speculate that they might function as Lewis acids [15]. It was envisioned that due to the positive charge on phosphorus and ability to form a pentacoordinate phosphorane-type structure, unlike their nitrogen-based counterparts, such species might be able to coordinate carbonyl compounds, allowing activation of the carbonyl carbon toward nucleophilic addition (Scheme 1). As a test case for this reaction, we investigated the addition of diethylzinc to benzaldehyde [16] in various phosphonium salt ILs. The addition of 2 equiv. of diethylzinc to 1 equiv. of benzaldehyde in toluene at 0 °C resulted in less than 2% conversion after 24 h. It could be observed that addition of 0.1 equiv. (10 mol%) of Cyphos IL 101 results in a 47% isolated yield of the addition product under otherwise identical conditions. Through further screening of available phosphonium salt ILs [8] we determined that trihexyl(tetradecyl)phosphonium decanoate (Cyphos IL 103) was superior, giving 71% isolated yield of the addition product [17]. Although it is not clear why the decanoate counterion is a superior catalyst, since this does not affect the solubility of the nucleophilic species (diethylzinc) present, phase-transfer catalysis does not appear to be an option. It is more likely that the electronically diffuse decanoate couterion allows for further ion pair separation from the phosphonium ion, resulting in increased Lewis acidity. It is clear that the phosphonium salt is able to function as a *mild* Lewis acid catalyst (7.1 turnovers) under these conditions. In comparison, the use of the stronger Lewis acid BCl_3–Me_2S resulted in 100% conversion in a matter of several minutes. A recent publication describing the addition of trimethylsilyl cyanide to aldehydes promoted by triphenyl(methyl)phosphonium iodide may also involve Lewis-acidic carbonyl activation, although no hypothesis as to the mode of action of the catalyst was put forward [18].



Scheme 1 Postulated mechanism of phosphonium salt mediated carbonyl activation.

A wide variety of metal-mediated hydrogenation and hydroformylation processes have been reported in nitrogen-based room-temperature ILs [1, 2, 5] (see also Section 5.2.2.2). Phosphonium tosylates also have now been employed as solvents in the rhodium-catalyzed hydroformylation of olefins [19]. In addition to the advantage of catalyst recovery demonstrated in this solvent-free process, these phosphonium salts exhibited unprecedented effects on the ratio of linear to branched aldehydes produced in the reaction. This ratio was also affected by the addition of further quantities of triphenylphosphine to the reaction. Given the need for hydroformylation catalysts that exhibit high regioselectivity, this process may prove to be of great significance and appears to be worth a thorough investigation. The rhodium-catalyzed transfer hydrogenation of ketones has also been reported in phosphonium tosylates [Eq. (3)] [20]. Once again the potential recyclability of the expensive catalyst and ability to perform the hydrogenation under solvent-free conditions are sufficiently powerful incentives for the development of this process, which does not appear to have been described when conducted in nitrogen-based ILs. Although the yields reported could most likely be improved, these authors report that the addition of the chiral bidentate phosphine (–)-DIOP results in the transfer hydrogenation of acetophenone with 92% *ee* (50% yield), a remarkable result given that this reaction was performed at 120 °C. Lastly, it should be noted that the tetra*alkyl*phosphonium salt was required to effect asymmetric induction in this hydrogenation process, as salts composed of phenyl- and *p*-tolylphosphonium salts gave essentially racemic alcohols. Precisely how the phosphonium salt is involved in the asymmetric hydrogen-transfer process in the presence of DIOP is a fascinating question, to be explored.



(3)

The Diels–Alder reaction is another valuable transformation that has been actively investigated in a number of nitrogen-based ILs [1, 5, 21] as well as phosphonium salts [22, 23]. The reaction has been investigated with both acyclic 1,3-dienes as well as cyclopentadiene and with a variety of acrolein and acrylic acid dienophiles. Product yields are generally good to high in both the imidazolium and phosphonium salt IL classes, but *exo:endo* ratios are often low. High *endo* selectivities were achieved in imidazolium salt ILs when an additional Lewis acid, such as ZnI_2 or BF_3–OEt_2, was added as a co-catalyst [21]. Asymmetric versions of the Diels–Alder reaction have also been attempted using chiral C_2-symmetrical imidazolium salts but have so far met with low asymmetric induction [24]. These results are of significance to the understanding of how such imidazolium ions activate the dienophile in the reaction and of their possible involvement in the transition state. Overall, the advantages or disadvantages of using nitrogen-based or phosphonium salts as solvents for these cycloaddition reactions are not as yet clear, given the handful of publications that have appeared in the area. Given the mild Lewis acidity of phosphonium salts demonstrated in the catalysis of carbonyl addition reactions described above, there appears to be much potential for phosphonium salts in general, as both catalyst and solvent for the reaction, and possibly chiral phosphonium salts in promoting asymmetric cycloadditions.

In conclusion, it has been shown that the investigation of phosphonium salt ILs as solvents and catalysts can reveal advantages in comparison to nitrogen-based systems that may be rationally conceived or that may be unpredictable beforehand. It was demonstrated that an active, stable, and recyclable palladium species is generated upon dissolution of $Pd_2(dba)_3$–$CHCl_3$ in phosphonium salt ILs. This recyclable catalyst offers advantages in both Suzuki and Heck coupling processes and will no doubt find applications in other palladium-mediated processes as well.

Furthermore, it has been shown that phosphonium salts can act as mild Lewis acids, resulting in the activation of carbonyl compounds toward nucleophilic addition reactions. The result with trihexyl(tetradecyl)phosphonium decanoate (Cyphos IL 103) is currently being extended to other carbonyl addition reactions, to cycloaddition reactions such as the Diels–Alder process, and to the corresponding asymmetric variations. At present, it has been aptly demonstrated that phosphonium salts can furnish reactivity that is different or not generally accessible with the use of nitrogen-based ILs. Unusual effects on the regioselectivity of the hydroformylation reaction and an unprecedented catalytic asymmetric transfer hydrogenation protocol have also been demonstrated in phosphonium tosylate solvents, the latter process requiring a tetraalkylphosphonium salt to achieve up to 92% *ee*.

The unique reactivity of phosphonium salt ILs both as recyclable, solvent-free media for metal-catalyzed reactions and as mild Lewis acids in catalytic processes represents fertile ground for research that is still in its infancy. The discovery and development of many new applications of this newer subset of ionic liquids will continue at an accelerated pace over the next few years.

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5.3
Commercial Applications and Aspects

5.3.1
Difasol^{TM} Process

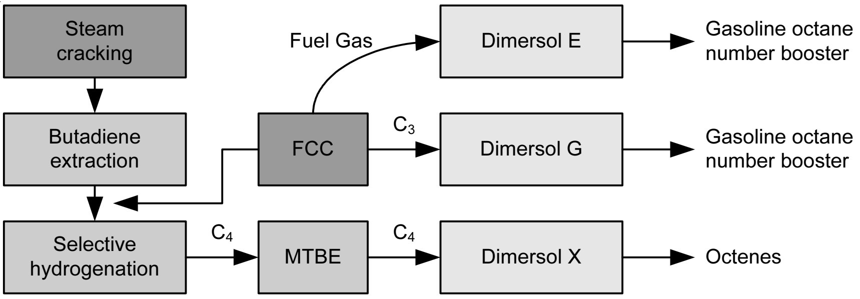
Alain Forestière and Frédéric Favre

5.3.1.1
Introduction

Refinery hydrocarbon cracking processes, such as steam cracking or catalytic cracking, produce significant amounts of light olefinic streams as co-products of ethylene/propene or gasoline. Dimerization and oligomerization reactions are widely used on an industrial scale to upgrade these light olefinic streams into heavier materials. These products find applications as fuels or as valuable petrochemicals [1].

In the mid-1970s, IFP developed such a process: the Dimersol^{TM} system. The homogeneous catalytic unit can be set out in different manners inside refinery and petrochemical complexes, depending on the available feedstock and desired products [2] (see Scheme 1).

- Dimersol G^{TM} converts a C_3 cut into a gasoline effluent having an excellent octane blending properties. This way, the dimerization reaction increases the yield of high-RON gasoline that can be obtained from a cracker.
- Dimersol E^{TM} is used to upgrade $C_2 + C_3$ fuel gas. Co-oligomerization of ethylene and propene leads to a gasoline stream very similar to the Dimersol G product. Mixed butenes are also obtained with Dimersol E (from ethylene dimerization). They can be used in paraffinic alkylation or to make propene through subsequent cross-metathesis reaction with ethylene.
- The Dimersol X^{TM} process has been developed to produce octenes as raw material for isononanol manufacture via oxo reaction.



Scheme 1 Dimersol units to upgrade light olefin cuts.

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5.3.1.2
One-Phase Butene Dimerization Process – Dimersol X^{TM}

5.3.1.2.1
The Reaction

Dimerization of *n*-butenes is carried out in a unique liquid-phase system, without any solvent, using a Ziegler-type catalyst based on nickel. The catalyst is activated by an alkylaluminum co-catalyst that acts as a Lewis-acidic alkylating agent on the nickel to produce a soluble nickel active species. In the case of a Ni(II) precursor, formation of the active species results from the transfer of an alkyl group from the aluminum to the nickel center, the β-elimination of an olefin, and the abstraction of an ionic ligand from the nickel center. The active species has been described by Wilke et al. in 1966 [3] as an ionic $[L_nNi(\mu^3allyl)]^+[AlCl_4]^-$ complex, where L is a two-electron donor ligand. This complex is submitted to a chemical equilibrium with its hydride equivalent $[L_nNi–H]^+[AlCl_4]^-$.

The ionic active nickel species initiates a degenerated polymerization mechanism (see Scheme 2, below). Olefin dimers predominate in the products due to a high rate of β-hydrogen abstraction on the organometallic intermediate. Trimers and tetramers are also produced, both by parallel growing chain reaction (involving the monomer) and by consecutive growing chain reaction (involving oligomers). Thus, at high monomer conversion, a high concentration of dimers induces increasing production of trimers and tetramers through the consecutive mechanism [4].

The overall kinetic of this dimerization reaction has already been described by Eq. (1), where the rate of reaction (r) is second order in monomer concentration ($[C_n]$) and first order in catalyst concentration ([Ni]):

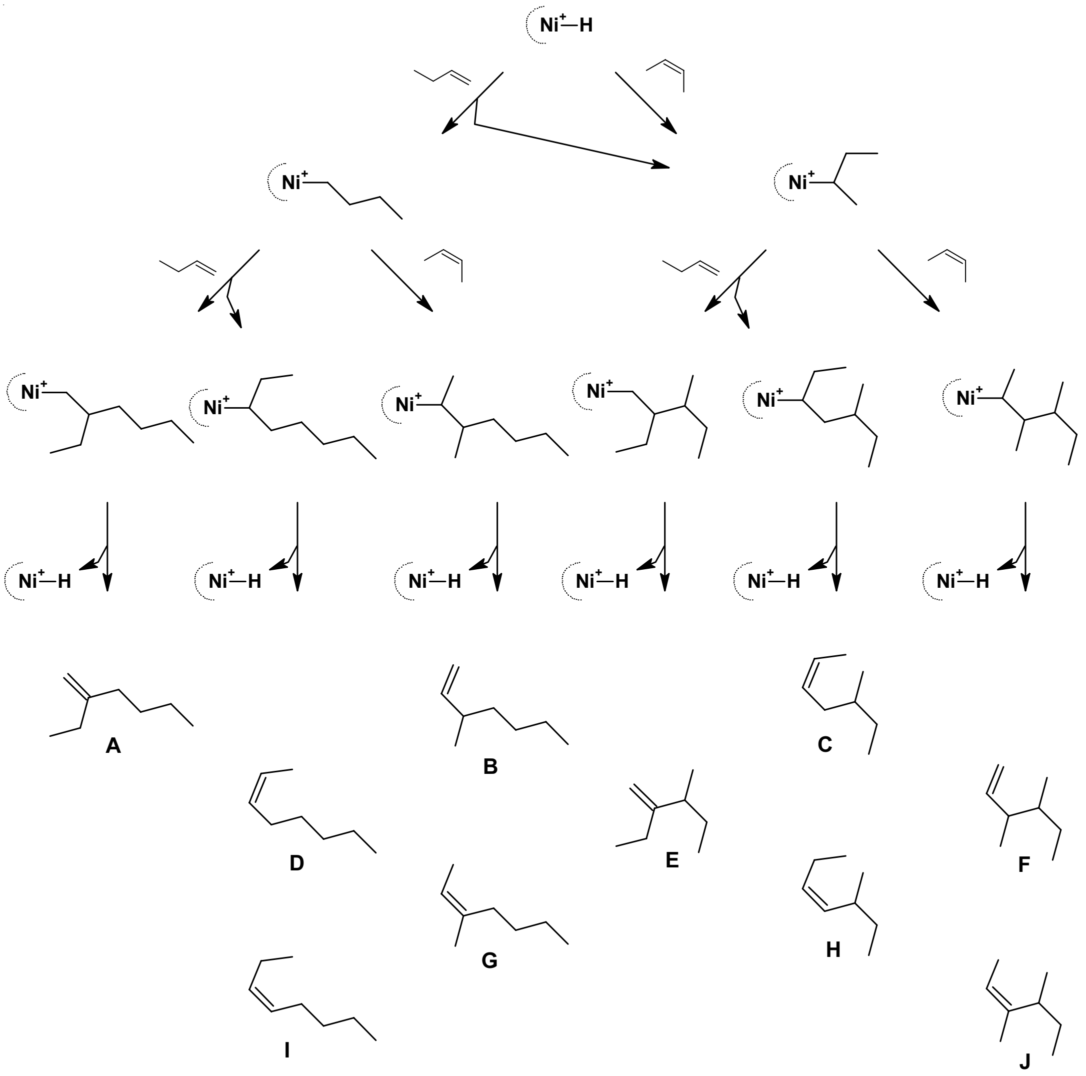
$$r = k_2\,[C_n]^2\,[\mathrm{Ni}]\ (n = 4, 8, \ldots) \qquad (1)$$

For any oligomer fraction, the distribution of isomers and the position of the double bond inside each structure depend on the catalyst composition [5]. Without any particular ligand introduced in the catalytic system, and for an isobutene-free feed, the C_8 isomers produced have the following distribution: 7% *n*-octenes, 58% methylheptenes, and 35% dimethylhexenes (see Scheme 2).

While the isobutene content in the C_4 feed is growing, the proportion of dimethylhexenes and higher branched isomers increases (Table 1), leading to an increase of the branched olefinic fraction.

Table 1 Composition of the Dimersol X^{TM} C_8 versus isobutene content in the feed.

Dimer produced	***Isobutene content in feed***	
	15%	***45%***
n-Octenes	5.5%	4.0%
Methylheptenes	53.5%	40.0%
Dimethylhexenes	39.0%	50.0%
Trimethylpentenes	2.0%	6.0%



Scheme 2 Butene dimerization by cationic nickel complexes. Reaction pathways for oligomer formation.

A 2-ethyl-1-hexene
B 3-methyl-1-heptene
C 5-methyl-2-heptene
D 2-octene
E 2-ethyl-3-methyl-1-pentene
F 3,4-dimethyl-1-hexene
G 3-methyl-2-heptene
H 5-methyl-3-heptene
I 3-octene
J 3,4-dimethyl-2-hexene

5.3.1.2.2
The Process [6]

In a typical refinery/petrochemical scheme, the crude cracker's C_4 cut is freed of its butadiene and selectively hydrogenated to remove acetylenics (Figure 1). The resulting raffinate-1 C_4 stream obtained is sent to an MTBE unit removing isobutene by reaction with methanol. The resulting raffinate-2, sometimes after de-iso-butanization, is a good feedstock for the Dimersol-X unit.

It should be noticed that the Dimersol catalytic system is sensitive to two types of impurities:

- Polyunsaturated hydrocarbons (dienes, acetylenics) that coordinate strongly to the Ni center and reduce its ability to coordinate olefins.
- Polar compounds (water, oxygen-, nitrogen-, and sulfur-containing compounds). They react with the organoaluminum co-catalyst (water, alcohols, amines, thiols), complex the aluminum center in a Lewis acid/base interaction (ketones, ethers, thioethers), or coordinate strongly to the nickel catalytic center (amines, sulfur compounds). They reduce the concentration of the active species and may be responsible of the formation of sludges in the reaction section.

Concentration of these impurities can usually be controlled through an MTBE plant by means of selective hydrogenation, dimethyl ether extraction, and drying of the feed. The C_4 cut generally engaged in a Dimersol-X plant contains from 70–90% olefins, the remaining part being paraffins.

The butene conversion level is highly dependent on its initial concentration. For instance, today commercial Dimersol-X technology achieves 80% conversion of butenes with up to 85% octene selectivity. A process flow diagram is depicted in Figure 1. The reaction takes place at low temperature (40–60 °C) in three or four consecutive well-mixed reactors. The pressure of 1.5 MPa is sufficient to maintain all reactants and products in the liquid state. Mixing and heat removal are ensured by an external recirculation loop over a heat exchanger system. The two components of the catalytic system are injected separately into this reaction loop under precise flow control. The residence time is between 5 and 10 h.

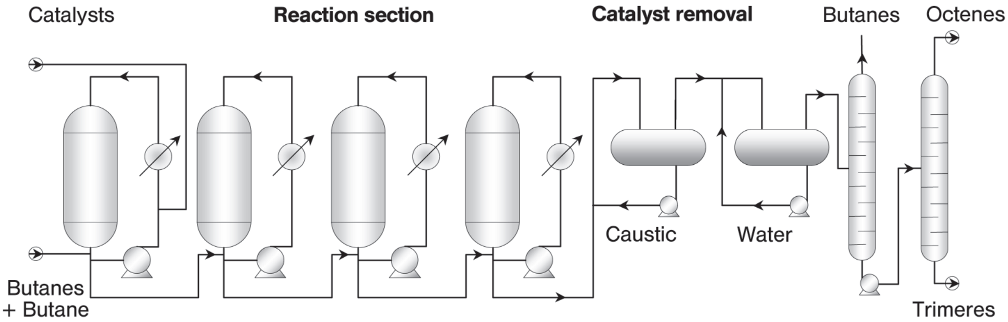


Figure 1 Dimersol scheme process.

At the output of the finishing reactor, the active catalyst is neutralized by anhydrous ammonia to avoid the formation of organic chlorides in the washing steps. Thereafter, the product stream is washed with a sodium hydroxide solution and water to remove the deactivated catalyst. The product stream is finally distillated to remove unreacted olefins and inert paraffins, which can be used as such (LPG) or sent back to the cracker. Octenes are also separated from the heavier oligomers. In some case, the trimers (dodecenes) can also be recovered.

5.3.1.2.3
Economics

Typical economics data are given in Table 2. Thirty-five Dimersol units treating various olefinic C_3 and C_4 cuts have been licensed, 25 of which are still in operation. Typical octene capacities range from 20 000 tpa up to 90 000 tpa.

In its present commercial form, Dimersol X produces octenes with a low branching index. This product quality allows higher reaction rates in subsequent hydroformylation units engaging octenes. It also leads to less branched isononyl alcohols and better plasticizer quality for PVC formulation. Furthermore, it should be noticed that Dimersol unit operation is quite flexible. The catalyst rate can be adjusted to the feed rate to maintain conversion and selectivity. As stated earlier, contamination of the feed can be accommodated partly by an increase in the catalyst injection rate. This contrasts with units using heterogeneous catalysts, where contamination of the feed can be irreversible and purity of the feed has to be higher.

Despite all these advantages, two limitations remain, i.e., the continuous catalyst carry-over by the products that implies disposal, and the conversion level for olefins is highly dependent on their initial concentration in the feed. These commercial limitations have been greatly overcome through Difasol two-phase catalysis technology.

Table 2 Dimersol economic data.

Feed [tpa]	
C_4 Raffinate-2 cut (75 wt.% *n*-butenes)	50 000
Products [tpa]	
LPG	18 200
Octenes	27 000
Dodecenes	3 200
Fuels	1 600
Battery limit costs[a)]	US$ 6 M
Utilities[b)]	
Electricity [kWh]	30
Cooling water [m^3]	50
MP steam [t]	0.5
Catalyst and chemicals[b)]	US$ 60

a) IBSL 2002 for a Gulf Coast Basis, excluding licenser fees and detailed engineering.
b) Per ton of octenes produced.

5.3.1.3
Two Phase Butenes Dimerization Process – Difasol^{TM}

5.3.1.3.1
The Biphasic System

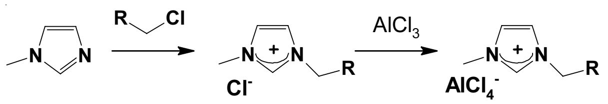
It has repeatedly been shown that biphasic liquid–liquid catalysis is highly attractive to solve the problem of homogeneous catalyst carry over [7]. The organometallic catalyst may be easily recovered in one liquid phase, whereas products and unconverted reactants remain in the second one. Thus, biphasic liquid–liquid reaction systems combine some advantages of heterogeneous and homogeneous catalytic systems; they allow a selective homogeneous-catalyst recycling (cf. Chapter 1).

Using such a catalytic system implies identifying a solvent that can achieve selective catalyst solubilization, with no impact on its activity. Two of these solvents are now used in industrial liquid–liquid biphasic catalytic processes: butane-1,4-diol in Shell's SHOP oligomerization process and water in Ruhrchemie/Rhône-Poulenc's olefin hydroformylation process.

Choosing a selective solvent for the catalyst is one of the most significant steps in the development of such a process. Due to moisture sensitivity and reactivity of the Dimersol alkylaluminum co-catalyst, protic media like butanediol or water are not suitable at all. At an early stage, Chauvin et al. anticipated that ionic liquids (ILs) could meet biphasic liquid–liquid solvent requirements [8].

Foreseeing the possibility of tuning the physico-chemical properties of these compounds by varying the nature of the anion and/or the cation, then taking into account the ionic state of the Dimersol catalyst, it was expected that ILs based on chloroalkyl aluminates would fit well. They do, indeed:

- Association of alkyl chloroaluminate anions with *N,N'*-dialkylimidazolium cations leads to salts that are liquid at low temperatures.
- These ILs are poorly miscible with octenes and longer olefins (this poor miscibility, actually, is the first prerequisite to form a biphasic system). Butene solubility is sufficient to stabilize the nickel active species and ensure high catalytic activity.
- These ILs can easily be prepared from commercially available *N*-alkylimidazolium, alkyl chlorides, and aluminum chloride (see below).
- These ILs can be turned acidic by adjusting the amount of aluminum chloride: Raman spectroscopy showed [9] that at $AlCl_3$/dialkylimidazolium molar ratios greater than 1, polynuclear $Al_2Cl_7^-$ and $Al_3Cl_{10}^-$ anions appear. They can dissociate into $AlCl_4^-$ and the Lewis acid $AlCl_3$.
- These chloroaluminate anions proved to be weakly coordinating toward nickel complex catalyst involved in our system. Moreover, the nickel active species is efficiently stabilized in the ionic medium, which plays both solvent and co-catalyst roles.
- The catalyst remains ionic and is retained without further modification.



Scheme 3 Imidazolium ionic liquid synthesis. R = H or alkyl group.

Chloroaluminate IL for IFP's Difasol reaction section can easily be prepared in two steps: firstly, the reaction of an alkyl chloride with *N*-alkylimidazole, and secondly, the direct reaction of the resulting *N,N'*-dialkylimidazolium chloride with aluminum chloride (Scheme 3). This synthesis has already been scaled up to several tens of kilograms using IFP's Lyon pilot plant facilities. The reaction conditions chosen allow an easy control of reaction exothermicity. Impurities or excess of volatile starting materials are removed during the reaction. The quality of the product obtained and the reasonable cost of the IL showed that production is ready for an industrial scale-up.

5.3.1.3.2
The Reaction

In the Difasol technology, the catalyst is dissolved in IL reaction products are poorly soluble. The reactants' miscibility remains adequate to ensure reaction. Batch laboratory experiments on butene dimerization demonstrated that no reaction occurs in the organic phase. This indicates that the reaction takes place at the interface or in the ionic liquid phase. Experiments also proved that rising the mixing efficiency increases the reaction rate but does not change the octene selectivity. So excellent mixing is necessary to ensure good conversion by rapid mass transfer and efficient interaction of the ionic catalyst with the substrate.

The main advantage of the biphasic Difasol process remains the ease of product separation that can be performed in a subsequent step. There is no co-miscibility between the products and the IL; thus, product separation by settling does not require heating and results in energy saving plus reduced loss of catalyst by thermal decomposition.

The Difasol biphasic system has been evaluated in terms of activity, selectivity, recyclability, and lifetime of the IL by continuous-flow pilot plant operation. During a typical run, feed in its liquid state enters continuously a well-mixed reactor that contains the ionic active phase. The effluent (a mixture of the two liquid phases) leaves the reactor via an overflow into a settler. The separation of the IL and the organic phase occurs rapidly and completely, favored by the difference in density. The IL containing the catalyst is recycled while the product stream is recovered and on line analyzed.

A first set of experiments showed that very small amounts of Al and Ni catalyst components are carried over by the organic stream. It appeared necessary to introduce continuously a nickel catalyst precursor and an alkylaluminum co-catalyst at a low rate to counterbalance this leaching. The flow rates of nickel and alkylaluminum are defined to maintain the butene conversion constant. As for

Dimersol, the active catalyst species is formed in situ in the reactor by alkylation of the nickel(II) salt introduced. It must be emphasized that, in this case, nickel consumption is lower than in a Dimersol system.

A continuous test-run engaging an industrially representative raffinate-2 feed (70% *n*-butenes, 2% isobutene, and 25% butanes) was then conducted. A productivity of 30 kg butenes converted/g Ni and 12 kg butenes converted/g IL was easily maintained over a period of 5500 h. During the whole test, butene conversion and octene selectivity were steady. The Difasol system achieved more than 70% butene conversion with 95% octene selectivity. This is five selectivity points higher than the classical Dimersol system. Moreover, unlike what is observed with Dimersol, octene selectivity remained higher than 90%, even at 80% butene conversion, which was easily obtained by increasing the catalyst concentration.

This steadiness of the selectivity with increased conversions can be ascribed to the low solubility of octenes in the ionic phase, compared to butene solubility. As soon as they are formed, octenes are extracted into the organic phase. The consecutive reactions involving the active nickel species dissolved in the IL are then minimized. Formation of trimers and tetramers is therefore disfavored.

Despite the importance of physical limitations such as solubility and mixing efficiency, an apparent reaction rate of order one relative to the olefin monomer could be determined experimentally. Another interesting result is the excellent activity obtained when diluted feedstocks are used. With Dimersol-X technology, olefin conversion is highly dependent on its concentration in the feed. In contrast, Difasol performances are maintained over a wide range of butene concentrations, without changing catalyst consumption (Table 3). Finally, whatever butene conversion is, for less than 2 wt.% isobutene in the feed, the C_8 isomer distribution remains equivalent to the distribution classically reported for the Dimerol process, i.e., 5.5% *n*-octenes, 55.5% methylheptenes, and 39.0% dimethylhexenes. Therefore low-branched octenes produced by the Difasol reaction have the same high quality and are good feedstock for oxo syntheses.

The test was deliberately stopped after 5500 h. Compared to the Dimersol one-phase system, the Difasol nickel consumption was ten times lower and the co-catalyst consumption twice as low. No additional fresh IL was required. This definitely demonstrated the stability of the chloroaluminate IL under dimerization conditions.

Table 3 Effect of butene feed dilution on Difasol catalytic performances.

Butene concentration [%]	*Conversion [%]*	*Dimer selectivity [%]*
20	65–70	> 92
40	65–70	> 92
60	65–70	> 92

5.3.1.3.3
The Process [10]

The Difasol reaction section (Figure 2) intended involves a mechanically stirred reactor and settlers. An injection of fresh catalyst components is defined to compensate the detrimental effects of accidental impurities present in the feed and slight carryover of the catalyst.

As the mixing of the two phases proved to be an important parameter for the reaction rate during experiments, it was concluded that the reactor should be mechanically stirred rather than a loop reactor. Mixing of the solvent phase and the organic phase will ensure advantageous butene conversion.

However, important stirring power conjugated with a high ratio of IL can result in longer decantation time. Therefore, in order to combine efficient decantation and a reasonable size for the settler, it has been proposed that the separation of the product phase should be performed in two distinct settling zones arranged in parallel [11]. One settler has a moderate residence time and returns the ionic phase to the reactor while the organic phase is recirculated via a pump through a heat exchanger. The other settler has a more limited residence time and sends product phase to the neutralization section.

The Difasol catalyst is concentrated and operates in the ionic phase, or maybe at the phase boundary. The reaction volume is therefore much lower than in the conventional one-phase Dimersol process, where the catalyst concentration is very low. The Difasol reactor volume can be downscaled 15-fold compared to the classical one-phase Dimersol-X process.

Several different process schemes including this Difasol reaction section have been envisioned.

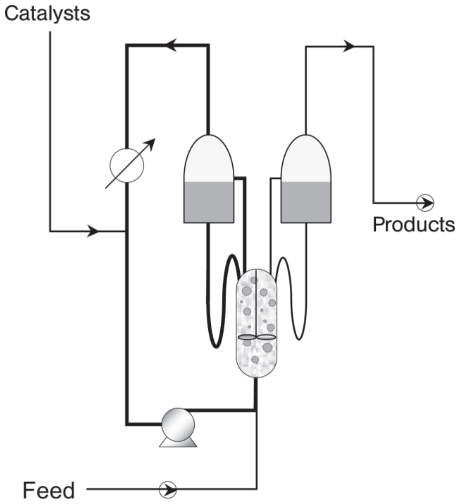


Figure 2 Difasol reaction section.

Dimersol and Difasol Package

In this scheme, Difasol is ideally placed as a finishing reaction section of a one-reactor Dimersol unit (Figure 3). The design consists of a first homogeneous Dimersol dimerization step (1), a vaporization–condensation section (2), and a biphasic dimerization section (3).

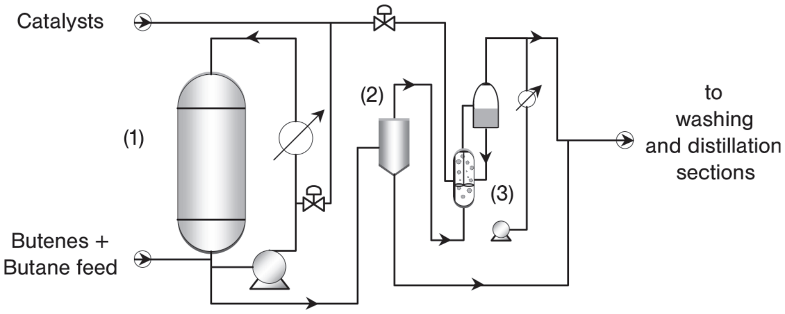


Figure 3 Dimersol + Difasol package reaction section scheme.
(1) Dimersol reactor; (2) Vaporization-condensation; (3) Difasol reactor.

The catalyst injection rate is decreased in the one-phase Dimersol reactor to provide low butene conversion. The effluent from the Dimersol reactor is partly vaporized to separate unconverted C_4 cuts from octenes. Products and catalyst are sent to the neutralization section while the vapor phase is condensed and sent to the Difasol reactor. Butene conversion is achieved with less catalyst and more selectivity, thanks to the biphasic system. This [Dimersol + Difasol] combination, which uses the same Dimersol catalytic system, improves the yield of octenes by about 10% with a lower consumption of nickel.

It should be noticed that, in such a combination, the one-phase Dimersol reaction totally purifies the Difasol feed from impurities that could potentially be accumulated in the IL.

This particular combination of a one-phase and a two-phase technology is possible because of high Difasol efficiency on the diluted feed recovered from the Dimersol reactor. This arrangement is suitable either for grass-roots units or for upgrading of existing Dimersol-X units. It considerably reduces the overall unit volume compared to existing (up to four-reactor) Dimersol-X units. It also induces lower catalyst consumption, i.e., lower catalyst and disposal costs (Table 4).

Table 4 Comparison of performances on 75 wt.% butenes feed.[a)]

	Dimersol (4 reactors)	*Dimersol/Difasol integrated concept (1 Dimersol + 1 Difasol reactor)*
C_8 yield	66%	73%
Relative nickel consumption	100%	70%

a) Nickel consumption is disclosed as a percentage comparison with the actual nickel consumption in an already existing Dimersol process (4 reactors).

Difasol Standalone System

In a second scheme, there may be only one Difasol reaction section. For such a grass-root unit, Difasol Standalone, the main concern is how to protect the chloroaluminate ionic liquid.

The proper pretreatments are highly dependent on the origin of the feed. Fortunately, the current poisons of chloroaluminates salts are similar to well-known Dimersol catalyst containments.

These are protic compounds (such as water and alcohols), nitriles (such as acetonitrile and propionitrile), common pollutants of FCC C_4 cuts, aprotic solvents (coming from butadiene extraction processes), oxygenates (namely dimethyl ether and *tert*-butyl ethers from the upstream isobutene extraction), mercaptans, sulfides, and disulfides. They all have to be eliminated. Acetylenics and dienes must be severely limited. The lower the content of these pollutants in Standalone Difasol feedstock, the longer the chloroaluminate IL lifetime.

The best arrangement, to remove these poisons as deeply as possible, includes a water wash with condensed or feed boiling water, followed by a water removal device. Currently a simple azeotropic and de-isobutanizer is recommended. The dry feed is then treated with the proper molecular sieves in order to remove both oxygenates and sulfur compounds. It should be noticed that all these feedstock treatments are also recommended to minimize classical Dimersol catalyst consumption, but using Standalone Difasol leads to more severe treatments and therefore higher investment and chemical expense. Table 5 summarises the main acceptable poison contents in the Dimersol + Difasol arrangement and in the Standalone Difasol configuration.

Table 5 Acceptable poison contents [ppm] in feedstocks.

	Water	*Nitrogen*	*Oxygenates*	*Sulfur*	*Dienes and acetylenes*
Dimersol + Difasol	0.5	5	5	1	10
Difasol Standalone	0.5	0.1	0.5	0.1	1

Comparisons

Rather than a purification section, a Standalone Difasol plant also requires a larger biphasic reactor than a Dimersol + Difasol unit. For instance, a 160 000 tpa C_4 cut unit requires a 50 m^3 Difasol reactor when it operates in Standalone mode and only a 30 m^3 reactor when it works as a conversion achiever. Table 6 shows a simplified mass-balance comparison for a Dimersol process, a Dimersol + Difasol arrangement, and a Standalone Difasol unit.

Both butene conversion and octene selectivity are clearly improved using Dimersol + Difasol arrangement, while Standalone Difasol appears to be able to achieve the best octene selectivity with the lowest butene conversions.

Table 6 Unit performances: butene conversion and oligomer selectivities.[a)]

	Dimersol unit (4 reactors)	*Dimersol (1 reactor) + Difasol arrangement*			*Difasol Standalone*
		Dimersol reactor	*Difasol reactor*	*Global arrangement*	
Conversion [%]	80	50	75	82	75
Selectivity [%]					
Octenes	82	89	91	90	91
Dodecenes	14	10	8.5	9	8.5
Hexadecenes	4	1	0.5	1	0.5

a) Feed 160 000 tpa; 75 wt.% butenes; isobutene max. 5%; iso-investment per ton of octenes.

In fact this last remark results from the constraint on iso-Capex per ton of octenes. Of course, Standalone Difasol can achieve higher butene conversion (more than 85% is feasible), still with 91% octene selectivity.

Table 7 gives a Capex comparison for the three unit arrangements mentioned above, taking into account the same constraint: all units have the same Capex per ton of octenes. Table 8 gives the Opex data for the three-unit arrangements using the same constraint. Clearly, both Dimersol/Difasol and Standalone Difasol furnish an interesting opex (operating expenditures – unit operating costs) economy.

Table 7 Unit Capex estimation.[a)]

	Unit configuration		
	Dimersol (4 reactors)	*Dimersol (2 reactors) + Difasol*	*Difasol Standalone*
Feed purification section [%]	10.3	10.3	25.5
Reaction section [%]	46.6	41.5	24.0
Distillation section [%]	20.2	20.2	20.2
Catalyst section [%]	5.0	5.0	5.0
Catalyst removal section [%]	17.9	17.9	17.9
Difasol cooling section [%]		7.7	11.0
Total unit investment [%] *(a)*	100	102.6	103.6
Butene conversion [%]	80	82	75
Octene selectivity [%]	82	90	91
Octene yield [%] *(b)*	66	73	68
Relative Capex per ton of octenes (a/b)	1.5	1.4	1.5

a) Feed 160 000 tpa; 75 wt.% butenes; isobutene max 5%; iso-investment per ton of octenes. Unit investment cost is disclosed as a percentage comparison with already existing Dimersol X process (4 reactors).

Table 8 Unit operating costs: chemicals and utilities consumption [%].[a)]

	Dimersol (4 reactors)	*Dimersol (2 reactors) + Difasol*	*Difasol Standalone*
Chemicals	90.7%	74.2%	46.6%
Cooling water	2.1%	2.1%	0.9%
Steam MP (distillation)	6.7%	9.7%	8.3%
Electricity	0.5%	0.7%	0.9%
Difasol cooling		3.9%	10.9%
Total unit	100.0%	90.5	67.6
Consumption per ton of octenes	1.5	1.3	1.0

a) Feed 160 000 tpa; 75 wt.% butenes; isobutene max. 5%; iso-investment per ton of octenes. Unit operating costs are disclosed as a percentage comparison with already existing Dimersol X process (4 reactors).

Standalone Difasol allows both interesting chemical consumption and flexibility in terms of octene production, just by tuning the chemical consumption, when compared with the classical Dimersol process.

5.3.1.4
Outlook for Higher Olefin Dimerization

For many years, oligomerization has been performed essentially using acidic catalysts economically interesting owing to their low price and low sensitivity to impurities. However, as envisioned here, biphasic IL dimerization reactions catalyzed by coordination catalysts offer the benefits of both homogeneous and heterogeneous catalysis. They combine mild operating conditions, high selectivity, and easy separation of catalyst from reaction products with better use of catalyst. The Difasol system makes it possible to reach a broader spectrum of activity and selectivity with optimized catalyst consumption and waste disposal.

Unlike Dimersol, the new biphasic system gives good results on less reactive feed such as C_5 cuts or mixtures of C_4 and C_5 cuts. Table 9 shows high conversion of one typical branched C_5 olefin during a batch test. Additional tests on a pilot plant indicate the possibility of achieving selectivity greater than 50% in nonenes and decenes through $C_4 + C_5$ co-dimerization.

Table 9 Dimerization of 2-methyl-2-butene: batch experiments.

Operating condition	*Dimersol*	*Difasol*
Ni engaged	1	0.33
Reaction time [h]	1	0.25
Conversion [%]	17	81
Dimer selectivity [%]	> 85	> 90

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5.3.2
BASIL^{TM} Process

Matthias Maase

5.3.2.1
Ionic Liquids in Industry

Since the end of the 1990s, ionic liquids (ILs) have faced a tremendous amount of interest from the scientific community [1]. They have turned out to be novel materials providing unusual new properties that simply had not been available before. In 1999, laboratory quantities of ILs became commercially available for the first time. This opened the door to the use of these materials for a whole variety of research groups, especially for those who do not concentrate on preparative chemistry but, for example, work on material science or physical properties. However, this initiated even more scientific work within the field, which can be measured by the more than exponentially growing number of scientific papers [2]. Numbers of potential applications of ILs have been described, and many suggestions have been made. For a long time only one of them – IFP's Difasol process (see Section 5.3.1) – had been developed to a pilot plant stage and offered for licensing [3]. Nevertheless, the scientific community expected the first large-scale application to appear very soon. What would most people have expected to be the first probable industrial application of ILs? Most likely a majority would have expected ILs to be used as alternative solvents replacing classical solvents in existing processes. This is how ILs are still perceived today: as alternative solvents. However, their potential is much greater than that and it is not surprising that BASIL$^{\mathrm{TM}}$ (biphasic acid scavenging utilizing ionic liquids), the first reported commercial process, utilizes them as functional materials. With BASIL$^{\mathrm{TM}}$ ILs are formed during a chemical reaction while performing a valuable function: they scavenge a byproduct that would decompose the desired one. They also influence the reaction rate and selectivity, and are subsequently exploited as a liquid – not a solvent – that entirely separates off from the product as an immiscible liquid phase.

Nobody would have predicted this application, but this shows that ILs can be smart and simple solutions to complex problems including chemistry, process engineering, and separation technology.

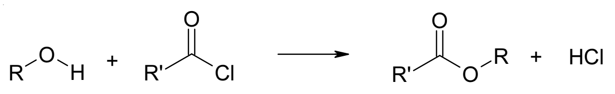
5.3.2.2
Solids and Suspensions

The handling of solids is a true challenge in large-scale industrial processes although it might not be obvious to academic groups. Perhaps it is even more challenging than the handling of volatile or highly reactive species as the problems related to solids, especially to suspensions, often do not occur in a reliable way. But what is wrong with suspensions?

- They often make reaction mixtures much more viscous, leading to insufficient mixing of the reactants.
- Heat transfer within large vessels containing suspensions is often less than satisfactory, so hot spots may occur.
- This in turn favors side reactions and lowers the yield of the desired product.
- It is difficult to transport suspensions through piping or to store them in tanks. In both cases a high flow rate or agitation is necessary to prevent the suspension from settling and plugging the system.
- Separation can also be an important issue. If a solid is formed during a reaction as an unwanted byproduct it must be removed afterwards.
- Reactors that are designed to deal with suspensions are usually more complex and expensive than those suitable for pure liquids.
- Finally, if a solid is generated during a reaction, scale-up is far from easy. One can hardly predict now the solid will appear when it is prepared in a 10 m^3 reactor rather than in a 100 mL flask. This can easily cause serious problems, for example, a solid that could be filtered off in a minute in the laboratory now takes two days on the large scale just because particles are several orders of magnitude smaller than expected.

5.3.2.3
Acid Scavenging

One example in which industrial chemists have to deal with suspensions is acid scavenging. Browsing organic textbooks one will find numerous reactions which liberate acids that have to be scavenged in order to prevent decomposition of the product or other side reactions. Equations (1) to (6) show some common acid – liberating reactions, namely esterfication, elimination, phosphorylation, sulfurylation, silylation, and deprotonation, respectively.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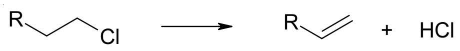
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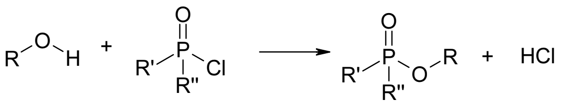
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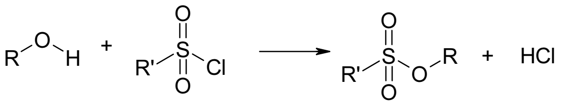
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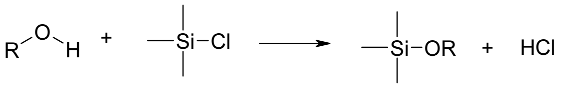
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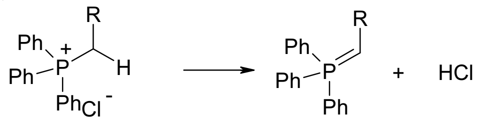
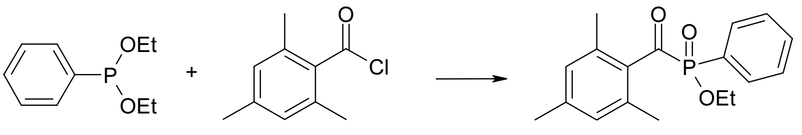

(6)

In some cases, acid scavenging is not used to stop further reactions of the acid, but to shift an existing equilibrium to the favored side. This is true for elimination reactions or the formation of ylids that are further used in Wittig reactions. Hydrochloric acid (HCl) is the acid most commonly formed. Usually, tertiary amines such as triethylamine are added to scavenge the acid. With the acid, these substances form solid salts which turn the reaction mixture into a suspension. The solid byproduct must then be removed. This can be done via a filtration step which requires expensive equipment, especially for precipitates with high filter resistances or continous filtration. If the product is inert to and insoluble in water, one can dissolve the solid by adding water to the reaction mixture, and remove the organic phase by a simple liquid–liquid separation. If the product is sensitive to acids and moisture, until now only filtration was left as a suitable means.

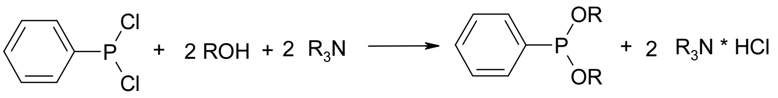
5.3.2.4
Synthesis of Alkoxyphenylphosphines

Alkoxyphenylphosphines are important raw materials in the production of BASF's Lucirines® [Eq. (7)], substances that are used as photoinitiators to cure coatings and printing inks by exposure to UV light (Figure 1).



(7)

HCl is formed during the synthesis of diethoxyphenylphosphine [Eq. (8)]. If the acid is not scavenged it undergoes an Arburzov-like reaction with the product to give the undesired ethyl ester of phenylphosphinic acid and chloroethane [Eq. (9)].



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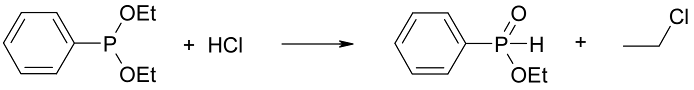
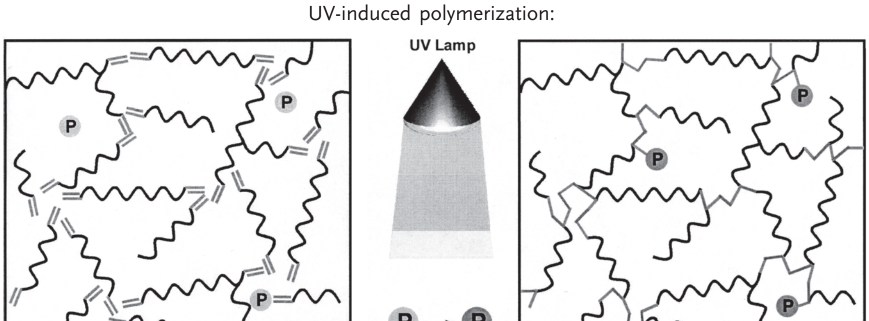


(9)

Scavenging with a tertiary amine results in a thick, nonstirrable slurry (Figure 2). The problems mentioned earlier significantly lower the yield and capacity of the process. In order to provide a minimum of mixing and heat transfer of the exothermal reaction, a solvent has usually to be added.


UV-induced polymerization:

Low molecular – liquid

Crosslinked-solid

Figure 1 Photocuring of coatings: a low molecular liquid containing olefinic unsaturated double bonds and a photoinitiator is irradiated with UV light. Upon irradiation the photoinitiator is cleaved into two radicals that start polymerization leading to a crosslinked polymeric solid (© BASF Aktiengesellschaft 2000).

Figure 2 Slurry that is formed when a tertiary amine is used as an acid scavenger (© BASF Aktiengesellschaft 2003).

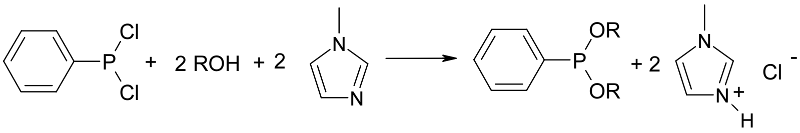
During the work-up of the reaction mixture the solid has to be removed via filtration. Alkoxyphenylphosphines are sensitive to hydrolysis, which makes addition of water in order to dissolve the salt unsuitable.

5.3.2.5
Ionic Liquids (Dis)solve the Problem

If an acid has to be scavenged with a base, the formation of a salt cannot be avoided, but why not form a liquid salt – a so-called ionic liquid? The properties of ILs (see Section 5.1) are:

- they are salts, consisting 100% of ions;
- they are liquid at temperatures below 100 °C.

As they are rather polar materials they often do not mix with solvents or nonpolar product molecules. Using the BASF product 1-methylimidazole as an acid scavenger, an ionic liquid is formed: 1-methylimidazolium chloride (HMIMCl), which has a melting point of about 75 °C [Eq. (10)].



(10)

After the reaction two clear liquid phases occur (Figure 3) that can easily be separated. The upper phase is the pure product – no solvent is needed any more – and the lower is the pure IL [2, 6]. HMIMCl as an IL has a great advantage over the classical dialkylated systems: it can be switched on and off just by protonation and deprotonation. This is crucial when recycling and purification of the ILs are considered. To distinguish the switchable ILs – the “HMIM” – from the conventional ones, Freemantle used the term “smart ionic liquids” in the context of the BASIL™ process [4].

Figure 3 The BASIL™ process. After the reaction two clear liquid phases are obtained; the upper one is the pure product and the lower is the ionic liquid HMIMCl (© BASF Aktiengesellschaft 2002).

5.3.2.6
Lesson Learned

Several success factors were responsible for BASIL™ being established in routine production so quickly.

- First of all there was an existing problem – the formation of unwanted solids – to which the unique properties of ILs offered a tailor-made solution.
- The lead structures of ionic liquids – the imidazoles – were known from academic research already, so industry did not have to reinvent the wheel.
- The material (1-methylimidazole) was available in large quantities within the company, since it was an existing BASF product.
- The process has been improved dramatically in terms of reliability and safety.
- There were clear economic benefits from BASIL™: higher chemical and higher space–time yields.
- BASIL™ was suitable as a drop-in solution with respect to the existing equipment and simultaneously provided a debottlenecking of the setup.

Finally, one should not forget to mention that luckily the chemistry worked as well. Further investigations revealed that BASIL™ is not restricted to phosphorylation chemistry but is a general solution to all kinds of acid scavenging [5]. Acylations and silylations have been run succesfully as well as an elimination reaction. BASIL™ is also applicable to extractive acid removal from organic phases, for example, for the purpose of purification.

5.3.2.7
BASIL^{TM} is More than Just Acid Scavenging

Methylimidazole is doing a perfect job by scavenging the acid. Looking closer at it, one may find that methylimidazole also helps in setting the acid free. In other words: it acts as an nucleophilic catalyst [7]. BASF has discovered that the phosphorylation reaction completes itself in less than a second. Having eliminated the possibility of the formation of any solids, and having increased the reaction rate, new reactor concepts were made possible. It is now possible to do the same reaction that has been done in a large vessel in a thumb-sized jet reactor. In this way the degree of productivity of the process has been risen by a factor of $8 \cdot 10^4$ to 690 000 kg m^{-3} h^{-1}.

This progress can be attributed to the existence of a new class of novel, promising materials: ionic liquids.

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5.3.3
Production (and Disposal) of ILs on a Large Scale

5.3.3.1
Industrial Aspects of Ionic Liquids

Markus Wagner and Marc Uerdingen

A growing number of scientists and engineers are attracted by the fascinating properties of ionic liquids (ILs) as they have begun the transition from curiosities to commodities [1].

The introduction of tetrafluoroborate [2] and hexafluorophosphate [3], based ionic liquids, and especially the development of their synthesis by means of metathesis from alkali salts [4], can be regarded as key steps toward commercial IL production.

This commercial availability of ionic liquids has become an important factor for the success of ILs methodology, as can be seen in the rising number of publications on ionic liquids (about 60 in 1998 to more than 1400 in 2003). Besides Solvent Innovation [5], the first commercial supplier, a number of others now offer ILs as well, the majority based on imidazolium cations.

Solvent Innovation currently commercializes 22 different ILs on a multi-kilogram scale. One of them, the quaternary ammonium sulfate ECOENG-500-™, is the first EINECS-registered IL which is available on a ton scale. We believe that one or two more ILs, most likely the halogen-free ones, will make their way through the registration process and be produced on a ton scale by 2006. Through the recently established strategic partnership of Solvent Innovation with Degussa, we will be able to fulfill all requests for quantities on a ton scale after a given lead time.

During 2003 we saw the first published process based on ILs [6]. In its BASIL process (see Section 5.3.2), BASF has disclosed the involvement of an imidazolium-based ionic-liquid in the production of alkoxyphenylphosphines. This constitutes an impressive demonstration that IL technology can result in significant financial savings. Another process said to be poised for licensing is the French Petroleum Institute's butene dimerization process, the Difasol process (see Section 5.3.1). Besides these, some more promising applications are currently under investigation, and are hoped to be disclosed in the near future. Notable examples of research areas are in electrochemistry (batteries), biocatalysis, and the application of ILs in extraction processes, e.g., the deep desulfurization of diesel oil.

The above-mentioned processes reflect the typical needs of industry before they establish ILs on an industrial scale [7]. The driving force is of course cost reduction which results from improved reaction rates and thus higher space–time yields. In this context the price of ILs can still be a limiting factor, but this cost has to be weighed against technological and economic benefits. We expect the prices of ILs to drop significantly when larger quantities are employed. The anticipated price of cation systems based on imidazole will be in the range of 50–100 Euros/kg. It should be possible to produce ILs with cheaper cation sources on a ton scale for prices below 25 Euros/kg. Halogen-free systems made from cheap anion sources are expected to meet this target first.

Before the scale-up of IL synthesis is attempted, a number of different criteria have to be considered. Quality of starting materials and products alike is a key factor. Furthermore, commercial availability and price of the starting materials have to be taken into account too. For the scale itself, aspects as the heat management (alkylation reactions are exothermic) and proper mass transport are crucial.

Another important issue is the disposal of ILs. So far very little research has been carried out into evaluation of the biological effects of ILs, but toxicological aspects are under investigation [8] (see also Section 5.4). It should be noted that for most applications ILs have very long lifetimes. However, if disposal should be necessary, combustion will probably be the method of choice (although ILs are not flammable, they can be burnt at temperatures above their decomposition temperature). This underlines again the advantages of halogen-free ILs as they cannot form HF under combustion conditions.

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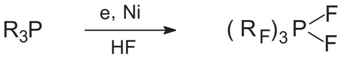
5.3.3.2
New Ionic Liquids with Stable Fluorinated Anions

Nikolai V. Ignatev and Urs Welz-Biermann

Commonly used ionic liquids (ILs) with hexafluorophosphate, PF_6^- (hydrophobic), or tetrafluoroborate, BF_4^- (hydrophilic), anions are hydrolytically unstable, especially when heated [1].

Recently, Merck KGaA (Darmstadt, Germany) has developed convenient methods of synthesis of ILs with the tris(perfluoroalkyl)trifluorophospate anion (FAP anion) as a replacement for PF_6^- and with the triflate, $CF_3SO_3^-$ anion, as replacement for BF_4^-.

The synthesis of the FAP anion is based on the electrochemical fluorination (industrial method) of trialkylphosphines [Eq. (1)] [2–4].



1

(1)

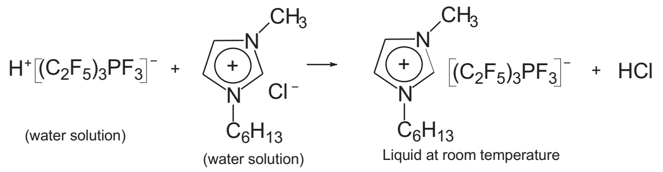
Yield: 49–74%

$R = C_2H_5$; C_3H_7; $n\text{–}C_4H_9$
$R_F = C_2F_5$; C_3F_7; $n\text{–}C_4F_9$

Tris(perfluoroalkyl)difluorophosphoranes (**1**) are very active compounds. They react readily with organic or inorganic fluorides [5–8] with formation of the corresponding salts with a FAP anion. The fluoride affinity of tris(perfluoroalkyl)difluorophosphoranes is so high that by the reaction with HF in water the hydrolysis of phosphoranes practically completely suppressed and the corresponding tris(perfluoroalkyl)trifluorophosphoric acid (**2**) is formed in nearly quantitative yield [Eq. (2)] [9].

$$(C_2F_5)_3PF_2 + HF + 5\,H_2O \longrightarrow \underset{\mathbf{2}}{[(C_2F_5)_3PF_3]^- H^+ \cdot 5\,H_2O} \qquad (2)$$

Acid (**2**) is a convenient starting material for the synthesis of various salts [9] with ILs properties, for instance by Eq. (3).

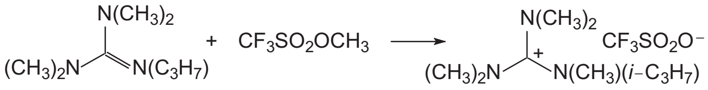


3

(3)

The salt **3** is not soluble in water and can be easily separated from the reaction mixture as the bottom liquid phase. After washing and drying, HMIM FAP **3** can be obtained with a very low content of chloride and residual water (10–15 ppm). HMIM FAP is a hydrophobic room-temperature IL, which possesses high hydrolytic stability (no detectable HF formation after 5 h of boiling in water) and a large electrochemical window (more than 5.5 V). The viscosity of HMIM FAP is comparable with the viscosity of HMIM BTFMS-imide.

Synthesis of ILs with triflate anion is based on direct alkylation of amines, phospines, or heterocyclic compounds with alkyl triflates, CF_3SO_2OR. The convenient synthesis of alkyl triflates was recently [10, 11] also developed by Merck KGaA. Alkyl carbonates are serving as a source of alkyl groups in the preparation of CF_3SO_2OR [10, 11]. Alkyl triflates are very strong and convenient alkylating reagents. By the action of these compounds on the organic bases the corresponding salts are formed in nearly quantitative yield within a short time [11, 12], for instance as in Eq. (4).



4

(4)

The guanidinium salt (**4**) has a low melting point (41–42 °C) and can be of interest as a new IL for extraction processes.

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5.3.3.3
Industrial Synthesis of Phosphonium Ionic Liquids

Al Robertson

5.3.3.3.1
Introduction

One of the first occurrences of a liquid organic salt in the literature goes back to 1914 where Walden reported the properties of ethylammonium nitrate [1], which melted at 14 °C. There was then a relatively large time gap until the work of Hurley and Wier on alkylpyridinium chloroaluminates in the late 1940s and early 1950s [2, 3]. In the early 1970s, there was ground-breaking work by Parshall on the use of low-melting ammonium and phosphonium stannates and germinate salts as solvents for palladium-catalyzed hydrogenation reactions [4, 5]. The range of liquid salts was later widened to include other nitrogen-based cations, such as alkyl methylimidazoles, through the efforts of Osteryoung, Hussy, and Wilkes. In addition, these investigators extended the applications into nonelectrochemical areas [6, 7].

While most of the early work on the pyridinium/imidazolium salts centered on electrochemical applications, mainly through the efforts of groups led by Seddon (The Queen's University, Belfast), Welton (Imperial College, London), Rogers (University of Alabama), Olivier-Bourbibou (IFP) and Wasserscheid (University of Aachen), the range of applications has been extended to include just about every class of organic chemical reactions [8]. Since about 1998, there has been a virtual explosion in ionic liquid publications and we have now what we would consider the first industrial application [9]. The current level of industrial and academic interest in ILs is evident from week-long ionic liquid symposia at each of the 2001, 2002 and 2003 ACS national meetings [10].

Of the volumes of IL publications, there have been relatively few on phosphonium-based salts – synthesis or applications – the main reason being that, historically, the key starting materials, tertiary alkylphosphines, have not been readily available. However, since 1970, Cytec Industries Ltd. have been commercially producing phosphine gas and derivatives thereof at its Niagara Falls, Ontario, facility.

The derivatives include tertiary alkylphosphines and phosphonium halides. Several of the latter are suitable IL candidates which are already being produced on ton scales and are currently on the major chemical inventories (e.g., EINECS).

Cytec has recently initiated an R&D program to considerably expand the list of potential phosphonium-based IL candidates, these are being marketed under the CYPHOS® IL trade name.

5.3.3.3.2
Synthesis and Applications

Phosphine readily adds to α-olefins in the presence of a free-radical initiator to yield tertiary alkylphosphines quantitatively [11]. Although these tertiary alkylphosphines have pK_as which are typically an order of magnitude lower than their amine counterparts and consequently are less basic, the more polarizable lone pair makes them much more nucleophilic than the corresponding amines [12, 13]. As a result, tertiary alkylphosphines readily undergo S_N2 nucleophilic addition to a variety of alkyl halides to yield tetraalkylphosphonium salts [13].

In theory, asymmetric tertiary alkylphosphines having generic formulaes $R_2R'P$ or $RR'R''P$ are available, but symmetric phosphines in which all alkyl substituents are identical (R_3P), because of the simple one-stem processing, are more economical to produce. Primary alkyl halides have the usual order of reactivity: $I > Br > Cl \gg F$. Typical reaction temperatures for iodides, bromides, and chlorides are 90, 110, and 150 °C respectively. The alkyl halide is generally added to the phosphine at the desired reaction temperature. Quantitative yields are obtained in 8–12 h. The products can be discharged as neat liquids or molten, low melting solids. Solvents are generally added to the higher melting products. Fluorides are too unreactive to consider.

Perfluoro or partially fluorinated olefinic raw materials, while somewhat expensive, are also available. Tertiary phosphines with generic formulaes

$$R_2P(\text{–}CH_2CH_2CH_2\text{–}O\text{–}CH_2C_nF_{2n+1}),\ RP(\text{–}CH_2CH_2CH_2\text{–}O\text{–}CH_2C_nF_{2n+1})_2,$$
$$P(\text{–}CH_2CH_2CH_2\text{–}O\text{–}CH_2C_nF_{2n+1})_3,\ R_2P(\text{–}CH_2CH_2\text{–}C_nF_{2n+1}),$$
$$RP(\text{–}CH_2CH_2\text{–}C_nF_{2n+1})_2,\ \text{and}\ P(\text{–}CH_2CH_2\text{–}C_nF_{2n+1})_3$$

can be prepared. They can also be quaternized with alkyl halides to yield salts with a much greater degree of hydrophobicity and which will have unusual miscibility characteristics.

Given the large number of possible available tertiary alkylphosphines and alkyl halides, there are an enormous number of potential tetraalkylphosphonium halides which can be prepared. While the majority are solids and many melt at > 100 °C, which would make them unsuitable as ILs even under the broadest definition, with a judicious selection of the alkyl halide and the alkyl substitutents on the phosphine one can produce low melting and even sub-ambient liquid phosphonium halides [13, 14].

The physical state and melting point of a phosphonium salt are a function of the crystal packing energy, which in turn is controlled mainly by a combination of the asymmetry of the cation and anion as well as the shielding and or delocalizing of

Table 1 Alkyl substituent and anion effects on the melting point of phosphonium halides for $[R_3R'P]^+$ $[X]^-$.

Entry	*R*	*R′*	*X*	*Melting point [°C]*
1	ethyl	ethyl	chloride	300
2	ethyl	ethyl	bromide	320
3	propyl	propyl	bromide	283
4	butyl	butyl	chloride	67
5	butyl	butyl	bromide	102
6	octyl	octyl	bromide	45
7	butyl	tetradecyl	chloride	56
8	pentyl	tetradecyl	chloride	liquid
9	hexyl	tetradecyl	chloride	liquid
10	hexyl	tetradecyl	bromide	liquid
11	hexyl	tetradecyl	chloride	liquid
12	butyl	hexadecyl	bromide	57

the respective charges. The effect of varying the alkyl substituents on the melting point of a series of phosphonium salts is indicated in Table 1.

The low melting and liquid halide salts in Table 1 have found utility as ILs. McNulty et al. have reported high yields for palladium cross-coupling reactions using entry 9 (CYPHOS® IL 101) as a recyclable solvent/catalyst system [15]. Similarly, Kaufmann et al. have reported that entry 12 can be used repeatedly with the same palladium catalyst to obtain high conversions of Heck coupling products [16]. Ramani has demonstrated that entry 9 can be successfully employed for a variety of reactions such as quantitative Michael addition of amines to acrylate esters [17], palladium-catalyzed carbonylation of iodobenzene to obtain ethyl benzoate [9], and Heck coupling of iodobenzene and ethyl acrylate [19].

While entry 5 (CYPHOS® IL 163) may be considered a borderline ionic, to date, of all the phosphonium-based ILs, it has received the most attention. Garayt et al. have patented a process to fluorinate aromatics [20]. Previously, Knifton, Lin et al. have published and patented an enormous number of petrochemical applications using entry 5 as the solvent – alcohols from syngas [21–29], synthesis of acetaldehyde and acetic acid from syngas [40–45], synthesis of esters from syngas [46, 47], and synthesis of formamides and amines [48, 49].

There have been no literature reports on applications of the corresponding chloride salt – entry 4 (CYPHOS IL 164). However, there is no reason to suspect that the identical reactions could not be carried out in this solvent. The chloride salt has the advantage of a 30 °C lower melting point; however, both are currently produced on a multi-ton scale by Cytec Industries and both are on the TSCA, EINECS, EEC, ENCS, ECL, PICC, and DSL inventories.

Phosphonium halides can be combined with $AlCl_3$ to form salts containing $[AlCl_4]^-/[Al_2Cl_7]^-$ anions. Additionally, many other metal halide salts such as $FeCl_3$, CuCl, $SnCl_3$, and $PdCl_2$ yield phosphonium salts with $[FeCl_4]^-$, $[CuCl_2]^-$, $[SnCl_4]^-$, and $[PdCl_4]^{2-}$ anions [50, 51]. Such anions when combined with entry 7 (CYPHOS IL 167) are liquids at room temperature.

Phosphonium halides such as entries 6, 9, 10 and 11, which are immiscible with water, are well suited as intermediates to salts which are essentially nonhalogenated with such anions as $[BF_4]^-$, $[PF_6]^-$, $[N(CN)]^-$,$[N(CS_2CF3)_2]^-$, $[R\text{-}CO_2]^-$, and $[R_2PO_2]^-$. The halide salts are converted via metathesis by simply stirring an aqueous salt of the desired anion with the phosphonium halide. Three aqueous washes reduces the halide content to < 1000 ppm [50, 51].

The bistriflamide salt (CYPHOS IL 109) prepared from entry 9 is particularly useful for catalytic Friedel–Crafts reactions [52] and for carrying out monoaromatic nitrations at less than 100 °C using essentially stoichiometric amounts of fuming nitric acid [53]. The bistriflamide, decanoate (CYPHOS IL 103) and phosphinate (CYPHOS IL 104) salts have also been reported to be excellent solvents for palladium-catalyzed reactions such as Heck and Suzuki coupling [54, 55].

Bis(2,4,4-trimethylpentyl)phosphinic acid (CYANEX® 272) is extremely selective toward extracting cobalt from aqueous cobalt/nickel solutions [56, 57], and consequently, the corresponding bis(2,4,4-trimethylpentyl)phosphinate salt prepared form entry 6 [58] may have some unique selective metal complexing properties.

Phosphonium salts manufactured by the above metathesis route will typically contain a few ppm of halogen anion. In many cases, this may be irrelevant, but if a totally halogen-free salt is required, they can readily be prepared in a simple one-pot procedure by heating a tertiary alkylphosphine with a tosylate, sulfate, or phosphate ester [51, 59, 60]. Examples are triisobutyl(methyl)phosphonium tosylate (CYPHOS IL 106), tributyl(methyl)phosphonium methylsulfate (CYPHOS IL 108), and tributyl(ethyl)phosphonium diethylphosphate (CYPHOS IL 169).

5.3.3.3.3
Thermal Analysis

Phosphonium salts are very thermally stable, as illustrated by the TGA plots for trihexyl(tetradecyl)phosphonium chloride (CYPHOS IL 101) in Figure 1. Under inert conditions, the weight loss onset occurs at approximately 310 °C whereas, even under oxidative conditions, the onset occurs at approximately 280 °C. These results are comparable to those for imidazolium salts with the same anion, but much higher than those for the corresponding ammonium salts [61].

While dynamic TGA plots are suitable for determining relative thermal stabilities, they do not provide good indications of absolute thermal stability. In addition to the atmospheric conditions over the sample, the weight loss onset is a function of the sample heating rate: higher heating rates result in higher apparent thermal stabilities. A more appropriate method is the use of isothermal TGA plots as presented in Figure 2 [61].

The TGA data presented in Figure 1 indicate relatively good stability even at 300 °C, whereas in fact there is a serious weight loss and associated decomposition, even at 210 °C. The true safe upper temperature limit would be closer to 150 °C as indicated in Figure 2. Similar results were obtained for the corresponding imidazolium and ammonium salts [61]. However, even 150 °C is perfectly adequate for the vast majority of IL applications.

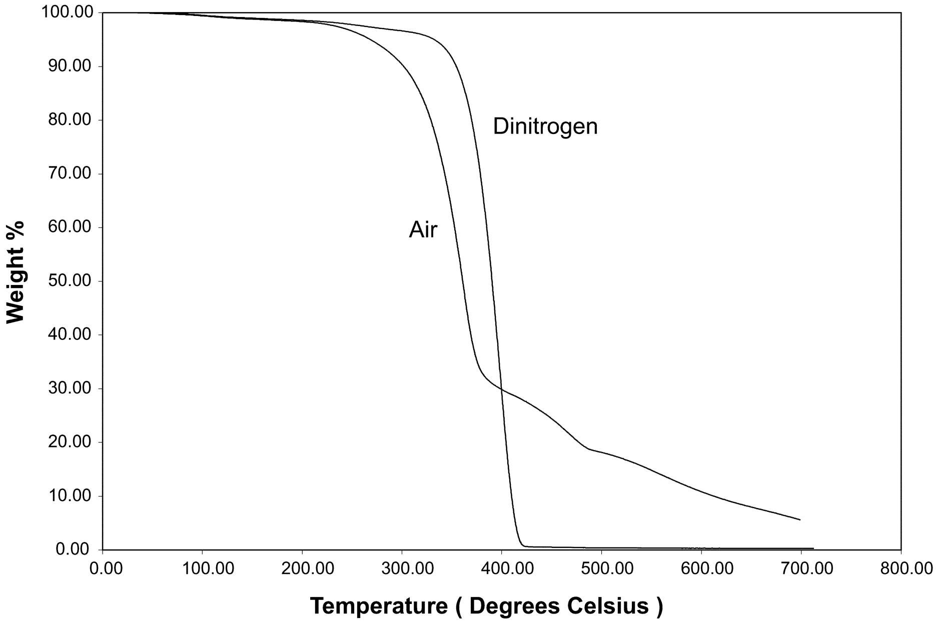

Figure 1 TGA plots for trihexyl(tetradecyl)phosphonium chloride (CYPHOS IL 101). Heating rate = 5 °C min^{-1} under air and dinitrogen atmospheres [51].

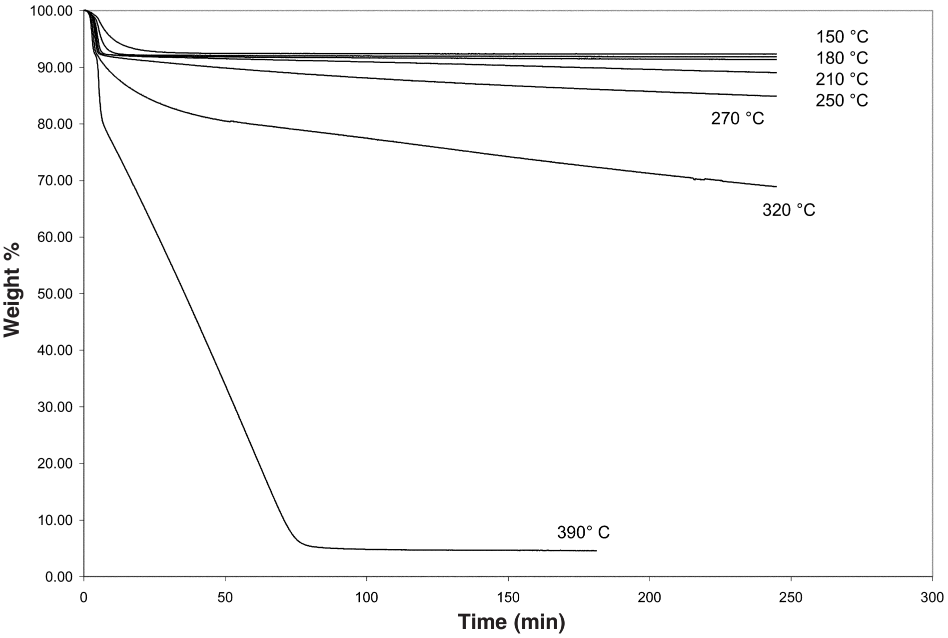

Figure 2 Isothermal TGA plots for trihexyl(tetradecyl)phosphonium chloride [62].

In general, the decomposition of phosphonium-based ILs is accompanied by an endothermic temperature; the only exceptions to date are the hexafluorophosphate salts. At a heating rate of 5 °C min^{-1} a 510 J g^{-1} exotherm beginning at 310 °C and with a maximum at 337 °C was noted [62]. In addition to the possible evolution of HF, the exothermic decomposition of hexafluorophosphate salts presents an added hazard when operating at or near the upper temperature limit. This is especially important to note when large volumes of such solvents are in service.

Viscosity

The viscosities of phosphonium-based ILs are generally greater that those of imidazolium salts. However, the addition of even minor levels of solutes results in dramatic lowering of the viscosity [63]. Additionally, the viscosity of ILs decreases exponentially with temperature. These effects are illustrated in Figure 3, which contains viscosity/temperature plots for trihexyl(tetradecyl)phosphonium chloride, initially containing 0.8% water. In the presence of a reactive substrate or reaction product and having been heated to a typical reaction temperature of 80 °C, phosphonium IL systems become water-like in viscosity.

The viscosity is also a function of the anion. Bistriflamide and dicyanamide anions result in relatively low viscosities, as shown in Figure 4. Given the same trihexyl-(tetradecyl)phosphonium cation, the viscosity of the dicyanamide salt is an order of magnitude lower than that of the salt with a chloride anion. Solute and temperature have a similar viscosity lowering effect.

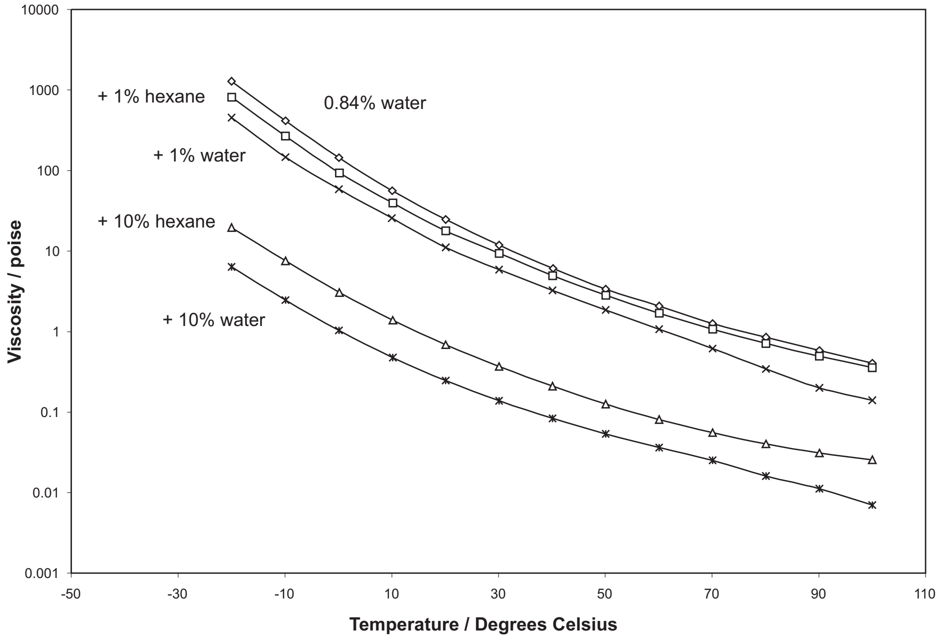

Figure 3 Effect of solute and temperature on trihexyl(tetradecyl)phosphonium chloride viscosity.

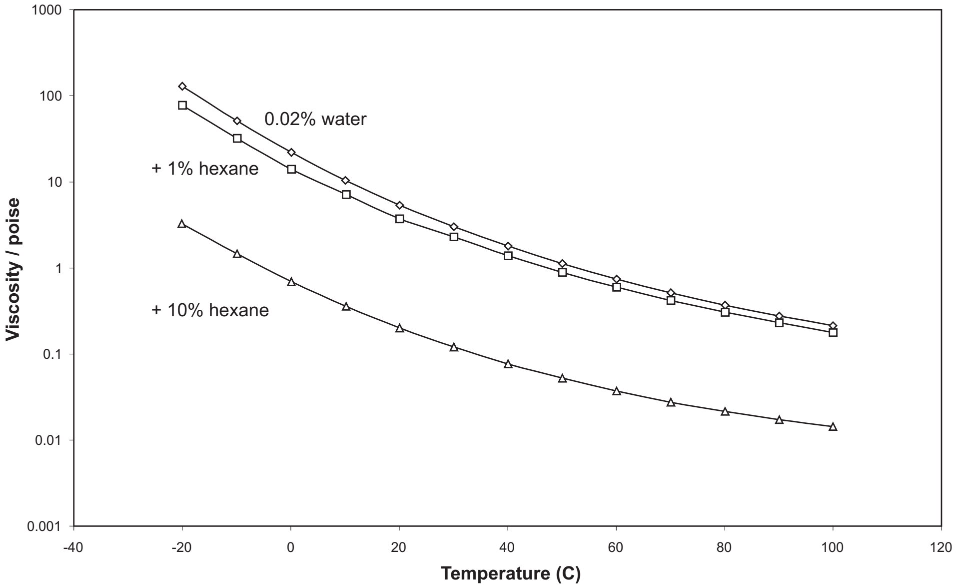

Figure 4 Effect of solute and temperature on trihexyl(tetradecyl)phosphonium dicyanamide viscosity.

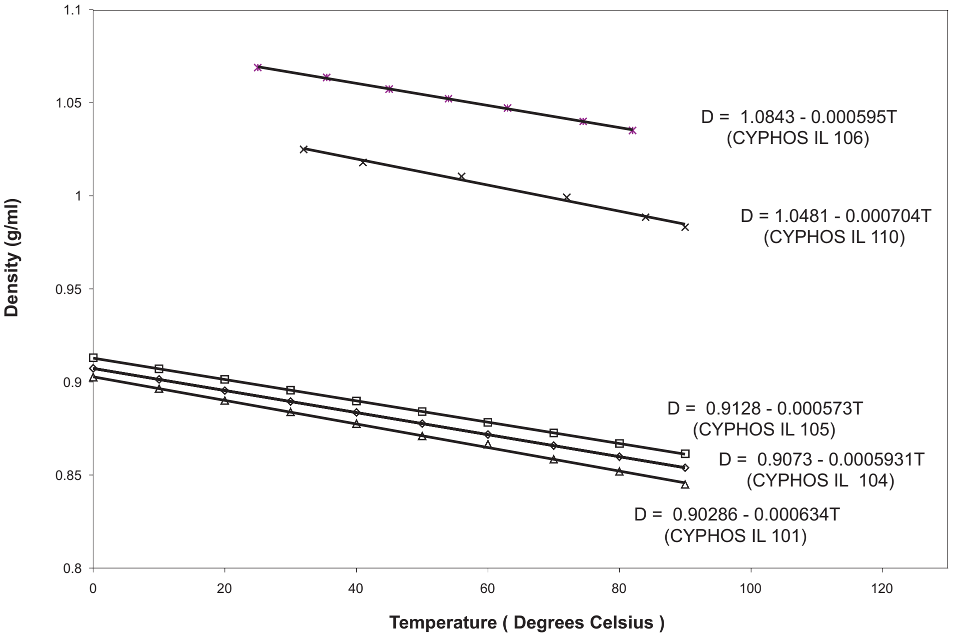

Figure 5 Phosphonium ionic liquid densities.

Density

In general, salts with alkylphosphonium cations are less dense than water. Densities as a function of temperature for trihexyl(tetradecyl)phosphonium chloride (CYPHOS IL 101), trihexyl(tetradecyl)phosphonium dicyanamide (CYPHOS IL 105) and trihexyl(tetradecyl)phosphonium bis(2,4,4-trimethylpentyl)phosphinate (CYPHOS IL 104) are found in Figure 5. Phosphonium salts with aromatic anions such as triisobutyl(methyl)phosphonium tosylate (CYPHOS IL 106) have densities greater than that of water. The density of trihexyl(tetradecyl)phosphonium hexafluorophosphate (CYPHOS IL 110) is unique in that, depending on the temperature, it may be greater or less than that of water.

Miscibility

Because of the wide range of alkyl substituents and anions, phosphonium salts can be very hydrophilic or hydrophobic; this in turn determines the miscibility of various solvents as outlined in Table 2. At the one extreme are salts such as the tetrabutylphosphonium halides which are hygroscopic solids which will form 80–85% aqueous solutions and which are very insoluble in nonpolar solvents such as hexane. At the other end of the scale are such salts as trihexyl(tetradecyl)phosphonium bistriflamide and hexafluorophosphate which are very hydrophobic and are totally miscible with nonpolar solvents.

Table 2 Miscibility of phosphonium salts.

Salt	*Hexane*	*Toluene*	*2-propanol*	*Water*
Tetrabutylphosphonium chloride	no	yes	yes	yes
Tetrabutylphosphonium bromide	no	yes	yes	yes
Triisobutyl(methyl)phosphonium tosylate	no	yes	yes	yes
Trihexyl(tetradecyl)phosphonium chloride	yes	yes	yes	no
Trihexyl(tetradecyl)phosphonium bromide	yes	yes	yes	no
Trihexyl(tetradecyl)phosphonium decanoate	yes	yes	yes	no
Trihexyl(tetradecyl)phosphonium bis-2,4,4-trimethylphosphinate	yes	yes	yes	no
Trihexyl(tetradecyl)phosphonium bistriflamide	yes	yes	yes	no
Trihexyl(tetradecyl)phosphonium tetrafluoroborate	yes	yes	yes	no
Trihexyl(tetradecyl)phosphonium hexafluorophosphate	yes	yes	yes	no
Tributyl(tetradecyl)phosphonium chloride	no	yes	yes	yes
Tetraoctylphosphonium bromide	yes	yes	yes	no

Table 3 Solubility of water in phosphonium ionic liquids.

Salt	*Water solubility [wt.%]*
Tetrabutylphosphonium chloride	14.0
Tetrabutylphosphonium bromide	4.5
Trihexyl(tetradecyl)phosphonium decanoate	21.1
Trihexyl(tetradecyl)phosphonium bis-2,4,4-trimethylphosphinate	20.6
Trihexyl(tetradecyl)phosphonium dicyanamide	3.1
Trihexyl(tetradecyl)phosphonium bistriflamide	0.7
Trihexyl(tetradecyl)phosphonium hexafluorophosphate	2.2
Trihexyl(tetradecyl)phosphonium tetrafluoroborate	1.8

While many phosphonium salts are not totally miscible with water, they are capable of dissolving a certain quantity of water as shown in Table 3. This unusual property offers an alternative means of separating nonpolar reaction products, ILs/ metal catalysts and salt byproducts. Having carried out a reaction such as a palladium-catalyzed Suzuki cross-coupling, a nonpolar alkane solvent can be added to the IL solution. At that point the mixture will be a single phase. Then on addition of an excess of water, three phases will form. The product will generally partition into the upper hydrocarbon layer. The palladium catalyst will remain in the middle IL layer and any byproduct salts will partition into the lower aqueous phase. The IL layer can be dried by vacuum stripping and subsequently recycled [15].

Electrochemical Window

The electrochemical window of an IL is determined by the reduction potential of the cation at the cathode and the oxidation potential of the anion at the anode. In general tetraalkylphosphonium cations are stable to –3.0 V. The total window will very much depend on the anion. In the case of the bistriflamine anion the oxidation potential is +2.5 V. Consequently the total electrical window for trihexyl(tetradecyl)phosphonium bistriflamide is 5.5 V. The cyclic voltammogram for this salt is shown in Figure 6 [64].

Compatibility with Strong Bases

J. Clyburne et al. while studying the reduction of imidazolium cations to carbenes, electrochemically and by treatment with potassium, have demonstrated the persistence of such carbenes in phosphonium ILs such as tetradecyl(trihexyl)phosphonium chloride [65]. The compatibility of phosphonium ILs with such strong bases prompted further investigations for the use of Grignard reagents and strong reducing reagents such as $NaBH_4$ in phosphonium ILs.

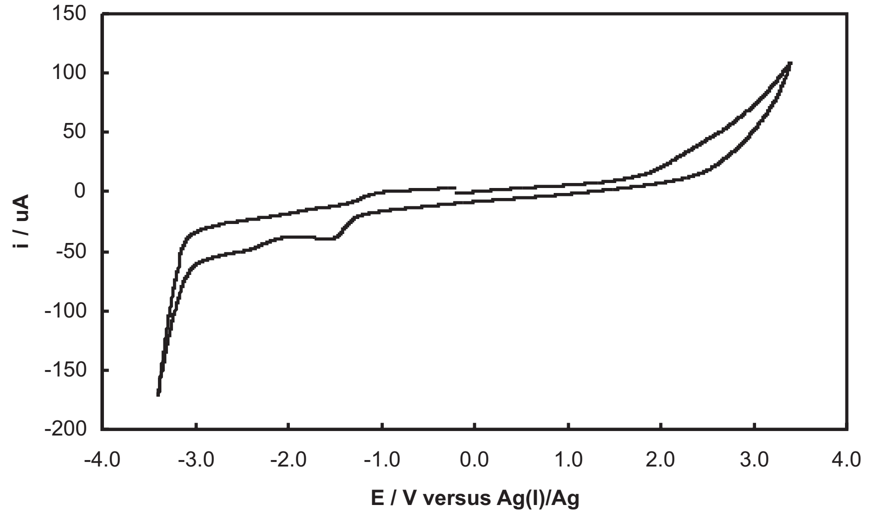

Figure 6 Cyclic voltammogram for trihexyl(tetradecyl)phosphonium bistriflamide.

In a subsequent paper [66], they report the inertness of phenylmagnesium bronide/THF solution in tetradecyl(trihexyl)phosphonium chloride. This Grignard solution was then successfully used to carry out a variety of standard Grignard reactions. In addition to the Grignard reactions, they successfully used $NaBH_4$ to reduce benzaldenyde to benzyl alcohol in the phosphonium IL. The work-up was made especially easy by adding water and a nonpolar solvent to the reaction mixture. Three phases formed, with the salts collection in the lower aqueous phase and the products being essentially extracted into the upper nonpolar organic phase.

The compatibility of phosphonium ILs such as tetradecyl(trihexyl)phosphonium chloride – CYPHOS® IL 101 – with strong bases such as $NaBH_4$, Grignard reagents and potassium metal, suggests that other applications which involve the use of alkali metals and even elemental phosphorus may be possible in phosphonium ILs.

Toxicity Data

Toxicity data for ILs are still generally lacking. However, B. Jastorff et al. have recently reported structure-activity relationship data on acetylcholinesterase inhibition for various classes of ILs [67]. Their conclusions indicated that ILs which contain imidazolium and pyridinium cations with longer alkyl substituents have EC_{50} values as low as 13 μM, where as phosphonium ILs containing bulky phosphonium cations such as tetradecyl(trihexyl)phosphonium have EC_{50} values of > 2000 μM.

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5.3.4
Industrial Production of Ionic Liquids

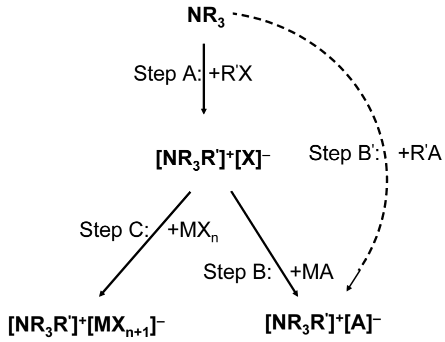
Christophe Vallée and Hélène Olivier-Bourbigou

5.3.4.1
Classical Methods for the Synthesis of Ionic Liquids

The nature of the cations of ionic liquids (ILs) is quite diverse, with the possibility of having a positive charge on a nitrogen, phosphorus, or sulfur atom. Numerous anions can be associated with these cations. A good idea of the extent of the field is given by the fact that today several hundreds of ILs are commercially available. Some new ILs have been presented in the preceding sections.

In spite of this diversity, most of ILs are synthesized using similar procedures. The nature of the reagents, as well as the conditions, are changed from one product to the other but the principle remains the same. As a consequence, this contribution will be limited to the synthesis of imidazolium ILs, because they are the most widely used ILs. Phosphonium-based ILs are reviewed in Section 5.3.3.2.

A detailed procedure for the synthesis and the purification of ILs can be found in [1] and references therein. As a consequence, it will be briefly mentioned here. As represented in Scheme 1, imidazolium ILs are generally prepared in a two-step synthesis.



Scheme 1

In the first step (Step A, Scheme 1), an imidazolium halide is formed by the reaction of an alkyl halide R′X with an *N*-alkylimidazole (a variety of *N*-alkylimidazoles are commercially available, while others can be obtained by reacting potassium imidazolide with 1 equiv. of an alkyl halide). The conditions of the reactions mainly depend on the nature of the alkyl halide: chloride reactants often require several hours at reflux, while it is necessary to manage the exothermicity of the reaction when bromide and iodide compounds are used.

The second step is the reaction of the imidazolium halide with MA, the metal salt or the conjugated acid of the appropriate anion, in a metathesis reaction (Step B, Scheme 1). This general method enables the synthesis of a practically unlimited variety of ILs $[NR_3R']^+[A]^-$ with numerous anion/cation combinations. The main problem of this reaction route is incomplete exchange of the halide in the metathesis step and thus contamination of the resultant IL with the strongly coordinating halide anion. One commonly used way to avoid such contamination is to transform the metal salt or the acid of the anion to its corresponding silver salt by treatment with silver nitrate. The reaction of the silver salt with the imidazolium halide in an organic solvent generally leads to complete removal of halide impurities but introduces the possibility of silver contamination.

To prevent these drawbacks, a simpler one-step route to an imidazolium low-temperature IL can be used for a more limited range of salt compositions (Step B′, Scheme 1). There are several classes of alkylating reagents R′A which are able both quaternize the imidazole ring and introduce the desired anion. Alkylating agents derived from alkyl triflate, tosylate, and trifluoroacetate were initially studied exclusively [2, 3]. The use of triethyloxonium tetrafluoroborate and triethyloxonium hexafluorophosphate was then reported [4]. Some other reagents have been described recently, such as alkyl sulfate [5, 6] and *N*-methyl bis[(perfluoroalkyl)sulfonyl]imides [7]. This one-step synthesis can be applied to the reaction of Brønsted acid (HA) with *N*-alkylimidazole base, providing protic ILs such as [BIM][NTf_2] (step B′, R′ = H).

Another synthesis of a narrow, yet potentially very useful, range of ILs is direct combination of an imidazolium halide salt with a Lewis-acidic metal halide MX_n (Step C, Scheme 1). Several anions were introduced this way, in particular halogenoaluminate(III), chlorocuprate(I), chlorostannate(II), chloroferrate(III), or chlorozincate(II) anions. According to the nature of the metal halide and to the stoichiometric ratio between the imidazolium salt and the metal halide, the formation of polynuclear anions is possible. Recently, this method has been extended to the synthesis of ionic liquids based on fluorinated anions. As an example, the acid–base reaction of [BMIM]$(HF)_{2.3}F$ IL with an excess of BF_3 (gas) leads to the formation of [BMIM][BF_4] ILs. No polynuclear anions such as $B_2F_7^-$ are formed [8].

Purity of the salts is essential for many solvent applications and for the characterization of their physical and chemical properties [9]. It is important to note that ILs are completely nonvolatile and thus cannot be purified by distillation. Chromatographic purification is also of very limited utility due to the tendency of the salts to absorb on a common stationary phase. Consequently the synthesis method chosen must necessarily be highly selective.

Common contaminants from these reactions are unreacted starting material: halide anions, alkaline cations, organic bases, and possibly solvent of reaction. Moreover, without a special drying procedure and handling in completely inert surroundings, water is omnipresent in ILs. Indeed, even hydrophobic ILs are to some degree hygroscopic. Some methods have consequently been developed to detect and quantify these impurities.

5.3.4.2
Purification and Analysis of Residual Impurities

Due to their coordinating properties, halide impurities can have disastrous effects on metal-catalyzed reactions, so special attention has to be given to the control of halide in ILs when they are obtained in a two-step synthesis. Halide impurities can be effectively removed from hydrophobic ILs by simply washing them several times with water. The preparation of water miscible ILs is a more demanding process: the IL can be dissolved in dichloromethane and washed with successive small portions of deionized water. However, this method results in a lowering of the yield and cannot be applied for the most hydrophilic ILs. In the latter case, the direct alkylation of *N*-alkyl imidazole should be preferred.

In practical terms, it is suggested that, in any application where the presence of halide ions may cause problems, the concentration of these be monitored to ensure the purity of ILs. The Vollhard procedure for halide ions or the use of a chloride-selective electrode are two methods which are well suited for the detection of amounts of halide in the region of 100 ppm [9]. The advantage of the chemical procedure is the ability to detect any halide anion. Recently ionic chromatography was developed to monitor the level of halide in ILs [10, 11]. The method enables a better detection of halide impurities, as the authors claim a detection limit in the range of a few parts per million.

Most of the time, residual alkaline cations are not detrimental to the application of ILs in catalysis. However, it has been demonstrated that physical properties such as density and viscosity can be radically altered by the presence of unwanted ions.

A sodium-selective electrode enables measurement of amounts of sodium around 100 ppm [9]. Ionic chromatography had been developed to monitor the quantity of sodium in chloroaluminate salt buffered with NaCl. The method was not developed for the detection of trace amounts of sodium: however, the sample was very dilute and it was possible to measure a sodium level as low as 2 ppm [12]. As a consequence, the method seems suitable if it is necessary to control the level of residual sodium in ILs.

In contrast to sodium, a residual Lewis base such as the starting *N*-alkylimidazole can severely poison organometallic catalysts. These compounds are coordinating bases and have been proven difficult to remove from ILs due to their high boiling points. A simple colorimetric method of detection was first developed, which is based on the complexation of *N*-methylimidazole with copper(II) chloride [13]. It enables monitoring of *N*-methylimidazole content in [EMI][Cl] to better than 0.2 mol%. More recently, capillary electrophoresis was applied for the detection of imidazole derivatives in 1-alkyl-3-methylimidazolium salts [14]. Using this technique, it is then possible to separate and identify the different *N*-alkylimidazole and imidazolium cations in the ILs.

Other main contaminants which can be present in ILs are residual solvents or water. Most of the time, traces of residual solvents can be easily removed by heating the IL under vacuum. The situation is much more delicate for water, and it is generally recommended that ILs be heated to at least 70 °C for several hours with stirring to achieve an acceptably low degree of water contamination. The residual water content is often measured by Karl–Fischer titration, and levels below 10 ppm can be achieved in the case of hydrophobic ILs.

5.3.4.3
Alternative Synthesis and Industrial Production

For academic researchers, it is possible and even desirable to try to obtain perfectly pure ILs, with negligible amounts of impurities. However, such achievement of purity would prevent the possible production of ILs on a large scale at a reasonable cost. Scientists in the industrial field have then to determine the specification in terms of purity which is required for each application and the corresponding production method.

Moreover, ILs are sometimes described as green solvents. However, the classical two-step synthesis uses a large amount of solvent and produces important byproducts. Some effort is therefore necessary to achieve simpler and greener synthesis of ILs. This situation has led to the development of some alternative syntheses which are likely to solve some of these difficulties.

The potential detrimental effect of halide has been described previously. A first alternative to the two-step synthesis is the direct alkylation of *N*-alkylimidazole. However, the range of available alkylating reagents is limited and they are sometimes expensive. Two-step syntheses of ILs which do not use imidazolium halide as an intermediate were then developed. For example, Seddon described the reaction of *N*-alkylimidazole with ethyl trifluoroacetate, which leads to imidazolium trifluoroacetate. The IL is then reacted with a Brønsted acid, e.g., HBF_4, which leads to the formation of imidazolium tetrafluoroborate and trifluoroacetic acid, the latter being removed in vacuum [15]. It is worth noting that the cost of using a fluorinated ester should not be prohibitively expensive as the carboxylic acid byproducts can be recycled. An analogous procedure is possible by alkylation of *N*-alkylimidazole with dimethyl sulfate, followed by an anionic metathesis. The remaining methyl sulfate sodium salt is eliminated by washing with water [16]. Both procedures give halide-free IL, but contamination by trifluoroacetic acid or methyl sulfate sodium salt cannot be excluded.

Another method has been described for the synthesis of halide-free ILs which uses an imidazolylidene carbene as an intermediate. The starting material is an imidazolium halide which is treated with sodium *tert*-butoxide to form an imidazolylidene carbene. The latter is distilled in a Kugelrohr apparatus, then reacted with a Brønsted acid. In this way, it is possible to obtain an IL free from halide contamination, but traces of *N*-alkylimidazole or acid may be present.

Some efforts have been devoted to the improvement of the classical syntheses. Indeed, the quaternization of *N*-alkylimidazole with alkyl halide via the conventional heating method in refluxing solvent requires several hours to afford reasonable yields and also uses a large excess of alkyl halides/organic solvent as the reaction medium. Similarly, the metathesis reactions are lengthy and generally result in reaction products which require purification.

A microwave-assisted preparation of a series of 1-alkyl-3-methylimidazolium halide ILs has been described [17]. The reaction is run in solvent-free conditions with a near-stoichiometric amount of reactants, and the imidazolium halides are obtained in high yield. It is also possible to perform the subsequent metathesis reaction with sodium hexafluorophosphate by means of microwave radiation and then to form the final product in a one-pot reaction [18]. Due to the fact that ILs absorb microwave energy in a very efficient way, they are believed to be well suited for large-scale microwave-assisted synthesis (that is, for reaction mixtures of more than 100 L).

Similarly Lévêque and co-workers claim that the use of ultrasonication makes it possible to improve the metathesis step [19, 20]. The reaction is performed in an organic solvent and its completion is followed by measuring the conductivity of the solution. ILs are obtained in 1 h with 80–90% yield and they are less colored than when prepared by simple stirring for several hours without ultrasonication.

Alternatively, an electrochemical process for producing ILs has been reported [21]. The electrochemical cell is charged with a first solution comprising the desired cation and a second solution comprising the desired anion. The electrolysis of the cell enables production of the desired IL. The authors claim it is possible to prepare ILs containing less than 100 ppm halide and 20 ppm sodium.

Other attempts have been made to simplify the synthesis of ILs and to increase the overall yield. For example, the synthesis of $[BMI][PF_6]$ was described using the desired product as solvent. Then the heating of a mixture of *N*-methylimidazole, chlorobutane, and sodium hexafluorophosphate for 35 h at 80 °C in $[BMI][PF_6]$ led to freshly formed [BMI][PF_6] with 80% yield. This method enables production of an IL without using volatile organic solvent. This advantage is nevertheless limited to hydrophobic ILs, as an organic solvent (for example, dichloromethane) is necessary to purify hydrophilic ILs of residual halide.

Similarly, a one-step procedure was proposed for a series of hydrophilic or hydrophobic ILs [22]. For example, a mixture of *N*-methylimidazole, ethyl bromide, and sodium tetrafluoroborate is heated at 70 °C for two weeks. The filtration of the solution allows collection of the IL in nearly 90% yield. Without any subsequent purification, the residual halide contamination is very low.

Some efforts have also been dedicated to the synthesis of haloaluminate ILs, in particular those containing trialkylammonium cations which have been developed for acid-catalyzed reactions (see Section 5.2.2.4). They are classically manufactured in a one-step synthesis by combination of the alkylamine hydrohalide salt with the metal halide. An improved preparation was described in a two-step process, which includes contacting an alkylamine with a hydrogen halide, preferably in the gaseous form, and then contacting the first reaction mixture with a metal halide [23]. The two-step process provides for easier handling of the reactant and is a more commercially viable manufacturing process.

IL production and commercialization have attracted the development of new companies or business. Recently installed in France, Solvionic [24] is a start-up that has focused its activity on the development and the production of ILs for catalysis and electrochemistry. Established chemical manufacturers have also introduced ILs in their commercial product lines. Some of them have filed patents on new formulations of ILs having specific properties, and often claim their use in different applications. Patents are also filed on alternative methods to produce them.

Nowadays, several IL producers claim their capabilities to fulfill all requested quantities on a ton scale. The questions of the price and availability of starting material have been considered, as well as the chemical processing aspects. Beyond this, the human and eco-toxicity of ILs has to be considered, as well as the way of disposing of “used” ILs.

Few data are available about the toxicity of ILs but toxicological aspects are under investigation (see Section 5.4). Some producers orient their choice of anion and cation toward relatively nontoxic compounds. For example, Sachem has recently introduced the Terrasail line of IL based upon the docusate (dioctylsulfosuccinate) anion because this anion is known to exhibit low mammalian toxicity and is widely used in food, drug, and cosmetic applications. However, the ILs registered in EINECS or equivalent inventories are still rare: we can quote the quaternary ammonium sulfate ECOENG-500™, commercialized by Solvent Innovation, or halide phosphonium commercialized by Cytec, such as CYPHOS® IL 163 and CYPHOS® IL 3563.

Concerning the disposal of “used” ILs, some producers such as Sachem have the experience of quaternary ammonium salt recycling program. Another possibility, as ILs often have very long lifetimes, is to dispose of them by way of combustion. For this solution, fluoride-free anions should be preferred as they would not generate HF.

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5.4
Preliminary (Eco-)Toxicological Risk Profiles of Ionic Liquids

Johannes Ranke, Frauke Stock, Reinhold Störmann, Kerstin Mölter, Jens Hoffmann, Bernd Ondruschka, and Bernd Jastorff

5.4.1
Background

Ionic liquids (ILs) are not only viewed as potent designer solvents for organic synthesis, they are also often cited in the context of the recently developed field of "green chemistry". The main rationale encountered for calling ILs "green" is their negligible vapor pressure, which, in comparison to conventional molecular organic solvents, reduces occupational health risks because of the limited exposure via air. Furthermore, the risk of explosions is limited because of the same property.

5.4.1.1
Green and Sustainable Chemistry

Looking more closely at the 12 principles of green chemistry [1] especially concerning the exchange of organic solvents for ILs, two of them especially are touched by this argument:

- Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
- Chemical products should be designed so that at the end of their function they do not persist in the environment but do break down into innocuous degradation products.

These two principles specifically address the substances to be used and produced in green chemistry. Just from these principles, some additional questions arise:

- If the "toxicity to human health" is reduced by virtually eliminating one important path of exposure, what about the "toxicity to the environment"?
- What about the persistence and degradation of ILs as compared to conventional solvents?

Another question also arises, of whether the "toxicity to human health" is really effectively reduced; different paths of exposure, especially dermal exposure, combined with a respective effect, could encompass a health risk that has to be taken into account.

Within the Organisation of Economic Cooperation and Development (OECD), several workshops have been held under the name of "Sustainable Chemistry". Alluding to the concept of sustainable development, the importance of long-term

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effects is again underlined as well as an equal relevance for economic, social, and ecological aspects.

While it is obvious that some of the above questions and aspects are not answered adequately by the current IL literature, the topic is complicated by the fact that there is a very large number of IL that have already been described, but an even larger number of such liquids that could be derived from known structures by a simple exchange of functional groups. Every IL has its own toxicity, and the lethal dose for oral application to mice or rats (LD_{50}) is only one measure for toxicity, not revealing much about such important effects as skin sensitization or genotoxicity.

5.4.1.2
Integrated and Sustainable Development of Products and Processes

At present, a wealth of applications of ILs are being developed, ranging from areas as different as fluids for thermal solar stations and suppression of tailing in HPLC. During such a development of processes or products, the design choices that can be made decrease constantly until the final, implemented result can only be changed with extraordinary effort. This has led to the concept of an integrated development of processes [2] and products [3]. This means that in the early design phases of new processes and products, environmental and health effects are simultaneously explored. In the Center of Environmental Science and Environmental Technology (UFT) of the University of Bremen/Germany, these aspects are recognized as being highly important for a sustainable development of chemistry in general. For the case of chemical products such as ILs, the concept of a sustainable design of chemicals has been sketched (Figure 1).

First, a so-called “test-kit” of compounds is being selected to represent the structural alternatives for the targeted technological purpose. Here, Structure–Activity Relationships (SARs) and Quantitative Structure–Activity Relationships (QSAR) help with the selection. The concept of “Thinking in Structure-Activity-Relationships” (T-SAR) means that a rationalization of the relationship between

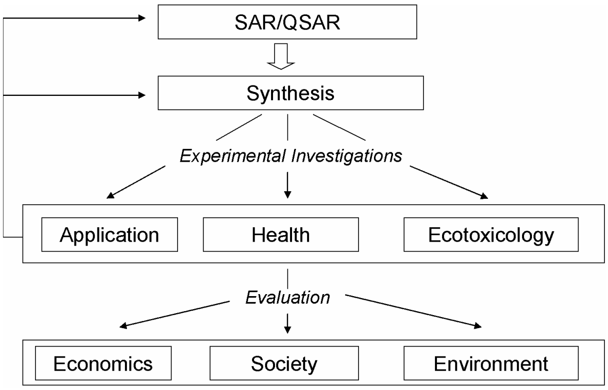


Figure 1 Sustainable design concept for chemicals.

the technological properties and the chemical structures is attempted and hypotheses about SARs and QSARs concerning environmental, and health effects are being generated. Then, the substances in the test-kit of substances have to be synthesized or requested from existing providers. In parallel, technical, environmental and health effects are being tested, leading to new knowledge about SARs of these compounds. A new test-kit can be formed or in-depth evaluations concerning economical, ecological, and social aspects can be carried out if a large-scale application is realistic. The idea of this iterative process is the motivation for our research strategy on ILs which has been detailed in [4].

In this section we report on the test-kit of substances that have been addressed by our work, we make a preliminary comparison of the (eco-)toxicological risk profiles of two of them as compared to a conventional solvent, and we summarize the first SAR and QSAR conclusions that could be generalized from the obtained data.

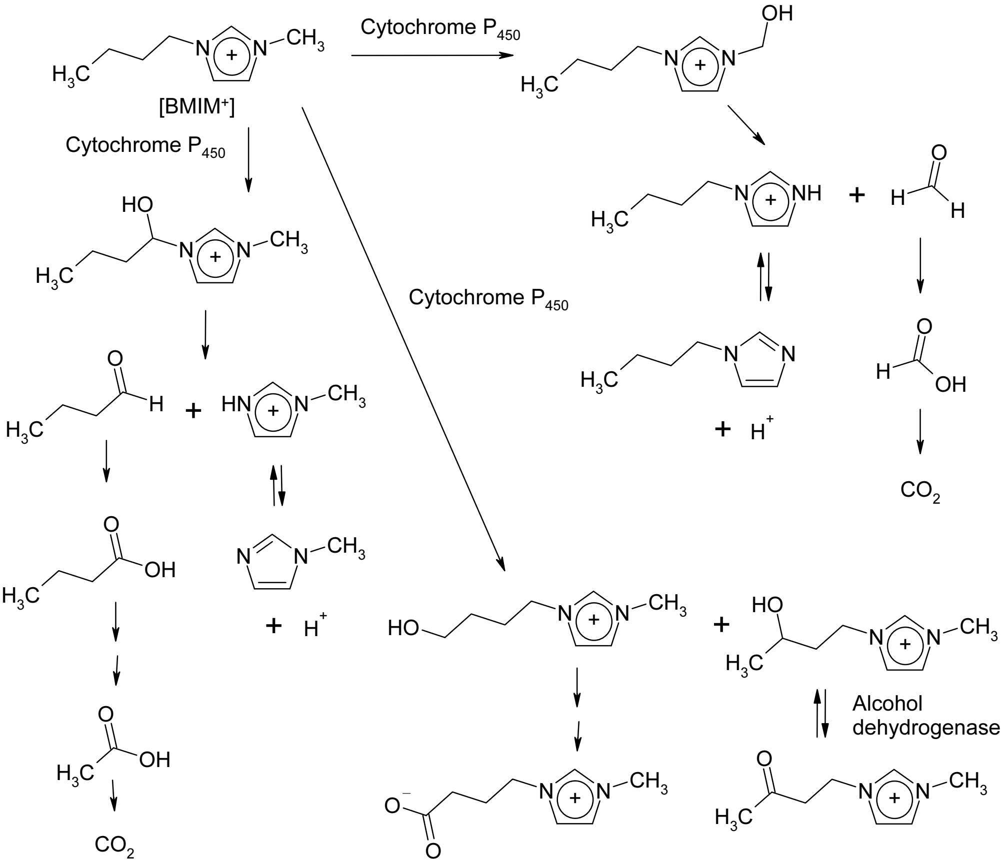
5.4.2
Description of Selected Substances

5.4.2.1
General

The first target class we concentrated on were imidazolium derivatives of ILs which exemplify our method of analysis. The central imidazolium ring is a delocalized aromatic system with high electron acceptor potential. Therefore, the nitrogen atoms are not able to form any hydrogen bonds. The system is very rigid and sterically inflexible (cf. Structure **8**). A methyl group in position R_2 does not change this sterically stable state. In contrast, elongation of residue R_1 (C_4 chain, C_{10} chain) leads to a continuous increase in flexibility, implying more conformational freedom. The R_1 residue of 2-phenylethyl-3-methylimidazolium chloride ([2-phenylethyl-MIM] [Cl]) contains an additional aromatic system. The phenyl ring shows a high electron density including electron donor potentials. Lipophilic parts within this molecule are the alkyl group and the phenyl structural element but some lipophilicity also resides in the aromatic imidazolium ring.

All three selected compounds reveal the steric feature of a flat cation which results in flexibility and prevents direct and easy binding of polar compounds. Within our systematic algorithm the prediction of possible metabolites has to be considered. According to this theoretical approach several points of action can be identified. If these ionic molecules actually reach the cytochrome P_{450} system located in the endoplasmatic reticulum of any cell, they can be oxidized in different positions of the alkyl side chains. The resulting metabolites can further be broken down metabolically to biocompatible fatty acids and imidazole. For part of this proposed metabolism for the 1-butyl-3-methylimidazolium ([BMIM]) cation see Scheme 1.

Of course it is possible that metabolites predicted theoretically may not be formed by nature. Nevertheless the prediction facilitates the analytical search for compounds while investigating the metabolic fate of ILs in biological test systems. Such studies are under way within a cooperating network.

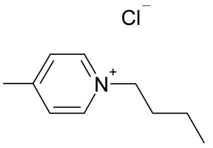


Scheme 1 Proposed metabolic pathways of the 1-butyl-3-methylimidazolium ([BMIM]) cation.

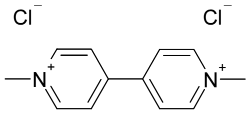
Finally, three examples will demonstrate the structure–activity relationship approach based on comparison of chemical structures. A pyridinium type of ionic liquid is presented in contrast to "Paraquat" (**4**), a herbicide which is considered to exhibit substantial toxicological and eco-toxicological risk (due to high acute toxicity and high persistence) and has therefore been banned in many countries.

In the same way 1-decyl-3-methylimidazolium chloride (**2**, [DMIM] [Cl]) and a patented plant growth regulator **4** are depicted side by side. A third example showing the structural similarity of some ILs to already existing chemicals are the quaternary alkylammonium compounds (quats) (**3** versus **6**). Some crystalline quats like dodecyltrimethylammonium bromide are commonly being used for disinfection or as preservatives, while tetrabutylammonium salts are easily accessible ILs.

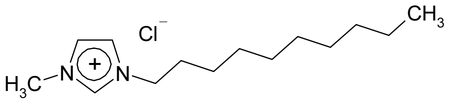
Because of the high variability and indefinite number of possible IL species, the choice of test compounds is difficult to perform. Therefore, we are using a so-called "test-kit concept" [5]. This concept has been used successfully over recent years to define nucleotide analogues as targets for systematic evaluation of enzymatic and cellular properties [6].



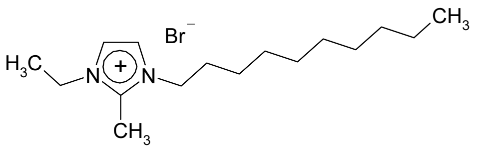
Ionic liquid
1



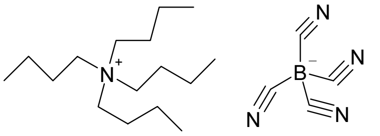
Herbicide Paraquat
4



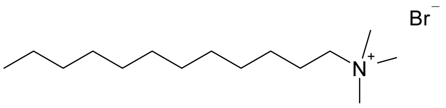
Ionic liquid
2



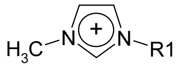
Patented plant growth regulator
5



Ionic liquid
3



Disinfectant / Preservative
6



R1= -$(CH_2)_n$-CH_3, n=3-10

Testkit 1a: Anion = $[BF_4]^-$

Testkit 1b: Anion = $[PF_6]^-$

7

R2= -CH_3, -C_2H_5

R1= -$(CH_2)_n$-CH_3, n=3, 5, 9

Testkit 2: Anion = $[BF_4]^-$

8

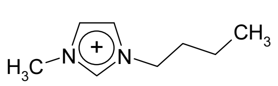
R1= -$(CH_2)_2$-C_6H_5, -CH_2-C_6H_5, -CH_2-C_6H_4-CH_3 (p-)

Testkit 3a: Anion = $[BF_4]^-$

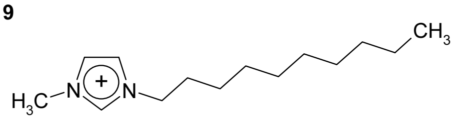
Testkit 3b: Anion = $[PF_6]^-$

Testkit 3c: Anion = Cl^-

9



Testkit 4a



Testkit 4b

Anion = $[BF_4]^-$, $[PF_6]^-$, Cl^-, Br^-, $[OTs]^-$

10

11

5.4.2.2
The Test-Kits

Starting from the chosen basic imidazolium structure, in general there are two possible ways to change residues. The first approach (**7**) is to increase chain length in the R_1 position keeping the R_2 residue constant (methyl group). Secondly (**8**), we keep R_1 constant but increase the length of R_2 from methyl to ethyl. The third set of test compounds (**9**) concentrated on imidazolium compounds with methyl groups in the R_1 position and side chains including a second aromatic ring (benzyl, phenylethyl, and *p*-methylbenzyl moieties) in the R_1 position. These considerations resulted in the test-kits 1, 2, and 3. Last but not least we systematically varied the anion, leaving the positively charged moiety constant (**10**, **11**), leading to test-kit 4.

5.4.2.3
Synthesis

Imidazolium chlorides were prepared at the ITUC in Jena by alkylation of *N*-methylimidazole or *N*-ethylimidazole with C3 to C10 alkyl chlorides (or alkyl bromides or *p*-toluenesulfonate alkyl esters) and successive washing with ethyl acetate plus drying with increasing vacuum in a similar manner to that described in [7–10]. The respective tetrafluoroborates were synthesized from the imidazolium chlorides by adding ammonium tetrafluoroborate in acetonitrile (cf. [11]). The hexafluorophosphates were obtained by dissolving the imidazolium chlorides in water, adding hexafluorophosphoric acid, washing with water, neutralizing with sodium bicarbonate solution, and washing with water again. The hexafluorophospates were then taken up in dichloromethane dried with magnesium sulfate, and the solvent was stripped off (cf. [12]). Substances were checked for volatile impurities with headspace and liquid injection gas chromatography.

5.4.3
First Results from Biological Testing

5.4.3.1
General

In a first screening study, toxicity levels of substances from test-kits 1, 2, and 4 toward two different mammalian cell lines and on *Vibrio fischeri* have been investigated [13]. The main questions addressed in this study were:

- How toxic are ILs in these systems?
- Is there an observable contribution of anions to toxicity?
- What is the (quantitative) influence of an increasing alkyl chain length on toxicity?

The use of mammalian cell cultures for a screening hazard assessment is an innovative approach in the environmental sciences, although they have been used in more mechanistic studies, e.g., for mode of action studies. The two cell cultures

Table 1 Toxicity of selected ionic liquids.

	IPC81 ***log$_{10}$ (EC$_{50}$ [μM])***	***C6*** ***log$_{10}$ (EC$_{50}$ [μM])***	***V. fischeri*** ***log$_{10}$ (EC$_{50}$ [μM])***
[EEIM] Br	> 3		
[PMIM] Cl	> 3		
[PMIM] [PF$_6$]	> 3	> 3	
[PMIM] [BF$_4$]	> 3		3.94 ± 0.06
[PEIM] Br	> 3		
[BMIM] Cl	> 3		3.4 ± 0.02
[BMIM] [PF$_6$]	> 3	> 3	
[BMIM] [BF$_4$]	3.14 ± 0.02	> 3	3.55 ± 0.04
[BMIM] Br	> 3	3.13 ± 0.2	3.07 ± 0.03
[BMIM] [OTs]	3.19 ± 0.2		3.52 ± 0.07
[BEIM] [BF$_4$]	> 3		2.8 ± 0.04
[AMIM] Cl	3.16 ± 0.06		
[AMIM] [PF$_6$]	3.07 ± 0.08	> 3	
[AMIM] [BF$_4$]	3.09 ± 0.05		3.14 ± 0.02
[HMIM] Cl	2.97 ± 0.07		
[HMIM] [PF$_6$]	> 3	> 3	
[HMIM] [BF$_4$]	2.95 ± 0.08		3.18 ± 0.03
[HEIM] Br	2.01 ± 0.06		
[HEIM] [BF$_4$]	2.26 ± 0.05		2.15 ± 0.05
[HpMIM] Cl	2.53 ± 0.05		
[HpMIM] [PF$_6$]	2.30 ± 0.06	3.08 ± 0.2	
[HpMIM] [BF$_4$]	2.58 ± 0.07		2.44 ± 0.06
[OMIM] Cl	2.01 ± 0.05		
[OMIM] [PF$_6$]	1.96 ± 0.07	2.76 ± 0.2	
[OMIM] [BF$_4$]	1.74 ± 0.06		1.41 ± 0.07
[NMIM] Cl	1.4 ± 0.04		
[NMIM] [PF$_6$]	1.85 ± 0.08	1.90 ± 0.08	
[NMIM] [BF$_4$]	1.65 ± 0.05		0.718 ± 0.04
[DMIM] Cl	1.34 ± 0.04		0.498 ± 0.07
[DMIM] [PF$_6$]	1.5 ± 0.04	1.69 ± 0.07	
[DMIM] [BF$_4$]	0.77 ± 0.08		–0.182 ± 0.06
[DEIM] Br	0.533 ± 0.07		

Table 2 Toxicity of some organic solvents.

	IPC81 ***log$_{10}$ (EC$_{50}$ [μM])***	***V. fischeri*** ***log$_{10}$ (EC$_{50}$ [μM])***
Methanol	6.2	7.0
Acetone	> 6.8	5.47
Acetonitrile	6.5	5.77
MTBE	> 5.6	3.89

used are from the hematopoietic system and from the central nervous system, therefore providing information from quite different physiological areas. They have been used previously for biochemical studies in our working group for some years. In general, cell cultures provide a quick and economical means to gain a first understanding about the biological activities of large numbers of substances.

This innovative method is combined with the *Vibrio fischeri* acute bioluminescence inhibition assay, for which a large database of effect concentrations is available. The bioluminescence inhibition assay for acute toxicity based on the bacterium *Vibrio fischeri* (formerly *Photobacterium phosphoreum*) is a standard eco-toxicological bioassay in Europe (DIN EN ISO 11348). Because this method is very rapid and cost-effective it has been widely used in environmental toxicity studies, e.g., routine screening of river and lake water or effluents, monitoring of bioremediated soils, or toxicity testing of chemicals [14].

Table 1 shows the results from testing test-kits 1,2 and 4 with the promyelocytic leukemia rat cell line IPC-81, the rat glioma cell line C6, and the luminescent bacteria *V. fischeri*. Details of the experimental procedure and the biometrical evaluation have been described previously [13]. For a first comparison, Table 2 shows data for selected conventional organic solvents (*V. fischeri* data from [15]). The solvents were chosen because of their widespread use. The comparison shows that, in the case of *V. fischeri*, ILs are more toxic than the conventional solvents tested, with the exception of MTBE, which has effect concentrations similar to the least toxic IL. In the case of the IPC-81 WST-1 assay, all ILs with detectable EC50 values are more toxic than the conventional solvents under investigation, while for the less toxic ILs no conclusion is possible on whether they are more toxic than conventional solvents or not.

5.4.3.2
The Influence of Different Anions

Although it has been stated that modifications of the anion are leading to changes in the chemical and physical properties of ILs [16], the test systems here showed no general systematic effect of the anion, and toxicity seems to be determined mainly by the cationic component; this could be explained by an intercalation of the lipophilic part of the molecules into the membrane, while their ionic head group is at least partially solvated in the aqueous solution, as proposed by Austin et al. [17].

For [PMIM] [PF_6] up to [AMIM] [PF_6] toxicity is even lower than that of the anion itself. It is assumed that in this case the anion and cation of the IL are associated, i.e., they form an ion pair, reducing [PF_6] uptake and hence toxicity. For [HMIM] [PF_6] and [HpMIM] [PF_6] toxicity is similar to that of the anion and compounds with [PF_6] are slightly more toxic than compounds with other anions. This could be due to the higher toxicity of [PF_6] compared to other anions, combined with an uptake of the anion together with lipophilic cations from the medium. Further investigations would be necessary to corroborate these hypotheses. For longer alkyl chain derivatives, the toxicity of the anion can be neglected in comparison to the effects caused by the corresponding cation. The uptake of the cation seems not to be influenced by the type of anion in the tested substance.

5.4.3.3
The Influence of Varying Chain Lengths

All test systems showed higher toxicity with increasing *n*-alkyl chain length.

Since ILs with longer alkyl chains possess more lipophilic properties [16], these results are in accordance with toxicity studies with other chemicals (e.g., Ref. [18]). In addition the structures of the compounds investigated show similarity to cationic surfactants, especially imidazolinium compounds. Cationic surfactants are known to increase membrane permeability and therefore cause narcotic effects with increasing chain length [19].

Furthermore, for some cationic surfactants, quantitative structure–activity relationships have been established for daphnids and fish. Increments used in the ECOSAR toxicity estimation software (Syracuse Research Center, freely available from the US Environmental Protection Agency as part of the software EPI Suite) are –0.13 and –0.37 for each carbon atom in monoalkyl quaternary ammonium surfactants in daphnids and fish, respectively. These increments are much smaller than the ones found here. Our increments for the *n*-alkyl chain in R_1 position are more in accordance with increments for CH_2 groups in *n*-octanol/water partitioning constant estimation procedures, which are, e.g., 0.66 and 0.49 in Hansch and Leo's method and Meylan and Howard's method, respectively [20]. This suggests that uptake into the cells is governed by lipophilicity, or maybe more exactly by membrane/water partitioning [21, 22].

It is interesting to note that, from the regression analysis data presented here, toxicity tends to increase more when the chain length in R_2 position is extended compared to elongation in R_1 position, especially in the IPC-81 assay. This effect might be explained with weaker water bonding of the imidazolium compounds to the end of the longer R_1 residues. This would mean that it takes less energy for the insertion of an additional CH_2 group at the tip of the longer R_1 residue and the hydrophobicity increase as well as the toxicity increase per CH_2 increment is smaller.

The dependence of toxicity on the chain length in the R_1 position is clearly visible for all biological systems that have been tested up to now.

5.4.4
Preliminary (Eco-)Toxicological Risk Profiles

5.4.4.1
General

Generally, ILs will be kept in more or less closed technical systems such as storage containers or batch reactors. It is clear that the risk for man and environment is connected with the possibility and magnitude of a release of the substance from these systems. The next factor determining the magnitude of the risk is the tendency of the substance including the products of its biotic and abiotic transformation to spread in space and time. Further, the tendency of the substance and its transformation products to be taken up by organisms (humans and others) determines the risk. Then the biological activity of the substances, once they have been taken up by organisms, is decisive. And last but not least, a contributor to the risk is the uncertainty in judging all these factors.

Thus the concept of eco-toxicological risk profiles has been derived; it has been described previously and applied [23, 24]. Here, this concept is used for a simplified aggregated risk comparison addressing the risk to man *and* the environment. The indicators making up the (eco-)toxicological risk profiles are Release (R), Spatiotemporal range (S), Bioaccumulation (B), Biological activity (A), and Uncertainty (U).

Such a multidimensional risk analysis is especially suitable for the comparison of chemical substances with a common scope of application. Since the imidazolium ILs under investigation are being used as alternatives for conventional organic solvents, a first screening risk comparison of two selected substances with the common solvent acetone is presented here as a preliminary example. The chosen substances are 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM] [BF_4]) and 1-decyl-3-methylimidazolium tetrafluoroborate ([DMIM] [BF_4]), one for its abundance in organic synthesis literature, the other for its increased toxicity (see below). Each risk indicator is evaluated on a qualitative scale from 1 to 4, signifying a very low (1), rather low (2), rather high (3), to very high (4) risk. Additionally, the uncertainty of each evaluation is evaluated on a scale from very low (A), rather low (B), rather high (C) and very high (D). The scales are intended to be representative for solvents used in organic synthesis. The resulting five-dimensional risk profiles are depicted in Figure 2.

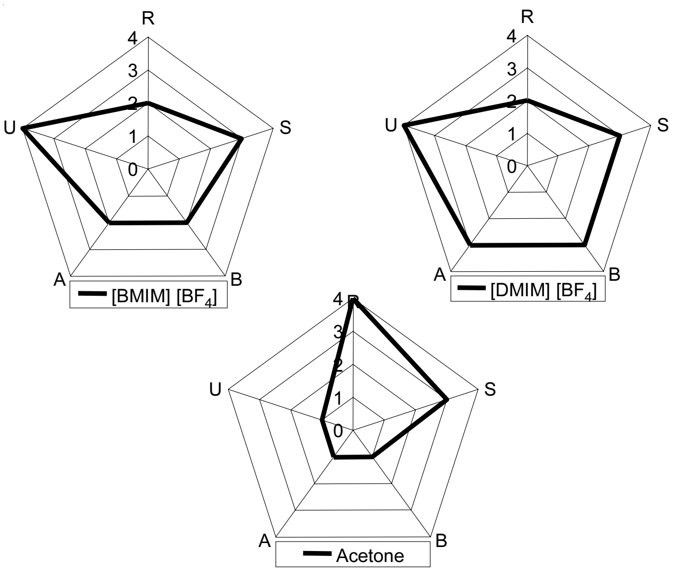


Figure 2 Five-dimensional risk profiles.

5.4.4.2
Release R

In order to provide a just risk comparison, only the application of acetone and imidazolium ILs as solvents for organic synthesis is taken into account. Acetone in general is a substance with a very high production volume, greater than one million tpy, but only a fraction is being used in organic synthesis. Because of its high volatility, its tendency to be released from technical systems is quite high. Contrarily, pure ILs are practically nonvolatile. Therefore, their release from technical systems via air can be assumed to be much smaller. However, their limited solubility in water makes a release via wastewater, potentially bypassing biological treatment, possible while acetone in wastewater will mainly be volatilized into air, the rest being mineralized. An additional pathway, not for the ILs themselves but for their decomposition products, is evaporation of dealkylated imidazole derivatives. In summary, release of acetone is found to be high, with very low uncertainty (4A), while release of imidazolium ILs [BMIM] [BF_4] and [DMIM] [BF_4] is expected to be rather low, with high uncertainty due to lack of information regarding decomposition reactions leading to volatilization and biodegradation in treatment facilities (2D).

5.4.4.3
Spatiotemporal Range S

The spatiotemporal range of the imidazolium ILs is presumably governed by the interplay between water solubility, biotic, and abiotic transformation, and sorption to solid phases. No quantitative information about decomposition and biodegradation of any of the ILs is accessible. Nevertheless it can be assumed that the [BF_4] anions eventually undergo hydrolysis. Also, the imidazolium cations can be expected to biodegrade eventually, following pathways similar to the ones suggested above, but in an unknown timeframe. Acetone will almost completely partition into air under environmental conditions. It is known to be decomposed by reaction with OH radicals and ozone in air with a half-life of ca. 10 to 22 days [13]. These two properties in combination let its spatiotemporal range appear rather high, with rather low uncertainty (3B). The imidazolium cations also are likely to have a rather high spatiotemporal range, definitely with a very high uncertainty (3D).

5.4.4.4
Bioaccumulation B

Acetone is highly volatile and readily biodegradable and therefore does not tend to bioaccumulate in the common sense. Therefore, the bioaccumulation of acetone from the environment is scored very low, with very low uncertainty (1A). The tendency of [BMIM] [BF_4] and [DMIM] [BF_4] to bioaccumulate is unknown. However, [DMIM] [BF_4] can be presumed to have a tendency to be incorporated into membranes, because of its structural similarity to membrane lipids, comprising a charged head group with a nonpolar tail. Generally, the existing water solubility of the imidazolium tetrafluoroborates does not suggest high bioaccumulation. Bioaccumulation of [BMIM] [BF_4] is scored rather low, with very high uncertainty (2D), and bioaccumulation of [DMIM] [BF_4] is scored rather high, with similarly high uncertainty (3D).

5.4.4.5
Biological Activity A

A first study of biological activities of test-kits 1, 2, and 4 has been conducted with three different test systems of the UFT test battery [13]. A distinct influence on toxicity of the length of the alkyl residues was found. In all the assays, ethylimidazolium compounds were significantly more toxic than analogous methylimidazolium compounds. Effect concentrations decreased by about 0.3 (IPC-81 leukemia cell lines) to about 0.6 (*Vibrio fischeri* luminescent bacteria) decadic log units for each additional carbon atom in the long *n*-alkyl chain. The biological activity of [DMIM] [BF_4] is therefore expected to be rather high, which is partially corroborated by some of the first results from terrestrial and aquatic plant tests, still with a rather high uncertainty, since the results from standard eco-toxicological tests are not available (3C). The biological activity of [BMIM] [BF_4] is rather low, also with a rather high uncertainty (2C). In comparison, the biological activity of acetone is very low, in our own tests as well as in standard eco-toxicological tests, with very low uncertainty (1A).

5.4.4.6
Uncertainty

From the above, the remaining uncertainty of the risk evaluation is clearly very low for acetone (1), but very high for both [BMIM] [BF_4] and [DMIM] [BF_4] (4). This shows that the risk comparison can only be very preliminary at this stage of knowledge. To compensate for this a clearly defined strategy to gather additional risk-relevant information is inevitable and it would be appropriate to apply such a strategy well in advance, before ILs will become high production volume chemicals.

5.4.5
Outlook

Regarding the sustainable development of ILs, the integration of companies and academic research from the very beginning will open up the chance to consider technological needs while avoiding hazardous structures in the early steps to development of new industrial chemical products. Together, chemists, biologists, and technologists have to find appropriate compounds based on T-SAR, QSARs and testing.

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5.5
Concluding Remarks and Outlook

Hélène Olivier-Bourbigou

Homogeneous catalysis will probably progress through the development of novel ligands and organometallic catalytic systems in order to improve reaction selectivities to get "purposeful" processes. But besides the catalyst design, the way the catalyst is used (liquid, gas–liquid-phase, or two-phase operation, presence or absence of solvents) can have a significant impact on the engineering of the process (reactor size and design, product separation, catalyst neutralization and disposal, etc.) and on its final cost.

Thus, the quest for novel solutions and technologies to carry out homogeneous catalysis remains a real preoccupation of scientists and engineers [1]. Two main approaches are still envisioned: catalyst immobilization on soluble or insoluble supports, and the operation in biphasic systems. In the biphasic (or multiphasic) approach, there is a large choice of possible liquid–liquid phase systems including aqueous–organic systems, fluorous–organic systems, supercritical carbon dioxide systems, ionic liquids–organic system, and combinations of these different possibilities. There is of course no universal solution. The solution has to be adapted to the reaction, the possible side reactions, the nature of the catalytic system, the products, and the byproducts. Conversely, the catalytic system may be adapted to the technology used.

Not very long ago, ionic liquids (ILs) were just considered as potential alternative solvents for multiphasic reactions and were mentioned in the "outlook" chapter of books dealing with this area, whereas water was already industrialized in key transition metal catalyzed processes [2]. ILs have now attracted more interest. It is possible to buy them, which probably promotes their use, and there are more and more physical data available on these solvents. The range of reactions that have been described in these media is probably wider than in $scCO_2$ or fluorous solvents. But it would not be realistic to assume that all catalyzed reactions can be transferred to ILs with benefits. The advantages of using ILs have been well described for some reactions which have been reported in this book, and just a few of them have been run on micro-pilot or pilot scale.

So why have ionic liquids gained so much interest since the mid-1990s? If the interest of ILs was first to offer "green" alternatives to volatile organic solvents, this is not the only reason for their wide development. Because of their unusual set of physico-chemical properties, they are very different from conventional organic solvents. They may give the opportunity to develop reactions that are not possible in other solvents. For example, they offer a nonaqueous environment to substrates and can be poorly miscible with organic compounds (see Section 5.4.5). But one would expect more than just physical solvents: "new chemistry" may be foreseen. It has indeed been proven that the nature of the IL may influence the outcome of chemical reactions [3, 4]. In many cases the use of IL contributes in improving

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reaction rate and selectivity. This is the case for biphasic systems in which organic reactants are more soluble in the catalyst ionic phase than are the products or reaction intermediates. Consecutive side reactions of products can be minimized (see Sections 5.4.1 to 5.4.4). Product separation can be made easier and less energy consuming. ILs also may stabilize catalyst and prevent their deactivation (see Section 5.4), leading to less catalyst consumption and waste.

In some cases, ILs act as both solvents and catalysts, which may simplify processes. Examples are given for reactions catalyzed by Lewis or Brønsted acids (see Section 5.4.4). They also open the way for association of different processes such as electrochemistry and catalysis, sonochemistry or microwaves and catalysis.

From an engineering point of view, ILs offer a great potential for separating reaction products and recycling catalysts. New reactors, much smaller than those used in homogeneous catalysis, can be designed (see Sections 5.3.1 and 5.3.2) which contribute in making processes more “environmentally friendly”. The physical properties of ILs, such as their viscosity, density, thermal stability or surface tension, are important to consider in the design of processes. For example, their viscosity remains in general rather high, even if it can be relatively varied according to the nature of cation and anion. For biphasic systems, important stirring power may be needed to ensure a good reaction rate. The demonstration of the thermal and chemical stability and the recyclability of ILs can only be proven through a continuous pilot-scale run. ILs biphasic systems may suffer from one drawback typical for heterogeneous catalysts: sensitivity to feed impurities that can accumulate in the ionic phase. In some applications feed pre-treatment is a main concern.

Examples of industrial development of ILs for catalysis are still scarce. Using IL for industrial reactions raises a series of specific questions (see Section 5.1). The scaling-up of IL synthesis procedures has been considered and is probably not the main difficulty. However, the commercialization and/or transport of these ILs raise the question of their registration (EINECS for Europe or equivalent). Disposal and eventual recycle of ILs are important concerns and should probably be considered case by case.

Examples of industrial applications or pilot-scale developments are also described. The reasons for the success and development of ILs are really specific to the reactions and specific to some properties of ILs. In the catalytic HF fluoration of trichloroethylene to 1,2-dichloro-2,2-difluoroethane and 1-chloro-2,2,2-trifluoroethane in the liquid phase, ILs based on $SbX_6^-/Sb_2X_{11}^-$ anions are used as sources of Sb(V) Lewis acid catalyst. The ILs proved to be superior to the typically used $SbCl_5$ catalyst because of their lower sensitivity to reduction to Sb(III) and not because they improve reaction activity. SbF_6^--based ILs may offer great potential for the substitution of $SbCl_5$ in all these processes. In the Difasol process, thanks to their unique solubility properties, ILs render possible the development of a biphasic system in which the unmodified homogeneous catalyst can be stabilized and recycled, thus decreasing global catalyst consumption. Because consecutive side reactions are minimized, reaction selectivity is increased, leading to an improvement in reaction yield. As a consequence, much smaller reactors are needed.

BASF’s Basil process uses ILs as functional materials and not as a solvent. The IL (e.g., methylimidazolium chlorhydrate) is formed during the chemical reaction while scavenging acid byproducts (e.g., HCl). The generation of IL leads to the formation of two clear phases in the reactor, thus solving the problem of separation of byproduct and the elimination of solid formation. This leads to an increase in reaction rate and productivity and a decrease in reactor volume.

Much remains to be done. A better understanding of the interactions between IL and reactants (or products) on one hand, and IL and catalyst on the other, should help in optimizing the choice of IL for a given reaction. The development of new ILs, with new properties, will make it possible to adjust the properties of ILs to each reaction.

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6
Catalysis using Supercritical Solvents

Walter Leitner (Ed.)

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6.1
Introduction

Aaron M. Scurto

6.1.1
Physico-Chemical Properties of Pure Supercritical Fluids

A supercritical fluid (SCF) is any compound above its critical point, which is the maximum in both temperature and pressure at which a gas and liquid can coexist. Above the critical point, isothermic compression yields a continuous increase in density without condensation to a liquid state. All substances theoretically have a critical point, but many experience thermal degradation well before reaching it. Figure 1 is the classic pressure–temperature (*PT*) representation of the phase changes of a pure component. There are three primary phases of pure components: solid, liquid, and vapor; solid–solid transitions, liquid crystal phases, etc., are also possible but will not be considered here. The solid lines represent the sublimation curve (solid→vapor), the vapor pressure curve (liquid→vapor), and the melting curve (solid→liquid) of the pure component. The triangle represents the triple point, in which a solid, liquid, and vapor coexist in equilibrium. The circle represents the pure component critical point, which begins the "supercritical" region.

The term "supercritical" is different for mixtures, although it is sometimes used similarly. Mixtures, e.g., of gases and liquids, are considered to be above their mixture critical point (supercritical) when the two phases become infinitely soluble or miscible. The mixture critical point for liquids and gases is always above the critical point of the pure gaseous component (vide infra).

Carbon dioxide is the most employed substance by far in supercritical fluid processes and will be the focus of much of the discussion here. Other substances have found use in certain circumstances; the most common fluids and their critical

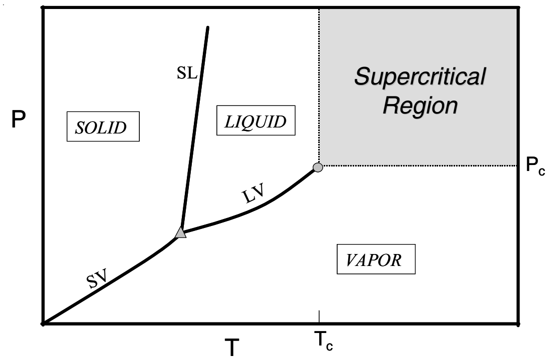

Figure 1 PT diagram of the phase transitions of a pure substance, illustrating the critical region; the circle represents the critical point and the triangle the triple point.

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Table 1 The critical properties of common fluids for supercritical fluid processes [1].

Substance	***MW*** ***[g mol^{-1}]***	***T_C*** ***[K]***	***P_C*** ***[MPa]***	***ρ_C*** ***[g mL^{-1}]***
Carbon dioxide	44.0	304	7.4	0.47
Ethane	30.1	305	4.9	0.21
Ethylene	28.1	282	5.0	0.21
Propane	44.1	370	4.3	0.22
Xenon	131.3	290	5.8	1.10
Ammonia	17.0	406	11.4	0.24
Nitrous oxide	44.0	310	7.2	0.43
Fluoroform	70.0	299	4.9	0.53
Water	18.0	647	22.1	0.32

points are listed in Table 1. CO_2 is the preferred SCF because it has mild critical constants, it is nontoxic, flammable, and inexpensive. While CO_2 may not be the "best" fluid in terms of absolute dissolving power, adjustable dielectric, etc., there are no other fluids which combine health and safety properties with low cost and availability. Water would be the one exception, but its critical properties are very high, i.e., T_C of 374 °C and P_C of 22.1 MPa. Despite the high critical point, supercritical water is utilized in large-scale processes for the destruction of hazardous wastes [2, 3].

When speaking of supercritical fluid technology, one most often wishes to indicate fluids above their critical point, yet within a regime of "liquid-like" densities. Reduced parameters are often used to describe these regions [Eq. (1)]:

$$T_R = \frac{T}{T_C} \qquad P_R = \frac{P}{P_C} \qquad \rho_R = \frac{\rho}{\rho_C} \tag{1}$$

Reduced temperatures T_R are usually within the range 0.9–1.2, therefore just below the critical temperature (usually the liquid state) to just above the critical temperature; when T_R reaches approximately 1.5, the pressure needed to achieve liquid-like densities usually becomes prohibitively high ($P_R \sim 10$) for most fluids. Reduced pressures P_R are usually > 1 and reduced densities from gas-like 0.1 to 2.5 [4]. In general, temperatures are usually below 150 °C and the pressure below 30 MPa.

6.1.1.1
Thermodynamic Properties

6.1.1.1.1
Density

Many physical and chemical properties are related to the density of the fluid. Properties such as the isothermal compressibility factor, κ_T, and the coefficient of thermal expansion, α, are simply derivatives of density (molar volume, V) with temperature or pressure [Eq. (2)].

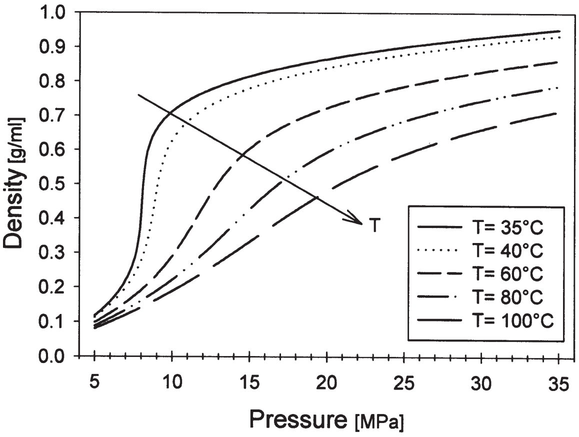

Figure 2 The change in density with pressure at various temperatures for CO_2 from the Span–Wagner equation of state [5].

$$\kappa_T = \frac{-1}{\underline{V}}\left(\frac{\partial \underline{V}}{\partial P}\right)_T \qquad \alpha = \frac{1}{\underline{V}}\left(\frac{\partial \underline{V}}{\partial T}\right)_P \tag{2}$$

As seen in Figure 2, the density of CO_2 changes dramatically in the near-critical regime. The isotherm at 35 °C (approx. 4 °C above T_C), illustrates the steep ascent within the 5–10 MPa range, followed by more modest increases in density with pressure. As the temperature is increased, the rate of change with pressure decreases. At roughly 20 MPa, the density at 100 °C is roughly half that at 35 °C. This highlights one of the reasons why most supercritical fluid processes are performed at temperatures of less than 150 °C.

6.1.1.1.2
Joule–Thomson Coefficient

Most supercritical fluid processes, whether extractions or reactions, involve pressure changes at some point, at times very large changes. Flow of supercritical fluids through valves from a region of higher pressure to lower pressure is quite common. This process is governed by the Joule–Thomson coefficient, μ_{JT}, which is defined as the change in temperature with the change in pressure at constant molar enthalpy, $\underline{H}$ [Eq. (3)]:

$$\mu_{JT} = \left(\frac{\partial T}{\partial P}\right)_{\underline{H}} = \frac{T\left(\frac{\partial V}{\partial T}\right)_P - \underline{V}}{C_P} \tag{3}$$

The Joule–Thomson coefficient of an ideal gas is zero, but in real gases, it can be very significant. The sign of the coefficient affects the temperature upon expansion: if $\mu_{JT} > 0$, then the temperature decreases, otherwise it increases. The Joule–

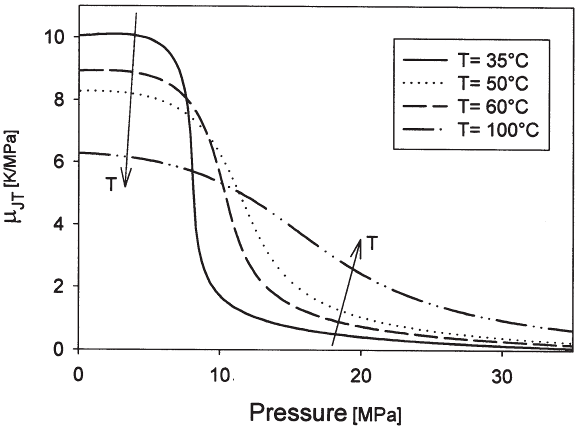

Figure 3 Variation of the Joule–Thomson coefficient, μ_{JT}, of CO_2 with temperature and pressure.

Thomson coefficient changes with both temperature and, to a lesser extent, pressure. The temperature at which the sign of the coefficient changes is called the Joule-Thompson inversion temperature. For most gases, the inversion temperature is well above ambient conditions, e.g., for air it is at 330 °C, and for methane 695 °C. Methane is a notable exception; it has a negative coefficient at ambient temperature and will warm upon venting (adding to the possibility of ignition). CO_2 has an exceptionally high μ_{JT} (0.55 K/(0.1 MPa) at 10.1 MPa and 50 °C [6]) and an inversion temperature of ~1230 °C; thus its expansion will always yield lower temperatures, even in the most extreme conditions associated with "supercritical" processes. Figure 3 illustrates the change in the Joule–Thomson coefficient with pressure for different isotherms. Obviously, in a real venting process, the coefficient would change with the drop in both temperature and pressure. Great care must be taken while venting CO_2, in order to avoid hypothermic exposure of laboratory workers. Another practical implication is that most valves involved with venting large quantities of CO_2 should be heated to avoid plugging due to the formation of "dry ice".

6.1.1.1.3
Heat Capacity

In general for gases, the constant-pressure heat capacity, C_P, decreases with increasing temperature and increases with increasing pressure (Figure 4). However, as with CO_2, there may be a maximum in C_P for pressures above the critical pressure. At the critical point, the heat capacity technically goes to infinity. The constant-volume heat capacity, C_V, is very insensitive to pressure and experiences only minor deviations in the near-critical regime.

The system expands as the temperature increases at constant pressure. Work is needed against the molecules and the atmosphere as they move apart. In the critical region the coefficient of thermal expansion at constant pressure is large and thus the effect on C_P is also large.

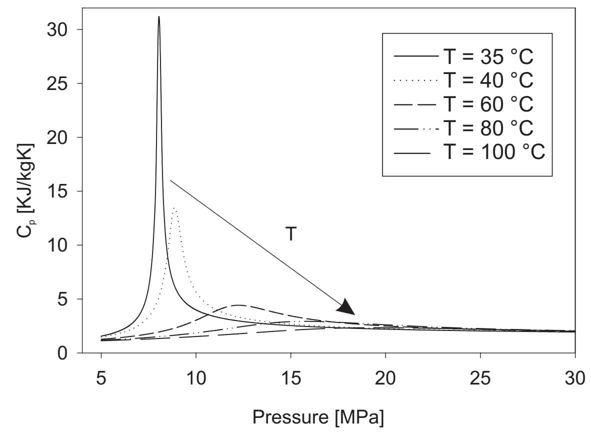

Figure 4 Isobaric heat capacity of CO_2 versus pressure in the near and far critical regimes from the Span–Wagner EOS [5].

6.1.1.1.4
Dielectric Constant

The dielectric constant is an important property for chemical reactions and reaction theory. Although it is not technically a thermodynamic property, it will be discussed here. For supercritical fluids such as CHF_3 and water, temperature and pressure can be adjusted to achieve large variations in the dielectric constant. For others, such as CO_2, the dielectric constant changes little between ambient pressure to several times the reduced pressure. Figure 5 illustrates the large differences in the dielectric constant between CO_2 and CHF_3. Both have similar qualitative behavior

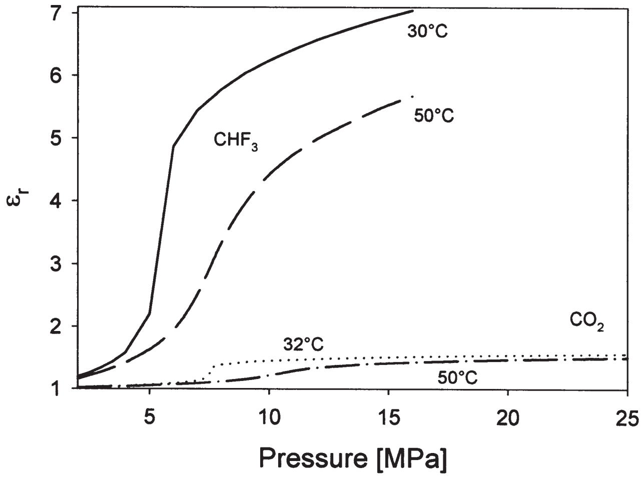

Figure 5 The dielectric constant of CHF_3 and CO_2 from the data of Makita et al. [7] and Moriyoshi et al. [8] respectively.

relative to their critical points, but CHF_3 has a much higher and much more tunable dielectric constant which will become apparent in its effect on reactions.

6.1.1.2
Transport Properties

The three most important transport properties for reactions and process design are diffusivity, viscosity, and thermal conductivity. Diffusion is the transport of molecules down a concentration gradient, or more exactly, down a chemical potential gradient. Viscosity is the transport of momentum along a transverse velocity gradient. Viscous forces are the frictional forces that attempt to equalize the velocity of all parts of a fluid. Thermal conductivity transports energy down a temperature gradient. Many of the advantages of supercritical fluids in practice are due to their advantageous transport parameters. Their properties are generally intermediate to those of liquids and gases.

6.1.1.2.1
Diffusivity

Generally, diffusivity is faster and viscosity lower for supercritical fluids than for liquids. A standard value of the diffusivity of solutes in liquids is roughly 10^{-5} cm^2 s^{-1} [4]; the diffusion coefficient of naphthalene in CO_2 at 10 MPa and 40 °C is $1.4 \cdot 10^{-5}$ cm^2 s^{-1} and the self-diffusion coefficient of CO_2 itself is two orders of magnitude higher than that of liquids [9]. The effect of temperature and pressure on the self-diffusivity of CO_2 is illustrated in Figure 6. Diffusivity is obviously a major consideration in reactions whether they be homogeneously, heterogeneously, or not catalyzed, and it will determine whether a reaction is controlled kinetically or by diffusion.

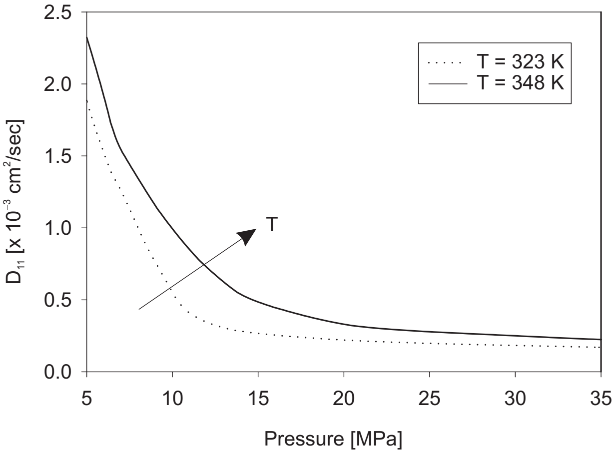

Figure 6 The self-diffusion coefficient, D_{11}, of CO_2 with temperature and pressure (according to Etesse et al. [10]).

6.1.1.2.2
Viscosity

Viscosity is only strongly influenced by pressure in certain ranges of temperature and pressure. Generally, pressure influences viscosity strongly at low reduced temperatures, T_R, and at high reduced pressures, P_R. Figure 7 illustrates the behavior of viscosity at different temperatures and pressures for CO_2. Under supercritical conditions and constant pressure, viscosity decreases to a minimum and then increases; the minimum is shifted to higher temperatures with increasing pressure. Under the most common conditions for supercritical processes, viscosity can generally be expected to decrease with temperature.

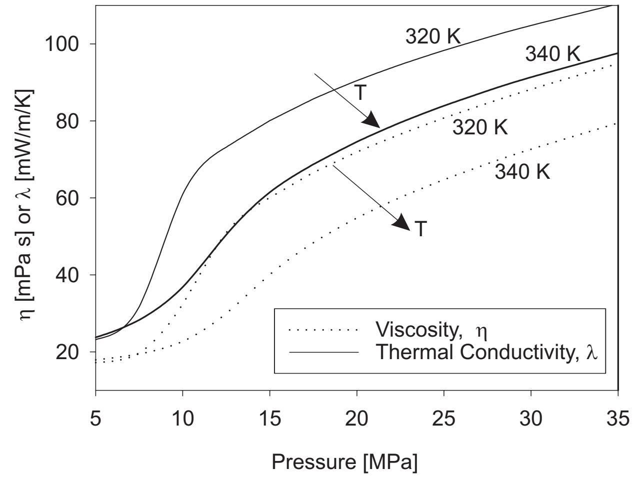

Figure 7 The similar behavior of viscosity and thermal conductivity of CO_2 with increasing pressure (from the correlations of Vesovic et al. [11]).

For mixtures of supercritical fluids with liquids, as the pressure increases and more of the supercritical fluid dissolves in the liquid phase the viscosity of the liquid phase decreases at constant temperature; an increase in temperature reduces the viscosity at constant pressure. The viscosity of the vapor phase increases with increasing concentrations of the liquid component. At higher pressures, more of the liquid component dissolves into the supercritical phase and the viscosity increases, but not to the same extent as the drop in viscosity with increasing concentration of the supercritical fluid.

6.1.1.2.3
Thermal Conductivity

Thermal conductivity is associated with the transport of energy at the molecular level and is thus intrinsically related to viscosity and heat capacity. For most gases in ambient conditions, thermal conductivity, λ, is between 0.01 and 0.025 W m^{-1} K^{-1}.

The thermal conductivity of CO_2 is illustrated in Figure 7. With increasing pressure, thermal conductivity increases at constant temperature. At constant pressure, thermal conductivity decreases with increasing temperature. Thermal conductivity exhibits a large (approximately seven-fold) spike near the critical point due to a similar increase in the constant-pressure heat capacity. Thermal conductivity is important for reactions for two main reasons. Depending on the heat of reaction, local hot (or cold) pockets could exist. It is also important for the rapid heating and cooling necessary for some processes.

6.1.2
Phase Behavior and Solubility in Supercritical Fluids

Knowledge of the phase behavior of high-pressure systems involving supercritical fluids such as carbon dioxide is extremely important. Failure to understand the effect of temperature, pressure, and concentration on the physical behavior (especially solubility) can lead to erroneous conclusions and subsequently poor process designs.

6.1.2.1
High-Pressure Phase Behavior of Mixtures

The study of high-pressure phase behavior in general has yielded rich and diverse phenomena that are interesting from both a theoretical and an application perspective. Development in this area has largely evolved from the petroleum and natural gas industries, which deal with multicomponent and multiphase mixtures over a wide range of conditions, from deep within the Earth to separations at a refinery. Ever increasing new applications have spawned serious interest in the subject, especially emanating from research on the use of supercritical fluids as environmentally benign solvents.

The mixing of substances can lead to many different types of phase transitions, beyond the three found with pure components. Phase behavior can be quite complex, especially with processes that change temperature, pressure, and composition. One can use a “metric” of this complexity with the Gibbs phase rule as expressed in terms of degrees of freedom: $F = C - P + 2$, where F is the number of degrees of freedom, C is the number of components, and P is the number of phases. For reacting systems, $F = C - P - M + 2$, where M is the number of independent reactions. The Gibbs phase rule relates the number of components, the number of phases and the number of field variables that characterize a system in thermodynamic equilibrium. It is customary to discuss phase behavior and mixtures in terms of directly or easily measurable quantities, such as the field variables: temperature, T, pressure, P, and composition (mole fraction), x_i. For example, a nonreacting two-component and a two-phase mixture yields two degrees of freedom, and, thus, is characterized by T and P, or T and one concentration, etc. One of the effects of two degrees of freedom is that on plots of Tx, Px, and PT, there will be a region (area) where two phases coexist, not a line as with one degree of freedom

(SV, SL, LV lines of Figure 1), nor as a point with zero degrees of freedom (the triple point of Figure 1). With two components and zero degrees of freedom, a maximum of four phases can coexist at a quadruple point, e.g., solid–liquid one-liquid two-vapor (SLLV) equilibrium; with three components a maximum of five phases can coexist, etc. The phase rule demonstrates that increasing the number of components substantially increases the possible complexity of the phase behavior.

The possible complexity of multicomponent systems cannot be overemphasized in the study of reactions in supercritical fluids. The simplest unimolecular, A → B, reaction in SCFs represents three components and thus a possible temperature, pressure, and conversion level (concentration) that would produce a five-phase system. For a more common situation, e.g., the hydrogenation of styrene with a rhodium complex, the system would consist of a solvent (CO_2), catalyst (a solid Rh complex), substrates (liquid styrene, gaseous hydrogen), and a product (ethylbenzene). This would yield a mixture with up to seven possible phases. Of course, systems with a large number of possible phases would probably only occur in a very limited T, P, and concentration space, if at all. However, without proper attention to the number of phases throughout the reaction, researchers may draw erroneous conclusions. If an extra phase is not taken into consideration, the necessary concentration and phase fraction of that extra phase would yield incorrect mass balances. Often, some of the additional phases may represent a very low fraction of the total mass, so that a mass balance of 95–99%, for example, may seem to be "closed", but may indeed indicate the presence of small amounts of additional phases. High-pressure viewcells are the best equipment to avoid such errors, where the number of phases can be visually inspected over the conversion range of the reaction. However, some phases may just comprise a few small droplets or crystals, etc. that are difficult to observe.

6.1.2.2
Phase Diagrams of Binary Mixtures: Liquids and Vapors

It is informative to familiarize oneself with binary phase diagrams of the supercritical fluids and liquids as they provide a basis from which to devise conditions for multicomponent reactions. One of the most common representations of the behavior or equilibrium of a vapor and a liquid is the pressure–composition (Px) diagram. The most common nomenclature uses x_i as the mole fraction composition of component i in the liquid phase and y_i as the mole fraction composition of i in the vapor phase; z_i is often used as an ambiguous loading composition, which is intended to split into one or more phases. Often, supercritical reactions are conducted isothermally and the behavior with pressure at constant temperature is of greater interest than an isobaric reaction; pressure is the easier of the two variables to change rapidly or control. Figure 8 illustrates a typical Px diagram as encountered with most liquids and CO_2 above the critical temperature of CO_2. The diagram yields a variety of information. At a mole fraction of zero CO_2 or equivalently a mole fraction of 1 for the liquid component, the "envelope" emerges from the vapor pressure of the liquid component; at pressures above P^{vap} the substance liquefies,

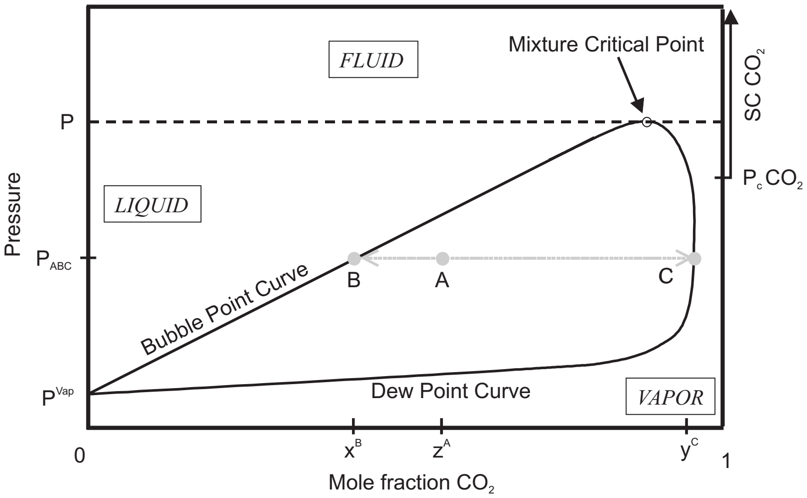

Figure 8 A typical *Px* phase diagram of a liquid and CO_2.

below it vaporizes. The rest of the "envelope" is constructed of two curves: the bubble point curve and the dew point curve; they separate the single-phase areas of completely liquid or completely vapor. The bubble point is the solubility of CO_2 in the liquid phase or alternatively it may be viewed as the first point at which the liquid will boil (form a bubble) as pressure is reduced from regions above the curve. The dew point is the solubility of the liquid component in the CO_2-rich phase or alternatively the first point at which vapor will condense (form dew) as the pressure is increased from regions below the curve. Any mixture of the two components that are constructed between concentrations of x^B and y^C, e.g., z^A, and pressurized to P_{ABC} would equilibrate to liquid and vapor phases with compositions of x^B and y^C respectively. The ratios of the line segments of AB, BC, and AC would yield the fraction of moles in each of the phases according to the Lever rule. If the overall (system) concentration is below x^B or above y^C, then only one phase can exist.

The bubble and dew points terminate at the mixture critical point (for temperatures above the critical temperature of the SCF). The mixture critical point is the greatest pressure and composition at a given temperature at which both liquid and vapor phases can coexist. Above the mixture critical point, a single fluid phase exists that is completely miscible in all proportions of the two components. As seen from the diagram, this pressure is always greater than the critical pressure of the pure SCF, e.g., CO_2.

For most researchers performing reactions, the most important information from this diagram is the mixture critical point. It gives the minimum pressure at a given temperature at which one can operate in a single-phase regime. It is the minimum pressure, because with the addition of other components the phase envelope shifts upward, requiring higher pressures to maintain a single phase. Now, as will be discussed later, control over the phase behavior will yield sensitive control over the reaction and subsequent separation. For multiphase processing, the kinetics and phase equilibrium might dictate a two-stage approach in which the first stage optimizes the phase behavior of the reactants in the reaction or catalyst phase, and is followed by a second stage that is optimized to partition the product out of that phase. Alternatively, the equilibrium may be such that reaction and separation may be possible in a single stage.

6.1.2.3
Phase Diagrams of Binary Mixtures: Solid–Fluid

The phase behavior and solubility of solids in supercritical fluids is quite different than that in liquids. First, it is assumed that the solubility of the fluid-phase component, such as supercritical CO_2, in the solid phase is negligible. This is unlike the equilibrium with liquids, where one must consider the mutual solubilities of both the liquid solute and the fluid phase. From thermodynamics, the mole fraction solubility of a solute in a supercritical fluid, y_2, is given by Eq. (4), where, P^{sub} is the sublimation pressure of the solid which is a function of temperature alone, the exponential term is called the Poynting correction (usual values are 1 to 4) to account for hydrostatic pressure, and the fugacity coefficient, ϕ, which accounts for the non-idealities of the fluid phase at a certain temperature, pressure, and concentration. At low pressures, the behavior is ideal and the solubility y_2 is equal to P^{sub}/P.

$$y_2 = \frac{P_2^{\mathrm{sub}} \exp\left[\dfrac{\underline{V}_2^{\mathrm{s}}\,(P - P_2^{\mathrm{sub}})}{RT}\right]}{\hat{\phi}_2^{\mathrm{scf}}\,P} \tag{4}$$

Figure 9 illustrates the behavior and solubility of a solid in a compressed gas. At low pressure (e.g., ~ < 1 MPa for CO_2), the solubility of a solid in a gas follows ideal behavior and is inversely proportional to the pressure. As the pressure approaches the sublimation pressure of the solid, the mole fraction solubility tends toward 1; below the sublimation pressure the solid completely vaporizes. Beyond the ideal region, the solubility experiences a minimum before becoming proportional to the

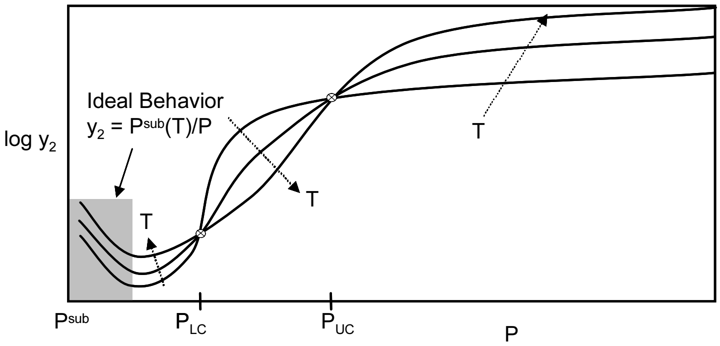

Figure 9 The solubility of solids in supercritical fluids.

pressure. This change is due to the non-idealities of the near- and supercritical fluid and is reflected in the low value of the fugacity coefficient. For some systems, the fugacity coefficient, ϕ, can approach values of less than 10^{-5}, reflecting the enhancement and the non-ideality under supercritical conditions [12]. At higher pressures, the marginal solubility decreases with pressure, and smaller enhancements with pressure are observed.

The effect of temperature on the solubility is quite interesting and can be divided into three regions. In the low-pressure and high-pressure regions, the solubility increases with increasing temperature at constant pressure. In the intermediate pressure region, the solubility surprisingly decreases with increasing temperature. The solubility itself is a balance of solvent effects and volatility effects. In the low- and high-pressure regions, the density does not change substantially with temperature and pressure (see Figure 2) and thus volatility effects dominate, i.e., P^{sub} increases with temperature. In the intermediate region, the large changes in the density (compressibility, etc.) dominate and thus solubility is proportional to density, which increases with decreasing temperature at constant pressure. As one traces the solubility at each of the three temperatures, the solubility of the three isotherms is equal at two pressures. These “crossover” points are called the lower (P_{LC}) and upper (P_{UC}) crossover pressures respectively [13]. At these points, the effects of density and volatility are equal. The crossover pressures, especially P_{UC}, can be of practical use in both reaction and separation steps. If a desired solubility of a solid reactant or catalyst is needed, knowledge of the upper crossover pressure would allow the researcher to know precisely whether an increase in temperature or pressure is needed. Otherwise, one may try intuitively to increase the solubility by increasing the temperature at constant pressure, which may have the opposite effect. With knowledge of the crossover points, solutes may be selectively precipitated, leading for example to the separation of isomers [14].

6.1.2.4
Global Fluid Phase Behavior of Liquids and Gases

Global phase behavior at elevated pressures can be quite diverse and complex. To date, there exist 16 different classes of unique global phase behavior diagrams for binary mixtures of liquids and gases. Most reaction mixtures comprise more than two components and would possibly have an even greater range of complexity. Whereas understanding and classifying phase behavior is a discipline unto itself, a general qualitative and phenomenological understanding would be quite useful to investigators who are most interested in performing reactions correctly.

Van Konynenburg and Scott [15] were the first to provide a uniform classification scheme for the global binary phase behavior of liquids and gases. High-pressure phase behavior of binary mixtures is usually illustrated by a pressure–temperature (*PT*) projection (see Figure 10), which is a two-dimensional representation of the salient aspects of the phase and critical phenomena taken from three-dimensional plots of temperature, pressure, and composition. They show the connectivity of the pure component phase transitions, especially mixture critical points, as one proceeds to increasing concentrations of one of the components. “Slices” through these *PT* projections would yield *Px* and *Tx* equilibrium diagrams (vide supra). In Scott and van Konynenburg’s scheme, all binary systems fall within one of five (later a sixth was added by Rowlinson and Swinton [16]) phase behavior types, although at present 16 exist. In 1998, Bolz et al. [17] proposed a new nomenclature system for the International Union of Pure and Applied Chemistry (IUPAC) based on a more descriptive nomenclature where the salient components (topology and connectivity of the critical curves) are represented in the classification identification number. Each phase behavior type has characteristic phase transitions.

6.1.2.5
Global Phase Behavior with Solid and Fluid Phases

All of the proposed phase behavior classification schemes describe liquids and gases. However, many of the systems related to reactions in SCFs involve solids, e.g., the reactant and especially the catalyst may be solid. One could imagine the added complexity of inserting solid-phase transitions into just the six types.

The pressure–temperature projection of a typical binary solvent–solid solute system is shown in Figure 10; the phase behavior of CO_2 and naphthalene is qualitatively similar to most of the diagram. This diagram shows a projection of all the salient features in the *P*–*T*-composition diagram, where the solid lines represent the pure-component phase transitions, i.e., melting, vaporization, and sublimation. Only the vaporization line of the pure gaseous solvent (ending at the critical point (c.p.)) is shown at lower temperatures in this figure. In the presence of the gaseous solvent, the melting curve of the pure solute can be lowered as shown by one of the dashed–dotted SLV curves (solid, liquid, and vapor in equilibrium) for Types I and II. They emanate from the triple point of the solute and terminate at the upper critical endpoint. It has been observed that the SLV curve can have a minimum in temperature on a *PT* projection (or can even have a maximum in pressure and become even lower at lower temperatures). This SLV line terminates in an upper critical endpoint (UCEP), indicated by a triangle, where the vapor and liquid phases become identical in the presence of the solid phase. Solid–liquid–vapor equilibrium can also occur at lower temperatures near the critical point of the less volatile component, as shown in the figure. However, this is more similar to boiling point elevation of the liquefied gaseous solvent, as the liquid phase is mostly composed of the solvent. Supercritical fluid extraction and reaction processes are usually operated at temperatures within about 100 °C of the pure fluid c.p., to take advantage of the high compressibility of the fluid in this region. If the UCEP is within this range of potential operating conditions, then the possibility of solid–liquid–vapor equilibria exists, which would impact on a reaction.

The detailed phase behavior at two different temperatures, labeled T_D and T_E in Figure 10 are shown in Figure 11. Figure 11 can be envisioned as “slices” in the third dimension of Figure 10. Similar discussion for a few of the labeled isotherms are given in Refs. [18–22]. At temperature T_D the behavior is similar to that in Figure 9, but plotted in a different manner. At temperatures above the UCEP

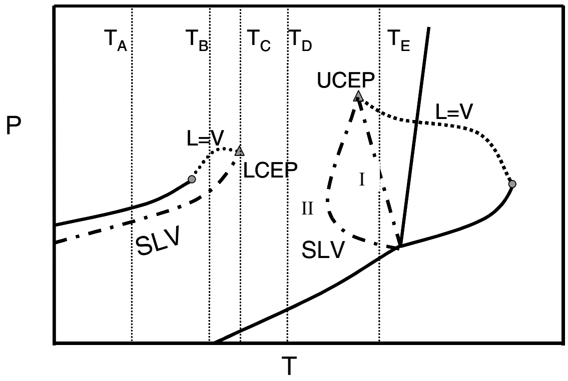

Figure 10 Pressure–temperature diagram of a typical solid solute–gaseous solvent system.

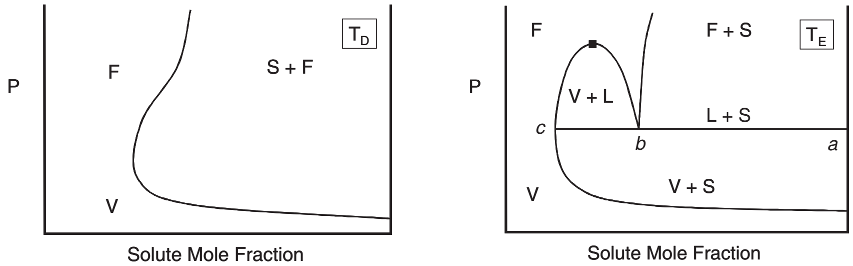

Figure 11 *Px* diagrams of two isotherms from Figure 10.

(Figure 11, temperature T_E), the diagram is qualitatively similar to one for temperatures between the c.p. of the solvent and the lower-critical endpoint (LCEP) (T_B, Figure 10). However, when SLV equilibrium exists, the liquid phase is composed mostly of the solute component. This phenomenon is also called melting point depression as the pressurized gas induces melting before the normal ambient pressure melting point; some gases actually increase the melting point, e.g., helium. At the pressure indicated by the SLV line, all three phases would exist over a very wide feed composition range: the pure solid at point *a*, a liquid with a composition indicated by point *b*, and a vapor with a composition indicated by point *c*. Above the SLV pressure the mixture can exist as solid–liquid equilibrium, vapor–liquid equilibrium, just a liquid or just a vapor, depending on the solute loading (the ratio of solid solute to gas). Notice that the vapor–liquid envelope is not connected at the pure solvent axis of the diagram, because the temperature is greater than the critical temperature.

The best studied example of this behavior is that of CO_2 and naphthalene (normal melting temperature 80.5 °C) [23–27]. Here, naphthalene can melt approximately 20 °C lower than its normal melting point at roughly 15 MPa of CO_2 pressure. It is sometimes difficult to detect transitions from SFE to SLVE and VLE without proper visual verification of phase behavior. This process can aid in reactions, as illustrated by Jessop et al. [28], who discovered that CO_2 pressure dramatically increased the reaction rate of vinylnaphthalene because it induced melting of the solid, which increased the mass transfer and mixing in the system.

6.1.2.6
Multicomponent Phase Behavior

Multiphase phenomenon is more frequently encountered in multicomponent mixtures, such as reaction mixtures. From a thermodynamic perspective, multiphase phenomena exist because multiple phases reduce the Gibbs free energy of the system. More components mean more ways and phases in which to partition this energy. Due to the Gibbs phase rule, a third component extends multiphase equilibrium as seen in binary mixtures, such as LLV and SLV equilibrium, from a *line* to a *region* of pressure and concentration at a given temperature.

As a general observation, a solid solute increases the likelihood of forming an additional liquid phase for two reasons. Assuming the fluid phase is composed of the supercritical solvent and an ambient liquid, the solid solute acts as an impurity inducing a form of "boiling point" elevation; higher pressures are needed in order to maintain a single fluid phase. Secondly, in this mixed fluid, the solid solute can melt more easily due to both the interaction with the pressurized gas and the liquid component present.

Figure 12 represents a typical scenario encountered when additional components (liquids or gases) at a certain initial concentration are added to a system with a solid component. These are ternary diagrams of a simple system, naphthalene, CO_2, and toluene, as adapted from Kikic et al. [29]. They illustrate the behavior with the composition of a mixture at a certain temperature and pressure. Each of the vertices is the pure component location. Each of the axes represents the phase equilibrium if the third component were absent, while lines parallel to the axes and moving toward the opposite vertex increase the concentration of the third component. To understand what may happen to a fluid mixture (with an original mixture ratio) as it comes in contact with the solid, a line of constant gaseous solvent/liquid ratio is drawn on the figure at about 10% toluene/CO_2, extending to the naphthalene vertex. By following this line, one may see into which equilibrium the mixture will split.

As seen from Figure 12, a large variety of phases and equilibria can occur, depending on the concentration of the components. Various permutations of a system which may have a solid, two liquids and a vapor phase appear, e.g., liquid–liquid–vapor equilibrium (L_1L_2V), various solid–liquid equilibria (SL_1E, SL_2E, SL_1L_2E), SLV, various vapor–liquid equilibria, etc. As the temperature and pressure are changed, these equilibria may undergo critical transitions with one or more of the other phases. *K* points occur when the vapor phase becomes critical with just one of the liquid phases. LCEPs occur when the liquid phases become miscible and form one liquid phase in equilibrium with a vapor phase. *Q* points occur when a solid phase is in equilibrium with two liquid phases and a vapor phase (Figure 12c), i.e., a SLLV equilibrium (one degree of freedom). The intersection of K points with LCEPs results in a single critical phase called the tri-critical point (Figure 12d).

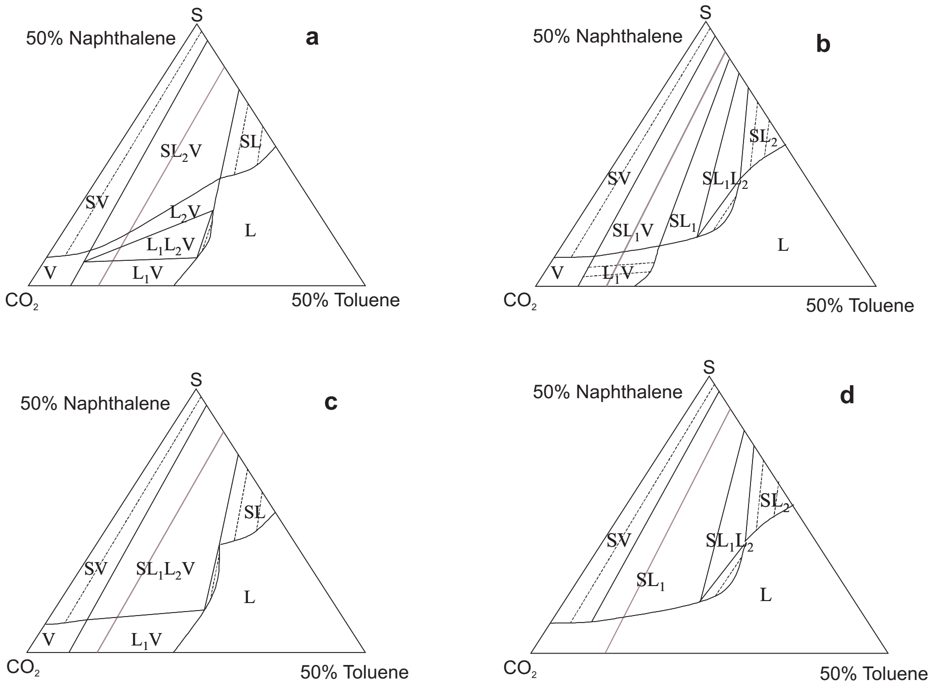

Figure 12 Ternary diagrams illustrating the phase behavior of naphthalene/CO_2/toluene under various conditions and at constant co-solvent to solvent loading.

6.1.2.7
Examples of Combined Reaction/Phase Behavior Studies

Stradi et al. [30] have performed a detailed phase equilibrium study of the binary and multicomponent mixtures of the reactants, products, and catalysts involved in the allylic epoxidation of *trans*-hexen-1-ol in $scCO_2$. Their studies indicate that, depending on the reaction conditions and conversion, vapor–liquid, vapor–liquid–liquid, and regions of multicomponent critical endpoints can exist. They were able to model the phase equilibrium with a reliable equation-of-state approach and were able to simulate different reaction conditions.

Baiker and co-workers [31, 32] investigated the role of phase behavior in the interpretation of the chemoselective oxidation of octyl alcohols in CO_2 and the enantioselective hydrogenation of ethyl pyruvate in supercritical ethane. They found that the effects of temperature and pressure and the concentration of the reaction gases (H_2 or O_2) had a large impact upon the selectivities. Only through careful consideration of the number of phases and their behavior through different conversion levels could the results be properly interpreted.

Ke et al. [33] considered how the mixture critical point changed with conversion in the hydroformylation of propene in CO_2. They found that as the conversion increased, the mixture critical temperature and pressure of this six-component mixture increased. This has ramifications for reaction engineering, as a higher pressure may be needed to maintain single-phase conditions for a batch reactor as opposed to a flow reactor.

Hou et al. [34] studied the synthesis of dimethyl carbonate from methanol and CO_2 as both solvent and reactant, with a methyl iodide promoter. They found that as the conversion increased, the mixture critical temperature and pressure increased. Thus, in order to maintain a single-phase mixture, the pressure needed to be increased or correctly chosen a priori. They also found that pressure affected the conversion differently, depending on whether the reaction was performed in a single phase or in a vapor–liquid regime. In a two-phase regime, an increase in pressure slightly increased the conversion, while the opposite was true in a single-phase mixture.

6.1.3
Phase Behavior for Catalyst Immobilization

Any method for the immobilization of organometallic catalysts in a fluid phase faces the paradoxical situation of combining intimate contact of reagents and catalyst during the reaction stage with a maximum of discrimination at the separation stage. Introducing phase boundaries and confined spaces will greatly facilitate separation, but will often create additional mass-transfer barriers reducing turnover rates and/or selectivities. A well-known example of this problem is the aqueous biphasic system for hydroformylation, which cannot be applied to long-chain olefins because of their insufficient aqueous solubility. Furthermore, catalyst leaching and cross-contamination between the substrate and catalyst phases are crucial factors for practical implementation. As will be discussed in more detail in the individual sections, the properties of $scCO_2$ can be beneficial in this context in various ways. The gas-like mass-transfer properties, for example, can facilitate exchange between catalyst and substrate phases. Cross-contamination of CO_2 into the catalyst phase is not an issue and the relatively poor solvent power of $scCO_2$ for organometallic compounds may reduce leaching as compared to classical organic solvents. Most importantly, the design of SCF-based continuous-flow systems that resemble gas-phase heterogeneous catalytic processes is a very attractive approach to reaction engineering of organometallic catalysis.

There are several ways in which multiphase processing can be utilized to facilitate facile separations and catalyst recovery. The tunability of the supercritical fluid can itself be used to “immobilize” the catalyst by allowing changes in temperature and pressure to separate the products from the catalyst to be recycled. One could immobilize the catalyst in a solid phase; this embodies either the well-known heterogeneous catalysts or the use of “heterogenized” organometallic catalysts that are anchored to a solid organic or inorganic support. Due to the infinite miscibility of reaction gases with SCFs and the moderate critical points of most liquid organic compounds in supercritical fluids, a truly biphasic (solid–supercritical fluid) reaction can occur. This is in sharp contrast to the situation with supported catalysts in organic solvents, where triphasic (solid–liquid–gas) reaction systems often lead to severe mass-transport limitations. The other approach is to use a liquid phase to dissolve and hold the catalyst. Most liquid organic compounds have moderate mixture critical points (becoming one phase) at pressures usually less than 15 MPa at temperatures under 100 °C. The nature of their phase behavior is described in Sections 6.1.1 and 6.1.2. The limited range in which two phases exist would preclude them from effective multiphase reactions and separation processes. However, Subramaniam and co-workers [35–37] have shown that simply using organic liquid phases that have been expanded with gaseous, liquid, or supercritical fluids can enable hetero- and homogeneously catalyzed reactions and separations to be performed with high efficacy under certain conditions. For multiphase processing, several exceptions exist to this generalization, namely, where water, polymers, and ionic liquids are involved. These compounds have ideal properties of high to nonexistent mixture critical points with SCFs, low to no cross-contamination, and the ease of processing that comes from liquid supports. Reactions using these immobilization phases will be discussed and examples will be highlighted in detail in Section 6.3. Here, their phase behavior with $scCO_2$ will be briefly discussed.

6.1.3.1
CO_2–Water

Figure 13 illustrates the phase behavior of CO_2 and water. As shown, the mutual solubilities (water in the CO_2 phase and CO_2 in the water phase) are small, i.e., < 5 mol%, and subsequent downstream contamination with H_2O in an actual process is usually neither detrimental nor hazardous. Depending on the temperature and pressure, the water–CO_2 system may exhibit liquid–liquid–vapor equilibrium (LLV, e.g., at 25 °C and 6.4 MPa), or LLE, etc. At temperatures above the critical temperature of CO_2, the mixture critical point reaches hyperbaric conditions (> 100 MPa) and therefore a one-phase mixture is impractical.

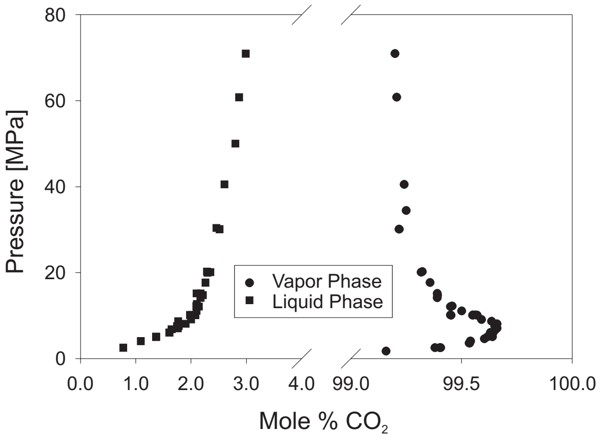

Figure 13 Phase equilibrium of water and CO_2 at 50 °C (from compilation of [42] and references therein).

This chemical and physico-chemical behavior of the binary H_2O–CO_2 mixture [38] suggests that water is an attractive liquid to be combined with supercritical carbon dioxide in multiphase catalysis. CO_2/H_2O systems have adequate mass-transfer properties, especially if emulsions or micro-emulsions can be formed ([39] and refs. therein). The low pH of aqueous phases in the presence of compressed CO_2 (pH ca. 3–3.5 [40]) must be considered and the use of buffered solutions can be beneficial in the design of suitable catalytic systems, as demonstrated for colloid-catalyzed arene hydrogenation in water–scCO_2 [41].

6.1.3.2
CO_2–Liquid Polymers

Polymers are usually used as a solid support for catalysts [44–47]. In general, they have a poor solubility in gases or supercritical fluids, especially CO_2 [12]. However, low-melting polymers, such as polysiloxane and poly(ethylene glycol) (PEG) may be used as a liquid immobilization phase. PEGs with average molecular weights above 1000 are waxy solids under ambient conditions. They have low melting points and can also melt under CO_2 pressure (SLV/melting point depression: see Figures 10 and 11) [48].

Figure 14 illustrates the phase equilibrium between CO_2 and PEG-1000 (average molecular weight: 1000) at 50 °C. As shown, CO_2 is very soluble in the PEG phase, while the PEG has a very low solubility in the CO_2 phase (< 0.1 wt.%). While the amount that dissolves in the fluid phase is finite it may not pose much of a problem, especially for food and pharmaceutical applications as PEG is a common food additive. As the molecular weight of the PEG is increased, the solubility in CO_2 decreases. The increase in molecular weight also raises the melting point, but this can be overcome by the CO_2 pressure which will induce melting point depression.

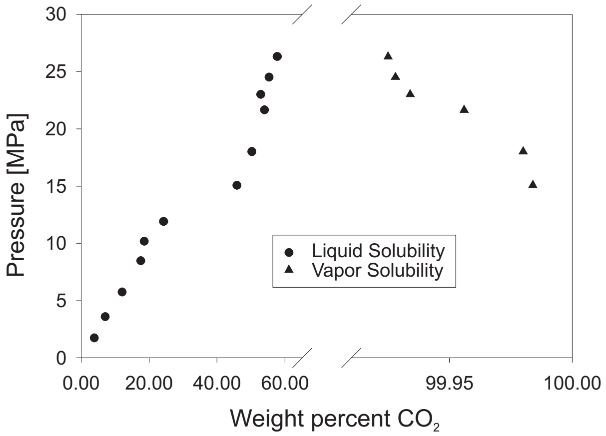

Figure 14 Phase equilibrium of PEG-1000/CO_2 at 50 °C (according to [43]).

6.1.3.3
CO_2–Ionic Liquids

Ionic liquids (ILs) are low melting (< 100 °C) salts of organic cations that are finding a large amount of interest as solvents for organometallic catalysis [49–51]. Consisting of discrete cations and anions, ILs exhibit no measurable vapor pressure and consequently they show generally no detectable solubility in pure $scCO_2$. Even with large amounts of co-solvents (10–30 mol%), the solubility is still very low, i.e., $\ll 10^{-4}$ mole fraction [52]. Carbon dioxide, however, has a remarkable affinity for ILs, leading to high concentrations of CO_2 in the liquid phase and rapid mass transfer between the two media [53]. Without a large expansion in volume (unlike organic liquids), an IL phase in contact with $scCO_2$ may contain up to > 0.6 mole fraction CO_2 and the supercritical fluid can be used to extract even high-boiling organic substances from the IL phase very efficiently [54]. These properties make IL–$scCO_2$ biphasic systems highly attractive for application in catalyst immobilization, especially under continuous flow conditions (for related examples in biocatalysis, see [55, 56]).

Figure 15 illustrates the vapor–liquid equilibrium of two imidazolium-based ILs. As seen with the solubility of CO_2 in 1-hexyl-3-methylimidazolium hexafluorophosphate, [HMIM][PF_6], large amounts of CO_2 dissolve in the liquid until the pressure reaches roughly 15 MPa, after which there is only a marginal amount of CO_2 addition with increasing pressure. Even at the highest pressure of 81.2 MPa, there still exist two phases. Blanchard et al. [57] have reported that the 1-butyl-3-methylimidazolium hexafluorophosphate system is still two phases at 310.3 MPa! This phase behavior makes them exceptionally matched candidates for biphasic catalysis with SCFs. However, it is interesting to note that the system of 1-ethyl-3-methylimidazolium hexafluorophosphate and $scCHF_3$ experiences a mixture critical point at approximately 26.9 MPa. This is the only known mixture critical point involving an organic IL and a gaseous solvent and is mostly likely due to the high dielectric constant of $scCHF_3$.

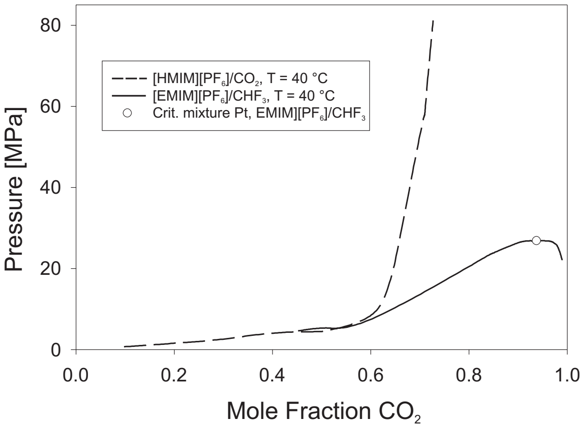

Figure 15 Vapor–liquid equilibrium of the imidazolium ILs with SCFs (from the smoothed data of Shariati and Peters [60, 61]).

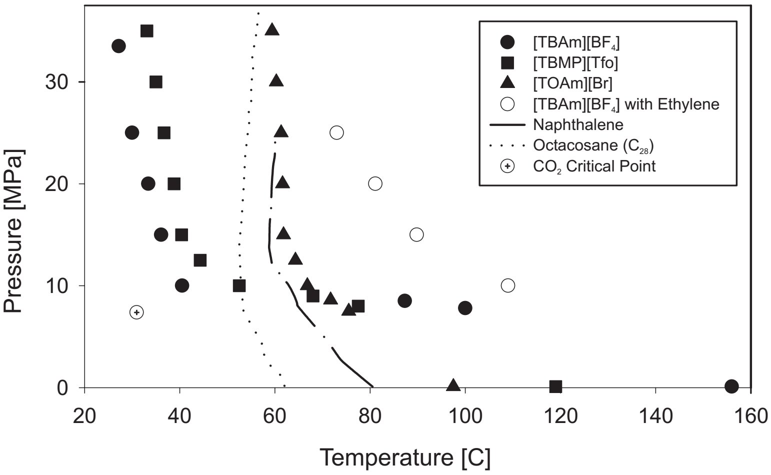

Figure 16 SLV equilibrium (melting point depression) of certain organic ionic solids with CO_2 and ethylene.
$[TBAm][BF_4]$ = tetrabutylammonium tetrafluoroborate;
[TBMP][Tfo] = tributylmethylphophonium trifluoromethylsulfonate;
[TOAm][Br] = tetraoctylammonium bromide.

Scurto et al. [58, 59] have also shown that gaseous, liquid, and supercritical CO_2 can be used to perform separations of ILs and organics or ILs and water. The dissolved CO_2 can be used to induce a phase separation of the components.

Recently, Scurto and Leitner [62] have shown that CO_2 can induce large melting point depressions in a variety of high-melting organic ionic salts, which can be used as an immobilization phase for organometallic catalysis. Most organic ionic salts are solids and very few can be used as “ionic liquids”, i.e., with $T_m < 100$ °C. However, CO_2 can greatly expand the number of possible ionic salts, especially ones that have been engineered with functional groups that are often solids. Kazarian et al. [63] have also shown that CO_2 can induce liquid-crystal phase transitions for long-chain ionic solids. This phenomenon is similar to the solid–liquid–vapor equilibrium as discussed above, with the exception that the CO_2 and ionic solid do not have a measurable critical point. Figure 16 illustrates this SLV behavior of several ILs and CO_2; the melting point depression is simply the difference between the normal melting point (SLV line as $P \to 0.1$ MPa) and the SLV at a particular pressure. The melting point depression of some of these ionic solids with CO_2 is the largest ever published. The different behaviors and lower extents of melting point depression of CO_2 with the wax, octacosane, and solid naphthalene are shown for comparison.

6.1.4
Conclusion

The unique physico-chemical properties of SCFs and in particular $scCO_2$ make these media highly attractive for application in multiphase catalysis. The rich phase behavior of multicomponent mixtures involving SCFs offers many opportunities, but also holds a major challenge for the control of reaction and separation stages. As will become evident in the following sections, there is emerging evidence for the practicability of SCF-based methodologies for the immobilization of organometallic catalysts in multiphase systems. The brief outline of the physico-chemical background provided in this introduction is hoped to contribute to better understanding of the fundamental principles and the engineering aspects associated with such applications in catalysis.

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6.2
State-of-the-Art (Applications of SCFs in Areas other than Catalysis)

Nils Theyssen

6.2.1
Introduction

In 2000 the number of processing plants that employ supercritical (sc) fluids (except ethylene polymerization) was slightly above 100 and it has been growing steadily. Most of the current plants use $scCO_2$ to process food in some way (extraction or fractionation), yet other types of plants have been or are being brought on stream (e.g., fluoropolymer synthesis by DuPont, hydrogenation or alkylation by Thomas Swan, coatings by Union Carbide, and polyurethane processing by Crain Industries) [1]. This chapter will focus on already or currently applied sc or compressed fluid-based processes (mostly $scCO_2$) in industries that are not related to catalysis (for industrial applications of SCFs in catalysis see Section 6.5).

6.2.2
Extractions with Supercritical Fluids

Commercial plants for solid extraction with SCFs have so far been used mainly in the food and pharmaceutical industry and employ solely carbon dioxide as the SCF component. The most important processes among them are described below. SCFs have also been used as solvents to separate liquid mixtures. One example is the *Residuum Oil Supercritical Extraction (ROSE)* process for extracting residual petroleum reservoirs with sc butane and/or pentane [2, 3].

6.2.2.1
Extraction of Caffeine

The oldest and at the same time the most profitable extraction process using SCFs is the decaffeinating of coffee beans by $scCO_2$. Its high diffusibility and low surface tension allows $scCO_2$ to penetrate deep into the beans, where 97–99% of the caffeine can be extracted, reducing the caffeine concentration from originally 0.8–2.5% to residual contents about 0.1% [4, 5]. In general, the process has the unusual advantage of producing a valuable extract (caffeine), as well as a valuable raffinate (decaffeinated coffee beans).

The decaffeinating process, as a prototypical example for the whole area of natural product extraction using $scCO_2$, was first discovered and developed by Kurt Zosel during the 1960s and 1970s [6, 7]. The Hag AG Corporation, a coffee company located in Bremen, Germany, acquired a patent license in 1976 and adapted Zosel's process by developing it to a full-sized commercial operation as soon as 1978. Maxwell House (a Philip Morris corporate), which now owns Hag, further enhanced

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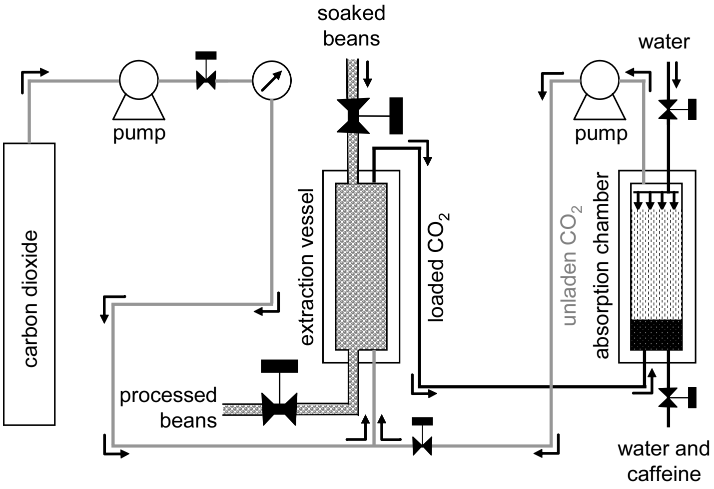

Figure 1 Simplified flow scheme for decaffeinating of coffee beans by $scCO_2$.

the process and built a large plant in the United States. Meanwhile, many other plants in the United States, Europe, and Japan produce supercritically decaffeinated coffee [8]; altogether they are responsible for annual estimate of more than 100 000 tpy today [9].

To date, the decaffeinating process has been done in a pulse manner (batchwise filling and continuous extraction) [8]. A truly continuous process, as is generally sought in CO_2 technology, is still not established due to the lack of an economically viable technology which allows continuous charge and discharge of larger solid fractions (here: the unground beans) into and out of a high pressure (> 10 MPa) regime [1]. Hence large extraction vessels are used, which may be more than 20 m high and up to 3 m in diameter [10, 11].

Since the solubility of caffeine in $scCO_2$ is not high enough, a separation by (isothermal) pressure reduction is not economical. Instead, the caffeine-loaded CO_2 phase is passed through an absorption chamber in the separator unit ($p\downarrow$). The caffeine is extracted out of the supercritical phase by a shower of water droplets, allowing the water-saturated CO_2 transport phase to move in a loop back into the reactor ($p\uparrow$) at a relatively constant pressure, making the separation process energy efficient. Another applied technology passes the caffeine-rich CO_2 through an activated charcoal bed, although the recovery of the desired pure caffeine is more difficult [1, 8].

Today caffeine extraction using $scCO_2$ is the most commonly operated technology and, besides the more expensive Swiss Water process (using only water – saturated with the coffee's own sugars and peptides – as an extracting agent [12]), it is the only one which is considered to be sustainable.

6.2.2.2
Other Extractions in the Food Industry

Due to its unique characteristics, carbon dioxide is the only supercritical fluid used in food industry. Research and development in this area has been prolific since the extraction of caffeine was patented in 1964 [13]. After its practical application in Germany in 1978 (by the Hag AG Corporation), commercial plants have been constructed [3, 14, 15] for extracting:

- hops (1982 and 1986 by SKW Trotsberg [since 2000: Degussa AG], 1984 by Barth and Co. as well as Natural Care Byproducts, and 1990 by Pitt–Des Moines and John Haas, Inc.);
- cholesterol and fat from egg yolk (Liquid Carbonic Supercritical and NutraSweet Co.);
- red pepper (1984 by Natural Care Byproducts);
- black tea (mid 1988 by SKW Trotsberg) and
- other spices (1990 by Raps and Co.).

With an estimated 10% yearly growth in the number of industrial SCFE plants, the food industry is the most developed and at the same time the most expanding industry sector using this technology today [16]. A more recent application of SCFE is the removal of superficially bonded pesticides and rice bran oil from rice [17], carried out for example at a large rice treatment plant in Taiwan. Surprisingly, due to the unexpected change in the rice structure caused by the extraction process, shorter cooking times are needed.

6.2.2.3
Extractions in the Pharmaceutical Industry

Although solvent residuals in the extracted material are of critical importance in the pharmaceutical industry, $scCO_2$ has found only a limited number of applications. First of all the lipophilic nature of $scCO_2$ has been a major limiting factor: many natural product classes which are of importance as pharmacologically active substances in medicinal plants, such as phenolics, alkaloids, and glycosidic compounds, are poorly soluble in carbon dioxide and hence almost not extractable [18]. However, the very high product quality has led to the isolation of therapeutic compounds of different categories by this method. To improve the solubility of polar solutes in carbon dioxide, other components are added. These more polar co-solvents are called modifiers or entrainers. For toxicity reasons ethanol is used almost exclusively as a co-solvent for the extraction of pharmacologically active compounds, which nowadays leads to a detailed understanding of the mixture's phase behavior [19].

One example of a commercial application is the isolation of diosgenin, the most important starting material for partial synthesis of steroids. Drivsun, a Chinese company, is isolating this compound on a scale of 300 tpy by SCFE from tubers of

Dioscorea species (dry content up to 6%), plants which grow in the wild and can be found in Mexico, China, India, and South Africa [20, 21].

6.2.3
Impregnations with Supercritical Carbon Dioxide

The interest in supercritical fluid impregnation of different materials stems from the opportunity to utilize the high diffusivity, low surface tension, and ease of solvent recovery for the preparation of new materials. In contrast to sc fluid extractions, where these intrinsic advantages have been used for a long time, pioneering work on impregnations with fluids was reported by Shim and Johnston only in 1989 [22]. The presented examples below are far from comprehensive, but give a good impression of the spectrum of current applications [23].

6.2.3.1
Impregnation of Woods with Biocides

Impregnation of wood with conventional fluids is generally limited by pits clogged with debris that make them resistant to fluid flow. Pit impermeability poses a major limitation to effective biocide treatment of many species containing high percentages of heartwood. Since $scCO_2$ functions as an effective biocide transport medium [23, 24], this methodology is of growing interest for wood treatments and was most recently established in the commercial application by the Austrian company Natex, with a yearly capacity of 60 000 m^3 [25, 26]. The postulated advantages are: (a) substitution of VOCs, (b) solvent and water-free method, (c) good penetrating ability (better and deeper impregnation for problematic woods), and (d) suitability for different biocides. To ensure a relatively uniform biocide distribution over a wide cross-section, carefully optimized process parameters are necessary. As in conventional treatments, collapse occurs for some wood species (due to pressure gradients inside the pores) which might be averted by further studies [24].

6.2.3.2
Textile Dyeing

Due to its high loading and large scale, wastewater treatment in the textile dyeing industry is laborious and expensive. Supercritical fluid dyeing technology has the potential to overcome this problem by eliminating wastewater flow completely [27]. Since results from numerous preliminary studies are very promising, a consortium of Scientists (DTNW, Germany), machine construction engineers (UHDE, Germany), and a textile finishing company (ADO, Germany) are currently planning the biggest pilot plant worldwide for textile dyeing in CO_2 (capacity: 100 kg per coloration). The process is achieved at temperatures between 100 and 140 °C and pressures between 20 and 30 MPa. Due to its nonpolar character, the CO_2-based technology is especially suited for dyeing hydrophobic synthetic fibers such as polyester. In the long run the consortium wants to expand this dye technology for natural fibers also, which demands the development of CO_2-adapted coloring matter [28].

6.2.3.3
Impregnation of Polymers with Drugs

Controlled-release products as a pharmaceutical formulation have recently received considerable attention. Today, such pharmaceutical forms are used for treatment of several diseases, ranging from diabetes to cancer. The controlled-release product must be free of any residual solvents (even nontoxic ones) to provide its property of constancy. Although $scCO_2$ is not yet applied industrially for this purpose, this medium meets the demands to a large extent. Such an impregnation process is feasible if the active substance (the solute) is soluble in the SCF, the polymer is swollen by the sc solution, and the partition coefficient is favorable enough to allow the matrix to be charged with enough solute [29, 30]. Recent research has shown that ibuprofene can be impregnated into polyvinylpyrrolidone – a common biomedical matrix – from $scCO_2$ solutions [31]. Limitations arise from the apolar character of CO_2: many of the bioactive compounds of interest are polar compounds (e.g., proteins) [32]. For such purposes polydimethylsiloxanes (PDMS) seem to be a suitable co-solvent class [33].

6.2.4
Polymer Synthesis and Processing

Some of the most successful commercial processes that employ CO_2 as a solvent involve polymeric substrates. Recently, SCF have been applied for polymerization, swelling, impregnation (see Chapter 7), fractionation, purification, and formation of powdered polymers. Due to the admittedly weak solvent power of CO_2, the general problem of the very low entropy of mixing in polymer/solvent binaries is magnified even more in the case of CO_2. However, the resulting poor solubility of most polymers is not a barrier here, as can be seen in the following numerous applications [1].

6.2.4.1
Polymer Synthesis

In general, polymerization using a condensed reaction medium can be done in four different modes. While processes for solution polymerizations are already commercialized, dispersion polymerization and emulsion polymerization are not. The reason lies in the difficulty of finding a suitable latex stabilizer or alternatively a surfactant that is capable of forming micelles. These additives should not only be CO_2-compatible but also inexpensive and sustainable. Hence, the fluorinated materials already developed– currently the only ones which perform satisfactorily – are not likely to be applied industrially. Since the present suspension polymerizations are both already relatively green and use inexpensive stabilizers, it is even more difficult to come up with a competitive transformation in CO_2.

Solution polymerization in scCO_2 is generally restricted by the solubility of polymers in this reaction medium. Only some fluoropolymers, silicones, and poly(ether-carbonates) have been found to be CO_2-philic. However, of exceptional importance is the free-radical polymerization of tetrafluoroethylene to PTFE (Teflon) which has been operated since 2002 by DuPont. The annual capacity amounts to over 1000 t of fluoropolymer, and plans have been announced to expand this capacity significantly by 2006. Compared to 1,1,2-trichloro-1,2,2-trifluoroethane or water, CO_2 offers many advantages: (a) no use of a highly expensive and harmful freon, (b) tetrafluorethylene is no longer explosive when mixed with CO_2, (c) easy and quantitative separation from solvent, (d) no buildup of unstable carbonic acid terminal groups (which occurs by chain transfer) in water, and (e) no need for surfactants as in the case of water. Moreover, the fluorinated copolymers produced in CO_2 exhibit superior performance during extrusion, owing to fewer gels and a tighter composition distribution. Hence, fluoropolymer polymerization in CO_2 is greener, safer, and offers product advantages [1, 34, 35].

6.2.4.2
Polymer Processing

Three intrinsic effects of SCFs are of great importance in polymer processing: their high penetrating ability (dissolution) even in the glassy state, the swelling of the polymer matrix (most significant in the case of CO_2), and the glass transition temperature (T_g) depression, simply called plasticization. For example, CO_2 concentrations of just 8–10 wt.% (maximal loading ranging typically from 10% to more than 30%) can depress the glass transition temperature of common glassy polymers from 80–100 °C to below room temperature. Compressed CO_2 also weakly solvates the molecular segments of the polymer, thus acting as a molecular lubricant. In general, plasticization reduces the viscosity of polymers, presumably due to the reduction of chain–chain interactions and increase in the interchain distance, which is a very important factor for the processing of polymers. High viscosity is a major obstacle to the processing of high molecular weight polymers. Usually this problem is solved by increasing the temperature and/or by the addition of plasticizing agents. However, increasing the temperature requires a higher energy consumption and may lead to thermal degradation. Added plasticizers usually remain in the product, thus affecting its properties and performance. Hence, the use of SCFs to reduce the viscosity of polymers may offer not only environmental advantages but also product advantages. Another example where the CO_2-induced viscosity reduction plays a role is the scCO_2-induced crystallization in certain polymers (e.g., in the case of polycarbonates): as a consequence of the higher mobility inside the polymer, the polymer chains have the possibility of rearranging into thermodynamically favored configurations, thus forming crystallites. Two important commercialized applications in polymer processing, which bear very interesting features, are described in more detail below [1, 36–39].

There has been much interest in the use of CO_2 as a solvent for the reduction of VOC emissions during spray coating. The conventional coating process employed polymer beads dispersed in a mixture of a good and a poor yet volatile solvent. The UniCarb process, developed by Union Carbide during the 1980s and 1990s, replaces the poor solvent with CO_2 while retaining the good solvent to maintain the stability of the dispersion. In general, reductions in VOC emissions of 30–70% are claimed.

In the process coating materials are dissolved (in either a two-phase or single-phase regime) and subsequently released through a specially designed nozzle from the spraying head, which produces a highly uniform spray with a narrow droplet size distribution (see Figure 2). Initial applications were in spraying paint on furniture, car parts, and industrial equipment. Now UniCarb systems are also spraying adhesion promoter on plastics, surfactants on nonwoven fabrics, lotion on facial tissue, coatings on aerospace parts, barrier coatings and chocolate on cookies, and additives on food.

The alternative to the addition of a good solvent is the use of stabilizers, similarly to their use in dispersion polymerization reactions. Finding a suitable stabilizer would lead to the elimination of any VOC emission. Taking advantage of the high solubility of perfluoropolyether, DeSimone has investigated the use of neat CO_2 as a solvent for spray coating of stone materials to achieve protective fluorocarbon coatings. The results are very promising although the synthesis of the perfluoropolyether is yet a limitation [1, 34, 36, 39, 40].

A variety of polymers are extrusion-foamed, including polyolefins, polystyrene, and polyesters: if the polymer is subjected to high-pressure gas, and the pressure is suddenly decreased or the temperature rapidly increased, the gas will try to escape from the polymer, causing antiplasticization. This rapid escape of gas can cause the nucleation and growth of bubbles within the polymer. Once a significant amount of gas escapes, the T_g of the polymer drops, and thus the structure formed is "frozen".

Prior to the late 1980s, chlorofluorcarbons (CFCs) were often employed as blowing agents (pore-forming agents) as these solvents are low boiling, nontoxic, and nonflammable. Subsequently to the acceptance of the Montreal protocols (1986), most foam producers switched from CFCs to hydrofluorocarbons, hydrocarbons, or mixtures of hydrocarbons and CO_2 as the blowing agent. For example, the foaming of polystyrene is often conducted using a mixture of CO_2 and an alkane,

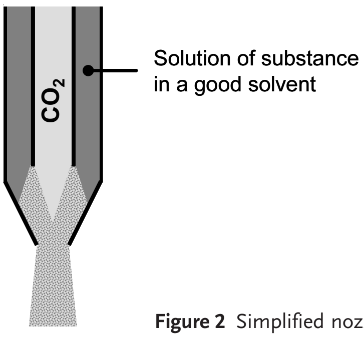

Figure 2 Simplified nozzle design for spray coating.

which is a more efficient route than employing either 100% alkane or 100% CO_2. Nevertheless, the generation of foamed thermoplastics using CO_2 as the sole blowing agent is most definitely green processsing, as the CO_2 replaces either organic or hydrofluorocarbon agents that would otherwise directly enter the atmosphere. Such technology has been commercialized in a number of cases (for example by Dow and by Trexel), yet the process is nonoptimal, as foam properties using CO_2 still do not always approach those when CFCs are employed as blowing agents [1, 36].

6.2.5
Dry Cleaning with Compressed Carbon Dioxide

Although numerous studies have shown perchloroethylene (perc) to be highly toxic and maybe even carcinogenic, today's dry cleaner use mostly perc (about 95%) as the primary processing solvent [41, 42]. At present, compressed carbon dioxide in conjunction with cleaning surfactants is considered as a substitute with high potential. Substantial work in this area was done by DeSimone et al. in the early 1990s, when his group found a detergent for liquid CO_2 with effective cleaning properties. These molecules build inverse micelles in that medium, whereby present impurities are encapsulated in the hydrophilic internal spaces. Such ensembles are then able to diffuse into the CO_2 phase, where they are continuously extracted. First prototypes of a cleaning machine that utilizes liquid CO_2 technology were built in 1997 [40, 43, 44]. The first dry cleaning facility to offer Micell's new process to customers was Hangers^{TM} in 1998. To date, millions of kilograms of clothing have been cleaned worldwide using this technology [45].

A competing CO_2 dry cleaning process was marketed by Global Technologies. Instead of a conventional basket unit, the system, called DryWash, uses jets of liquid CO_2 to agitate clothing [40].

6.2.6
Utilisation in Semiconductor Processing and Cleaning

The use of carbon dioxide in its various states for processing and cleaning in semiconductor fabrication and related electronic devices is of enormous potential. The extremely low surface tension of $scCO_2$ is a favorable property in terms of its rapid and complete removal from the substrate after a treatment has been effected. Another reason for CO_2's unique attractiveness is its environmental compatibility. There are currently four different approaches which have the potential to utilize CO_2 for semiconductor technology. All of them have been intensively investigated but have not yet been applied in industrial production [42, 46–49]:

6.2.6.1
Photoresist Stripping

Photoresist stripping and residue removal will probably be the first microelectronics supercritical fluid applications integrated into IC (integrated circuit) processing.

Several companies have already installed such CO_2-based technology in their research laboratories, since the commercial technology using water and VOCs in the lithography process is reaching its limit. Due to the comparable high surface tension of these solvents and the high capillary forces present in small-circuit architectures, complete removal is a serious problem if line widths of 180 nm or less are focussd. Due its extremely low surface tension, which allows effective wetting, supercritical CO_2 might be a potent photoresist stripping agent. Unfortunately, neat CO_2 is not sufficient to remove the soluble parts (either light-exposed or -unexposed) of commercial photoresists, but the addition of small amounts of co-solvents and pressure fluctuations has been shown to work efficiently by several groups. A further development is the design of specialized photoresists with enhanced solubility in compressed CO_2. These would allow a practically dry process, thereby reducing dramatically the huge amount of effluent stream [1, 34, 46–48].

6.2.6.2
Chemical Fluid Deposition (CFD)

The use of critical fluid media for film deposition is a relatively new technology. Through the precise control of CO_2 solution evaporation rates and the low surface tension and low viscosity, it is possible, in a very uniform manner, to cover very fine features (e.g., 100 nm wide by 1 μm deep) with metal precursors that have been reduced in situ [50]. Such a filling is not possible with the classical chemical vapor deposition method (CVD). In the CFD process high-purity films are facilitated by the high solubility of ligand byproducts in CO_2. A disadvantage is the limit in the temperature range: reduction must proceed somewhere between 40 and 80 °C because at higher temperatures CO_2 densities in an applicable pressure regime would be too low to dissolve the metallic precursors [42, 46, 47].

6.2.6.3
Drying

Compressed CO_2 has a small, but finite, solubility for water over an extended range of temperatures and pressures [51]. Together with the good solubility for most organic solvents these properties can be used for unrivalled drying processes in microelectronic processing. Pattern collapse (deformation or bending) of structures, a phenomenon which is directly related to the surface tension of rinse solution, can be avoided even for very small spacers and features. Not surprisingly, commercial systems are already available [46, 47].

6.2.6.4
Snow Gun Cleaning

The snow gun cleaning method uses solid CO_2 ice crystals as a jet medium. With its combination of mechanical (ablation), thermal (freezing), and chemical (dissolution) properties, CO_2 snow is able to gently detach and remove a whole variety of surface contamination – of course, not only in the microelectronics. This cleaning method is reminiscent of sandblasting, but in contrast to this widespread technology the CO_2-based one is much milder and residue-free. The essential component in CO_2 snow-jet technology is the cleaning head, which consists of a two-component concentric nozzle. The liquid or scCO_2 ($20\,°C < T < 100\,°C$, $5 < p < 40$ MPa) flowing toward the inner line of the nozzle expands as it exits to become a mixture of snow and gas which forms the core jet (consumption: 0.1–0.25 L min^{-1} liquid CO_2). In addition, compressed air is fed in a ring shape and forms a jacketed jet which bundles the CO_2 snow crystals and accelerates them to velocities of about 500 m s^{-1} (consumption: 0.4–1.0 m^3 min^{-1} gas) [52]. The distance from the nozzle to the target is usually kept between 4 mm and several centimeters. Efficient ablation is achieved by a nozzle angle of 60° relative to the surface [46].

6.2.7
Formation of Fine Particles Using CO_2

The controlled formation of defined particles (particle size, particle size distribution, composition, etc.) is important to several kinds of production lines, including those in the pharmaceutical, pigment and catalyst industries. Milling and crystallization are the most commonly used microionization processes here, but these methods suffer from some limitations: (a) it is difficult to control particle size and particle size distribution; (b) recrystallization leads to solvent-contaminated compounds; and (c) milling is not suitable for the treatment of heat- or even of shock-sensitive substances, or for highly viscous or sticky products.

Applying sc fluids in various precipitation processes may overcome some of the drawbacks of conventional technologies, providing a better performance and sometimes even a higher grade of sustainability. The most popular processes for formation of solid particles using dense gases for micronization are described below [1, 53–55].

6.2.7.1
Rapid Expansions of Supercritical Solutions (RESS)

In the RESS process a homogeneous solution of one compound or a mixture of compounds in SCF (mostly scCO_2) is depressurized through a heated nozzle (heating avoids plugging by the precipitate; see also Figure 2) into a low pressure chamber (see Figure 3). Through this spontaneous pressure drop, the solvent strength is drastically reduced; this results in an extremely rapid nucleation of the substrate(s). Its morphology depends on both the material structure created (crystalline or amorphous, composite or pure) and on the RESS parameters (temperature, pressure drop, nozzle construction, time of flight to surface, etc.). By varying these parameters, small particles with a narrow size distribution (0.5–20 μm) as well as fibers or films can be produced. RESS has been demonstrated for a wide variety of materials, including polymers, dyes, pharmaceuticals, and inorganic substrates. However, a major limitation of this process is that the solubility

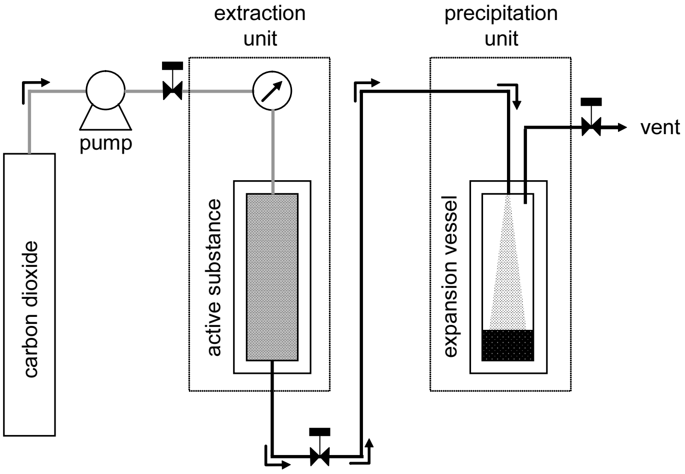

Figure 3 Simplified flow scheme for the RESS process.

of many materials in pure SCF are usually too low, which makes profitability difficult, thus restricting industrial-scale production to date – but maybe it will be used for specialities in the future. Nevertheless, if the solute has a significant solubility in the SCF (e.g., in the case of DiSimone's fluoropolymer coatings; see Chapter 7), the RESS process will be the first choice for particle design because of its simplicity and controllability [53–55].

Nanosized drugs are processed by a special variant [57].

6.2.7.2
Gas Anti-Solvent Precipitation (GASP and Related Methods)

This method exploits the ability of gases to dissolve in organic liquids, thereby lowering solvent power of the liquid for the compounds in solution, and thus causing the solids to precipitate. Many different approaches have been developed which differ in the way the contact between solution and anti-solvent is achieved – for details see Ref. [53]. Also, in these processes the particle sizes are easily controlled and very small particles may be produced (submicron to a few microns). The biggest advantage is the great flexibility of this methodology for almost any kind of compound. One commercialized application is the UniCarb process of Union Carbide (see Section 6.2.4.2). However, other fields of application are at present foreseen only for high-value products (pharmaceuticals, cosmetics, superconductors, etc.) with productions ranging from 1 to 500 tpy [1, 53, 54].

6.2.7.3
Particles from Gas-Saturated Solutions (PGSS)

This process takes advantage of the high solubility of compressed gases (especially $scCO_2$) in a broad range of solid materials (see Section 6.2.4). The pressure which is required to create a concentrated solution is significantly lower than that to create a solution of substrate in CO_2 (2–5 MPa instead of 15–50 MPa as in the RESS case). The gas-saturated material is then rapidly expanded through an expansion unit, whereby the gas phase evaporates. Due to the Joule–Thomson effect, and the work accomplished of gas expansion, the solution cools to below the solidification temperature of the solute, leading to the formation of fine particles or thin films. The advantages of the PGSS process over conventional methods are numerous: (a) it is a versatile process, applicable to several substances; (b) it uses moderate pressures; (c) it has low gas consumption; (d) it gives solvent-free and fine powders with a narrow size distribution; (e) it is suitable for highly viscous or sticky products; and (f) it is easy to scale up. Due to the low processing costs, PGSS can be used not only for highly valuable but also for commodity products. The process already runs in pilot plants with a capacity of some hundreds kilograms per hour. So far, processed materials have been polymers, resins, waxes, surface-active compounds, and pharmaceuticals [53, 54].

6.2.8
CO_2 as a Working Fluid for Heat Pump Systems

Due to the very high global warming potential (GWP) of hydrofluorocarbons (HFCs), which is 1000–3000 times higher than the value for carbon dioxide, there is an increasing interest in using alternative media as working fluids in heat pump systems. The common refrigeration principal (evaporation (heat extraction) → gas compression (additional heat formation) → condensation/heat transfer → depressurization → and so on) is also possible for CO_2, as long as one can realize a subcritical temperature ($T < 31\ °C$) at the heat sink. As a consequence, this technology might not indeed be the first choice for refrigerators but there are several other applications, such as using heat pumps for heating tapwater or residential buildings. Against the background of limited resources, such technologies will be of crucial importance. As a consequence, a huge number of experimental results at laboratory and technical scale, as well as theoretical calculations in this area, exist which show that CO_2 is an excellent alternative working fluid to HFCs. Of course, components for much higher design pressures (typically 15 MPa) are needed, which might be a limiting factor. However, due to the high volumetric capacity in the high-pressure regime, advantages such as significant reduction of component size are obtained. Especially in applications where the toxicity and flammability of ammonia or hydrocarbons which are currently used as substitutes to a broad extent are a problem, CO_2 has the potential to become the fluid of choice [56].

6.2.9
Conclusion

The large number and the broad variety of successful industrial applications of $scCO_2$ summarized in this section illustrate well the technology platform available for the engineering of supercritical fluid processes on various scales. Many of the technologies described above can be readily adjusted to catalytic processes for screening, laboratory, and pilot-plant operation. The value of many of the products produced with these technologies is well within the range of fine and special chemicals, indicating that no principal economic barrier should exist to adopt this technology, at least in this sector of the chemical industry. Looking at the pace of the development, it becomes apparent that after a start in natural product extraction, many other fields are being added with increasing speed. It is hoped that catalytic chemistry and multiphase catalysis will open yet another possible market for supercritical fluid technology in the near future.

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6.3
Homogeneous Catalysis in Supercritical Solvents as a Special Unit Operation

Charles M. Gordon and Walter Leitner

6.3.1
Introduction

The application of supercritical fluids (SCFs) as reaction media with homogeneous catalysts has been investigated on a laboratory scale by a number of research groups in recent years. The technology discussed in previous sections for the use of SCFs in other applications, notably separations and extractions, has been used extensively in the development of this work. Many aspects of such processes on an industrial scale are already well understood (Section 6.2), particularly in the processing and extraction of reaction products, having been utilized in applications such as natural product extraction [1, 2], wood impregnation [3], wafer production, and dry cleaning [4]. A commercial-scale multipurpose plant for heterogeneous catalysis involving $scCO_2$ has recently entered operation [5] (see Section 6.4.2). Examples of organometallic catalysis in supercritical fluids are by no means restricted to CO_2 [6], but only this medium has been used to date in applications focusing on catalyst immobilization. Supercritical fluids offer a range of potential advantages for applications in homogeneous catalysis, as outlined in Table 1. As many of the potential benefits of CO_2 for multiphase catalysis are also retained in the near-critical liquid region, operation at or even below room temperature may be possible in many cases. In certain cases, low-density CO_2 at temperatures above T_c can also be used for separation purposes, but generally densities $d \geq d_c$ are required to exploit the solvent properties.

The high miscibility of $scCO_2$ with reaction gases, combined with its liquid-like solvation properties for many organic solutes, can be advantageous in important transformations such as hydrogenation, oxidation, or carbonylation reactions. The balance between reactivity and inertness of the CO_2 molecule provides another significant difference from classical solvent systems if suitably exploited. The possibility of significantly altering solvent properties through relatively small

Table 1 Potential reaction benefits and corresponding physico-chemical properties for compressed CO_2 as the reaction medium in transition metal catalyzed organic synthesis.

Potential benefit	***Physico-chemical property***
Higher rates	Miscibility with gases, rapid mass transfer
Different selectivities	Weak coordination, pressure tuning
Fewer reaction steps	In-situ protection of amines
Additional safety	No toxicity, inertness, good heat transfer
Enhanced separation	Tunable solvent properties, multiphase systems
Continuous-flow operation	Multiphase systems, mass transfer

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changes in pressure adds an additional parameter for control of rate and selectivity in certain cases. In more general terms, this pressure tuning allows also the control of solubility in $scCO_2$ and novel separation schemes can be envisaged on the basis of this phenomenon. The combination with CO_2-insoluble materials offers interesting strategies for multiphase catalysis which are facilitated by the gas-like mass-transfer properties of the supercritical state. These themes have emerged individually or in combination for a large number of transition metal catalyzed reactions in $scCO_2$ reaction media since the mid-1990s [6, 7]. The aim of the present section is to describe the general principles of reaction engineering for the different methodologies. Detailed descriptions and typical examples of each approach are discussed in Section 6.4.

Any method for the immobilization of organometallic catalysts faces the paradoxical requirements for intimate contact of reagents and catalyst during the reaction, but a maximum of discrimination at the separation stage. Separation can be facilitated by introducing phase boundaries and confined spaces, but this approach will often create additional mass-transfer barriers, thus reducing turnover rates and/or selectivities. This problem is illustrated by the existing aqueous biphasic hydroformylation system, which cannot be applied to long-chain olefins because of their low solubility in the catalyst-containing aqueous phase. Furthermore, catalyst leaching and cross-contamination between the substrate and catalyst phases are crucial factors for practical implementation of some biphasic approaches. As will be discussed in more detail in the following sections, the properties of $scCO_2$ can be beneficial in this context. The gas-like mass-transfer properties, for example, can facilitate exchange between catalyst and substrate phases. Cross-contamination of CO_2 into the catalyst phase is not a problem if the catalyst is chemically inert toward CO_2. Indeed, this is often an important requirement for efficient mixing during the reaction, as the CO_2 will generally act as the mobile phase bringing reactants to, and separating products from, the catalyst. The relatively poor solvent power of $scCO_2$ for most organometallic compounds generally leads to reduced leaching compared with classical organic solvents. Most importantly, the design of SCF-based continuous-flow systems that resemble gas-phase heterogeneous catalytic processes is a very attractive new approach to reaction engineering of organometallic catalysis.

Three fundamentally different approaches to catalyst immobilization involving SCFs can be distinguished; they are depicted schematically in Figure 1. First, the tunable solvent properties of the SCF are used to control the solubility of the organometallic catalyst in the reaction medium with no additional support or solvent (Figure 1a). In certain cases, these systems operate under truly monophasic supercritical conditions during the reaction stage. We refer to these methods as "catalysis and extraction using supercritical solutions" (CESS). Such processes are reminiscent of the temperature-controlled catalysts in conventional solvents sometimes referred to as "smart catalysts". The second approach is liquid/supercritical multiphase catalysis (Figure 1b), where the traditional counterpart is in fact triphasic (liquid–liquid–gas) if gaseous reagents are involved. Finally, the organometallic catalyst can be anchored to a solid organic or inorganic support

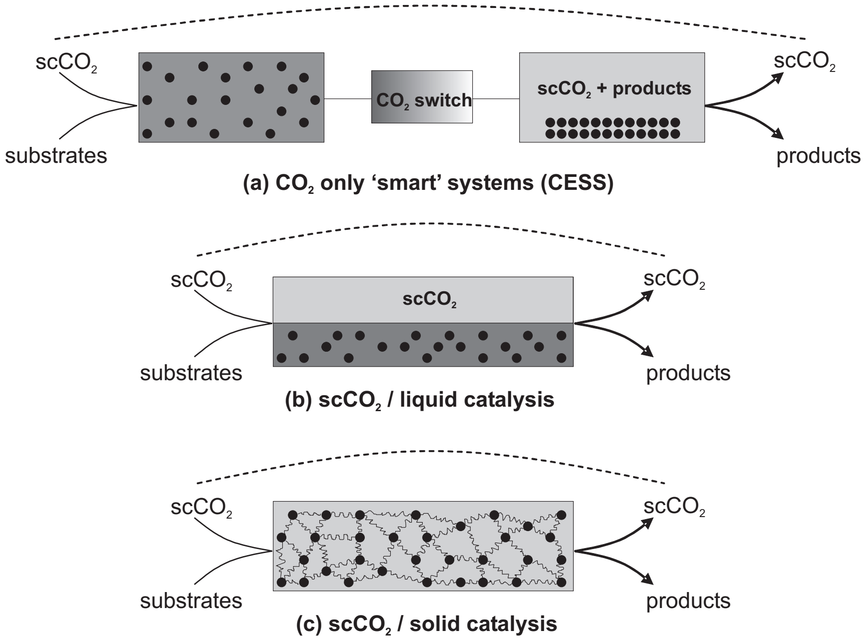


Figure 1 Schematic representation of the three approaches discussed in this section.

which is then contacted with the supercritical reaction medium (Figure 1c). Again, such a reaction is truly biphasic (solid–supercritical fluid) in nature, whether additional gaseous reagents are present or not. This is in sharp contrast to the situation with supported catalysts in organic solvents, where triphasic (solid–liquid–gas) reaction systems often lead to severe mass-transport limitations.

Most examples to date have concentrated on $scCO_2$ as the phase containing substrates and/or products, corresponding to the mobile phase in continuous-flow operation. Recently, however, the reverse situation where the catalyst is retained in the $scCO_2$ phase has also found increasing interest. These systems have been referred to as "inverted" biphasic catalysis. In this section we will use the notation "phase/$scCO_2$" to indicate that the catalyst is contained in the non-CO_2 phase, and "$scCO_2$/phase" when the catalyst is in the $scCO_2$ (i.e., "inverted").

6.3.2
Supercritical CO_2-Based Approaches to Catalyst Immobilization

6.3.2.1
General Considerations

As noted in Section 6.3.1, supercritical CO_2 offers three fundamentally different procedures, each of which can be carried out in conventional or inverted biphasic systems. Concentrating initially on methods using $scCO_2$ as the product stream (i.e., conventional systems), the major difference results from the nature of the catalyst phase. Using the CESS procedure the catalyst is homogeneously dissolved in the $scCO_2$ phase during the reaction stage, whereas liquid–$scCO_2$ systems and solid–$scCO_2$ systems are biphasic in nature. Consequently, different approaches must be considered for continuous-flow operation in each case. Although all three approaches share many features in common, especially with regard to isolation and purification of products, it is also important to be aware of how each presents different potential advantages and difficulties. In most cases a flow reactor setup would be preferred if possible, as this would prevent the need for large reactor volumes and a costly pressurization step between reaction and separation.

The successful implementation of unit operations employing supercritical fluids will ultimately depend on their being able to compete on a commercial level with more conventional methods. The fact that several applications of $scCO_2$ for separation processes have already been demonstrated, especially in extraction technology, is an advantage since much of the equipment used is available commercially. Furthermore, the parts which are unique to homogeneous catalysis such as suitable reactors can easily be adapted from existing high-pressure autoclave technology. However, a number of specific processing issues must be addressed for industrial application to be successful, notably:

- *Catalyst activity:* does the catalyst provide a high enough TOF for the given substrate residence time in the reactor?
- *Catalyst stability:* does the catalyst retain its activity or selectivity on extended use?
- *Catalyst immobilization:* can leaching of catalyst into the product stream be minimized?

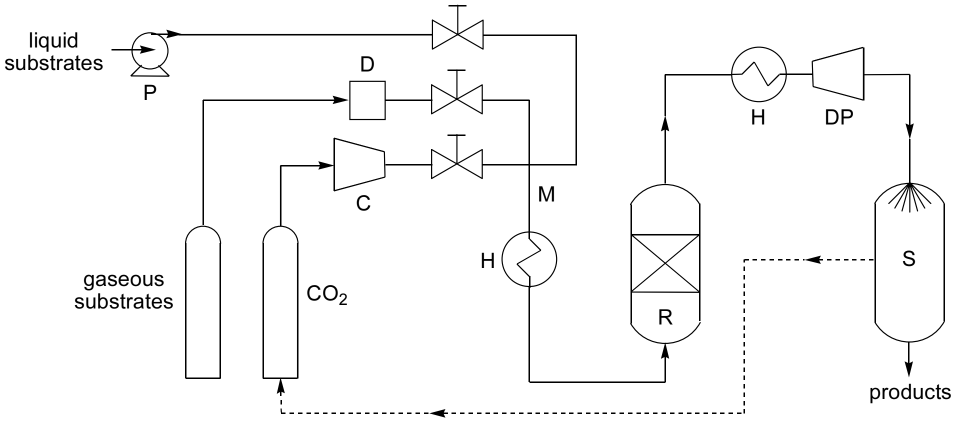


Figure 2 General reactor scheme for homogeneous catalysis using SCFs.
P = HPLC pump; D = dosimeter; C = compressor; M = mixing chamber;
H = heat exchanger; R = reactor; DP = depressurizer; S = separation/collection chamber.
The dotted line represents possible recycling of the CO_2.
Similar recycling of unreacted substrates could also be performed.

The general setup for all non-inverted catalytic processes carried out using SCFs will be as shown in Figure 2. Here it can be seen that one or more substrate streams will be mixed and led into the reactor (most likely using the CO_2 feed), which is charged with the catalyst and the desired pressure of CO_2. The residence time of the substrate in the reactor will depend on the activity of the catalyst. The products and any unreacted substrate will then be carried out of the reactor by the CO_2 stream, and isolated by reduction of the CO_2 pressure. Although in most test systems reported to date the CO_2 is simply vented, in industrial applications it is likely to be repressurized and re-used. One unique feature of SCFs is the ability to control its solvent properties by altering its density (i.e., temperature or pressure). This means that product mixtures may be separated, in principle at least, by selective phase separation from CO_2.

One factor that is of great importance in systems based on supercritical fluids is effective control of phase behavior. As has been discussed in Section 6.1, the critical point in mixtures can be very different from that in the pure SCF. It is therefore important that the development of catalytic methods is supported by investigations of the critical points of mixtures. A recent example of this was the use of acoustic measurements to determine the critical point of a model hydroformylation system containing six components (CO_2/propene/CO/H_2/*n*-butanal/isobutanal) [8]. The critical point was measured for different composition ratios corresponding to different levels of conversion, from which it was found that the critical point rose by up to 35 °C and 3.0 MPa relative to pure CO_2. The problem is likely to be more pronounced in systems involving batch reactors where the pressure and composition of the mixture will change during the course of the reaction as reactants are consumed and products formed. In such cases it will be important that the initial pressure is high enough to retain a supercritical phase, even at maximum conversion. There is less of a problem in continuous-flow systems as the pressure and composition should remain constant once the system has reached equilibrium. Other reactions for which such critical point investigations have been carried out include hydrogenation [9], and an eight-component system for allylic epoxidation in $scCO_2$ [10].

6.3.2.2
Immobilization Methods Using CO_2 Only

The variation in critical data for complex reaction mixtures can be problematic, but at the same time it can also permit operating conditions in which a condensed phase is in equilibrium with a compressed CO_2-rich phase at temperatures and pressures beyond the critical point of pure CO_2. Although the whole mixture is then not supercritical, the solvent properties of the compressed CO_2 phase will be like those of a supercritical fluid. Any component in such a mixture will partition between the condensed and the supercritical phase, depending on its molecular structure as well as the pressure and temperature of the system. This ability to control the partitioning of substrates and catalysts allows the design of integrated reaction/separation schemes that rely on CO_2 as the only mass separating agent.

It has been found that the solvent properties of a supercritical fluid depend most importantly on its bulk density, which depends in turn on the pressure and temperature. In general a higher density of the SCF corresponds to stronger solvation power, whereas a lower density results in a weaker solvent. The solubility of a solute in $scCO_2$ is extremely dependent on its structure, with three features of paramount importance: low polarity compounds are more soluble than very polar substances or salts; solubility increases with increasing vapor pressure of the solute; specific functional groups like perfluoroalkyl and polysiloxane substituents, or polyether/polycarbonate copolymers give enhanced CO_2 solublity. The latter "CO_2-philic" substituents can lead to dramatic solubility enhancements, thus allowing control of the phase preference of reaction components at different stages of a reaction/separation process.

Many organic substrates and products have significant solubilities in $scCO_2$, whereas the majority of organometallic catalysts are very poorly soluble in this medium. Attempts have been made to exploit this factor if the main grounds for using $scCO_2$ lie simply in allowing effective catalyst recycling and product isolation. In such cases it is not necessarily essential to work under fully homogeneous conditions during the reaction. In some cases the reaction is carried out in the absence of CO_2, which is used only in the separation step and for downstream processing. An early example of this approach is provided by a BASF patent proposing to regenerate phosphine-modified rhodium hydroformylation catalysts via extraction of the so-called "heavy ends" after the more volatile short-chain aldehyde products have been removed by conventional distillation [11]. More recently, the hydroformylation of long-chain olefins was carried out using CO_2-insoluble catalysts in a substrate–$scCO_2$ biphasic system. At the end of the reaction, the products were separated by supercritical fluid extraction, allowing repeated re-use of the catalyst [12]. In order to fully exploit the potential benefits of the supercritical state for both reaction and separation, it may be preferable to carry out the reaction in a fully homogeneous single phase, and only afterward to induce phase separation. In particular, the importance of homogeneity of substrates, catalysts, and intermediates in a single phase for high conversion and selectivity in catalytic processes has been noted in several studies [13].

Most organometallic complexes are too insoluble in $scCO_2$ for catalytic applications under single-phase conditions. This problem can be overcome by the introduction of perfluoroalkyl groups into the ligand periphery of metal catalysts bearing this type of ligand [14]. Again, these catalysts are soluble in $scCO_2$ at high density, but become insoluble at lower density [15], resulting in separation from the reaction mixture or partitioning into a liquid phase (if present) upon density reduction. The efficiency of this type of regulated system for catalyst immobilization has been demonstrated with a rhodium catalyst bearing fluoro-substituted triphenylphosphine derivatives such as $P[m\text{-}F(CF_2)_6(CH_2)_2C_6H_4]_3$ (3-H^2F^6-TPP) for the hydroformylation of long-chain olefins [16]. Using this system in a batch process, a turnover frequency of 430 h^{-1} was obtained for the hydroformylation of 1-octene, with an *n*/*i* ratio of over 5 : 1 in the products and almost complete suppression of olefin isomerization. The products were collected by careful depressurization of the reactor, and were found to contain only trace amounts of Rh in the range of 1 ppm under optimized conditions. The catalyst itself could be re-used for five successive catalytic runs with no significant change in selectivity or turnover number.

A batch system of this type (the so-called CESS approach) is still not ideal, however, it requires full depressurization and repressurization, the latter being a very energy-intensive process. A fully integrated system can be envisaged on the basis of a loop technology to combine the reaction and separation steps into one quasi-continuous process. Although partial depressurization is required to isolate the products, it is an improvement over the early experiments which required full depressurization to atmospheric pressure. This is the most capital-intensive of the methods described in this section, and can be regarded also as the most complex scenario with regard to operating costs of processes employing $scCO_2$.

A potential flow sheet for hydroformylation of 1-octene in a semicontinuous CESS process as a prototypical catalytic transformation is illustrated in Figure 3, with the operating specifications summarized in Table 2. The 1-octene feed is heated to 65 °C in E101, then pumped into the reactor R101. At the same time the syngas and CO_2 pass through compressors C101 and C102 respectively, are mixed with the recycle stream from V101, heated to 65 °C and fed into R101 at a total pressure of 20.0 MPa. The product stream from R101 is then heated to 125 °C in E103, after which the pressure is reduced in C103 to 11.0 MPa and the stream passes into separator S101. In this vessel 20% of the product precipitates as a liquid phase containing the catalyst. This stream is pumped back into R101 by P102, at the same time being returned to 65 °C in E104. The remainder of the product stream is then cooled to 25 °C in E105, the pressure is adjusted to 5.0 MPa by C104, and then the stream passes into isolation chamber V101. At this stage, the liquid product is separated by gravity, while the remaining gas stream is recompressed to 20.0 MPa by C105, whereupon it rejoins the feed stream. The isolated aldehyde mixture can be subjected directly to a conventional *n*/*i* distillation without the need for further purification.

Such an approach clearly requires advanced engineering. Large costs are associated with the energy of compression, a feature that has to be considered in all three approaches involving $scCO_2$. This problem can be somewhat ameliorated

Table 2 Process and reactor specifications for hydroformylation of 1-octene.

Reaction pressure (P_1)	20.0 MPa
Reaction temperature (T_1)	65 °C
Separation pressure (P_2)	14.0 MPa
Separation temperature (T_2)	125 °C
Isolation pressure (P_3)	5.0 MPa
Isolation temperature (T_3)	25 °C
Rh/L/substrate [mol]	1 : 10 : 5000
1-Octene conversion per pass	90%

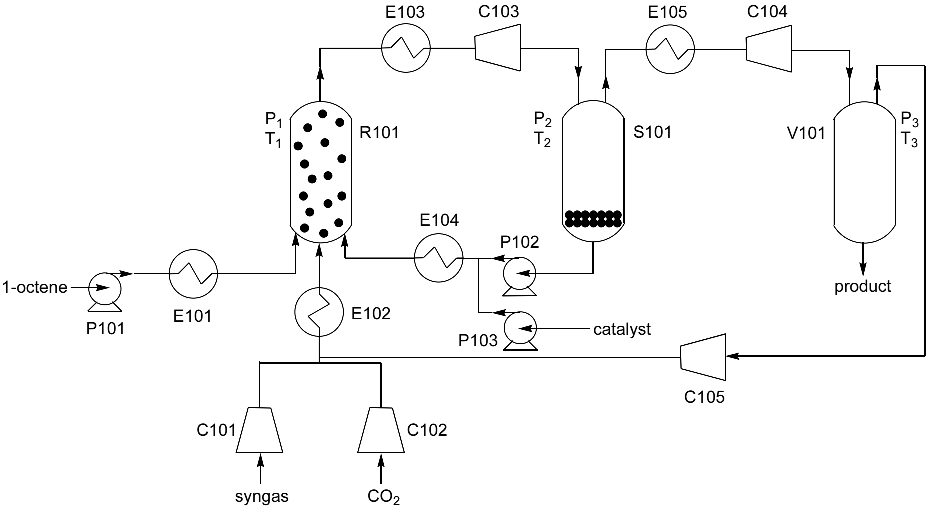
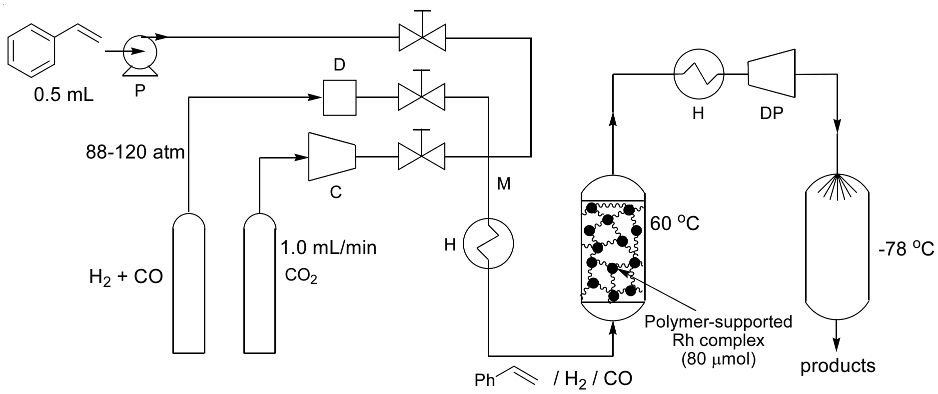


Figure 3 Process flow sheet for hydroformylation of 1-octene to 1-nonanal using the CESS approach. The black circles (●) represent catalyst molecules.

by the use of temperature to control the density, and hence the solubility, thus reducing the need for drastic alterations in pressure. The existing examples of industrial-scale processes employing pressurized CO_2 demonstrate that the cost of generating such pressures need not be prohibitive, and additionally provide a technical framework on which new methods may be developed. Whereas the CESS procedure seems to be particularly applicable to high value-added products, the other two approaches described later in this section could potentially reach the bulk and commodity businesses if suitably optimized. A major advantage of using $scCO_2$ for catalyst immobilization is the effectively solventless generation of the final products. Thus, all downstream processing related to solvent removal, recycling, or disposal is avoided. This can be especially important in cases such as fragrances, food additives, or pharmaceuticals, where even trace amounts of solvent residues must be avoided.

6.3.2.3
Solid–$scCO_2$ Systems

Catalysis using solid–$scCO_2$ systems could be accomplished by straightforward fixed-bed technology as already implemented on a commercial scale for *heterogeneous* hydrogenation [5]. Examples have already been reported using both inorganic (e.g., silica, alumina) and organic (e.g., polystyrene) supports for catalysts, ligands, or reagents in reactions involving $scCO_2$. Compared with conventional solution-phase systems employing solid-phase reagents, SCFs offer the potential for much more rapid mass-transfer rates, especially in reactions containing both gaseous and liquid substrates.



Step 1 Incubation: H_2/CO total 8.8-12 MPa, 15 min.
Step 2 Reaction: styrene, H_2/CO/CO_2 8.8-12 MPa, 30 min
Step 3 Sweeping: $scCO_2$ 12 MPa, 15 min

Figure 4 Experimental setup for polystyrene-supported (*R,S*)-BINAPHOS–rhodium-catalyzed asymmetric hydroformylation of styrene (adapted from [18]).

Examples of this approach has been described by Poliakoff and co-workers for the hydroformylation of 1-octene using a silica-immobilized rhodium–phosphine complex [17], and by Nozaki and co-workers for the asymmetric hydroformylation of styrene using a polystyrene-supported (*R,S*)-BINAPHOS–rhodium complex [18]. A range of operating conditions was tested, giving a maximum TOF of 160 h^{-1} when the reaction was carried out at 90 °C. This was approximately half of the TOF in an equivalent fully homogeneous system [19]. Although the degree of octene conversion was relatively low (14.3% at this reaction temperature), the selectivity toward the linear isomer was very good (33 : 1). The system proved to be extremely robust for successive reactions, with no loss of activity or catalyst leaching being observed over six runs. One important benefit of using $scCO_2$ as the mobile phase was the ability to separate ca. 90% of the 1-octene from the reaction product simply by using a two-step depressurization approach, similar to that employed in the CESS system described above. The experimental setup used by Nozaki and co-workers is illustrated in Figure 4. In this case $scCO_2$ was found to be the most efficient mobile phase for the process, which was operated using successive incubation, reaction, and sweeping steps, in which the gas flow consisted of H_2/CO, H_2/CO/CO_2, and CO_2 only, respectively.

6.3.2.4
Liquid–SCF Systems

In liquid–supercritical systems, the liquid phase most commonly acts as a support to retain the catalyst rather than using the selective solubility properties of $scCO_2$ as for the CESS approach described below. Thus, there is a permanent phase separation between the mobile phase which is (usually, but not exclusively) CO_2 and the "stationary" liquid phase. The fact that the catalyst is molecularly dispersed in the liquid phase means that the environment resembles the typical situation of homogeneous catalysis. In order to immobilize the catalyst efficiently, the solubility of the organometallic species in the liquid phase must be greatly favored over their solubility in the supercritical phase. Fortunately, $scCO_2$ is a rather poor solvent for many organometallic catalysts in the absence of suitable ligands [14]. Therefore, the risk of catalyst leaching should be reduced, compared with similar liquid–liquid multiphase systems such as water–organic, fluorous–organic, or ionic liquid–organic. However, it may still be advantageous to design the catalyst or ligands to enhance their retention in the stationary phase.

It is also important to note that in most cases the stationary phase cannot be regarded as an "innocent" component of the reaction mixture. The interactions of substrates, catalyst, or CO_2 with the stationary phase can all influence the course of the reaction. In optimal cases this can be a useful factor, for example in the hydrovinylation system discussed below, where the ionic liquid (IL) acts as a catalyst activator which must otherwise be added separately. In water–CO_2 systems, however, the formation of carbonic acid when CO_2 is dissolved in water means that the pH of the aqueous phase can be as low as 3. Thus all reagents and catalysts must be stable under acidic conditions when using this approach.

Except for water as the stationary phase, no significant cross-contamination of the liquid phase into CO_2 can be tolerated, as this would result in its depletion during continuous-flow operation, along with contamination of the product. The mixture critical points of most organic solvents are in the vicinity of those of the pure solvents. They would thus be at least partially miscible with the SCF and would not form a stable stationary phase for catalyst immobilization. As has been noted previously, the solubility of a compound in $scCO_2$ is determined not only by its polarity, but also by its vapor pressure. Therefore, highly polar and/or very nonvolatile liquids, which do not become miscible with CO_2 until hyperbaric conditions, are the most useful candidates for liquid catalyst phases together with $scCO_2$. Three different approaches that are receiving particular interest are discussed in detail in Section 6.4, using water, ILs, and liquid or low melting polymers as the liquid phase. To date it is mainly $scCO_2$ that has been applied to these systems, but there is in principle no reason why alternative SCFs cannot be used. All of these materials share a small to negligible solubility in CO_2, thus allowing efficient phase separation. In most applications reported so far, the CO_2 acts as a mobile phase, bringing substrates into the system and removing products, while the other liquid is a stationary catalyst-containing phase. This need not always be the case, and there is increasing interest in so-called "inverted" systems where the catalyst is immobilized in the CO_2 phase, while the other liquid acts as mobile phase. A schematic representation of the conventional and inverted systems for CO_2/H_2O is given in Figure 5.

A continuously stirred tank reactor (CSTR) would probably be the reactor vessel of choice for most liquid–$scCO_2$ systems, to ensure that efficient mixing of the phases occurs. Apart from this, the setup is likely to be similar to that employed for solid–CO_2 applications with regard to product isolation. A typical reactor setup for laboratory-scale exploratory explorations is depicted in Figure 6. Examples of continuous-flow systems using IL–$scCO_2$ mixtures using apparatus of this type

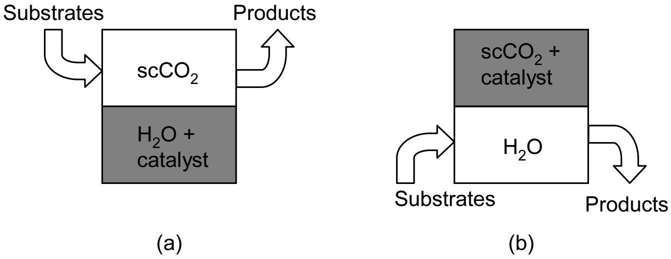


Figure 5 Schematic representation of (a) conventional (H_2O–$scCO_2$), and (b) inverted ($scCO_2$–H_2O) catalyst systems.

have been reported for enantioselective hydrovinylation [20], hydroformylation [21], and enzyme-catalyzed reactions [22]. Although the latter is not strictly homogeneous catalysis, the approach employed would be entirely identical. In the example shown in Figure 6, the CO_2 passes through the IL from beneath to ensure the maximum contact between the two phases. In more recent examples this approach has been modified by the delivery of CO_2 through a capillary from the top to minimize physical extrusion of the liquid phase [22c]. A very similar setup can also be used for the other $scCO_2$–liquid systems discussed in this section.

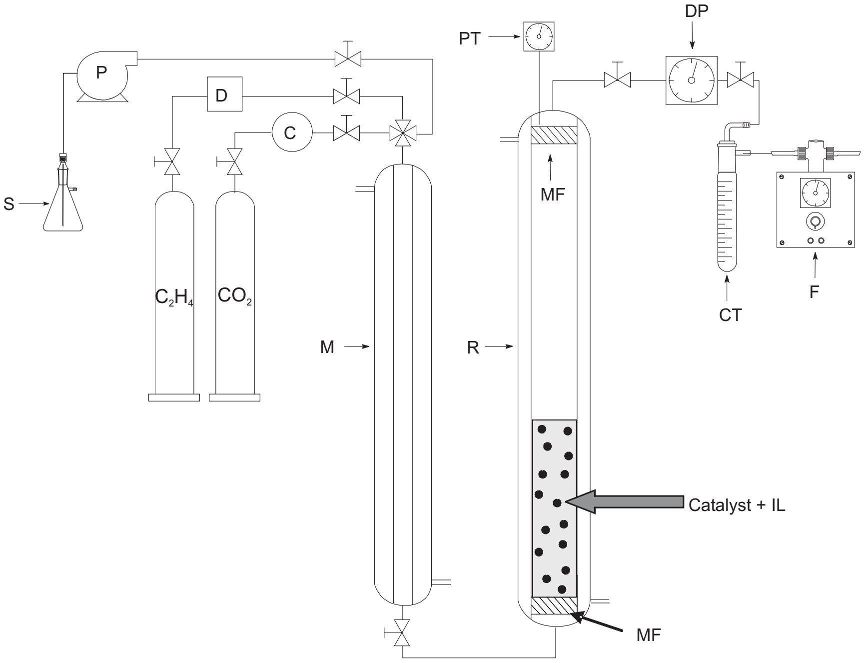


Figure 6 Schematic view of continuous-flow reaction setup for IL–$scCO_2$ systems (adapted from [20]).
C = compressor; CT = cold trap; D = dosimeter; DP = depressurizer;
F = flow meter; M = mixer; MF = metal filter; P = HPLC pump;
PT = pressure transducer and thermocouple; R = reactor; S = styrene.

The low solubility of most organometallic catalysts in CO_2 means that in ideal cases no modification catalyst is required, provided it is sufficiently soluble in the IL. This was found to be the case for the hydrovinylation system which employed a nickel-based chiral catalyst first reported by Wilke and co-workers [23]. In the case of the hydroformylation system, however, the activity was found to be highest when using [Rh(acac)$(CO)_2$] combined with a sulfonated triphenylphosphine analogue that had an imidazolium cation as its counterion. In practice it is likely that neutral catalysts may require charged ligands, while those which are themselves charged can be used unmodified.

The nature of the IL itself is also important in the development of a flow system. In particular, it is important that it remains completely stable under the reaction conditions to ensure that no product contamination occurs. Another important aspect is the possibility of interaction of the cation or anion with the catalyst: in ideal circumstances this can be used to enhance the activity of the system. This was clearly demonstrated in the hydrovinylation system, where the IL acted both as catalyst support and activator [20].

In the case of the hydroformylation reaction, 46.5 mg (0.180 mmol) [Rh(acac)$(CO)_2$] and 1.31 g [Prmim][TPPMS] (Prmim = 1-propyl-3-methylimidazolium; TPPMS = triphenylphosphine monosulfonate) were dissolved in 12 mL IL in a 30 mL CSTR. The CO/H_2 mixture was added at 4.0 MPa (1 : 1 ratio of gases), the reactor was heated to the operating temperature (70–100 °C), and the pressure was made up to 20.0 MPa with CO_2. The reaction was optimized by varying factors such as the IL employed, the substrate flow rate, the reaction temperature, and the gas composition. Although the catalyst retained activity over a relatively long period of continuous reaction, its slow but steady deactivation was noted. This was ascribed to slow oxidation of the phosphine ligand caused by traces of oxygen in the CO_2 stream. Clearly this is a problem that could occur in any flow system employing $scCO_2$ where the catalyst or ligands are oxygen-sensitive. Another example of this problem is noted later in this section.

The use of poly(ethylene glycol) as the stationary phase is the least developed of the three CO_2–liquid phase systems. Liquid PEG of low to moderate molecular weight serves as a reasonably good solvent for many typical organometallic catalysts, but these systems are still soluble in $scCO_2$ or form emulsion-type mixtures, which may be interesting media for catalysis in their own right [24]. For multiphase catalysis the use of high molecular weight PEG is preferred, however, owing to its low solubility in $scCO_2$. PEGs with average molecular weights above 1000 are waxy solids under ambient conditions, but they melt under CO_2 pressure to become liquids under typical conditions of $scCO_2$ catalysis [25]. The approach has been demonstrated for the rhodium-catalyzed hydrogenation of styrene as a test reaction using Wilkinson's complex [$(PPh_3)_3RhCl$] as the catalyst [26]. The reactor setup for such an approach is likely to be very similar to that already described for IL–$scCO_2$ systems in the previous sections. Although the solubility of high molecular weight PEGs is very low in $scCO_2$, for long-term operation it may still be necessary to ensure that any lost in the product stream is replaced, and that significant quantities do not build up in the product. If greater affinity between the catalyst and the PEG is required, phosphine-substituted PEGs have been prepared which may also be applied as ligands.

6.3.2.4
Other Developments

A further approach that permits the use of an entirely homogeneous reaction, but also efficient catalyst separation, is the use of a membrane reactor. In such systems, the reaction mixture is passed through a membrane whose pores are small enough to trap the catalyst but also large enough to permit transit of the products and reaction solvent. Such an approach has recently been reported by Goetheer et al. for the hydrogenation of alkenes [27]. In principle, the properties of supercritical fluids should be ideal for the application of membrane reactors, most notably the small size of the most common SCF materials, and their low viscosity compared with many organic solvents. Inorganic membranes are likely to be more suitable for use in reactors of this type owing to their higher thermal and chemical stability than most organic membranes. There is also the possibility of swelling of organic membranes by the SCF.

The system reported by Goetheer et al. used a silica membrane with pore sizes of 0.5–0.8 nm [27]. The requirement to attach fluorous substituents to the ligands to gain sufficient CO_2 solubility is in fact beneficial in this application as it increases the size of the ligand, and thus reduces the likelihood that it will pass through the membrane. In the application reported, a modified version of Wilkinson's catalyst ($RhCl(PPh_3)_3$) was employed. The fluorous triphenylphosphine ligand had the structure $P[C_6H_4\text{-}p\text{-}SiMe_2CH_2CH_2(CF_2)_8F]_3$, giving a complex whose diameter was estimated to be 2–4 nm, and thus much larger than the pores in the membrane. The hydrophobic nature of the ligands was expected to ensure also that the catalyst was not adsorbed on the hydrophilic membrane surface. The membrane reactor setup was as shown in Figure 7.

Before catalytic tests, the flux of CO_2 and 1-butene through the membrane were measured at operating temperature and pressure to ensure that satisfactory reaction conditions were established. It is important in such systems that the pressure on the product side of the membrane remains high enough to transport the products and any unreacted starting materials into the collection vessel at a reasonable rate.

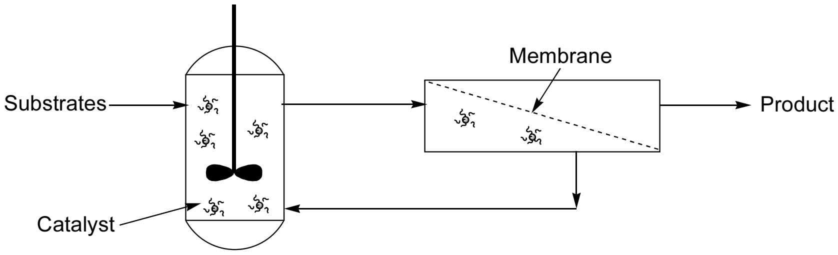


Figure 7 Membrane reactor for continuous homogeneously catalyzed reactions in $scCO_2$ (adapted from [27]).

The hydrogenation of 1-butene to butane was run using this reactor for a total of 32 h, with a starting conversion of ca. 40% which dropped to about 33% after 32 h reaction. Overall the reaction gave a total turnover number (TTN) of $1.2 \cdot 10^5$. The decrease in reactivity was thought not to result from catalyst leaching, but instead from slow decomposition caused by the presence of oxygen in the CO_2 or the feed gas. The problem has already been noted for the biphasic $scCO_2$–IL hydroformylation reaction, and is one that will need to be solved if such systems are to be applied on an industrial scale. One potential solution to the problem is efficient oxygen scrubbing of the CO_2 or feed mixtures, which would increase the cost of the process. A better long-term solution might be the development of catalysts that display higher oxygen stability, since this would make such systems more robust overall. One interesting feature of the membrane reactor system was the use of online analysis to monitor catalyst leaching.

6.3.3
Summary

Although no industrial processes have yet been reported in which homogeneous organometallic catalysts are employed in combination with SCFs, an increasing number of examples have been published that could potentially be developed for this purpose. Both batch and flow systems have been shown to be applicable, and the existing systems are limited more by the chemistry than by engineering aspects. Some closely related catalytic systems not involving organometallic catalysts are discussed in Section 6.5 [9]. Probably the most pressing problem, noted in some of the examples given in this section, is the long-term stability of homogeneous catalysts. Even the presence of very small amounts of oxygen in the reaction stream can result in an undesirable degree of catalyst decomposition. One solution is to ensure that feed streams are kept scrupulously oxygen-free, but a better one is the development of catalysts with greater oxygen stability. Overall, however, this is an area of huge promise which is likely to develop in parallel with related examples of heterogeneous catalysis using CO_2 as a mobile phase.

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6.4
Typical Reactions

6.4.1
Catalyst Immobilization using SCFs as the Only Mass-Separating Agent

Charles M. Gordon and Walter Leitner

6.4.1.1
Introduction

Homogeneous catalysis employing $scCO_2$ is an extremely promising approach that has been attracting considerable interest in recent years. This section will outline approaches to homogeneous catalysis where CO_2 is the only mass separating agent present.

The opportunity to operate under truly homogeneous conditions is probably the main incentive for using $scCO_2$ as the reaction medium in molecular catalysis. Following traditional approaches, homogeneously catalyzed reactions employing gaseous reagents are, strictly speaking, two-phase processes, owing to the presence of phase boundaries. Reactions such as hydrogenation, hydroformylation, or carbonylation may suffer from mass-transfer limitations owing to restricted gas solubility in the liquid phase. In contrast, $scCO_2$ is completely miscible over all composition ranges with the majority of reactive gases used in chemical synthesis, thus offering a truly homogeneous single-phase medium. Furthermore, the density of the medium may be controlled through alteration of pressure or temperature, thus allowing very fine control of the solvent properties. Finally, in certain cases CO_2 may interact chemically with the solutes; this effect may be used to aid the system, for example where it acts as a protecting group.

Apart from these potential benefits for the chemical transformation, compressed (gaseous or supercritical) CO_2 offers the opportunity of optimizing catalyst recycling in a process. This topic has been intensively investigated in the last few years, and three different approaches have been envisaged which explore compressed CO_2 as a solubility trigger for catalyst recycling, as described below and illustrated graphically in Figure 1.

- *CO_2 as anti-solvent*: In this approach the reaction is performed under conventional conditions in an organic solvent or neat substrate. When the reaction is complete, CO_2 is added. This causes a volume expansion as well as a decrease in polarity of the reaction medium. Under these altered conditions the catalyst is precipitated, and the products can be flushed out of the reactor and the catalyst re-used.

- *CO_2 as co-solvent*: In this case CO_2 is present during the reaction to ensure the solubilization of the catalyst. After the reaction, CO_2 is released leading to catalyst precipitation and easy product separation.

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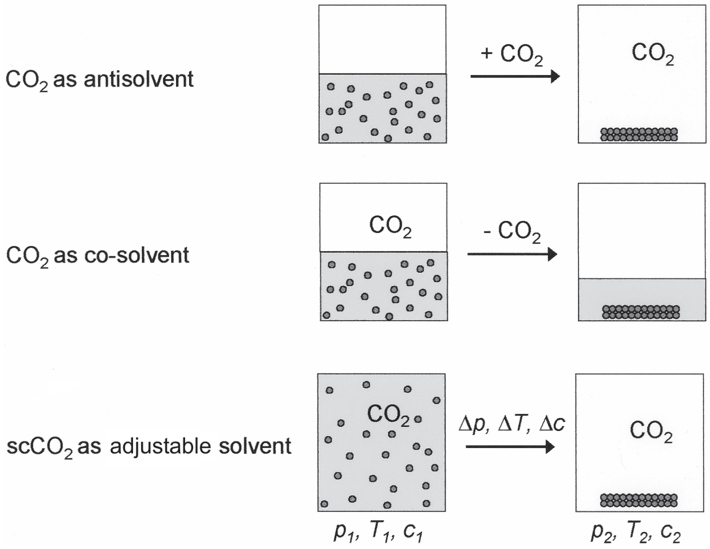


Figure 1 Different approaches to application of CO_2 to homogeneous catalysis for catalyst recycling.

- *CO_2 as adjustable solvent*: Here, both the reaction and the separation step are performed in the presence of CO_2, no other solvents being required. This unique procedure is enabled thanks to the tunable solvent properties of $scCO_2$. A high density of CO_2 allows the reaction to proceed under fully homogeneous conditions. When the reaction is complete, through suitable variation of pressure and/or temperature in the reactor vessel, the catalyst forms a separate phase, while the more volatile products remain in the CO_2 phase and can be selectively extracted. In some cases, simply the change in composition during the course of the reaction induces the catalyst precipitation. These approaches have been referred to as CESS (*c*atalysis and *e*xtraction using *s*upercritical *s*olutions).

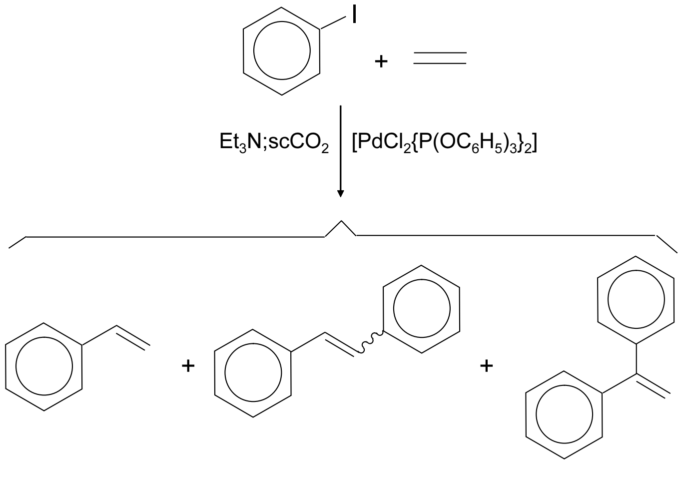
This systematic classification of recycling methods can be related directly to the solubility properties of the organometallic catalysts. The majority of these are poorly soluble in CO_2, which therefore acts as an anti-solvent for solutions containing such species. However, either substrates or products may act as "entrainers" which serve to enhance the CO_2 solubility, so in some cases additional catalyst modification may be necessary to render them sufficiently "CO_2-phobic" for efficient separation. In the other two approaches, the catalysts need to be "CO_2-philic" to ensure sufficient solubility in the CO_2-based media under the reaction conditions. This behavior is exhibited by certain volatile and nonpolar complexes such as transition metal carbonyl complexes, and also by metal complexes containing suitably modified ligands (e.g., containing perfluoroalkyl groups).

6.4.1.2
ScCO$_2$ Insoluble Catalysts

The most obvious case of catalyst immobilization relies on using a catalyst that is insoluble in scCO$_2$. In such cases the products can be extracted either by employing batchwise procedures or continuously. This classification includes the entire class of biocatalysts that is beyond the scope of this article [1]. In this section we will discuss methods for catalyst immobilization where this poor solubility is exploited directly, as well as those where CO$_2$ is used to alter the solvent properties of conventional solvents (the so-called "expanded solvent" approach). The simplest approach to using CO$_2$ in homogeneously catalyzed processes is to use it simply for clean extraction of reaction products. In such cases the lack of scCO$_2$ solubility of most organometallic catalysts is advantageous, since there is a reduced likelihood of catalyst contamination of the product. An early example of this approach is provided by a BASF patent proposing to regenerate phosphine-modified rhodium hydroformylation catalysts via extraction of the so-called "heavy ends" after the more volatile short-chain aldehyde products have been removed by conventional distillation [2].

In the above example, CO$_2$ is added after the reaction to facilitate only the separation. It can, however, be advantageous to add compressed CO$_2$ during the reaction stage, even if it cannot dissolve the catalyst. Ikariya and co-workers reported an example of enhanced product selectivity in the Mizoroki–Heck reaction of ethylene with aryl halides under CO$_2$–liquid biphasic conditions [3]. In such reactions, the initially formed styrene derivatives can react with another aryl halide molecule to form stilbenes and 1,1-diphenylethylenes (Scheme 1).

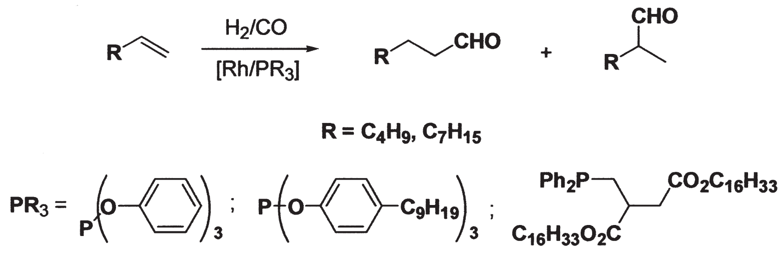
Styrene and its derivatives have a significant solubility in scCO$_2$, so the authors reasoned that it should partition into the CO$_2$ phase, thus suppressing further



Scheme 1 Mizoroki–Heck reaction of ethylene with iodobenzene under CO$_2$–liquid biphasic conditions.

reactions. The catalyst employed was $PdCl_2[P(OC_6H_5)_3]_2$, which is insoluble in $scCO_2$, dissolved in a liquid phase consisting of the aryl halide and triethylamine. For the reaction of iodobenzene with ethylene at a pressure of 0.1 MPa at 130 °C, in the absence of CO_2 a conversion of 95% was obtained, but with a styrene selectivity of only 57%. When instead the reaction was carried out under 10 MPa CO_2 at the same temperature, the conversion remained excellent at > 99%, but the styrene selectivity was increased to 83%. Increasing the CO_2 pressure gave further enhancement in the selectivity, but at the cost of greatly reduced levels of conversion, presumably because of the very high solubility of the substrates in the CO_2 phase under these conditions, resulting in reduced contact times with the catalyst. No attempts to recycle the catalyst were reported in this study.

Cole-Hamilton and co-workers reported the hydroformylation of long-chain olefins using CO_2-insoluble catalysts in a substrate–$scCO_2$ system [Eq. (1)] [4]. The catalysts were based on $[Rh_2(OAc)_4]$ combined with either phosphine or phosphite ligands, and were insoluble in $scCO_2$ under the conditions used for either reaction or product extraction (see **1**–**3**). When the reactions were carried out under $scCO_2$, the yields were lower than in its absence, but a higher selectivity toward the linear product was observed. At the end of the reaction, the products were separated by supercritical fluid extraction with effectively no rhodium content (< 0.01%). Recycling studies showed that conversion levels remained similar over five reaction steps, although the linear/branched ratio decreased, an observation thought to result from hydrolysis of the phosphite ligand. The authors suggested that the catalysis resulted from formation of a two-phase system, with the excess ligand acting as a solvent for the catalytic reaction, or alternatively by reaction at the phase boundary between the $scCO_2$ and the catalyst.



(1)

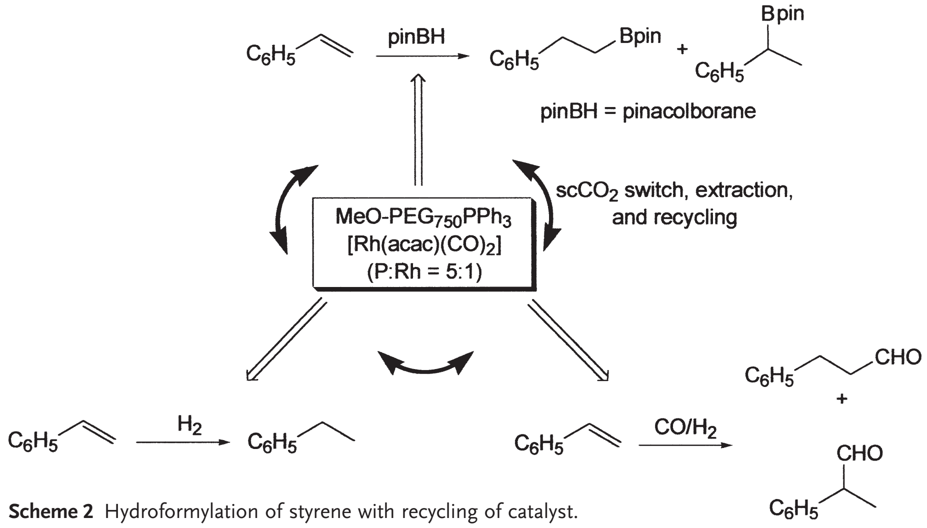
1 **2** **3**

More recently, the Cole-Hamilton group has been able to develop a continuous-flow process on the basis of a similar concept, using phosphine ligands modified with ionic side groups to disperse and immobilize the catalyst in the liquid product phase [5].

An interesting recent development is the use of PEG-substituted phosphine ligands which are completely insoluble in $scCO_2$, but soluble in the organic substrates involved in the reaction. Leitner and co-workers have described this approach using the ligand MeO-$PEG_{750}PPh_2$ (**1**) [6]. In initial experiments, it was demonstrated that the hydroformylation of 1-octene catalyzed by a catalyst formed in situ from **1** and $[Rh(acac)(CO)_2]$ (acac = acetylacetonate; P/Rh = 5 : 1) could be "switched off" completely with the introduction of CO_2 into the reactor. For example, conversion after 2 h of reaction time ($T = 70$ °C, p (H_2/CO) = 5 MPa) dropped from 99% in the absence of CO_2 to 66.4% at a density d (CO_2) = 0.35 g mL^{-1} to 0% at d (CO_2) = 0.57 g mL^{-1}. This halting of the reaction on addition of CO_2 was accompanied by precipitation of a yellow-orange solid, demonstrating the efficient separation of catalyst and substrate. The same separation was induced in the product mixture if CO_2 was introduced after the 2 h reaction time.

The potential of this approach for catalyst recycling was demonstrated by its application as a "cartridge" system for the hydroformylation of a range of different alkenes using a single batch of catalyst. In total the same batch of catalyst was applied for nine consecutive catalytic cycles using four different alkenes, with effectively quantitative conversion in all cases, along with unchanged selectivity. The loss of catalyst components with the product stream was determined as 1.2% for rhodium and 2.4% for phosphorus in total over the nine reaction steps. Perhaps even more significant was the demonstration that different reactions could be carried out using the same batch of catalyst without significant cross-contamination. In this case, styrene was subjected to hydroboration, hydroformylation, hydrogenation, and finally hydroboration once more, all using the same rhodium catalyst system (Scheme 2).

At the end of each reaction cycle the products were thoroughly extracted using $scCO_2$, after which the reactor was charged with fresh substrate. The conversion and selectivity obtained in these studies can be seen in Figure 2, and it is clear that the catalyst is as active for the second hydroboration cycle as for the first. No significant cross-contamination in the products of the three different reaction types was observed, and once again the degree of catalyst leaching in the products was very low. As the modification of achiral and chiral ligands with PEG chains is synthetically straightforward, this approach could open a widely applicable



Scheme 2 Hydroformylation of styrene with recycling of catalyst.

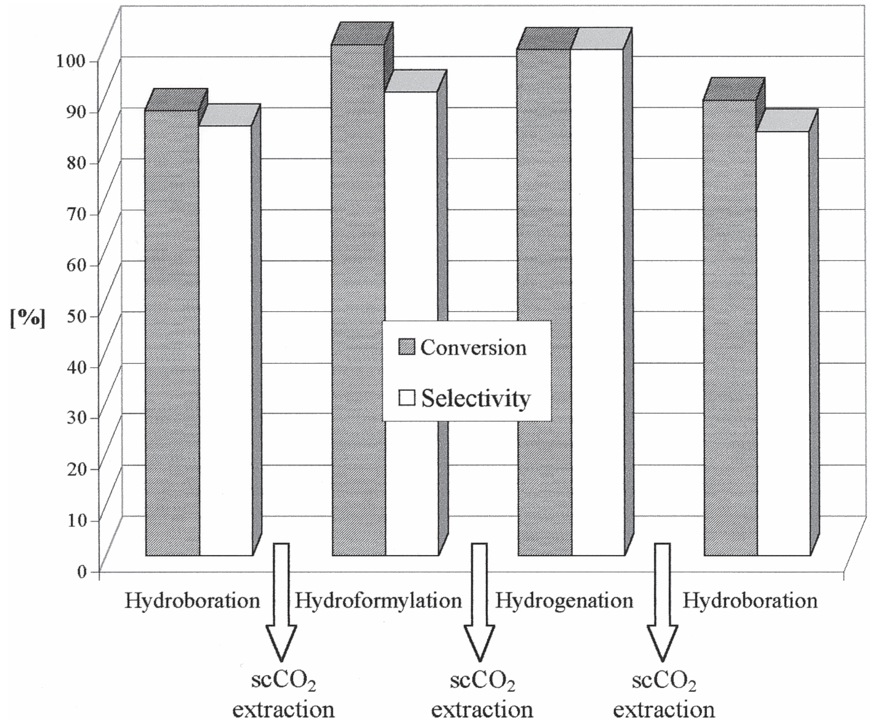


Figure 2 Results for a series of different catalytic reactions linked sequentially with the cartridge system **1**/[Rh(acac)(CO)$_2$]/scCO$_2$.

methodology for the synthesis of solvent and metal-free fine chemicals and pharmaceuticals on various scales.

The ability of scCO$_2$ to alter properties such as melting point, viscosity, diffusion coefficient, solvation ability, or dielectric constant in organic materials has been known for some time. A noncatalytic application of this technology is found in CO$_2$-induced melting processes for polymer processing, or for the precipitation of particles of uniform morphology and size (*p*articles from *g*as-*s*aturated *s*olution, PGSS). Exploiting this physical phenomenon, Jessop and co-workers showed that the addition of compressed CO$_2$ can allow transformation of solid organic substrates in solventless catalytic hydrogenation and hydroformylation reactions at temperatures well below their natural melting points [7]. When the reagent, or reagent and product mixture, is solid at the reaction temperature, the addition of gaseous CO$_2$ induces a melting point depression. The degree of lowering of the melting point is dependent on the solubility of the gas in the material. The liquid phase thus generated acts as a solvent for the catalyst, allowing the reaction to occur. As proof of principle, they carried out the hydrogenation and hydroformylation of 2-vinylnaphthalene (mp 65–66 °C) at 33 °C using Wilkinson's catalyst, RhCl(PPh$_3$)$_3$. The results showed that under solventless conditions and in the absence of CO$_2$ almost no reaction occurred in the solid state, whereas with the addition of 5.5 MPa of gaseous CO_2 the reactions proceeded smoothly in the molten substrate–product mixture. Similar rate enhancements were also observed for the heterogeneously catalyzed hydrogenation of oleic acid to stearic acid [7].

The addition of near-critical or $scCO_2$ to an organic solvent induces expansion of the solvent caused by uptake of gas, and consequently greatly increases the solubility of other gases in the solvent. At the same time the solvation power of the medium for solid or liquid substrates is reduced. This phenomenon has been proposed as an approach for the immobilization and recycling of organometallic catalysts. In this "expanded solvents" approach, a certain amount of CO_2 is added to the system during the reaction step to aid the solvation of gaseous reactants, and at the end of the reaction the pressure is increased to induce precipitation of the catalyst (Figure 3). The method is derived from a related technique in materials science known as *p*recipitation with a *c*ompressed *a*ntisolvent (PCA). It is important here to point out the difference between a CO_2-expanded solvent and co-solvents. A co-solvent will generally be present only in very small quantities (typically 1–2 vol%) and is added simply to enhance the solubility of compounds that are generally insoluble in pure CO_2. When considering CO_2-expanded solvents, the organic solvent is the starting point, but even in the presence of dense CO_2 will be present in quantities on the order of 20–50 vol%.

This approach was applied to the catalytic asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)acrylic acid to *S*-Naproxen using Ru(BINAP)-type catalysts in methanol solution [8]. The rate and selectivity of such reactions is very dependent on the concentration of H_2 in solution, with a higher concentration leading to improvements in both. The concentration of pure H_2 in methanol is relatively low, thus limiting the reaction rate. The addition of CO_2, however, results in expansion of the methanol and a corresponding large increase in the concentration of H_2 present in solution. The authors first studied the degree of expansion of methanol over a range of temperatures and CO_2 pressures in order to ascertain the optimum reaction conditions. The catalytic studies showed that a higher reaction rate was observed under a total gas pressure of ca. 10 MPa (pH_2 = 5 MPa) than under a pressure of 5 MPa H_2 alone. Unfortunately attempts to recycle the catalyst were

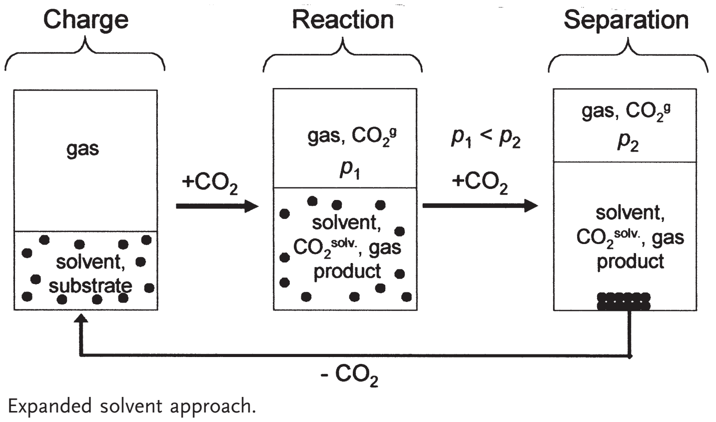


Figure 3 Expanded solvent approach.

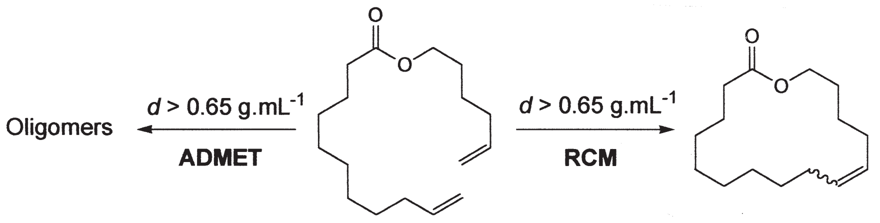
hindered by its deactivation over the course of the reaction, thought to occur as a result of oxygen poisoning.

Subramaniam and co-workers have reported the use of CO_2-expanded solvents for homogeneous catalytic oxidation reactions [9]. A for H_2, the solubility of O_2 in organic solvents can be greatly enhanced by the presence of CO_2. An important part of these studies was the determination of the “maximum expansion limit”, the point at which the catalyst solubility in the expanded organic solvent drops to the point at which it is precipitated. The reaction chosen was the oxidation of 2,6-di-*tert*-butylphenol (DTBP) by O_2 catalyzed by Co(salen) and iron porphyrin complexes. In the case of the cobalt complexes, the TOFs in expanded CH_3CN were between one and two orders of magnitude higher than the equivalent reactions in $scCO_2$. Such reactions cannot be easily carried out under high O_2 pressures in neat CH_3CN owing to the risk of forming explosive mixtures. The iron complex showed higher activity and selectivity in the CO_2-expanded CH_3CN than in $scCO_2$. Furthermore, much lower overall pressures were required to carry out the reaction (9 MPa as against 34.5 MPa). When the activity of the iron complex was compared in neat CH_3CN and CO_2-expanded CH_3CN, a much shorter induction period of 4 h was observed in the latter compared with 16 h in the former. This observation was ascribed to the higher O_2 solubility in the expanded solvent. In this case no attempts at recycling the transition metal catalysts were reported.

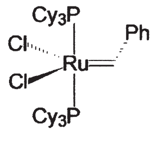
6.4.1.3
$ScCO_2$-Soluble Catalysts

Increasing interest has focused in recent years on the development of catalyst systems which are soluble in $scCO_2$. As has been previously noted, conventional organometallic catalysts, with a few notable exceptions, are not sufficiently soluble in $scCO_2$ under all normally accessible conditions to allow for efficient catalysis in solution. A number of different approaches have now been developed which can be used to enhance the CO_2 solubility of these complexes.

As aliphatic compounds are in general more soluble than aromatic ones, the (partial) hydrogenation of the aromatic backbone of a ligand can increase the solubility of the complex in $scCO_2$ sufficiently for catalytic purposes in some cases. Certain ligands, such as PEt_3, PBu_3, or PCy_3, can be used directly to generate metal complexes that dissolve in $scCO_2$ to some extent. An example of such a situation was reported by Leitner and co-workers for olefin metathesis in $scCO_2$ using ruthenium carbene complexes bearing PCy_3 or N-heterocyclic carbene ligands [10]. These complexes were at best sparingly CO_2-soluble, but it was thought unlikely that the catalysis occurred in a purely heterogeneous manner. Both *r*ing-*o*pening *m*etathesis *p*olymerization (ROMP) and *r*ing-*c*losing *m*etathesis (RCM) reactions were studied. The $scCO_2$ also proved to have a more profound effect on the outcome of the reaction, depending on its density. At lower CO_2 densities the main products formed were oligomers resulting from an intermolecular reaction pathway (*a*cyclic *d*iene *m*etathesis (ADMET) polymerization), while the RCM product was only formed in significant quantities at $d\,(CO_2) > 0.65\ g\ L^{-1}$ (Scheme 3).

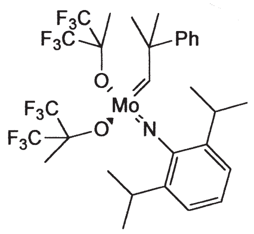


Scheme 3 Olefin metathesis in $scCO_2$.



sparingly soluble in $scCO_2$

4



highly soluble in $scCO_2$

5

This was postulated to result from a combination of decreasing the mole fraction of substrate with increasing density, and clustering of monomer molecules at lower CO_2 densities. A further interesting observation from this work was the ability of CO_2 to act as a protecting group under supercritical conditions when it was coordinated with an amine functional group to form a carbamic acid. In RCM reactions, a wide range of dienes were cyclized successfully, and the catalyst remained active after extraction of the products, as was confirmed in recycling studies. The very low CO_2 solubility of the Ru catalysts (confirmed by UV–Vis spectroscopy) meant that separation of the products free of Ru was easily accomplished.

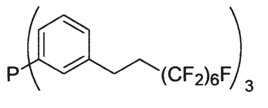
The results obtained using the Ru catalysts were further compared with those obtained using a molybdenum–alkylidene complex that was entirely CO_2-soluble under the reaction conditions [10]. The RCM reaction also proceeded successfully using this fully homogeneous system, although no recycling of this catalyst was reported. The CO_2-philicity of this complex arose from the presence of trifluoromethyl substituents in ligands attached to the Mo center. This observation is an example of a more general approach to the generation of CO_2-philic ligands where functional groups with high affinity for the reaction medium are introduced, ideally without altering the main structure and properties of the parent ligand. Perfluorinated alkyl chains have been found to greatly enhance the solubility in CO_2 for a broad range of materials [11]. The attachment of such CO_2-philic substituents in the periphery of ligands has been shown to enhance the solubility of the corresponding complex by more than two orders of magnitude [12]. The amount of fluorine in the ligand required to enhance solubility in $scCO_2$ is much lower than that required for solubility in fluorinated liquid solvents [13]. It has also been demonstrated that the number of CO_2-philic groups is more decisive for solubilization in $scCO_2$ than the length of the perfluoro groups [14].

The factors which lead to enhanced CO_2 solubility are still not fully understood, but have been reviewed recently by Beckman, particularly with regard to polymeric molecules [11]. The most important appear to be:

- weak self-interaction;
- specific interactions with CO_2;
- flexible, high free-volume molecules.

Fluoroalkyl groups exhibit all of these properties, although the interactions with CO_2 are relatively weak and have most recently been assigned to polar–quadrupole interactions. It would be advantageous to be able also to produce nonfluorous CO_2-philic ligands. Recently, it has been demonstrated that polyether chains [15] and silicone and acetate groups [16] also confer improved CO_2-philicity to otherwise insoluble materials. The oxygen-containing functional groups in particular show promise as these can interact with CO_2, and alter the acidity of neighboring protons, but at the same time add little to the self-interaction strength of the solute. To date, however, few nonfluorous CO_2-philic ligands have been reported.

Examples of fluoroalkyl-containing phosphorous ligands employed for catalysis in $scCO_2$ are given with the Structures **6–10**. In general the synthesis of these species need not be significantly more complex than that of the nonfluorinated analogues, with the only extra steps necessary being those involved in linking the fluoroalkyl group to the starting material. An example of this is the synthesis of (*R,S*)-3-H^2F^6-BINAPHOS [17], illustrated in Scheme 4, where the only step not present in the standard synthesis of unfluorinated (*R,S*)-BINAPHOS is the Grignard reaction mediated introduction of the R_f chain.



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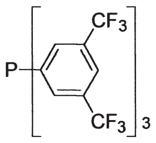

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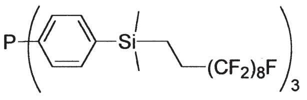

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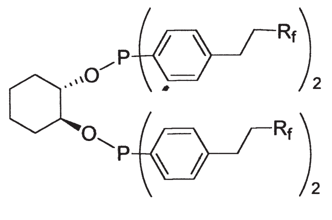
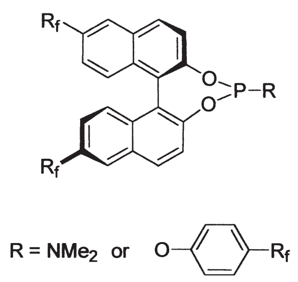


$R_f = (CF_2)_6F$

9



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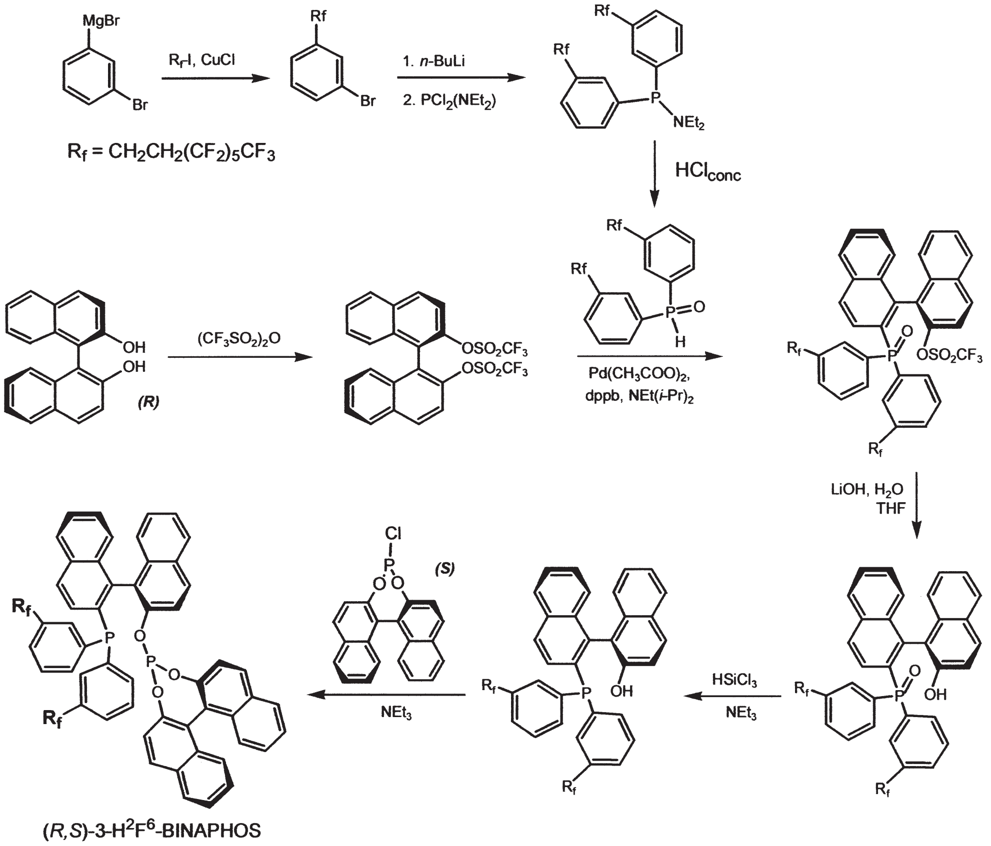


(R,S)-3-H^{2}F^6-BINAPHOS

Scheme 4 Synthesis of (R,S)-3-H^{2}F^6-BINAPHOS.

A number of groups have reported the use of CO_2-philic catalysts for palladium-catalyzed cross-coupling reactions. In some cases the reaction mixtures were truly homogeneous in nature, but often it appears likely that the catalyst was only partially soluble at best. In an early example, Tumas and co-workers demonstrated that higher yields were obtained for Stille and Heck reactions in $scCO_2$ using $Pd_2(dba)_3$ in combination with the CO_2-philic ligand $P[3,5\text{-}(CF_3)_2C_6H_3]_3$ than with conventional triarylphosphines such as PPh_3 [18]. High activities were also reported using tris(2-furyl)phosphine, although it was not indicated whether the presence of ether linkages in this ligand resulted in the solubilization of the resulting Pd complex. In all cases the reactions were carried out under 34.5 MPa CO_2 at 90 °C, corresponding to a relatively high CO_2 density ($d \sim 0.7$ g mL^{-1}). Although no quantitative solubility studies were carried out, the authors reported that when the ligand $P[3,5\text{-}(CF_3)_2C_6H_3]_3$ was used, a visually homogeneous mixture was formed, whereas significant precipitation was observed using PPh_3. A similar study was published simultaneously by Carroll and Holmes, who demonstrated that $Pd(OAc)_2$ combined with $(C_6F_{13}CH_2CH_2)_2PPh$ was soluble in $scCO_2$ and could be employed to catalyze

Heck, Suzuki, and Sonogashira coupling reactions [19]. The same group later described an $scCO_2$-soluble nonfluorinated catalyst system formed by the combination of $Pd(OAc)_2$ with $PBu^t{}_3$, which was applied to Heck and Suzuki coupling reactions [20].

An alternative approach to the generation of CO_2-soluble Pd catalysts was described by Rayner and co-workers, who used the commercially available palladium complexes $[Pd(CF_3CO_2)_2]$ and $[Pd(hfacac)_2]$ in combination with nonfluorinated phosphine ligands for the catalysis of Heck coupling reactions [21]. These systems were found to be significantly more active in $scCO_2$ than their nonfluorinated analogues, requiring shorter reaction times and lower catalyst concentrations to obtain good levels of conversion. As in the work described by Tumas et al., tris(2-furyl)phosphine proved to be a particularly good ligand for these reactions. No indication was given whether the increased catalyst activity in the fluorous systems resulted from increased $scCO_2$ solubility. In this case the reaction conditions were ~80 °C and ~11 MPa, corresponding to $d\ (CO_2) = \sim 0.25\ g\ mL^{-1}$. Such low densities of CO_2 make it unlikely that the system was truly homogeneous. The same authors subsequently reported that catalyst systems of this type can be used to suppress double bond isomerization in intramolecular Heck reactions [22]. For example, in the cyclization of an aryl butenyl ether the exocyclic product predominated when the reaction was carried out in $scCO_2$, while in CH_3CN the major product was the isomeric form with the double bond within the ring. Increasing the pressure resulted in little alteration in the isomer ratio, although at pressures of over ca. 13 MPa the conversion levels fell rapidly.

Fluoroalkyl-substituted phosphine ligands were also used as ligands in Pd-catalyzed Stille couplings in $scCO_2$ [23]. In general, good yields were obtained for a range of substrates and ligands, although the reaction times were reported to be longer compared with the same reactions carried out in a fluorous biphase system. Recycling of the catalyst system was achieved through the addition of perfluorocyclohexane and DMF to the system after extraction of the products with $scCO_2$, the catalyst partitioning into the fluorous solvent. One observation that was at first sight unexpected, however, was the fact that almost equally high yields were obtained using the $scCO_2$-insoluble complex $Pd(PPh_3)_2Cl_2$. It is possible, however, that this is simply an indication that the reaction was occurring under multiphasic conditions, although the authors did not comment on this.

One problem that remains to be addressed in all of the examples of Pd-catalyzed cross-coupling reactions in $scCO_2$ reported to date is the possibility of recycling the catalyst. In the absence of such data, the process remains considerably less well developed than many of the other catalytic systems carried out in $scCO_2$, such as hydrogenation or hydroformylation. The requirement to separate not only the catalyst and product, but also the salt byproducts, has probably contributed to the lack of development in this direction.

Capitalizing on the fact that perfluoroalkyl-substituted CO_2-philic catalysts are soluble in high-density CO_2 (good solvation), but still poorly soluble at low density (weak solvation), a unique approach to multiphase catalysis was developed by Leitner and co-workers for exploring the density-dependent solvent behavior of CO_2.

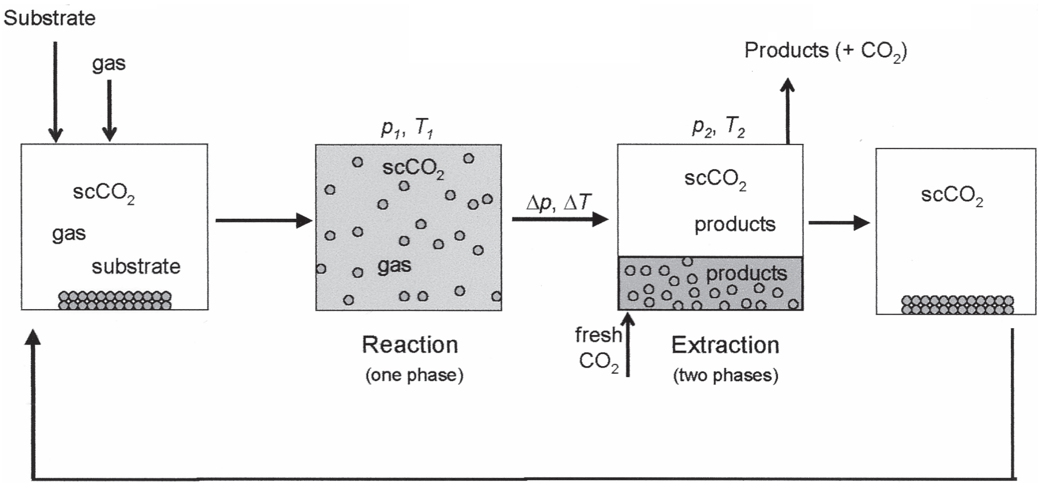


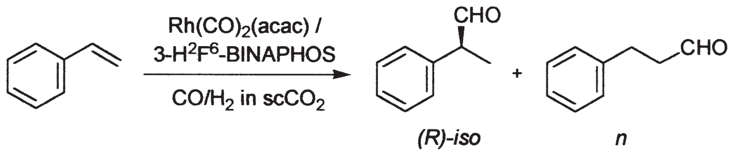
Figure 4 Schematic representation of the CESS process.

The CESS process (*c*atalysis and *e*xtraction using *s*upercritical *s*olutions) is a repetitive batchwise procedure based on $scCO_2$ as the only reaction *and* extraction medium. It comprises two different process steps, one for reaction and one for extraction. The reaction step involves a fully homogeneous single phase for any combination of solid, liquid, or gaseous substrates. Phase separation for extraction of products is induced by choosing a different operation point in the p,T diagram, as illustrated in Figure 4.

The most important feature of this procedure is a switch from the conditions under which the reaction occurs, characterized by a high density of CO_2 where both catalyst and organic species are soluble in this phase, to a regime characterized by low pressure and high temperature where the volatility of the materials governs the solubility in the CO_2 phase. Under the latter conditions, a liquid phase containing most of the product mixture and all the catalyst separates. Only the more volatile organics will partition between the liquid phase and the low-density $scCO_2$ phase, this being the prerequisite for performing a selective extraction of products with fresh CO_2, leaving the catalyst behind. The reduction in density is achieved on the laboratory scale either by careful release of gaseous CO_2 at room temperature or, if a variable volume reactor is available, by augmenting the reactor volume.

The first example of homogeneous catalysis using this approach was in the rhodium-catalyzed hydroformylation of 1-octene in $scCO_2$ [24]. The catalysts used in this reaction were formed *in situ* from rhodium complexes such as (cyclooctadiene)rhodium (hexafluoroacetylacetonate) along with fluorinated phosphine and phosphite ligands such as **6**–**10**. Although the rhodium complex on its own gave improved activity for hydroformylation in $scCO_2$ compared with that observed in toluene solution, the n/i selectivity was poor, as is typical for unmodified rhodium catalysts. Furthermore, the separation efficiency was not sufficient to apply the CESS procedure owing to the high volatility (and hence high CO_2 solubility) of rhodium carbonyl complexes. The addition of fluorinated triarylphosphorus ligands gave much improved linear selectivity, up to a maximum n/i ratio of 5.6 : 1 for [P]/[Rh] = 10 : 1, and allowed for efficient separation and recycling (< 1 ppm Rh in product under optimized conditions).

Equation (2) exemplifies the CESS approach for batchwise rhodium-catalyzed asymmetric hydroformylation of styrene using the CO_2-philic chiral ligand 3-H^2F^6-BINAPHOS [25]. Eight successive runs were performed and the system was still active after a total turnover number of more than 12 000 catalytic cycles per rhodium center. A noticeable decrease in the enantiomeric excess was encountered after the fourth run, but regioselectivity and conversion remained uniformly high. The decrease in the enantiomeric excess may be attributed partly to racemization of the product under the experimental conditions [26]. Chemical instability of the phosphite unit in the ligand framework seems to play a more important role in this case, however, as indicated by the fact that the initial high level of enantioselectivity was restored in the final run by the addition of fresh ligand.

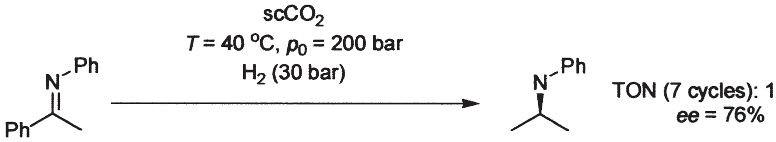


(2)

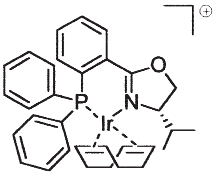
Conversion >90% in eight consecutive runs
Total TON >12,000

Even with simple laboratory equipment, the CESS procedure allowed quantitative recovery of the product free of solvent, and with rhodium contents ranging from 0.36 to 1.94 ppm (determined by atomic absorption measurements). Furthermore, by this approach removal of unreacted starting material or side products from the product is possible during extraction from the catalyst, since even small structural differences can result in significant differences in CO_2 solubility. For example, the desired branched aldehyde formed upon hydroformylation of vinylnaphthalene is considerably more soluble in $scCO_2$ than its linear isomer. Therefore, the ratio of the branched to linear product increased from approximately 90 : 10 in the condensed phase to up to 98 : 2 in the CO_2 phase in a single extraction step under the low-density conditions of catalyst separation. Another example of enantioselective catalysis by the CESS approach was the hydrovinylation of styrene in liquid or $scCO_2$, using a chiral Ni catalyst along with a range of co-catalysts [27]. The most effective co-catalyst was found to be the CO_2-soluble salt sodium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (NaBARF).

Many organometallic catalysts and especially many chiral catalysts are cationic, and modification of the anion has been found to be very effective for enhancing their solubility in $scCO_2$ without the requirement for ligand alteration. Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (BARF) was an early example of such an anion which has proven extremely useful for this purpose [28], and very pronounced anion effects on the activity and selectivity of the catalysts are observed in many other cases [27, 29]. Using the BARF-modified "CO_2-philic" chiral iridium catalyst shown in Eq. (3) and Structures **11** and **12**, catalytic efficiency was greatly enhanced and almost identical *ee* values were observed for the enantioselective hydrogenation of imines upon changing from CH_2Cl_2 to $scCO_2$ as the solvent [29b].



(3)



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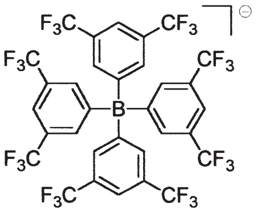

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Interestingly, the phase separation in this case results from a change in the composition of the reaction mixture rather than temperature or pressure. The iridium catalyst was found to be sufficiently soluble for catalysis in the form of the substrate complex, but it was precipitated quantitatively once all substrate has been consumed. Supercritical fluid extraction at that stage yielded the solvent- and metal-free product in crystalline form, leaving the active and selective catalyst behind for further use. Under batch operation, noticeable deactivation occurred after the fourth cycle, but this might be avoided by working in a closed system. Recently, ionic liquids have been found to stabilize the iridium catalyst for better recycling in a two-phase approach [30].

A different approach taken by Jessop and co-workers, who demonstrated the possibility of using CO_2 as a solubility switch for fluorinated catalysts in organic solvents. In an initial paper, they described a crystallization procedure for highly fluorinated compounds in organic solvents, involving the addition of CO_2, followed by its slow release [31]. Crystals of highly fluorinated complexes suitable for structural determination have been grown by adopting this methodology. Moreover, the dissolution of complexes employed in this study is reversible. This observation served as inspiration for a novel immobilization process. Using cyclohexane as the solvent, $[Rh_2(O_2C(CF_2)_9F)_4]$ as the catalyst precursor, and CO_2 as the solubility trigger, the same group attempted to perform repeated cycles of cyclopropanation of styrene with diazoacetate [32]. However, recycling was frustrated by the fact that the catalyst resting state was much more soluble in the organic solvent than the catalyst precursor. The same group subsequently investigated the hydrogenation of styrene to ethylbenzene using $[RhCl[P(C_6H_4)\text{-}p\text{-}CH_2CH_2(CF_2)_6F)_3]_3]$ as the catalyst precursor, along with fluorous silica gel as a catalyst sponge. When expanded with CO_2, the catalyst dissolved in the cyclohexane phase. Upon CO_2 release, however, it became quantitatively trapped in the fluorous silica (Figure 5). In recycling experiments

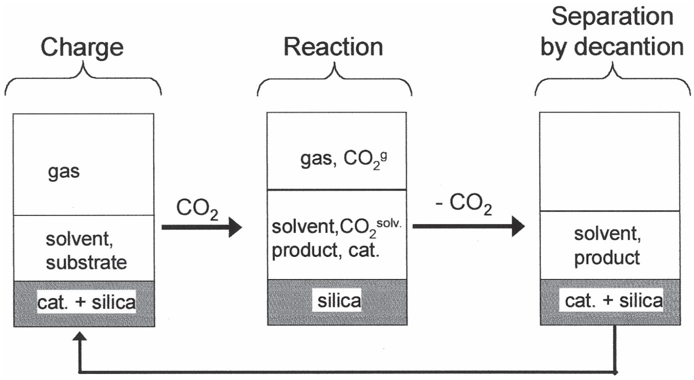

Figure 5 Schematic representation of the use of fluorinated silica as a "trap" for fluorous catalysts.

employing this system, the fluorous Wilkinson's catalyst showed only marginal decrease in activity over five cycles. If extended to further examples, this elegant methodology, which completely avoids the use of fluorous solvent, would represent a valuable alternative to fluorous biphasic catalysis.

A somewhat different method has been pioneered by van den Broeke and co-workers, who suggested the use of a microporous silica membrane for the immobilization of a CO_2-soluble catalyst in the hydrogenation of 1-butene [33]. The technical aspects of this system are discussed in Section 6.3.2.4, but some comments are appropriate here. The catalyst employed was a (1*H*,1*H*,2*H*,2*H*-perfluoroalkyl)dimethylsilyl-substituted analogue of Wilkinson's catalyst, formed in situ by the reaction of $[RhCl(cod)]_2$ (cod = *cis,cis*-1,5-cyclooctadiene) with the corresponding phosphine. The catalyst is immobilized because it is much larger (ca. 2–4 nm diameter) that the pore size (0.5–0.8 nm) of the silica membrane. The great advantage of this system is that it may be easily employed in a continuous-flow system, and a turnover number of $1.2 \cdot 10^5$ was reported over 32 h reaction time. The resulting turnover frequencies were considerably higher than those observed for equivalent reactions carried out in organic solvents.

6.4.1.4
Conclusions

In this section we have summarized the potential for using pressurized CO_2 alone as a reaction medium for homogeneous catalysis. Intriguingly, CO_2 can be used either as an anti-solvent or a co-solvent to trigger catalyst solubility. Furthermore, the unusual ability to vary solvation strength through alteration of either temperature or pressure presents the opportunity to carry out selective separation of reaction products from catalysts, as demonstrated for example in the CESS procedure. It should be noted, however, that the systems discussed in this section have generally been carried out as batch processes (see Section 6.3). It would be desirable to identify systems where the separation occurs under reaction conditions, so that they could be adapted for continuous-flow systems. The “holy grail” in this area will be the development of a flow system that uses only $scCO_2$ in combination with a homogeneous catalyst.

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6.4.2
SCFs and Liquid Polymers

Philip G. Jessop

6.4.2.1
Introduction

Ideal solvents for biphasic homogeneous catalysis would be inexpensive, nontoxic, environmentally benign, and easy to remove from the product, and they would have properties and reactivity compatible with the needs of the catalytic system. The requirement that they be environmentally benign (which will be increasingly important in the future) eliminates from contention all halogenated solvents and disadvantages all volatile organic solvents. Volatile organic compounds (VOC) are to be avoided because of the negative economic, environmental, and occupational safety consequences of volatile emissions and solvent flammability. Therefore, the remaining choices are volatile inorganic solvents (especially water and CO_2) and nonvolatile organic solvents (principally ionic liquids and liquid polymers). In an auto-separating system (i.e., one in which the product is immiscible with the solvent), any one of these four solvents, water, CO_2, ionic liquids, and liquid polymers, could serve as the sole solvent. In a binary solvent system, in which the product partitions preferentially into one of the two solvents while the catalyst partitions into the other, a pair of these solvents must be used. Table 1 summarizes some of the options for solvent pairs. Note that the use of a nonvolatile liquid as the product-bearing phase is not shown in Table 1 because removal of the product from the nonvolatile liquid would require a further, potentially difficult, separation step. This section is concerned with liquid polymers as solvents for catalysis and biphasic catalysis with the liquid polymer/CO_2 solvent pair.

Many advantages are inherent in a liquid polymer/CO_2 solvent pair. CO_2 and poly(ethylene glycol) (PEG), the most commonly used liquid polymer solvent, are both approved in the US as food or beverage additives [11]. Liquid polymers are far less expensive than ionic liquids, their main competition in the area of nonvolatile liquids. Polymers are tunable over a very wide polarity range. Compared to water, liquid polymers are also presumably less susceptible to acidification by CO_2, although this has not yet been confirmed experimentally.

Table 1 Solvent pairs for VOC-free biphasic catalysis (see also other sections in this chapter).

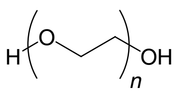
Product-bearing phase	***Catalyst-bearing phase***	***Catalyst modification***	***Example reference***
H_2O	ionic liquid	none	1,2
H_2O[a]	H_2O[a]	water-soluble	3
H_2O	$scCO_2$	CO_2-soluble	4
$scCO_2$	H_2O	water-soluble	5
$scCO_2$	ionic liquid	none[b]	6–9
$scCO_2$	liquid polymer	none[b]	10

a) Aqueous biphasic systems contain two aqueous phases, typically one being an aqueous solution of a polymer and the other being an aqueous solution of a salt.

b) Catalyst modification from the original hydrophobic complex is optional, but could help prevent leaching.

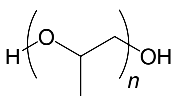
Other nonvolatile nonionic organic solvents are available, but they are less likely to succeed in combination with CO_2. For successful biphasic homogeneous catalysis, the catalyst-bearing solvent must not be soluble in the product-bearing phase (in this case, CO_2). Therefore nonvolatile solvents that have significant solubility in supercritical CO_2 ($scCO_2$) or liquid CO_2 can be immediately rejected. For example, heavy alkanes such as eicosane, polyols such as 1,2,6-hexanetriol, and even one liquid polymer, poly(dimethylsiloxane) (PDMS) can be rejected for this reason. Glycerol, on the other hand, is a nonvolatile liquid with negligible solubility in $scCO_2$ [12] but it must be rejected because it is incapable of dissolving many homogeneous catalyst precursors. As a result, in this section only liquid polymers will be considered.

The polymers that will be discussed are poly(ethylene glycol) (PEG, **1**), poly(ethylene glycol) 4-nonylphenyl monoether (PEG-NPE), poly(propylene glycol) (PPG, **2**), poly(tetrahydrofuran) (PTHF, **3**), and poly(methylphenylsiloxane) (PMPS, **5**). PDMS (**4**) will also be mentioned because it is one of the most studied liquid polymers, even though the most commonly used molar mass fractions of PDMS are not appropriate for this application because they are too CO_2-soluble. Numbers given after a hyphen following an acronym are the nominal average molar masses of the polymers. Variations upon these polymers are possible, including (a) versions with ether or ester groups at the termini, (b) block copolymers, and (c) versions with modified side chains, especially for the siloxanes.



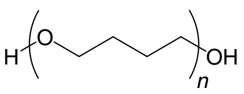
PEG
poly(ethylene glycol)

1



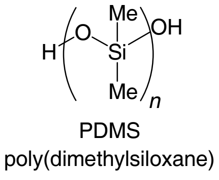
PPG
poly(propylene glycol)

2



PTHF
poly(tetrayhdrofuran)

3



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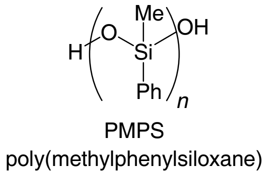

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6.4.2.2
CO_2-Insoluble Liquid Polymers

6.4.2.2.1
Physical Properties

The polymers under consideration are either low-melting solids or viscous liquids. Around room temperature, PEG and PTHF are solids if the average molar mass is above approximately 700 (see Figure 1). The melts are highly viscous, especially at temperatures only slightly above the melting point. Commercially available PPG fractions (up to 3500 g mol^{-1}) are all liquid. Whatever its molar mass, PDMS is a liquid, with pour points typically between –60 and –40 °C [13]. PMPS is a liquid unless it is prepared with carefully controlled tacticity [14]. Commercial samples of PTHF are commonly stabilized against oxidation with ~0.06% BHT. PEG and PPG may also have stabilizers.

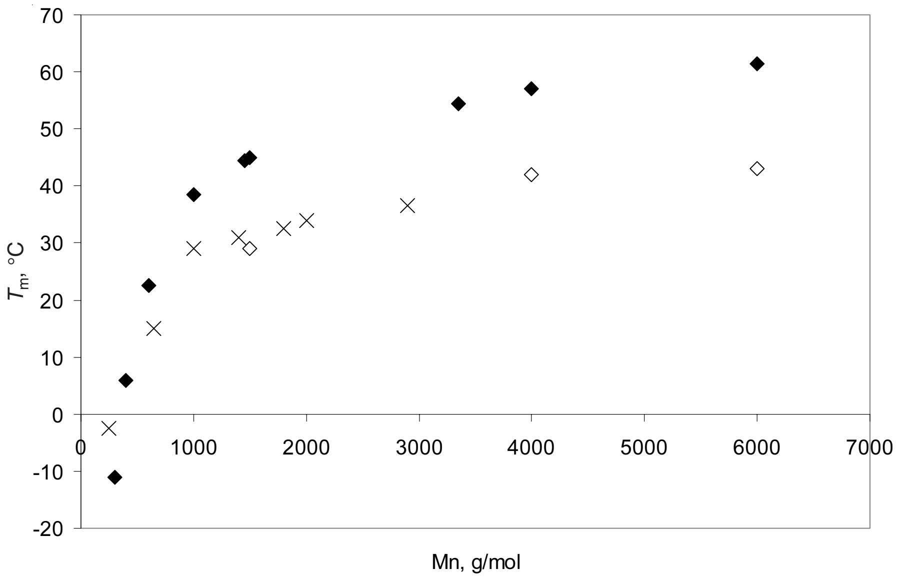


Figure 1 The mean melting points T_m of (◆) PEG [15, 16] (◇) CO_2-expanded PEG at > 10 MPa [16, 17], and (×) commercially available fractions of PTHF [18], as functions of M_n. Note that the melting points are typically melting ranges rather than sharp points.

Polarity varies widely from one polymer to the next. PDMS has a dielectric constant of only 2.8 [13], meaning that its polarity is close to that of toluene. Solid PEG has a Kamlett–Taft π^* (polarity/polarizability) value of 0.86 and an $E_T(30)$ value of 45.7 [19]. The $E_T(30)$ value implies a polarity comparable to MeCN or DMSO while the π^* value is surprisingly high for an entirely saturated structure. Ohno and Kawanabe showed that the $E_T(30)$ of a polyether increases with molar mass and calculated that the $E_T(30)$ values of PEG and PPG with infinite chain lengths would be 46.6 and 38.5 kcal mol^{-1} [20]. Thus PPG is significantly less polar, matching the polarity of butyl acetate.

PEG and other polyethers are inherently coordinating. PEG can bind metal centers in a multidentate structure similar to a crown ether [15]. The coordinating ability can significantly affect reaction performance. The presence of dimethoxylated PEG has been shown to enhance the enantioselectivity and TON of the alkylation of benzaldehydes catalyzed by chiral amino alcohols [21]. While siloxanes are generally less coordinating and much less polar than the polyethers, polar and coordinating siloxanes, such as nitrilesiloxanes, are known [22].

Liquid polymers, like ionic liquids, are not always particularly good at dissolving permanent gases. The solubility of N_2 in PEG-1500 is only 0.4 wt.% at 18.8 MPa and 50 °C [23]. In contrast, the solubility of O_2 in PDMS-77000 is 0.4 wt.% at only 2.2 MPa [24]. Although this data set is rather limited, it seems that careful choice of liquid solvent could allow high reagent gas concentrations. In such a discussion, one must note that mass transfer of reagent gases into the reaction phase is also important, and liquid polymers may in general not compare favorably in that respect. There is some evidence that surfactants can help for a reaction involving reagent gas transfer into PEG [25], but it was not clear in that report whether the rate increase was due to increased gas-transfer rates or other factors.

6.4.2.2.2
Phase Behavior of CO_2/Liquid Polymer Mixtures

Low molar mass fractions of PEG are somewhat soluble in $scCO_2$. PEG-400 has even been used as a surfactant for enhancing the solubility of substrates in $scCO_2$ [26, 27]. The solubility of PEG-400 in $scCO_2$ is 2.1 wt.% at 27 MPa and 50 °C [28]. However, for the purposes of biphasic catalysis in PEG/$scCO_2$ mixtures, a fraction of PEG with less solubility in CO_2 is desired. Fortunately, the solubility of PEG in $scCO_2$ drops off rapidly as the molar mass increases (Figure 2). The solubilities of PEG-600 and PEG-1000 are only 0.2 and 0.08 wt.%, respectively, at the same conditions (26–27 MPa and 50 °C) [28]. The solubility of PEG-NPE-2500 at roughly similar conditions (23 MPa and 45 °C) is 0.03 wt.% [29]. Of course, the average molar mass of the solubilized fraction of a polymer is lower than that of the parent polymer [29, 30].

Most other liquid polymers are expected to show similar behavior, with the higher molar mass fractions having very low solubility in $scCO_2$. Lower fractions of PDMS are quite soluble, but again the higher fractions are not. Garg et al. [31] reported that PDMS-308 000 is essentially insoluble. Unfortunately, there are few or no solubility data for other liquid polymers in CO_2.

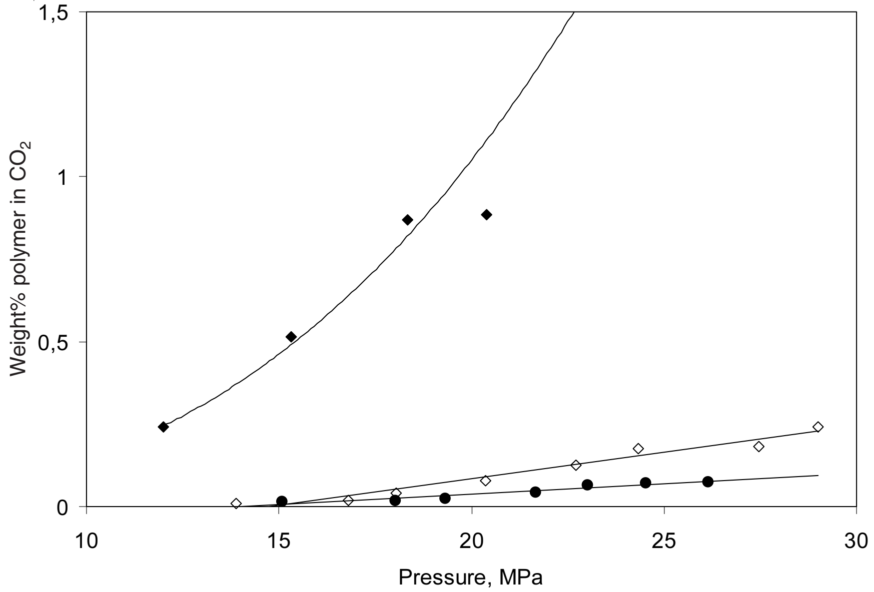


Figure 2 Solubility of PEG-400 (♦), PEG-600 (◊), and PEG-1000 (•) in $scCO_2$ at 50 °C [28].

Carbon dioxide is very soluble in some of these polymers (Figure 3). For example, in PDMS-308 000, the CO_2 content of the condensed phase reaches 40% mass fraction at only 26 MPa and 50 °C [31]. The solubility of CO_2 in PEG is slightly lower than in PDMS. Weidner et al. [16] found only 29 wt.% CO_2 in PEG-1500 at those conditions. Similar values have been found for PEG-400, PEG-600, and PEG-4000 [23, 32]. Daneshvar et al. [28] obtained much higher values but it has been suggested that equilibrium had not been reached in those experiments [16]. The solubility of CO_2 in PEG and PDMS is significantly lower at higher temperatures. Unfortunately there seem to be few data for other liquid polymers.

The volumetric expansion ratio (expanded volume/original volume) of a volatile organic solvent upon exposure to compressed CO_2 can be over 10 [33], but the ratio is far lower for liquid polymers. PEG-NPE-2500 at 50 °C reaches a ratio of only 1.17 and only when the CO_2 pressure reaches as high as 16 MPa. At higher temperatures, greater expansion is observed (a ratio of 1.20 at 16 MPa and 70 °C) [34]. Liquid PDMS-308 000 expands considerably more, reaching a ratio of 1.7 at 50 °C and 20 MPa [31]. However, in the case of PDMS, the expansion is lower at higher temperatures.

Partitioning of solutes between the $scCO_2$ phase and the polymer phase has been studied for cross-linked PDMS and poly(cyanopropylmethylsiloxane) (PCPMS). It has ben shown that naphthalene, acridine, and 2-naphthol partition preferentially into the polymer phase, but the partition constant drops from 10^2–10^3 below 75 bar to only 1–5 at higher pressures [35, 36]. One would anticipate, therefore, that heavy polyaromatic compounds will be difficult to extract from liquid polymers with $scCO_2$. Extraction of lighter compounds is relatively facile [10].

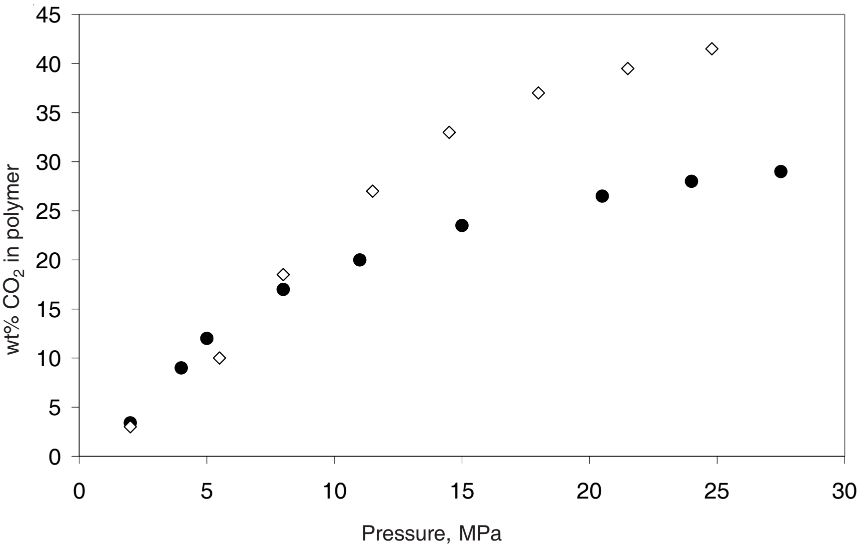


Figure 3 Solubility of CO_2 in PDMS-308 000 [31] (◊) and PEG-1500 [16] (•) at 50 °C.

If the ligands on a catalyst in the liquid polymer have multiple aromatic rings, then leaching of the ligand or the catalyst from the polymer phase is less likely to be a problem. Washing a PEG solution of Wilkinson's catalyst ($RhCl(PPh_3)_3$) with $scCO_2$ for 4 h extracted only 0.06 equiv. of PPh_3 [10]. Nevertheless, it may be necessary to use modified ligands to prevent leaching over extended periods of time. Either a ligand attached to a soluble polymer, or a phase-tagged ligand such as TPPTS (tris(3-sulfonatophenyl)phosphine trisodium salt), may be necessary. Naughton and Drago used the latter for hydroformylation reactions in PEG [25].

6.4.2.2.3
Physical Properties of CO_2-Expanded Liquid Polymers

Volumetric expansion caused by dissolution of CO_2 into liquid polymers is accompanied by significant changes in the physical properties of the condensed phase. Properties that change include the melting point, viscosity, interfacial tension, diffusion coefficients, and potentially solubilities of other species and the polarity of the liquid phase.

The melting point of PEG is decreased when CO_2 dissolves into the polymer (Figure 1). As the CO_2 pressure increases, the melting point lowers to 15–20 °C below the normal melting point. This is true even for molar masses as high as 35 000. Beyond a certain pressure, typically 7–10 MPa [17], no further melting point decrease is observed.

Viscosity changes have been extensively documented. The viscosity of PEG-400 is lowered by 10-fold upon addition of 25 MPa of CO_2 at 40 °C [37]. In contrast, a similar viscosity drop is observed in PPG-2700 at 35 °C when it is exposed to a CO_2 pressure of only 4 MPa [38]. It was suggested that the more rapid drop in viscosity for the PPG may be related to the lower temperature and the greater molar mass. A viscosity drop in PEG-NPE-2500 at increasing CO_2 pressure has also been reported [34] but the viscosity of the polymer in the absence of CO_2 was not measured. Data show that the viscosity of PDMS-380000 at 50 °C drops by 55–58% if enough CO_2 pressure (9 MPa) is put upon it to give 21 wt.% CO_2 in the liquid phase [39].

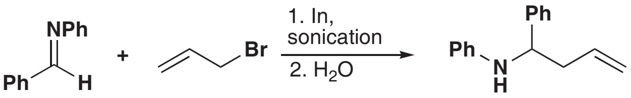
Other mass-transfer properties also improve with increasing CO_2 content in a liquid polymer. The interfacial tension in a PEG-NPE-2500/$scCO_2$ biphasic system at 50 °C decreases from just above 17 dyne cm^{-1} to only 9 dyne cm^{-1} when the $scCO_2$ pressure is increased from 9 to 20 MPa [34]. The diffusion coefficient of CO_2 in PEG-12 000 at 62 °C drops by about half when the CO_2 pressure is raised from 5 MPa to 29 MPa [17].

There seem to be no data available currently relating to the polarity or solubilizing properties of CO_2-expanded liquid polymers, or to measurements of the solubility of catalysts, reagents, or reagent gases in these media. One could expect that gases would be more soluble in the CO_2-expanded polymers than in the pure polymer. These property changes caused by the dissolution of CO_2 in the liquid polymer could directly affect the performance of reactions in the liquid phase. There are literature examples of reactions that have shown modified selectivities or rates when performed in low molar mass liquids expanded by CO_2 or related gases [40–45].

6.4.2.3
Catalysis and Reactions in Liquid Polymer/$scCO_2$ and Related Systems

Liquid polymers have been used for some time as solvents for uncatalyzed organic transformations. Santaniello et al. [46] in 1979 were the first to report the use of liquid PEG, in which they performed oxidations and nucleophilic substitutions of alkyl bromides, and the $NaBH_4$ reduction of a ketone. They suggested that PEG was an ideal solvent because of its strong ability to solubilize alkali metal salts. They recovered the products either by extraction with pentane or by distillation of the product from the PEG.

Reports of uncatalyzed reactions in liquid polymers continue to appear occasionally. For a recent example, a synthesis of homoallylic amines by a Barbier-type reaction in dried PPG [Eq. (1)] was recently reported by Andrews et al. [47]. Indium powder was used in stoichiometric quantities. The yields were comparable to those in VOC solvents. The products were isolated by vacuum distillation from the polymer, which was subsequently washed by water and dried by $MgSO_4$ before re-use.

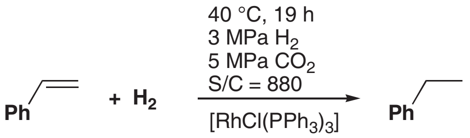


(1)

Tundo et al. in the 1980s developed a method called “gas–liquid phase transfer catalysis” in which PEG-6000 serves as both a liquid polymer solvent and as a phase-transfer catalyst [48]. Substrates were heated until they vaporized; the vapors were then passed through a bed of liquid PEG containing a solid salt reagent. Products were removed in the vapor phase. A variety of reactions were performed, including halide and pseudo-halide exchanges. Even though the continuous-flow nature of the process is appealing, the high temperatures required (typically 170 °C) preclude application to most transition metal catalyzed reactions. In hindsight it is easy to speculate that the addition of $scCO_2$ to this process would have enhanced the volatility of the reagents so much that the process would have become possible at significantly lower temperatures.

Reactions in nonvolatile liquid polymers inherently pose a problem when it comes to product isolation because the solvent is nonvolatile and therefore cannot be removed by distillation. The product can be isolated by distillation, extraction with organic solvent, or extraction with CO_2. Those reactions which produce a CO_2-soluble product could be performed in a polymer/$scCO_2$ biphasic system, provided of course that CO_2 does not chemically interfere with the reaction.

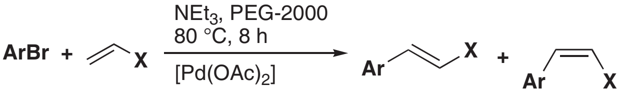
Heldebrant and Jessop [10] performed a homogeneously catalyzed hydrogenation of styrene in PEG-900 [Eq. (2)]. The product was isolated by extraction with $scCO_2$ and the catalyst solution in PEG was re-used, by addition of fresh styrene and H_2, for a total of five cycles. Conversion was > 99% each cycle. Product recovery was 79% in the fifth cycle but lower in earlier cycles. The Rh content of the extracted material was found to be < 1 ppm (S/C = substrate to catalyst molar ratio).



(2)

Although Eq. (2) is the only organometallically catalyzed reaction to have been studied in liquid polymers with product isolation with $scCO_2$, it demonstrates an intriguing potential for biphasic catalysis and continuous-flow applications. For this reason, the following sections briefly summarize additional examples of catalysis in liquid polymers with and without the additional use of CO_2. It is evident from this literature that reactions in these polymers can behave differently from those in ionic liquids or traditional solvents. It is equally evident that more research is needed before we can predict when polymers will be preferable to other solvents and where a combination with $scCO_2$ as mass separating agent and/or reaction medium will provide additional benefits.

Heck coupling of aryl bromides with alkenes in PEG-2000 [Eq. (3)] was reported by Chandrasekhar et al. [49]. The product isolation was achieved by extraction with ether at 0 °C and the catalyst was used for five cycles with an overall Pd loss of 10%. Yields were high and the regioselectivity was 100% for the reaction between phenyl bromide and butyl vinyl ether, giving exclusive coupling at the β-carbon of the vinyl group, with predominantly *E* geometry. In contrast [50], coupling has been found to take place at the α-carbon in ionic liquids (in the presence of a phosphine), while mixtures are obtained in traditional organic solvents.

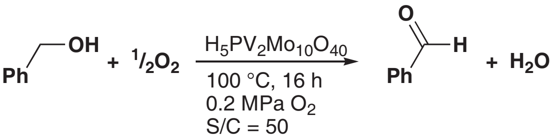


(3)

Suzuki coupling has also been tested in PEG [Eq. (4)]. Namboodiri and Varma [51] used PEG-400 as a solvent for a microwave-assisted coupling, with product isolation by extraction with ether. The catalyst/PEG solution could be recycled by addition of fresh substrate; no yield decrease was observed over three cycles. The reaction could also be performed with conventional heating to 100 °C for 15 min.

$$\mathrm{ArBr} + (\mathrm{HO})_2\mathrm{BAr'} \xrightarrow[\text{[PdCl}_2\text{], KF}]{\text{PEG-400, microwave}} \mathrm{Ar\text{-}Ar'} \tag{4}$$

Oxometallate-catalyzed oxidations of benzyl alcohols to benzaldehydes in PEG-200 were reported by Haimov and Neumann [Eq. (5)] [52]. The product was obtained by extraction with cyclohexane or by vacuum distillation, and the catalyst/PEG solution was re-used. Some decomposition of the PEG solvent to dioxolane was observed, giving a weight loss of 5% per cycle.

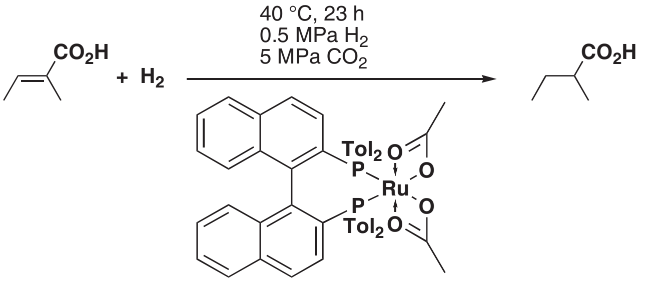


(5)

Hydrogenation reactions have been more extensively tested. Da Rosa et al. [53] performed the hydrogenation of 1-hexene to hexane catalyzed by [Rh(cod)(dppe)]PF_6 (cod = 1,5-cyclooctadiene, dppe = 1,2-bis(diphenylphosphino)ethane) in a monophasic solution of PEG in MeOH. The TOF was 240 h^{-1} at room temperature. The product was isolated by extraction with heptane. The catalyst was recycled with only 0.08% Rh loss.

Heldebrant and Jessop have investigated several hydrogenations in liquid polymers. The asymmetric hydrogenation of tiglic acid [Eq. (6)] proceeded in reasonable conversion and enantioselectivity (88% *ee*) in PEG-2000 dimethyl ether, but gave poor enantioselectivity in PPG-3500, PMPS-710 and PTHF-2900 [54]. In each case, the CO_2-expanded solvent was used, although afterward the product was extracted with hexane.

The reduction and coupling of CO_2 with H_2 and diethylamine to give diethylformamide has not, in the past, been a facile reaction [55]. However, the reaction [Eq. (7)] has recently been found to proceed in ≥ 99% conversion in CO_2-expanded PPG-3500, PTHF-2900, and PMPS-710 but not in PEG-2000 dimethyl ether or PEG-1000 [54]. The product was extracted with hexane or, in the case of PMPS, with water.



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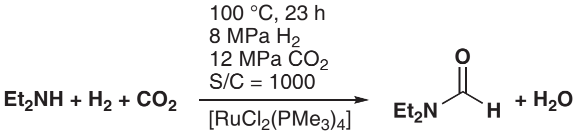
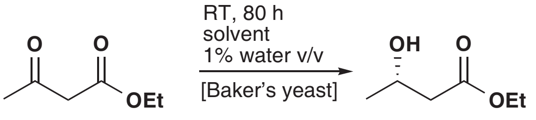


(7)

Notably, the use of liquid polymers in multiphase catalysis with $scCO_2$ is not restricted to transition metal catalysts. Biocatalysts can also be used in this environment, as demonstrated by the yeast-catalyzed reduction of a β-ketoester that gave excellent (99%) enantioselectivity in PMPS-710 and the ionic liquid $[P(Me)(Bu)_3][^iBu)_3][O_3SC_6H_4pMe]$ [Eq. (8)]. The product was isolated by extraction with water or $scCO_2$, respectively [54].



(8)

Furthermore, the use of PEG in catalyst immobilization is of course not limited to the liquid phase only. Naughton and Drago described a technique which they termed "supported homogeneous film catalysis". They coated silica gel with a thin layer of PEG-600 and the complex $[RhH(CO)(TPPTS)_3]$, dissolved in this layer, catalyzed the hydroformylation of 1-hexene [25]. The continuous or extracting phase was the neat substrate, 1-hexene. Catalyst leaching was believed to be negligible, as shown by the fact that the liquid used to wash the supported catalyst was afterward found to have no catalytic activity. A large increase in rate was found when a surfactant was added, presumably because mass transfer between phases was accelerated. There is also a report of solid PEG-3350 being used to encapsulate and then precipitate a homogeneous catalyst after a reaction in a VOC solvent. The PEG-encapsulated catalyst could then be re-used in a subsequent run [56]. In yet another approach, direct attachment of PEG chains to ligands or catalysts has been used to ensure that the catalyst stays in the polar phase of an organic/organic biphasic system [57, 58] or to ensure that the catalyst is not extracted by $scCO_2$ along with a product [59]. Reviews of the large area of catalysts supported on soluble polymers have been published [60–63] and the topic is discussed in more detail in Chapter 7.

6.4.2.4
Conclusions and Outlook

Catalyst recycling and solvent recycling are both desirable from economic and environmental points of view. Biphasic catalysis offers an opportunity to achieve both, and will be most benign and inexpensive if the solvents involved are carefully selected with cost and environmental impact in mind. Biphasic catalysis, with water as the catalyst-bearing phase and supercritical fluid as the product-bearing phase, is already an industrial reality [64]. The work described in this section and related sections in this book shows that biphasic catalysis can be performed in dual-solvent systems with the use of nonvolatile organic solvents.

For biphasic catalysis in two solvents, with $scCO_2$ as the product-bearing phase, the three most obvious choices of catalyst-bearing phase are water, ionic liquid, and liquid polymer. In particular, the use of the liquid polymer/$scCO_2$ system has the advantages of low solvent cost, very low toxicity, low environmental impact, high ability to dissolve gases (for siloxanes at least), and very clean separations. The disadvantages are the cost of CO_2 pressurization, the possibility of polymer degradation at higher temperatures, the potential chelation of catalytic metal centers by polyethers, and the fact that we know very little about the properties of CO_2-expanded liquid polymers.

Further research is needed in the area of liquid polymer solvent modification by (a) the use of end-caps or different monomers, (b) the addition of surfactants, or (c) expansion of the polymer with CO_2. In each of these cases, measurement of solvent physical properties and evaluation of reaction performance are needed. Reaction performance in supported PEG phases with CO_2 as the product-bearing phase, especially as a continuous-flow system, should also be investigated. One may anticipate greater ease of handling of the catalyst plus improved mass transfer between phases as a result of a greater surface area.

Although the literature in the area of polymeric solvents is quite limited, the reports summarized in this brief section suggest that a range of catalytic reactions should be possible in liquid polymers. All of the products reported in the examples of Section 6.4.2.3 can in principle be extracted from the polymer with $scCO_2$. Overall, the new $scCO_2$-based biphasic catalysis methods offer industry viable new options for catalyst and solvent recycling.

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6.4.3
SCFs and Ionic Liquids

David J. Cole-Hamilton, Thulani E. Kunene, and Paul B. Webb

6.4.3.1
Introduction

The environmentally acceptable nature of supercritical carbon dioxide has already been discussed in this chapter, but another type of solvent which is generating great interest as a possible replacement for volatile organic compounds is ionic liquids. A detailed account of ionic liquids and their application for catalyst immobilization is the subject of Chapter 5, edited by H. Olivier, in this handbook. In essence, ionic liquids are involatile, of low toxicity, and very stable, and are therefore seen as having a low environmental impact. The very different properties of supercritical carbon dioxide and ionic liquids makes them ideally suited for use in combination to provide an environmentally acceptable form of two-phase catalysis, which might be carried out as a continuous-flow process.

Ionic liquids (ILs) are organic salts that are liquid at ambient conditions and possess properties that are akin to conventional organic solvents, not least in their ability to solvate an extended range of solutes [1–3]. Ionic liquids provide potential as environmentally benign replacements to volatile organic compounds (VOCs), primarily because of the lack of any measurable vapor pressure, a property that is not exhibited by classical solvents. The vanishingly small vapor pressures of ILs ensure that their use as solvents is not complicated by evaporation into the environment or worker exposure. However, in terms of the development of a generic separation technology, distillation and aqueous extraction cannot be applied to all solutes, in particular lipophillic and high molecular weight organics. Volatile organic solvents such as Et_2O and hexane, which are immiscible with a number of ILs, can be employed in liquid–liquid extraction, although this somewhat negates the use of an IL in the first place. Liquid–liquid extractions may also present further separation problems due to the finite solubility of the IL in the aqueous or organic extractant.

6.4.3.2
Interaction of Supercritical Carbon Dioxide with Ionic Liquids

The pioneering work of Brennecke, Beckman, and co-workers has prompted research into a new field of separation technology [4]. They demonstrated that $scCO_2$ exhibits high solubility in ILs whereas the gas-rich phase remains free of IL [4]. ILs have easily modified structures and properties and are often designated as "designer" solvents. Both ILs and CO_2 therefore represent tunable solvents, a factor which broadens the scope of their use as a general methodology for biphasic catalyst separation.

An understanding of phase behavior is key to multiphase chemical processes, and biphasic systems involving ILs are no exception. Brennecke, Beckman, and co-workers paved the way for a new means of biphasic separation with groundbreaking observations that $scCO_2$ dissolves extensively in the IL [BMIM][PF_6] (BMIM = 1-butyl-3-methylimidazolium) whereas the gas-rich phase remains essentially pure CO_2 [4]. Using naphthalene as a solute, they also demonstrated, for the first time, that $scCO_2$ could be used to extract organic species from an IL solution without cross-contamination of the gas phase with IL [4]. Recovery of the organic solute was near-quantitative and brought about by simple expansion of the gas phase downstream. This efficient exchange between the two phases, coupled with the lack of mutual solubility, is ideal for product separation and provides the basis for the use of these systems in biphasic catalysis which will be discussed below.

In subsequent work, Blanchard et al. [5] carried out a systematic study on the phase behavior of CO_2 with a number of imidazolium, and pyridinium-based ILs. The solubility of CO_2 in [BMIM][PF_6] was found to increase with increasing pressure reaching 0.72 mole fraction CO_2 at 40 °C and 9.3 MPa, as illustrated in Figure 1. Conversely, the solubility of the IL in CO_2 was determined to be less than $5 \cdot 10^{-7}$ mole fraction. Perhaps the best indication of solubility within $scCO_2$ is vapor pressure: the more volatile a solute, the more soluble it will be. The absence of IL dissolution within the gas-rich phase therefore reflects the vanishingly small vapor pressure of these materials and the inability of CO_2 to solvate charge-separated salts.

Two-phase immiscibility regions were found to exist for all ILs studied by Blanchard et al. [5], even at pressures where the phase envelope begins to close in typical organic liquid–CO_2 systems [6]. Figure 1, in which the nonlinear extrapolation represents a qualitative prediction of phase behavior to high pressures, clearly illustrates the large immiscibility gap over an extended range. More recently, Shariati and Peters [7] confirmed this qualitative prediction experimentally through

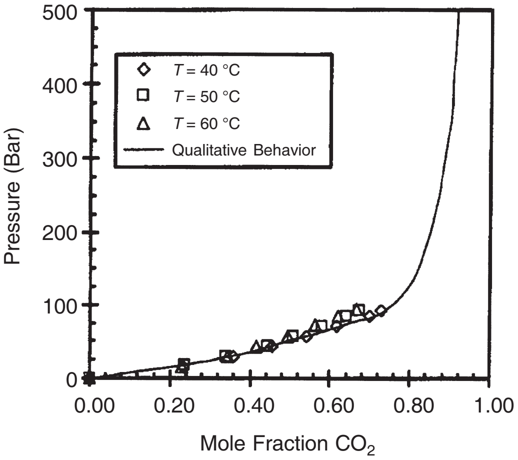


Figure 1 Liquid-phase compositions of $[BMIM]PF_6$–CO_2 at 40, 50, and 60 °C. (Reprinted with permission from [5], © 2001 American Chemical Society).

measurements of $[EMIM][PF_6]$–CO_2 phase behavior at higher pressures. This extended two-phase immiscibility region is an unusual property for liquid–CO_2 systems [6]. When high concentrations of CO_2 dissolve in a liquid at low pressures a two-phase envelope with a mixture critical point, at moderate pressures, is normally observed. CO_2–IL phase behavior is therefore very much different from normal organic liquid–CO_2 phase behavior, as clearly illustrated in Figure 2, which compares the mole fraction solubility of CO_2 in $[BMIM][PF_6]$ and *N*-methylimidazole [5].

The shapes of the liquid-phase composition curves are seen to differ significantly. The *N*-methylimidazole curve is concave and typical of many organic liquid–CO_2 systems [6]. This concave correlation implies the presence of a mixture critical

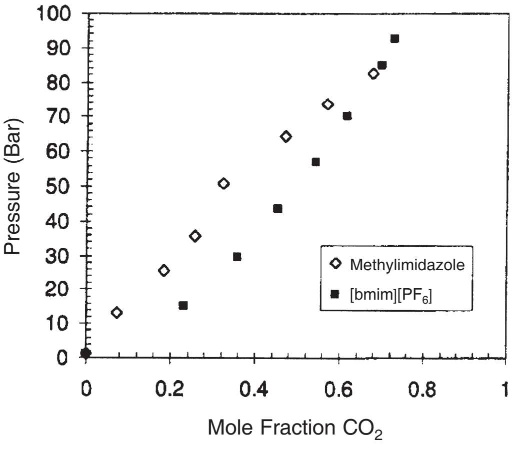


Figure 2 Liquid-phase compositions of the $[BMIM]PF_6$–CO_2 and *N*-methylimidazole–CO_2 systems at 40 °C. (Reprinted with permission from [5], © 2001 American Chemical Society).

Table 1 Mole fraction solubility of CO_2 in several ILs and the corresponding mixture molar volumes at 50 °C and ca. 9.2 MPa.

Ionic liquid [a]	***T = 50 °C***			
	p [MPa]	X_{CO_2}	***mL [mol]***	***Ref.***
[OctMIM][PF_6]	9.267	0.705	103.0	[5]
[BMIM][PF_6]	9.246	0.675	83.9	[5]
[EMIM][PF_6]	9.260	0.449	–	[7]
[OctMIM][BF_4]	9.228	0.671	106.1	[5]
[*N*-Bupy][BF_4]	9.235	0.581	92.2	[5]
[BMIM][NO_3]	9.262	0.530	95.0	[5]
[EMIM]$EtSO_4$	9.427	0.403	124.6	[5]

a) Oct = octyl, EMIM = 1-ethyl-3-methylimidazolium, *N*-Bupy = *N*-butylpyridinium.

point above which a single gas phase exists. Conversely, the IL–CO_2 system is convex in behavior and indicates a two-phase region extending to very high pressures and the absence of a mixture critical point.

The solubility of CO_2 in several ILs is listed in Table 1 [5, 7]. In all cases the solubility is found to increase with increasing pressure and although the extent of dissolution varies significantly, the phase behavior shown in Figure 1 is representative of all ILs studied by Blanchard et al. [5] and Sheriati and Peters [7]. The extent of CO_2 dissolution is seen to be largely dependent on the degree of fluorination in the anion, following the general trend [BMIM][PF_6] > [BMIM][BF_4] > [BMIM][NO_3] [5].

Welton and co-workers used a series of solvatochromic dyes to determine the Kamlet–Taft parameters of various ILs [11]. The ability of various imidazolium based ILs to hydrogen-bond to solutes was found to be greater for ILs possessing a proton (as opposed to methyl) on the C2 carbon of the imidazole ring. Cadena et al. [8] studied the effect of the C2 proton on gas solubility by comparing the solubility of CO_2 in [BMIM][PF_6] and its C2-Me analogue ([BMMIM][PF_6]). Although differences in CO_2 solubility were observed, such differences were found to be very small. This is consistent with spectroscopic evidence, which demonstrates that the solubility of CO_2 in both [BMIM][PF_6] and [BMIM][BF_4] is governed primarily by interactions with the anion [12].

The effect of temperature on gas solubility has also been determined [5, 7, 13]. Temperature can have a considerable effect on the solubility of a gas within a liquid phase and in general an increase in temperature will cause a drop in gas solubility. ILs are no exception to this general observation although the temperature dependence was found to be quite small over the temperature and pressure ranges studied [5, 7, 13].

The presence of water in ILs can have a considerable effect on the solubility of CO_2 [5], an important observation considering that ILs can be notoriously difficult to dry.

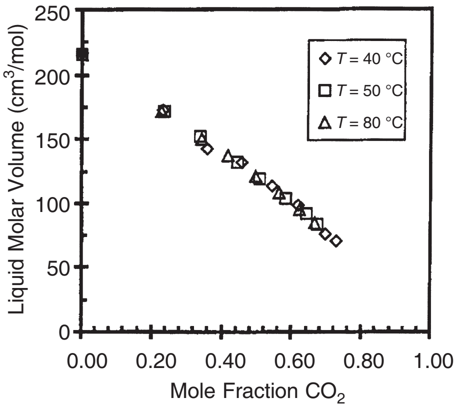


Figure 3 Liquid molar volumes as a function of CO_2 composition at 40, 50 and 60 °C. (Reprinted with permission from [5], © 2001 American Chemical Society).

Another remarkable property of these biphasic systems is the unusual volumetric behavior illustrated for [BMIM][PF_6] in Figure 3 [5]. The volume expansion of the IL is comparatively small even at high mole fractions of dissolved CO_2. This phenomenon is represented in Figure 3 by a dramatic drop in mixture molar volume, which simply reflects a negligible liquid volume expansion. Similarly to the gas solubility, a weak temperature dependence is observed.

This volumetric behavior is again uncommon to nonionic organic–CO_2 systems, where high gas solubility causes considerable volume expansion of the liquid phase. Large volume expansions are common and cause a decrease in the solvent strength of the expanded liquid, a phenomenon that is exploited in solute precipitation technology known as GAS (gas anti-solvent precipitation) [14]. Similar behavior is demonstrated by other ILs, with the largest volume expansion observed for ILs with the largest molar volume [5].

Blanchard et al. [5] assigned this lack of volume expansion to strong coulombic forces between ion pairs whose separation, and therefore expansion, is thermodynamically unfavorable. The existence of a two-phase region, which extends to high pressures, and the lack of mutual solubility can be attributed to this limited volume expansion. Increasing the CO_2 pressure will cause the pure gas phase to increase in density but since the liquid phase does not expand to any great extent, the two phases will never become identical and a mixture critical point will not be reached.

6.4.3.3
Extraction of Organic Compounds from Ionic Liquids using Supercritical Fluids

For viability as a means of separation it is important that the desirable phase behavior in IL–CO_2 systems does not become disrupted by a third component representing the solute. Blanchard and Brennecke [15] performed a systematic study on the recovery of organic solutes from [BMIM][PF_6] with scCO_2 and demonstrated the generality of CO_2–IL biphasic systems as a new separation technology. Recovery rates of a wide range of aromatic and aliphatic solutes, of varying chemical functionality, were measured by spectroscopic and gravimetric analysis. Of all solutes studied a greater than 95% recovery was obtained, with the ease and rate of extraction corresponding to the relative partition coefficients of the solutes. High volatility and low polarity favors high solubility in CO_2, whereas high polarity and aromaticity will favour solubility in the IL-rich phase. Not surprisingly, the more polar the solute the more difficult the extraction becomes, reflecting the relative solubility of the solute between the two distinct and very different phases. In terms of biphasic catalysis, however, the IL, the operating pressure, and partial pressures of permanent gases can all be tailored to improve liquid substrate partition coefficients [16]. Blanchard and Brennecke [15] also demonstrated the separation of comparably involatile solutes with the successful extraction of 1,4-butanediol, a solute representative of a high-boiling organic for which separation on the basis of its vapor pressure alone (i.e. distillation) would not be a feasible option.

Scurto et al. [17] exploited the insolubility of ILs in CO_2 to effect a separation switch in IL–organic mixtures, and demonstrated the complex phase behavior of IL–organic–CO_2 ternary systems. Using mixtures of methanol and [BMIM][PF_6], which are miscible in all proportions under ambient conditions, the separation of methanol could be effected by the addition of CO_2 and is illustrated in Figure 4.

At low CO_2 pressures, the IL-methanol mixture exists as a single phase, but as the pressure is increased a second liquid phase separates. The system now comprises a dense IL-rich phase (L_1), a methanol-rich phase (L_2), and a vapor phase consisting mostly of CO_2. For a given temperature and given volumes of methanol and [BMIM][PF_6], the pressure at which the phase transition is induced is termed the lower critical end point (LCEP). At pressures above the LCEP, the methanol-rich phase begins to expand significantly while the volume of the IL-rich phase remains largely unaffected, as discussed previously. This expansion reduces the solvating capacity of the methanol rich phase causing further separation of the IL. As the pressure is increased further a second critical point, the K-point, is reached where the methanol-rich phase merges with the vapor phase, precipitating the remaining

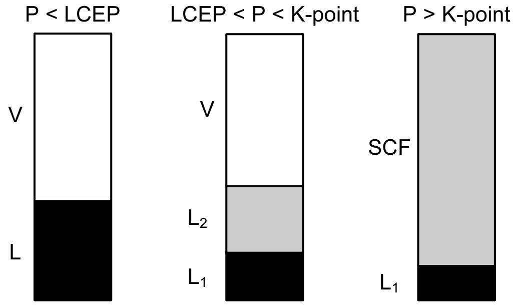


Figure 4 Schematic illustration of [BMIM][PF_6]–methanol–CO_2 phase behavior with increasing CO_2 pressure. (Reprinted with permission from [17], © 2002 American Chemical Society).

dissolved IL and completing the separation. The vapor phase was found to contain no detectable IL. The K-point pressure in the IL–methanol–CO_2 system was found to be identical to the mixture critical point of methanol and CO_2, providing further evidence that the IL remains absent from the gas-rich phase [17].

At higher IL concentrations it is not possible to induce a liquid–liquid separation by the addition of CO_2, i.e., no LCEP is observed [17]. This complex phase behavior has certain implications for the use of these biphasic systems as reaction/separation media. If large concentrations of reactants and products are present, relative to the IL itself, an additional liquid phase might occur. A liquid–liquid phase split may then be detrimental in homogeneously catalyzed reactions, introducing additional mass-transport limitations.

Other studies seem to indicate, however, that care must be exercised when such ternary systems include small, polar solutes. Low molecular weight, polar solvents, in particular alcohols, are used extensively as co-solvents in natural products and other extractions employing $scCO_2$ [18]. The polar solvent acts as a modifier of gas-phase polarity and enhances the solubility of polar species that would otherwise exhibit limited solubility in CO_2. The effect of solvents such as ethanol and acetone was investigated [13, 19] by measuring the solubility of [BMIM][PF_6] in CO_2 in the presence of these solvents (Figure 5).

Figure 5 suggests that the solubility of [BMIM][PF_6] in both CO_2–ethanol and CO_2–acetone mixtures is considerable and strongly dependent on the concentration of the organic solvent. These experiments [13, 19] serve as an important warning to future practitioners of CO_2–IL biphasic systems. If reactants or products are small, polar solutes, care must be taken to operate under conditions where the mole fraction solubility of the solute is low enough not to disrupt the otherwise mutual immiscibility of the two phases.

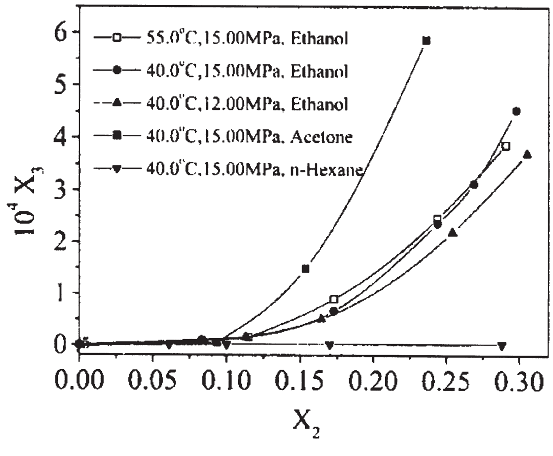


Figure 5 Mole fraction solubility (X_3) of [BMIM][PF_6] in $scCO_2$–organic mixtures as a function of the mole fraction of organic present in the gas phase (X_2). (Reprinted with permission of the Royal Society of Chemistry [19]).

6.4.3.4
Solubility of Gases in Ionic Liquids

A number of industrially important reactions, including hydrogenations, hydroformylations, carbonylations, and oxidations, involve the reaction of permanent or condensable gases. For reactions in CO_2–IL biphasic systems, the partial pressure of an additional reactant gas will affect both the reaction kinetics and the thermodynamic behavior. In terms of reaction kinetics, a low gas solubility in the IL may result in mass-transport limitations as a rate-determining factor. The additional gas will also cause expansion of the $scCO_2$, reducing its solvating capacity and its ability to extract reaction products, although the effects on solvent characteristics can be used to an advantage [16]. The solubilities of both permanent and condensable gases (other than CO_2) in ILs have been measured [20–24], but research into the effects of the additional gas on phase behavior is limited [16]. Henry's constants for several gases in $[BMIM]PF_6$ are listed in Table 2 in the order of decreasing solubility (i.e., increasing Henry's constant).

In general, gas solubility is found to be small, compared to the high solubility observed for CO_2. Additionally, and with the exception of CO_2, the solubility of gases in $[BMIM][PF_6]$ is considerably lower than solubilities normally observed in conventional solvents [21]. The trend in gas solubility correlates well with the polarizability of all gases except CO_2. This correlation implies that solubility is governed largely by dispersive forces and not specific interactions with the solvent (as observed in the case of CO_2) [21]. A systematic investigation on the solubility of CO in a series of ILs revealed that IL structure plays an important role in gas solubility [23]. For the [BMIM] cation the solubility of CO increases according to the series NTf_2 ($Tf = CF_3SO_3$) > CF_3CO_2 > SbF_6 > PF_6 > BF_4 [23], a trend that is identical to that observed for CO_2 solubility [5, 8]. CO solubility is also affected by the chain length of the alkyl substituent in pyridinium and imidazolium ILs; an increase in chain length enhances gas solubility.

Table 2 Henry's constants for gases in $[BMIM][PF_6]$ at 298 K.

Gas	*H_1 [MPa]*	*Ref.*
CO_2	5.34 ± 0.03	[21]
C_2H_4	17.3 ± 1.7	[21]
C_2H_6	35.5 ± 3.6	[21]
CH_4	169 ± 1.8	[21]
CO	327	[23]
H_2	538	[23]
H_2	570	[24]
O_2	800 ± 540[a)]	[21]

a) More accurate measurements are available for $[BMIM][BF_4]$ [20].

High concentrations of CO_2 in the IL may enhance the solubility of reactant gases and this may explain, at least partly, observations that the presence of CO_2 appears to overcome mass-transport limitations [25]. The solubility of hydrogen as a reactant gas in ILs has been determined in the presence of compressed CO_2 very recently [26]. Indeed, a remarkable increase in concentration of the hydrogen at constant H_2 partial pressure has been observed with increasing CO_2 pressure. These data could be correlated with an increase in hydrogenation efficiency for the iridium-catalyzed asymmetric hydrogenation of imines.

In general, however, the effect of different gas solubilities in different ILs on reaction rates is still difficult to predict.

6.4.3.5
Continuous-Flow Homogeneous Catalysis using Supercritical Carbon Dioxide–Ionic Liquid Biphasic Systems

6.4.3.5.1
General Considerations and Background

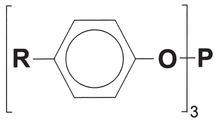
The ideal catalytic reaction would selectively produce a single desired product with 100% atom economy in a continuous-flow process which left the catalyst within the reactor under its optimum operating conditions at all times. There would be no volatile organic compounds, no waste, and no byproducts (see, e.g., [28, 29]).

Although the reactions in [28] and [29] show the possibility of approaching the ideal situation, the number of processes where this can be realized is very small because, in general, reaction products are not sufficiently volatile to be distilled from the reaction mixture at temperatures below the decomposition temperature of the catalyst. In most cases, this problem is circumvented by removing some of the reaction mixture and carrying out the separation ex situ by low-pressure distillation, phase separation, etc. However, this means that, at all times, some of the catalyst is outside the reactor and is held under conditions for which it has not been optimized. This can lead to catalyst precipitation, deactivation, or decomposition. In extreme cases, attractive reactions have not been commercialized because the separation problem has not been solved.

A possible alternative, which would exploit the ability of supercritical fluids (SCFs) to dissolve organic compounds and hence impart to them gas-like flow behavior below their boiling points, would involve a catalyst which is insoluble in an SCF, dissolved in a liquid which is also insoluble in the SCF. The SCF could be then used to transport substrates into and products out of a reaction mixture; hence systems could be designed which are very close to the ideal described above. The product would then be recovered from the SCF by decompression, and the SCF could be recycled.

An example of such a process concerns the hydroformylation of medium chain alkenes using rhodium–triarylphosphite complexes (**1**) [30].

During the course of studies [27, 30, 31] on a range of different phosphines and phosphites for solubilizing rhodium-based hydroformylation catalysts in $scCO_2$, it



Structures 1: R = H; **2**: R = C_9H_{19}

was discovered [30] that ligands **1** and **2** gave reasonable conversions and selectivities in the hydroformylation of 1-hexene (**1**: TOF = 32 h^{-1}, $l/b = 6.8$; **2**: TOF = 30 h^{-1}, $l/b = 5.5$; $l/b = n/i$). Observations through a viewing window in the reactor showed, however, that a significant liquid phase was present and that there was little or no coloration of the supercritical phase. Assuming that the liquid phase consisted of the catalyst dissolved in excess ligand and that the product would be dissolved in the $scCO_2$ phase, the upper phase was removed by flushing with more $scCO_2$ at the reaction temperature and pressure, and the product was collected by decompressing into a second autoclave held at room temperature. Once all the product had been removed, the reactor was vented, opened, charged with more substrate, repressurized with CO/H_2, and reheated. No rhodium was detected in the collected products (< 0.2 ppm, < 0.01% of rhodium charged after product extraction). The catalyst involving ligand **2** was used five times, but a reduction in l/b ratio in cycles 4 and 5 together with the detection of the phenol from which ligand **2** is derived suggested that the phosphite was being removed or more likely hydrolyzed. The rather high l/b selectivities (some as high as 26 : 1) observed in these studies, compared with those under similar conditions in toluene (TOF = 49 h^{-1}, $l/b = 1.4$), suggest that the catalysis occurs in the liquid phase where the local concentration of phosphite is very high. This method of catalyst recycling will be referred to hereafter as repetitive batch reactions.

Although the results described above are of interest, the instability of the phosphites used as ligands which are important for the catalyst immobilization makes them unsuitable for continuous operation. However, the very interesting properties of $scCO_2$–IL biphasic systems described in Sections 6.4.3.3–6.4.3.5 suggest a generic approach to carrying out homogeneous catalytic reactions under continuous-flow conditions. All that would be required is that the catalyst should dissolve in the IL but not in the SCF and that the products should be soluble in the SCF. A diagrammatic representation of such a process is shown in Figure 6.

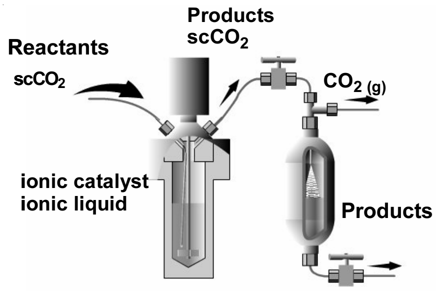
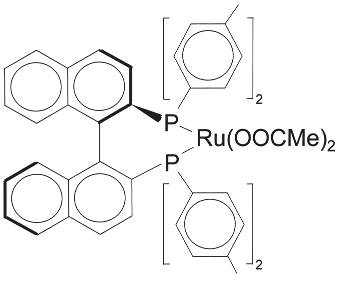


Figure 6 Schematic diagram of a continuous-flow $scCO_2$–IL catalytic process.

Following the elegant work of Brennecke, Beckman, and co-workers on phase behavior and separation [4, 15], a number of groups have investigated SCF–IL biphasic systems; for other reviews cf. [32–36].

6.4.3.5.2
Hydrogenation

Jessop et al. [37–40] were the first to report on organometallic catalytic reactions utilizing IL biphasic systems for product recovery and catalyst recycling. They investigated the asymmetric hydrogenation of tiglic acid catalyzed by [Ru(O_2CMe)$_2$((*R*)-tolBINAP)] (**3**) in [BMIM][PF_6] with added water [Eq. (1)]. The reaction was performed in the IL (25 °C, H_2 0.5 MPa, 18 h) followed by extraction with scCO_2 (35 °C, 17.5 MPa, 1 cm^3 min^{-1}, 18 h). The product was recovered by downstream decompression of the CO_2.



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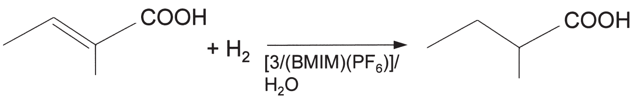


(1)

The reaction gave high enantioselectivity (85% *ee*) and conversion (99%) to 2-methylbutanoic acid. Following product isolation by scCO_2 extraction, the catalyst could be re-used at least five times without losing its activity, which suggests insignificant catalyst leaching, although this was not measured. Interestingly, there was a slight increase in *ee* on the first recycle (to 90%) and this was retained in later cycles. One advantage of this system over the use of fluorous biphasic or aqueous biphasic reactions is that the ligands, which have been optimized for organic solvents, do not need to be modified because they are soluble in the IL but much less so in the SCF. Supercritical carbon dioxide is not present during the reaction because the acidity it generates in the added water deactivates the catalyst.

Jessop et al. recently reported a comparison of asymmetric hydrogenation reactions in several solvent systems, namely scCO_2, [BMIM]PF_6, and an scCO_2 [BMIM]PF_6 biphasic system [38]. Some substrates (Class I) give high *ee* values when the availability of H_2 is high, while others (Class II) perform better under conditions of hydrogen starvation. A typical Class I substrate, atropic acid ((*E*)-MeC(H)=C(Me)COOH), gave a high *ee* when the hydrogenation was carried out in

Table 3 The effect of CO_2 on the *ee* of products from enantioselective hydrogenation of different substrate types catalyzed by **3** in [BMIM][PF_6] [38].

Substrate	***Type***	***H_2 [MPa]***	***CO_2 [MPa]***	***ee %***
Tiglic acid	Class I	0.5	0	93
		0.5	7	85
Atropic acid	Class II	5	0	32
		5	5	57

$scCO_2$, while the class II substrate, tiglic acid ((*E*)-MeC(H)=C(Ph)COOH), gave higher *ee* values in ILs. This observation arises because the mass transport of hydrogen to the catalyst is favored in $scCO_2$, whereas the very low solubility of hydrogen in the IL makes mass transport slow. Because $scCO_2$ reduces the viscosity of the IL (at 50 °C the viscosity of [BMIM][PF_6] drops from 60.4 cp to 28.5 cp when 0.64 mole fraction of CO_2 is present [13]) and increases the hydrogen mass transport, the $scCO_2$–IL system is better for tiglic acid than the IL on its own, while the *ee* drops for atropic acid when CO_2 is added to the IL (see Table 3).

Although the transport of hydrogen appears to be an important factor in determining the outcome of the reaction under different conditions, studies using different ILs show that it is not the only effect. If it were, class I substrates would give higher *ee* values in less viscous ILs for which H_2 mass transport is better, whereas the reverse would be true for class II substrates. In practice, both substrates give higher *ee* values in the less viscous ILs, although these reactions did not include CO_2 [38].

The hydrogenation of simple alkenes, 1-decene and cyclohexene [41], to decane and cyclohexane respectively has also been investigated in the $scCO_2$–[BMIM][PF_6] biphasic system using Wilkinson's catalyst [$RhCl(PPh_3)_3$] (50 °C, 4.8 MPa H_2, total pressure 20.7 MPa, 1 h). The catalyst activity was found to be the same in both $scCO_2$–[BMIM]PF_6 and hexane–[BMIM]PF_6, but the products from 1-decene hydrogenation were removed, when using $scCO_2$, by flushing with $scCO_2$ at the reactor temperature and pressure and operating repetitive batch reactions. The yield remained at 98% in each of five reactions using the same batch of catalyst.

Noyori and co-workers [42, 43] reported the hydrogenation of CO_2 in the presence of dialkylamines to produce *N,N*-dialkylformamides using $scCO_2$-soluble catalysts derived from [$RuCl_2(PMe_3)_3$] [Eqs. (2)–(6)]. More recently, Liu et al. have studied the same reaction using [$RuCl_2(dppe)_2$] (dppe = bis(diphenylphosphino)ethane) as catalyst in $scCO_2$–IL systems (80 °C, 0.5 MPa H_2, total pressure 27.6 MPa, 1 h) [41]. In the $scCO_2$–[BMIM][PF_6] system, much higher selectivities to higher alkylformamides were found than when using [$RuCl_2(PMe_3)_3$] in $scCO_2$ alone, probably because the intermediate carbamates and alkylammonium formates produced in Eqs. (3) and (4) would be expected to be more soluble in the IL phase than the $scCO_2$ phase [41]. When using Pr_2NH, extraction of the product *N,N*-dipropylformamide with $scCO_2$ was initially poor (5% recovery); however, the success of the recovery process improved considerably on the second (61%) and subsequent (almost quantitative) cycles of a series of repetitive batch reactions. Clearly, the partition coefficient of the formamide into the $scCO_2$ from the IL is low, but once the IL is saturated, successful extraction occurs [41]. This would appear to be a good candidate reaction for continuous processing.

$$CO_2 + H_2 \xrightleftharpoons{\text{Cat}} HCO_2H \tag{2}$$

$$HCO_2H + NHR_2 \rightleftharpoons [NH_2R_2]^+[HCO_2]^- \tag{3}$$

$$HNR_2 + CO_2 \rightleftharpoons R_2NCO_2H \tag{4}$$

$$R_2NCO_2H + NHR_2 \rightleftharpoons [NH_2R_2]^+[O_2CNR_2]^- \tag{5}$$

$$[NH_2R_2]^+[O_2CNR_2]^- + 2\ HCO_2H \rightleftharpoons 2\ HC(O)NR_2 + 2\ H_2O + CO_2 \tag{6}$$

6.4.3.5.3
Hydroformylation

The first description of a continuous-flow reaction being carried out in an $scCO_2$–IL mixture concerned the hydroformylation of medium-chain alkenes [16, 25, 44]. Initially, repetitive batch reactions were carried out using triphenylphosphite modified rhodium catalysts in [BMIM][PF_6]. The catalyst could be re-used two or three times, but then deactivated because water, probably generated by aldol condensation of the product, hydrolyzed the $[PF_6]^-$ anion to produce $[O_2PF_2]^-$ and HF, which in turn reacted with the phosphite to give fluorinated phosphines. Better results were obtained for repetitive batch reactions using $[Rh_2(OAc)_4]$/[BMIM][$Ph_2P(3\text{-}C_6H_4SO_3)$] (not the sodium salt [45] because it has low solubility in the IL) [16]. Rhodium leaching (< 0.003%) was not observed until the ninth cycle [16]. The gradual drop in selectivity and the rhodium leaching after the ninth cycle was attributed to oxidation of the ligand so that the active species becomes $[RhH(CO)_4]$, which is soluble in $scCO_2$ and gives more isomerization and lower *l*/*b* ratios [10]..

Based on these results, a system for continuous processing was devised using a catalyst formed from $[Rh(acac)(CO)_2]$ (acac = 2,4-pentanedionato) and [PrMIM]-[$Ph_2P(3\text{-}C_6H_4SO_3)$] in [BMIM][$PF_6$], with a steady rate and *l*/*b* ratio being observed for up to 72 h (100 °C, total pressure 20 MPa) [25]. The rates (TOF = 5–10 h^{-1}) of these initial reactions were rather low and product recovery was only about 20%. In subsequent optimization studies [16], very significant improvements were realized so that rates comparable to those pertaining in commercial systems have now been achieved.

The product collection efficiency was improved to > 90% by altering the decompression system so that the product was collected after the first decompression valve at a pressure of ca. 0.5 MPa rather than after a two-stage decompression at a pressure of 0.1 MPa. A diagram of the apparatus design is shown in Figure 7.

The problem of low conversion was largely caused by poor mass transport of the substrate into the IL, where the catalyst resides. Significant improvements were obtained by increasing the chain length of the 1-alkyl in the imidazolium cations (Figure 8) probably because of the known increase in alkene solubility [3].

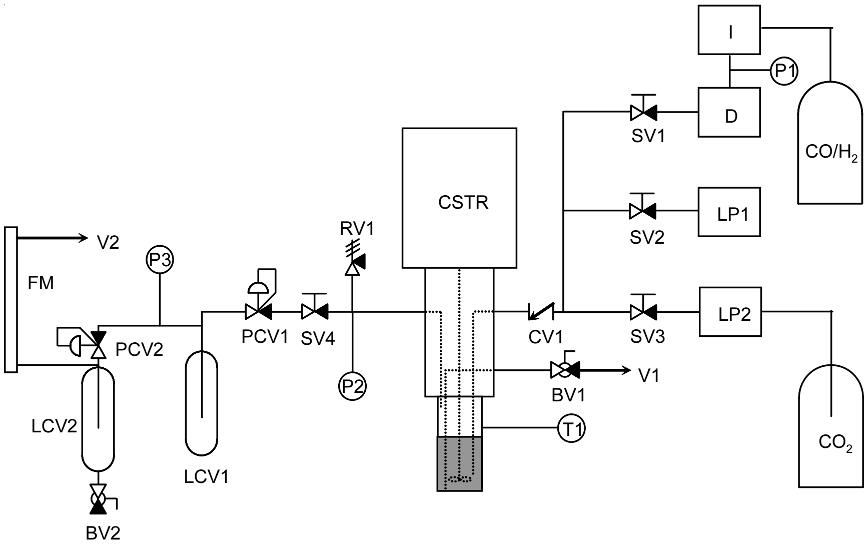


Figure 7 Reactor for continuous-flow hydroformylation.
CSTR = continuously stirred tank reactor; CV = check valve; D = dosimeter;
FM = flow meter; I = intensifier; LCV = liquid collection vessel; LP = liquid pump;
P = pressure transducer; PCV = pressure control valve; RV = relief valve;
T = thermocouple; SV = shut-off valve; V = vent.
(Reprinted with permission from [16], © 2003 American Chemical Society).

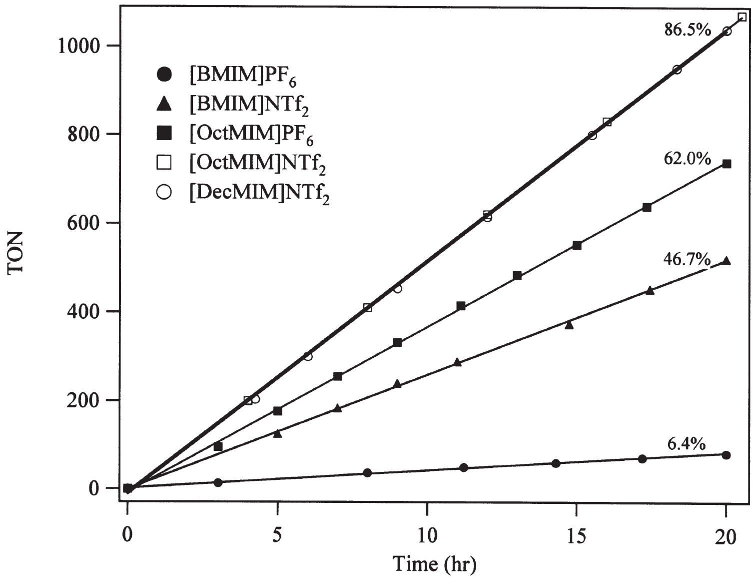


Figure 8 Hydroformylation of 1-dodecene catalyzed by Rh/[PrMIM][$Ph_2P(3\text{-}C_6H_4SO_3)$] in a variety of ILs. The percentages are conversions of 1-dodecene in the isolated fractions. (Reprinted with permission from [16], © 2003 American Chemical Society).

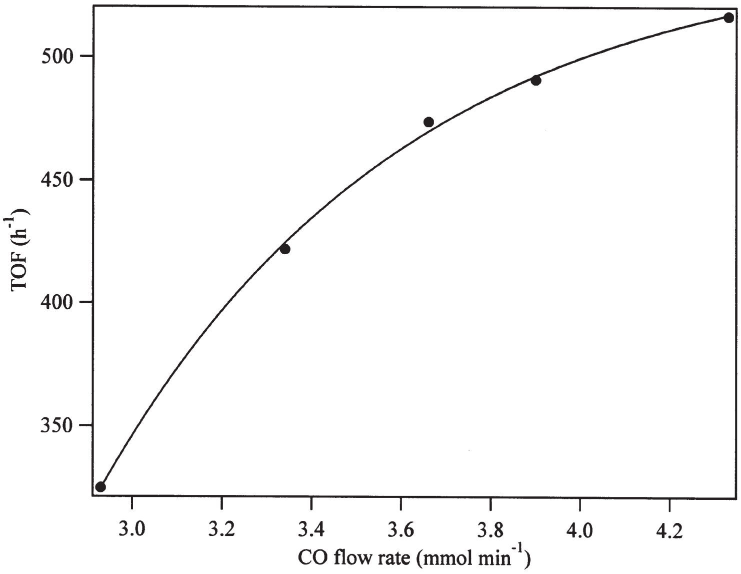


Figure 9 Effect of CO/H_2 flow rate on continuous-flow hydroformylation of 1-octene catalyzed by Rh/[PMIM][$Ph_2P(3\text{-}C_6H_4SO_3)$] in the [OctMIM][$NTf_2$]-$scCO_2$ biphasic system. (Reprinted with permission from [16], © 2003 American Chemical Society).

Further rate increases were obtained by changing the reaction parameters, the most important being substrate flow rate and the partial pressure of the permanent gases. Increasing the flow rate and hence the partial pressure of CO/H_2 increases the turnover frequency (Figure 9) because the solvating power of the mobile phase decreases and more substrate partitions into the IL phase where the catalyst resides. However, there is a limit to the partial pressure of permanent gases which can be used effectively, and this is determined by the ability of the mobile phase to extract reaction products. At very high CO/H_2 partial pressures, the mobile phase cannot solubilize the product sufficiently to remove it at a rate equivalent to that at which it is formed. Nevertheless, TOFs up to 500, comparable to those for the commercial rhodium-catalyzed hydroformylation of alkenes [28, 29], were observed under the optimum conditions. A partial decrease in the solvating power of the sc phase, caused by the permanent gases, offers further advantages in that the solubility of the catalyst is also suppressed [16].

Figure 10 shows how the reaction rate and rhodium extraction are affected by the partial pressure of CO and H_2 during the continuous hydroformylation of 1-octene. Decreasing the partial pressure (flow rate) of the permanent gases causes a decrease in rate and an increase in rhodium leaching because the supercritical phase is a better solvent for both the substrate and the catalyst. The effect is completely reversible by increasing the partial pressure of the permanent gases. Under the optimum conditions of Figure 9, the concentration of rhodium in the collected fractions was 12 ppb, which amounts to 1 g of Rh in 40 tonnes of product aldehyde. The catalyst was very stable, with constant rates and *l*/*b* selectivities being

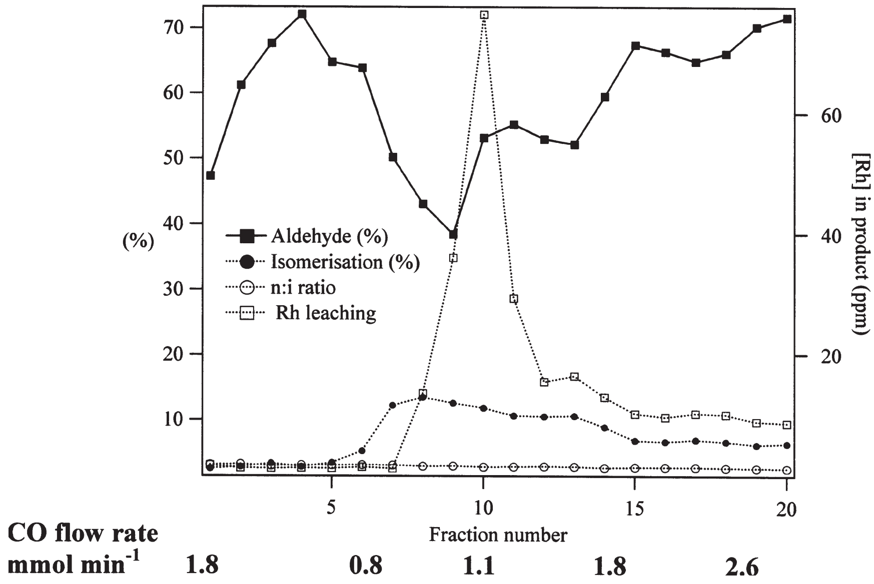
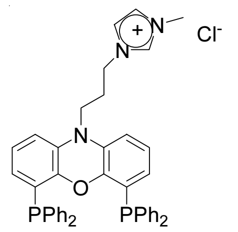


Figure 10 Effect of changing the partial pressure through variation of the flow rates of CO/H_2 during the continuous hydroformylation of 1-octene in $[OctMIM][NTf_2]$. (Reprinted with permission from [16], © 2003 American Chemical Society).

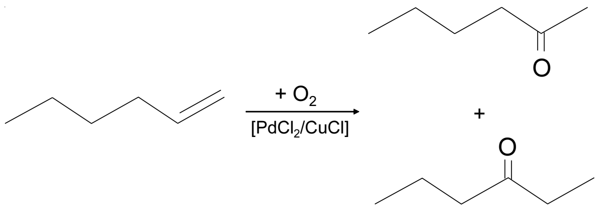
observed for up to 72 h of continuous operation, and good activity after four weeks at the reaction temperature and pressure in the presence of product aldehydes [16]. Using $[PrMIM][Ph_2P(3\text{-}C_6H_4SO_3)]$ as the ligand the *l*/*b* ratio was only modest (*l*/*b* = 3–3.5), but the Xanthphos-type ligand (4) gave *l*/*b* ratios of 40 at TOFs of 286 h^{-1}. Rhodium leaching was slightly higher in this case, at 0.2 ppm.



4

6.4.3.5.4
Oxidation of Alkenes

Oxidation of alkenes to methyl ketones using oxygen has been developed in both synthetic organic chemistry and industrial processes. A well-known example is the Wacker process using $PdCl_2$ and $CuCl_2$ as catalysts in acidic water or an organic solvent [Eq. (7)].



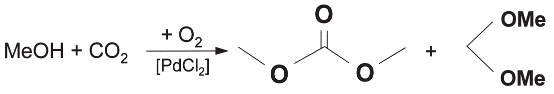
(7)

Wacker oxidation of 1-hexene has been carried out in $scCO_2$–[BMIM][PF_6] at 40 °C and 12.5 MPa total pressure (2.1 MPa O_2) [47]. The main products for this reaction were 2-hexanone and 3-hexanone, with 2-hexanone being the desired product. The conversion approached 100% after 17 h in all the solvent systems studied ($scCO_2$ only, [BMIM][PF_6] only, $scCO_2$–[BMIM][PF_6]) as well as in a solventless reaction. Very similar rates were observed in $scCO_2$ and in $scCO_2$–[BMIM][PF_6].

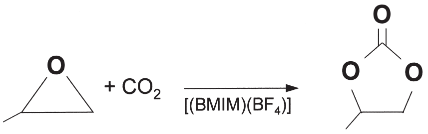
The selectivity to 2-hexanone was found to be the highest in the $scCO_2$–[BMIM][PF_6] biphasic system. The reaction mostly takes place in the IL phase since $PdCl_2$ and $CuCl_2$ are insoluble in the $scCO_2$ phase but soluble in the IL phase. 1-Hexene is soluble in both phases, and thus distributes between them. The improved selectivity in the $scCO_2$–IL system suggests that the rate of alkene isomerization is reduced, because 3-hexanone is the oxidation product from isomerized 1-hexene. This has been attributed to the alkene residing preferentially in the $scCO_2$ and not being in contact with the catalyst so that isomerization does not occur. However, this should not only slow the isomerization, but also the oxidation. If both reactions are catalyzed by the same Pd complex, the effect of this partition should be the same on the rate of both reactions. The difference may arise because different species catalyze the two different reactions (oxidation and isomerization) and the speciation between them is affected by some parameter such as mass transport of oxygen. The reaction could be repeated up to six times in repetitive batch mode, with the products being flushed from the reactor using CO_2 at 160 °C and 11 MPa. For complete extraction 100 g of CO_2 was required. The reaction rate and selectivity were reported to decrease over the six cycles.

6.4.3.5.5
Carbonate Formation

A system has been described for the formation of dimethyl carbonate via the phosgene-free route of oxidative carbonylation of methanol [(Eq. (8)] catalyzed by $PdCl_2$ in [BMIM][PF_6] (110 °C, total pressure 10 MPa, 1 h) [48]. Conversions were generally low (< 7%) and did not improve with increased reaction time, although the selectivity to dimethyl carbonate dropped. Dimethoxymethane was the major product but selectivities of dimethyl carbonate of up to 25% were possible with an O_2/CO_2 ratio of 29 : 71. Neither the pressure nor the temperature had dramatic effects upon the yield or selectivity, although the reaction was slower at lower temperatures. The reaction was repeated three times under the optimum conditions in a repetitive batch process. The rate remained constant, but there was a slight drop in selectivity.

 (8)

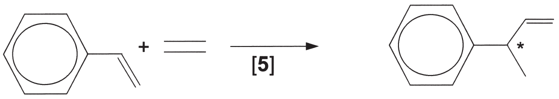
Cyclic carbonates can be prepared by chemical fixation of CO_2, which is a much more environmentally acceptable process than that using phosgene. The formation of propene carbonate has been achieved in CO_2–IL systems, whereby CO_2 serves as a reagent rather than a reaction medium [Eq. (9)] [49]. The production of cyclic carbonates has suffered in the past from serious disadvantages of separating the catalyst [50, 51], while the activity of heterogeneous catalysts is generally very poor [52].

 (9)

It had been shown earlier that the synthesis of cyclic carbonates from epoxides and CO_2 takes place in $scCO_2$ using small amounts of DMF as an $scCO_2$-soluble, acid–base catalyst [53, 54]. However, long reaction times (about 12 h) were required because of the poor catalytic activity of DMF. The reaction time could be reduced to 5 min by replacing the DMF with a catalytic amount of an IL, which acted as an acid–base catalyst and a solvent [49]. As expected, the reaction rate was higher at higher CO_2 pressure, because CO_2 is a reagent, but was still low in cations of imidazolium salts with short alkyl chains such as $[EMIM]^+$, although the rate increased in the order $[BF_4]^- > [NO_3]^- = [PF_6]^- > [CF_3SO_3]^-$. Increasing the chain length of the IL to C_4 ($[BMIM][BF_4]$) gave much better activity and this is again attributed to the better solubility of the epoxide in the IL. Under these conditions, the reaction was successful at temperatures as low as 60 °C, but not at 40 °C. The reaction medium could be re-used at least twice, but the rate of reaction dropped markedly in successive cycles.

6.4.3.5.6
Alkene Coupling Reactions

Hydrovinylation is the transition metal catalyzed codimerization of alkenes with ethylene to yield 3-sustituted 1-butenes [Eq. (10)]. This is an interesting reaction because there are issues relating to chemoselectivity (dimer vs. oligomer formation), regioselectivity, and enantioselectivity. The reaction can be achieved with high enantioselectivity using Wilke's complex (**5**) as the catalyst precursor [55]. The main problem with this reaction in conventional solvents is the fact that the catalyst must be activated by chloride abstraction using highly flammable $Et_3Al_2Cl_3$ at temperatures below –60 °C [56]. Some of these problems were overcome by carrying out the reaction in liquid or $scCO_2$ with the catalyst being activated by an alkali salt of a weakly coordinating anion such as Na[BArF] (BArF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) [57].

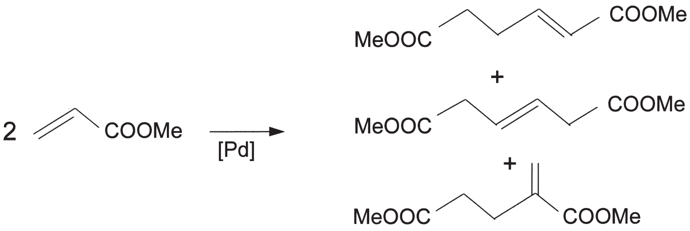


(10)

Further improvements were obtained by using an $scCO_2$–IL biphasic system in which the IL acts as both solvent and chloride abstractor [58]. It was noted that the effectiveness of the catalyst activation depends on the nature of the anion of the IL. The conversion drops in the order $[BArF]^- > [Al\{OC(CF_3)_2Ph\}_4]^- > [NTf_2]^- > [BF_4]^-$ with $[EMIM]^+$ as the cation, a trend that is consistent with the nucleophilicity/coordination strength of the anion. In terms of enantioselectivity, the IL which most effectively activated the catalyst also gave the highest *ee*: The cation was also found to have an influence on the enantionselectivity of the catalyst, with [4-MBP]-$[BF_4]$ giving a higher *ee* (44.2%) than $[EMIM][BF_4]$ (34.2%), although the effect is reversed for the bistrifluoromethylsulfonamides, with *ee* values. of 58.4% and 53.4% in $[4\text{-}MBP][NTf_2]$ and $[EMIM][NTf_2]$ respectively. The best *ee* (89.4%) was obtained with [EMIM][BArF], but this was at the expense of a poorer chemo- (10% oligomers) and regioselectivity (26.2% of undesired isomers). Overall, the best performance was obtained with $[EMIM][Al\{OC(CF_3)_2Ph\}_4]$, which allowed 90.5% conversion with 96.7% selectivity to the desired 3-phenyl-1-butene (*ee* = 78.2%).

After optimizing the reaction temperature and pressure, the reaction was carried out in a repetitive batch mode, the product being extracted with $scCO_2$ after the reaction. However, the active species deactivated rapidly after three to four batchwise cycles. This was also observed when using only $scCO_2$ as a solvent [57]. It was suggested that the deactivation is related to the instability of the active species in the absence of substrate. In this case continuous operation should improve the stability because substrate is always present. Continuous-flow operation was therefore demonstrated in $[EMIM][NTf_2]$ [58] and the catalyst was found to be stable for over 61 h (conversions 75–80%) with the *ee* dropping slightly (65–58%) over the long reaction period. The great advantages of this system over conventional IL/organic liquid systems are the facile separation of the mobile solvent, CO_2, from the product by simple decompression and the use of more environmentally acceptable solvents.

The head-to-head dimerization of methyl acrylate (MA) to dimethyl Δ2- and Δ3-dihydromuconate (DHMs) [Eq. (11)] leads to an intermediate which can be transformed to nylon-6,6 via adipic acid. An $scCO_2$–$[BMIM][BF_4]$ biphasic system for methyl acrylate dimerization using a catalyst formed from $[Pd(acac)_2]$, $[Bu_3PH][BF_4]$, and $[Et_2OH][BF_4]$ has recently been reported [59].

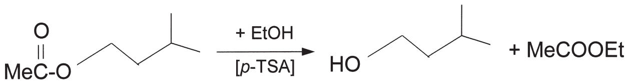


(11)

Phase behavior studies showed that the substrate methyl acrylate is fully miscible with CO_2 in the pressure range 9–29.5 MPa, whereas the product dihydromuconates are only fully miscible at the concentrations required above a density of 0.4 g cm^{-3} (15 MPa at 80 °C). The biphasic reactions were therefore carried out at 20 MPa and 83 °C. The conversion (73%), selectivity (> 98%) and TOF (95 h^{-1}) were found to be similar to those obtained in monophasic (IL only) conditions. This is somewhat surprising since the concentration of substrate in the IL is expected to be much lower when the $scCO_2$ is present. The catalyst stability was determined by cooling down the reaction after 6 h and then, after 60 h, heating the system to the reaction temperature, introducing fresh methyl acrylate, and re-running the reaction under the same conditions. The results showed that the catalyst was still active, although at a lower rate, and still gave the same selectivity. The product was extracted from the IL phase using $scCO_2$. Fractionation of the reaction mixture, by stepwise depressurization of the supercritical solvent, enabled separation of DHMs and unreacted MA (DHMs precipitate first as they are less soluble in $scCO_2$ than MA) [59].

6.4.3.5.7
Transesterification

The equilibrium for the transesterification of isoamyl acetate by ethanol can be affected by the solvent system. This reaction was studied in $scCO_2$, the IL [BMIM][PF_6] and the $scCO_2$–[BMIM][PF_6] biphasic system at 65 °C using *p*-xylenesulfonic acid (*p*-TSA) as a catalyst [Eq. (12)] [60].

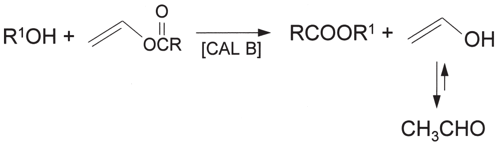


(12)

It was found that the equilibrium conversion in the $scCO_2$–IL biphasic system was lower than that observed in either $scCO_2$ or the IL alone. In $scCO_2$, the conversion at equilibrium depends on the phase behavior. When two phases are present (80 °C, 12 MPa), i.e., a CO_2-rich gas phase and a liquid phase comprising the reaction mixture, the equilibrium conversion is 45%, while above the critical pressure of the system (14 MPa), when only a single phase exists, the conversion is only 25%. Similar differences occur when the IL is present. At 8 MPa, when three phases occur (predominantly containing IL, liquid organic compounds and a gas-rich phase), the conversion amounts to 20% while at higher pressures (12–14 MPa), where only two phases are present, the conversion drops to only 15% at equilibrium compared to 28% in the absence of CO_2. It also takes longer for equilibrium to be established in the $scCO_2$–IL system [60].

Transesterification has also been used to demonstrate that enzyme catalysis can be carried out in SCF–IL biphasic systems. ILs can stabilize enzymes, thereby enabling their use at higher temperatures [61, 62]. $ScCO_2$, on the other hand, may cause reductions in activity for enzymes either because of changes in pH, as a result of the acidic CO_2 dissolving in water, or as a result of conformational changes that occur during pressurization and depressurization [63]. Many enzyme-catalyzed reactions suffer from product inhibition, or even inactivation, so continuous-flow operation in which the product is continuously removed offers the possibility of improved performance and/or lifetime. Over-reaction might also be avoided in this way.

Lozano et al. [64–67], and Reetz, Leitner and co-workers [68, 69], simultaneously reported $scCO_2$–IL biphasic, biocatalytic systems for lipase-catalyzed transesterifications using vinyl esters as the transesterification agent [Eq. (13)]. Vinyl butyrate was used because the product vinyl alcohol tautomerizes to acetaldehyde and hence the reaction is irreversible.



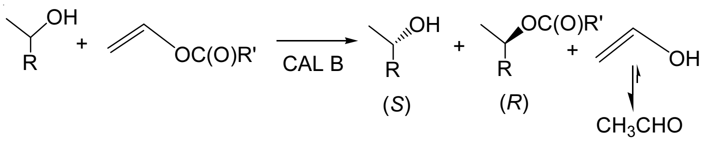
(13)

Lozano et al. [64, 65, 67] used an aqueous solution of *Candida antarctica* lipase B (CAL B) dissolved in $[EMIM][NTf_2]$ or $[BMIM][NTf_2]$ and then supported on celite as a catalyst. The reactions were run continuously at 25 °C and 1.5–15 MPa using CO_2 as a transport vector for 4 h and then stored for 20 h at atmospheric pressure before being re-used. They found that the specific activity and selectivity of the enzyme increased with increasing temperature for the synthesis of butyl butyrate from vinyl butyrate and 1-butanol [Eq. (13), R = butyl, R′ = propyl]. This observation was attributed to a reduction in water solubility in the IL phase, although simple Arrhenius behavior would also be expected to give higher rates at higher temperatures. The increase in specific activity could also be related to a reduction in CO_2 density with increasing temperature (constant pressure) because a lower CO_2 density enhances the activity of the enzyme [63]. Carbon dioxide can be detrimental to enzymes [63, 70] and indeed the reaction rates in the SCF–IL system are only about 10% of those in the IL alone [62].

The decrease in gas-phase density will also shift the equilibrium partitioning of the substrate toward the IL phase, which favors the enzyme action, as has been suggested from comparative work using ILs (see below). The enzyme deactivates with time, the rate of decay increasing with temperature. After ten cycles at 40 °C, the activity is still 85% of that initially observed, and even at 100 °C has only dropped to 40%. Studies in which the IL is varied show that, for all straight-chain alcohol substrates, the activity of the enzyme is higher in $[BuMe_3N][NTf_2]$ than in $[\{NC(CH_2)_3\}Me_3N][NTf_2]$. The reverse is true in the ILs in the absence of $scCO_2$, an observation that has been attributed to the different viscosities of the ILs. Viscosity cannot explain the results obtained in the presence of $scCO_2$ where the relative rates arise because the substrates are more soluble in $[BuMe_3N][NTf_2]$ than in the IL containing the cyanopropyl group. The observed rate differences are probably then brought about by different rates of mass transport across the SCF–IL interface [67].

The acylation of 1-octanol by vinyl acetate catalyzed by CAL B in an $scCO_2$-IL biphasic system [Eq. (13), R = octyl, R′ = methyl] was studied in the work by Reetz et al. [68]. The reactants were added directly to a suspension of the enzyme in [BMIM][NTf_2]. Initially, repetitive batch reactions were carried out in the absence of CO_2 for 30 min and the products were extracted at 39°C and 9.5 MPa $scCO_2$ over 1 h. Complete conversion was achieved in four consecutive cycles and octyl acetate was collected in yields ranging from 92–98%. With evidence that the enzyme did not lose its activity, continuous-flow processing was performed. A reactor was charged with [BMIM][NTf_2] and CAL B, and flushed with CO_2 at 45 °C and 10.5 MPa [68]. The substrates, octanol and vinyl acetate, were injected into the system using an HPLC pump. After passing through the reactor, the CO_2 stream was depressurized and the organic components were collected in a cold trap. The system required about 10 min to reach a steady state, after which good mass balance was achieved. The total yield of octyl acetate was 93.9% after 24 h at a rate corresponding to 0.1 kg (L of reactor volume)$^{-1}$, and a specific activity of the enzyme of 26 μmol min^{-1} g^{-1}.

Both groups also studied the kinetic resolution of *rac*-1-phenylethanol by vinyl propanoate [64, 65, 67], vinyl acetate [68, 69] or vinyl dodecanoate [68, 69] [Eq. (14), R = Ph, R′ = Me, Pr or undecyl]. The specific activity of CAL B toward the kinetic resolution of *rac*-1-phenylethanol by vinyl propanoate was lower than for butyl butyrate synthesis because of the lower nucleophilicity of the secondary alcohol, although the activity was found to be eight times greater than when the enzyme was immobilized on celite in the absence of an IL [64, 67]. The enzyme gave high enantioselectivity (> 99.9%) to (*R*)-1-phenylethyl propanoate and little difference was observed between [EMIM][NTf_2] and [BMIM][NTf_2] at 50 °C, although the rate was higher for the shorter-chain IL at 100 °C. In both cases lower activity was observed at 100 °C than at 50 °C and the activity dropped by half after > 20 cycles at 50 °C, but < 20 cycles at 100 °C (eight cycles for [BMIM][NTf_2]) [64].



(14)

Reetz t al. [68, 69] observed similar results (about 99% (*R*)-1-phenylethyl acetate isomer) using vinyl acetate and the same enzyme, but suspended directly in [BMIM][NTf_2] and using $scCO_2$ for product separation (40 °C, 11 MPa) in a batchwise mode. The time to 45% conversion increased from 1 h to about 12 h on the fourth cycle [68]. Substantial loss of activity appeared to have occurred between the third and fourth cycles. Higher yields were obtained with [BMIM][NTf_2] than with [BMIM][PF_6] or [BMIM][BF_4]. The enzyme could be used in free suspension or on a support; supported enzymes are preferred because they do not promote transesterification beyond 50% making for very high *ee* values in the recovered alcohol and the product ester. The reaction was also successful with a variety of other secondary alcohol substrates [68].

In an attempt to separate the unreacted (*S*)-alcohol from the product (*R*)-ester, lower pressures were used for the extraction. This gave some enrichment of the ester (1-phenylethyl acetate/1-phenylethanol = 1.4 : 1 at 60 °C and 9 MPa) in the liquid fractions collected downstream because of the higher solubility of acetates compared with the corresponding alcohols. After extraction of 65% of the ester formed, an alcohol-rich fraction was obtained (1-phenylethyl acetate/1-phenylethanol = 1 : 3) when the CO_2 pressure was increased to 15 MPa [69]. A more successful separation was achieved when vinyl acetate was replaced by vinyl dodecanoate in the initial reaction and 2-octanol was the substrate [Eq. (14), R = 1-hexyl, R′ = undecyl]. In this case, the high molecular weight ester is less soluble in $scCO_2$ than the alcohol. Extraction at 9 MPa and 60 °C initially gave fractions that were highly enriched in the alcohol (ester/alcohol = 1 : 18), whereas the ester was enhanced in later fractions (21 : 1; see Figure 11).

A two-step extraction procedure, typically 9–10.5 MPa CO_2 at 60 °C, dropping to 8 MPa in the collector, over 90 h to extract the alcohol followed by 20 MPa and 45 °C also worked well for other secondary alcohol substrates so that yields of each of the unreacted alcohol and the recovered ester can be > 90% with *ee* values > 90%. The *ee* is generally lower for the ester than for the recovered alcohol, the exception being $PhCH_2CH_2CH(OH)CH_3$, where only 72.5% of the ester was recovered (*ee* 88.2%). The recovered alcohol (92.4%) had an *ee* of only 65% [69].

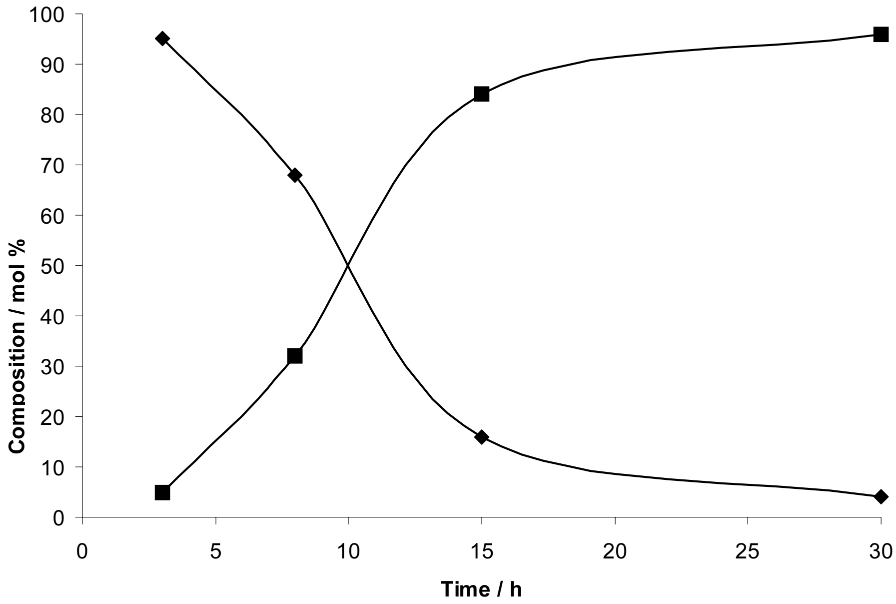
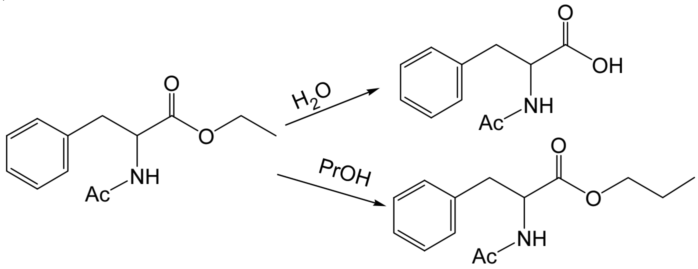


Figure 11 Separation of (*S*)-2-octanol from (*R*)-2-methylhexyl dodecanoate from CAL B catalyzed kinetic resolution in [BMIM][NTf_2] by extraction with CO_2 (60 °C, 9 MPa) [69].

Finally, the teams of Reetz and Leitner operated a reaction using 2-phenylethanol and vinyl dodecanoate continuously in a reactor consisting of two consecutive autoclaves containing the enzyme–IL suspension, to ensure high conversion, and two decompression chambers with a liquid recycling system and the ability to add further CO_2 independently [69]. The process was performed at 50 °C and 2 MPa with a mixed substrate flow rate (33% alcohol) of 0.6 cm^3 min^{-1}. The CO_2 stream leaving the reactor was decompressed to 1.3 MPa at 50 °C in a first chamber, where extra CO_2 was added to help remove the alcohol into the second chamber (100 °C, 10 MPa). Finally, the stream was passed into a cryotrap. The liquid collected in the second chamber was periodically recycled to the first so that the alcohol ended up mostly in the cryotrap, while the ester was recovered from the first collection chamber. After 112 h of continuous operation, the alcohol (81%, > 97% *ee*) containing < 0.1% of ester was recovered from the cryotrap, while the first extraction vessel contained ester (97%, > 97% *ee*) contaminated by < 0.5% of alcohol. After resuming the substrate and CO_2 flows, identical activities and selectivities were obtained. Acetaldehyde would have been vented from the system because of its high volatility, but the unreacted vinyl dodecanoate, which was used in excess, is of intermediate volatility and was contained in both product fractions.

Enzymes other than CAL B have also been reported to operate under the biphasic conditions. CAL A and CAL B or a lipase from *Mucor miehei* were tested for the kinetic resolution of glycidol using vinyl acetate or vinyl butyrate. The enzymes were used either suspended in the free ILs or immobilized, when the reactions were carried out in [EMIM][NTf_2] [71]. CAL A was inactive, but the other two enzymes showed activity, albeit at 10–20% of that in the absence of CO_2 whether they were free or immobilized. In general, the supported enzymes showed superior performance [71]. Chymotripsin, a specific protease for aromatic amino acids, was found to catalyze the hydrolysis or transesterification of the ethyl ester of *N*-acetylphenylalanine with propanol in $scCO_2$–[RMIM][PF_6] (R = butyl or octyl) with or without added water [Eq. (15)].



(15)

Interestingly, the addition of $scCO_2$ improved the reactivity relative to that in the IL alone, or when chymotripsin was employed in $scCO_2$ without the IL. Addition of 1% water to the mixture improved the reaction rate of transesterification, but some hydrolysis was also observed. In this case, [BMIM][PF_6] proved to be superior to [OctMIM][PF_6], whereas the opposite was true for reactions carried out in the absence of $scCO_2$.

6.4.3.6
Recent Developments

SCF–ionic liquid-based processes have enormous potential for development, given that commercially interesting rates, selectivities, catalyst lifetimes, and separations can be achieved once optimization has been carried out [16, 44, 69]. However, there is still scope for improvement because of residual concerns pertaining to ILs. ILs are generally considered to be environmentally benign because of their high stability and negligible vapor pressure. However, little attention has been paid to their very long term stability, although a commercial process using an IL has been in operation since 1997 without any loss or replenishment of the original charge of solvent [73]. There must still be some doubt about the disposal of ILs, particularly for those with anions containing fluorine, which can sometimes react with water to give HF, and whose incineration can be difficult [16, 25, 46]. Although studies show that there are certainly examples with acceptable toxicity, imidazolium salts with long alkyl chains are skin irritants [72] and can be toxic to nematodes, albeit at fairly high dose levels ($LD_{50} < 1$ mg cm^{-3} for [tetradecyl MIM]Cl, between 2.5 and 5 mg cm^{-3} for [OctMIM]Cl, and > 5 mg cm^{-3} for [BMIM]Cl) [75].

There are also economic concerns about the use of ILs in SCF–IL biphasic systems. If a process has been designed to give high rates, this generally means that the IL has been chosen to dissolve the substrate effectively. Often this will then mean that the product is also very soluble, so that high rates of extraction require high SCF pressures (typically 20 MPa) [16] which could make the process prohibitively expensive for all but the most valuable products. The cost of ILs themselves is also currently high, particularly when the anion contains fluorine, and this may limit their use in bulk and commodity chemical processes. Consideration is therefore being given to systems in which the IL is replaced by a liquid polymer which is insoluble in the SCF (see Section 6.4.2), or omitted altogether.

An approach to obviating the need for the IL simply involves dissolving the catalyst, which has similar solubility characteristics to other catalysts used successfully with the IL, in the steady-state mixture of reactants and products that develops during the reaction. This approach has been demonstrated for the continuous hydroformylation of 1-octene using $scCO_2$ as a transport vector for reactants and products [76]. The catalyst was initially dissolved in pure nonanal with flow rates balanced so that the rate of product extraction matched the rate of its continuous formation. Initially, only 1-nonanal was recovered downstream (it was the starting solvent) but the *l*/*b* ratio changed smoothly toward a steady-state value of 3.2 : 1, characteristic of the product distribution expected using PPh_3-type ligands.

The substitution pattern in the ligand periphery was found to be crucial for the successful operation. If the ligand was too lipophilic, e.g., [OctMIM]-[$Ph_2P(3\text{-}C_6H_4SO_3)$], significant extraction of the active species occurred. Conversely, if the ligand was too polar, e.g., [PrMIM][$Ph_2P(3\text{-}C_6H_4SO_3)$], it was not sufficiently soluble in the product phase. As a result, an unmodified rhodium complex was formed, which was CO_2-soluble, and the rhodium was rapidly lost from the system. Even with the intermediate-polarity ligand [PentMIM][$Ph_2P(3\text{-}C_6H_4SO_3)$], the process conditions had to be controlled carefully. Too high a flow rate of 1-octene led to higher levels of 1-octene in the system, reducing polarity. This caused some of the catalyst to precipitate and the conversion to drop. Further catalyst then precipitated, leading to a negative feedback loop and very poor catalysis. Nevertheless, with only preliminary optimization, the operating pressure for the new continuous-flow process was reduced from 20 MPa when using an IL solvent [16] to 12.5 MPa.

6.4.3.7
Outlook and Conclusions

The facile separation of products from both reaction solvent and catalyst is of principal importance if the commercial viability of homogeneously catalyzed reactions is to be fully realized. A number of commercial processes rely on liquid–liquid biphasic systems to effect catalyst separation but this approach has its limitations (the limited solubility of organics in water, for example). The unusual phase behavior of supercritical fluid–IL systems makes them excellent candidates for use in continuous-flow biphasic catalysis. ILs and $scCO_2$ are tunable solvents and therefore represent a more generic approach to the catalyst separation problem. This is exemplified by the diversity of the reactions that have already been demonstrated in these systems. Often, these reactions have been carried out as repetitive batch processes and, in these cases, the throughput is probably too low to be of commercial interest. However, in a few examples true continuous-flow operation has been demonstrated over prolonged periods with commercially significant rates, good product selectivities, good catalyst stability, and very low catalyst leaching [1, 16, 69].

In principle, SCF–IL and related systems could be operated as totally emissionless processes, but this would require recycling of the SCF. This has not been demonstrated in any of the catalytic systems reported so far, but is carried out, e.g., in coffee decaffination [18], continuous hydrogenation in SCFs over heterogeneous catalysts [77] and the conservation of archaeological wood by supercritical drying [78]. In the latter process, water in the wood is exchanged for methanol, which is then removed by extraction with $scCO_2$. This prevents crossing of any phase boundaries and avoids the surface tension forces that lead to collapse of the cells within the wood. The extraction can take several days, so the methanol is precipitated from the $scCO_2$ by decompression before the CO_2 is recompressed and recycled [78].

A similar procedure could be used when there are no permanent gases involved in a catalytic reaction, but when gases are used, the recycling will be more complex. A possible process design is shown in Figure 12. Product recovery is achieved by simple expansion of the gas phase downstream. The remaining gas phase is cooled or recompressed to liquefy the CO_2 and any remaining organics. This liquid phase can then be recycled to the reactor. The gaseous phase from the liquefier, containing CO_2 and any remaining permanent gases, is heated above its critical temperature and pumped as a gas back into the system.

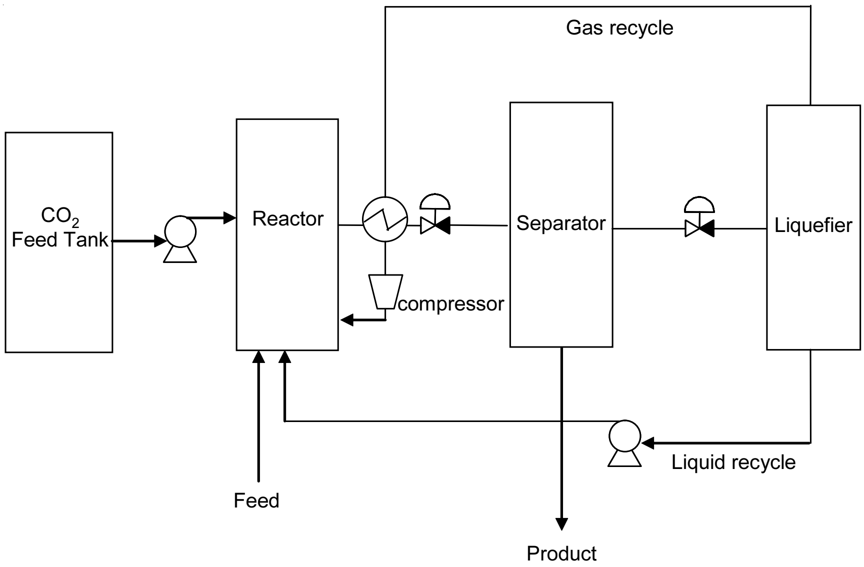


Figure 12 Prototypical process design for continuous operation with full recycling using $scCO_2$–IL biphasic systems.

The very exciting initial studies summarized in this section should be developed further, with special emphasis being placed on reducing the overall pressure so that recycling of the SCF can be economically attractive. It is important to note that similar process considerations apply to most continuous-flow systems involving $scCO_2$ as the transport vector.

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6.4.4
SCFs and Water

Walter Leitner and Katja Burgemeister

6.4.4.1
Physico-chemical Properties of the $scCO_2/H_2O$ System

The basic physico-chemical properties of the binary mixture carbon dioxide/water are well investigated owing to its great importance in several scientific and technological fields (see Section 6.1). For example, carbon dioxide and water are often found together in natural gas streams and also in oil reservoirs as part of enhanced oil recovery. In addition, the system plays an important role with regard

Table 1 Critical properties of the pure compounds CO_2 and H_2O.

Compound	*p_C [MPa]*	*T_C [°C]*	*V_C [m^3 kg mol^{-1}]*
Water	22.048	347.15	0.056
Carbon dioxide	7.377	31.05	0.094

to geochemistry, e.g., in the analysis of CO_2-bearing fluid inclusions in minerals [1]. Extraction processes with $scCO_2$ from aqueous phases are of interest to natural product isolation and water purification (Section 6.2). The knowledge of the chemical and physio-chemical behavior of the binary mixture emerging from these studies provides an excellent basis for the concept of using the combination of compressed carbon dioxide and aqueous phases for biphasic catalytic systems.

The carbon dioxide/water biphasic system is an example of binary mixtures consisting of components with widely separated critical temperatures. The critical properties of the pure compounds are given in Table 1. The typical phase diagram for such mixtures can be complex, including the possibility for areas of three-phase coexistence (LLV). For applications in biphasic catalysis, however, the key parameters to be discussed are solubility and cross-contamination, mass transfer, and chemical changes.

The mutual solubilities are not very high, as factors such as vapor pressure and polarity are quite different for the two components. The solubility of carbon dioxide in pure water as a function of pressure and temperature is presented in Figure 1 [2]. As expected, the solubility increases with increasing pressure at a given temperature and decreases with temperature under isobaric conditions. At near-

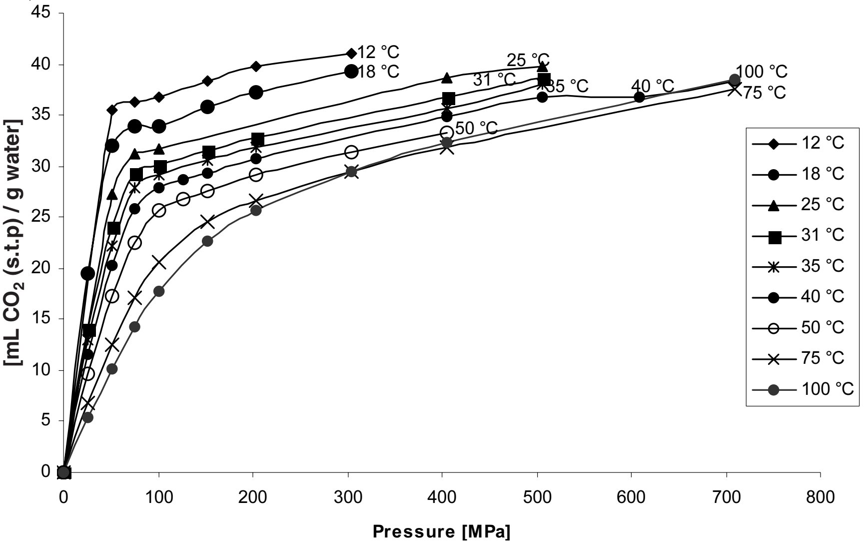


Figure 1 Solubility of CO_2 in the water-rich phase in a biphasic water/CO_2 system as a function of pressure and temperature (data taken from [2]).

critical temperatures, the increase with pressure is very steep up to approximately 100 MPa and reaches a plateau between 30 and 35 mL CO_2 per gram of water (ca. 1.5 M) under practical pressure conditions.

A review combining and discussing 25 literature studies concerning the solubility of CO_2 in water has been published recently [3]. The data were analyzed critically and correlated using a thermodynamic model based on Henry's law and recent high-accuracy equations of state. After refinement of the model with an empirical correction function, the experimental data could be reproduced within less than 2% deviation. The model is available as a computer code [4] allowing estimation of a large set of physico-chemical properties of the CO_2-containing aqueous phase including activity coefficients, partial molar volumes, and chemical potentials.

Even though the solubility of water in CO_2 is low (< 1 mol% under most practical conditions), it cannot be neglected in catalytic applications and especially under continuous-flow conditions. Again, the water content in the gas phase of the CO_2 water system is a function of temperature and pressure. In subcritical conditions, the water content decreases with an increase in the system pressure at constant temperature. In supercritical conditions the same behavior occurs up to a certain pressure, but then an increase in the system pressure leads to an increase in the water content [5, 6]. Obviously, the solubility is determined by vapor pressure in the first region, whereas fluid density is the dominant factor in the second region. Although this means that cross-contamination between the stationary phase and the $scCO_2$ phase cannot be fully avoided in these biphasic systems, this is not a problem from an ecological or toxicological viewpoint owing to the benign nature of water. It can be an issue, however, for downstream processing and product isolation/drying.

The presence of small amounts of water in the $scCO_2$ phase alters the solubility properties of this phase significantly. Water is known to act as an entrainer that makes the CO_2 phase much more polar, and engages in hydrogen bonding with solutes, thus rendering it a better solvent for functionalized organic materials [7]. The density of the CO_2 phase, another important parameter related to its solubility properties, is hardly affected by dissolved water in the range of 1–30 MPa and 284–332 K [8]. The density of the water-rich liquid phase shows a noticeable dependence on pressure and temperature, whereby the density increases with dissolved CO_2 as depicted in Figure 2.

One disadvantage of the concept of phase segregation in multiphase catalysis is the limitation of mass transfer across the phase boundaries (see also Section 2.3.1). Although a supercritical/liquid system has already much better mass-transfer properties than a classical gas/liquid/liquid system for organometallic catalysis, the presence of separated phases during the reaction can still be unfavorable for the chemical transformation, or limit the range of possible substrates. In an approach to overcome this problem for reactive CO_2/aqueous biphasic systems, the formation of high-surface emulsions and microemulsions between water and supercritical carbon dioxide has been investigated intensively [9].

Microemulsions are thermodynamically stable dispersions of one fluid phase in a second continuous phase, stabilized by an interfacial film of surfactant (see

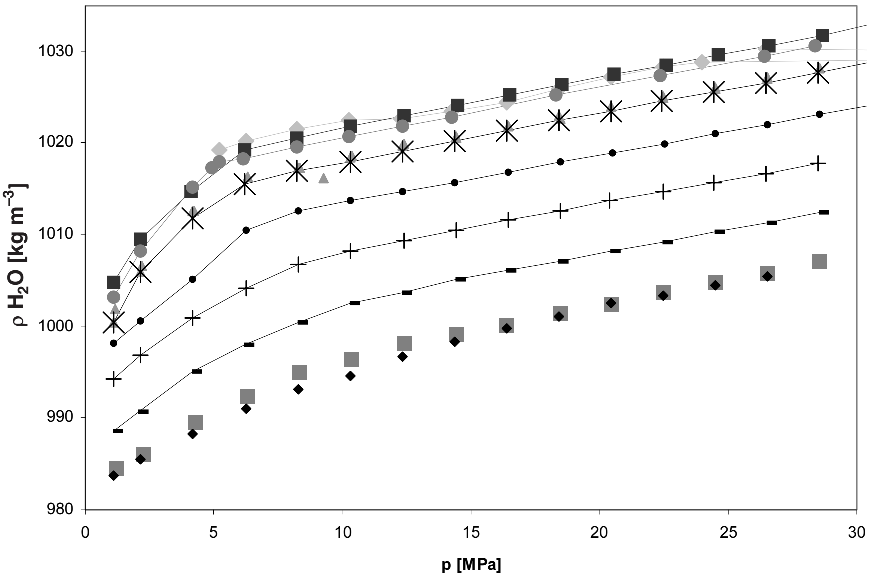


Figure 2 Density of the water-rich phase in a CO_2/aqueous biphasic system as a function of the system pressure and temperature (data taken from [8]).

Section 2.3.4). This dispersion may be either CO_2-in-water or water-in-CO_2. Microemulsions are typically clear solutions, as the droplet diameter is approximately 100 nm or less. The interfacial tension between the two phases is extremely low. Emulsions (or macroemulsions) are in contrast thermodynamically unstable and the suspended droplets will eventually agglomerate, causing the dispersed phases to separate. Emulsion droplet sizes are much larger, typically 1 μm or more, resulting in a cloudy or milky dispersion. The nature of an emulsion may depend on the order of mixing of the ingredients and the amount of energy put into the mixing process. The final microemulsion state will not depend on order of mixing, and the energy input determines only the time to reach the equilibrium state.

Compared to pure CO_2 as a solvent, aqueous emulsions and microemulsions offer increasing solubility of nonvolatile hydrophilic substances, including even proteins and ions. With the design of surfactants for the interface between water and CO_2, new opportunities in polymer and protein chemistry as well as in chemical engineering and environmental science are emerging. Examples of applications in organometallic catalysis and related reactions are summarized for individual examples (see sections below). Suffice it to say here that even the protein bovine serum albumin (BSA) with a molecular weight of 67 000 has been successfully dissolved in a water/carbon dioxide microemulsion using nontoxic ammonium carboxylate perfluoropolyether as surfactant [9]. In general, carboxylate perfluoropolyether (PFPE) surfactants with molecular weights between 2500 and 7500 are soluble in carbon dioxide at pressures below 30 MPa. The development of surfactants for water/CO_2 microemulsions is an ongoing area of research and recent examples include anionic [10], cationic [11], and nonionic substances [12].

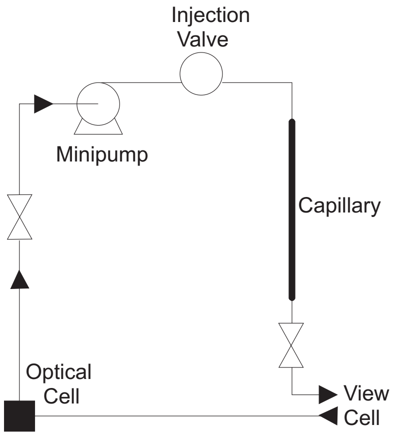


Figure 3 Experimental setup for phase behavior measurement of water/CO_2 microemulsions.

The phase behavior of water/CO_2 microemulsions can be determined using a setup such as that shown in Figure 3. At high pressure, the system becomes transparent after a certain time of mixing. In some cases it can take several hours to dissolve an aliquot of water, even though the surfactants generally dissolve within minutes. Then, the pressure is lowered slowly until a distinct cloud point is observed visually or by laser detection. The pressure and temperature boundaries are analyzed for a given water content and then another increment of solute is injected to repeat the process.

The cloud point data of water/CO_2 microemulsions are presented in Figure 4 for a typical $[PFPECOO]^-[NH_4]^+$ surfactant [13, 14]. For a given composition, the pressure has to be increased with increasing temperature to keep the density of CO_2 high enough for sufficient surfactant solubility. For a given amount of surfactant, the pressure has to be raised, to increase the water/surfactant ratio w_0.

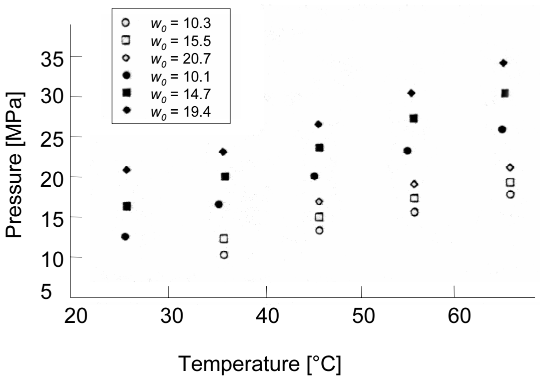


Figure 4 Cloud point data for CO_2/water microemulsion using a $[PFPE\ COO]^-[NH_4]^+$ surfactant (data taken from [13, 14]).

Neutron scattering has been used to measure the droplet size in these water/CO_2 microemulsions and the droplet diameter was found to increase from 20 to 36 Å for w_0 values of 14 and 35, respectively [15]. Droplet size and w_0 depend only weakly on pressure, unless the pressure is reduced to that pressure where the phase boundary droplets aggregate.

Water-in-CO_2 and CO_2-in-water emulsions can be formed by using similar surfactants to those for the microemulsions but with high-pressure emulsifiers to provide high-shear mixing of all compounds. A surfactant-free method for emulsification of near-critical CO_2/water biphasic systems using ultrasound irradiation has been described recently [16]. To distinguish between water and CO_2 as the continuous phase, conductivity measurements and dielectric constants can be utilized. For CO_2 as the continuous phase in an emulsion, the conductivity will be very low and the dielectric constant should be similar to that of CO_2 (~1.2). For a water-continuous emulsion, considerable conductivities are observed in the presence of ionic solutes and the dielectric constant should approach that of water (~80). Using these methods, stable water/CO_2 emulsions formed with $[PFPECOO]^-[NH_4]^+$ as surfactant were found to show an inversion from CO_2 to water as the continuous phase with a decrease in pressure, resulting most probably from a decrease in CO_2 density [14].

Another useful method for investigations of water/CO_2 emulsions and microemulsions is electron paramagnetic resonance (EPR) spectroscopy, because no transparent samples are necessary [9, 13]. Furthermore, data from EPR experiments can provide information about the polarity of the local environment of the EPR-active compound. The diagnostic unpaired electron(s) can be introduced either through stable free radicals or by using transition metal ions such as Mn^{2+}. The active moieties may be incorporated directly in the surfactant [17, 18] or added as a soluble probe molecule such as TEMPO (4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl) [9].

In addition to the phase behavior and the mixing state of the water/CO_2 biphasic system, the pH value must be considered as an important process parameter. In general, the system has quite an acidic nature due to the formation and dissociation of carbonic acid (Scheme 1). The second dissociation, of bicarbonate to a proton and carbonate, lies far to the left and does not contribute strongly to the pH value. Typically, the pH of unbuffered water at elevated pressures of CO_2 is in the range of 2.8–3.0 [19].

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^- \rightleftharpoons 2\ H^+ + CO_3^{2-}$$

Scheme 1 Equilibria in water/CO_2 biphasic systems.

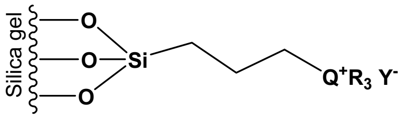
One way to obtain neutral or nearly neutral supercritical fluid/water systems is the use of gases other than CO_2, such as lower alkanes, fluorinated hydrocarbons, or SF_6. This may not always be applicable and these materials are likely to find less acceptance for a potential synthetic application. The inherent condition of low pH in the presence of compressed CO_2 can be addressed by the addition of buffer systems. For example, the buffer MOPS (γ-morpholinopropansulfonic acid) has been successfully introduced to keep aqueous solutions at pH 5.5 under CO_2 pressures in the range of 5 MPa [20]. The addition of organic and inorganic buffers to water/CO_2 microemulsions and emulsions has also been reported to result in an increase in pH to values of 5–7 [21]. Influences of pressure, temperature, and buffer type were investigated and predicted with thermodynamic models. An initial pH step was already observed with small buffer concentrations, but large amounts of base were required to increase the pH further, due to the buffer capacity of the carbonic acid/bicarbonate equilibrium. In another study, pH switches greater than 1.5 were obtained by shifting the CO_2 pressure over a range of 40 MPa with aqueous solutions of NaOH as the base [22].

In summary, the physico-chemical properties of the binary mixture water/CO_2 are well understood and the brief overview given in this section indicates that this biphasic system has a promising potential for application in biphasic catalysis, either in the form of segregated phases or as emulsion-type mixtures.

6.4.4.2
Organic and Inorganic Synthesis in H_2O/CO_2 Biphasic Systems

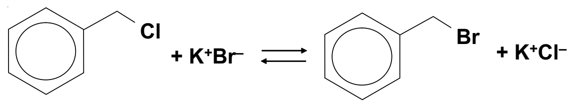
For nucleophilic substitution reactions involving hydrophilic nucleophiles and hydrophobic substrates, the biphasic H_2O/CO_2 system enables the reaction to take place without requiring toxic organic solvents. The nucleophilic displacement of *n*-octylmesylate with bromide and iodide anions has been investigated in a water/CO_2 system under phase-transfer catalysis conditions [Eq. (1)] [23]. Silica-supported onium salts were used as phase-transfer catalysts (**1**). Complete conversion was achieved using, for example, silica-supported $[n\text{-}Bu_4P]^+Br^-$ at 70 °C after 3 h. The conversion is mainly controlled by substrate concentration in the $scCO_2$ phase. Thus the density and hence the operating pressure play an important role in order to ensure sufficiently high concentrations [24].

$$n\text{-}C_8H_{17}OSO_2CH_3 + KY \xrightarrow{\text{PTC}} n\text{-}C_8H_{17}Y + CH_3OSO_2^-K^+ \qquad (1)$$



Y = I⁻, Br⁻
Q = N, P
R = H, Me, *n*-Bu

Similar transformations were used to demonstrate the possibility of using water/CO_2 microemulsions as reaction media, which were stabilized using the anionic perfluoropolyether ammonium carboxylate surfactant $[PFPECOO]^-[NH_4]^+$ [25]. No additional phase transfer catalysts are necessary under these conditions. For example, the reaction between potassium bromide and benzyl chloride to form benzyl bromide [Eqs. (2)–(4)] resulted in a much better yield in the H_2O/CO_2 system than in a conventional water-in-oil microemulsion.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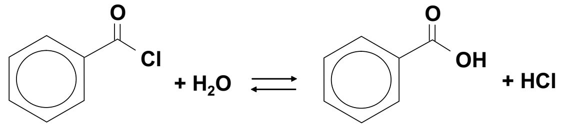
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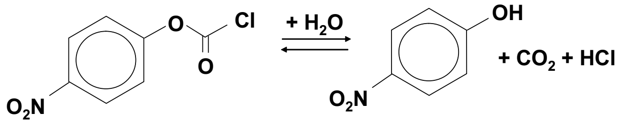

(4)

Hydrolysis reactions of benzoyl chloride and *p*-nitrophenyl chloroformate were successfully carried out under similar conditions.

As an example of inorganic synthesis in a water-in-CO_2 microemulsion, the preparation of semiconductor cadmium sulfide nanoparticles has been described [26]. In general, the mean radii of water droplets in mircoemulsions are proportional to the water surfactant molar ratio w_0 [27]. Because particle growth occurs within the water droplets, the size of the water core can be used to control the particle size, providing a kind of nanoreactor. At the same time, the $scCO_2$ density can be manipulated by variation of temperature and pressure values, making this system highly tunable. Microemulsions based on $[PFPECOO]^-[NH_4]^+$ as the surfactant generated at w_0 ratios of 5 and 10 led to nanoparticles with radii of 0.9 and 1.8 nm, respectively. Using a similar approach, metallic silver nanoparticles with diameters from 5 to 15 nm have been generated in water-in-CO_2 microemulsions using sodium bis(2-ethylhexyl)sulfosuccinate (AOT) and perfluoropolyether-phosphate surfactants [28].

6.4.4.3
Catalysis in H_2O/CO_2 Biphasic Systems

As outlined in general in Section 6.3, two distinct engineering concepts can be envisaged for transition metal catalysis in $scCO_2$-based biphasic systems. In one case the compressed CO_2 phase is used as the compartment for substrates and/or products, whereas the catalyst is contained in the liquid phase, in the present case water. We will refer to this scenario as $H_2O/scCO_2$ biphasic catalysis and examples are discussed in this section. In the other case, carbon dioxide is used as the catalyst-containing phase, whereas substrates and products are retained in the polar aqueous phase. We refer to this system as “inverted biphasic catalysis”, denoted as $scCO_2/H_2O$, and it will be subject of the discussion in Section 6.4.4.4.

In the more conventional setup, a polar hydrophilic catalyst is immobilized in the aqueous phase, whereas hydrophobic substrates (S) and products (P) as well as gases (if present) are dissolved and transported in the compressed carbon dioxide

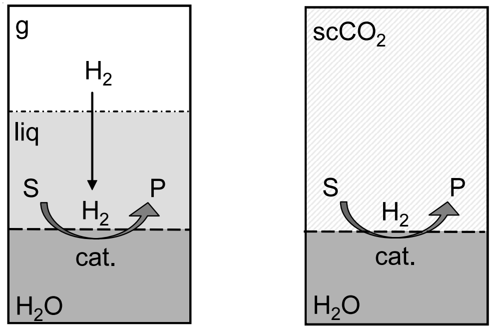
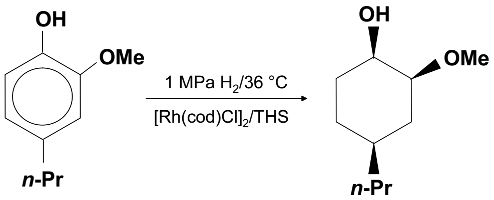


Figure 5 "Biphasic" catalysis in the classical water/organic (left) and water/CO_2 (right) system. Note that the traditional setup leads to a triphasic reaction system in the presence of a gaseous reactant such as H_2, whereas the $H_2O/scCO_2$ system remains truly biphasic.

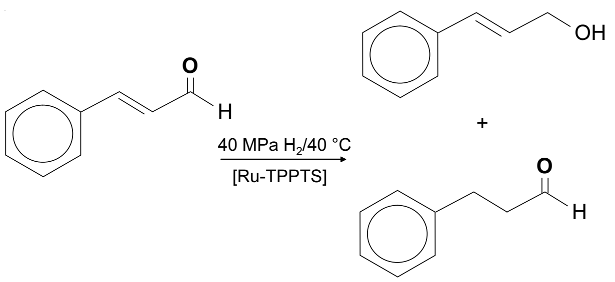
phase. The situation is schematically depicted for a hydrogenation reaction as a prototypical example in Figure 5. The design and development of water-soluble organometallic catalysts can follow well-established guidelines from the area of classical aqueous/organic "biphasic" catalysis, which is in fact triphasic (LLG) in the presence of reacting gases. It is important to note that leaching of a given catalyst from the aqueous into the mobile phase is likely to be strongly reduced with CO_2 as compared to organic phases, because $scCO_2$ is known to be a feeble solvent for polar and low-volatility organometallic compounds. This method is not restricted to CO_2 as the supercritical phase, as will be highlighted below, but the vast majority of examples has concentrated on this combination so far.

Biphasic systems consisting of an aqueous phase and a supercritical phase have been used for the colloid-catalyzed hydrogenation of arenes [29], including the lignin model compound 2-methoxy-4-propylphenol [Eq. (5)]. The rhodium colloids were generated in situ from the precursor [$\{Rh(cod)Cl\}_2$] (cod = 1,5-cyclooctadiene) using tetrabutylammonium hydrogensulfate (THS) as a stabilizer to disperse the particles in the aqueous phase (Rh : THS = 1 : 3). The resulting catalysts are known to require a pH between 7.4 and 7.6 as the region for optimum activity. Consequently the hydrogenation did not proceed in the aqueous/$scCO_2$ biphasic system, even if buffer systems were used to raise the pH. Hydrogenation was achieved, however, using ethane as the supercritical fluid and quantitative conversion was obtained within a 72 h reaction time at a substrate/rhodium ratio of 10 : 1. The all-*cis* product was formed preferentially with approximately 90% stereoselectivity.



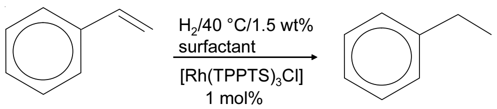
(5)

The hydrogenation of α,β-unsaturated aldehydes was examined in a water/$scCO_2$ biphasic system using molecular ruthenium catalysts based on the trisulfonated triphenylphosphine ligand TPPTS [30]. Cinnamaldehyde was chosen as a test substrate to assess the chemoselectivity between C=C and C=O double-bond hydrogenation [Eq. (6); TPPTS = $p(m\text{-}C_6H_9SO_3Na)_3$]. In addition to cinnamyl alcohol and the saturated aldehyde, the saturated alcohol would also be a possible reaction product. The biphasic water/$scCO_2$ system gave significantly better conversion and chemoselectivity for the unsaturated alcohol than conventional biphasic systems, such as water/toluene- or single-solvent systems, e.g., pure toluene or $scCO_2$. The beneficial effect of $scCO_2$ was qualitatively attributed to the absence of the gas/liquid phase boundary and improved mass-transport properties.



(6)

The potential of microemulsions for organometallic-catalyzed hydrogenations in water/$scCO_2$ biphasic systems has been assessed using the rhodium-catalyzed hydrogenation of styrene as a common test reaction [Eq. (7)] [31]. The water-soluble Wilkinson complex $[RhCl(TPPTS)_3]$ was applied as catalyst precursor together with anionic perfluoropolyether carboxylates, cationic Lodyne A, or nonionic poly(butene oxide)-*b*-poly(ethylene oxide) surfactants. The interfacial tension is small in the presence of the supercritical fluid and small amounts of surfactant (0.1–2.0 wt.%) suffice to form stable microemulsions. The droplet diameter of the microemulsions varied between 0.5 and 15 µm and a surface area of up to 10^5 m^2 was obtained.



(7)

Table 2 shows the turnover frequencies observed under the conditions of Eq. (7) using a two-phase water/toluene system, a water/$scCO_2$ system, or the surfactant-stabilized microemulsions. To compare the relative catalyst activities, a standardized turnover frequency was defined as the amount of substrate converted per mole of catalyst per hour at 50% conversion. Indeed, a significantly higher activity was found for the aqueous/$scCO_2$ emulsion compared to the other two systems. The activity in the microemulsion system is comparable to the single-phase homogeneous reaction in organic solvents using Wilkinson's catalyst $[RhCl(PPh_3)_3]$ [32].

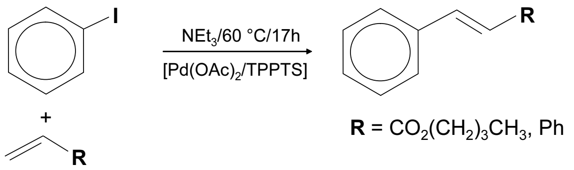
Table 2 Catalyst activity for hydrogenation of styrene using [Rh(TPPTS)$_3$Cl] in various biphasic systems.

System	*TOF*[a)] *[h^{-1}]*
H_2O/toluene	4
H_2O/scCO_2	26
H_2O/scCO_2/surfactant	300

a) Mole substrate per mole rhodium divided by reaction time at 50% conversion.

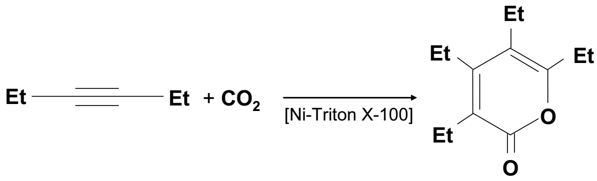
Another advantage of the surfactant-stabilized water/scCO_2 systems over common water/organic emulsions is that they can be broken up readily by pressure variation. In the styrene hydrogenation, reducing the total pressure from 25 to 7 MPa afforded clean separation and it was possible to recycle the catalyst phase at least three times after extracting the product with CO_2 under these conditions.

Another example of a successful transfer of a TPPTS-based catalytic system into water/CO_2 media is the Heck vinylation reaction [Eq. (8)] [33, 34]. Butyl acrylate and styrene were coupled successfully with iodobenzene using a [Pd(OAc)$_2$]/TPPTS catalyst in situ in the presence of scCO_2 at different pressures. The reaction was carried out at 60 °C for 17 h using triethylamine as a base. With a catalyst/substrate ratio of 1 : 200, a maximum turnover number of 36 at a moderate CO_2 pressure of 8 MPa was reached. With ethylene glycol as polar co-solvent instead of water, turnovers of up to 135 could be obtained. Catalyst recycling was achieved by phase separation after complete decompression of the reaction mixture, yielding similar conversions at least three times. Very little metal leaching into the product phase was observed with palladium contaminations below 0.1 ppm.



(8)

Most recently an example of a C–C bond forming reaction in water/scCO_2 emulsion-type systems was also reported for the coupling reaction between 3-hexyne and carbon dioxide forming tetraethylpyrone [Eq. (9)] [35]. A water-in-CO_2 emulsion was employed as the reaction medium, which was formed using a nickel complex of Triton X-100 ($C_8H_{17}C_6H_4O(CH_2CH_2O)_{9.5}H$) as surfactant. In this example the nickel complex acted on the one hand as an emulsion-forming surfactant, but on the other hand also as a water-soluble catalyst. In addition CO_2 has a dual role as the reaction medium and reactant. A yield of 69% after 72 h was obtained, using a surfactant ratio of 0.3 wt.%. This example highlights nicely the possibility of multifunctional solvent systems in catalysis.



(9)

An early example of the use of transition metal complexes as molecular catalysts in water/$scCO_2$ systems is the two-phase oxidation of alcohols, alkenes, and other substrates using high-valent ruthenium oxo species (Figure 6). In this case, the active metal component is not permanently fixed as a catalyst in the aqueous phase, but mediates a stoichiometric oxidation in one phase before it is regenerated in the second phase. Initially, the active species RuO_4 is formed from $RuCl_3 \cdot n\ H_2O$ and the terminal oxidant NaOCl, $NaBrO_3$, or $NaIO_4$ in the aqueous phase. Owing to its volatility, RuO_4 can transfer into the $scCO_2$ phase, where it reacts with the substrate under C=C bond cleavage. The oxidative cleavage of the cyclic alkene to give the corresponding diacid occurs with high selectivity in the presence of water. The reduced metal oxide RuO_2 can return to the aqueous phase, where it is re-oxidized to close the catalytic cycle. Catalytic efficiency was limited to five turnovers after 10 h at 40 °C, which was attributed to deactivation by formation of ruthenium carboxylate and carbamate salts.

The application of aqueous/supercritical biphasic media is not restricted to metal complex catalysis but has proven effective also for enzymatic and whole-cell biocatalysis [36]. In general, water plays an important role in connection with biocatalysis. If water is completely absent, enzymes are often not catalytically active under supercritical conditions [37]. In the literature many examples of biocatalysis with supercritical fluids containing various amounts of water are known and a detailed account of this field is outside the scope of the present discussion. One example to highlight the use of a true biphasic system is the carboxylation of pyrrole

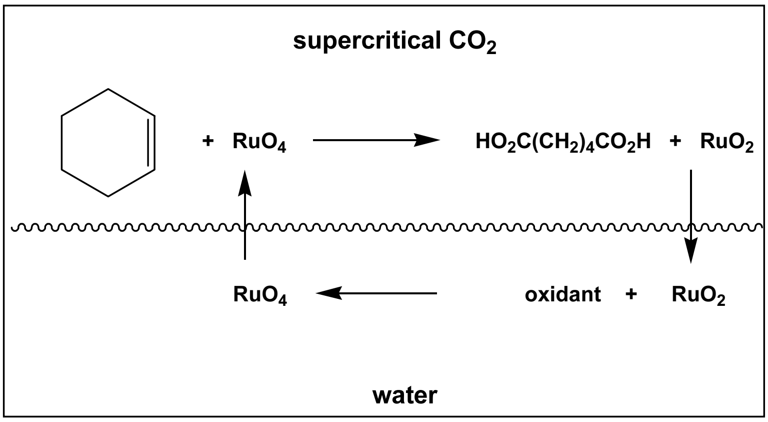
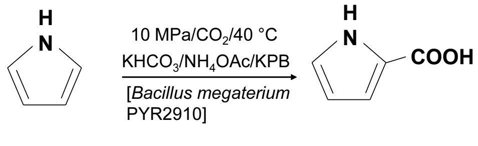


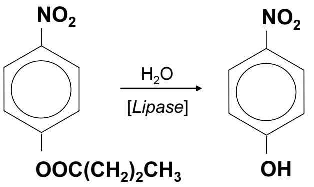
Figure 6 Ruthenium-mediated oxidation of alkenes in $H_2O/scCO_2$.

to pyrrole-2-carboxylate in the presence of $scCO_2$ [38]. The reaction mixture comprised pyrrole, potassium phosphate buffer (KPB), $KHCO_3$, and an aqueous solution of ammonium acetate [Eq. (10)]. Cells of *Bacillus megaterium* PYR 2910 catalyzed the CO_2 fixation from the supercritical state, with the yield of the carboxylation reaction under these conditions being 12 times higher than under atmospheric pressure.

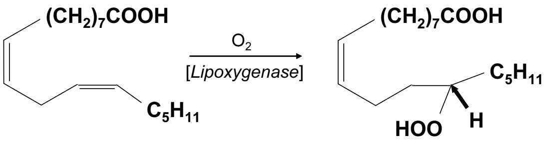


(10)

Bioconversion can also be conducted in water-in-CO_2 microemulsions. In one case, fluorinated two-chain sulfosuccinate surfactants have been used to stabilize microemulsions in which the enzyme was located within the dispersed water droplets [39]. Two reactions, a lipase-catalyzed hydrolysis of *p*-nitrophenol butyrate and a lipoxygenase-catalyzed peroxidation of linoleic acid, were investigated [Eqs. (11) and (12)]. The pH was controlled by the buffer MES [2-(*N*-morpholino)ethanesulfonic acid] in the range of 5–6. Both enzymes showed good activity in the water-in-CO_2 microemulsion, largely identical to that observed in water-in-heptane microemulsions.



(11)



(12)

6.4.4.4
Catalysis in Inverted Biphasic Systems of Type $scCO_2/H_2O$

Catalysis in an inverted biphasic $scCO_2/H_2O$ system forms an interesting alternative to the classical two-phase systems described in the Section 6.4.4.3. It offers especially a possibility of synthesis and conversion of highly polar substances, which is otherwise a general limitation of $scCO_2$-based methodologies. As there are many industrial important examples of fine chemicals and biologically active compounds that are hydrophilic in nature, a method of synthesizing these compounds without the problems of product separation and catalyst recycling seems highly attractive.

From a process engineering point of view, the inverted system has the advantage that the catalyst is immobilized in the supercritical phase, which consequently does not leave the reactor and is not depressurized during the process. This removes one of the most energy- and cost-effective steps from the overall process (see Section 6.3). Cross-contamination of the stationary-phase CO_2 into the mobile-phase H_2O will of course occur, owing to the solubility of CO_2 in water, but is expected to cause no significant problems in any downstream processing. The CO_2-philic catalysts, which require enough absolute solubility and a high partition coefficient in the CO_2 phase to minimize leaching, can be obtained by techniques that are largely identical to those developed for applications under monophasic supercritical conditions (see Section 6.4.1).

A general scenario for exploratory investigations of catalysis in inverted $scCO_2$/aqueous media is shown in Figure 7. The CO_2-philic catalyst is added as a solid to a window-equipped high-pressure reactor that is then charged with CO_2 using a compressor or another mode of CO_2 delivery. Once the catalyst has been dissolved, the aqueous solution of substrates and reagents is added via an HPLC pump to provide the biphasic medium. After the reaction is complete, the aqueous product layer can be removed using a capillary valve or an outlet at the bottom of the reactor. After adjusting the pressure again for possible loss CO_2 if necessary, the reactor is charged again with a new aqueous substrate phase for repeated use of the catalyst phase. Obviously, the system is readily applicable to continuous-flow processing using countercurrent flow techniques as established in liquid/supercritical extraction processes [40].

The principal applicability of this system for catalytic conversion of polar hydrophilic substrates was demonstrated for hydroformylation of bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid monomethyl ester as a model substrate [Eq. (13)] [41]. A CO_2-philic rhodium catalyst was generated using the *para*-subsituted fluoroalkyl derivative of triphenylphosphine, 4-H^2F^6-TPP (**2**). Emulsion-type mixtures were formed under the reaction conditions upon stirring, but the two layers separated rapidly when stirring was stopped. Complete conversion to aldehyde was obtained in 20 h using a rhodium/phosphine/substrate ratio of 1 : 10 : 500. The catalyst was recycled three times without any loss of activity and without the requirement of expansion/recompression of the CO_2 phase, giving a total turnover number of nearly 1500 in three consecutive runs.

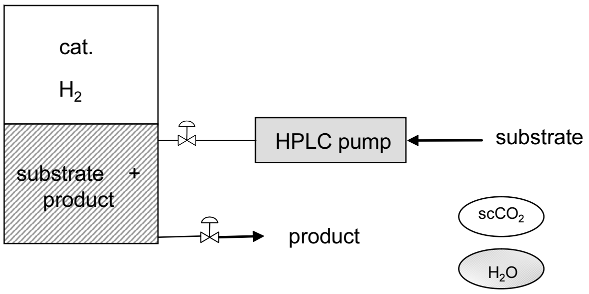
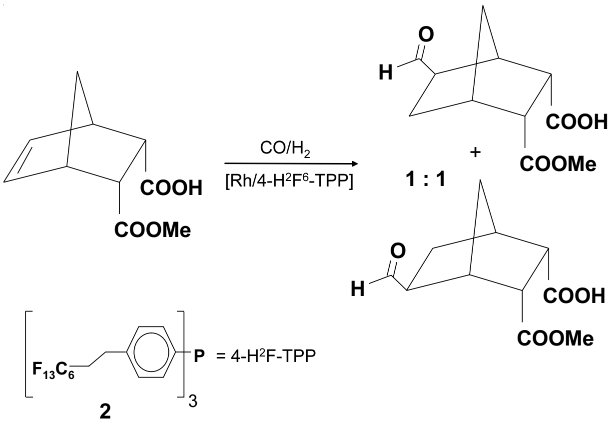
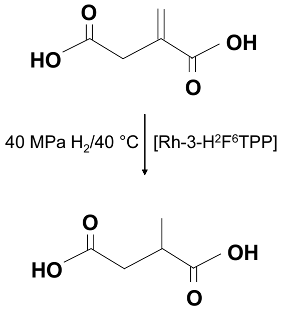


Figure 7 Laboratory-scale setup for catalysis in inverted $scCO_2/H_2O$ biphasic systems.



(13)

At lower rhodium concentrations, the activity of the catalyst decreases, the decrease is probably caused by the low pH of the aqueous solution in the presence of carbon dioxide and the limited stability of the active species of the hydroformylation cycle under acidic conditions. More recently, it has been shown that similar catalytic systems show excellent activity and very promising recycling characteristics in the hydrogenation of α,β-unsaturated carboxylic acids such as itaconic acid [Eq. (14)] [42].



(14)

The generation of hydrogen peroxide directly from H_2 and O_2 in an inverted $scCO_2/H_2O$ system has also been reported [43]. No water-soluble substrate is involved in this case, but the direct reaction of the delicate H_2/O_2 mixture in the safe environment of a large excess of CO_2 is intriguing. Catalysts generated from Pd(II) and Pd(0) precursors in the presence of CO_2-philic ligands such as the one shown in Eq. (13) were explored for the homogeneous formation of hydrogen peroxide in carbon dioxide. The product forms in the supercritical phase but is transferred into the aqueous phase immediately (Figure 8). As H_2O_2 is handled, shipped, and used in aqueous solution, no further work-up of the water phase is required if the conversions are high enough.

An interesting extension of this concept is to use a $CO_2/H_2/O_2/H_2O$ mixture containing a catalyst for H_2O_2 formation in the CO_2 phase directly for the epoxidation of alkenes [44], e.g., in a direct synthesis of propene oxide (Scheme 2) [45]. It has been shown that H_2O_2 will react with aqueous bicarbonate to form percarbonate

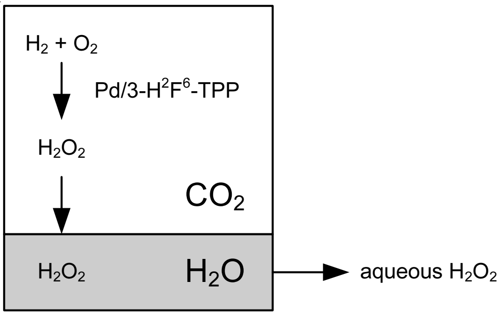
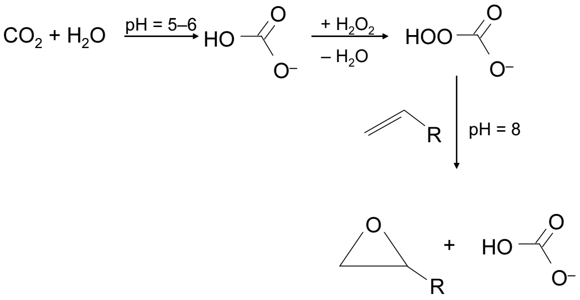


Figure 8 Catalytic reaction of hydrogen and oxygen to give aqueous hydrogen peroxide in an inverted biphasic $scCO_2/H_2O$ system.

(HCO_4^-) and that this species will perform epoxidations of hydrophilic alkenes in the presence of base [46]. To reduce transport limitations between the hydrophobic alkenes in CO_2 and the reactant formed in situ in the aqueous layer, phase-transfer catalysts such as tetraheptylammonium bromide may be used and increase the reaction rate. Similarly to what has been found for conventional $scCO_2/H_2O$ systems, it is also possible to increase the interfacial area by addition of fluorinated surfactants.



Scheme 2 $H_2O_2/H_2O/CO_2$ formed in situ as an epoxidizing agent.

6.4.4.5
Outlook and Conclusion

The combination of $scCO_2$ and water provides a truly benign reaction environment for sustainable chemical synthesis. This “green” biphasic mixture does not impose any environmental or toxicological hazards and will result in products that are *a priori* free of any organic solvent residues. The possibility of varying the position of catalyst and substrate in the more conventional or the inverted setup makes it possible to process substances of a wide range of polarities, including highly functionalized hydrophilic compounds. Together with the advantageous mass-transfer properties, the system seems to be an attractive alternative to classical aqueous/organic media for fine chemical and pharmaceutical synthesis, especially in cases where gaseous reagents are involved.

In addition, to demonstrate the reaction principle for a wider range of applications including in particular asymmetric catalysis, future efforts will be directed toward the utilization of the chemical characteristics of the system in synthetic procedures. The carbonic acid equilibria (Scheme 1) provide many opportunities to interact directly with substrates, products, or catalytically active intermediates as, for example, demonstrated in Scheme 2. Up to now, the main focus has been to avoid detrimental interference of such processes in the reactions under scrutiny. As our understanding of the mechanisms and catalytic cycles in this medium increases, it should, however, become more and more possible to take advantage of the CO_2/H_2O reactivity similarly to the interaction of $scCO_2$ with secondary amines [47, 48].

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6.5
Economics and Scale-Up

Peter Licence and Martyn Poliakoff

6.5.1
Introduction

The preceding examples in Chapter 6 of biphasic catalysis using supercritical fluids (SCFs) include, inter alia, hydroformylation [1, 2], hydrovinylation [3], and enzymatic resolution [4]. Unfortunately, technical elegance is not enough! There are numerous examples in the electronics industry, including personal computers, VCRs, etc., where the ultimate market leader was not necessarily the most elegant of the competing technologies.

In chemical manufacturing, the situation is very much worse. It is inherently a rather conservative industry that is currently under attack on all fronts: the increasing price of oil is raising the costs of both feedstocks and energy; some industrial sectors already have an overcapacity in their existing facilities; the public perception of chemicals has never been lower, and the weight of environmental legislation is ever increasing; the cost of waste disposal is soaring; traditional chemicals manufacturers are being undercut by new manufacturers in developing countries whose plants are often newer and therefore more efficient. It is against this background that SCF processes must make the leap from laboratory to commercial plant.

Not everything is gloomy. Supercritical CO_2 ($scCO_2$) already has several profitable commercial – not chemical related – applications (see Section 6.2) [5, 6].

Some years ago, Beckman and co-workers listed a series of desirable process characteristics (1) and key constraints (2) that they believed were prerequisites for commercial success [7].

(1) Process Characteristics that May be Amenable to the Application of $scCO_2$

a) *Food/Pharmaceutical processing*: the application of FDA-approved CO_2 can minimize regulatory hurdles and concerns of liability.
b) *Application of gaseous reagents*: elimination of the gas–liquid interface can lead to a considerable acceleration in reaction kinetics as mass transport is minimized.
c) *Minimization of environmentally damaging solvent emission*: CO_2 could be used in polymer foaming, dry cleaning, paints and coatings, etc.
d) *Contact between hydrophilic and hydrophobic phases:* $scCO_2$ technology could minimize cross-contamination.
e) *Sequestration of CO_2:* if CO_2 could be successfully activated, it would become a wonderfully attractive, renewable C_1 building block.
f) *Polymer processing:* $scCO_2$ provides a benign and reversible methodology, ideal for application with thermally labile systems.

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(2) Process Constraints that Aid the Reduction of Both Capital and Energy Costs

a) *Minimization of the operating pressure:* employing CO_2-philic materials whenever possible can greatly reduce capital costs.
b) *Avoidance of large pressure reduction steps:* this would result in cost reduction in product recovery and recompression.
c) *Recycling of CO_2-philic materials whenever possible:* they are often much more expensive than their conventional analogues.
d) *Application of continuous processes*: in general, this greatly reduces the volume of reactors.
e) *Minimization of CO_2 flow rate:* operation in more concentrated solution will reduce the size of the reactor and pumps, thereby reducing the capital cost.

If one considers these key points, it can be seen that decaffeination exhibits characteristics 1 a), 1 c) and 1 d), and constraints 2 b) and 2 d) are also obeyed. The whole situation was succinctly captured by SCF pioneer Val Krukonis, who stated, “There is no point in doing something in a supercritical fluid just because it’s neat. Using the fluids must have some real advantage.” And in this case, advantage does not just mean “technical or scientific elegance”.

6.5.2
Technical Issues

There are a number of issues that make the scale-up of SCF processes somewhat different from the scale-up of more traditional chemical processes. The first is that SCF processes must necessarily be continuous, largely because the cost of large-scale batch reactors would make the cost of all but the smallest plants economically unfeasible (Beckman’s constraint 2 d). That said, vessels of up to 500 L are regularly used in SCF extraction but they are not subject to the corrosive conditions that accompany many chemical processes. Continuous reactors demand that processes should be run at the highest possible temperature, thereby maximizing the throughput of a reactor of a given size. High temperatures may add further costs or constraints on the construction of the reactor and inevitably on day-to-day energy costs.

By far the most complicated aspect of SCF reactions is that of phase behavior, or more accurately vapor–liquid equilibria. Of course, by its very nature, biphasic catalysis will involve two phases. However, as explained in more detail in Section 6.1, the “SCF phase” may itself consist of both a vapor and a liquid phase. Initial phase equilibria studies have demonstrated that these are not necessarily pure $scCO_2$ and liquid organic phases, but complex mixtures of CO_2, reactants, products, and additional catalyst phases such as ionic liquids. Indeed some reactions, e.g., the acid-catalyzed condensation of simple alcohols, can also give rise to an aqueous phase. Furthermore the composition and whole phase equilibrium will change as a reaction proceeds [8a]. This means that, in a batch reactor, the phase behavior will change with time, whereas, in a continuous reactor, it will change along the length of the reactor.

The key point is that, in general, the phase behavior of a given reaction system will not be known prior to the development of that process. Moreover, in those cases where data are available in the literature, they often refer to mixtures far more dilute than would be used in a commercial process. In such a process, energy and plant costs will clearly dictate that the reaction mixture should contain the minimum amount of SCF (see Beckman's constraint 2 e). This contrasts with SCF extraction, where the concentration of the extract dissolved in the SCF is determined, at least in part, by the mass-transport kinetics on the matrix material. All of these factors mean that the phase behavior of the reaction mixture will usually have to be determined by experimental methods.

Knowledge of the relevant phase behavior is important for several reasons. Much of the detailed chemical engineering of the plant will depend upon the phase state of the reaction mixture. In the present case, totally different separation strategies will clearly be needed for a system where the catalyst is in a liquid phase with all other components being in the gas phase, and a system with two (or more) liquid phases plus a gas phase. In addition, heat transfer is phase-dependent; liquids conduct heat much better than gases and the thermal capacity of reaction mixtures close to their critical point can be anomalous. Finally, the outcome of a few reactions is phase-dependent, with SCF biphasic systems giving different products from homogeneous monophasic systems.

The need to understand phase behavior itself gives rise to a number of technical problems. Firstly, all SCF experiments are carried out under relatively high pressures, typically 5–20 MPa, and most high-pressure equipment is made of opaque materials, e.g., stainless steel. Although it has recently been demonstrated that phase separation can be detected with sensors [8b], most phase observations are made with the help of windows, usually sapphire or borosilicate glass [6, 9]. However, even when high-pressure apparatus does incorporate windows, the windows rarely allow the whole reactor volume to be observed and so phase separation could be occurring in a "hidden" part of the system. Chemical engineers frequently rely on calculations to predict the phase state of reaction mixtures but, unfortunately, many of the databases used for such calculations do not reproduce accurate phase behavior (or other properties) close to the critical point. This is an area which clearly needs to be resolved because phase observations are too time-consuming to be made for every possible case and reliable calculations are vital to the rapid progress of supercritical reactor engineering.

Beckman's point 1 b) highlights the potential advantage in using gaseous reagents, such as H_2 for hydrogenation, in $scCO_2$ reactions. The original rationale for using gaseous reagents was the complete miscibility of permanent gases with SCFs, which gives rise to enhanced concentrations of dissolved gas, often up to one order of magnitude higher than in conventional solvents. Experiments by Nunes da Ponte's group [10–12] and recent calculations by Beckman and co-workers [13] have shown that this view is simplistic (see below for more discussion of this point). However, it remains true that $scCO_2$ and other SCFs do appear to enhance reaction rates dramatically through a complicated set of synergistic effects which together cause a dramatic increase in rates of interphase transport. $scCO_2$ has a further advantage in the case of oxidation with gaseous O_2, namely that unlike most traditional solvents, CO_2 is oxidatively inert and therefore nonflammable.

There are further technical issues which need to be addressed before SCF reactions can be scaled-up effectively and SCF processes can become widespread. For example, some of the reactions described in Section 6.3 have involved sophisticated catalysts which have only been prepared on a “research scale” and scaling their production up to commercial scale might in itself present technical challenges. Some of these reactions use ionic liquids to immobilize the catalysts and, as has been widely mentioned, there are still significant uncertainties in the toxicological issues surrounding the large-scale use of these liquids as well as a more general life-cycle assessment of their use. Finally, a recent UK report by the CRYSTAL Faraday Partnership highlighted the lack of “readily available bench top trial equipment” as one of the key barriers to the wider implementation of new, greener technologies in the chemical industry [14]. There is a clear need for increasing efforts in this area to create more widespread acceptance of SCF technology in catalysis.

6.5.3
Economic Issues

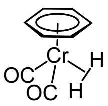
The principal economic factors facing the introduction of SCF processes into the chemical manufacturing industry are similar to those facing any new technology. In a paraphrase of Krukonis’s statement (see above), “being green is not enough; any successful SCF process has to give real economic advantage or a greatly improved product”. Unfortunately, there are few precedents in the form of processes that are already operating, on which engineers can base their projections of the costs of new SCF processes. Obviously, a dominant cost is likely to be energy and, therefore, energy-efficient design will always be crucial.

There are, however, also other aspects in chemical manufacture that govern the economics of a process to a large extent. It can be, for example, a particular intermediate or by-product which is extremely troublesome to remove from the final product, so that any process which reduces or eliminates the formation of this compound could revolutionize the manufacture of that product. Unfortunately, even other chemical manufacturers are not necessarily aware of the key problem in the production of a given compound. Therefore, it is not surprising that most academic researchers do not know which problem currently dominates the economics of any given chemical process. However, the implication is that an SCF process could offset the increased cost of high-pressure processing by generation of such increased purity, thereby reducing the complexity of downstream processing, or even totally eliminating the need for it. Indeed it was this aspect that led to the success of the hydrogenation of isophorone, one of the relatively few SCF reactions which has made the transition from laboratory to production scale, in this case 1000 tpy (see Section 6.5.4). Thus, although the isophorone process involves heterogeneous rather than biphasic catalysis, we describe it here to highlight some of the generic problems which are likely to occur in the scale-up of most SCF processes [15].

6.5.4
The Commercial Scale-Up of the Hydrogenation of Isophorone

6.5.4.1
The Starting Point

The implementation of the hydrogenation of isophorone on a technical scale is a good example of successful new technologies [16, 17]. Originally, however, our motivation for carrying out chemical reactions under supercritical conditions was to provide a better route for the photochemical generation of unstable organometallic dihydrogen [18] and dinitrogen [19, 20] complexes such as **1**–**3** [19]. One of the keys to the success of this early work was the relatively high concentrations of H_2 and N_2 that could be readily achieved because, as explained above, such gases are totally miscible with most SCFs. This concentration effect was later exploited for catalytic hydrogenation in SCFs by Noyori [21] and others [22].



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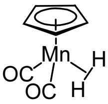

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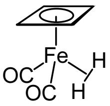

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All of these reactions [19] were initially carried out in small spectroscopic cells (volume < 2 mL) which afforded little chance of isolating the "unstable" products, even though many of them appeared to be surprisingly long-lived. This meant that miniature continuous reactors had to be devised for carrying out such reactions on a preparative scale [23–25], which subsequently enabled a number of novel ethene and dihydrogen complexes to be isolated, one of the few occasions when *new* compounds have been successfully isolated with the aid of SCFs [19].

A key aspect to scale-up was a strong and effective collaboration between academia and industry. In this case, collaboration began in a most unusual way. The organometallic work at the University of Nottingham was included by David Bradley in his *New Scientist* feature article [26] on SCFs entitled "Solvents get the Big Squeeze". The article covered a number of applications of SCFs, ranging from the decaffeination of coffee [5] to the development of new reactions and polymerization techniques [27]. Crucially to this project, it also included M. Poliakoff's semi-humorous vision of SCF chemistry in the future as being "as simple as operating a drinks vending machine. The chemist will simply press a button and the machine will add the appropriate reagents to the supercritical CO_2 and pump the mixture into the reactor." This frivolous statement caught the eye of Professor Tom Swan, owner of the fine chemicals manufacturer, Thomas Swan and Co. Ltd., who recognized the potential that such "dial a chemical" technology could bring to his business. He was also attracted by $scCO_2$ as a cleaner solvent because, at that time, it was feared that all chlorinated solvents might be banned. He contacted us at the University of Nottingham, nine months of discussions began, and a collaboration was set up.

6.5.4.2
The Strategy

It was decided to target continuous hydrogenation in $scCO_2$ using heterogeneous catalysts. This built on existing expertise [23, 24] in constructing flow reactors involving H_2. Thomas Swan and Co. Ltd., did not have any hydrogenation equipment and therefore, if successful, the project would lead to a new capability for the company. This again was an important point; it is always easier to introduce a new technology if there is no need to justify the replacement of pre-existing equipment. Heterogeneous rather than homogeneous catalysis was chosen because it was experimentally simpler and there were more obvious routes to scale-up under high-pressure conditions. The objectives were ambitious.

It rapidly became clear that a multidisciplinary team would be required, including organic chemists, high-pressure engineers, and catalyst developers. Thus, links were formed, at an early stage, with the German catalyst manufacturers Degussa AG, who had experience of catalysis in SCFs [28], and with Dr K.-H. Pickel, whose company, NWA GmbH, specializes in the manufacture of high-pressure SCF apparatus [29, 30].

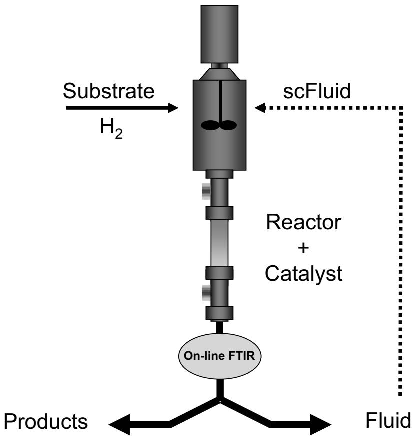
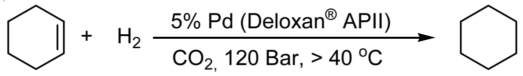


Figure 1 Block diagram of the key components of the continuous reactor for hydrogenation of organic compounds at Nottingham [31]. $scCO_2$, H_2 and the organic substrate were mixed in a heated mixer. The mixture was then passed through a reactor containing a fixed bed catalyst (usually a supported noble metal). There was optional on-line FTIR monitoring before the product and CO_2 were separated by expansion. More recent reactors have used static rather than mechanical premixers.

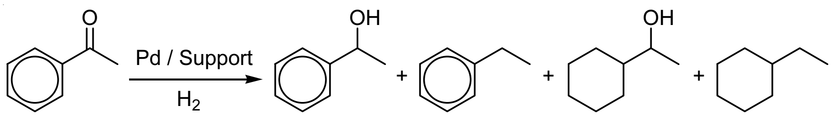
6.5.4.3
Proof of Concept

The project started in November 1995. The first reaction involved the hydrogenation of cyclohexene in $scCO_2$ [Eq. (1)]. The results were striking, with a quantitative conversion being observed. The reaction proceeded with a very high linear hourly space velocity (LHSV) (e.g., 300 h^{-1} from a 5 mL reactor) [31, 32], equivalent to a rate of 1200 mL h^{-1} or 7.5 tpy.



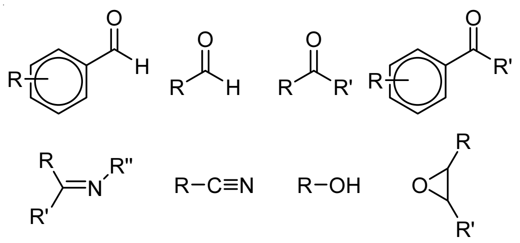
(1)

These results complemented those of Härröd and co-workers, who were working on the hydrogenation of oleochemicals in sc propane [33, 34]. A detailed investigation at the University of Nottingham into the hydrogenation of acetophenone [Eq. (2)] showed that $scCO_2$ allowed reaction conditions to be optimized very effectively to maximize the yield of particular hydrogenation products [31]. An interesting aspect was that the reactor delivered product free from any solvent. Thus, early in this project, all analysis was performed merely by diluting the product with deuterated solvent and running the ^1H NMR spectrum [31, 32]. Later, the analysis was switched to more conventional methods, e.g., GC-FID and GC-MS.



(2)

The range of functionalities which could be hydrogenated in this way was quickly extended [31] and soon included those shown in Scheme 1. Most of these could be hydrogenated with high selectivity. There were some limitations, inherent to $scCO_2$, particularly the fact that aliphatic amines react with CO_2 to form insoluble carbamates [6, 35], which effectively terminate the reactions by precipitating and blocking the reactor.



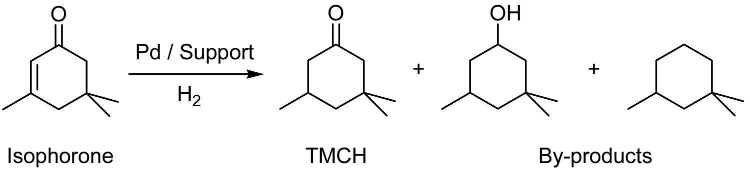
Scheme 1 Some of the functionalities that have been successfully hydrogenated under supercritical conditions as part of our project.

6.5.4.4
Extending the Chemistry

It was quickly realized that the SCF reactor was not restricted to hydrogenation reactions and could, in principle, be adapted to any type of solid or supported catalyst. Successful reactions included Friedel–Crafts alkylation [36], etherification [37], hydroformylation [38], and base-catalyzed transesterification [39].

6.5.4.5
Development of the Process

It was now important to identify a model compound, which could be used by the two laboratories, at the University of Nottingham and Thomas Swan and Co., as the basis for developing a viable SCF process. It was also important to choose a reaction of potential commercial interest where the ease of optimization in $scCO_2$ could be exploited. The chosen reaction was the hydrogenation of isophorone to trimethylcyclohexanone (TMCH) [Eq. (3)] [40]. This reaction is a good model because the industrial end-users require high-purity product. The problem with conventional hydrogenation technologies is that they can easily lead to a mixture of TMCH and the over-hydrogenated byproducts, trimethylcyclohexanol and trimethylcyclohexane. All of these compounds, and isophorone itself, have similar boiling points, and the need to separate and purify TMCH from these mixtures adds greatly to both the cost and the environmental impact of the overall process.



(3)

The reaction was initially carried out on a laboratory scale at the University of Nottingham, where it was found that conditions in $scCO_2$ could be adjusted to give quantitative conversion of isophorone to TMCH at a rate of up to 7 mL min^{-1} [40]. Clearly, if this process could be scaled up, one would eliminate the need for any purification steps following the hydrogenation.

6.5.4.5.1
Choice of Catalyst

The initial studies were carried out using catalysts supported on Deloxan®, a polysiloxane material from Degussa [28]. Deloxan® was found to be very durable and gave a good catalyst lifetime with up to 3 kg of product produced per gram of catalyst without significant loss of selectivity [40].

Then, there was a major setback. The Deloxan® range of catalysts was suddenly withdrawn from commercial production; an alternative source of catalysts was urgently required. After a variety of catalysts had been screened, it was evident that a wide range of conversions and catalyst lifetimes could be obtained for a given noble metal, depending on the nature of the support. It was quickly recognized that the key criterion was the yield of TMCH *per g of Pd* rather than the yield *per g of catalyst*. These results supported previous work carried out by Hutchenson et al. in that Deloxan® outperformed most other catalysts with respect to conversion [42]. Eventually, alternative catalysts were identified that gave excellent catalyst life whilst retaining a level of conversion and product selectivity comparable to those of

Table 1 Catalyst screening results for the selective hydrogenation of isophorone to trimethylcyclohexanone (TMCH).

Catalyst	*Pd loading [%]*	*Yield*		*Selectivity [%]*
		[kg TMCH/g cat.]	*[kg TMCH/g Pd]*	
Deloxan®	Pd 5	3.0	60	100
A	Pd 5	0.4	8	91
B	Pd 2	1.2	60	100
C	Pd 2	1.1	55	> 99
D	Pd 5	3.0	60	98
E	Pd 2	0.05	1	94

Deloxan®; see Table 1. Here again, there is an important lesson for scale-up of biphasic catalysis. An apparently small change in catalyst supplier caused a major change in the process economics.

6.5.4.5.2
Reaction Optimization

Reaction optimization was accomplished in a reactor device (optimized conditions: 0.85 cm × 25 cm long; catalyst 2% Pd; temperature at inlet 56 °C, at outlet 100 °C; hydrogen 1.7–2.75 equiv.; substrate feed 2–48 wt.%). Supercritical reactions generally involve high pressures and considerable compression costs, in contravention of the sixth principle of Green Chemistry [16, 43].

6.5.4.5.3
Phase Behavior

Considerable scientific argument has arisen around the question of whether supercritical hydrogenation reactions proceed faster and more efficiently in either a single or multiple phases; indeed conflicting reports have been published [44–47]. Much of this debate has revolved around the LHSV of a reaction, but this parameter only addresses part of the issue from an industrial perspective. Other important factors which have to be taken into account include catalyst lifetime, overall conversion, and product selectivity, as well as the solvent compression costs need. The situation has been at least partly resolved by a key paper by Nunes da Ponte and co-workers [10]. They have shown that biphasic reactions can sometimes be faster than monophasic ones, because the concentration of substrate (as opposed to H_2) is lower under monophasic conditions.

A study was undertaken of the phase behavior of four mixtures of varying isophorone/CO_2/H_2 composition across six experimentally determined isotherms at 40, 60, 80, 100, 120, and 140 °C. This established the boundary between the one- and two-phase regions of the phase diagram for this system; see Figure 2.

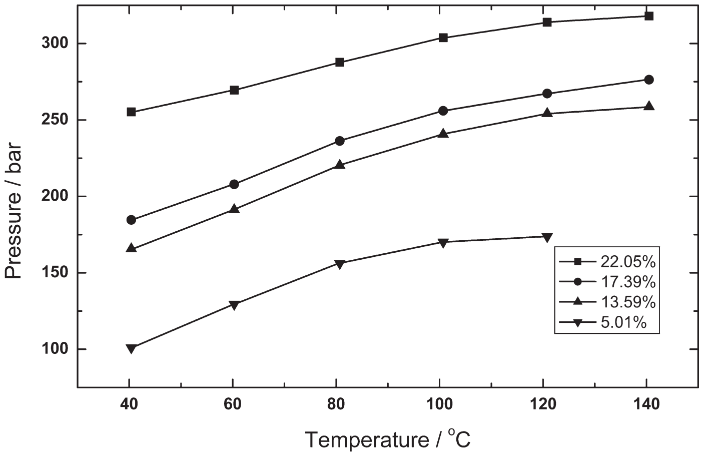


Figure 2 Experimentally determined phase boundaries of four mixtures of isophorone/CO_2/H_2 of varying composition (isophorone 5–22% wt.%; isophorone/hydrogen molar ratio was fixed at 1 : 1.7). N.B. 100 bar = 10 MPa.

The measurement of these phase equilibria clearly reveals that, for mixtures with a composition in excess of around 5% isophorone, quite substantial pressures and temperatures are required to render the system monophasic, a condition that has been reported to be essential for efficient and rapid hydrogenation [46]. By contrast, it has been shown that this reaction can be carried out with excellent selectivity and conversion with as much as 50% isophorone in the reaction stream, conditions that are clearly not single-phase. Furthermore, when conditions that facilitate single phase reactions are employed, a loss of desired product selectivity is observed as the high temperatures that are required often lead to the formation of unwanted side products.

6.5.4.6
The Plant

Figure 3 shows the schematic design of the plant. It has a production capacity of ca. 100 kg h^{-1} (1000 tpy). It therefore represents a ×400 scale-up of the laboratory reactor in terms of production.

The plant is multipurpose. The catalysts within the reactor can be changed to alter the chemistry. A view of the actual reactors may be seen in Figure 4. The plant, which is designed to work only with CO_2 as the SCF, went on stream in June 2002 (a rather smaller plant for reactions in supercritical propane has recently been built in Göteborg [46]).

The hydrogenation of isophorone was the first reaction to be run on the plant. The optimized conditions are catalyst 2% Pd; temperature isothermal 104–16 °C; hydrogen 1.7 equiv.; substrate feed 9–17 wt.%. It is immediately clear that these conditions are very close to the optimized conditions in the laboratory. If this transferability applies to other reactions, it will have considerable significance;

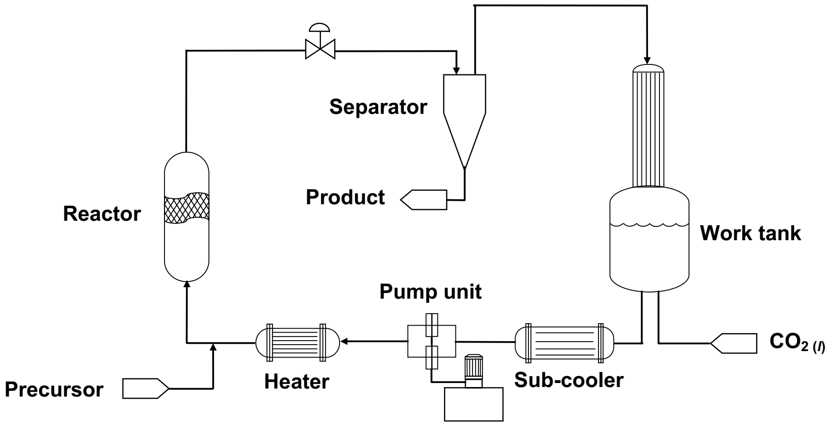


Figure 3 Schematic flow diagram of the SCF plant at Thomas Swan and Co. Ltd., constructed by Chematur Engineering.

Figure 4 The reactor array in the SCF reactions plant at Thomas Swan and Co. Ltd.

reactions can be optimized in the laboratory and transferred almost directly to the plant. It is not always apparent to academic researchers that the specification of a commercial chemical product can be much wider than the purity criteria used in typical journal publications. Thus Table 2 summarizes the customer specifications for TMCH and an actual analysis of the raw product, direct from the plant.

Table 2 Customer specification and product analysis for TMCH produced under supercritical conditions.

Specification	*Customer*	*Swan SCF*
Colour [Hazen scale]	10 max	< 10
Assay [%]	99 min	99.4
Trimethylcyclohexanols [%]	1 max	0.3
Isophorone [%]	0.4 max	0.08
Acid value [(mg KOH) g^{-1}]	0.1 max	0.08[a)]

a) Value measured after discharge of dissolved CO_2; corresponding value before discharge was 8.

It can be seen that the product exceeded the specification in all five categories, although the acid value is only reached after residual CO_2 is removed by a brief application of vacuum. Thus, in the case of TMCH, SCF technology has eliminated the need for any downstream purification of the product.

6.5.5
Conclusions

Overall, this project has demonstrated what can be achieved by a committed academic/industrial partnership. Much of the success has been due to the drive and vision of a relatively small private company which was unfettered by the demands of public stockholders. Most SCF processes, including those described in this chapter, will have to face more conventional economic tests. Therefore, the most exciting phase is just beginning for our process. The technology works; now the key is to demonstrate whether it is commercially competitive. Such demonstrations are vital to the future of multiphase catalysis and Green Chemistry. New and cleaner methodologies will only result in sustainable technology if they also provide genuine commercial advantages.

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6.6
The Way Ahead: What Should be Done in the Future?

Walter Leitner

Research in the area of using supercritical carbon dioxide ($scCO_2$) for organometallic catalysis has been prolific since the mid-1990s, and a broad range of reaction types can be performed effectively in CO_2 to date. In a significant number of cases, catalyst performance is observed to have been improved compared to conventional organic solvents, and certain general patterns are starting to emerge of which reactions might benefit most from the unique physico-chemical properties of this reaction medium. The examples discussed in the previous sections of this chapter are not intended to give a comprehensive overview of these various potential improvements, but concentrate on catalyst immobilization as the most general theme associated with the use of $scCO_2$ and its tunable solvent properties. Nevertheless, several key features should become evident also from this selection.

Clearly, the use of $scCO_2$ as an innocuous material can have straight practical advantages over toxic, ecotoxic, flammable, or otherwise potentially hazardous solvents. However, these advantages have to be balanced against the requirements of using high-pressure technology and the energy input necessary for compression of large volumes of gas. If a process runs perfectly in toluene under ambient pressure at moderate temperatures, there will be little impetus to substitute this with any unconventional reaction medium. If a reaction is severely limited by mass-transfer issues or if a delicate reaction mixture involving, for example, molecular oxygen has to be handled, it may well be justified to contemplate the use of $scCO_2$ to ameliorate such problems. It may well be that additional benefits such as pressure tuning, altered selectivities, or using CO_2 as a protective medium can be identified if research is invested into such systems.

Most importantly, however, it seems that the utilization of $scCO_2$ in catalysis holds considerable promise in a paradigm shift that is ongoing in process development in various areas of chemical production. There is a strong tendency to look for intensified processes that enable chemical transformations on various scales in flexible continuous-flow processes where reaction and separation techniques can be integrated and automated in a compact unit. Here, the combination of gas-like mobility properties and liquid-like solvent properties of $scCO_2$ are of particular value. Flow reactor concepts that would previously have been restricted to gaseous reactants can now be adopted for liquid or even solid substrates, provided that they have sufficient solubility in the supercritical mobile phase. The highly increased space–time yields of such approaches compared to classical batchwise techniques makes the use of high-pressure equipment less of a hurdle. Notably, the equipment required for such systems is available from supercritical chromatography or natural product extraction on various scales almost “off the shelf”.

Nevertheless, the engineering aspects of organometallic catalysis in $scCO_2$ have received little attention so far. Whereas the principle set up for solid-phase-bonded

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organometallic catalysts in $scCO_2$ would be largely identical to that already used on a technical scale for heterogeneous catalysis, reactive liquid/supercritical biphasic systems are less well understood. There are very few data on diffusion rates and mass-transfer properties in such systems, factors which are of course crucial for transporting substrates to and products from the active centers in the stationary phase. These parameters will strongly depend on the nature of the liquid support as well as the conditions (temperature, density) of the mobile CO_2 phase. Fundamental investigations of this type on real reacting systems would help to provide important background for possible engineering solutions.

An intriguing bridge between the liquid/supercritical and solid/supercritical systems is provided by the use of so-called supported liquid-phase catalysts. In these systems, a thin film of a generally polar and low-volatile liquid is dispersed on the surface of a solid support. The catalyst is then dissolved in this liquid film, but the morphology of the material is governed by the properties of the support. Interestingly, the liquids used in such systems include water, PEG, and most recently also ionic liquids. So far, these systems have been successfully introduced with organic solvents, and it appears highly attractive to combine them also with $scCO_2$ as mobile phase.

Another area of continuing importance is the design and synthesis of organometallic complexes with the correct solubility properties to partition with high specificity into the desired phase. The classical "similis similibis solvuntur" principle applies also to $scCO_2$/liquid biphasic systems, but the requirements to render a complex "CO_2-philic" or "IL-philic" are significantly different from those in conventional solvents. A frequently encountered case is the persistent myth that low polarity will always be equivalent to high $scCO_2$ solubility. In fact, it has long been known that volatility is another, at least equally important factor: whereas a methyl or ethyl group in the right position may still enhance CO_2 solubility, longer alkyl chains beyond C_5 will rapidly decrease the solubility even below that of the parent compound. It is also a challenge to develop efficient and economic synthetic strategies to generate the desired structures.

The mechanistic understanding of the chemical transformation in $scCO_2$ either alone or in combination with another phase is also a prerequisite for further progress in this field. In-situ spectroscopic techniques as well as indirect methods such as kinetic measurements or labeling studies can help to unravel the molecular interactions. In many cases, they will not be fundamentally different from those in conventional solvents, but even seemingly small shifts in equilibria or changes in rate constants of individual steps can result in dramatic effects on the overall catalytic cycle. Furthermore, the established reactivity of CO_2 toward many organometallic fragments indicates that $scCO_2$ will not always behave just as an innocent solvent but may get directly involved in the reactions.

Although the main focus of the present volume is organometallic catalysis, it has been noted on several occasions that the principles discussed here and the challenges outlined above are not restricted to this subdiscipline of catalysis. For example, it may be interesting to note that $scCO_2$ has found attention as a reaction medium for biocatalysis even before the first reports on organometallic catalysis in this medium were published. This area is likely to see a flourishing development as only a limited range of enzymatic reactions – mainly lipase-based – have been explored so far. Furthermore, the rapidly expanding field of organocatalysis is faced with almost identical engineering problems to those of homogeneous organometallic catalysis. Again, $scCO_2$ may hold much promise there.

It should be obvious, from the discussion in this brief summary, that only an interdisciplinary approach will lead to significant progress in the field of catalysis in $scCO_2$. Synthetic chemists, engineers, biochemists, physico-chemists – they all can make important contributions in this area. All these efforts are necessary, but not sufficient to carry this area from science to innovation. This will require in addition the willingness and devotion of individuals to take risks and to introduce novel technologies. The examples described in Sections 6.2 and 6.5 of this chapter seem to strongly support the optimistic view that this is a worthy challenge.

7

Soluble Polymer-Bound Catalysts

Stefan Mecking (Ed.)

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7.1
Introduction

Stefan Mecking

7.1.1
General Background

The immobilization of metal complexes to be used in homogeneous catalysis was investigated at an early stage, in order to adapt their handling and separation from the products after a catalytic reaction to resemble those operations for the more widespread heterogeneous catalysts. Very soon after the discovery of Wilkinson's complex and its catalytic properties [1], the heterogenization of well-defined transition metal complexes on solid supports was already being investigated intensively [2]. Since then most approaches for immobilization of metal complexes have employed microporous organic or inorganic solids [3–5]. However, such heterogeneous catalyst systems are of limited practical utility to date. A limited diffusion of the substrates within the microporous support materials is disadvantageous. Also, the cross-linked copolymers used mostly as organic supports possess a heterogeneous structure consisting of domains of greatly differing composition, and their mechanical stability is limited in longer-term use [6]. As a possible alternative, binding of metal complexes to soluble polymers and other colloidally dispersed systems has captured the interest of academic as well as industrial research groups.

The concept of binding catalytically active metal complexes to soluble metal complexes was brought forward by Manassen in the 1970s [7]. Results of hydroformylation and hydrogenation with rhodium complexes bound to phosphine-modified soluble polystyrenes were communicated by Bayer and Schurig soon afterward [8, 9]. It was not until ten years later that Bergbreiter initiated a broader investigation of the topic [10, 11], and since the mid-1990s the field has begun to attract a broader interest in academia as well as industry [12–14].

The separation of polymer-bound catalysts from a (single-phase, homogeneous) reaction solution after catalysis by means of properties specific to macromolecules is an alternative to homogeneous two- or multiphase catalysis as described in Chapters 2 to 6. Such specific properties, allowing for differentiation between the polymer-bound catalysts and low molecular weight compounds in the reaction mixture (products, substrates, and solvent), could be the dependence of polymer solubility on solvent composition or temperature. Another option is a separation based on the large difference in "size" of the dissolved species, by means of ultrafiltration. These approaches, which are the subject of this chapter, can be differentiated from the use of polymers as mere solubility-impeding groups in ligands for two- or multiphase catalysis. An example of the latter is the replacement of the sulfonate groups in the archetypical TPPTS by nonionic poly(ethylene glycol) chains. Such catalyst systems are treated in various other sections of this book and are beyond the scope of this chapter.

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7.1.2
Structure and Synthesis of Soluble Polymeric Supports

In linear polymers, catalyst binding can occur by coordination of the metal centers with two functional end-groups or with functional moieties (S) pendant on the polymer backbone chain (Figure 1). The latter approach obviously offers the advantage of higher possible loadings. A somewhat less common case is the coordination of the metal centers by heteroatoms which are directly part of the polymer backbone. The most prominent examples of the latter are (linear or branched) poly(ethylene imine)s with repeat units $–CH_2CH_2NR–$.

A variety of linear polymers have been employed as catalyst supports with functional groups serving as ligands covalently attached as end-groups or to the polymer backbone, e.g., polystyrene [8] and low molecular weight polyethylenes [15], and also polymers which can be water-soluble, such as poly(ethylene glycols) [16] or poly(*n*-alkylacrylamides) [17]. In addition to these organic polymers, polymers with an inorganic backbone have also been studied, most notably polysiloxanes [18, 19].

Concerning polymer synthesis in general, the functional groups which will represent the ligands for the metal center at a later stage in catalysis can be introduced by homo- or copolymerization of the corresponding substituted monomers, or by post-polymerization functionalization reactions of preformed polymers. An example of the former approach is the synthesis of polyvinylpyridine by polymerization of vinylpyridine. The choice of functional groups is somewhat restricted, as they must be compatible with the reaction conditions of polymerization, unless additional protection/deprotection steps are introduced. Depending on polymerization type, this translates to the presence of reactive radicals and temperatures around ca. 70 °C in free-radical polymerization, to reactive carbanions in anionic polymerization,

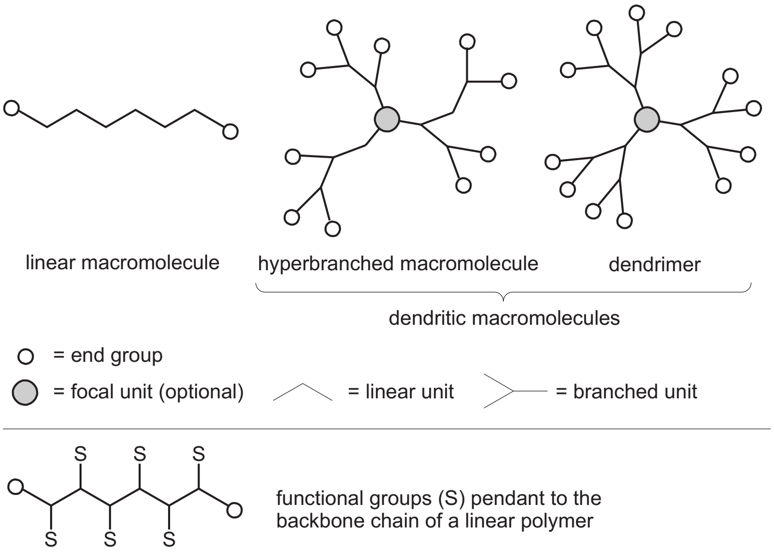
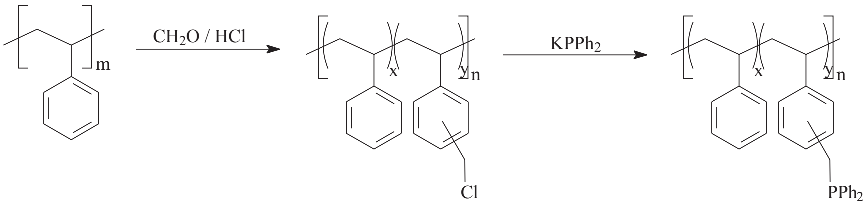


Figure 1 Schematic structure of linear and branched polymers.

or to compatibility with transition metal catalysts in catalytic polymerization, to name the most common polymerization types employed.

More often, post-polymerization functionalization, also termed polymer-analogous reactions, is utilized. As the classical example [8], the synthesis of phosphine-substituted polystyrene by chloromethylation of styrene and subsequent reaction with potassium diphenylphosphide is depicted in Scheme 1. Polymer-analogous reactions are subject to some general restrictions. The high viscosity of polymer solutions at the concentrations of typical organic syntheses is problematic. Achieving full conversion is difficult in many polymer-analogous reactions. As a sideline of the properties of highly branched polymers in the context of catalyst supports, the high solubility, low viscosity, and good accessibility of functional end-groups can be of particular interest for catalyst synthesis by polymer-analogous reactions.

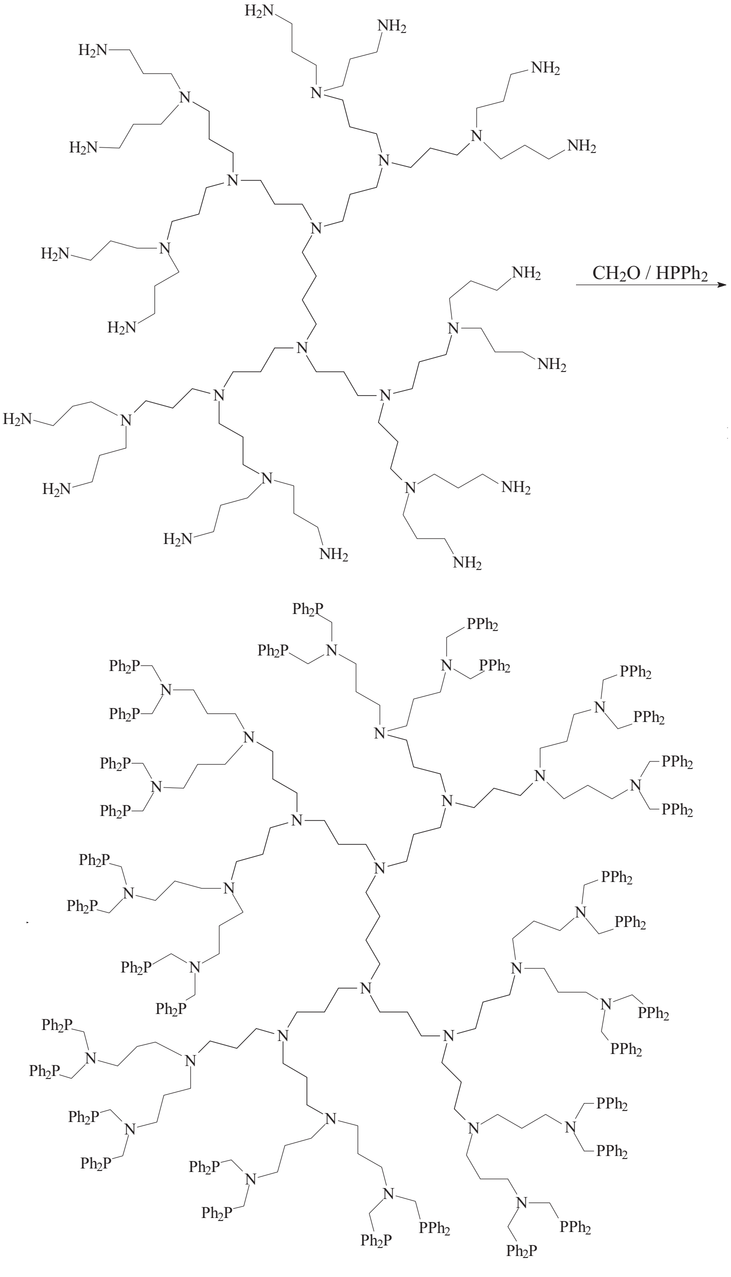


Scheme 1 Synthesis of phosphine-substituted polystyrene by a polymer-analogous reaction.

It can be noted that the degree of functionalization of a polymer with ligand moieties is usually limited in order to control the solubility properties of the polymer.

Whereas linear polymers have been employed the most, highly branched dendrimers [20–22] [Figure 1 and Eq. (2)] have also found considerable interest recently as soluble supports for metal complex catalysts [12, 13]. In this context it should be noted that, unlike frequently implied, dendrimers per se do not possess a spherical structure with a dense shell of end-groups on the outer surface of the molecules in solution. Rather, there is evidence that the solution structure varies with generation number, and that lower generations are very flexible molecules. For example, for a urea-functionalized G4 polypropyleneimine dendrimer (vide infra) the end-groups are mostly folded back into the interior of the molecule, in accordance with a dense-core picture of dendrimers [23, 24]. By contrast, for a G7 PAMAM dendrimer there is some experimental evidence that the end-groups are located at the periphery of the molecule [25]. Detailed experimental [24] and theoretical [26] investigations show that the earlier assumption [27] of a dense shell of dendrimers is not applicable. Rather, the density of dendrimers in solution usually decreases with increasing distance from the center of gravity of the molecule.

Clear advantages of highly branched macromolecules by comparison to linear polymers are their inability to crystallize and their corresponding high solubility, which is advantageous in catalyst synthesis as well as for the use of the resulting catalysts in solution. Also, the absence of chain entanglements results in low solution viscosities, which again are advantageous, particularly during polymer modification and catalyst synthesis [Eq. (1)] [44]. Polypropyleneimine dendrimers [28–30] (abbreviated PPI also termed DAB dendrimers, trade name Astramol® of DSM;



(1)

cf. Figure 2) and polyamidoamine dendrimers [31, 32] (abbreviated PAMAM, trade name Starburst® by Dendritech) are commercially available up to generation G4 (PPI) and G10 (PAMAM) respectively, corresponding to 64 and 4096 functional NH_2 or OH end-groups respectively. A G10 PAMAM dendrimer has a molecular weight of $M = 934\,720$ g mol^{-1}.

An ideal dendrimer structure without defects features only branched units and end-groups, in addition to the core (Figure 1). The molecules are monodisperse, i.e., they all possess the same molecular weight. While this perfect structure is not required for catalysis and recovery in principle, it enables the precise characterization of polymer-bound catalyst precursors. MALDI-TOF is a particularly useful technique. This well-defined nature of dendrimer-bound catalysts is advantageous also for systematic studies of their catalytic properties.

The synthesis of dendrimers, using either convergent [33] or divergent [31] routes, requires tedious multistep procedures. Therefore, so-called hyperbranched polymers [34] have found increasing attention recently [35–40].

In addition to the branching units and end-groups of dendrimers, hyperbranched polymers also contain linear units (Figure 1). The branching of a polymer molecule can be expressed illustratively by the degree of branching $DB = 2\,D\,/\,(2\,D + L)$, D representing the number of dendritic, i.e., branching units and L being the number of linear units [40]. For a linear molecule the degree of branching is zero, whereas it is 100% for a perfect dendrimer. On this scale, typical hyperbranched polymers have a degree of branching of ca. 60–70%. Dendrimers and hyperbranched polymers are generally termed dendritic polymers.

By contast to dendrimers, hyperbranched polymers can be obtained in one-step procedures. As a drawback, molecular weight distributions are often extremely broad. However, certain hyperbranched polymers can be prepared with reasonably narrow molecular distributions if suitable reaction conditions are employed. Hyperbranched polyethyleneimine, a polyamine with NH_2 end-groups, is produced on a large scale industrially [41]. Hyperbranched polyesteramides with, e.g., terminal OH groups (trade name Hybrane® by DSM) and hyperbranched polyglycerol, a polyether-polyol with terminal OH groups, are currently available as specialty products on a kilogram scale [39, 42]. For molecular weights around M_n 5000 g mol^{-1}, polyethyleneimine and polyglycerol are available routinely with polydispersities of $M_w/M_n \leq 1.3$ [41, 43]; higher molecular weight samples are more broadly distributed.

7.1.3
Binding of Catalytically Active Complexes

The attachment of metal complexes to the polymer most often occurs via coordinating functional groups (ligands) bound the polymer in a covalent fashion as outlined in Section 7.1.2, but various types of noncovalent attachement are also well documented (Figure 2). The latter can be achieved, for instance, by means of electrostatic interactions [45, 46], physisorption by amphiphilic polymer micelles (either as common association micelles or as unimolecular micelles) [47–49], by hydrogen bonding [50], or by specific interactions of proteins with a molecule [51]. Noncovalent attachment can offer the advantage of a lower synthetic effort in the catalyst preparation. On the other hand, it can be assumed that the resulting catalysts will often be restricted to a comparatively narrow range of organic solvents for reasons of solubility (electrostatic interactions) or leaching (physisorption and

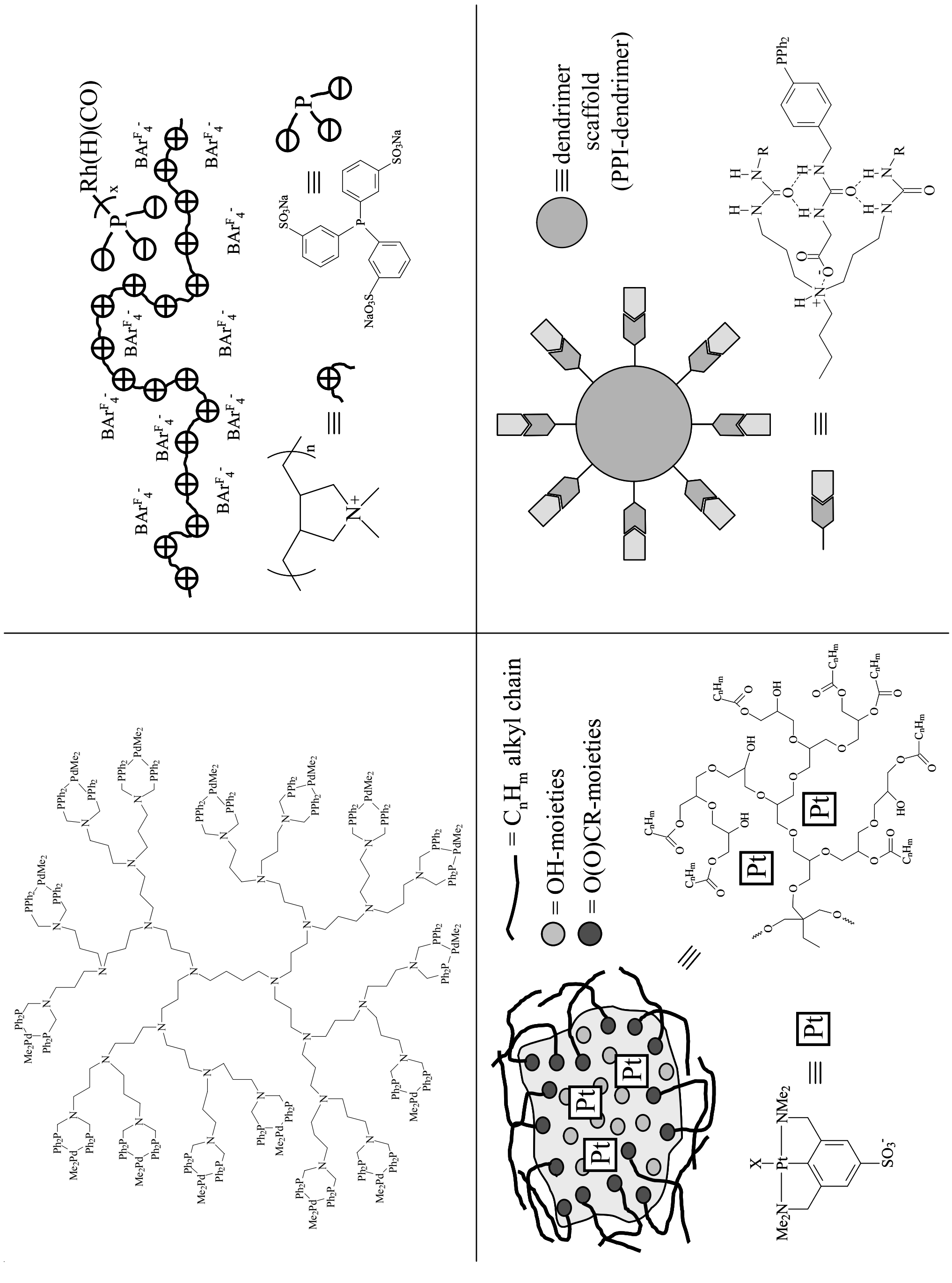


Figure 2 (legend see page 759)

hydrogen bonding), and an enhanced sensitivity to temperature and changes in the solvent composition of the latter two types of binding versus covalent attachment or electrostatic interactions must be considered.

As for the synthetic protocol in general, the catalytically active metal center itself will be introduced only to the already prepared polymer, with very rare exceptions. A metal center which is sufficiently reactive to perform useful catalytic reactions will be susceptible to side reactions in most polymerization procedures.

7.1.4
Metal Colloids

Metal colloids, i.e., colloidally stable dispersions of metal particles in the size range of 1–10 nm, are often considered to be intermediate between classical homogeneous and heterogeneous catalysts. Like heterogeneous catalysts such colloids contain more than one phase: in them, the solid nanoparticles are dispersed in a liquid medium. In terms of practical handling they are more similar to homogeneous catalysts in resembling single-phase “solutions”. In terms of catalytic reactivity, metal colloids are known to catalyze a variety of reactions, such as hydrogenation, C–C coupling, and hydrosilylation, to name the most prominent. Most interest to date has certainly been devoted to catalytic hydrogenation with metal colloids. Generally speaking, the reactivities and activities observed are roughly similar to hydrogenations with standard heterogeneous catalysts, albeit in detail colloids can offer advantages in some cases [52, 53]. In terms of reaction mechanisms, hydrogenation by “soluble metal colloids” do not appear to differ from the well-known mechanism of hydrogenation on metal surfaces of heterogeneous catalysts. By contrast, the role of colloids in C–C coupling reactions, especially the Heck and Suzuki reaction, is currently the topic of debate [54–57]. Possible mechanistic pathways include the colloidal particles being in equilibrium with mononuclear complexes, which are the active species (Figure 3a), or reaction occurring directly on colloid particle surface atoms (Figure 3b). For hydrosilylation, the importance of platinum colloids has long been recognized [58].

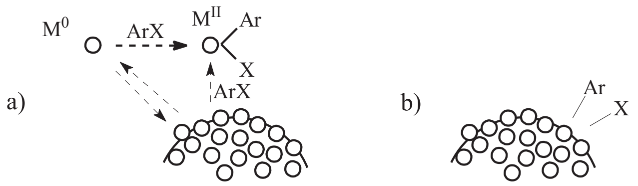


Figure 3 Possible mechanisms of C–C coupling with soluble metal colloids.

Figure 2 Schematic representation of various modes of attachment of catalytically active complexes to soluble polymers: covalent binding to a PPI dendrimer (upper left); electrostatic binding to linear poly(diallyldimethylammonium chloride) (upper right); physisorption in a unimolecular micelle of amphiphillically modified hyperbranched polyglycerol (lower left); specific hydrogen-bonding to a urea functionalized PPI dendrimer.

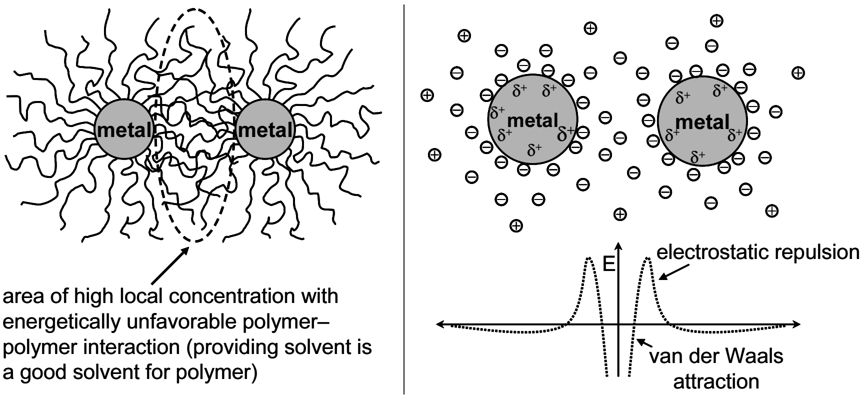


Figure 4 Steric stabilization of colloidal metal particles by a polymer layer (left) and electrostatic stabilization of colloidal particles (right).

The synthesis of metal particles and their properties have attracted considerable attention for more than a century [59, 60]. They are usually prepared by reduction of metal salts in the presence of suitable, low molecular weight or polymeric stabilizers [60], and electrochemical preparation [61–63] and decomposition of organometallic precursors [64, 65] have also been investigated intensively. Most often spherical particles with sizes in the range of 1–10 nm are obtained. However, it is interesting to note that geometrically regular particles can also be obtained under suitable conditions [66–70]. Electrostatic or steric stabilization is required to prevent coagulation to the thermodynamically preferred bulk metal (Figure 4). Steric stabilization by polymers has been widely applied to the stabilization of catalytically active metal colloids [71–73]. By comparison to electrostatic stabilization, steric stabilization is less sensitive to the nature of the solvent (as long as it is a good solvent for the polymer) and to charged substrates, which is advantageous in view of catalytic reactions.

By comparison to homogeneous catalysts based on metal complexes, the properties of which can be tuned via the ligands coordinating to the metal center, the scope of reactions and viable substrates is certainly less broad for metal colloids. The strong interest in metal colloids as catalysts which exists nonetheless (beyond the current surge of interest in nanoparticles for their own sake) can be traced to several, partially overlapping, aspects:

- Metal colloids can represent precursors for highly active catalysts for some reactions, which cannot be performed on heterogeneous catalysts (albeit the actual active species is not always clear).
- In many reactions catalyzed by metal complexes, colloids also are formed.
- In reactions catalyzed by metal complexes, irreversible formation of bulk metal is frequently a major catalyst deactivation roure, e.g., in nearly any reaction involving palladium complexes. Stopping the aggregation at the stage of small particles in combination with a re-oxidation step can enhance catalyst activity.
- As a model for reactions on heterogeneous catalysts, colloids can be advantageous in some cases.

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7.2
State-of-the-Art

Stefan Mecking

First studies on the recovery of transition metal catalysts bound to soluble polymers were already being reported in the 1970s [1]. At the time, hydroformylation and hydrogenation with polystyrene-bound complexes of rhodium and other metals was being studied. The principle of ultrafiltration recovery was demonstrated. This first pioneering work, carried out in academia, received little attention. Only in the second half of the 1980s did the first publications on the topic begin to appear again [2]. Today, a broad range of reactions comprising carbonylations and other C–C linkage reactions, C–C coupling of aryl halides and other reagents, catalytic oxidations, and hydrogenations have been reported with polymer-bound soluble catalysts [3, 4]. Some of these reactions have also been performed enantioselectively. Generally speaking, catalyst activities and selectivities are comparable to those of homogeneous analogues that are not polymer-bound. With much of this work having been carried out in academia, actual catalyst recovery and recycling have been investigated and reported only in a portion of this expanding body of literature, and most often solvent precipitation, a method that is rather unattractive beyond small-scale laboratory batch experiments, has been employed.

Catalysts based on a variety of linear, and since the mid-1990s also highly branched, dendritic polymers, have been studied. For a large part, the polymer-bound ligands for catalysis have been prepared from commercially available polymers by polymer-analogous reactions (see Section 7.1.2) with only one or two synthetic steps.

Industrial interest in soluble polymer-bound catalysts has been closely linked to the development of ultrafiltration membranes with sufficient long-term stability in organic solvents. Membranes fulfilling these requirements were prepared first in the late 1980s. Today, solvent-stable flat sheet membranes and membrane modules are available from several suppliers. As for the viability of ultrafiltration in organic solvents, rhodium-catalyzed hydroformylation of dicyclopentadiene with continuous catalyst recovery and recycling has been demonstrated successfully on a pilot plant scale over an extended period of time [5]. The synthesis of other fine chemicals by asymmetric reduction and other reactions has also been carried out in continuously operated membrane reactors (also cf. Section 7.5) [6–9]. The extent of commercial interest in catalysts bound to soluble polymers appears to fluctuate at intervals. Amongst other factors, the price of precious metals can be a driver.

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7.3
Homogeneous Catalysis with Soluble Polymer-Bound Catalysts as a Unit Operation

Stefan Mecking

7.3.1
Overview and General Considerations

Homogeneous catalysis with soluble polymer-bound catalysts has been carried out by a variety of academic and industrial research groups. These investigations have been performed on a laboratory scale in a batchwise fashion for the most part. In several cases, reactions have also been performed on a pilot plant scale, however (cf. Section 7.5). From the published data, no general systematic differences from catalysis with conventional catalysts that are not polymer-bound are evident regarding the reaction conditions of catalysis. The increased solution viscosity of polymer solutions by comparison to solutions of low molecular weight compounds should usually not be a major issue in view of the rather limited concentrations required for catalysts. The high local concentration of metal centers in polymer-bound catalysts represents a difference from non-polymer-bound homogeneous catalysts. This can result in an enhancement of undesirable bimolecular deactivation reactions in polymer-bound catalysts [1]. Differences in the catalytic properties by comparison to non-polymer-bound analogues, which were observed in same cases, have also been ascribed to the polymer coil representing a local different "solvent" composition.

Thus, the unit operations most characteristic of catalysis with soluble polymer-bound catalysts apply to the separation and recycling step rather than to the actual catalytic reaction (as a special case, both can be carried out at the same time, e.g., in a continuously operated membrane reactor; vide infra). As mentioned previously, the separation of polymer-bound catalysts makes use of properties specific to macromolecules, in order to differentiate between the polymer-bound catalyst and the low molecular weight reaction products of the catalytic reaction and unreacted substrates in the recycling step. The miscibility of polymers with low molecular weight compounds, i.e., the solubility in the reaction solvent (which can also be the neat substrate), is such a property. For most polymer/solvent combinations, a non-solvent can easily be identified which precipitates the polymer-bound catalyst when added in sufficient amounts, while the reaction products of catalysis stay in solution. For example, the common support poly(ethylene glycol) is insoluble in diethyl ether, and polystyrene can be precipitated with methanol. However, while this approach may be useful on a laboratory scale, from a chemical engineering point of view it is not very elegant and practical, requiring the recycling and fractionation by distillation of large amounts of solvent. Alternatives are the utilization of the temperature [2–4] or pH dependence [5, 6] of the solubility of polymers. The miscibility of many polymer/solvent combinations is strongly dependent upon temperature [7]. Thus polyethylenes are soluble in aromatic hydrocarbons only at elevated temperatures.

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Whereas mostly systems rely on an upper critical solution temperature, some, such as aqueous solutions of poly(ethylene glycol) or poly(*N*-alkylacrylamide)s, also separate upon increasing the temperature [8]. This unusual temperature dependance has been termed "smart behavior". A restriction of temperature-dependent solubility is that the solvent (containing the dissolved substrate and product)/polymer combination must be chosen individually for each substrate. pH-dependent solubility is focused on catalytic conversions of water-soluble substrates with aqueous solutions of polymer-bound catalysts, a rather specific case given that most organic substrates are not water-soluble. As a sideline it is worth noting that, for technical viability, all these separation methods require the polymer to separate in a physical form suitable for filtration. Separation as a highly viscous goo, which is not uncommon, poses problems. All these separations utilizing polymer-specific solubility behavior rely on general standard unit operations, which will not be discussed further here.

A different approach of major practical importance is the separation of polymer-bound catalysts from low molecular weight products and substrates by means of appropriate nano- or ultrafiltration membranes. For porous membranes, the larger "size" of the dissolved macromolecules, which prevents permeation through the pores, can be regarded as the underlying principle. In nonporous membranes, the solubility of the macromolecules in the membrane material in combination with the diffusion coefficent can be considered as the physical basis. The unit operations for membrane separation are discussed in the following Section 7.3.2.

7.3.2
Membrane Ultrafiltration Techniques

Membrane separation techniques are employed on a large scale today, the most important applications being in the food industry and in water desalination [9]. According to the driving force of the separation step and the size of the retained species, membrane separations can be classified into osmosis and dialysis (driving force: osmotic pressure and concentration gradient respectively), microfiltration, ultrafiltration, nanofiltration, and reverse osmosis (driving force: external hydraulic pressure). The latter, hydraulic pressure driven processes, which are of particular importance for industrial applications, can be divided according to the size of the retained species, as outlined in Figure 1. Ultrafiltration retains macromolecules, i.e., species with sizes greater than about 1–20 nm, corresponding to molecular weights of 10^3–10^6 g mol^{-1}. Thus it is of interest for the separation of polymer-bound soluble catalysts. Only moderate pressures are required, ranging from a slight overpressure to ca. 3–4 MPa as the upper limit. It should be noted that the terms ultrafiltration, nanofiltration, and even reverse osmosis are not strictly differentiated in use in the literature, and they are often used interchangeably.

Conventional filtration processes are usually performed in a "dead-end" mode. By contrast, membrane separations are designed to be operated in a cross-flow mode (Figure 2). Such a turbulent cross-flow prevents an undesired concentration–polarization of the membrane, i.e., a concentration of solutes at the membrane

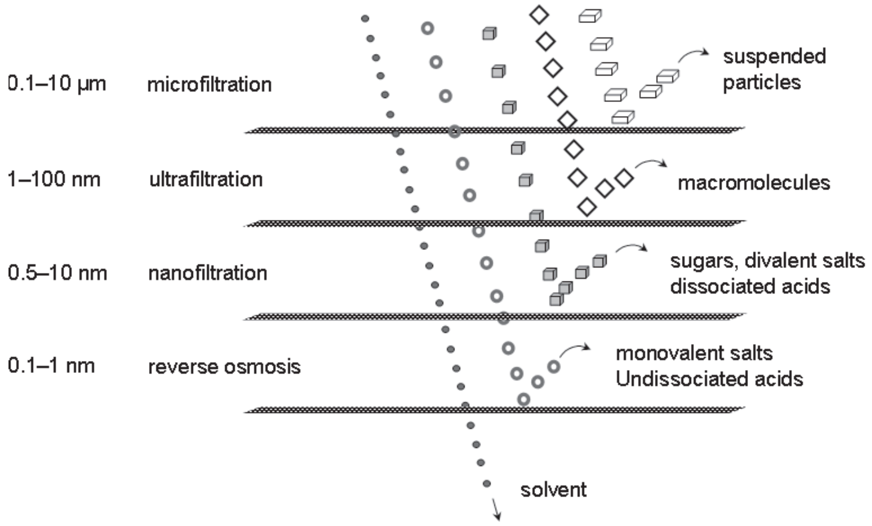

Figure 1 Pressure-driven membrane separation techniques [9].

surface, and reduces membrane fouling. The most common membrane designs are flat sheet membranes, or hollow fibers. In industrial applications membranes are integrated in modules which possess a high membrane surface per module space. Common designs are hollow fiber bundles, or spiral-wound modules (cf. Figure 7). Laboratory-scale exploratory research on catalyst recovery usually requires a frequent replacement of the membranes to avoid possible contamination upon

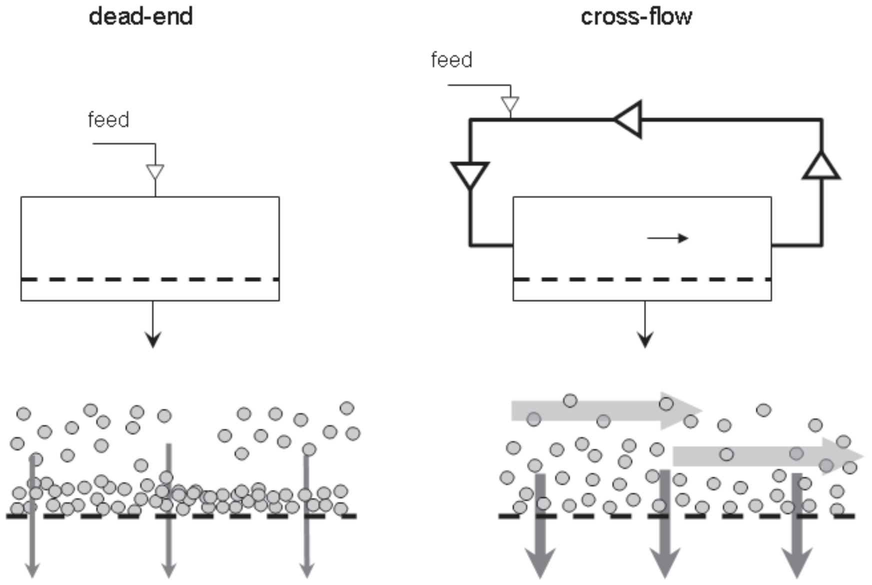

Figure 2 Cross-flow vs. dead-end mode filtration.

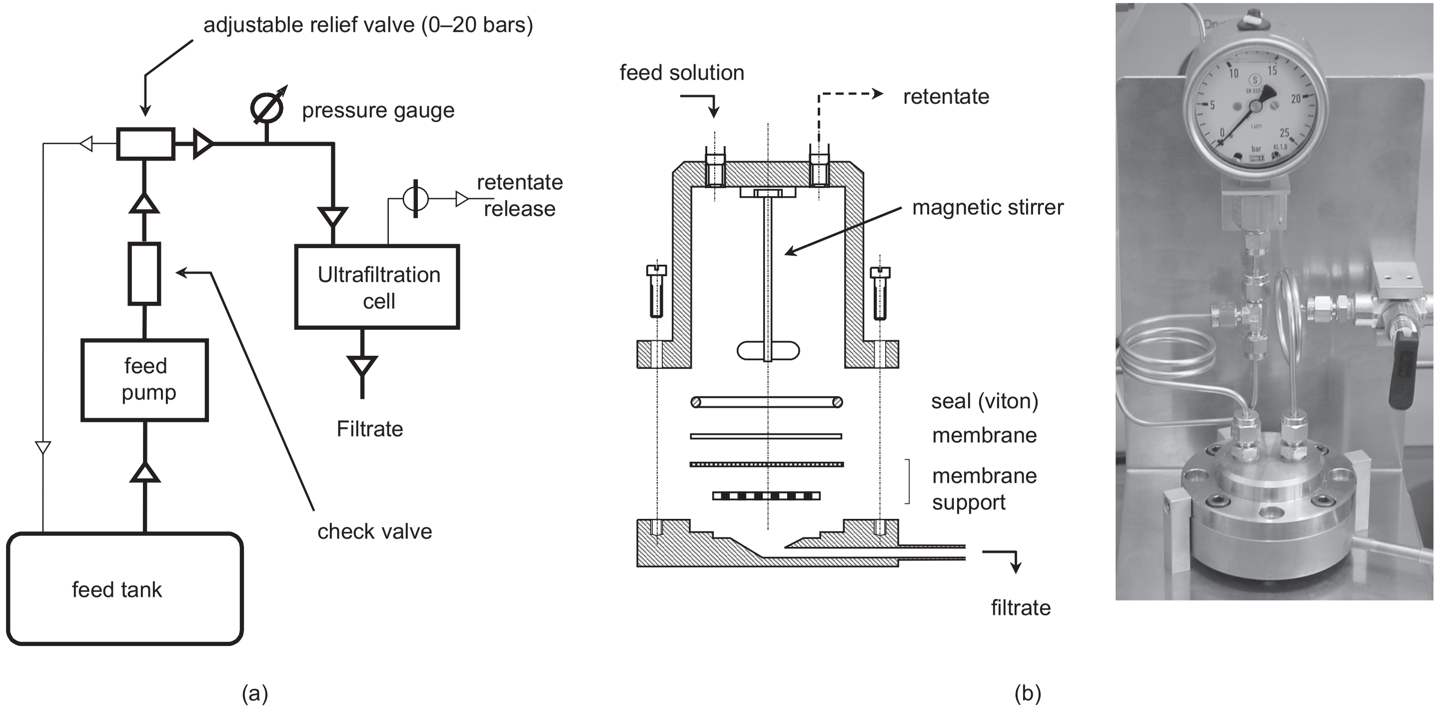

Figure 3 Simple laboratory-scale ultrafiltration setup. (a) Schematic setup, (b) ultrafiltration cell [10].

changing to other substrate feeds, to exclude any possible damage to the membranes which would lead to misinterpretation of experimental results, etc. Therefore, flat sheet membranes are usually used as such in simple test filtration setups (Figure 3) [10], rather than much more costly membrane modules.

Most ultrafiltration, nanofiltration, or reverse osmosis membranes possess an asymmetric structure. A thin layer with an extension of the order of 1 μm on the surface of the membrane is responsible for the separation characteristics. It is supported by an underlying layer which may contain larger voids. Depending on the method of membrane preparation, the thin surface layer may be porous, as depicted in Figure 4, or it can be nonporous. The entire structure can be supported by further, thicker layers providing mechanical stability to form a multilayer membrane. Typical materials for the active separating layer are polyacrylonitrile, cellulose acetate, polysulfone or polyimide [11]. In addition to these polymeric membranes, inorganic membranes have been commercialized since the 1980s. Inorganic membranes, also termed ceramic membranes, are most often composed of alumina and titania. Like polymeric membranes, they possess an asymmetric structure.

The separation characteristics of an ultrafiltration membrane are usually expressed as the molecular weight cutoff (MWCO), i.e., the molecular weight of a solute of which 90% is retained in one filtration step. However, it is well known that the retention characteristics are determined not only by the mere molecular weight of the solute, but also by its solution conformation, chemical nature, etc., and by the solvent employed. Dextrans, certain proteins, and – on the lower molecular weight end – dyes are often used as test substrates, but frequently MWCOs are given in membrane suppliers' data sheets or in the literature without specification of the test solute used. Moreover, there are no general standard conditions with respect to solvent, temperature, transmembrane pressure, concentration of the solute, flow rates, etc. Therefore, MWCOs are sometimes designated as nominal molecular weight cutoffs (NMWCOs) and they should be regarded rather as an order-of-magnitude information. Albeit the results cannot be transferred directly to the issue of ultrafiltration of polymers as a catalyst support because membrane pore sizes are not uniform and the interaction of the polymer with the membrane material is not trivial to quantify, it is nonetheless interesting to note that polymer

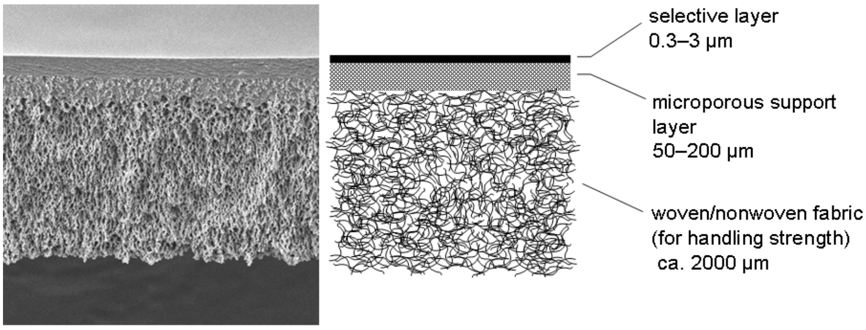

Figure 4 Structure of an ultrafiltration membrane.

translocation through nanometer-sized pores has also been considered on a fundamental level [12, 13].

Physico-chemical phenomena associated with membranes have contributed immensely to the understanding of the nature and behavior of colloids and dissolved molecules or ions. For example, Abbé Nollet had already observed the phenomenon later termed osmosis in the 18th century, when he found that water diffuses from a dilute to a more concentrated solution across a semipermeable membrane (a pig bladder in this case). By contrast, larger industrial applications have only emerged since the 1960s. A major enabling breakthrough was the development of suitable asymmetric membranes by Sourirajan and Loeb [14]. Reverse osmosis for seawater desalination was the first large application. In specific regard to the chemical industry, membrane techniques are employed primarily for the production of ultrapure feed water and for gas separation (nitrogen from air, hydrogen separation from refinery gas streams, and also hydrocarbons from waste gas streams) [15].

Major applications of ultrafiltration are the recovery of electropaint particles from rinsing water in electrocoating paint processes and the fractionation of cheese whey in the dairy industry. As in most other applications of ultrafiltration, aqueous systems are treated in these two examples. By contrast, the separation of polymer-bound catalysts will usually be performed in organic solvents, requiring solvent-stable membranes. In this context, an interesting application of membrane filtration which has already reached the commercial stage is the separation of organic solvents from larger-molecule hydrocarbons in refinery operations by reverse osmosis. In a refinery, vast amounts of residual oils from vacuum distillation are dissolved in organic solvents such as toluene and methyl ethyl ketone; cooling of the solutions results in the precipitation of wax components, which are isolated. Subsequently, the solvents are stripped by distillation. As an energy-saving alternative for the removal of a large part of the solvent, ExxonMobil and Grace have jointly developed a reverse osmosis process termed Max-Dewax^{TM} (Figure 5) [15–17]. Polyimide

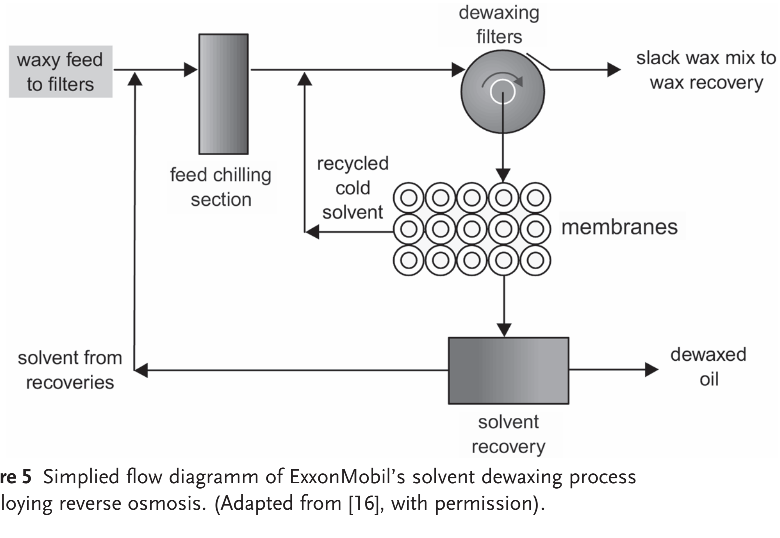

Figure 5 Simplied flow diagramm of ExxonMobil's solvent dewaxing process employing reverse osmosis. (Adapted from [16], with permission).

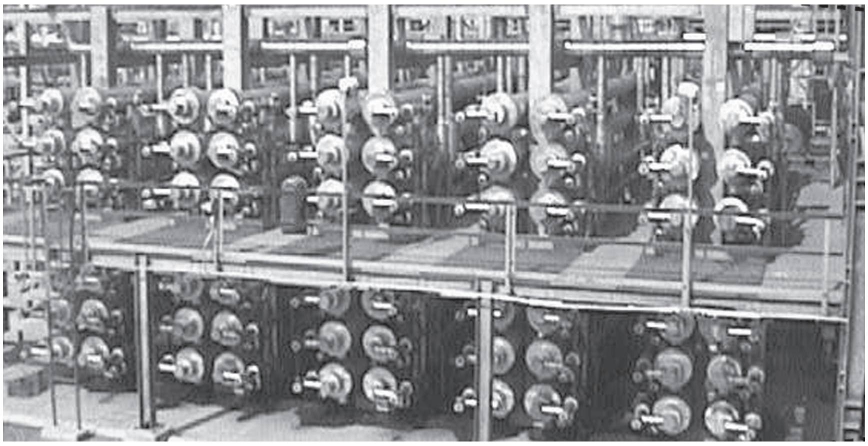

Figure 6 Membrane filtration unit for solvent dewaxing.
(Photograph by courtesy of ExxonMobil Research and Engineering Company).

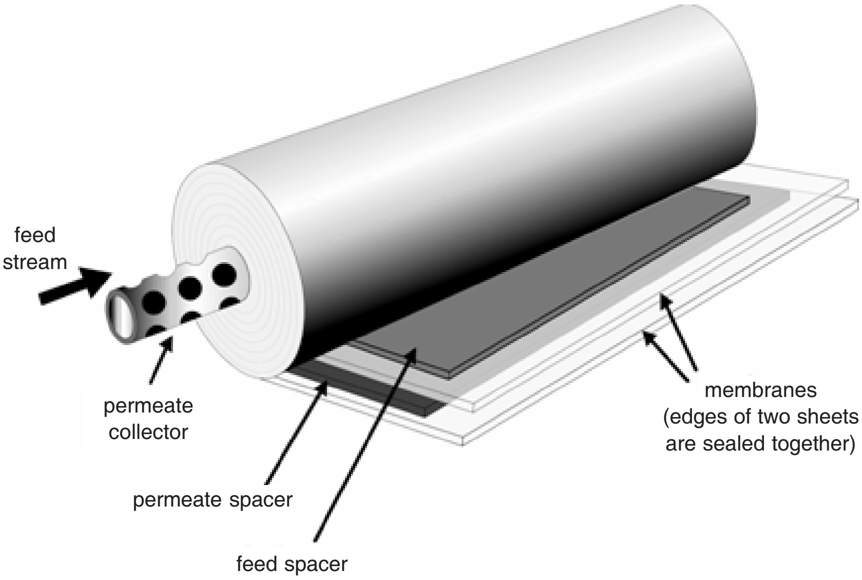

Figure 7 Cross-section of a spiral-wound module. (Adapted from [16], with permission).

membranes with a molecular weight cutoff of 300 Da are employed in the form of spiral-wound modules (Figures 6 and 7). Operation conditions are around 3.5 MPa and –18 to 0 °C. A first commercial unit, processing 5800 m^3 of lube oil filtrate per day, was installed at ExxonMobil's refinery in Beaumont (Tx) in 1998. This example illustrates the viability of membrane filtration in an organic solvent on a large industrial scale.

Polymeric ultrafiltration membranes stable to organic solvents were developed by Linder, Perry, and co-workers. As a separating layer, cross-linked polyacrylonitriles or halomethylated poly(phenylene oxides), for example, are mentioned in patents [18–21]. These products, under the name SelRO®, are now marketed by Koch industries [22, 23]. Flat sheet membranes as well as tubular and spiral modules are available. Two flat membranes, MPF-50 and MPF-60 with NMWCOs of 700 and 400 Da, respectively, are supplied. Both membranes are hydrophobic, with an asymmetric structure. The nature of the crucial separating layer is not disclosed, but from the patents it can be inferred that cross-linked polyacrylonitrile or polyethyleneimine, or bromomethylated phenylene oxide cross-linked with ammonia, may be involved. Another producer of solvent-stable polymeric membranes is the aforementioned Grace Davison; the products are marketed under the trade name Starmem™ by Membrane Extraction Technology [24]. Again, flat membrane sheets as well as modules are available with NMWCOs ranging from 200 to 400 Da. According to the supplier, these are polyimide membranes. The operating conditions recommended for SelRO® and for Starmem™ are roughly similar. Maximum temperatures are 40 to 60 °C and typical transmembrane pressures are 3 MPa. Flow rates are around 30 $m^2\ l^{-1}\ h^{-1}$ at this pressure. The membranes are stable toward solvents such as toluene, ethyl acetate, methyl ethyl ketone, hexane, or methylene chloride [22, 24]. It can be noted that polyaramide ultrafiltration membranes were also investigated intensively at Hoechst AG in the 1980s, and were made available for some time to academic research institutions [25].

For ultrafiltration as a unit operation for the separation of polymer-bound soluble catalysts in particular, the recovery process for a rhodium catalyst from the hydroformylation of dicyclopentadiene is an illustrative example (for another detailed example, see Section 7.5) [26, 27]. Toluene can be used as a solvent with the polyaramide membrane employed. TPPTS or also a sulfonated bidentate phosphine with large ammonium counterions, are used as ligands. For efficient recovery, molecular weights of the catalyst of more than 3000 g mol^{-1} were required on the membrane used. Separation is performed in two steps [28]. A pilot plant was run successfully over an extended period of time of three months.

Other examples of ultrafiltration as a separation operation on a laboratory scale employing continuously operated membrane reactors (vide infra) have been reported [1, 29, 30]. These examples will be discussed throughout Section 7.4. Continuous ultrafiltration of polymer-stabilized metal colloids, in addition to polymer-bound metal complexes, has also been studied [31].

Due to their high stability toward organic media, inorganic membranes [32] appear particularly suited for separations in organic solvents including the recovery of polymer-bound catalysts. To date they have found only limited attention for such purposes. The non-inorganic materials in modules, i.e., the seals, gaskets, and O-rings which hold the membrane elements in their housing, impose limitations. The brittleness of the ceramics requires relatively careful handling. Large pumping capacities are required to achieve the required flow rates in modules. Pore sizes of most commercial inorganic membranes are too large for efficient catalyst retention, although nanofiltration membranes are also available now [9]. There is also some effort directed at the development of flat sheet inorganic membranes, which would be of particular interest for laboratory-scale research on catalyst recovery [33]. However, the pore sizes attainable in a defect-free fashion currently are still too large. While the aforementioned limitations may be a hurdle, particularly for academic laboratories not geared toward engineering, they pose no major limitations, and inorganic membranes certainly provide attractive future opportunities for soluble catalyst recovery (see also Section 7.4.1).

The recovery of homogeneous catalysts can be performed batchwise, subjecting the catalyst alternately to a catalytic reaction in a batch reactor and to a batch ultrafiltration (e.g., using an apparatus as depicted in Figure 3 for the filtration), or it can be carried out in a continuous fashion. Continuous filtration units comprise continuously operated membrane reactors, or loop reactors (Figure 8).

In many applications of a membrane filtration step, a completely selective retention of a given substrate is not in general mandatory, but rather an enrichment of the substrate is achieved (e.g., in the aforementioned Max-Dewax process). In other applications a complete retention is necessary. Even when defining "complete" as ≥ 99%, the latter requirement is much less demanding by comparison to the recovery and recycling of a polymer-bound soluble catalyst: in membrane applications in general the solution to be filtered is usually subjected to the filtration process only once. By contrast, a catalyst has to run through the "filtration step" many times (either in the form of a discrete filtration step, or by continuous filtration, such as in a continously operated membrane reactor; cf. Figure 8). For a continuously operated membrane reactor of volume V_0, the retention of the solute being considered, i.e., the polymer-bound catalyst, and the proportion remaining after the passing of $n = V_S/V_0$ reactor cell volumes of solvent (i.e., the substrate feed stream) through the reactor cell may be calculated from Eqs. (1) and (2).

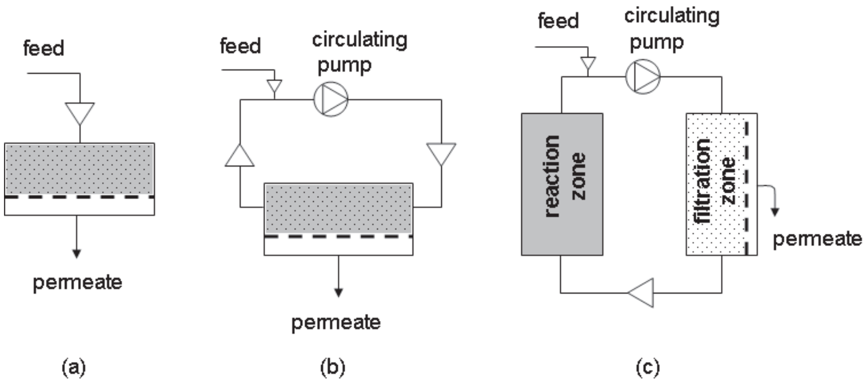

Figure 8 Schematic representation of different reactor types for the continuous recovery of soluble polymer-bound catalyst:
(a) dead-end continosly operated membrane reactor;
(b) cross-flow continuously operated membrane reactor;
(c) loop reactor.

$$\text{Retention } R' = \frac{c_r - c_p}{c_r} = 1 - \frac{1}{(V_S/V_0)} \ln \frac{c_r(0)}{c_r(V_S)} \tag{1}$$

c_r, c_p = concentration of solute in retentate and permeate respectively at any given time; R' corresponds to retention per cell volume (for $R' >$ ca. 0.95)
V_0 = cell volume
V_S = volume of solvent pumped through cell
$c_r(0)$ = initial solute concentration
$c_r(V_S)$ = solute concentration in retentate after passing of V_S

The portion of solute retained in the cell after passing of V_S is obtained from Eq. (2).

$$\frac{c_r(V_S)}{c_r(0)} = e^{[-(1-R')V_S/V_0]} \tag{2}$$

To retain 99% of the catalyst after $n = 100$ exchanged reactor volumes (i.e., a 1% catalyst loss from the reactor), a retention of $R' = 99.99\%$ per exchanged reactor cell volume is required (Figure 9). For commercial viability of continuously operated filtration, a minium retention per exchanged reaction volume of $R' > 99.9\%$ (small-scale synthesis) to $R' > 99.999\%$ (bulk chemicals) can be estimated. It can be noted that noncontinuous filtration, e.g., to remove high-boiling side products from a catalyst from time to time, poses less stringent requirements on retention. In any case it is evident that appropriately designed catalysts in combination with suitable membranes and engineering of the filtration unit must be used.

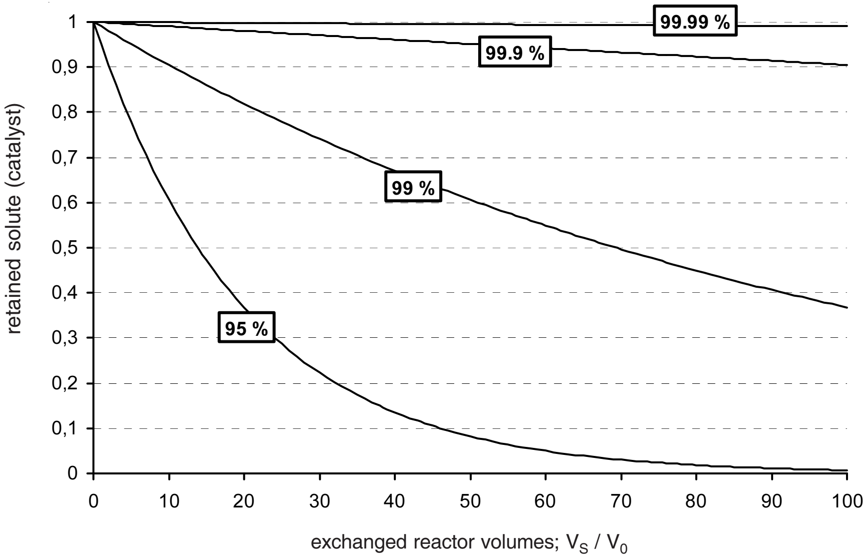

Figure 9 Proportion of a soluble catalyst remaining in the reactor vs. the number of exchanged reactor volumes in a continuously operated membrane reactor for different catalyst retentions (R′ = 99.99%, 99.9%, 99%, and 95%).

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Multiphase Homogeneous Catalysis
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7.4
Typical Reactions

7.4.1
C–C Linkage Reactions by Formal Addition to Unsaturated Compounds

Christian Müller and Dieter Vogt

7.4.1.1
Introduction

C–C linkage reactions by formal addition to unsaturated compounds are frequently used for the transformation of cheap carbon feedstocks into a variety of valuable bulk and fine chemicals as well as pharmaceuticals. The contribution of homogeneous catalysts to these types of C–C coupling reactions is significant and a number of important large-scale processes are nowadays based on homogeneous catalysis. Nevertheless, the separation and recovery of the catalyst from the product mixture remains a crucial feature for the commercialization of a catalytic process and there is currently considerable interest in the development of organometallic catalysts anchored on different supports. This section exclusively focuses on soluble polymer- as well as dendrimer-bound homogeneous catalysts. Their application in transformation reactions of unsaturated compounds in monophasic and thermophasic systems is described and the separation and recovery of the catalyst by means of membrane separation and water-induced liquid/liquid phase separation is demonstrated.

It should be noted here that a number of excellent review articles on recoverable catalysts using recyclable polymer- and dendrimer-based supports have recently been published [1].

7.4.1.2
Soluble Polymer- and Dendrimer-Bound Catalysts

Table 1 gives an overview of addition reactions to unsaturated compounds. C–C coupling reactions such as Heck, Suzuki and Sonogashira coupling are described in Section 7.4.2.

First attempts on the concept of binding catalytically active metal complexes to soluble supports were reported by Manassen in the 1970s, when Rh-containing polymers were successfully applied as hydrogenation catalysts [2]. Soon afterward, Bayer and Schurig used molecularly enlarged rhodium complexes for the homogeneous hydroformylation of alkenes to aldehydes. Soluble polystyrenes (non-cross-linked linear PS, MW ca. 100 000), poly(ethylene glycol)s, polyvinylpyrrolidones, or poly(vinyl chloride)s were functionalized with phosphine groups and converted into the corresponding Rh complexes by reaction with RhH(CO)(PPh$_3$)$_3$ [Eqs. (1) and (2)].

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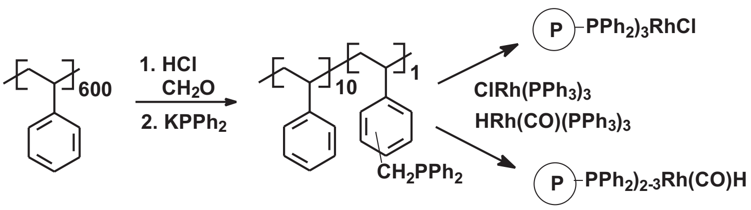
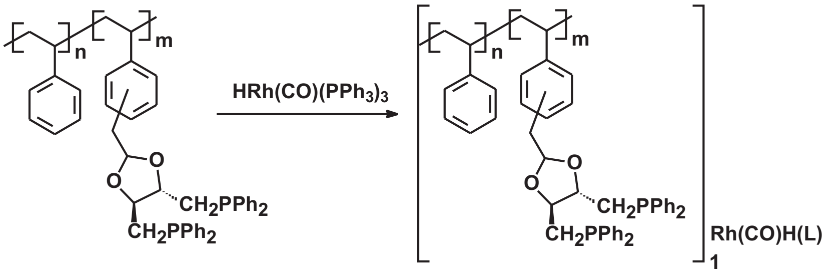
Table 1

Type of reaction	*Catalytic system*	*Ref.*
Hydroformylation	Rh/linear polystyrene, polyethylene, polyelectrolytes, dendrimers	[2–8]
Diethylzinc addition to benzaldehyde	Organo-catalyst/polyphenyl ether, polymethacrylate, dendrimers	[9, 10]
Allylic substitution	Pd/dendrimers	[11–14]
Hydrovinylation	Pd/dendrimers	[16]
ATRA, Kharasch addition	Ni/dendrimer	[17, 18]
Aldol condensation	Pd/hyperbranched polytriallylsilanes	[19]
Ring-closing metathesis	Ru/poly(ethylene glycol)	[20]
Diels–Alder	Cu/poly(ethylene glycol)bisoxazolines	[21]
Cyclopropanation	Cu/poly(ethylene glycol)bisoxazolines	[21]
Ene reactions	Cu/poly(ethylene glycol)bisoxazolines	[21]
Michael addition	Organo-catalyst/poly(*t*-butylstyrene)	[22, 23]
Oligomerization of C_2H_4	Ni/dendrimers	[25]



(1)



(2)

1-Pentene was hydroformylated to C_6 aldehydes at 22 °C under 0.1 MPa H_2/CO. The reaction solution was membrane-filtered and the products (77% *n*-hexanal and 23% methylpentanal) were analyzed by GC. The retained catalyst could be recycled twice [3]. Along with Ohkubo et al., Bayer and Schurig also reported on soluble polymers as supports for asymmetric catalytic systems. The soluble polystyrene-bound analogue of DIOP (4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxalane) was used for the asymmetric Rh-catalyzed hydroformylation of styrene but the *ee* of the predominantly obtained branched product was only 2% [Eq. (2)].

Bergbreiter, Karakhanov, and their respective co-workers used the temperature-dependent solubility of polyethylene oligomers to design recoverable catalysts. Polyethylene-diphenylphosphine ligands were used for the Rh-catalyzed hydroformylation of 1-dodecene, cyclododecene, styrene, and 1,5-cyclooctadiene. Catalyst solutions with excess oligomeric ligand showed up to 87% linear product in 1-dodecene hydroformylation as well as an increased stability of the catalyst solution, which could be recycled successfully at least 10 times using a precipitation/filtration protocol (Figure 1) [4]. In this procedure, the polyethylene-ligated catalyst is homogeneous in a hot solution of substrate, but insoluble and thus separable from the products at room temperature.

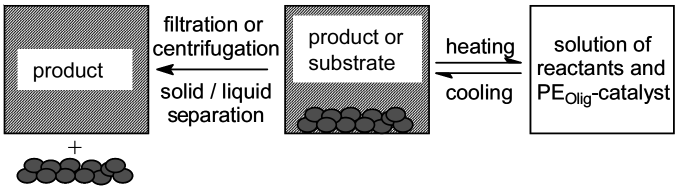


Figure 1 Catalyst recovery and product separation by temperature-dependent solubility of polyethylene oligomers. (Reprinted with permission of ACS from [1a], © 2002).

Mecking et al. also carried out hydroformylation reactions with Rh(I) complexes ionically tethered to soluble polyelectrolytes (Figure 2) [5]. The noncovalently bound catalyst was prepared by reacting poly(diallyldimethylammonium chloride) (PDADMA–Cl) with $NaBAr_4^F$ to form PDAMA–BAr_4^F. Exchanging multiple BAr_4^{F-} anions by reaction with $[HRh(CO)(NaTPPTS)_3]$ generated a methanol-soluble polymer with electrostatically bound Rh(I) fragments. This molecularly enlarged catalyst was used for the hydroformylation of 1-hexene and the activity (TOF = 160 mol h^{-1}) was comparable to that of an unsupported catalyst. The catalyst was subsequently separated from the products by means of ultrafiltration, using a poly(ether sulfone) membrane with a molecular weight cutoff (MWCO) of 50 kDa

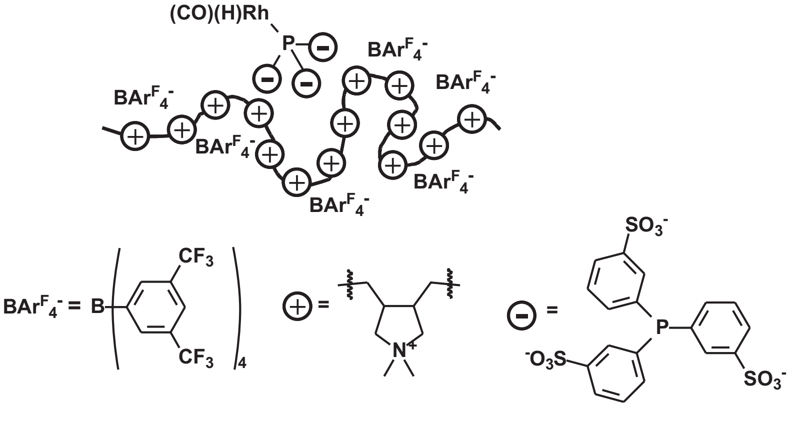
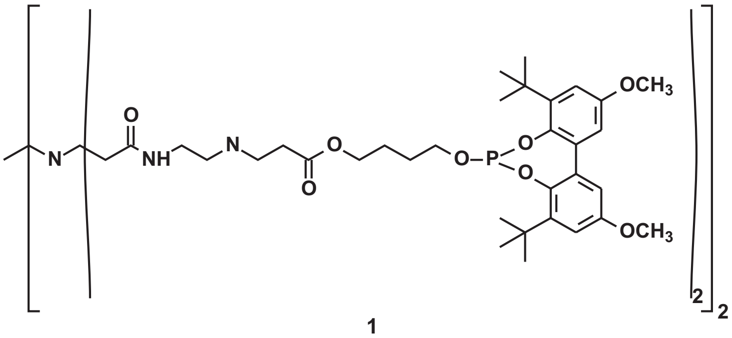


Figure 2 Soluble polyelectrolytes for Rh-catalyzed hydroformylations.

supplied by Sartorius. Interestingly, retention of 99.8% was found and repetitive recycling experiments in which virtually the same catalytic activity was observed showed 2–7% loss of rhodium. This was probably due to partial oxidation of the phosphine ligand and could most likely be suppressed in a continuous-flow membrane reactor.

Dendrimer-based organophosphites, organophosphonites, and organophosphinites, as well as their corresponding metal complexes, were described and patented by Tulchinsky and Miller for the hydroformylation of propene in batch processes [6]. The recovery of the catalysts by means of nanofiltration was described for phosphite-substituted PAMAM dendrimers of generations G0–G4 (**1**).



1

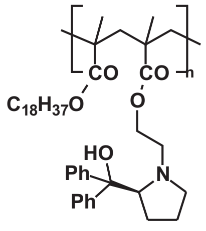
After the hydroformylation run, the reaction mixture was passed through nanofiltration membranes (reverse osmosis) of the MPF-50 type or cross-linked GKSS [7] membranes. The dendrimers were stable under hydroformylation conditions and no detectable amount of dendritic material was found in the permeate solutions. The highest retention for Rh (99.96%) was achieved by using GKSS (10 μm) membranes and the third-generation PAMAM dendrimer. Even higher retentions of Rh and flux rates were found for nanofiltration experiments using a 50 Å ultrafiltration membrane and the fourth-generation PAMAM system (99.997%).

Van Leeuwen and co-workers synthesized and applied diphenylphosphine-functionalized carbosilane dendrimers of different generations (G0–G2) in the Rh-catalyzed hydroformylation of 1-octene. In batch reactions, the same selectivities toward the linear and branched aldehyde were observed for the dendritic systems as for the model compounds $(H_3C)_3SiCH_2PPh_2$ and $(H_3C)_2Si(CH_2PPh_2)_2$. However, activities of the catalysts were largely influenced by the size and flexibility of the dendritic ligand. Preliminary experiments using a commercially available membrane (Koch/SelRO MPF-60 NF) showed that the membrane was not compatible with standard hydroformylation conditions [8].

Even though the hydroformylation of alkenes is an important reaction for the functionalization of unsaturated compounds with enormous potential, the above mentioned examples already show the limitations of using molecularly enlarged catalysts in combination with membrane filtration; the hydroformylation reaction is typically performed at elevated temperature (40–80 °C) as well as under a syngas pressure of 1–2 MPa. Typical reactors and membranes are not designed yet for use with certain organic solvents, high temperature, and/or high pressure. Therefore, C–C linkage reactions involving the consumption of one or more gases are usually performed in a batchwise process with subsequent filtration through a membrane in order to separate the molecularly enlarged catalyst from the product. In the case of hydrogenations, the saturation of the solvent with hydrogen is in most cases sufficient to run the reaction in a continuous way. However, the design of suitable reactors for applications under more drastic reaction conditions (e.g., elevated temperature and pressure) is obviously desirable.

Wandrey and co-workers pioneered the use of homogeneous catalysts bound to soluble supports in continuously operating membrane reactors (CFMRs). In 1996 Kragl and Dreisbach reported on a chiral polymer-enlarged homogeneous catalyst, which was used for the enantioselective addition of diethylzinc to benzaldehyde [Eq. (3)] [9]. The catalyst consisted of a soluble polymeric support, a copolymer of 2-hydroxyethylmethacrylate and octadecyl methacrylate, combined with α,α-diphenyl-L-prolinol as the active organocatalytic site (**2**).

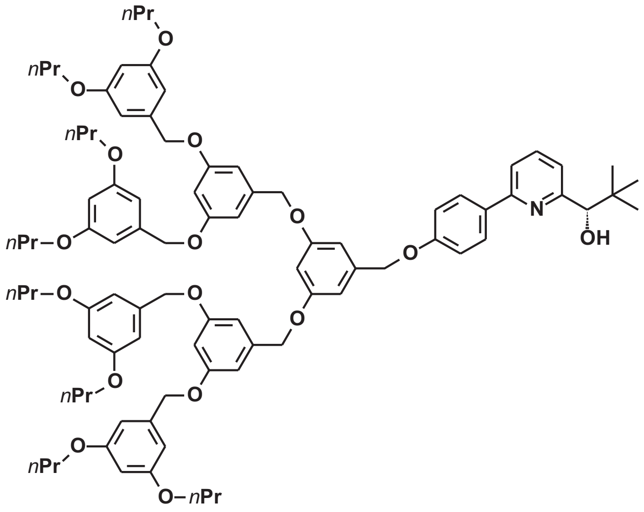
(3)



2

The reaction was carried out continuously by using an ultrafiltration membrane (Hoechst Nadir UF-PA20). The authors found a retention of the polymeric support of more than 99.8%. Even though the *ee* achieved with the molecularly enlarged catalyst was lower (80%) compared to the unsupported analogue (97%) the principle of running the reaction in a continuous way was proven. Interestingly, the total turnover number (tTON) of the chiral organocatalyst under continuous conditions could be raised by a factor of 10, to 500. After seven days, no deactivation of the catalyst occurred.

Bolm and co-workers also studied diethylzinc addition to benzaldehyde with soluble polymeric catalysts [10]. Dendritic chiral catalysts consisting of poly(benzyl ethers) and chiral pyridyl alcohols (**3**) were used as organocatalysts for the asymmetric C–C linkage reaction. The enantiocontrol by the dendritic systems was slightly lower than that of the parent pyridyl alcohols (2–3% drop in *ee*) but the conversion toward the chiral secondary alcohol was actually slightly higher for the largest dendritic catalyst (84% versus 80% yield after 3 h of reaction time). In more recent work by Bolm et al., polymeric multivalent chiral catalysts were prepared via ring opening metathesis polymerization (ROMP) of strained bicyclic olefins. The polymers containing a chiral pyridyl alcohol as a catalytically active subunit were applied in the addition of $ZnEt_2$ to benzaldehyde (**4** and **5**). The optically active 1-phenylpropanol was obtained in good yields. The activity of the polymeric catalysts as well as the enantiocontrol was slightly decreased compared to the parent pyridyl alcohol. However, applications of these systems in a continuous-flow membrane reactor have not been reported yet.



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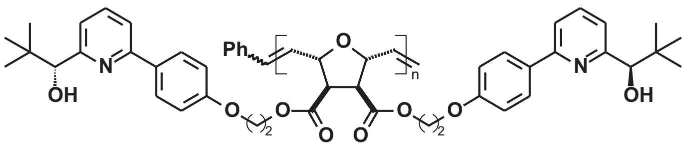
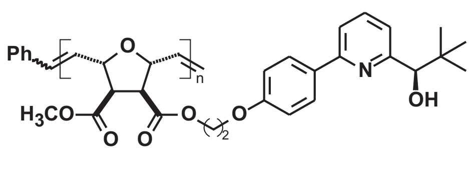


P1: n = 20; **P2**: n = 50; **P3**: n = 100

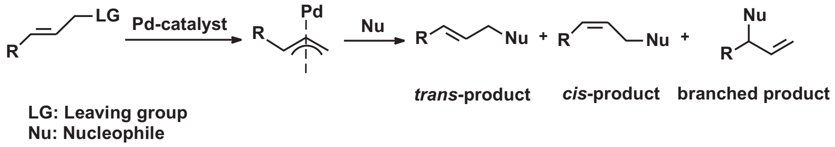
4



P4: n = 50

5

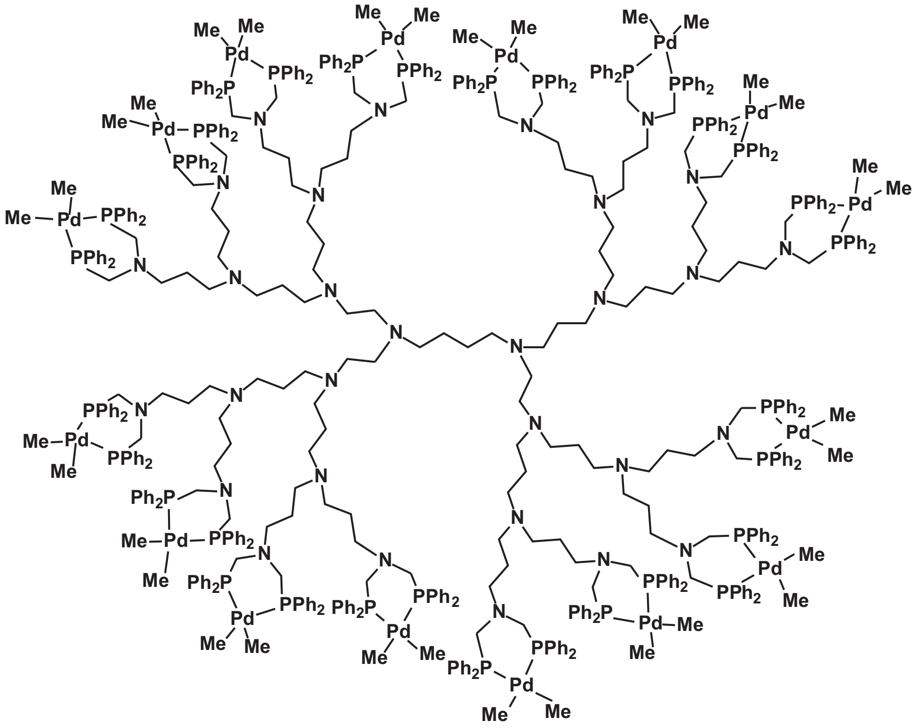
Allylic substitution reactions, such as allylic alkylations or allylic aminations, have recently attracted interest as suitable C–C and C–N bond-forming reactions in continuously operating membrane reactors. Oxidative addition of the starting material to a Pd center leads to an (η^3-allyl)Pd(II) species, which, after attack of the nucleophile, forms the substituted product [Eq. (4)].



(4)

Reetz and co-workers reported on a DAB dendrimer as a soluble support, functionalized with diphenylphosphine groups at the periphery. The corresponding Pd complexes were used for Pd-catalyzed allylic amination to yield N-[3-phenyl-2-propenyl]morpholine in a continuous membrane reactor (**6**) [11].

Fourth- and fifth-generation phosphine-functionalized DAB dendrimers were applied, for which 100% conversion was obtained at the beginning. A 20% decrease was observed after 100 h, as well as palladium leaching between 0.07 and 0.14% per residence time. The soluble support, on the other hand, was completely retained in the membrane reactor.



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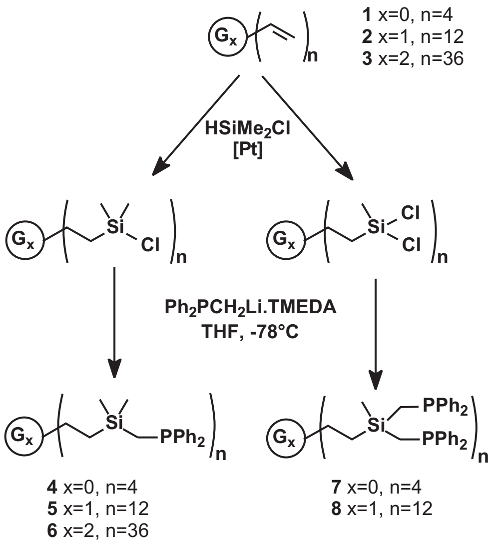
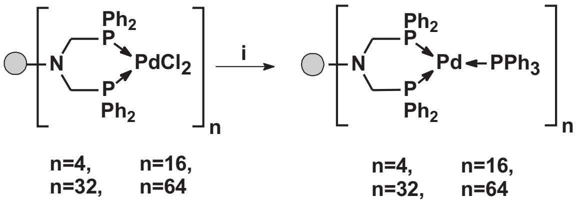


Scheme 1 Preparation of carbosilane dendrimers of different generations.

Van Leeuwen and co-workers synthesized phosphine-functionalized carbosilane dendrimers of different generations and applied the corresponding Pd(allyl) complexes in the allylic alkylation reaction of allyl trifluoroacetate with sodium diethyl-2-methylmalonate (Scheme 1) [12]. While the retention of the dendrimer was 98.1%, the Pd complexes decomposed under continuous-flow conditions and the space–time yield dropped to zero after 15 residence times. In the Pd-catalyzed allylic amination reaction between crotyl acetate and piperidine, the dendritic systems with $Si(CH_2PPh_2)_2$ end-groups showed a rapid drop in yield under continuous conditions due to catalyst deactivation, whereas stable catalysts were obtained for dendritic ligands with $SiCH_2CH_2PPh_2$ end-groups. These systems were successfully applied in a continuous-flow membrane reactor and retentions of 98.5–99% were reached. Obviously, small changes in the dendritic ligand structure had a large impact on catalyst stability, which is pivotal for successful applications in continuous-flow membrane reactors [13].

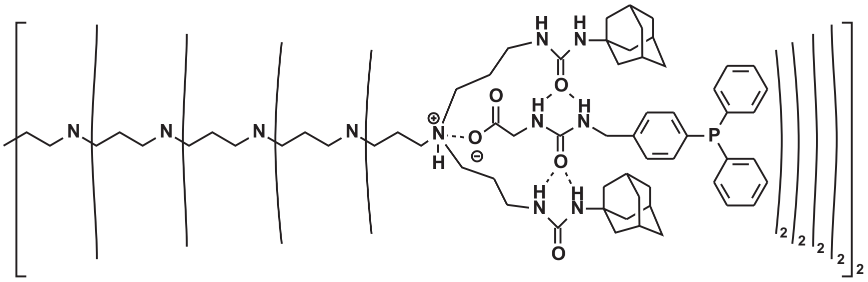
The first application of dendrimers in a thermomorphic system was described by Kaneda and co-workers. Poly(propylene imine) dendrimer-bound Pd(0) complexes were synthesized by reduction of dendritic Pd(II) systems with hydrazine and used for the allylic substitution of *trans*-cinnamyl acetate with dibutylamine [Eq. (5)] [14].



(5)

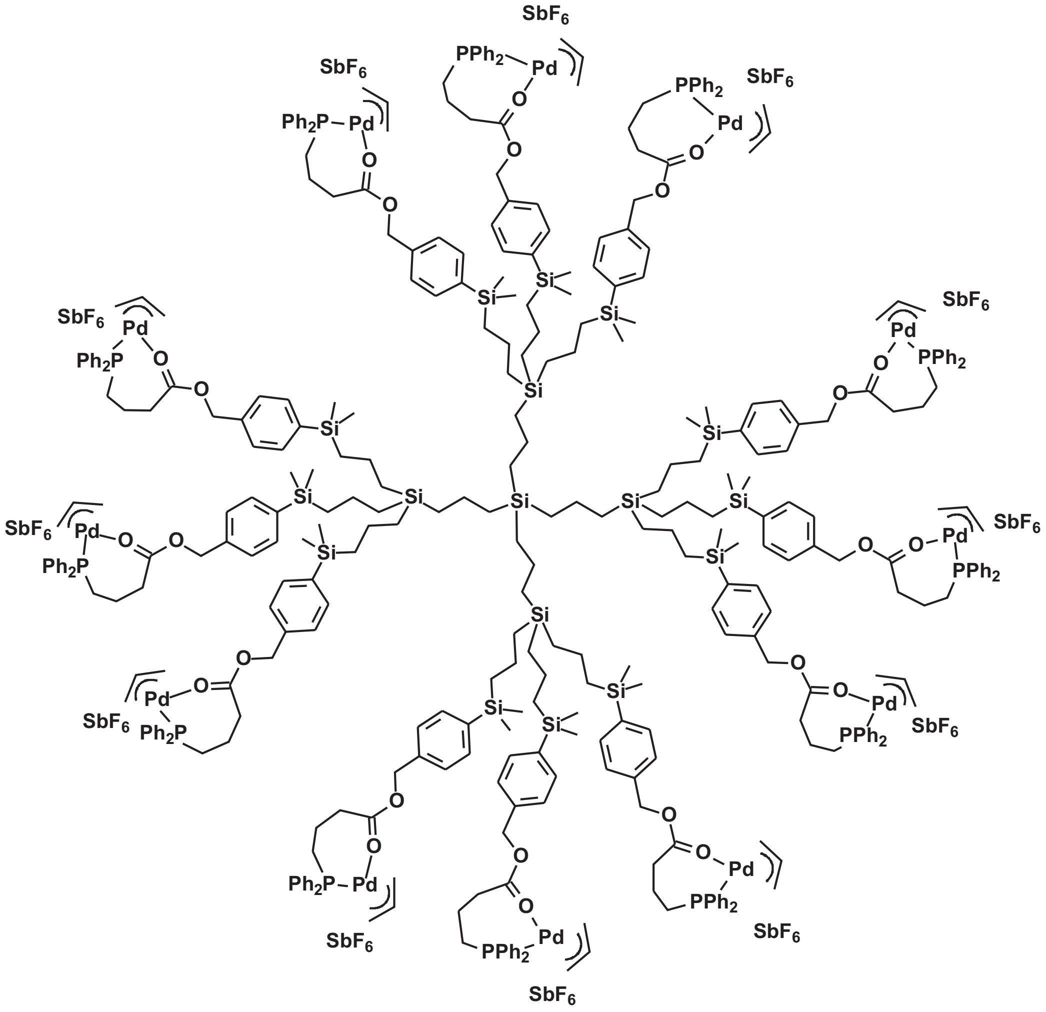
The Pd complexes were efficiently recycled by running the reaction in a thermomorphic system at 75 °C: under these conditions a biphasic system consisting of DMF and heptane became homogeneous. Phase separation occurred again when the reaction medium was cooled to room temperature (see also Figure 1, above). The dendritic catalyst system was almost completely insoluble in heptane and was transferred to the polar DMF phase, while the heptane solution containing the products could easily be decanted. Furthermore, the stereoselectivity for the *cis* product [see Eq. (4)] increased with the generation of the dendrimers. Up to 94% *cis* selectivity was observed for the fifth-generation dendrimer, while only a slight excess of *cis* product was observed for the unsupported $Pd(PPh_3)_4$ complex. As an explanation, steric congestion at the periphery of the dendrimer was suggested which led to steric steering of the nucleophilic attack to a surface (π-allyl)Pd intermediate and strong shielding from the *endo* attack of the nucleophile at the active center.

Allylic amination reactions with a supramolecular host–guest catalyst were studied by van Leeuwen et al. A noncovalently functionalized dendrimer with 32 phosphine ligands was generated by reaction of PPI (poly(propylene imine)) dendrimers equipped with urea adamantyl groups and phosphorus ligands functionalized with urea acetic acid groups (**7**). This supramolecular complex was applied in the Pd-catalyzed reaction between crotyl acetate and piperidine under continuous conditions. A maximum conversion of approximately 80% was reached after 1.5 h and only a slight decrease in conversion was observed during the course of the experiment due to slow catalyst deactivation. Remarkably, a retention of 99.4% for the supramolecular host–guest Pd complex was found which demonstrates that the noncovalently assembled systems are indeed suitable soluble supports for continuous-flow applications [15].

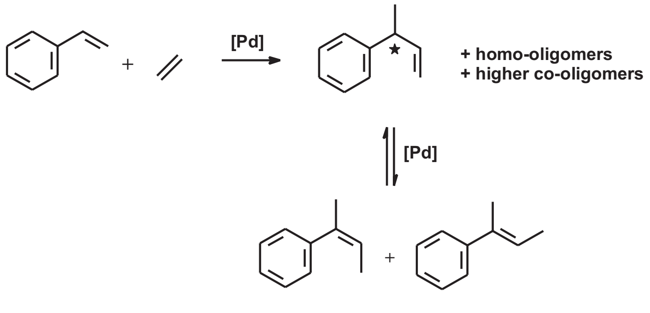


7

Pd complexes of soluble P,O-functionalized carbosilane dendrimers (**8**) were used by Vogt and co-workers for the hydrovinylation reaction (codimerization of ethylene and styrene). This C–C coupling reaction is of great interest, because it opens an easy access to building blocks for fine chemicals as well as pharmaceuticals [Eq. (6)] [16].


SbF$_6$
Pd
PPh$_2$
Ph$_2$P
O
Si

8


[Pd]
+ homo-oligomers
+ higher co-oligomers
[Pd]
+

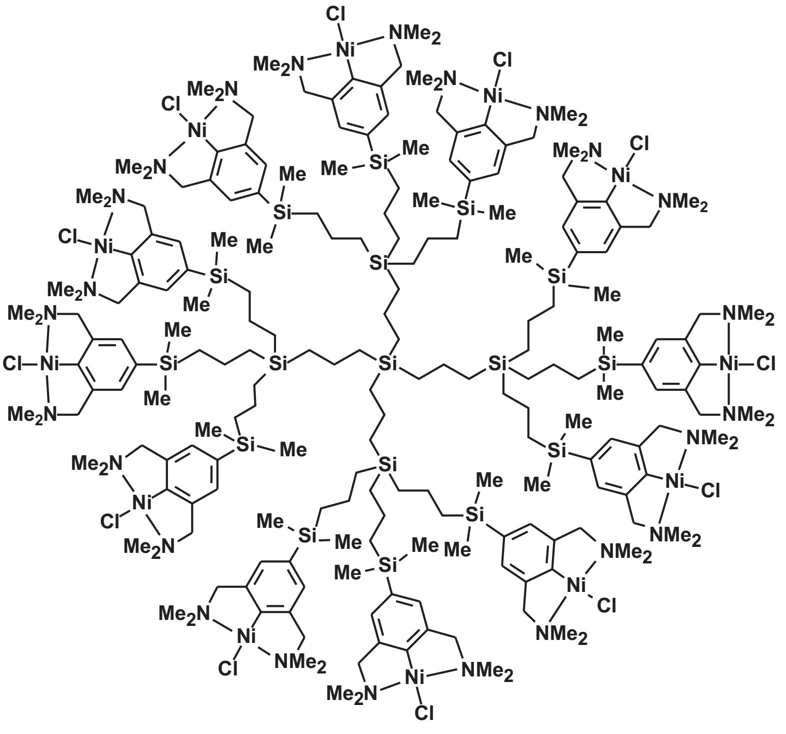
(6)

For the codimerization of ethylene and styrene, a pressure membrane reactor was developed and the reaction ran almost without any isomerization of the products or formation of side products. These undesired side reactions are often observed at high conversion. Nevertheless, the space–time yield dropped to zero within 15 residence times and low retention of the dendrimer as well as precipitation of palladium on the membrane were found. Larger dendritic catalysts with higher retentions did not show much improvement, indicating that catalyst deactivation was indeed the major problem.

A soluble dendritic Ni catalyst for the atom-transfer radical addition (ATRA, i.e., polyhalogenated alkane addition to olefins, the Kharasch addition) was described by van Leeuwen and van Koten et al. in 1994 [17]. G0 and G1 carbosilane dendrimers, functionalized with NCN pincer–nickel(II) groups, were synthesized and applied as homogeneous catalysts for the addition of organic halides to alkenes [Eq. (7)].

(7)

Slightly modified systems were subsequently used in a continuous-flow membrane reactor for the atom-transfer radical addition of carbon tetrachloride to methyl methacrylate (**9**) [18].



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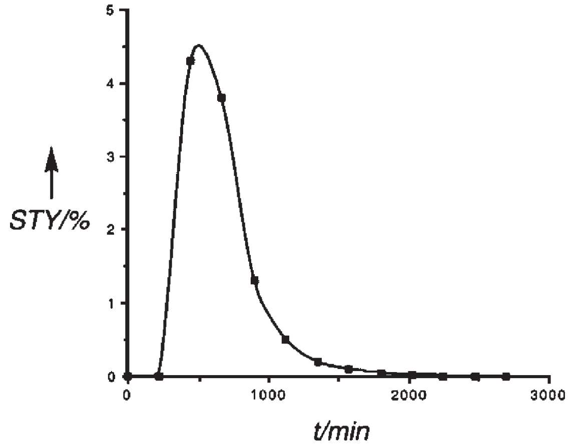
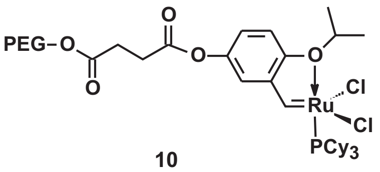


Figure 3 Kharasch addition reaction in a CFMR.
(Reprinted with permission of ACS from [18c], © 2000).

While retentions of the molecularly enlarged systems of up to 99.75% were observed, the formation of insoluble purple species occurred under continuous-flow conditions. Addition of $[Bu_4N]Br$ prevented catalyst precipitation but a fast decrease in the conversion was detected. After 45 cycles, the activity of the catalyst dropped to almost zero, while the retention of the catalyst under the applied conditions was 98.6% (Figure 3). The authors state that the main decrease in activity was due to formation of inactive Ni(III) species. Furthermore, the carbosilane support plays a pivotal role in the accessibility of the active sites: surface congestion can lead to the formation of mixed-valence Ni(II)/Ni(III) complexes on the dendrimer periphery that compete for reactions with substrate radicals.

Hyperbranched polytriallylsilanes functionalized with NCN $[C_6H_3X(CH_2NMe_2)_2$-2,6] ligands were reported by van Koten and Frey [19]. The soluble supports were used as ligands for the Pd-catalyzed aldol condensation of benzaldehyde and methyl isocyanate. Activities similar to that of parent NCN–Pd complexes were observed (Scheme 2). The hyperbranched polymeric systems showed similar properties to those of analogous dendritic compounds, indicating that structural perfection is not always required. The polymers were purified by means of dialysis, showing a potential application in continuous-flow membrane reactors.

Yao described stable and soluble poly(ethylene glycol)-bound Ru catalysts (**10**) for the ring-closing metathesis (RCM) of a variety of dienes. Bidentate non-phosphine ligands are in fact promising candidates for the recycling of Ru–carbene complexes, since the formation of chelates is entropically favored at the end of the reaction [Eq. (8)] [20].



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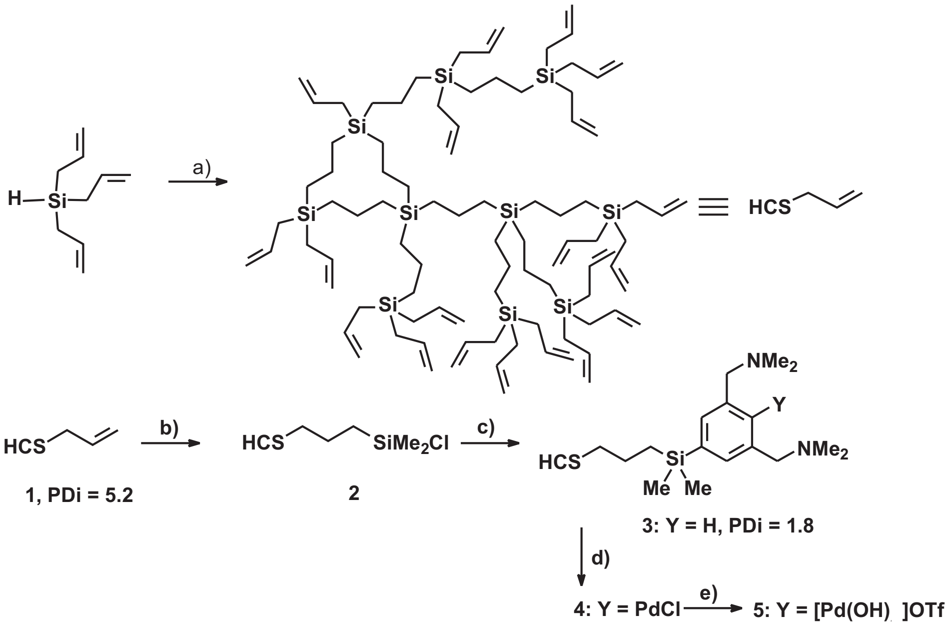
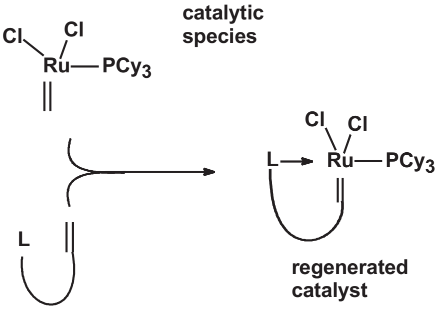


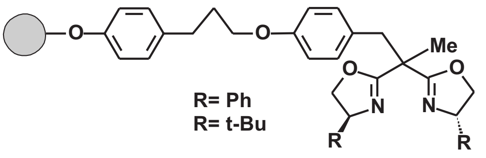
Scheme 2 Preparation of hyperbranched polytriallylsilanes.



(8)

Indeed, Ru complexes which could be repeatedly used in the metathesis of various diene substrates could be prepared and showed only a slight decrease of activity during recycle experiments. However, this concept cannot be applied for continuous conditions: the intermediate in the ring-closing metathesis reaction is not necessarily bound to the chelate, because one ligand has to dissociate from the Ru center in order to provide a free coordination site for the incoming alkene. Therefore, a constant stream of substrate would ultimately lead to a loss of catalyst across the membrane.

Soluble, poly(ethylene glycol)-supported bisoxazolines were used as ligands for enantioselective Diels–Alder as well as cyclopropanation and ene reactions (**11**) [21].



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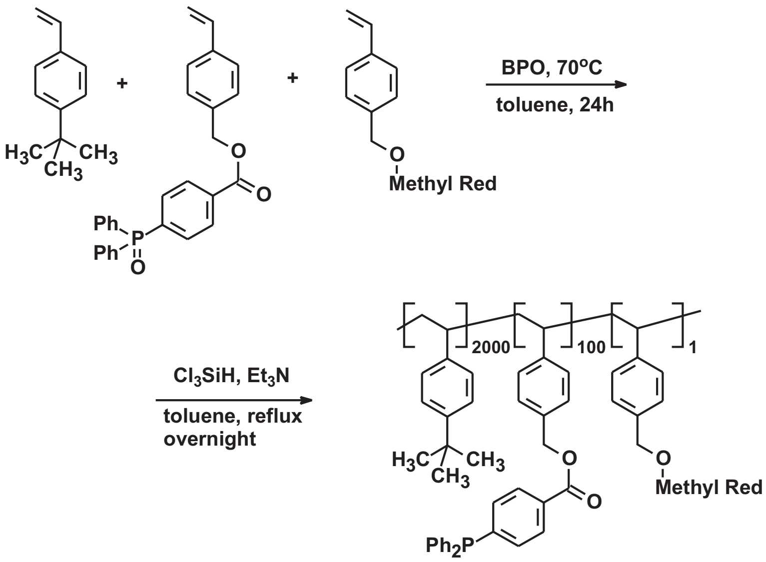
In combination with Cu(II) and Cu(I) salts, the polymer-anchored, enantiomerically pure bisoxazolines showed only poor enantioselectivity in the Diels–Alder cycloaddition between *N*-acryloyloxazolidinone and cyclopentadiene (up to 45% *ee*). Better stereocontrol was found in the cyclopropanations of styrene and 1,1-diphenylethylene with ethyl diazoacetate (up to 93% *ee*) and in the ene reactions between ethyl glyoxalate and α-methylstyrene or methylenecyclohexane (up to 95% *ee*), which was comparable to the structurally related, unsupported ligands. Only a slight decrease in activity and in stereocontrol was observed upon recovery and recycling of the catalyst. The catalytic transformations were as efficient as if performed with the corresponding catalysts supported on insoluble polymers.

Michael additions of 2-nitropropane to methyl acrylate with soluble, diphenylphosphine-functionalized poly(4-*tert*-butylstyrene) copolymers as nucleophilic catalysts were investigated by Bergbreiter and Li [Eq. (9)] [22]. The catalytic reactions were performed in a monophasic system consisting of a mixture of ethanol and heptane at room temperature. After 24 h, a small amount of water was added and phase separation occurred. With this water-induced liquid/liquid phase separation, the polymeric catalyst could be recycled and successfully applied again in a catalytic cycle. UV-Vis spectroscopy showed that the catalyst was quantitatively dissolved in the nonpolar, heptane-rich phase.



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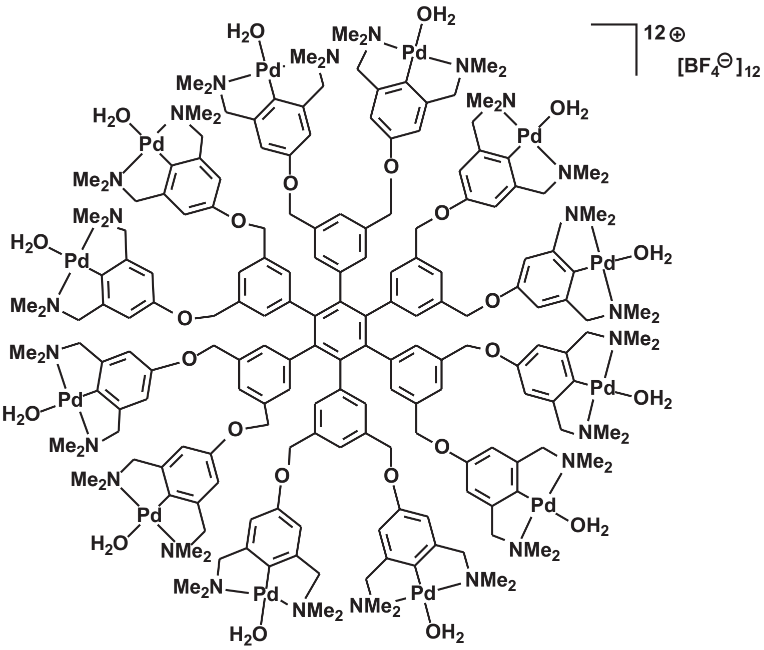

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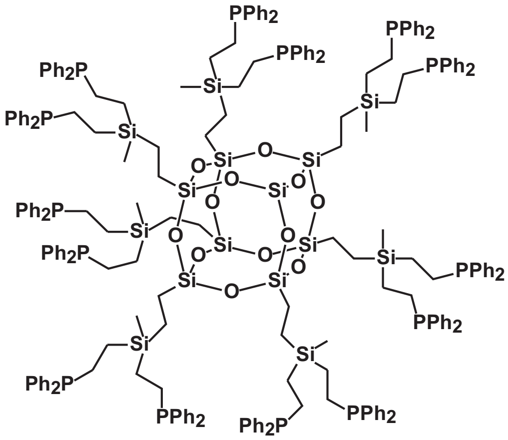
Double Michael addition reactions between methyl vinyl ketone (MVK) and ethyl α-cyanoacetate under continuous conditions (dead-end reactor) were performed with a dodecakis(NCN–Pd^{II}) catalyst by the van Koten group (**12**). A high productivity and retention (99.5%) of the catalyst for more than 24 h was observed, but slow deactivation of the system occurred after a stable conversion level had been reached [23].

It should be mentioned here that soluble supports are not always innocent systems but can in fact alter the reaction in rather unexpected ways: Cole-Hamilton and co-workers reported on dendrimers with 16 PPh_2 groups on the periphery. This system was applied in the Rh-catalyzed hydroformylation of 1-octene and linear/branched ratios (*l*/*b*) of 13.9 were obtained, while a small-molecule analogue showed an *l*/*b* ratio of 3.8 (**13**) [24].

Van Leeuwen and co-workers synthesized dendrimer-substituted P,O ligands for the Ni-catalyzed oligomerization and polymerization of ethylene (SHOP process; cf. also Chapter 3). Interestingly, a clear positive dendritic effect was obvious. The dendritic system showed a much higher productivity in toluene as the solvent than the unsupported *o*-hydroxyphenyl (diphenylphosphine)-Ni catalyst (**14**). In more polar solvents (methanol, THF), the parent compound was catalytically inactive due to formation of Ni bischelates, while the molecularly enlarged system produced mainly oligoethylenes. The presence of mainly monoligated dendritic Ni species under catalytic conditions was verified by high-pressure NMR spectroscopy [25].



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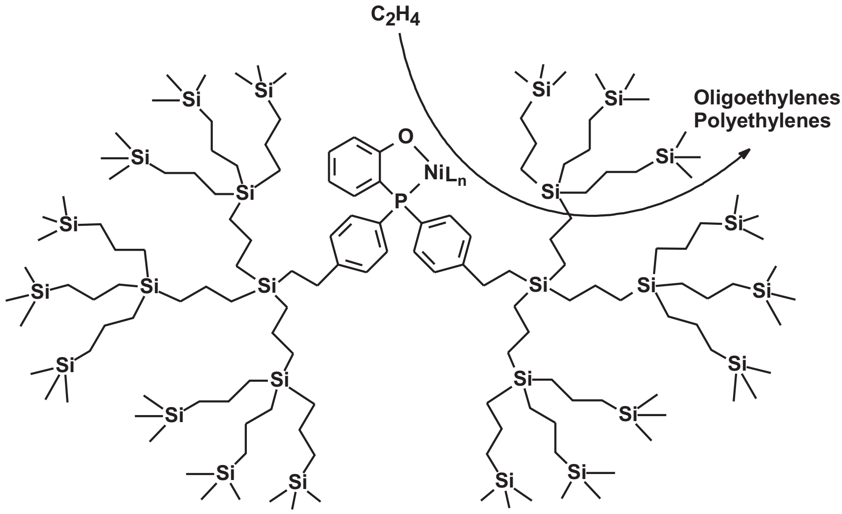

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7.4.1.3
Outlook

The binding of catalysts to soluble supports has the advantage that the catalytically active sites are uniformly distributed throughout the reaction media, as for the unsupported homogeneous counterparts. Furthermore, supported catalysts – especially dendritic systems – can sometimes show even higher selectivities than their small-molecule counterparts. Dendrimers as soluble supports, however, are not always easy to synthesize and usually require tedious synthetic protocols.

Therefore, easy-to-synthesize, robust, and inert materials which are soluble in common solvents and large enough to be retained by membranes have to be developed. At the same time, they should be accessible in large quantities, yet at affordable costs. Nanostructured supports such as polyoxometallates, hybrid inorganic/organic composites, or polyhedral oligosilsesquioxanes (POSS) are promising candidates for the molecular weight enlargement of homogeneous catalysts and their application in continuous-flow membrane reactors. Intensive research in the field of POSS-substituted metal complexes is currently being performed in our laboratories. However, the design of new membranes and reactors which are compatible with organic solvents and organometallic reagents under more drastic reaction conditions (elevated temperature, pressure) are required to develop this fascinating area of homogeneous catalysts supported on soluble materials to its full potential.

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7.4.2
Coupling Reactions

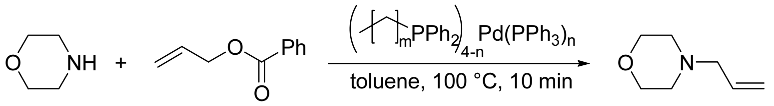
Stefan Mecking and Ulf Schlotterbeck

Coupling reactions, most prominently Heck and Suzuki coupling but also Sonogashira coupling and allylic substitution, are established catalytic transformations for the synthesis of fine chemicals. The recovery of catalytically active complexes from such coupling reactions, by the concept of covalent binding to soluble polymers, has been studied by various research groups. This research, addressed in the following section, has been carried out for the largest part only since the late 1990s. On a different level, since approximately the same time, coupling reactions with palladium colloids as catalysts have also attracted substantial interest. In addition to the synthetic utility and also catalyst re-use, the challenging question of the mechanistic function of colloids has been the focus of attention. The colloids employed are usually stabilized either by polymers or by low molecular weight surfactants. Coupling reactions with colloids are discussed in Sections 7.4.2.2 and 7.4.2.3.

7.4.2.1
Polymer-Bound Metal Complexes as Catalysts for C–C and C–N Coupling

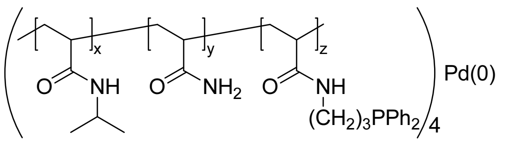
In an early report dating from 1989, Bergbreiter et al. reported on phosphine-terminated ethylene oligomers (M_n = 1400–2000 g mol^{-1}) as ligands for Pd(0) complexes, used as precursors for allylic substitution of allyl esters with secondary amines [Eq. (1)]. The reactions were carried out at elevated temperatures around 100 °C, at which the polymeric ligand is soluble (complete conversion in 10 min at

100 °C in toluene, 2 mol% palladium). Upon cooling to room temperature the complex was precipitated and could be separated by centrifugation. Repeated recycling over nine cycles was possible without an observed reduction in activity or loss of palladium (< 0.001%) [1].



(1)

Allylic substitutions were also carried out with Pd(0) complexes as catalyst precursors with phosphine ligands bound covalently to polar polymers, namely random copolymers of acrylamide and *N*-isopropylacrylamide (PNIPAM) (**1a**, $M_v = 500\,000$, determined by viscometry). After the catalytic reaction, the polymer-bound catalysts were precipitated by adding the reaction mixture to an apolar solvent and could be re-used for further cycles (with an average of 93% conversion in ten consecutive reaction cycles, each 6 h at 50 °C in THF/H_2O 1 : 1, 1 mol% palladium) [2].



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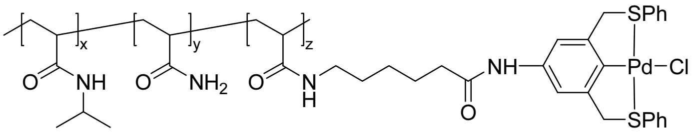

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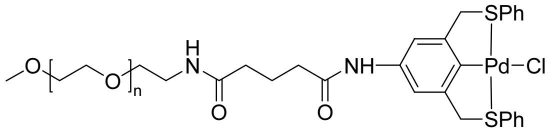
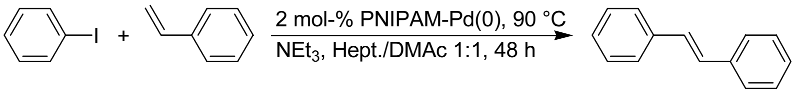


1c

After 15 consecutive reaction cycles, only a slight loss in productivity was observed, which was ascribed to a partial oxidation of the phosphine ligand. The fact that these polymers were no longer soluble in neat water above a certain temperature was used as an alternative for separating this catalyst; the polymers were precipitated upon heating and could be separated. However, this concept required the catalytic reaction to be performed at lower temperatures (10 °C), consequently resulting in longer reaction times [2].

A further possible way to separate the catalyst is to employ a biphasic system, in which the polymer-bound complex is soluble selectively only in one phase, while the substrates and products are soluble in the other phase. Fluorinated polymers are, for example, selectively soluble in fluorous solvents or in supercritical CO_2. By phase separation the catalyst can be recovered (cf. also Chapters 4 and 6). A variation of these permanently biphasic mixtures is, e.g., a polar and an apolar phase which are miscible at elevated temperatures to form a single phase. Such solvent combinations have been termed “thermomorphic”.

The aforementioned PNIPAM-bound palladium(0) complexes (**1a**) were employed as catalyst precursors for Heck and Suzuki coupling under “thermomorphic” conditions in heptane/DMAc or heptane/EtOH/water, respectively [Eqs. (2) and (3); DMAc = dimethylacetamide] [3]. After cooling to room temperature, the heptane-rich phase formed was separated from the polar phase containing the polymer-bound catalyst. New heptane solution of the substrate was added to the catalyst phase. In three consecutive cycles, no loss in activity was observed.



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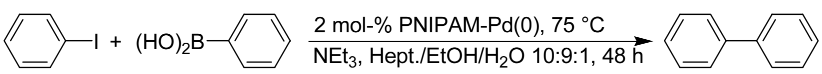


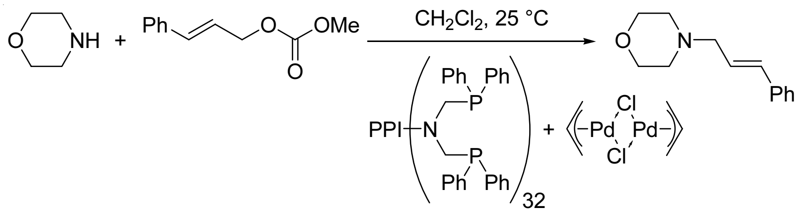
(3)

In allylic substitutions, a similar behavior was observed in “thermomorphic” solvent mixtures to that in the aforementioned reaction in toluene (100% conversion in five consecutive reaction cycles, each 11 h at 70 °C in heptane/EtOH/H_2O, 10 : 9 : 1) [4].

PNIPAM- and PEO-bound Pd(II) pincer complexes (**1b**: M_v = 870 000 g mol^{-1}; **1c**: M_n(PEG) = 5000 g mol^{-1}) were used for the same reactions (20 h at 95 °C, 0.2 mol% palladium, NEt_3) in heptane/DMAc/H_2O (20 : 9 : 1). In contrast to the Pd(0) phosphine complexes, these catalyst precursors are not sensitive to oxidation (to the phosphine oxides). Again, over five consecutive cycles under the reaction conditions chosen, no decrease in catalyst activity is evident [3].

Very recently, Plenio and co-workers investigated Sonogashira and Suzuki coupling in biphasic organic systems, such as DMSO/cyclohexane, with catalysts formed in situ from complexes [$(RCN)_2PdCl_2$] and polymers substituted with bulky electron-rich diadamantylphosphine moieties. Depending on the preference of the substrate for either of the two phases, the catalyst was made soluble in the other phase by choice of poly(ethylene glycol) or polymethylstyrene, respectively, as the soluble polymeric support. For example, in the Sonogashira coupling of bromoacetophenone with phenylacetylene, a very small reduction in catalyst activity from an average TO of 220 h^{-1} in the first cycle to 210 h^{-1} in the fifth cycle was observed. High yields were obtained for various substrates (cyclohexane/DMSO; 60 °C; 1 mol% catalyst; 5000 g mol^{-1} phosphine-substituted polymethylstyrene) [5]. Reactions were also run in a bubble-column type reactor in continuous mode with similar results [6]. Palladium losses were determined to be less than 0.005% with DMSO as the catalyst phase by means of total reflection X-ray fluorescence [7].

Continuous catalyst recovery by means of ultrafiltration in a membrane reactor was described by Kragl and Reetz for an allylic substitution reaction [Eq. (4)] [8].

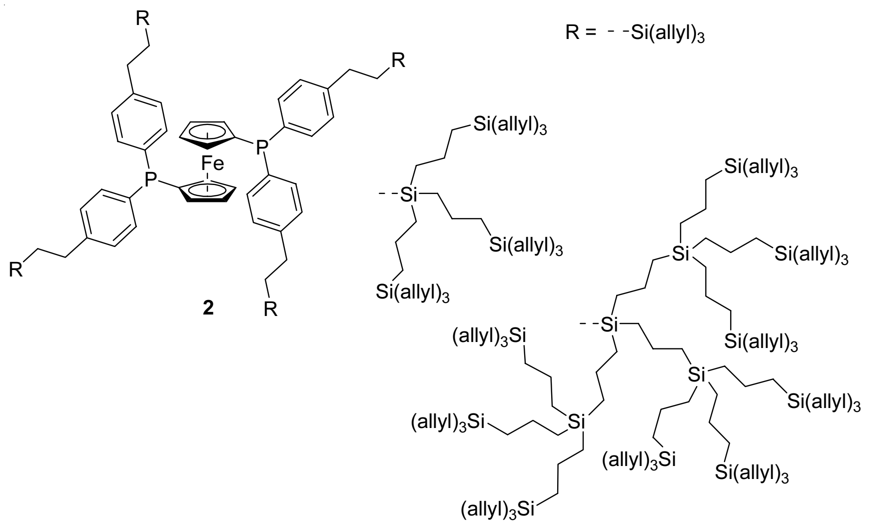


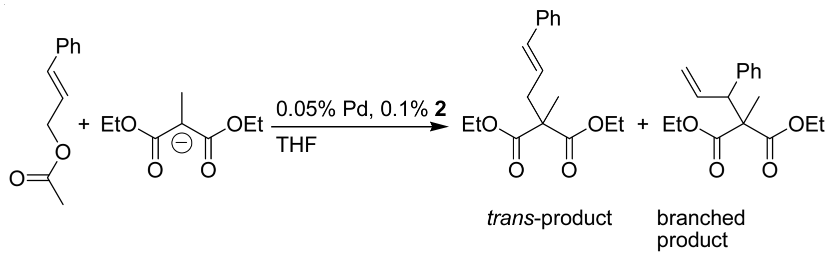
(4)

A second- or third-generation poly(propylene imine) dendrimer substituted with diphosphine end-groups was utilized as a polymeric ligand. The catalyst was prepared in situ with either the dimeric allylpalladium(II) chloride as a palladium source, or the well-defined complex PPI(G2)-[(diphosphine)PdMe$_2$]$_{16}$. For the former, solutions of the substrates methyl 3-phenylprop-2-enyl carbonate (30 mmol L^{-1}) and morpholine (60 mmol L^{-1}) in methylene chloride were pumped into the reactor continuously at a rate of 20 mL h^{-1}, with a catalyst concentration of 30 mmol L^{-1} palladium in the membrane reactor. Palladium losses of 0.07% to 0.14% per exchanged reactor volume were observed. The observed slight decrease in conversion from full conversion to 75% after 100 exchanged reactor volumes could not be ascribed to palladium losses by leaching alone. A part of the catalyst was apparently deactivated by other pathways. The TTN in the aforementioned experiment corresponded to 95. Nonetheless, the catalyst displayed a considerable stability under the reaction conditions.

The same catalyst precursor PPI(G2)-[(diphosphine)PdMe$_2$]$_{16}$ was employed by Reetz and co-workers for Heck reactions [9]. By addition of diethyl ether the polymer-bound catalyst could be precipitated and isolated by filtration. Upon its repeated use for catalysis, a slight decrease in activity was observed. By contrast to analogous low molecular-weight catalysts that were not polymer-bound, no formation of palladium black was observed with the dendrimer-bound catalyst.

In addition to the utilization of dendrimers as multifunctional polymeric supports for catalytically active complexes by means of their end-groups, core-functionalized dendrimers have also been investigated. By comparison, in the latter approach the molar mass per active site is rather high. However, selectivity induced by shielding of the metal center may be of interest. Van Leeuwen et al. prepared carbosilane dendrimers of various generations with a bidentate ferrocenylphosphine as the core unit (**2**). These ligands were employed in the palladium-catalyzed allylic alkylation of 3-phenylallyl acetate with sodium diethyl 2-methylmalonate [Eq. (5); complete conversion at room temperature within 24 h; 0.05 mol% palladium]. With increasing generation number, a slight change of the regioselectivity in favor of the branched product was observed [10]. A possible explanation is an increase in the steric demand of the ligand with increasing dendrimer generation, or also the increasingly apolar local environment of the active site.





(5)

7.4.2.2
C–C Coupling by Palladium Colloids

This section describes C–C coupling by "soluble" palladium colloids, i.e., palladium nanoparticles dipersed in a liquid phase, the particles being colloidally stabilized by polymers. As they do not differ fundamentally either in terms of selectivity and activity in catalysis or in physical properties, e.g., those relevant for catalyst recovery, palladium colloids stabilized by low molecular weight surfactants and ligands are also included.

There is evidence in some cases that C–C coupling by heterogeneous catalysts also occurs by soluble metal colloids (or smaller species) leached from solid supports, such as silica. In the 1970s, the catalytic activity of palladium black for C–C coupling was already reported by Mizoroki et al. [11, 12]. Various examples of Heck reactions with "heterogeneous" catalysts have been reported since then [13]. Therefore, while heterogeneous catalysts are not the main focus of this section, they are addressed where appropriate.

C–C coupling by metal colloids has only received attention since about the mid-1990s. In 1996, Beller et al. reported on Heck coupling by palladium colloids [14].

The latter were prepared by reducing $PdCl_2$ with tetraalkylammonium triethylborohydride [15]. High activities were observed only with activated aryl bromides, in particular with 4-bromoacetophenone in coupling with butyl acrylate. Adding a freshly prepared colloid to the reaction mixture resulted in a temperature increase of 20 °C within 5 min at a low catalyst loading (97% conversion; 0.05 mol% palladium; DMAc as a solvent; 140 °C; activity, TO ca. 24 000 h^{-1}) (Table 1). Only with freshly prepared colloids were high conversions observed. Irreproducible results were obtained when the colloid was added prior to heating the reaction mixture to the reaction temperature; these were ascribed to a thermal instability of the colloids.

Reetz et al. reported on catalytically active solvent-stabilized colloids in propylene carbonate, which were prepared electrochemically or by thermal decomposition of $[Pd(OAc)_2]$ assisted by ultrasound. The colloidal particles had sizes of 8 to 10 nm, as determined by TEM. After addition of aryl bromide, styrene, and base to the colloid solution, satisfactory conversions were obtained within reaction times of 5–20 h. Isolation of the particles stabilized by propylene carbonate was not possible, however [16]. The same authors also reported Suzuki and Heck reactions with electrochemically prepared Pd or Pd/Ni colloids stabilized by tetraalkylammonium, as well as polyvinylpyrrolidone (PVP)-stabilized palladium colloids prepared by hydrogen reduction (Table 1) [17]. It was assumed that the reaction occurs on the nanoparticle surfaces.

In 1997, Antonietti et al. reported on catalytically active palladium nanoparticles prepared by reduction of palladium(II) compounds in inverse block copolymer micelles, namely polystyrene-*b*-poly(4-vinylpyridine) (PS-*b*-P4VP). Activated aryl bromides were coupled reproducibly in Heck reactions [18]. Small particle sizes were a prerequisite for high conversions, as indicated by qualitative TEM investigations. Very high total turnovers were reported (0.0012 mol% palladium, 68% conversion in five days, corresponding to 56 000 TO) (Table 1). Catalyst activity was found to be dependent on the structure of the block copolymer employed, which was attributed to a better accessibility of the metal particles in smaller micelles with a high surfacer area and thinner polystyrene layer.

Bradley et al. employed PVP-stabilized palladium colloids, which were "pretreated" with the base and the olefin at the reaction temperature prior to addition of the aryl halide (Table 1) [19]. The colloids were prepared by stirring $[Pd(dba)_2]$ in the presence of PVP at variable hydrogen pressures, affording particles of different average particle size (diameter 1.7 ± 0.5 nm to 3.7 ± 0.3 nm). The initial activities of Heck reactions catalyzed by these colloids of different average particle size were correlated with the number of low-coordinated atoms, i.e., corner and edge atoms in the palladium particles rather than all surface atoms. A general difficulty in such considerations is that the particles are not monodisperse, and also are not ideal cuboctahedra.

El-Sayed and co-workers more recently reported on the catalytic activity of PVP-stabilized aqueous palladium colloids in Suzuki reactions (substrates: 2-iodothiophene or phenyl iodide and 2-thiophene boronic acid or phenylboronic acid; 0.3 mol% palladium; 12 h reflux) (Table 1) [20]. They did not find such a clear

Table 1 Examples of C–C coupling reactions catalyzed by palladium colloids stabilized by polymers or surfactants.

Ref.	*Stabilizer*	*Solvent*	*Cat. [mol%]*	*d_{TEM} [nm]*	*Substrates*	*Base*	*T [°C]*	*Time [h]*	*Conv. [%]*	*Reaction type*
[14]	$Oct_4N^+Cl^-$/b	DMAc	0.05	n.d.	BrAc; BuA	NaOAc	140	0.08	97	HE
[16]	PC	PC	3.5	8–10	BrNi; S	NEt_3	130	21	96	HE
[17]	$Oct_4N^+Br^-$/b	DMAc	2[a)]	2–3	BrB; PhB	KOAc	120	2.5	100	SU
[17]	PVP	DMAc	0.5	n.d.	BrB; PhB	KOAc	100	3.5	100	SU
[17]	$Oct_4N^+Br^-$/e	DMF	1	3	IB; BuA	$NaHCO_3$[b)]	30	14	~100	HE
[18]	PS-*b*-P4VP	xylene	0.05	n.d.	BrAc; BuA	NBu_3	140	48	93	HE
[19]	PVP	DMAc	0.025	2–4	BrBA; BuA	NaOAc	140	1	> 95	HE
[20]	PVP	H_2O[c)]	0.3	3.6	IB; PhB	Na_3PO_4	R[d)]	12	95	SU
[29]	$Oct_4N^+HCO_2^-$	DMF	2[e)]	2	BrNi; PhB	K_2CO_3	110	2	100	SU
[22]	PAMAM-OH	EtOH	0.055	3.2	IB; TB	K_2CO_3	R[d)]	18	98	SU
[26]	star-PS-*b*-P2VP	xylene	0.5	2–3	BrNi; BuA	NBu_3	125	2	96	HE
[27]	polyacrylate microgel	DMAc	0.1	4.2	BrAc; BuA	NaOAc	120	1	89	HE

Stabilizer: $Oct_4N^+Cl^-$/b, colloid prepared by reduction with $[Oct_4N]^+[BEt_3H]^-$; PC, propylene carbonate; $Oct_4N^+Br^-$/e, prepared electrochemically; PS-*b*-P4VP, block copolymer polystyrene-*b*-poly(4-vinylpyridine); $Oct_4N^+HCO_2^-$, colloid prepared by reduction with $[Oct_4N]^+[HCO_2]^-$; PAMAM-OH, hydroxy-terminated PAMAM dendrimer; star-PS-*b*-P2VP, star polymer with cross-linked polystyrene core; acrylate microgel, cross-linked acrylate microgel partially substituted with amines.

Substrates: BrAc, 4-bromoacetophenone; BrB, bromobenzene; BrBA, 4-bromobenzaldehyde; BrNi, 4-bromonitrobenzene; BuA, butyl acrylate; IB, iodobenzene; PhB, phenylboronic acid; S, styrene; TB, 4-tolylboronic acid.

Reaction type: HE, Heck reaction; SU, Suzuki reaction.

a) Pd/Ni bimetallic colloid (1 : 3).

b) $NaHCO_3/Bu_4NBr$.

c) H_2O : EtOH 6 : 4 (v/v).

d) Reflux.

e) Pd/Cu bimetallic colloid (1 : 1).

correlation of particle size and activity. In addition to PVP, hydroxy-terminated PAMAM dendrimers or polystyrene-*block*-poly(sodium acrylate) also stabilized colloids, which were catalytically active [21, 22]. Colloids stabilized by the G4 dendrimer were found to be more stable than those stabilized with the G3 dendrimer or the linear polymers, but they also possessed a lower activity. This was attributed to a more efficient shielding of the metal particles by the higher-generation dendrimer, findings similar to those on hydrogenations of various allyl alcohols [23]. Reasonable conversions were only observed with aryl iodides however.

Suzuki reactions of phenylboronic acid with phenyl iodide were investigated further, employing PVP-stabilized palladium particles of different average sizes from 3 to 7 nm [24]. TEM investigations reveal that particle sizes increase under reaction conditions. Beyond this, results concerning effects of particle sizes and colloid concentrations on reaction rates are not straightforward, and various explanations have been brought forward to account for experimental observations [24, 25].

Fréchet and Hawker prepared polystyrene-*block*-poly(2-vinylpyridine) (PS-*b*-P2VP) block copolymers with an alkoxyamine moiety on the P2VP block by nitroxide-mediated controlled free-radical polymerization. In a second step, star polymers with ca. 40 to 50 arms and a cross-linked polystyrene core were prepared by terpolymerization of these block copolymers with styrene and divinylbenzene (1 : 4 : 10). The resulting polymers solubilized [$Pd(OAc)_2$] and stabilized palladium colloids formed upon heating with ethanol as a reducing agent [26]. The colloids were active for the Heck reaction of activated aryl bromides with butyl acrylate (Table 1). No undesired formation of palladium black was observed, and the colloids retained an identical performance upon recycling by preciptiation with methanol over four repeated cycles.

Biffis et al. employed soluble microgels to stabilize colloidal palladium particles [27, 28]. These cross-linked polyacrylates, characterized by gel permeation chromatography, contained amino groups, which coordinate palladium ions. Reduction results in colloids with particle sizes of 3 to 9 nm. Particle sizes can be influenced by the degree of crosslinking of the microgel. Heck reactions of activated aryl bromides proceed with high activities (Table 1).

In 2002, Rothenberg et al. reported on Suzuki reactions catalyzed by surfactant-stabilized colloids of Cu, Pd, Pt, or Ru or bimetallic combinations of these metals [29]. The colloids were prepared of metal salt solutions in DMF with tetraoctylammonium formate, which served as a reducing agent as well as a stabilizer. Interestingly, ruthenium and even copper colloids were found to convert aryl iodides completely to the corresponding biphenyls, albeit more slowly than palladium colloids.

Gedanken et al. prepared palladium nanoparticles by decomposition of [$Pd_2(dba)_3$] or [$Pd(OAc)_2$]/$Me_3(C_{14}H_{29})NBr$ by extended exposure to ultrasound. In the case of [$Pd_2(dba)_3$], the colloidal metal particles were stabilized by amorphous carbon formed from dba. Activities of the soluble colloids in the Heck reaction were comparable to those of the "heterogeneous" catalyst palladium on charcoal (Table 2) [30, 31].

Table 2 Examples of C–C coupling reactions with colloids stabilized by other means than polymers or surfactants and Heck coupling with heterogeneous catalysts.

Ref.	***Stabilizer***	***Solvent***	***Cat. [mol%]***	***d_{TEM} [nm]***	***Substrates***	***Base***	***T [°C]***	***Time [h]***	***Conv. [%]***	***Reaction type***
[30]	$C_{amorphous}$	DMF	~1.6	~2	BrB; S	KOAc	125	20	30	HE
[32]	$[PW_{11}O_{39}]^{7-}$	H_2O[a)]	0.01	15[b)]	BrAc; PhB	*i*Pr_2NH	85	12	92	SU
[32]	$[PW_{11}O_{39}]^{7-}$	H_2O[a]	0.01	15[b)]	TBr; S	*i*Pr_2NH	85	16	95	HE
[34]	$(bbim)^+X^-$	$(bbim)^+X^-$	1	~2	IB; EtA	NaOAc	30	1.5	87	HE
[35]	$Bu_4N^+X^-$	$Bu_4N^+Br^-$	1.5	3.3	TBr; ZE	$Bu_4N^+OAc^-$	130	1	95	HE
[36]	PPI-F	FC-75/org[c)]	3–5	2	IB; BuA	NEt_3	90	24	70	HE
[54]	Pd/C	NMP	0.005	3	BrB; S	NaOAc	140	2	90	HE
[52]	Pd/C	NMP	1.5	5	IB; MA	Na_2CO_3/NEt_3	160	0.5	100	HE

Stabilizer: $C_{amorphous}$, amorphous carbon; $[PW_{11}O_{39}]^{7-}$, Keggin ion; $(bbim)^+X^-$, dibutylimidazolium salt (ionic liquid); $Bu_4N^+X^-$, ionic liquid; PPI-F, perfluoroalkyl-substituted PPI dendrimer; Pd/C, palladium on charcoal.
Substrates: BrAc, 4-bromoacetophenone; BrB, bromobenzene; BuA, butyl acrlyate; EtA, ethyl acrylate; IB, iodobenzene; MA, methyl acrylate; PhB, phenylboronic acid; S, styrene; TBr, 4-tolylbromide; ZE, *E*-ethyl cinnamate.
Reaction type: HE, Heck reaction; SU, Suzuki reaction.

a) $H_2O/EtOH$ (2 : 8) (v/v).
b) Incl. stabilizer.
c) Perfluoro-2-butyl-THF (FC-75)/heptane/benzene (2 : 1 : 1).

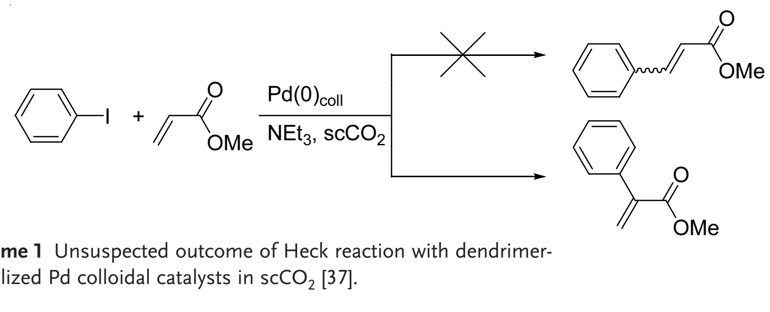
In addition to surfactants and polymers, other compounds have also been studied as stabilizers. Water-soluble polyoxometallate-stabilized nanoparticles display satisfactory activities in Suzuki, Heck and Stille reactions in aqueous solution (Table 2) [32]. Thiol-substituted cyclodextrins have been employed as stabilizers for palladium colloids, which were active in Suzuki reactions, although the stability was limited [33].

Examples of C–C coupling with palladium colloids in *biphasic* systems have also been reported. Heck-coupling and copper-free Sonogashira coupling with [Pd(OAc)$_2$] in ionic liquids have been studied (Table 2) [34]. Under ultrasound, high conversions were obtained within 1.5 to 3 h. The product was isolated from the ionic liquid phase by extraction with organic solvents. A palladium—carbene complex formed under the reaction conditions of C–C coupling was assumed to be the source of colloidal palladium particles, as TEM investigations of a reaction mixture after a Heck reaction suggest. The catalytic system is active only toward aryl iodides (see also Section 2.4.4.4).

Another report on Heck reactions in ionic liquids also confirms that, in Bu$_4$NBr as an ionic liquid, [Pd(OAc)$_2$] rapidly reacts to form catalytically active colloidal particles [35]. The authors point out that it is unclear whether the palladium particles are the actual active species or whether they are a precursor to the latter.

Polypropylene imine dendrimers with covalently attached perfluorinated poly(propylene oxide) end-groups have been employed for the stabilization of palladium colloids in Heck reactions in fluorous solvents by Crooks et al. [36] (Table 2). Relatively low activities were obtained, which were further reduced upon re-use of the fluorous phase in a second cycle. From the results of repeated Heck reactions without an added base, it can be assumed that the reduction in activity upon recycling is due to protonation of the dendrimer scaffold, serving as a base. No leaching of palladium from the fluorous phase was detected (< 0.01 ppm); however, this value was not related to the overall palladium loading (cf. also Section 4.2).

Employing the same dendrimer-stabilized palladium colloids for Heck reactions in supercritical carbon dioxide, after 24 h reaction time and 55% conversion no further reaction was observed for reasons not clarified. Remarkably, methyl 2-phenylacrylate was formed exclusively instead of the expected methyl cinnamate (Scheme 1) [37].



Scheme 1 Unsuspected outcome of Heck reaction with dendrimer-stabilized Pd colloidal catalysts in scCO$_2$ [37].

7.4.2.3
Homogeneous or Heterogeneous Catalysis in C–C Coupling by Palladium Colloids?

The importance of colloids in C–C coupling reactions is generally accepted today. The open question remains whether colloidal particles themselves represent the true active species, or whether they are a precursor to smaller structures – ultimately mononuclear soluble metal complexes – as the active species. Along the same lines, for homogeneous catalysis with defined metal complexes as a precursor, it is debatable whether colloidal particles form as the true active species (Figure 1). The topic is attractive due to its relevance for the fundamental understanding of such catalytic reactions, as well as its practical importance. Ultimately answering the aforementioned questions is very difficult, as the actual active species can have very high activities of millions of turnovers per hour [13], making them hard to detect in the very low concentrations in which they are present.

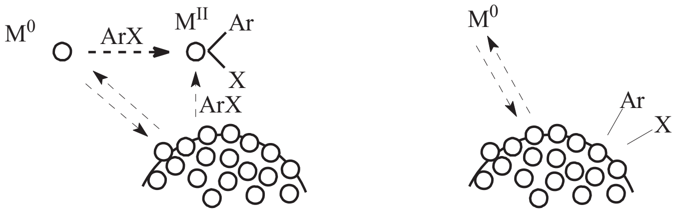


Figure 1 True active species (colloidal vs. smaller structures).

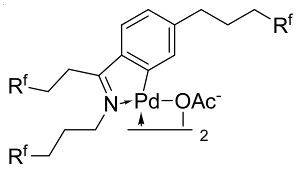
Mizoroki et al. demonstrated as early as 1971 that palladium black is active for the reaction of iodobenzene with styrene [11]. Beyond 2 mol% palladium black, no increase in activity was observed upon increasing the amount of catalyst [12]. The authors concluded that the reaction does not occur on the surface of palladium black in a heterogeneous fashion, but that the aryl halide reacts with palladium to form a soluble species. The low solubility of such compounds in the methanol solvent used was assumed to result in saturation by the soluble active species at low concentrations, accounting for the lack of effect of further increases in the amount of palladium black. At the same time, Julia et al. investigated the catalytic activity of palladium on charcoal for the Heck reactions, but focusing on the reactivity of aryl chlorides rather than mechanistic aspects [38, 39].

Reetz et al. addressed the function of palladium colloids in palladium-catalyzed C–C coupling reactions [40]. The homogeneous catalyst system $[PdCl_2(PhCN)_2]$/*N,N*-dimethylglycine (DMG) shows a clear induction period of ca. 1 h. Only after this time were colloidal 1.6 ± 0.3 nm palladium particles also detected by TEM of the reaction solutions. Nanoparticles are formed too in phosphine-free Heck reactions with addition of Bu_4NBr (Jeffrey conditions) as well as in Suzuki coupling utilizing only $[Pd(OAc)_2]$. On the other hand, with $[Pd(OAc)_2]/PPh_3$ or Herrmann's palladacycle [41] no nanoparticles were observed in the reaction solutions. Also, the tetraalkylammonium-stabilized colloids used in some investigations were found to react with aryl iodide to form soluble palladium(II) species (Ar–Pd–X_n), even with stoichiometic amounts [42].

In their investigations of Heck reactions of aryl bromides with very active “ligand-free” catalysts, based on [Pd(OAc)$_2$], de Vries et al. found that turnover frequencies increase strongly with decreasing catalyst concentration in the range 0.01–0.1 mol% palladium under a given set of conditions (135 °C; reaction of phenyl bromide with butyl acrylate) [43]. At a high concentration of 1 mol%, the reaction stops at an early stage and virtually no conversion is observed. These observations were ascribed to the active species being in equilibrium with (inactive) soluble palladium colloid particles, which can aggregate to palladium black. Thus, high catalyst concentrations would favor deactivation.

Extended X-ray absorption fine structure (EXAFS) analysis has been employed recently for the investigation of the role of colloids in catalysis. For Heck reactions with Herrmann’s palladacycle or with [Pd(OAc)$_2$]/P(*tert*-Bu)$_3$, no indication of formation of colloidal palladium was found [44]. By contrast, Koningsberger and co-workers found that in allylic amination with allylpalladium complexes with bidentate phosphine ligands, from the early stages of the reaction onward, deactivation occurs by formation of di- and trinuclear clusters, which aggregate to larger clusters and finally to palladium black [45].

A further well-documented example of the occurrence of metal colloids in homogeneous catalysts derived from defined transition metal complexes is provided by investigations by Gladysz et al. of Heck reactions with perfluro-substituted palladacycles (**3** and **4**) [46, 47]. The complexes are soluble in DMF at elevated temperatures, display high activities, and can be recovered by precipitation upon cooling. The course over time of the reaction, which has an induction period, the recycling behavior, and finally TEM images of the DMF solution after the Heck reaction suggest that colloidal palladium particles are the active species. As a stabilizer, $Et_3NH^+X^-$ formed in the Heck reaction was suggested.



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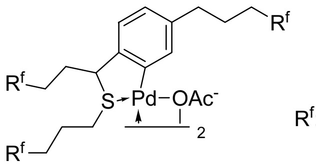

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R^f: *n*-C_8F_{17}

Studies on C–C coupling reactions with heterogeneous palladium catalysts are also of interest in the context of the role of palladium colloids in such reactions. In early studies Augustine and O’Leary concluded that Heck reactions with supported palladium catalysts occurred in a heterogeneous fashion [48, 49]. By contrast, the occurrence of soluble palladium compounds also with heterogeneous palladium catalysts has been demonstrated in recent years by different research groups. In the examples investigated, the onset of the reaction was accompanied by significant “leaching” of palladium species into the liquid phase [50].

Biffis et al. concluded that, in C–C coupling reactions, heterogeneous catalysts are only a source of the actual soluble active species, which is formed under reaction conditions by interaction of the catalyst with one or more of the reagents [50]. They argued that the finding of a correlation of the number of corner and surface atoms with the catalyst activity of colloids in Heck reactions [19] and Suzuki reactions [24, 25] could also be explained by these atoms being particularly susceptible to dissolution as (mononuclear) complexes.

Arai et al. investigated Heck coupling of iodobenzene with methyl acrylate by heterogeneous palladium catalysts based on silica or charcoal as a support. Under reaction conditions a substantial portion of the palladium was already present in the liquid phase in the early stages of the reaction, and activities correlated with the palladium concentration in solution [51, 52]. The presence of only base or olefin did not result in detectable palladium concentrations. By comparison to silica, charcoal had a stronger propensity for readsorbing palladium from solution. Under appropriate conditions, a catalyst could be recycled without loss in activity [53].

In investigations of Heck reactions with different palladium-on-charcoal heterogeneous catalysts, Köhler and co-workers found that among other factors the palladium particle size had a strong effect [54]. A high degree of dispersion resulted in stronger leaching under reaction conditions, and consequently higher activities. Palladium concentrations in the liquid phase were highest in the early stages of the reaction. At the end of the reaction, the palladium was adsorbed onto the solid support again nearly completely. Palladium particle sizes on the support were significantly increased after the reaction, as studied by TEM. Consequently, activities upon re-using these catalysts were significantly lowered by comparison to the first run.

In summary, palladium colloids are precursors to highly active catalysts for C–C coupling reactions. Whether the colloidal metal nanoparticles are the active species, or whether catalysis occurs by soluble metal complexes formed from the colloids under reaction conditions, cannot be answered unambiguously in a general sense to date.

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7.4.3
Oxidation Reactions

Ana M. Santos and Fritz E. Kühn

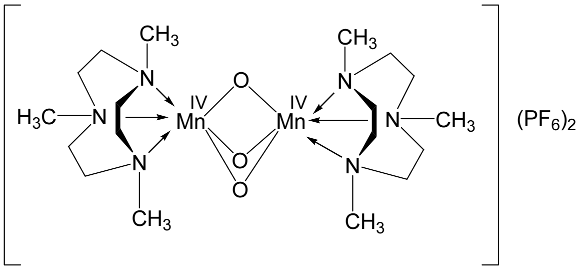
7.4.3.1
Introduction

Oxidation reactions are a field of outstanding importance within the possible application areas of catalysts. For several decades catalysts for oxidation reactions have been under intensive investigation, again spanning a broad field including heterogeneous catalysts [1], homogeneous catalysts [2], surface-bound organometallic catalysts [3], etc. More recently, the use of polymers as anchoring units for catalysts also came into the scope of oxidation catalysis. Most of the reported materials, however, are not soluble but act as heterogeneous carrier materials with defined catalysts in a certain, fixed concentration bound to their surface [4]. As polymeric catalyst supports, a wide range of materials, such as polymers with organic and organometallic functional groups, ion-exchange resins, membranes, and polyelectrolytes have been employed, and several methods have been developed to functionalize polymers for catalyst attachment [5]. Furthermore, transition metal complexes or metal ions anchored to polymer matrixes represent useful model systems of natural metalloenzymes [6]. Oxidation catalysts have been successfully anchored on polymers and applied as heterogeneous catalyst systems that are defined and comparatively easy to remove from the product/substrate fractions [7]. Nevertheless, the use of polymeric soluble systems is not yet very well developed, despite the fact that the major usefulness of this approach also in oxidation catalysis is evident. However, there is a clear increase in the research efforts made in this field, most of the studies having been performed quite recently.

The applications reported for polymer-supported, soluble oxidation catalysts are the use of poly(vinylbenzyl)trimethylammonium chloride for the autooxidation of 2,6-di-*tert*-butylphenol [8], of copper polyaniline nanocomposites for the Wacker oxidation reaction [9], of cationic polymers containing cobalt(II) phthalocyanate for the autooxidation of 2-mercaptoethanol [10] and oxidation of olefins [11], of polymer-bound phthalocyanines for oxidative decomposition of polychlorophenols [12], and of a norbornene-based polymer with polymer-fixed manganese(IV) complexes for the catalytic oxidation of alkanes [13]. Noncatalytic processes can also be found, such as the use of soluble polystyrene-based sulfoxide reagents for Swern oxidation [14]. The reactions listed above will be described in more detail in the following paragraphs.

7.4.3.2
Oxidation of Olefins

The oxidation of olefins has been of considerable industrial interest since the early 1970s and a broad variety of both heterogeneous and homogeneous catalysts have been investigated and employed in both industrial and research laboratories [15]. The main oxidizing agents employed are currently TBHP (*tert*-butyl hydroperoxide), H_2O_2, and O_2 [16]. From an environmental point of view, H_2O_2 (forming H_2O as a byproduct) and O_2 (no byproduct) are of significant interest as oxidants. Among the systems utilizing H_2O_2 as the oxidizing agent, manganese–triazacyclononane complexes have received considerable attention in recent years [17]. A report was first published in 1994 that manganese complexes derived from 1,4,7-trimethyl-1,4,7-triazacyclononane and related ligand systems act as highly active catalysts for the bleaching of stains by hydrogen peroxide at comparatively low temperatures in water [18]. H_2O_2, the traditional bleaching agent, was known to lose its activity as the washing temperature decreased. Therefore, peroxyacetic acid, maintaining an acceptable bleaching activity down to 40 °C, was often applied, but still lower temperatures would be desirable. The above-mentioned manganese compound, used as a catalyst, made it possible to apply the environmentally quite safe and cost-effective H_2O_2 at lower temperatures. Despite the fact that some disadvantages of this particular catalyst as an ingredient of detergents have been pointed out since then, several other applications in oxidation catalysis, among them epoxidation reactions, have been found and described for the catalyst **1** and some closely related systems [19].



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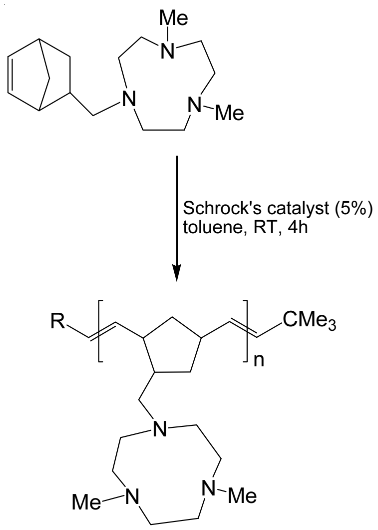
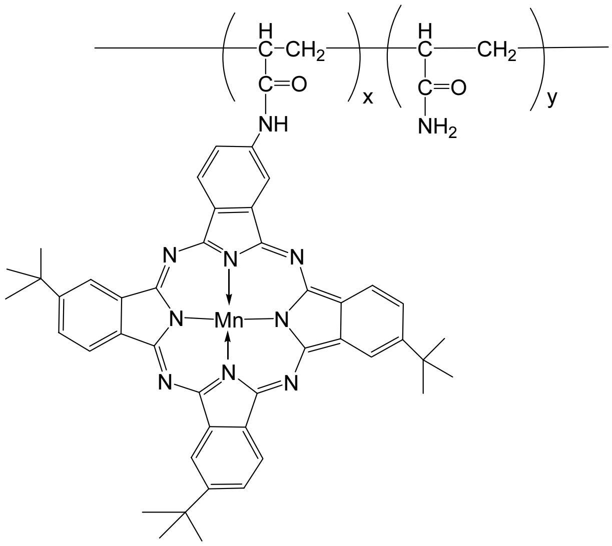
Dinuclear Mn(IV) catalysts were successfully applied for the epoxidation of 4-benzoic acid and styrene in aqueous systems [18], for the epoxidation of styrene and dodecene in two-phase systems [19g] as well as in methanol and acetone [17d, 19b,g,h], and for the epoxidation of olefins in acetonitrile [19i], aqueous acetonitrile [17f, 19c], acetone [17d, 19b,h], methanol [19i], and acetone–methanol–water mixtures [19j]. Enantioselective epoxidations of olefins have been reported for chiral triazacyclononane derivatives bound to $Mn(OAc_2) \cdot 4\,(H_2O)$ in methanol [19k]. Heterogenization of the Mn catalysts on silica for the epoxidation of styrene and cyclohexene, on zeolites for olefin epoxidation, and on a solid $MnSO_4 \cdot H_2O$ also for olefin epoxidation [20] has also been described. A polymeric structure bearing a dense arrangement of 1,4,7-triazacyclononane moieties can be synthesized by application of ROMP (Ring-Opening Metathesis Polymerization) [21]. With hydrogen peroxide as terminal oxidant, manganese complexes of such polymeric ligands efficiently catalyze epoxidations of simple olefins, exhibiting activities and selectivities which are comparable to those of the monomeric systems [11a]. Allylic and benzylic alcohols can also be oxidized; in the case of conjugated alkenes, other oxidation products such as diols are also formed. The Schrock molybdenum-based catalyst reacts with the free triamine rapidly and efficiently, allowing the preparation of the desired polymer in quantitative yield [Eq. (1)].



(1)

The catalytic runs employ 1 mol% of catalyst formed in situ from $Mn(OAc)_2 \cdot 4\,H_2O$ and the triazacyclononane-containing polymer. Both the ligand and the manganese compound are soluble in aqueous acetone–methanol–H_2O_2 mixtures. The presence of sodium oxalate as co-ligand proved essential for the efficiency of the reaction. An interesting observation is that the conversion of the substrates was negligible in the absence of the triazacyclononane-containing polymers. The performance of the polymeric systems in catalyzing the oxidation reactions was in most cases comparable or even superior to that of the monomeric azacycle. Simple aromatic olefins, e.g., styrene, α-methylstyrene, β-methylstyrene, and indene, were converted efficiently to the corresponding epoxides. In the case of α-methylstyrene and indene, notable amounts of diols were formed. Aliphatic alkenes were also epoxidized. In particular, internal (*Z*) systems reacted more effectively than terminal or (*E*) olefins [11a].

Manganese was also used for the catalytic oxygenation of cyclohexene, with a water-soluble polymer containing a manganese–phthalocyanine complex (MnPc). The cyclohexene was oxidized using H_2O_2 or sodium hypochlorite as oxidant in the presence of a nitrogen base. The polymer catalyst was an acrylamide polymer containing MnPc in the side chain, which was prepared by radical polymerization. The structure of the polymer (**2**) is shown [22].



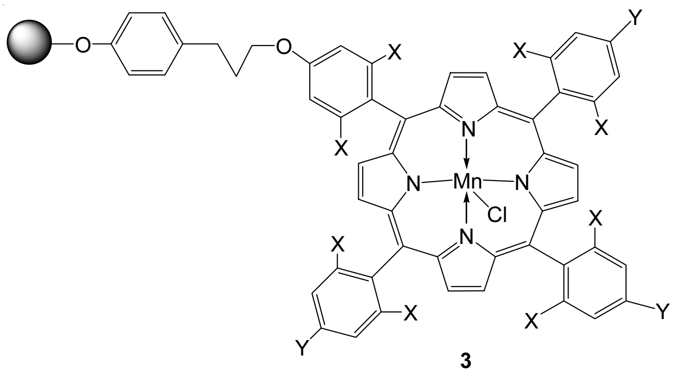
2

The reaction was conducted at room temperature, and with H_2O_2 only moderate yields of 46% were achieved. With sodium hypochlorite, yields of diol of 90% were obtained after a 4 h reaction time. Nevertheless, this system is not very efficient, since good results can only be achieved with a non-environmentally friendly oxidant.

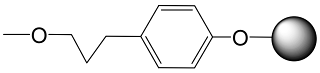
Another system studied pertains to the use of polyethylene glycol (PEG)-supported manganese(III)–porphyrin complexes for the epoxidation of olefins [23]. PEG polymers are inexpensive, readily functionalized and soluble in most organic solvents, but they can be easily precipitated in ethanol, allowing easy catalyst recovery. This represents an important advantage for catalytic systems containing porphyrins, since these ligands are difficult to synthesize and low-yielding [24]. The catalysts are obtained by reaction of the PEG-supported porphyrins with $Mn(OAc)_2$ in 70% yield (**3**).

The compounds were tested as catalysts in the epoxidation of several olefins (cycloooctene, styrene, 1-dodecene, cyclohexene, and indene) with iodosyl benzene (PhIO) or 30% aq. H_2O_2 as terminal oxidants. The higher yields were obtained with compound **3**, since the presence of bulky, electron-withdrawing substituents enhances their catalytic activity and stability, analogously to what had already been observed with the unsupported catalysts [25]. Quantitative yields were obtained for cyclooctene with PhIO as oxidant, and up to 10 000 turnovers were attained in a 28 h reaction using 0.01 equiv. of catalyst. The yield obtained with H_2O_2 was lower (70%); this oxidant requires the use of very robust metalloporphyrins, which can withstand this strongly oxidizing environment [26]. Good results were also obtained for the other substrates, except for 1-dodecene, a poorly reactive terminal alkene.

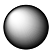
With supported Mn(III)–salen complexes [27], the use of polymer-bound catalysts for the asymmetric epoxidation of olefins is possible, allowing once more the easy recovery of the catalyst by precipitation with a suitable solvent [28]. Poly(ethylene



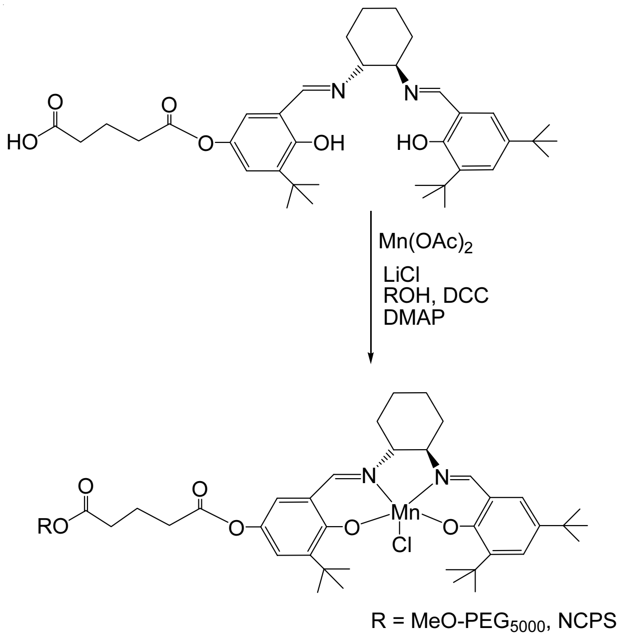
3

3a X = H, Y = 

3b X = Cl, Y = H

 = $CH_3O(CH_2CH_2O)_nCH_2CH_2^-$

glycol) monomethyl ether (MeO-PEG) and non-cross-linked polystyrene (NCPS) were used as soluble supports, and the polymers were linked to the salen catalyst through a glutarate spacer, as depicted in Eq. (2).



(2)

Styrene, *cis*-β-methylstyrene and dihydronaphthalene were used as substrates and in the case of cis-β-methylstyrene, conversions and *ee* values up to 85% could be achieved; these are comparable to the values obtained with a commercially available Mn–salen catalyst.

7.4.3.3
Oxidation of Alkanes

Another application of a catalytic system containing manganese is the oxidation of alkanes, e.g., cyclohexane or isooctane [13]. Several transition metal complexes are capable of catalyzing hydrocarbon oxidations (C–H activation reactions) by various oxygen donors, among them H_2O_2 and hydrogen peroxide [29]. In the particular case of manganese(IV) complexes with polymer-bound 1,4,7-triazacyclononanes as ligands, the catalytic oxidation reaction of alkanes is performed in acetonitrile at room and lower temperatures (5, 16 and 25 °C) with hydrogen peroxide as oxidant. It is interesting to note that the yields obtained are higher at lower temperatures. The catalytically active species is formed by reaction of the compound depicted in Eq. (1) with $MnCl_2$ followed by addition of H_2O_2 in an ethanol/water mixture and in the presence of NaOH. The catalyst, which is a Mn(IV) complex of the polymeric ligand, is obtained as a red solid in almost quantitative yields (95%).

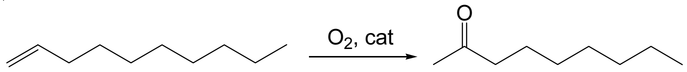
The corresponding alkyl hydroperoxides are obtained as main products in the initial period of the reaction. The addition of triphenylphosphine to quench the reaction leads to the formation of the corresponding alcohols or ketones. The reaction has to be performed in the presence of a small amount of acetic acid. In fact, the initial rate of the oxidation grows with increasing acetic acid concentration up to 0.5 mol L^{-1}. Both the oxidation rate and the total product yield grow with increasing H_2O_2 concentration, and the reaction follows first-order kinetics [13]. However, this system is quite a weak catalyst for the epoxidation of olefins, although related systems, such as a binuclear manganese(IV) complex ($[LMn^{IV}(O)_3Mn^{IV}L]^{2+}$) (**1**) have shown high activities for this reaction (see Section 7.4.2) [17–19]. This might, according to the authors, indicate that the polymer-bound system and the free dinuclear Mn(IV) complex oxidize organic substrates via different mechanisms [13].

Despite the fact that several related complexes of other metals have been described [30], only Mn triazacyclononane derivatives have been fixed onto soluble polymers and successfully applied in alkane oxidation so far [31].

7.4.3.4
Wacker-Type Oxidation Reactions

The oxidation of olefins to carbonyl compounds (the Wacker process; in technical concerns, also called the Hoechst–Wacker process) was of great importance for the recognition of the usefulness of organometallic homogeneous catalysis in the bulk chemicals industry [32]. The Wacker ethylene oxidation is one of the key steps in industrial homogeneous catalysis. Palladium catalysts are usually applied and have proven most versatile and useful. However, the future of the commercial acetaldehyde processes depends mainly on the availability of cheap ethylene. Only the low price of ethylene keeps the Wacker process for the preparation of acetaldehyde industrially attractive still. Among the newer processes for the manufacture of acetic acid from ethylene is a one-step process utilizing a Pd–heteropolyacid catalyst, allowing a gas-phase oxidation [32, 33]. Nevertheless, ongoing research focuses on finding better conditions for the oxidation in solution of longer-chain olefins to aldehydes and ketones. Nanocomposites of conducting polymers and noble metals are of particular interest as catalysts since they provide a large surface area and present a selective catalytic activity [34]. The efficiency of a catalyst depends in these cases exclusively on efficient particle stabilization and a smooth, reversible redox cycle of the complex catalyst. All these features can be achieved by using suitable polymers such as polyaniline, polypyrrole and polythiophene. Several methods are available for synthesizing nanoclusters of noble metals [35].

Copper nanoclusters applicable for Wacker-type oxidation reactions were synthesized by a chemical reduction of an aqueous copper salt solution containing $Cu(NO_3)_2 \cdot 3\,H_2O$ by sodium borohydride ($NaBH_4$). A polyaniline nanocomposite containing copper nanoclusters was prepared by polymerizing a monomeric aniline hydrochloride solution containing the copper nanoclusters using ammonium persulfate as an oxidizing agent [9]. The nanocomposite shows a higher solubility than the polyaniline. The synthesized nanocomposite was used to catalyze the Wacker reaction for the conversion of 1-decene to 2-decanone in the presence of molecular oxygen [Eq. (3)].

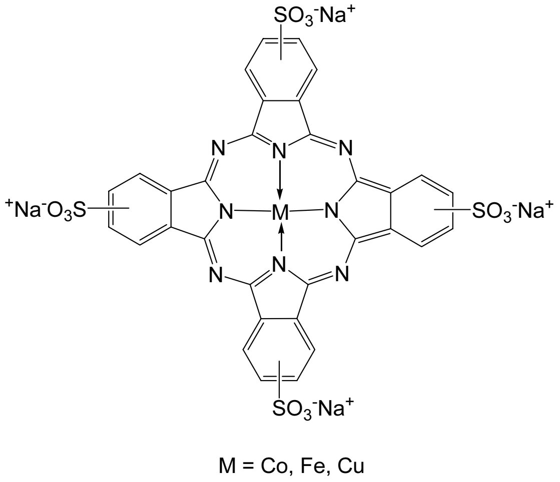


(3)

The Wacker reaction was chosen as a representative reaction since in this case the conversion of an alkene to a ketone or an aldehyde can be achieved in one step, which is of industrial relevance. The reaction was carried out in a biphasic water/acetonitrile system at 50–60 °C in an oxygen atmosphere, using the copper/polyaniline nanocomposite, as well as a bare copper nanocluster. In the system, copper is present in the zero-valent state supported by polyaniline. Although 2-decanone is the only product formed, the yield obtained is still relatively low. It has to be mentioned in this context that the reaction carried out in the presence of bare copper nanoclusters showed no evidence for the presence of 2-decanone, indicating that those copper nanoclusters alone do not bring about the oxidation of 1-decene.

7.4.3.5
Autoxidation of 2,6-Di-*tert*-butylphenol

Autoxidation reactions of organic compounds are quite widespread and Co(III) is among the most generally active metal ions serving as a catalyst in such reactions [36]. Cobalt–phthalocyanine tetrasulfonate bound cationic latexes have been employed as colloidal catalysts for the autoxidation of several water-soluble and -insoluble alcohols and thiols [37]. Furthermore, the catalytic activity of ionene-bound cobalt–phthalocyanine tetrasulfonate for the autoxidation of water-soluble 2-mercaptoethanol has been studied in some detail [38]. Soluble poly(vinylbenzyl)trimethylammonium chloride polyelectrolytes (PVBTMA Cl) and 2,6- and 2,10-ionenes were synthesized and used as catalyst supports for cobalt–, iron–, and copper–phthalocyanine tetrasulfonates (4) in the autoxidation of 2,6-di-*tert*-butylphenol (DTBP) in water by molecular oxygen [Eq. (4)] [8].



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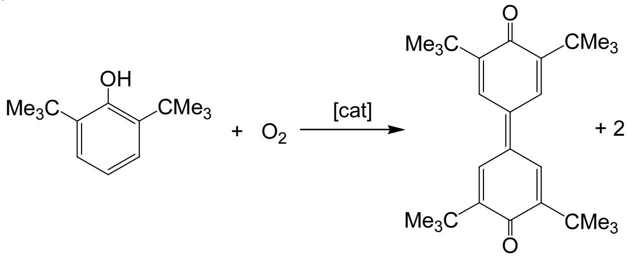


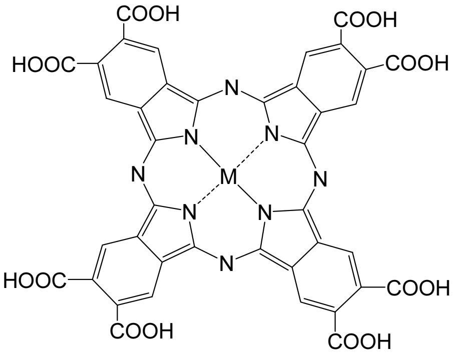
(4)

Soluble PVBTMA Cl is prepared in two steps using an emulsion polymerization technique [39]. The ionenes and soluble PVBTMA Cl give clear solutions and no solubility problem of these supports occurs, according to the authors. The water-insoluble DTBP is oxidized by O_2 gas dissolved in the aqueous phase, where the supported metallophthalocyanine tetrasulfonate is found. The ionenes and polymers used in the reaction mixtures serve not only as a support for the catalysts, but also attract the DTBP due to their organic nature, being of utmost importance for the mass-transfer step of the reaction. Accordingly, the conversions of the reaction were higher for the supported catalysts than for unsupported ones. Polyelectrolytesupported cobalt–phthalocyanine tetrasulfonate shows the highest activity (73%) in comparison with the supported analogues of iron (39%) and copper–phthalocyanine tetrasulfonates (5%).

The reaction yielded 3,3′,5,5′-tetra-*tert*-butyl-4,4′-diphenoquinone as the only oxidation product of 2,6-di-*tert*-butylphenol. The activity was found to increase with the temperature: the best results were obtained at 75 °C, and at room temperature almost no conversion took place. Higher pH values also had a positive effect on the conversion, and the authors ascribe this to a higher stability of the M–O_2 species [8].

7.4.3.6
Oxidative Decomposition of Polychlorophenols

The widespread presence of halogenated compounds in marine waters and in soils is a matter of severe environmental concern, and there has been much research done on decomposition of these hazardous compounds by electrochemical, biochemical, and chemical methods [40]. Oxidative decomposition of 2,4,6-trichlorophenol (TCP) has been reported using metalloporphyrins and phthalocyanines electrostatically bound to ion-exchange resins [41]. If the complexes are covalently bound to the polymer chain, however, higher activities are to be expected. Several phthalocyanine complexes (iron, manganese and cobalt, Mpc) covalently bound to a water-soluble polymer having a pyridinium side chain were synthesized to act as catalysts for the decomposition of TCP (**5** and **6**) [12]. The polymer main chain inhibits the formation of aggregates of phthalocyanine complexes and the cationic side chains concentrate both substrate and oxidant around the phthalocyanine catalysts, leading to a high turnover in the decomposition of TCP.



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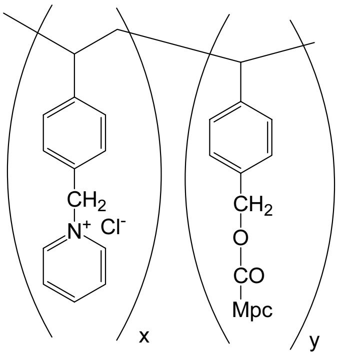

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The reaction was conducted in acetonitrile in the presence of a phosphate buffer at pH 7 (the catalytic activity is reported to be highest at this pH and drops sharply on both sides of this optimal value); hydrogen peroxide and $KHSO_5$ were used as oxidants. Although the highest activities were obtained with the latter oxidant, H_2O_2

would be preferable, since the use of $KHSO_5$ results in sulfur-containing byproducts after the oxidation. With iron as the central metal, it is possible to obtain quantitative conversions after 10 min of reaction time using H_2O_2 as the oxidizing agent. During the initial period of the TCP decomposition 2,6-dichloro-*p*-benzoquinone was detected, which was further oxidized and dechlorinated to yield formic acid and oxalic acid, among other products formed in minor amounts [12].

In comparison to other systems applied for the same purpose, the metallophtallocyanine shows quite a good activity when it is covalently bound to water-soluble polymers having pyridinum side chains. The polymer main chain helps to inhibit the formation of phthalocyanine complex aggregates. The side chains help to concentrate both oxidizing agent and substrate around the catalytic sites. Thus, a high turnover in TCP decomposition and efficient dechlorination of the aromatic ring are achieved [12].

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7.4.4
Hydrogenation and Other Reduction Reactions

Lasse Greiner and Andreas Liese

7.4.4.1
Introduction

In Nature, hydrogenations have been mastered in whole cells. Such reactions have been performed for many thousands of years and they are utilized for the production of millions of tons of products worldwide. The technology used in Nature is due to homogeneously soluble macromolecular catalysts, the enzymes. These biocatalysts are applied for direct hydrogenation with molecular hydrogen, transfer hydrogenation, and mediated hydrogenation utilizing nicotinamide cofactors, NAD(P)H, as mediators. Even humankind has been using this biocatalytic hydrogenation power in beer and wine brewing for several thousands of years. Ethanol is produced from glucose by yeast, wherein the final step is hydrogenation of acetaldehyde to ethanol catalyzed by an alcohol dehydrogenase.

In chemistry, the pioneering work in the field of homogeneously soluble polymeric ligands for homogeneous catalysis was first reported by Bayer and Schurig [1, 2]. They describe the functionalization of linear polystyrene (molecular weight $1 \cdot 10^5$ g mol^{-1}) via chloromethylation, and subsequently with potassium diphenylphosphide. Four of the six catalysts described were used for hydrogenation of 1-pentene. Besides employing palladium and platinum as active metals, the use of Wilkinson's catalyst $Rh(PPh_3)_3Cl$ as a metal precursor is described in detail. The catalyst was purified by ultrafiltration prior to use. The polymeric analogue of $Rh(PPh_3)_3Cl$ showed an initial TOF of 17 h^{-1} (50% conversion after 3 h) and was recycled five times by ultrafiltration. Thus TTN = 600 was reached. Even though no quantification of a possible metal leaching was carried out, the authors state that the reaction times were prolonged to reach quantitative conversion. In a later contribution they report the extension of this concept [3]. Here the cobalt-catalyzed lithium borohydride reduction is briefly mentioned. This was the starting point for hydrogenations with homogeneously soluble macromolecular catalysts. The recent developments were the topic of different reviews.

Bergbreiter gave a critical review mainly of work carried out in his own laboratory [4]. An overview of soluble polymers as supports for catalysts has been given by Dickerson et al. [5]. Polymer enlargement as a means for tuning catalyst properties toward hydrophilic solubility was covered by Sinou [6] and other chapters of Cornils' and Herrmann's books [7, 8].

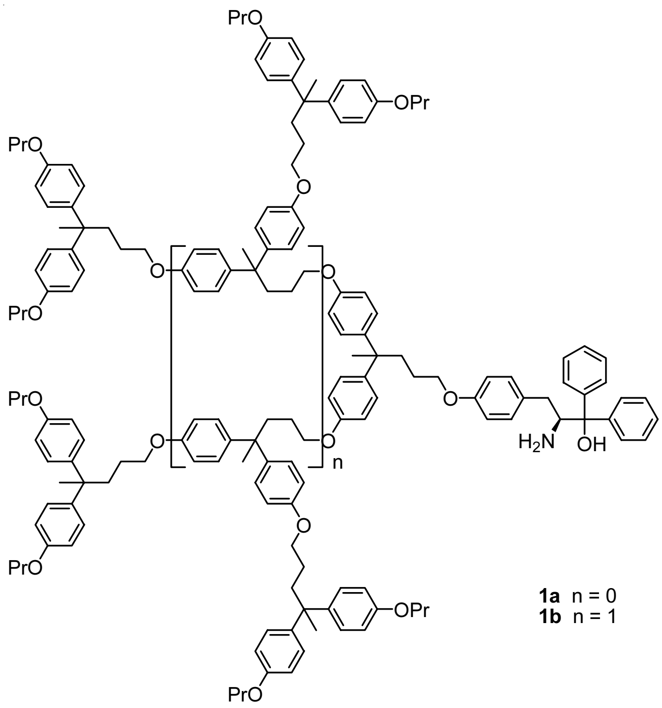
Fan et al. give an extensive review of immobilized asymmetric catalysts according to reaction classes and the kind of support [9]. Saluzzo and Lemaire reviewed the use of polymer-supported BINAP for hydrogenation and hydrogen-transfer reduction with diamines or amino alcohols, respectively [10]. The immobilization and recycling of chiral catalysts was the topic of a recent book [11]. Dendritic catalysts were reviewed by Kreiter et al. [12]. The use of dendrimers for the recycling of catalysts was covered by two recent reviews: one is focused mainly on modes of recycling [13], whereas the other is grouped according to catalyzed reactions [14].

A concise overview of recycling modes for chiral catalysts, including enzymes, is given by Kragl et al. [15]. The technical aspects of the application of continuously operated chemical membrane reactors was covered by Wöltinger et al. [16, 17].

In the following sections, developments since 1999 are discussed in detail, subdivided according to the source of hydrogen equivalents applied for reduction.

7.4.4.2
Borane Reduction

Bolm and co-workers reported a chiral amino alcohol attached to the focal points of two different dendritic wedges (**1**) for the catalytic reduction of ketones with $BH_3 \cdot SMe_2$ as hydride donor [Eq. (1)] [18]. All the reactions carried out at room temperature and with THF as solvent yielded TTNs of 10. The best results concerning enantioselectivity were reached for the reduction of chloroacetophenone with *ee* = 96% (*er* = 49) employing the amino alcohol attached to the second-generation dendrimeric wedge 2, compared to 87% (14) of the non-enlarged system. The authors reasoned that enantioselectivity fell as steric crowding decreased, i.e., at a higher number of generations, but increased with lower rigidity of the wedge, corresponding to a lower number of generations.



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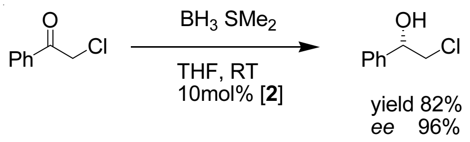
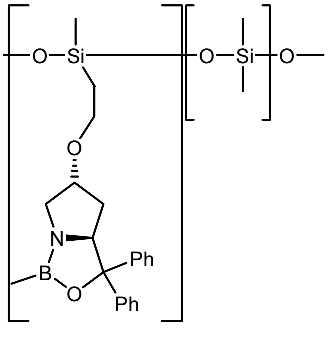


(1)

Wandrey and co-workers optimized the synthesis of their previous polysiloxane and linear polystyrene-bound oxazaborolidine catalysts **2** and **3** [17]. They also switched from the previously employed borane to methylboranes, for higher catalyst robustness. Both homogeneously soluble macromolecular catalysts were employed in a continuously operated membrane reactor for the reduction of tetralon to tetralol with $BH_3 \cdot THF$ in THF at room temperature [Eq. (2)]. With the polysiloxane-based macromolecular catalyst, *ee* values higher than 97% (*er* = 66) could be obtained for more than 200 residence times (> 200 h), resulting in a TTN of 320. For the polystyrene scaffold the number of residence times for which the *ee* was higher than 97% exceeded 355 (355 h), giving a TTN of 1370. The polystyrene-based catalyst showed a higher retention (99.94%) compared to the polysiloxane one with a retention of 98.50%. Thus half-lives of the respective catalysts due to loss of catalyst, within 1156 residence times and 46 residence times, were reasoned to account for the increase in TTN being more than the fourfold.

Rico-Lattes and co-workers reported on the functionalization of commercially available PAMAM dendrimers with up to 32 gluconic acid residues [19]. Reduction



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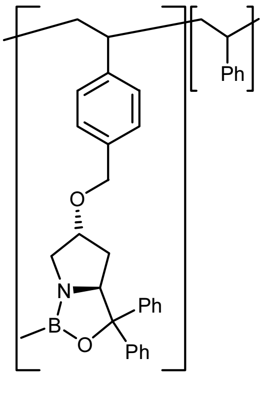

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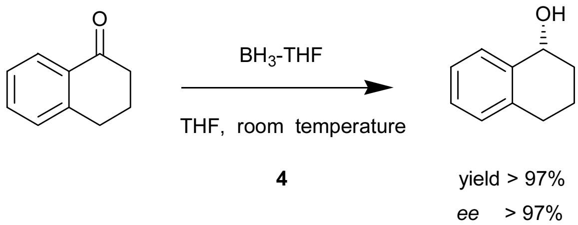
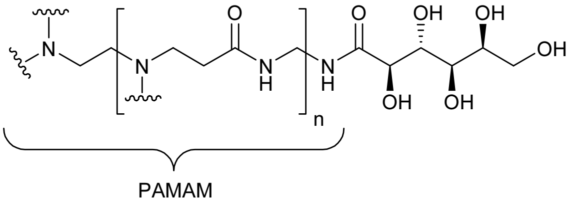
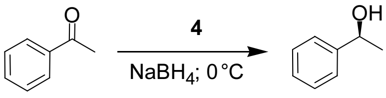


(2)

of an aqueous saturated solution of acetophenone employing the respective third-generation dendrimer gave phenylethanol with *ee* = 50% (*er* = 3), which increased to *ee* = 98% (*er* = 99) for the fourth-generation dendrimer. Under heterogeneous conditions in THF the highest *ee* for acetophenone was obtained for the third-generation dendrimer **4** with *ee* = 97% (*er* = 199), which dropped to *ee* = 3% (*er* = 1.06) [Eq. (3)]. Other ketones, such as cyclohexyl phenyl ketone, gave an *ee* of 50% (*er* = 3) in aqueous solution and 97% (*er* = 66) in THF. The first- and second-generation dendrimers as well as gluconic acid bound to other nonpolymeric residues gave no asymmetric induction under either set of conditions. The third-generation dendrimers were recovered by ultrafiltration with no loss of activity and selectivity during up to 10 cycles under the reaction conditions.



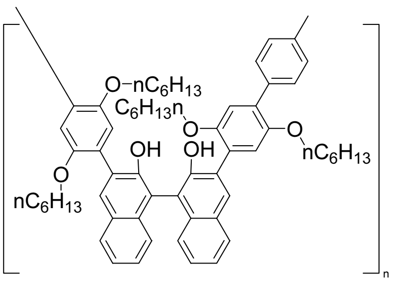
4 n = 3



(3)

water (homogeneous)	yield	95%
	ee	50%
THF (heterogeneous)	yield	97%
	ee	97%

Several polymeric BINOL ligands were synthesized by Pu and co-workers [20]. Two (**5**: $M_w = 10.0 \cdot 10^3$ g mol^{-1}, $M_n = 4.6 \cdot 10^3$ g mol^{-1}; **6**: $M_w = 25.8 \cdot 10^3$ g mol^{-1}, $M_n = 14.3 \cdot 10^3$ g mol^{-1}) were employed in the borane reduction of aryl ketones at –30 °C giving a maximum *ee* of 80% (*er* = 9), with TTN = 20 in the presence of 10 mol% Et_2Zn [Eq. (4)]. Recycling of the catalyst was not described.



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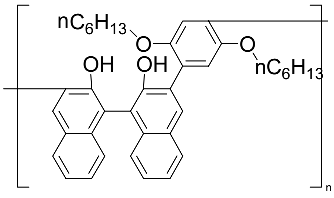

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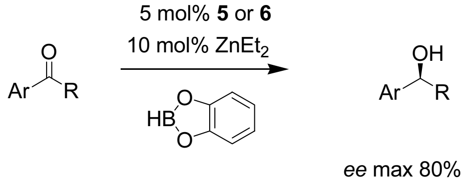
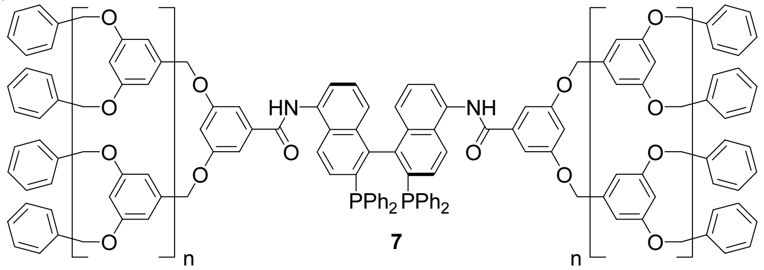


(4)

7.4.4.3
Molecular Hydrogen

Fan et al. reported the synthesis of Fréchet-type BINAP ligands **7** and their use in catalytic hydrogenation of 2-[4-(2-methylpropyl)phenyl]acrylic acid to ibuprofen with TTN = 125 [Eq. (5)] [21]. The TOF for the zero- and first-generation catalyst were comparable with BINAP (TOF = 6, 6, and 8 h^{-1}); the second-generation catalyst was more than three times faster than BINAP per metal site (TOF = 21 h^{-1}). The enantioselectivity of the dendrimeric catalyst was slightly increased on comparing BINAP with the dendrimers, from *ee* = 89.8% (*er* = 18.6) to maximum *ee* = 92.6% (*er* = 26.0) for the first-generation catalyst ($n = 2$). The authors attribute acceleration to an altered dihedral angle compared to free BINAP. The second-generation catalyst ($n = 3$) was precipitated by adding methanol to the methanol/toluene (1 : 1) reaction mixture and re-used three times with no apparent loss in activity and selectivity. The same dendrimeric ligands were used with enantiopure diphenylethylenediamine **8** as a modifier in the reduction of aryl methyl ketones [Eq. (6)] [22]. Here it turned out that the zeroth-generation ligand exhibits the same level of enantioselectivity as the parent BINAP ligand. The highest selectivity was obtained by the reduction of 5-naphthyl methyl ketone with *ee* = 96% (*er* = 49). With higher generations a decrease of selectivity was observed in all the tested substrates. The catalyst was prepared in situ from the Ru salt and the amine. The third-generation catalyst was precipitated after the reaction by the addition of methanol, and re-used twice for the reduction of acetophenone with a decrease in enantioselectivity from 75 to 72% (*er* = 7 and 6, respectively). In the fourth cycle conversion was not quantitative after 20 h resulting in an overall TTN of 1750.



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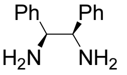

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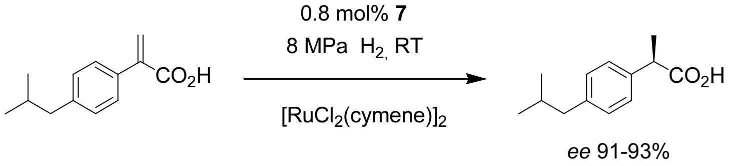
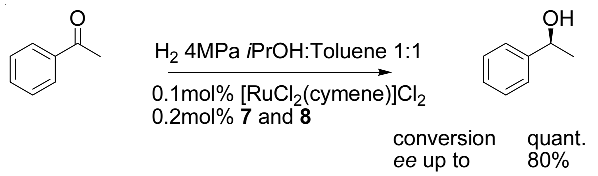
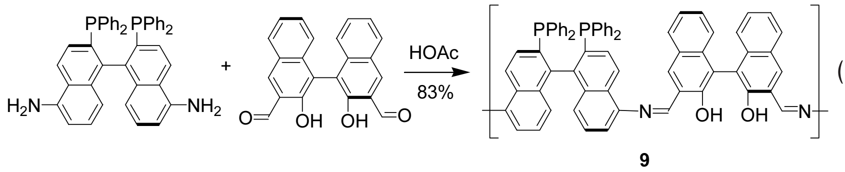


(5)

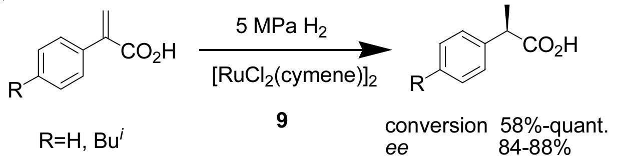


(6)

Pu [23] prepared soluble irregular copolymers, and Fan [24] regular ones (**9**), of BINAP and BINOL that were incorporated into the polymer chain [Eq. (7)]. The ruthenium complexes were used for catalytic hydrogenation of arylacrylic acid [Eq. (8)]. The maximum *ee* of 88% (*er* = 16) with TTN = 100 is lower than with BINAP under comparable conditions. No recycling of the hydrogenation catalyst is reported, whereas for diethylzinc addition to benzaldehyde the catalyst was recycled by precipitation with methanol.

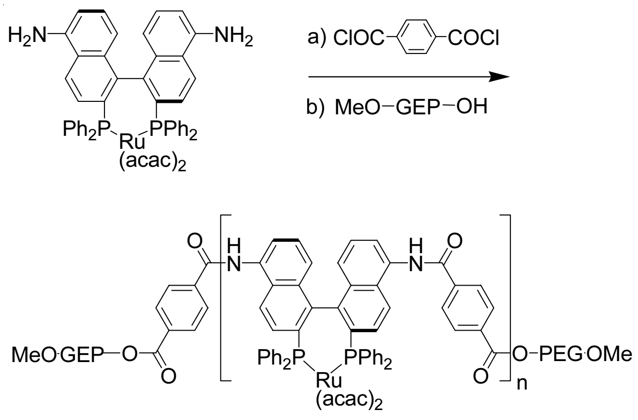


(7)



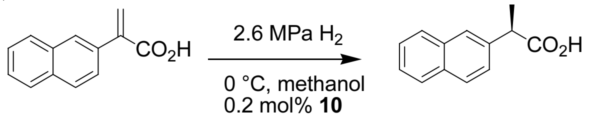
(8)

Oligomer chains with incorporated BINAP were end-functionalized with PEG-OMe [Eq. (9)] [11, 25, 26]. The Ru(acac)$_2$ complex **10** shows higher activity than the RuCl$_2$(cymene) complex in the hydrogenation of 2-(6-methoxy-2-naphthyl)propionic acid to naproxen [Eq. (10)]. The former, with a molecular weight of $1.9 \cdot 10^4$ g mol^{-1} ($M_w/M_n = 3.10$) with *ee* = 96% (*er* = 49), was recycled once by precipitation, giving an overall TTN of 2000 with maximum TOF = 1.67 h^{-1}. The latter, with a molecular weight of $1.2 \cdot 10^4$ g mol^{-1} ($M_w/M_n = 1.24$), yielded an overall TTN of 300 when recycled twice (*ee* = 96%) [11, 25, 26].



(9)

10

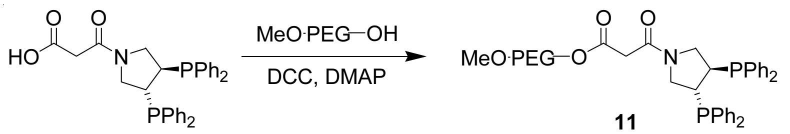


(10)

conversion quant.
ee 95.8 and 95.6%

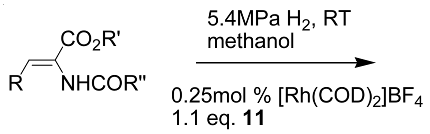
In the same paper [25] the authors present a MeOPEG-bound pyrphos ligand **11** derived from PEG with molecular weight of $5 \cdot 10^3$ g mol^{-1} attached to the pyrrolidinone nitrogen via butanediole acid (succinic acid) [Eq. (11)]. The Rh complex of this polymer-enlarged ligand was compared to the precursor of the polymer attachment. Both catalysts show comparable enantioselectivity toward hydrogenation of several prochiral enamides [Eq. (12)]. The polymer-enlarged catalyst was recycled three times by precipitation and filtration, resulting in an overall TTN of 1600.

Malmstöm and Andersson reported a pyrphos ligand [27] **12** and a PPM ligand [28] (PPM: 4-phenylphosphino-2-(diphenylphosphinomethyl)pyrrolidine) bound to



11

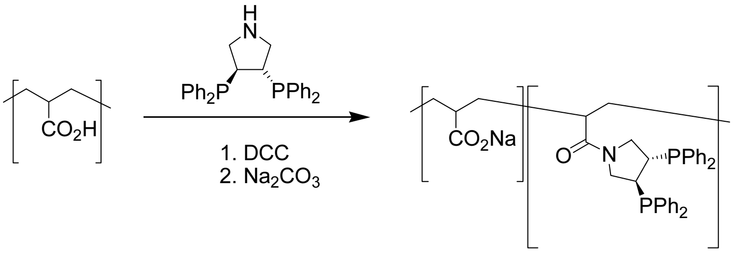
(11)



(12)

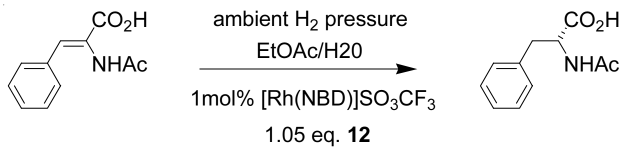
R=Ph
conversion quant.
ee 94.0-96.0%

polyacrylic acid by DCC coupling (DCC = dicyclohexylcarbodiimide) [Eq. (13)]. The goal in either case was to derive water-soluble catalyst systems. The rhodium complexes of three different scaffolds were used for hydrogenation in a three-phase system (water/EtOAc/hydrogen) [Eq. (14)]. Whereas for the PPM system a systematic influence of ligand loading and ionic strength was observed, for the pyrphos system no rationalization of these influences was found.



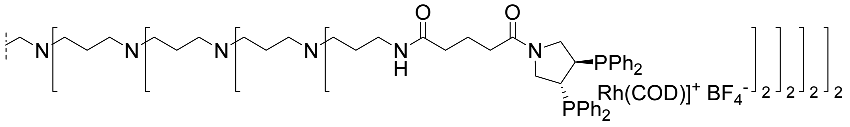
12

(13)



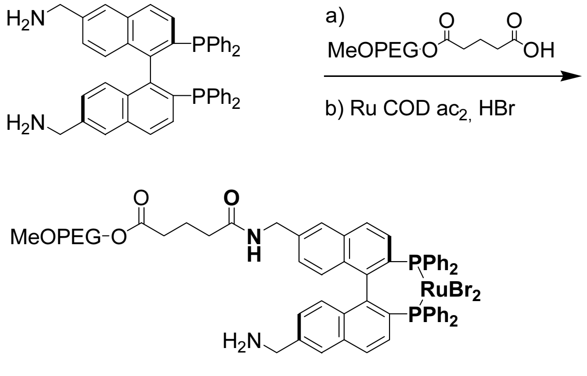
(14)

A similar coupling technique utilizing *N,N*-dimethylaminopropylcarbodiimide was used to attach a glutaric acid derivative of pyrphos to the core of up to fourth-generation diaminobutyl (DAB) dendrimers by Gade and co-workers (**13**) [29]. The $[Rh(COD)]BF_4$ were prepared and utilized for the hydrogenation of (*Z*)-methyl-α-acetamidocinnamate and itaconic acid (3.0 MPa, 25 °C, methanol, TTN = 400). For both substrates TOF and enantioselectivity decreased with the generation number. The *ee* dropped from 93% to 88% (*er* = 28 to 16) and from 77% to 60% (*er* = 8 to 4), respectively. For the cinnamate higher-generation catalysts showed prolonged activation times and TOFs decreased approximately tenfold.



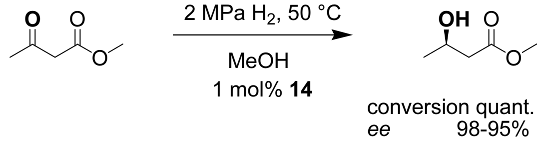
13

Genêt and co-workers reported the synthesis of a PEG (molecular weight = 5000)-attached BINAP ligand **14** [Eq. (15)] [30]. The ruthenium complex was used for the hydrogenation of 3-ketobutanoic (methyl aceroacetate) acid methyl ester with a quantitative yield and *ee* = 98% (*er* = 99) in methanol [Eq. (16)]. The catalyst was recycled three times by precipitation and successive filtration, giving an overall TTN of 400. Whereas conversion in each run was still quantitative, the *ee* dropped from 98% (*er* = 99) in the first two runs to 96% (49) and 95% (39) in the next two runs.



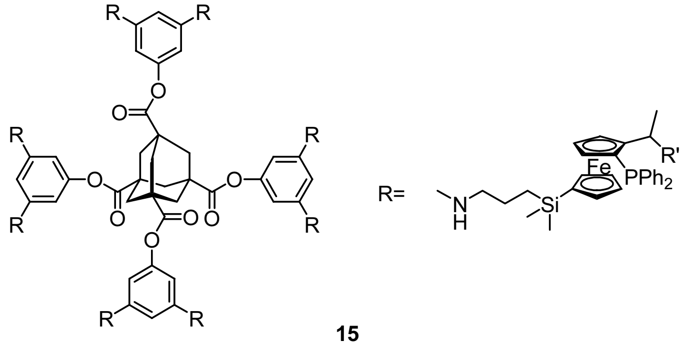
(15)

14



(16)

The synthesis of dendrimers bearing core functionalization with chiral ferrocenyl ligands was described by Togni and co-workers. Based on an adamantyl center, up to 24 “Josiphos” ligand entities were attached to the core of the dendrimer (**15**) [14, 31, 32]. Compared to free Josiphos, when it was a ligand for rhodium a decrease in enantioselectivity in the catalytic hydrogenation of itaconic acid from *ee* = 99% (*er* = 199) to 98% (*er* = 99) was observed. This was independent of dendrimer size, so that steric hindrance was not considered to be an issue. In reaction conditions a TOF of at least 300 h^{-1} can be deduced at room temperature and atmospheric hydrogen pressure. Further work was carried out with the dendrimeric polymeric backbone based on cyclophosphazenes as the center (**16** and **17**) [14, 31, 33]. It was hinted that retention by means of nanofiltration was high enough to allow continuous application.



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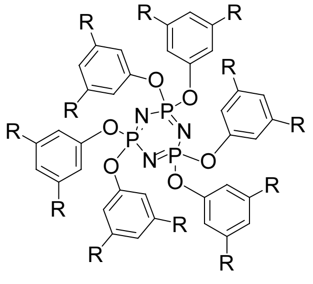

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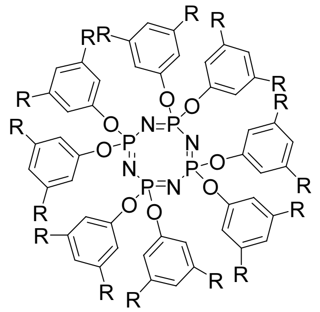

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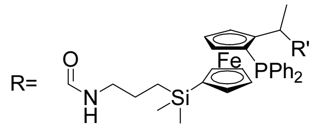
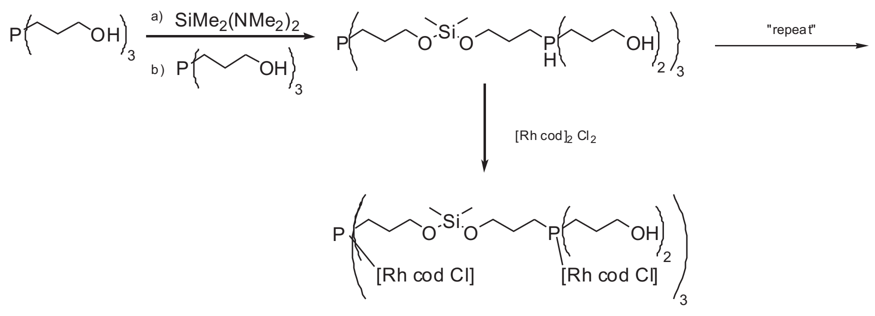


Dendrimer-encapsulated catalysts are another area of active research for polymer-supported catalysts. The nanoparticles are stabilized by the dendrimers preventing precipitation and agglomeration. Bimetallic nanoparticles with encapsulated metals (dendrimer-encapsulated catalyst: DEC) from commercially available fourth-generation PAMAM dendrimers and palladium and platinum metal salts were prepared via reduction by Crooks and co-workers [34], following previous work in this area [35]. The simultaneous incorporation of Pt and Pd reflects the concentrations in solution. The bimetallic DECs are more active than the physical mixture of single-metal DEC [35, 36] in the case of the hydrogenation of allyl alcohol in water, with a maximum TOF of 230 h^{-1} compared to TOF = 190 h^{-1} obtained for monometallic palladium nanoparticles (platinum TOF = 50 h^{-1}).

A Fréchet-type dendrimeric dppf (diphenylphosphinoferrocene) was used as a ligand for rhodium-catalyzed hydrogenation [37]. No difference in activity was found for the comparable low molecular weight dendrimer in relation to non-enlarged dppf as a ligand. The reaction was carried out in a continuously operated membrane reactor for 35 residence times. Retention for the dendritic ligand was 99.8%, and the loss was found to be identical to the amount of metal leaching from the reactor. The authors conclude that a strong ligand–metal bonding suppresses additional loss of precious metal from the reactor.

Up to fourth-generation dendrimers with phosphane branching points were used as ligands for Rh(I) (Scheme 1) [38]. The resulting catalysts were used for the catalytic hydrogenation of 1-decene with TTN = 200, TOF = 400 h^{-1} in THF [Eq. (17)]. A slight decrease in activity was observed in the case of higher generations, probably because of diffusion limitations. The fourth-generation dendrimer was extracted from the reaction mixture with pentane and recrystallized from THF/hexane, yielding 95% of the initial activity. Although this type of dendrimer is easy accessible, it was pointed out that Si–O bonds are labile and the resulting catalysts may be unsuitable for continuous applications [14]. However, stability is increased compared to the monomeric system.



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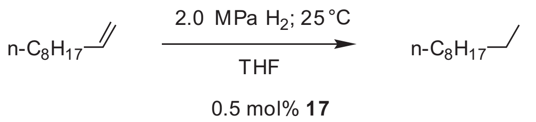
Scheme 1 Synthesis of fourth-generation dendrimeric Rh catalyst with phosphane branching points [15, 38].

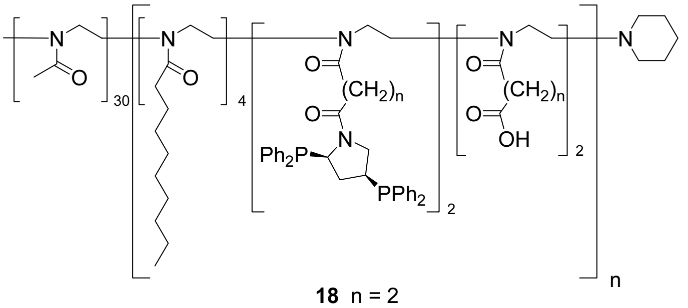


(17)

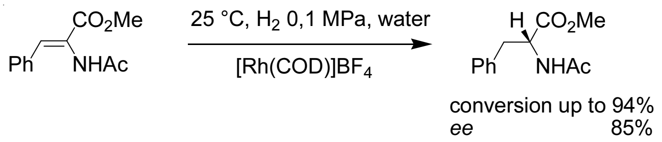
Dendrimeric enlargement was used for restricting a ruthenium–BINAP catalyst in one phase [39]. Reaction was performed in a homogeneous 1 : 1 mixture of ethanol/hexane. Phase separation followed the addition of water. The C_{10} tails render the catalyst insoluble in ethanol/water. The catalyst was re-used twice with a minor decrease in selectivity and activity.

Oehme and co-workers pioneered the addition of amphiphiles to the reaction mixture. An increase in rate and selectivity is due embedment of the catalyst and substrate into micelles. Weitbrecht et al. investigated the kinetics of the hydrogenation in different reaction media and temperatures at 0.11 MPa hydrogen pressure [40]. They found that the rate-determining steps in methanol are different from those in micellar systems in water. In methanol a pre-equlibrium between substrate and catalyst micelles has to be taken into account, whereas for water this step can be neglected. The authors argue that the local concentration of substrate in the micelles is so high relative to that in water that pre-equilibrium is almost completely shifted toward the substrate–catalyst complex.

The concept of micelle-enclosed catalyst was extended by Weberskirch and co-workers by attaching PPM as a ligand to amphiphilic diblock copolymers (**18** and **19**) [41]. The micellar environment is thus given by the polymeric support itself. The rhodium complex of the two polymers synthesized was used in the catalytic hydrogenation of (*Z*)-2-acetamidocinnamic acid and the corresponding methyl ester in water as the solvent [Eq. (18)]. The hydrogenation of the ester was fast and a TOF of up to 140 h^{-1} was obtained with 85% *ee* (*er* = 12). The length of the spacer and amphiphilic side chain had no apparent effect on either TOF or selectivity. The hydrogenation of the acid was slow for both polymers, probably due to low solubility in the micelles. The aqueous phase was extracted and re-used for a second hydrogenation with the same level of enantioselectivity. The loss of activity (ca. 10%) and leaching of Rh (3–4%) were attributed to the water solubility in ethyl acetate as the organic phase and induced loss of the polymeric ligand.



18 n = 2
19 n = 4



(18)

Commercially available third-generation DAB dendrimers were core-functionalized with methylene diphenylphosphane and $PdCl_2$ complexes. The resulting catalyst was used for the catalytic hydrogenation of various conjugated dienes [42]. Higher TOFs were obtained when compared to monomeric catalyst and polystyrene-bound catalyst. The authors believe this to be due to basicity of the dendrimeric backbone, as activity of the monomeric catalyst was enhanced by addition of triethylamine. Selectivity was higher for single hydrogenation of cyclopentadiene. As concluded from the hydrogen uptake rate, the first hydrogenation step to cyclopentene was accelerated compared to the monomer, whereas the successive step was slower than with the monomeric catalyst.

Oosterom et al. reported core-functionalized mono- and diphospines as ligands for rhodium-catalyzed hydroformylation and hydrogenation [43]. Based on triphenylphosphine, dppf (diphenylphosphine ferrocene), and xantophos (9,10-dihydro-9,9-dimethyl-4,5-bis(diphenylphosphino)acridophosphine) with three generations of dendritic wedges, nine different ligands were synthesized (**20**–**22**). The dppf-based ligands were tested for hydrogenation with $[Rh(nbd)_2]ClO_4$ as metal precursor. In batchwise operation conversions > 97% were obtained within 4 h (TOF = 25 h^{-1}) [Eq. (19)]. The second-generation ligand was utilized in a continuous membrane reactor. Retention was found to be 99.4% compared to 87.5% for the unmodified dppf ligand. The loss of precious metal was found to be of the same order of magnitude as the leaching of ligand for both dppf and dendrimer. The authors conclude that complexation of the metal is strong. However, this was determined independently and not under reaction conditions. The membrane reactor was operated for more than 35 residence times (residence time 20 min) with a maximum conversion higher than 80%. This results in a maximum space–time yield of approximately 370 g L^{-1} d^{-1}.

PR_3

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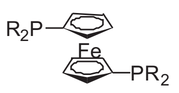

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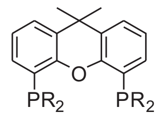

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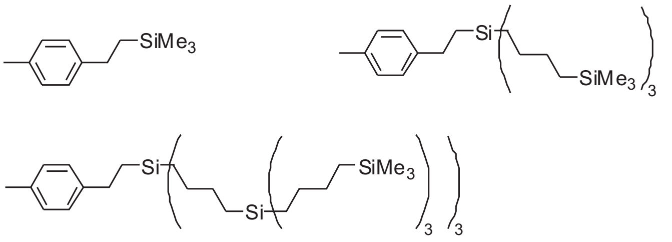
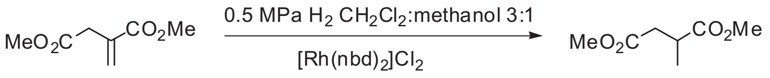
R=

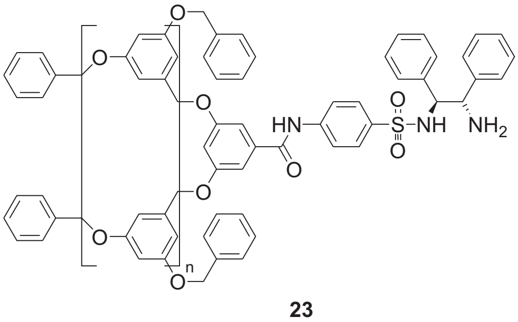




(19)

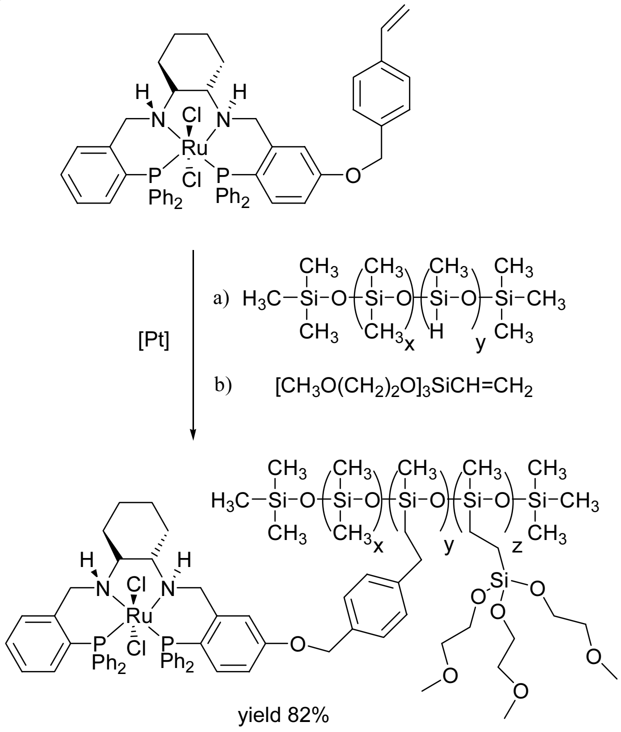
7.4.4.4
Transfer Hydrogenation

A dendrimeric catalyst for transfer hydrogenation was synthesized and used for the reduction of acetophenone [44]. Up to the fourth generation of the polybenzyl ether, dendritic wedges were attached to the TsDPEN ligand (**23**). The cymene–ruthenium chloride complex was used for catalysis. The reactions were performed in dichloromethane with formic acid as hydride donor. The enantioselectivity (*ee* > 96%) was independent of the generation of the wedge (*er* > 49). After removal of the solvent under reduced pressure and washing with methanol, the catalyst was re-used. The stability was found to be the highest for the fourth-generation wedge, which could be re-used up to six times before the activity and enantiomeric excess dropped.



23

Polysiloxane-bound ruthenium-based hydrogen-transfer catalysts were reported by Liese et al. [45] [Eq. (20)]. The ruthenium-bound system was used for the asymmetric reduction of acetophenone in a continuously operated membrane reactor for the reduction of acetophenone to (*S*)-phenylethanol. With a constant dosage of base and an initial catalyst concentration of 0.5%, a stable operation was possible for more than 150 h (residence time 1 h). The maximum space–time yield was 580 g L^{-1} d^{-1} for the membrane reactor for more than 200 residence times, with a maximum *ee* of 92% (*er* = 24).



(20)

7.4.4.5
Conclusion

This review shows that transferring Nature's principle of homogeneously soluble macromolecular catalysts to hydrogenations in fine chemicals synthesis leads to astonishing new results. There has been a clear trend since the mid 1990s in the direction of the synthesis and application of such biomimetic catalysts, especially in reductions utilizing borane or molecular hydrogen as reduction equivalents.

The next topics to be addressed with a view to an industrial application will be stability, TOF, and TTN. If these features can be improved significantly, we might see the application of homogeneously soluble macromolecular catalysts in industry in the future.

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7.5
Toward Economic Applications

Uwe Dingerdissen and Juan Almena

7.5.1
Introduction

From the economic point of view, processes with catalyst recycling and re-use without changes in the catalyst's productivity and selectivity will be preferred in industry.

A heterogeneously catalyzed step offers the possibility of catalyst recycling, but it often lacks selectivity, activity, and the possibility of substrate variations in the production of chiral pharmaceutical intermediates, in contrast to homogeneous catalysis. As previously described, the combination of a polymer and a catalytically active center derived from a homogeneous catalyst circumvents the drawbacks of heterogeneous catalysis but at the same time could take advantage of the separation and recycling of the catalyst. Among the different ways to recycle a catalyst, those methods which do not imply any perturbation or changes in the catalytic system are preferred because an extra reaction step is avoided, namely the recovery of the active form of the catalyst, which afterward could be either used again or recycled differently.

Following this concept and taking advantage of our expertise in the use of membrane reactors for the production of amino acids, the so-called enzyme membrane reactors, Degussa has been active in the field of polymer-enlarged soluble catalysts since 1996. As a result of our work, a pilot process for the production of chiral alcohols and the application of this technology to other reaction types have been established.

The principle of the enzyme membrane reactor technology (developed in a collaboration between Degussa AG and Professor Wandrey's group at the Research Institute Jülich, and in operation since 1980), and thus the principle of the Chemzyme membrane reactor, is depicted in Figure 1.

Taking advantage of the enormous differences in molecular weight (and hydrodynamic volume) between the catalyst (an enzyme) and the substrates or the products, it is possible to confine the catalyst in a membrane reactor while the reagents and products can be selectively extracted from the reaction mixture without modifying the catalytic active intermediate. Remarkably, the Chemzyme membrane reactor concept allows a productivity per gram of catalyst which could be higher than in the case of enzymes because the polymers can be multifunctionalized with several active centers [1].

In the field of enantioselective catalysis we present here two pilot plant examples developed in our laboratories: a metal-free catalysis process and a metal-catalyzed reaction.

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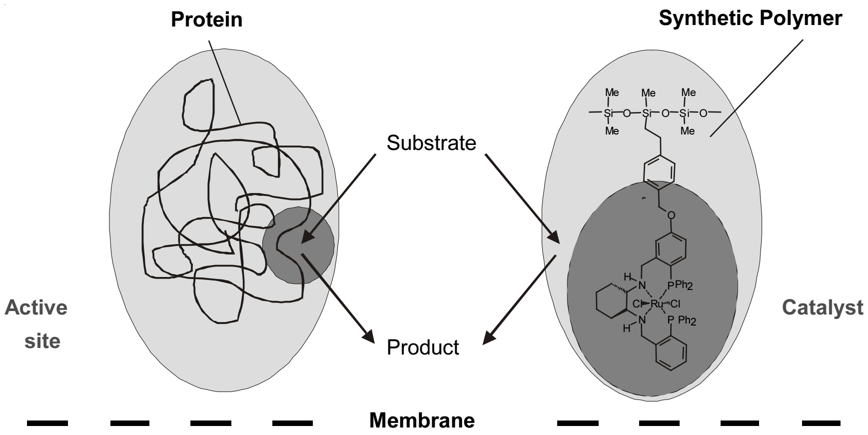
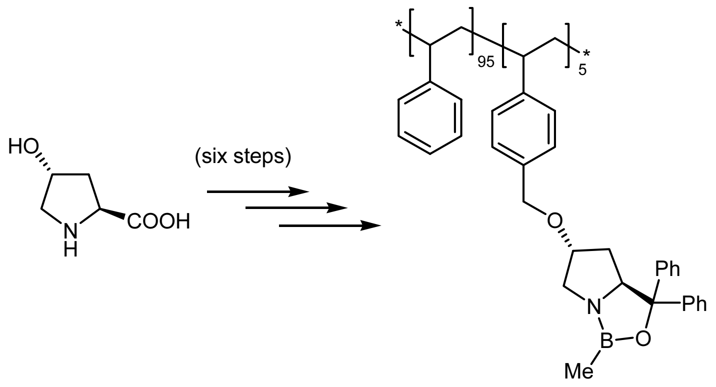


Figure 1 Principle of the enzyme reactor (left) and the Chemzyme membrane reactor (right).

7.5.2
Enantioselective Borane Reduction of Ketones

The enantioselective reduction of ketones has become a key reaction not only for the production of chiral alcohols, but for the production of functionalized compounds in general, thanks to the versatility of the hydroxyl functionality. The oxazaborolidine-catalyzed borane reduction of ketones [2] has become an important reaction due to the fact that the stereochemistry of the alcohols can be predicted and because of the wide substrate acceptance of this catalytic system (it works with aromatic as well as with aliphatic ketones). Among all the known oxazaborolidine catalysts, the proline-based one is very interesting not only because it is one of the most selective catalysts, but also because another related reagent, the 4-hydroproline, is commercially available and possesses a functional group which could be used for the linkage to a polymer.

As a continuation of our collaboration with the Research Institute Jülich, a pilot process based on the described reaction has been optimized successfully in our facilities. Starting from L-hydroxyproline it was possible to obtain a polymer-bound oxazaborolidine-based catalyst on a 300 g scale in six steps [Eq. (1)].



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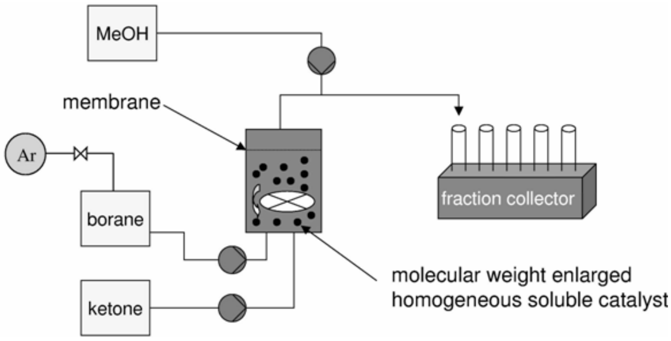


Figure 2 Simplified schematic representation of the pilot plant.

Using 30 g of this catalyst, which was approximately 5% functionalized with oxazaborolidine centers, 4 kg of tetralone were converted to (*R*)-(–)-tetralol in a continuous reaction during 10 days. From the beginning a high conversion was observed. The enantiomeric excess could be increased from 35% to 95% during the process optimization. This was mainly achieved by changing the feedstock supply, i.e., by introducing the borane and the ketone streams separately into the reactor. Therefore the initially observed undesired uncatalyzed reduction of the ketone was avoided. After reaction work-up, (*R*)-(–)-tetralol was isolated with a purity of > 99% *ee* [3] (Figure 3). This small setup is appropriate for production on a kilogram scale for the synthesis of expensive pharmaceutical intermediates.

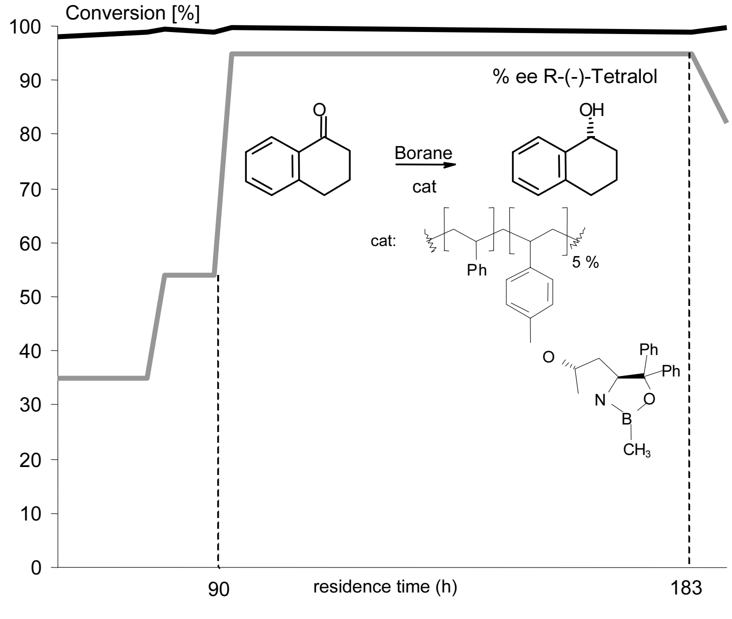
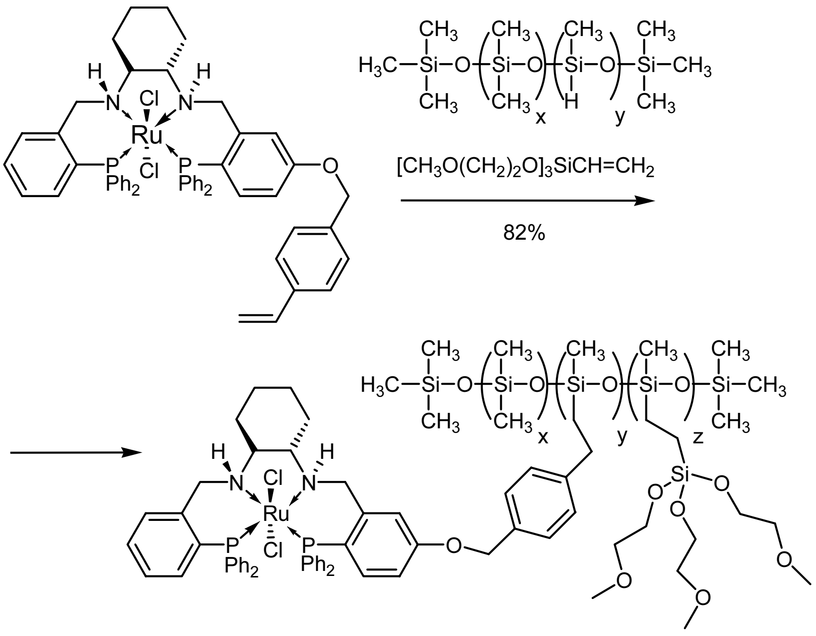


Figure 3 Conversion and enantiomeric excess over time in the reduction of tetralone with borane in a continuously operated Chemzyme membrane reactor.

7.5.3
Asymmetric Transfer Hydrogenations

From an engineering point of view, the transfer hydrogenation of ketones is a very simple reaction which does not require the use of high-value equipment. Instead of hydrogen gas, an hydrogen source that is easier to handle is used (e.g., isopropanol or formic acid). Several ligands have been applied successfully in the transfer hydrogenation of ketones. To avoid metal leaching during the reaction, the use of tetradentate ligands, described in 1996 by Gao and Noyori [5], has been studied to prove the concept of polymer-bound ligands.

To enable the attachment to a polymer, the original Gao–Noyori catalyst was tethered as shown in Eq. (2) and described in the literature [4]. As polymer backbone a polysiloxane polymer was chosen simply because the attachment of the monomer through its vinylic functionality by means of a hydrosilylation reaction could easily be achieved [Eq. (2)].



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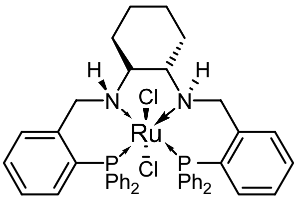
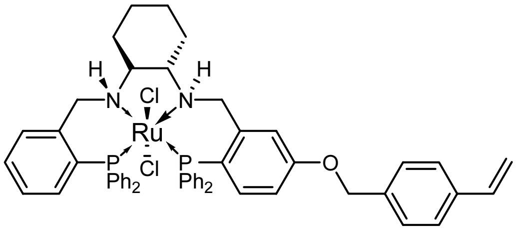


Gao-Noyori

1



Modified monomer

2

It has been found that 99.8% of the catalyst could be retained within a reactor setup using the same schematic approach as described previously. This catalyst was used in a continuous process with acetophenone as the substrate for a period of six days. During the optimization phase it was necessary to supply continuously a 0.001 M base solution in order to overcome the deactivation of the catalyst by the presence of accumulated amounts of water. By removing the water from the reaction mixture formation of the original catalyst was achieved continuously. Under those modified conditions the retention of the catalyst in the reactor slightly decreased (down to 99.5% in 50 h) because of the degradation of the polysiloxane polymer as a result of the base dosage. Therefore, a continuous loss of catalyst at a constant rate $k_{des} = 0.005\ h^{-1}$ took place. These losses (referred to as leaching of catalyst) were compensated by continuously supplementing 0.5% polymeric catalyst per residence time. By doing this a stationary catalytic process (79% conversion and 91% enantioselectivity using a 0.25 M solution of acetophenone, a residence time of 60 min, an initial catalyst concentration of 0.015 M, and a continuous supply of catalyst in a 0.075 mM concentration feedstock) was obtained. After 75 residence times running under the optimized conditions a productivity of $578\ g\ L^{-1}\ d^{-1}$ of 1-phenylethanol and a total turnover number (TON) of 2633 mol substrate per mole catalyst were calculated (the TON is calculated as the ratio of the concentration of the product flow to the concentration of the catalyst supply flow).

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7.6
What Should be Done in the Future?

Stefan Mecking

Polymer-bound catalysts offer various attractive properties in combination with membrane separation techniques:

- Catalyst recovery can be performed in an energy-efficient way by reducing the volume of distillation streams.
- Temperature-sensititve catalysts can be recovered at relatively mild temperatures from high boiling compounds.
- By enabling continuous operation, reactions can be run under steady-state conditions, e.g., at limited conversions.
- Catalysts based on expensive metals or ligands can be recovered effectively.

A broad range of organic reactions catalyzed by polymer-bound catalysts have been described since the mid-1990s. Selectivities and activities can generally compete with those of the analogous catalysts that are not polymer-bound. Synthetic routes to a multitude of polymeric ligands are well worked out on a laboratory scale. Beyond these various proofs of principle, basic issues remain open in most instances, however. For example, in repeated recycling runs often the reaction is not followed over time but only a final conversion is given, telling little about changes in catalyst performance. The metal content in the filtrate from catalyst separation is usually taken as an indication of recovery efficiency, but the polymer content of the filtrate is rarely reported. Thus, catalyst decomposition or other reactions resulting in low molecular weight species containing metals cannot be differentiated from insufficient recovery of the polymer itself. On a more sophisticated level, a mechanistic understanding on a molecular level of catalyst deactivation is a decisive and also a scientifically attractive topic. When recycling the catalyst by means of binding to a soluble polymer, its stability over time becomes a much more critical issue by comparison to batch reactions without recycling. Moreover, deactivation reactions can also be specific to polymer-bound catalysts, due to the high local concentrations of the polymer-bound metal centers, and also due to different concentrations of reagents and products in continuously operated reactions by comparison to traditional batch mode.

Membrane filtration techniques are effective in the recovery of polymer-bound soluble catalysts. This is contrasted by the scarceness of published systematic data on membrane properties and stability in organic solvents. Even the composition of the commercially available membranes used is often unclear. The nominal molecular weight cutoffs for solvent-stable membranes are usually given for aqueous or methanol solutions, although it is evident that membrane swelling and other properties in different solvents can affect the retention characteristics by orders of magnitude. Phenomenological studies of the retention in different organic solvents for a range of model solutes varying in molecular weight, chemical composition

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(and thus affinity for the membrane surface), and molecular architecture (e.g., linear versus branched) would already be helpful to describe a given membrane systematically. In particular, the comparison between different membranes calls for a precise definition of experimental conditions concerning solvent flow rates, solute concentrations, transmembrane pressure, and experimental setup. With polymer-bound catalysts, interactions with the membrane such as adsorption on or in the separating layer have received little attention, although they can strongly affect membrane performance. In the larger scheme of things, the development of organic as well as inorganic membranes with a high mechanical stability and stability of separation characteristics in organic solvents is a decisive issue. This applies to the development of flat sheet membranes as well as modules with their seals and other elements. Finally, engineering of the overall separation unit in combination with the reaction space is just as crucial for separation performance. Working with gaseous reagents in continuous mode adds to these challenges.

Commercial applications have advanced to the pilot plant scale so far. It can be speculated that in the overall scheme the aforementioned issues of catalyst stability and membrane stability and performance are critical issues. In the particular case of rhodium-catalyzed hydroformylation (for higher alkenes or functional olefins) for the synthesis of fine chemicals it can be assumed that, as a nonscientific and nontechnical driver, the price of rhodium will contribute to the commercial success.

An attractive aspect which has received little attention so far is the aforementioned possibility of running reactions in continuous mode under steady-state conditions concerning reactant concentrations by means of membrane techniques. The potential for directing reactions by suppressing side reactions or otherwise controlling selectivities has attractive potential. It must be realized that for applications in the synthesis of fine chemicals such a concept requires additional development (costing time and money) by comparison to established conventional batch processes, and therefore will only be realistic for well-chosen problems with sufficient reward.

Overall, by comparison to the state-of-the-art in two-phase techniques, polymer-bound catalysts are at an earlier stage. Combining expertise in catalysis, polymer synthesis, and characterization, membrane technology and particularly engineering is required to advance this attractive field.

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8
Multiphase Processes as the Future of Homogeneous Catalysis

Boy Cornils and Wolfgang A. Herrmann (Eds.)

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8
Multiphase Processes as the Future of Homogeneous Catalysis

Boy Cornils and Wolfgang A. Herrmann (Eds.)

Dudukovic, Larachi, and Mills [1] recently stated that multiphase systems

> "are ever present in the process industry and are found in a number of diverse areas of commerce. Typical application areas include the manufacture of petroleum-based products ..., the production of commodity and specialty chemicals, ..., and pollution abatement."

Although this was aimed at *heterogeneous* catalytic processes, we are convinced that in only a few years this statement will be also true for multiphase *homogeneous* catalysis. The advantages of biphasic methodologies for homogeneous catalysis have been summarized by Chaudhari et al. [2] and Drießen-Hölscher et al. [3] as follows:

> "The most important advantage ... is the easy separation of catalysts and products by simple phase separation ..."
>
> "Containment of catalysts with products is minimized and helps in preventing deactivation ..." or
>
> "For substance inhibited kinetics, higher activity is achievable ... as the concentration of reactants in the catalyst phase can be controlled taking advantage of the solubility limitations."

Above all, tremendous efforts have been made to replace the solvents, which are required to be fully miscible with the catalyst and the products, by alternative reaction media. These encompass water, immiscible organics, supercritical media, perfluorinated fluids, ionic liquids, and soluble polymers – as described in the preceding chapters. Although all approaches share many features in commom, it is also important to be aware of how much each presents different potential advantages and difficulties. The general outline of a process (or a process proposal) is relatively simple and comprises the components described in Figure 1.

The figure displays the procedure, which is basically similar with organic/organic solvent pairs, ionic liquids, supercritical fluids, fluorous solvents/catalysts, and polymer-soluble catalysts (route **1**): these techniques have in common that during chemical reaction a homogeneous mixture of solvent, reactant, catalyst, and product

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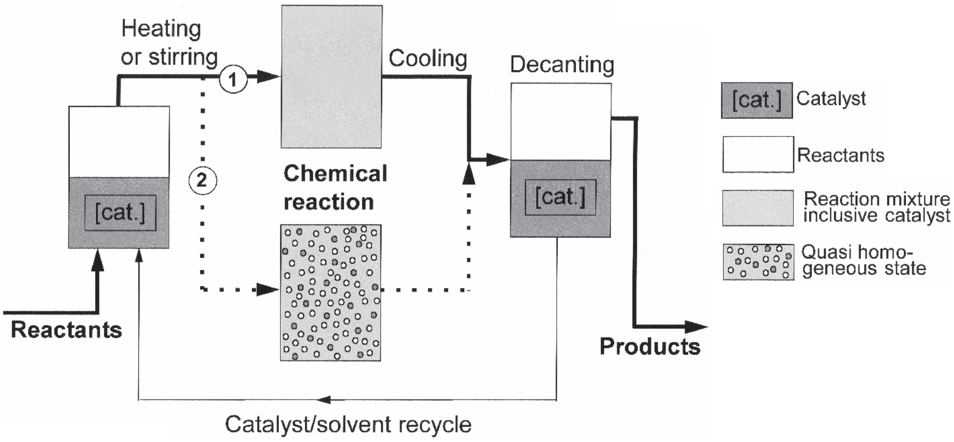

Figure 1 Principle of a simple work-up procedure when using biphasic techniques [4].

exists. Mass-transfer barriers are thus minimized. This is different from the aqueous biphasic process (route **2**) where the reaction vessel contains a more or less "quasi-homogeneous" liquid, consisting of the bulk of the reactants, catalyst phase, and reaction products finely distributed in each other as droplets (not considered possible) gas bubbles. Reaction occurs at the interface between the reactants and the aqueous catalyst solution, emerging with the known restrictions as far as the reactivity of higher molecular weight reactants is concerned. On the other hand, separation can be facilitated by the presence of phase boundaries. To reach a summarizing judgment of the various multiphase homogeneously catalyzed processes, the single process steps of the unit operation *and* the solvents, ligands, etc., have to be discussed.

Throughout the preceding pages the cornucopia of research and development work on homogeneous catalysis has been opened: besides basic research (on theory, ligands, central atoms, new ideas about applications, etc., in homogeneous catalysis) the focal point of progress is at the intersection of development and industrial (and commercial) application. With knowledge of the ongoing homogeneous catalysis research, the main areas of industrially relevant work quite obviously focus on multiphase operations as described in Chapters 2 to 7 with

- aqueous biphasic processes,
- organic/organic biphasic processes,
- syntheses in/with ionic liquids,
- the application of supercritical solvents, mainly supercritical carbon dioxide ($scCO_2$),
- catalysis with fluorous compounds, and
- the use of polymer-supported homogeneous catalysts.

The details which have been disclosed in the previous sections are summarized on the basis of the condensed details as given in Tables 1 and 2.

Table 1 Comparative approach to all processes with multiphasic operation: Solvents–ligands–catalysts.

<table>
<tr><th></th><th>Aqueous biphase</th><th>Organic biphase</th><th>Ionic liquids</th><th>scCO₂</th><th>Fluorous biphase</th><th>Polymer-supported</th></tr>
<tr><td>Solvents</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Availability</td><td>high</td><td>high</td><td>medium</td><td>high</td><td>low</td><td>low</td></tr>
<tr><td>Costs</td><td>low</td><td>medium</td><td>high</td><td>low</td><td>high</td><td>high</td></tr>
<tr><td>Flammability</td><td>none</td><td>high</td><td>high</td><td>none[a]</td><td>none</td><td>high</td></tr>
<tr><td>Thermal stability</td><td>high</td><td>medium</td><td>medium[c]</td><td>high</td><td>high[b]</td><td>low</td></tr>
<tr><td>Toxicity</td><td>none</td><td>various</td><td>various[c]</td><td>none</td><td>various</td><td>various</td></tr>
<tr><td>Ligands</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Availability</td><td>high</td><td>various</td><td colspan="4">low to medium</td></tr>
<tr><td>Price</td><td>low</td><td>various</td><td colspan="3">high</td><td>various</td></tr>
<tr><td>Catalysts</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Variability</td><td>medium</td><td>high</td><td colspan="3">medium</td><td>unknown</td></tr>
<tr><td>Activity</td><td colspan="5">high</td><td>unknown</td></tr>
<tr><td>Service life</td><td>high</td><td>high</td><td colspan="3">various</td><td>unknown</td></tr>
<tr><td>Recyclability</td><td colspan="2">proven</td><td colspan="3">probable</td><td>unknown</td></tr>
</table>

a) Valid only for $scCO_2d$ and scH_2O.
b) Except for atmospheric Ozone Depletion Potential of perfluorinated compounds.
c) Except for corrosive effects and potential toxicity.

Table 2 Comparative approach to all processes with multiphasic operation: Chemical engineering aspects.

<table>
<tr><th></th><th>Aqueous biphase</th><th>Organic biphase</th><th>Ionic liquids</th><th>scCO₂</th><th>Fluorous biphase</th><th>Polymer-supported</th></tr>
<tr><td>Process</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Variability of reactants</td><td colspan="2">limited</td><td colspan="3">unknown/limited</td><td>limited</td></tr>
<tr><td>Sensitivity to poisons</td><td>low</td><td colspan="5">unknown</td></tr>
<tr><td>Environmental concerns</td><td colspan="2">none</td><td colspan="2">medium</td><td>high</td><td>low</td></tr>
<tr><td>Economical recyclability</td><td colspan="2">proven</td><td colspan="3">probable</td><td>unknown</td></tr>
<tr><td>Scale-up</td><td colspan="2">proven</td><td colspan="2">probable</td><td colspan="2">unknown</td></tr>
<tr><td>Need for additional equipment</td><td colspan="5">none</td><td>yes</td></tr>
<tr><td>Ranking</td><td>1</td><td>2</td><td>3</td><td>3</td><td>4</td><td>5</td></tr>
</table>

The processes are ordered within the Tables according to their industrial relevance, starting with the two commercial processes – Ruhrchemie/Rhône-Poulenc's oxo process and the SHOP process of Shell [5]. As has been described in the preceding chapters, all other developments are more or less "proposals" rather than processes: they are on the way from laboratory scale to first pilot plant applications and finally to industrial scale – some are in an advanced stage of realization, such as the Difasol process of IFP, BASIL of BASF, or Swan's TMCH process. For both tables, the "degree of realization" depends on a few criteria, but decisive ones, which will be discussed below.

Table 1 concentrates on solvents, ligands, and catalysts of the various processes. According to earlier statements, ideal solvents would be inexpensive, environmentally benign, and easy to remove from the products, and have properties compatible with the needs of the catalytic system. The environmental requirements eliminate from contention all halogenated solvents; this also includes – basically – fluorinated solvents. Volatile organic compounds (VOCs) are to be avoided because of the negative economic, environmental, and occupational safety consequences of volatile emissions and flammability. Quite obviously, water and carbon dioxide are the most suitable solvents, the fluid of the SHOP process is proven but flammable, and ionic liquids are (at least at the moment) not fully available for industrial consideration. The solvents (and ligands) for fluorous biphase operation (as halogenated compounds) and polymer-supported catalysts (as highly flammable systems) are actually forbidden for commercial use and special efforts would be required to use them (the situation with highly flammable supercritical hydrocarbons as often proposed is uncertain). Flammability and thermal stability requirements of the solvents as working media are thus most inline with the properties of water and $scCO_2$ – the first choice for supercritical operation when other proposals fail with their great demands as far as "green" properties are concerned – in contrast to Roesky's provocative question: "Is water a friend or foe in organometallic chemistry?" [6]. By the way: two of the editors (BC and WAH) do not share the general community's enthusiastic attitude to the "greening" of chemical reactions, and do not use the term "green" so excessively; the reasons for this opinion are outlined in Section 2.7.

The stability of some ionic liquids is under discussion: for example, one of the most widely used of the ILs ($[C_4mim][PF_6]$) can decompose under the conditions used for its preparation and application (mainly acidic reactions) to give toxic HF (not to mention its corrosive properties). Additionally, partially fluorinated or perfluorinated solvents are very stable and inert materials, so they can very easily raise questions about their presence and the consequences in the atmosphere, which include ozone depletion or the greenhouse warming potential of fluorine compounds as known from the discussions of the chemistry and environmental tolerability of fluorinated hydrocarbons and the fate of even traces of them during any further processing steps – for example, recycling, work-up, etc. This area between stability and toxicity is of the utmost importance for both environmental suitability and health: the toxicity must be close to zero in commercial applications. The importance of the choice of solvents is underlined when considering their costs.

Ligands have to be considered from both sides: availability and price (which may depend on each other). TPPTS, the standard ligand for aqueous multiphase rhodium- and other transition metal-based catalyzes, is readily available and can now be delivered even by external, commercial suppliers. This is due to the fact that it is based on two inexpensive items: triphenylphosphine (on which a variety other processes also are based) and the low-cost technique of sulfonation. If we look at the organic/organic approach, the situation is presumably more severe as far as the availability and the price of diphenylphosphinobenzoic acids are concerned. The higher earnings of α-alkenes (compared to *n*-butanal) and the in-house consumption of Shell's SHOP products may be helpful for calculation purposes. The price difference between rhodium and nickel is of no importance (except from the inventory): experience has shown that the costs of the losses of Rh (parts per billion in the case of the hydroformylation reaction) are negligible.

The development of ligands for the application of ionic liquids, $scCO_2$, and fluorous fluids is still in its infancy. Because of similar polarities, partially fluorinated or perfluorinated spacers or "ponytails" are the state-of-the-art of ligands for supercritical and fluorous-phase catalysis. A similar status exists for ionic liquid catalysis: the catalysts tested so far were designed to have a certain tolerance of the ILs (e.g., by substitution of the anionic part of the IL molecule by phenylphosphino groups, sulfonated phosphines, or even surfactats [7] which might be able to form active complexes with the transition metal catalysts). The tuning of the various catalysts to the appropriate (and most suitable) ILs will be a hard job. Therefore, a judgment about the availability and costs of ligands which will be used industrially at a later stage is not possible at the moment. Because of the multitude of possible polymers (as far as the types of polymers and their surrounding solvents, the molecular weights, molecular weight distributions, viscosities, etc., might be concerned), polymer-bound, homogeneous catalysts are also far from being confirmed experiences with proven systems (although the idea of soluble polymers as "macroligands" of the whole system is impressive and enticing [8]).

The status of the catalysts that are to be judged as composites of central atoms and ligands also differs widely: the rhodium/TPPTS catalyst systems (Ruhrchemie/Rhône-Poulenc) and nickel/diphosphines (Shell SHOP) are highly available and commercially proven. Their service life is high and – especially as far as the aqueous biphasic mode is concerned – many varieties have been tested. For catalyses in ionic liquids, in $scCO_2$, and in fluorous phases active catalysts are known although they are not being tested for several series of applications and various combinations of solvents. The knowledge base for polymer-supported catalysts is still too small.

To judge the different "processes" of multiphase catalyzes is rather unfair because of the wide range in the status of the variants, which include commercially operating processes such as Ruhrchemie/Rhône-Poulenc and SHOP, some processes that are in the first stages of commercial demonstration of their reliabilty, and what are more or less "process proposals" in the other cases. This is specially relevant when economic figures have to be compared. But it is possible to recognize and distinguish basic trends.

For example, for reasons discussed in Chapter 2, there is a limited variety of reactants suitable for the aqueous-phase mode – a drawback which hampers the scope of application. The same is true for the organic/organic variant, due to the inadequate number of solvent pairs that act suitably. Although there is much recent information available [9], it is difficult to find (or develop) suitable solvent/solvent mixtures or solvent pairs. A reliable assessment, however, is not yet possible. The same is true for the sensitivity to poisons, with the exception of the aqueous-phase process, which is extremely insensitive. Because of very limited publicity, the status of the SHOP process is unknown.

What about environmental concerns about the various processes? Although the suitability of water as a process solvent is – astonishingly enough – still debatable (see Section 2.1) [10, 11], there is no doubt that both commercially proven processes are environmentally benign and in no need of discussion. On the solvent side, this applies also for supercritcal carbon dioxide (or scH_2O) provided that the catalysts or ligands do not require perfluoro "ponytails" [12]. In that case, the concerns of the community would be the same as with fluorous ligands: partially fluorinated or perfluorinated solvents are very stable and inert materials and the uncertainty about their presence in the atmosphere and their inertness would surely prevent the authorities from giving approval for commercial realizations: ozone depletion or the greenhouse warming potential of fluorine compounds would once more raise questions about the fate of even traces of losses during any further processing steps (for example, recycling, work-up, etc.).

Besides the processes of IFP and BASF (Difasol and Basil) that have been mentioned, and as far as ionic liquids are concerned the situation is still uncertain: under laboratory and pilot plant testing are some 20 ionic liquids with no preference for any of these solvents. Although their industrial availability is just a matter of time, the main rationale encountered for calling ILs "green" is their negligible vapor pressure, which reduces occupational risks because of the limited exposure. One of the requirements for solvents in multiphase homogeneous catalysis is that they do not persist in the environment; they break down into innocuous degradation products at the end of their service life (cf. Section 5.4). Some of the existing ILs do not fulfill these requirements as they can decompose under the conditions used for their preparation and application, i.e., under acidic and/or aqueous environments they can release toxic HF or other corrosive halogen compounds. In any case, polymer-supported systems for homogeneous catalysis have to cope with the flammability.

As far as other chemical engineering aspects are concerned, the scaling-up of the newer proposals for a multiphasic operation ought to be scrutinized. Once more, the commercial processes are out of the discussion. All new processes, ionic liquids, $scCO_2$, and fluorous systems, should be able to be scaled up without problems. Unless serious developments occur, this seems to be valid also for polymer-bound systems – with the prerequisite of membrane devices for the separation of the products from the composite of polymer and catalyst. Moreover, imdustrial interest in soluble polymer-bound catalysts has been closely linked to the development of membranes with sufficient long-term stability in organic solvents. The discoveries attained with polymer-bound catalysts may fertilize new recycling concepts with other multiphase processes, but in any case they represent an additional step – additional equipment – of processing, which means additional costs! This holds especially for membrane separation units if they will be necessary for the handling of soluble polymer-bound catalysts [13–15].

It is obvious that this is commercially impossible for the industrial production of bulk chemicals such as butanal or α-alkenes, since additional manufacturing costs of cents (or even fractions of cents) per kilogram are prohibitive. The maximum permissible burden for fine chemicals might be higher, and may render this equipment possible for realization of new ideas about the recycling of multiphase catalysts.

In the eyes of the editors, a ranking of the various processes of multiphase homogeneous catalyzes might be as indicated in Table 2: the aqueous-phase and the organic/organic processes are in front of supercritical carbon dioxide and ionic liquids, which are both on the way to their first commercial qualification and demonstration of reliability. The use of fluorous systems will be restricted to highly prized specialties or to separation problems, without consideration of whether catalytic reactions are concerned or not. Polymer-bound homogeneous catalysts have good potential, provided that the immense experimental effort can be narrowed down to several systems with promising horizons, as long as availability of the polymer base and its commercial operationability can be secured. As described in various of the previous sections, hybrid systems (e.g., aqueous/polymer-bound, aqueous/scCO_2, etc. [16–18]; even in the presence of enzymes [19]) may stimulate attention, especially if the manufacture of highly prized specialty chemicals (e.g., enantiopure building blocks) is concerned (see, e.g., [20, 21]).

In any case, sophisticated catalysts which have only been prepared on a research scale and tested in laboratory-scale operation must prove their scaling-up to commercial production – which might often be a technical challenge: a successful implementation of unit operations employing the new proposals will ultimately depend on their being able to compete on a commercial level with more conventional methods. The not-proven process proposals must necessarily be continuous, largely because the cost of large-scale batch reactors (or other reactors) would make the cost of all but the biggest plants economically unfeasible. Because there are mostly substantial uncertainties in the toxicological and environmental issues surrounding the large-scale use of the reactants, catalysts, and solvents, the life-cycle assessment is indispensable [22]. Remember Krukonis's statement (as cited in Licence and Poliakoff's contribution in Section 6.5: "... being green is not enough ..." and they continue: "... any successful ... process has to give real economic advantage or a greatly improved product ...".

Keim, one of the prophets of multiphase homogeneous catalysis, cites in one of his reviewing contributions [23] on this topic the famous Max Planck (unfortunately without reference):

> "If a new scientific discovery doesn't triumph because the opponents are convinced, it will win when the opponents finally die"

and he concludes by stating his belief that the future will hold much promise for the biphasic approach – and that Max Planck may be wrong. We hope so, too.

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