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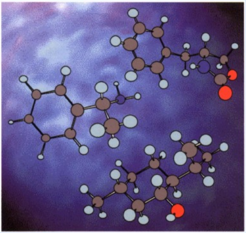

Karola Rück-Braun, Horst Kunz

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Library of Congress Card No. applied for.

A catalogue record for this book is available from the British Library.

Deutsche Bibliothek Cataloguing-in-Publication Data:
Rück-Braun, Karola:
Chiral auxiliaries in cycloadditions / Karola Rück-Braun ; Horst Kunz. -
Weinheim ; New York ; Chichester ; Brisbane ; Singapore ; Toronto : WILEY-VCH, 1999
ISBN 3-527-29386-8

Printed on acid-free and chlorine-free paper.

Printing: betz-druck gmbh, D-64291 Darmstadt.
Bookbinding: J. Schäffer GmbH & Co. KG., D-67269 Grünstadt.
Printed in the Federal Republic of Germany.

Preface

This book is considered to be a handbook about the application of chiral auxiliaries in selected areas of cycloaddition reactions. We hope it will serve as a useful tool for those working in the field of organic synthesis, e.g. the stereoselective synthesis of cycloalkanes and heterocycles.

A discussion of the theoretical backround of diastereoselective synthesis is not included. In the chapters 1 to 5 the reader will find brief introductions to the reactions and examples chosen. For most of the selected reactions reviews and references dealing with the mechanism, stereoselectivity and applications are especially addressed. Considerable effort was made to give the presentation of the data collected in tables a uniform design despite the diversity of the reactions covered. It was not our intention to indicate in detail the absolute stereochemistry or the substitution pattern of the products formed for each given auxiliary. This information can easily be gathered from the cited literature. Where it seemed reasonable, detailed information about the removal of the chiral auxiliaries or the reaction conditions, e.g. Lewis acids, is provided. Auxiliaries of broader applicability or those displaying unique structural features of general interest are assigned a number in the tables and compiled in chapter 6. In this chapter cross-reference to other chapters and references guiding the reader to the synthesis of the compounds are given.

The vast amount of data was collected to the best of our knowledge. But we are well aware and regret that possibly not all contributions in the field are included. Of course, we would appreciate comments from the readers to rectify omissions in future editions.

K. R.-B. is deeply grateful to Matthias Braun for his support to complete this book.

We wish to thank Georg Fuchs (Chapter 5), Ingo Ganz (Chapter 2), Arnulf Lauterbach (Chapter 1), Mark Mikulàs (Chapter 6) and Markus Weymann (Chapter 3 and Chapter 4) for their assistance in gathering the literature.

Mainz, Oktober 1998

Karola Rück-Braun   Horst Kunz

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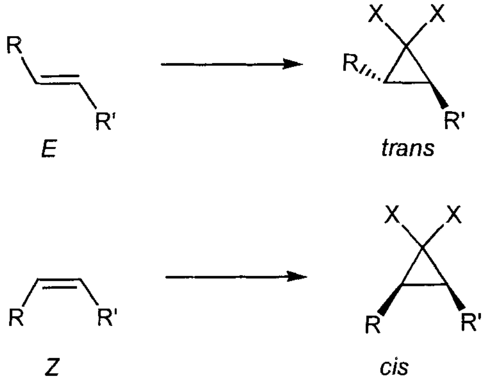
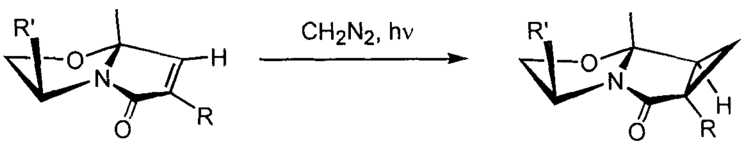
Chiral Auxiliaries in Cycloadditions
Karola Rück-Braun, Horst Kunz

1 [2+1] Cycloadditions (Cyclopropanations)

By stereoselective additions of carbenes or carbene equivalents to alkenes optically pure cyclopropanes are obtained.[1-7] In concerted [2+1] cycloadditions the stereochemistry of the alkene is conserved in the products. (*Z*)-configurated alkenes lead stereospecifically to *cis*-cyclopropanes. So far, compared to [2+1] cycloadditions involving alkenes bearing the chiral auxiliary, asymmetric reactions involving chiral carbene precursors proved to be less efficient.
Besides transition metal-catalyzed methylenations with diazomethane, diastereoselective Simmons-Smith cyclopropanations have been extensively studied.[6,7]



In addition, cyclopropanes are accessible diastereoselectively by 1,3-dipolar cycloaddition of diazomethane followed by photodecomposition of the pyrazolidine intermediate as shown below for the bicyclic α,β-unsaturated γ-lactams developed by Meyers et al. as chiral inductors for asymmetric synthesis.[8-10] Similarly, highly diastereoselective reactions of diketopiperazines have been reported in the literature.[7]

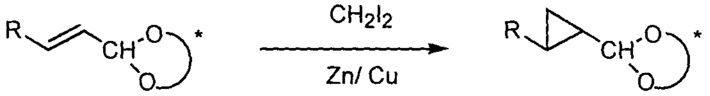


1.1 Simmons-Smith Reactions

Cyclopropanes are efficiently obtained from alkenes by Simmons-Smith reaction applying CH_2I_2/Zn-Cu couple or CH_2I_2/Et_2Zn as reagents.[6,11] A variety of compounds bearing a chiral moiety have been studied, as for example α,β-unsaturated acetals and oxazolidines, enolethers, allylic alcohols, alkenylboronic esters as well as α,β-unsaturated carbonyl compounds.

Chiral Acetals and Ketals

Easily accessible acetals and ketals of α,β-unsaturated aldehydes and ketones derived from C_2-symmetric chiral 1,2-diols have been successfully used with Simmons-Smith reagents furnishing cyclopropane aldehydes with high selectivity and recovery of the auxiliary.[12] Thus, dialkyl tartrates proved to be superior compared to 1,2-diphenylethanediols as chiral auxiliaries in reactions of α,β-unsaturated aldehydes.



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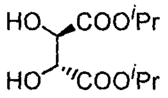
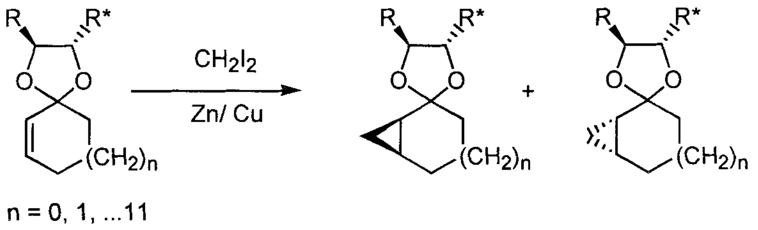
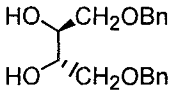
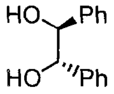
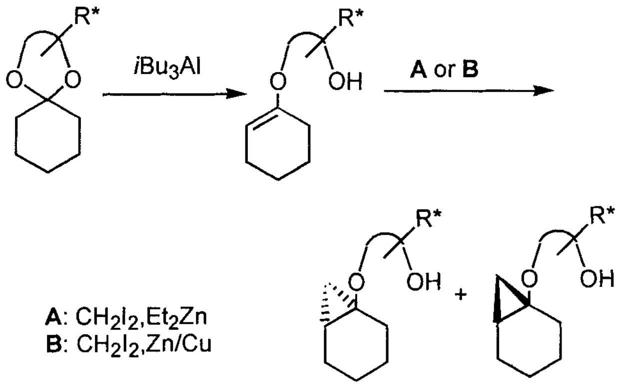
	**58**	87-94%		80-95%%	13-15

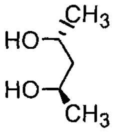
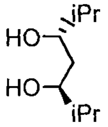


auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**60**	67:33-95:5		37-98%	[16,17]
	**54**	> 93:7		66-90%	[18]

Chiral Vinylethers

By treatment of acetals, obtained from chiral 1,3-diols and cyclic α,β-unsaturated ketones with *i*Bu$_3$Al, enolethers are obtained bearing an alcohol functionality, which proved to be necessary to obtain high diastereoselectivity.[19]

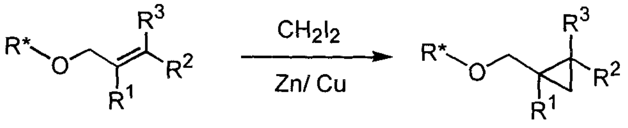


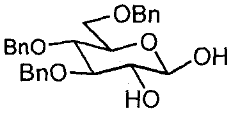
auxiliary	no.	method	d.r. or *de*	yield	ref.
	**55**		14-95%	56-70%	19
	**56**	**A**	95-99%	59-86%	19
		B	53-69%	81-94%	

Similarly, allylethers with free alcohol functionalities in close proximity to the alkene moiety have been successfully examined as outlined below.

Chiral Allylethers

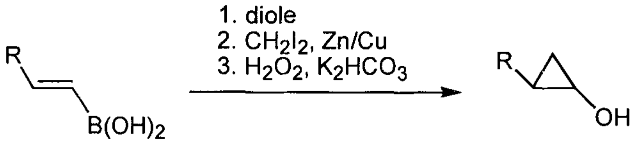
Besides monoallylethers of chiral alcohols, allylglycosides bearing a free alcohol functionality have been applied in asymmetric syntheses of enantiomerically pure cyclopropanemethanols with success.[11] The cleavage of the chiral carbohydrate-derived auxiliary was achieved by treatment of the cycloadducts with a. Tf_2O, pyridine; b. DMF/H_2O, pyridine, whereas for the compounds derived from **57** a. Tf_2O, Bu_4NI and b. *n*BuLi were applied.

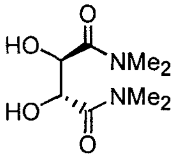


auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
		> 98:2		>97%	20
	**57**	> 15:1		68-97%	20,11

Chiral Alkenylboronic Esters

Chiral alkenylboronic esters are accessible *in situ* from the appropriate chiral diol and the desired alkenylboronic acid. Simmons-Smith reaction and subsequent treatment with $H_2O_2/KHCO_3$ lead to cyclopropanols with high selectivity.

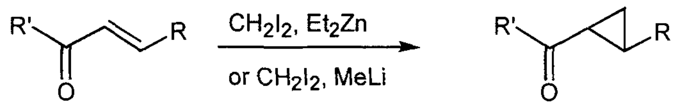


auxiliary	no.	*ee*	yield	ref.
	**61**	89-94%	46-48%	21

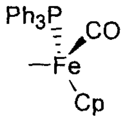
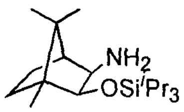
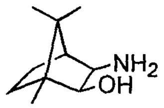
Chiral α,β-Unsaturated Carbonyl Compounds

Considering α,β-unsaturated carbonyl compounds, the application of α,β-unsaturated chiral menthylesters proved to be less effective (<3% *ee*).[22]

However, chiral at iron complexes have been established successfully by Davies et al. in asymmetric syntheses of cyclopropanes.[23] α,β-Unsaturated acylcomplexes were reacted with $CH_2I_2/ZnEt_2$ or $CH_2I_2/MeLi$ to obtain cyclopropanecarboxylates in high selectivity.

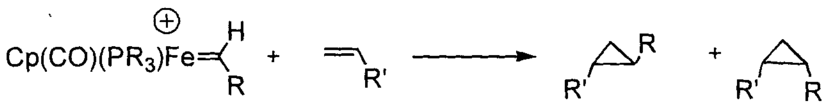


R' = R*, OR*, NRR*

auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
		>91:9 - > 98:2		61-85%	23
		78:22-90:10		72-83%	24
	**29**	90:10- >99:1		10-72%	24

1.2 Cyclopropanations with Carbene Equivalents

Enantiomerically pure iron carbene complexes have been used for carbene transfer reactions to alkenes, e.g. vinyl acetate and styrene, at low temperature to furnish cyclopropanes with moderate *cis/trans* selectivity in high optical yield (75-95% *ee*). A two-step reaction mechanism has been proposed to explain the origin of enantioselectivity.[25]

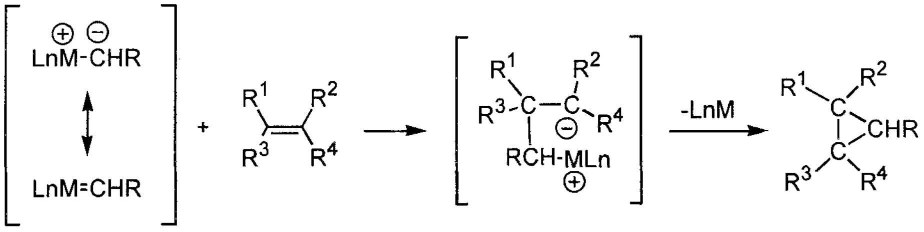


trans : *cis* = 3.5:1

83% *ee*, 75%

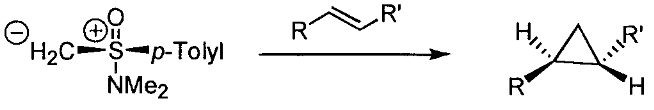
1.3 Cyclopropanations with Ylide Reagents

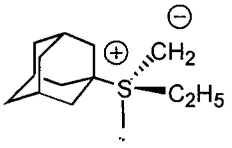
Asymmetric ylide cyclopropanations have been studied since 1960 and have been intensively discussed and documented in the literature.[26] Besides chiral aminosulfoxonium ylides, chiral sulfonium as well as chiral sulfoxonium ylides have been examined in reagent-controlled asymmetric cyclopropanations. However, asymmetric ylide cyclopropanations with alkenes bearing the chiral inductor proved to be more efficient.

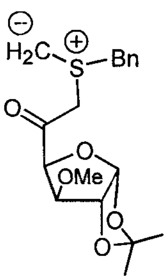


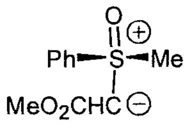
1.3.1 Chiral Ylide Reagents

Chiral aminosulfoxonium ylides react with electron-deficient alkenes, e.g. α,β-unsaturated ketones and esters, to cyclopropanes in moderate to high yields (56-94%) and up to 34% *ee*.[27] The chiral sulfur ylides **A**,[28] **B**[29] and **C**[30,31] were reacted with various Michael acceptors, whereby enantioselectivities up to 53% were achieved.





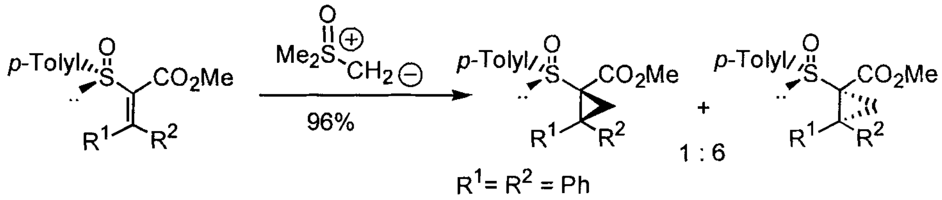




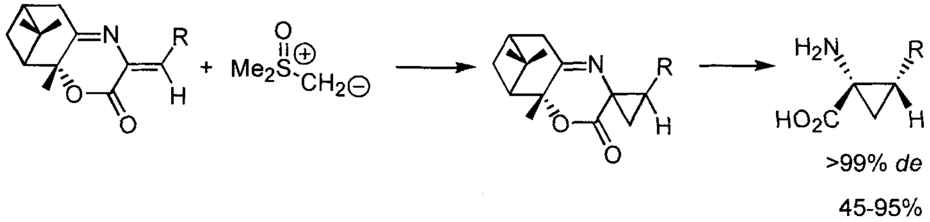
A **B** **C**

1.3.2 Chiral Alkenes

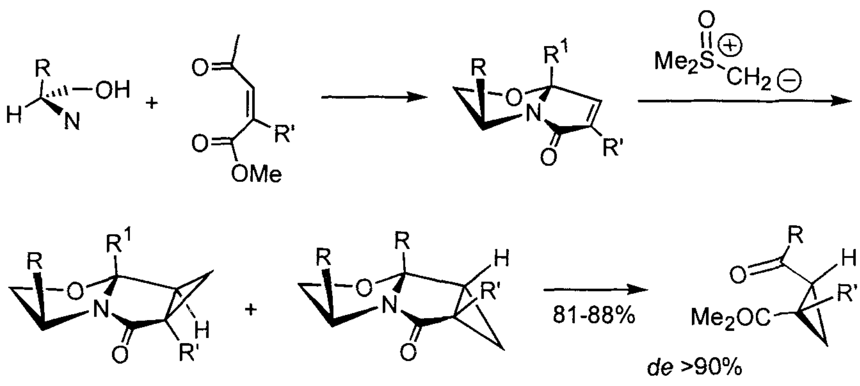
In asymmetric ylide cyclopropanations with achiral ylides vinylsulfoxides,[32] bicyclic γ-lactams[33] as well as *exo*-cyclic methylene compounds[34] were examined as chiral Michael acceptors. Bicyclic compounds proved to be most efficient.



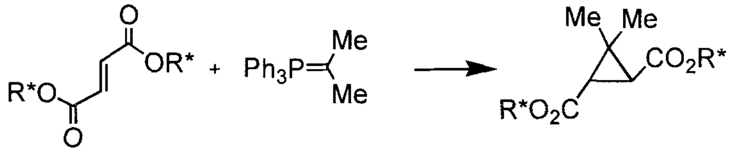
Dehydroamino acid derivatives derived from 2-hydroxypinan-3-one were found to react smoothly with dimethylsulfoxoniummethylide to give optically pure cyclopropanes in 45-96% yield.[34]



Meyers bicyclic lactams, derived from easily accessible chiral amino alcohols, have been used in the Corey-Chaykovsky reaction with $CH_2S(O)Me$ to yield chiral cyclopropanes with high diastereoselecitvity.[33]

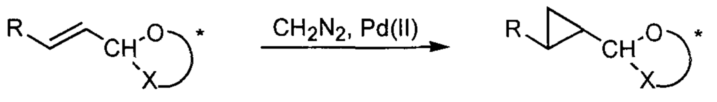


Phosphoranes were applied in highly diastereoselective reactions with (-)-8-phenylmenthylfumarates at low temperature.[35]

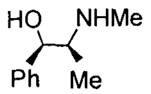


1.4 Transition Metal-Catalyzed Reactions of Diazo Compounds

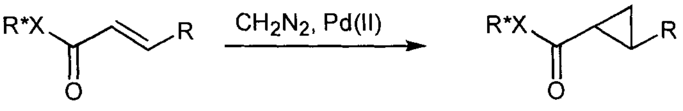
Palladium-catalyzed as well as photochemical reactions of diazoalkanes with optically pure oxazolidines derived from 1,2-amino alcohols and α,β-unsaturated aldehydes were found to be highly selective.



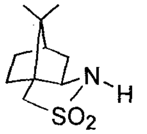
X = O, NR

auxiliary	no.	d.r. or *de*	yield	ref.
	**26**	> 95:5	55-100%	[36,21]

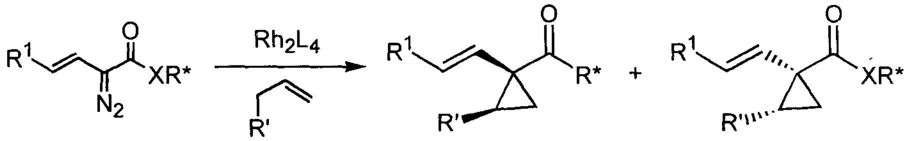
In palladium-catalyzed reactions with diazomethane *N*-enoylsultams have been successfully used for the synthesis of cyclopropane carboxylic acid derivatives. The cleavage of the auxiliary was achieved by treatment of the cycloadducts with a. Ti(O^{i}Pr)$_4$, $PhCH_2OH$; b. $NaOH/H_2O$.



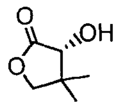
R* = O, NR

auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**63**	86:14-95:5		62-73%	37,38

In rhodium-catalyzed reactions[39,40] of vinyldiazoesters with alkenes various chiral alcohols have been examined, whereby (*R*)-pantolactone was found to be the best choice for the synthesis of *trans* cyclopropanecarboxylates. Cleavage of the auxiliary was achieved with 6N HCl.



X = O, NR
R' = Aryl, OAlkyl, OAc
L = OAc

auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**19**	47-95%		71-91%	41

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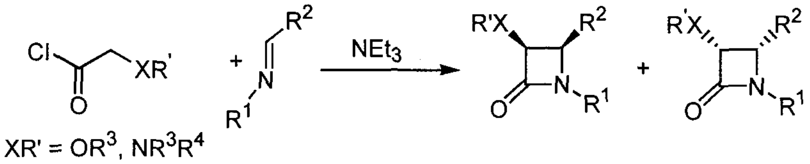
Chiral Auxiliaries in Cycloadditions
Karola Rück-Braun, Horst Kunz

2 [2+2] Cycloadditions

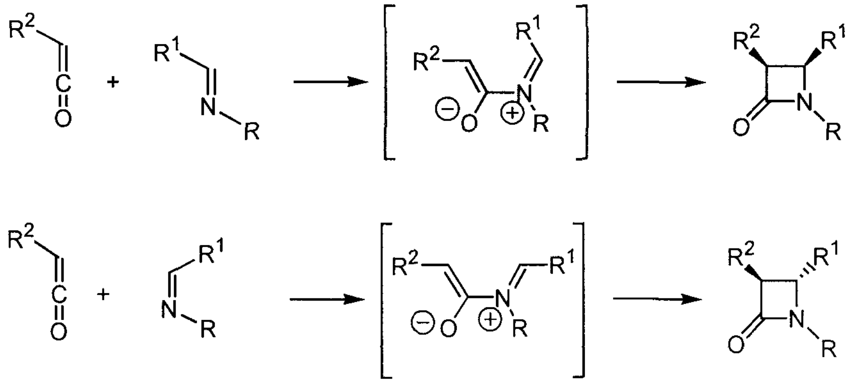
According to the Woodward-Hoffmann rules, concerted thermal [2+2] cycloadditions are symmetry-forbidden, but should proceed via supra-antarafacial attack of the reactants. [2+2] cycloadditions of ketenes and related reactive intermediates generated *in situ* proceed by a stepwise mechanism.[1-4] Photochemical [2+2] cycloadditions are symmetry-allowed.[2] Asymmetric [2+2] cycloadditions leading to 4-membered heterocycles, e.g. Staudinger reactions or Paterno-Büchi reactions, have been extensively studied in the past.

2.1 Reactions of Imines with Ketenes (Staudinger Reaction)

The reaction of ketenes with imines opens up a useful route for the synthesis of β-lactams. The two-step mechanism involving a dipolar intermediate is outlined in the scheme below.[5-8]

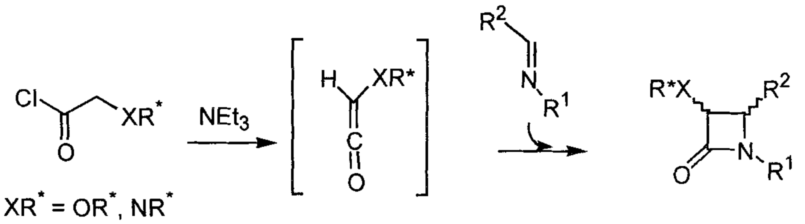


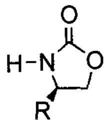
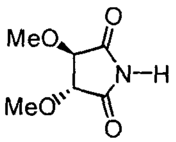
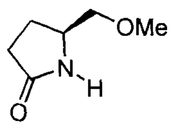
In the second reaction step the *cis/trans* stereochemistry of the product is determined. In general, *trans*-β-lactams are formed starting from cyclic (*Z*)-imines by conrotatory ring closure of the zwitterionic intermediate.[5-7,8]

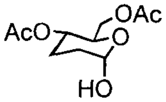


2.1.1 Chiral Ketenes

The use of chiral ketenes and imines has been examined, whereby the latter proved to be less efficient regarding *cis/trans* and face selectivity. The ketenes are generated *in situ* by treatment of acyl chlorides with triethylamine at –78°C. *N*-Acetyl chlorides are for instance appropriate precursor molecules. *Cis*-β-lactams are accessible diastereoselectively by intermolecular reactions of chiral ketenes derived from oxazolidinones with imines. In general, the cleavage of these compounds is achieved with Li/NH_3 under recovery of the chiral auxiliaries.

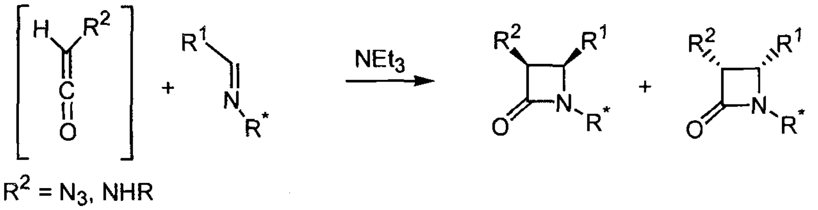


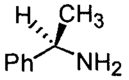
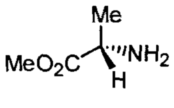
auxiliary	no.	*cis* : *trans*	d.r. or *de*	*ee*	yield	ref.
amine derivatives						
	**62**	70:30 - >98:2	95:5-97:3		48-82%	9-12
	**38**	0:100	84:16-86:14		47%	5
	37	84:16	97:3		71%	13

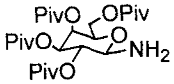
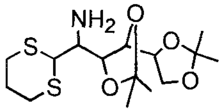
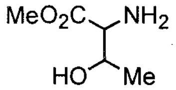
auxiliary	no.	*cis : trans*	d.r. or *de*	*ee*	yield	ref.
alcohol derivatives						
				70%	52%	[14]

2.1.2 Chiral Imines

Besides imines bearing a chiral (1-naphthyl)-ethyl group, glycosylamine-derived imines as well as amino acid ester derivatives have been examined as chiral inductors in diastereoselective Staudinger reactions.

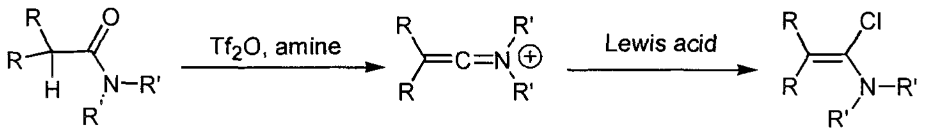


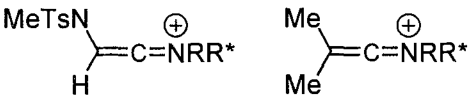
auxiliary	no.	cleavage	d.r. or *de*	*ee*	yield	ref.
	31	$(NH_4)_2S_2O_8$, H_2O/CH_3CN	80:20- 90:10		59-74%	[15-17]
		Li/NH_3	50:50- >99:1		76-92%	[11]

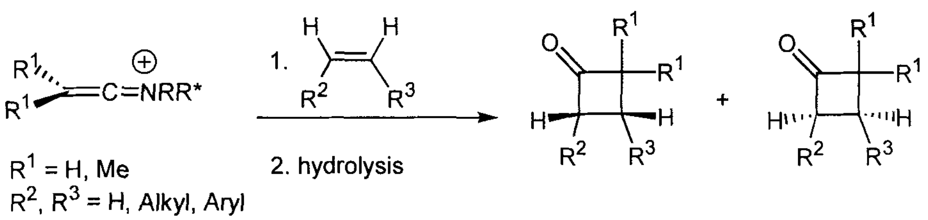
auxiliary	no.	cleavage	d.r. or *de*	*ee*	yield	ref.
	**33**	6N HCl/MeOH	>99:1		75%	18
			2:1 -100:0		92-94%	19
			95:5		50-60%	20

2.2 Reactions of Keteniminium Salts with Alkenes

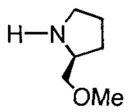
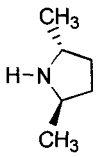
Keteniminium salts, generated *in situ* from dialkylamides or α-haloenamines, are more reactive compared to ketenes and react with alkenes in a stepwise cycloaddition to give cyclobutanones. However, the cycloaddition is limited to mono- and 1,2-disubstituted alkenes.







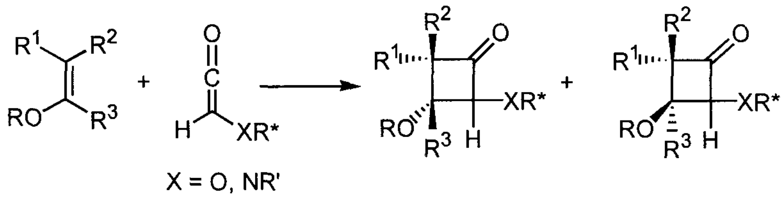
C_2-Symmetric pyrrolidines have been employed as chiral auxiliaries effectively. Intramolecular cycloadditions of keteniminium salts as well as reactions with imines furnishing β-lactams have been reported in the literature.[21-23,3]

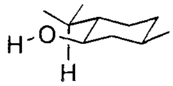
auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**40**	55-97%		30-70%%	21,22
	**41**	48-96%		51-81%	23

2.3 Reactions of Ketenes with Electronrich Alkenes

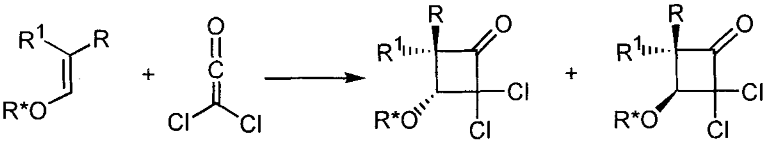
Reactions of ketenes, e.g. dihaloketenes, with electron-rich alkenes bearing the chiral auxiliary, for example enolethers, carbohydrate-derived anomeric enolethers or ketene acetals, lead to cyclobutanones with moderate stereoselectivities.

2.3.1 Chiral Ketenes

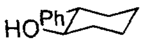
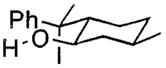
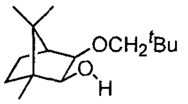
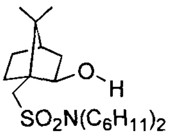


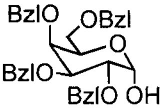
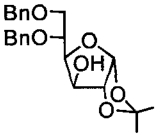
auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**10**	3:1 - 5:1		50-65%	24

2.3.2 Chiral Vinylethers



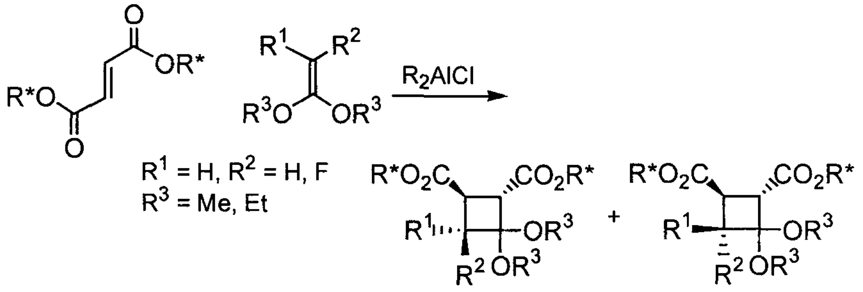
By treatment of the cycloadducts with CH_2N_2 cyclopentanones are regioselectively accessible, whereas upon oxidation with MCPBA γ-butyrolactones are formed.

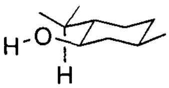
auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**12**	90:10 - 95:5		65-92%	25-27
	**11**	55:45 - 90:10		(60)	28
	**6**	10:90		60%	28
	**9**	90:10		60%	29

auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
		80:20		72%	29
		83:17		35%	29

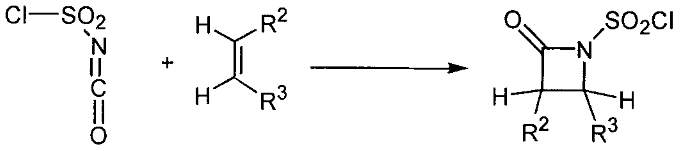
2.3.3 Miscellaneous Reactions

Asymmetric [2+2] cycloaddition reactions of fumarates bearing a chiral moiety with ketene acetals lead to optically active substituted cyclobutane ring systems under Lewis acid catalysis.

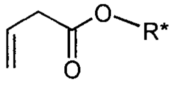


auxiliary	no.	*cis* : *trans*	d.r. or *de*	yield	ref.
	**10**		3:1-95:5	50-98%	30,31

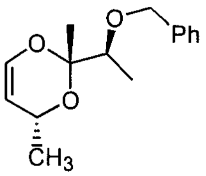
2.4 Reactions of Isocyanates with Alkenes



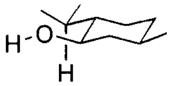
Types of Chiral Alkenes

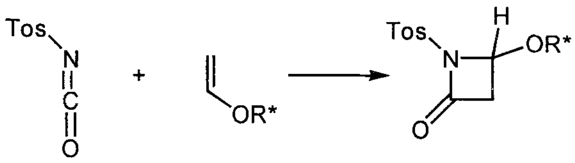


A



B

type of alkene	auxiliary	no.	*cis* : *trans*	d.r. or *de*	yield	ref.
A		**10**		1:1	28%	32
B			100:0	98:2	56%	33



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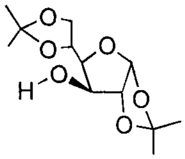
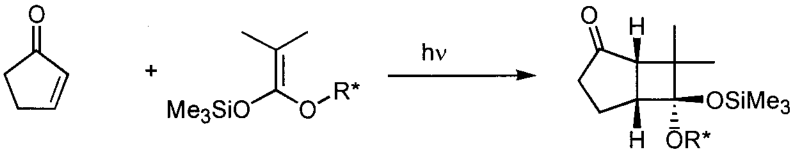
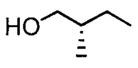
	**20**		86:14	50%	34

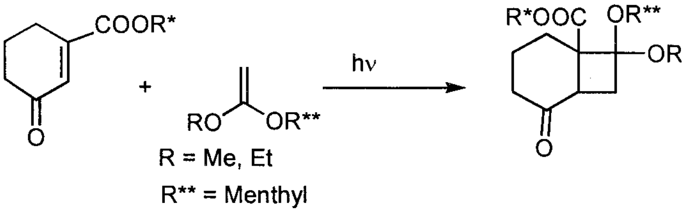
2.5 Photochemically Induced [2+2] Cycloadditions

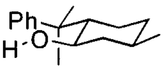
Reactions of α,β-Unsaturated Carbonyl Compounds

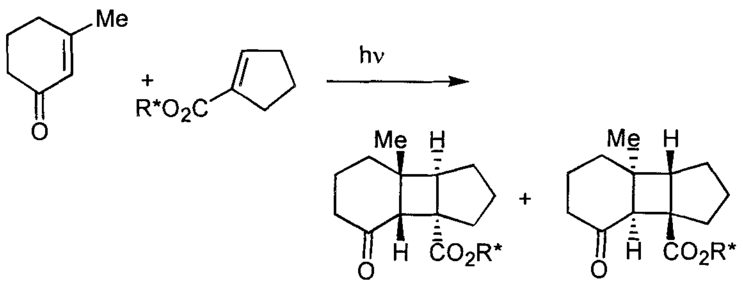
Stereoselective [2+2] photocycloadditions of alkenes are a powerful tool for the synthesis of cyclobutanes.[1,2,4] However, in diastereoselective reactions cyclic enones have been intensively examined with moderate success. By double stereodifferentiation an increase in selectivity was achieved.

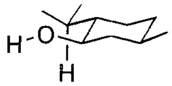
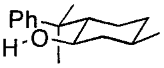
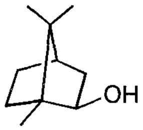


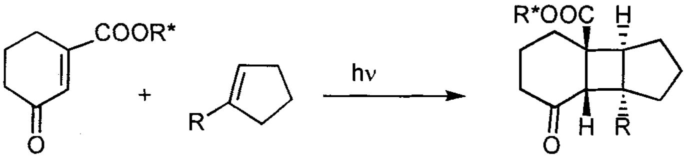
auxiliary	no.	d.r. or *de*	*ee*	ref.
			33%	2

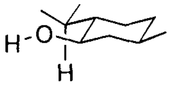
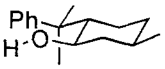


auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**11**	56%		51%	35

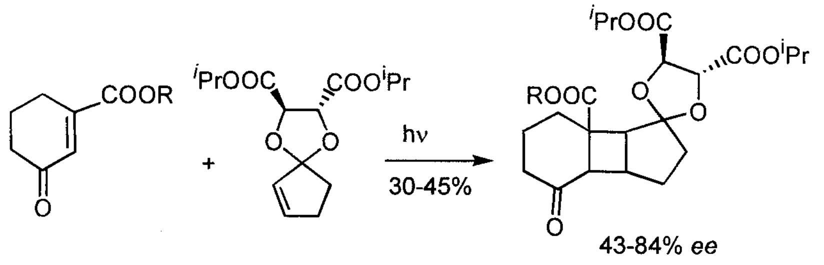


auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**10**	13%		54%	36
	**11**	56%		51%	36
	**3**	19%		57%	36

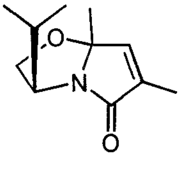


auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**10**	70:30		18-23%	36
	**11**	60:40		30-70%	36

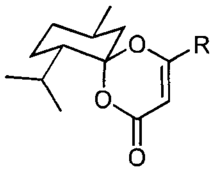
In [2+2] photocycloadditions of α,β-unsaturated ketals derived from C_2-symmetric 1,2-diols tartaric acid derivatives (**58**) proved to be efficient to yield the cycloadducts in up to 84% *de.*[37]



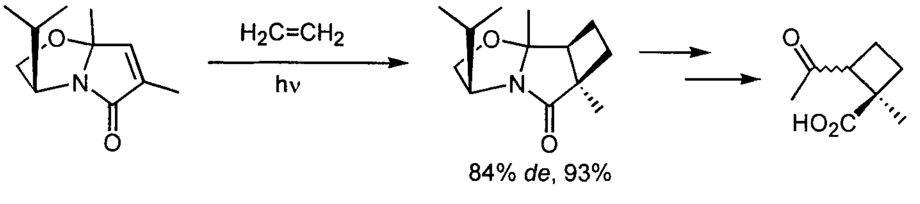
In photocycloadditions of 1,2-dioxine-4-ones **A** derived from menthone with unsymmetrically substituted alkenes moderate regioselectivity was observed. However, the cycloaddition reaction with cyclopentene proceeded highly stereoselective.[38-40] Chiral bicyclic lactams diastereoselectively react with ethylene furnishing optically active cyclobutanes.[41]



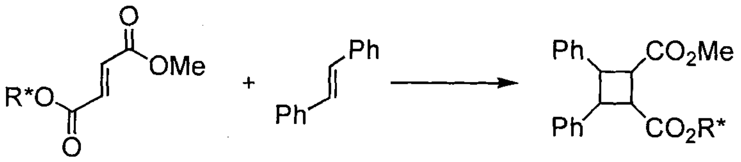
A

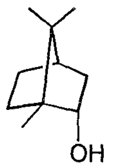


B



Reactions of α,β-unsaturated ester derivatives with alkenes have been investigated leading to cyclobutanones with moderate stereoselectivity.[42]

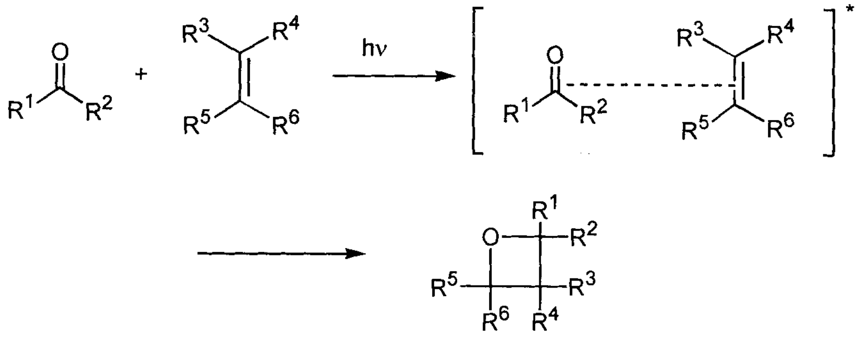


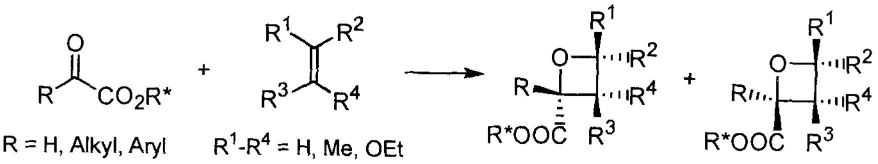
auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**2**	20-90%		20-35%	42

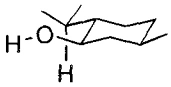
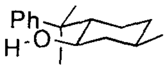
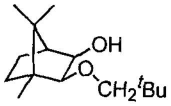
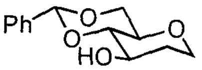
2.5.1 Paterno-Büchi Reactions

The photochemically induced [2+2] cycloaddition (Paterno-Büchi reaction) of carbonyl compounds with alkenes gives oxetanes.[43-45]

Glyoxylates of chiral alcohols have been intensively studied as carbonyl components. According to the mechanistic studies of Scharf and coworkers, the outcome of the cycloaddition is in particular depending upon the reaction temperature (isoinversions principle).[43]

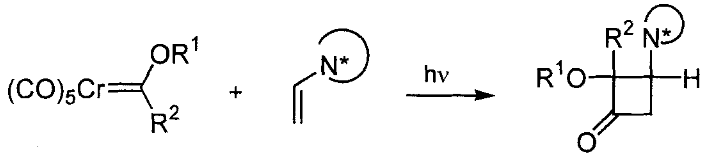


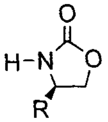


auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**10**	25-67%		>70%	47
	**11**	76 - > 96%		72-93%	48
	**7**	> 96%		>70%	48
		90:10		80%	48b

2.5.2 Application of Chromium Carbene Complexes

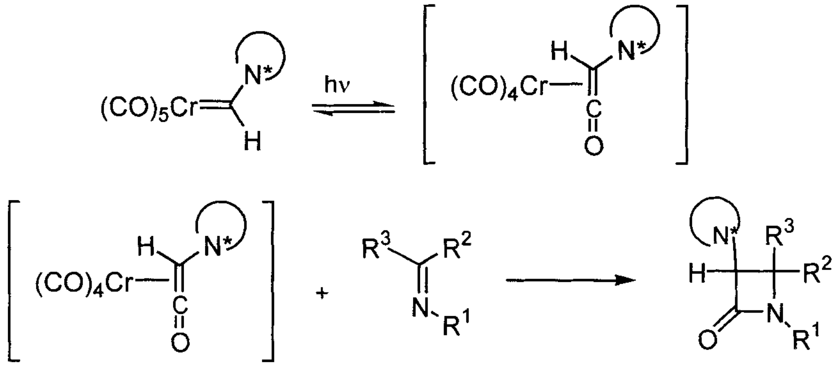
By photolysis of achiral heteroatom-stabilized chromium carbene complexes chromium-ketene species are generated[49] that undergo [2+2] cycloaddition with chiral alkenes diastereoselectively.[50]

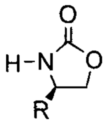
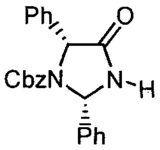
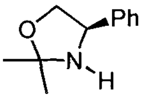


auxiliary	no.	*cis : trans*	d.r. or *de*	*ee*	yield	ref.
	**62**	>97%	>99%		90%	50

Staudinger-type Reactions

Chromium-complexed ketenes are obtained by irradiation of chromium aminocarbene complexes derived from chiral oxazolidines (CO pressure). These ketenes were found to react with imines diastereoselectively furnishing *trans*-β-lactams, exclusively.[49,51]



auxiliary	no.	*cis : trans*	d.r. or *de*	*ee*	yield	ref.
	**62**	>97%	>99%		90%	51
		100:0	60:40-100:0		90%	51
		0:100	> 97%		75-94%	51

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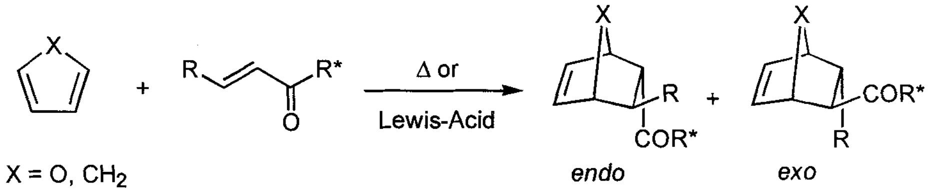
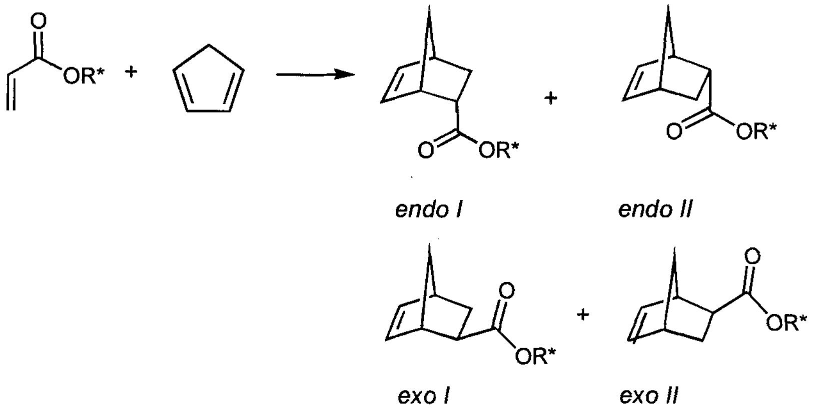
Chiral Auxiliaries in Cycloadditions
Karola Rück-Braun, Horst Kunz

3 [4+2] Cycloadditions (Diels-Alder Reactions)

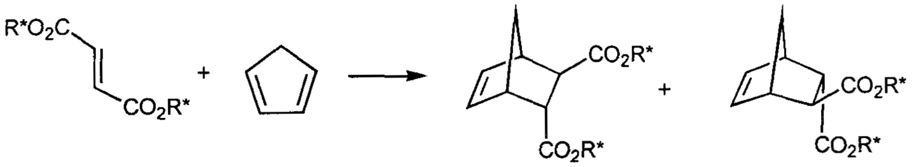
In thermal and Lewis acid-catalyzed Diels-Alder cycloaddition reactions diene and dienophile react in a suprafacial concerted process predicted by the Woodward-Hoffmann rules.[1-9] Therefore, the double bond configuration of the dienophile is retained in the cycloadducts. In asymmetric Diels-Alder reactions up to four stereogenic centers can be formed stereoselectively in a single reaction step.



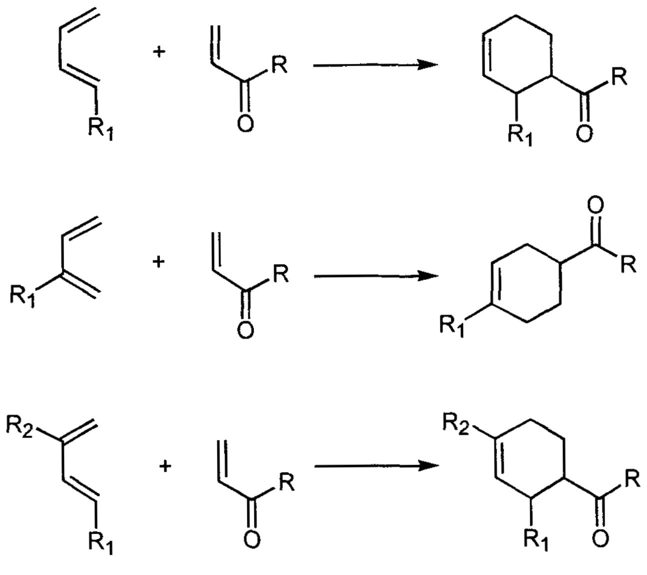
In cycloaddition reactions of dienophiles with cyclic dienes generally a preference for the *endo* adduct is observed due to secondary orbital interactions.[6,7] Also, the regioselectivity observed in Diels-Alder reactions originates in orbital interactions of the two reactants and can well be rationalized by molecular orbital calculations.



Endo/*exo* selectivity can be influenced by Lewis acids, the solvent or for example high pressure. The stereoselectivity of Diels-Alder reactions can be controlled and even altered by the appropriate use of chelating and non-chelating Lewis acids, too. Thus, by effective shielding of one of the enantiotopic faces of the diene or dienophile attached to a chiral auxiliary, asymmetric induction leading to the formation of only one product can be achieved.



In frontier orbital terms the regioselectivity of Diels-Alder reactions is mainly controlled by the atomic orbital coefficients of the frontier orbitals of both reaction partners. The regioselectivity observed for substituted dienes with α,β-unsaturated carbonyl compounds is shown below. With substituents at C-1 of the diene the 3,4-disubstituted cyclohex-1-enes are preferably obtained. The formation of 1,4-disubstituted cyclohex-1-enes is favored in cycloaddition reactions of C-2-substituted dienes. In cycloaddition reactions of electron-poor alkenes with 1,3-disubstituted dienes generally a preference for the 1,3,4-trisubstituted cyclohex-1-enes is observed.



3.1 Thermal Reactions

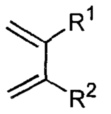
3.1.1 Reactions of Chiral Dienophiles

In asymmetric Diels-Alder reactions of chiral electron-poor alkenes the dienes compiled in the schemes given below have been used as indicated in the tables on the following pages.

Types of Dienes

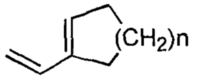
X = O, (CH_2)

1



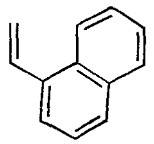
R^1 = H, Me
R^2 = H, Me

2

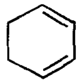


n = 1,2

3



3



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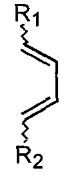

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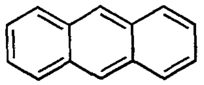

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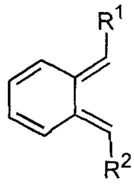
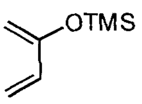


R^1, R^2 = H;
R^1 = OH, R^2 = H

7

Heteroatom-substituted Dienes



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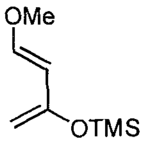

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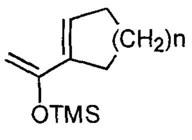

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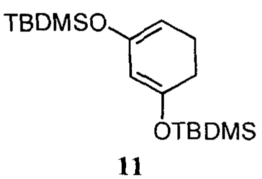

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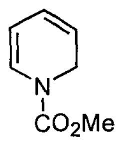

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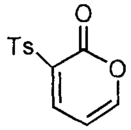

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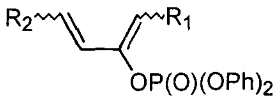

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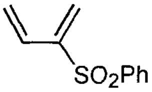
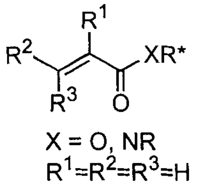
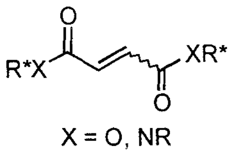


15

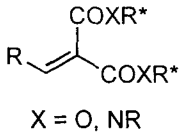
Types of Dienophiles



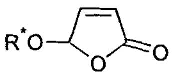
A



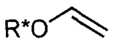
B



C



D

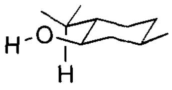
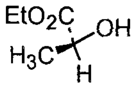
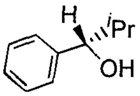
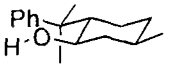
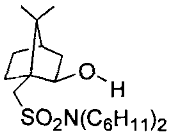


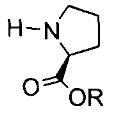
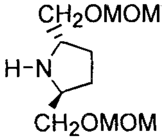
E

In thermal cycloaddition reactions of acrylates (type **A**, table: column 3) only moderate *endo/exo* selectivities and diastereoselectivities have been observed.[10-19] Mixtures of regioisomers have often been obtained with isoprene as the diene component. Reactions of chiral fumarates (**B**) derived from (*S*)-lactate **15** with a variety of dienes (table: column 4) lead to moderate to high selectivities.

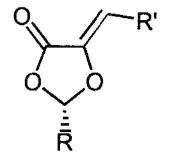
Asymmetric Diels-Alder reactions of the chiral dienophile 5-(alkyloxy)-5*H*-2-furanone (**D**), derived from the chiral auxiliary **10**, with a variety of dienes have been studied in toluene at 120°C. Thereby, diastereoselectivities up to 96% *de* were determined. From cyclic dienes with exocyclic or vinylic double bonds, such as (3), substituted decalins were obtained as optically pure cycloadducts.

In non-catalyzed [4+2] cycloadditions of chiral acrylamides (**A**), e.g. prolinates, in toluene or water/ethanol mixtures at room temperature moderate to high selectivities have been determined.[19] Removal of the chiral auxiliary **43** is achieved by treatment with I_2 in H_2O/dimethoxyethane.

auxiliary	no.	type	dienes	*endo : exo*	d.r. or *de*	yield	ref.
alcohol derivatives							
	**10**	A	1,2		3.8%	93%	10
		B			4–12%	76-100%	11
		D	1,2,3, 8,9	> 97%	> 96%	44-65%	12
		E	1,3,5	77:23		89%	13
	**15**	A	1,6,4,7	63:37–77:23	80:20-85:15	62–99%	14
		B			75:25-98:2	96-99%	15
	**17**	E	13,15		92:8	94%	13
	**11**	C	1	82:18	0%		16
	**9**	B	6		34-60%	68-90%	17

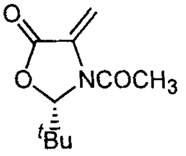
auxiliary	no.	type	dienes	*endo : exo*	d.r. or *de*	yield	ref.
amide derivatives							
 R = Bzl		A	1,2	57:43-78:22	64:36-82:18	27-43%	18
		B			67:33-94:6	30-100%	
	**43**	A	1	95:5	69:31	73-76%	19

Chiral exo-Methylene Compounds and related Derivatives

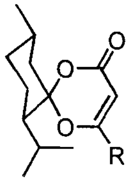


R' = H, CO_2Et
R = ^{t}Bu, Cyclohexyl

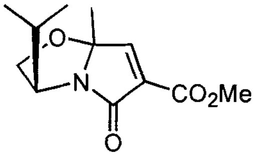
A



B



C



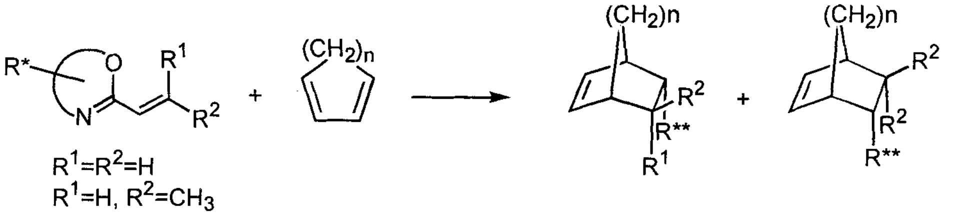
D

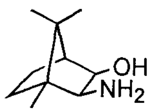
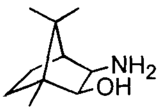
Chiral, optically pure *exo*-methylene compounds, as for example dioxolanes **A**[20,21] and 1,3-oxazolidinones **B**[21], have been successfully examined as dienophiles in thermal Diels-Alder reactions with 1,3-butadiene or cyclopentadiene. Similarly highly diastereoselective reactions of dioxinones **C**[9] with cyclopentadiene in benzene at 80°C have been reported in the literature. Non-catalyzed cycloaddition reactions of Meyers' bicyclic lactam **D**[22] with acyclic dienes proceed at moderate temperature (60°C) highly stereoselective furnishing the products in excellent yield. Equally high *endo*/*exo* selectivities and diastereoselectivities were reported for the reactions that have been carried out at low temperature in the presence of Lewis acids, e.g. $ZnCl_2$.[22]

compound	*endo* : *exo*	d.r. or *de*	yield	ref.
A	88:12-100:0	55:45-100:0	65-93%	20,21
B	82:18-93:7	100:0	67%	21
C	0:100	93:7-100:0	64-66%	9
D		>98%	98%	22

α,β-Unsaturated Oxazolidines

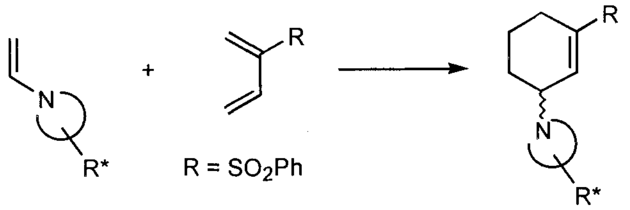
In Diels-Alder reactions α,β-unsaturated oxazolines react with various dienes (1, 2, 12, 14) stereoselectively via the acyl iminium salts derived by *N*-acylation with trifluoroacetic anhydride.

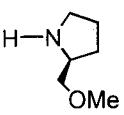


auxiliary	no.	*endo* : *exo*	d.r. or *de*	yield	ref.
	**30**	50:50- >100:0	84:16- >99:1	47-82%	23
	**29**	100:0	64:36-86:14	61-72%	23

Chiral Enamines

Inverse-electron demand cycloaddition reactions of chiral enamines with 2-phenylsulfonyl-1,3-diene in toluene at high temperature have been studied, furnishing the cycloadducts in moderate yield and selectivity

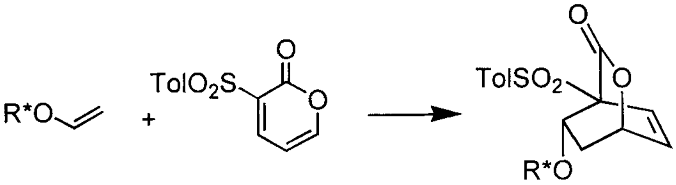


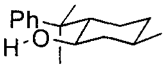
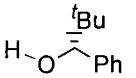
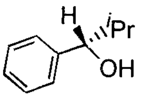
auxiliary	no.	type	*endo : exo*	d.r. or *de*	*ee*	yield	ref.
	**40**			80:20-86:14		32-60%	24

Chiral Vinylethers

Inverse-electron demand Diels-Alder reactions between electron-rich dienophiles, e.g. vinylethers or enamines, are controlled by dienophile-HOMO/diene-LUMO orbital interactions.

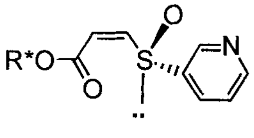
The highly reactive diene 3-tosyl-2*H*-pyran-2-one reacts with chiral alkyl vinylethers at moderate temperatures furnishing the cycloadducts in excellent yield and diastereoselectivity. With a variety of well-known auxiliaries, such as **11**, only moderate selectivities were obtained.



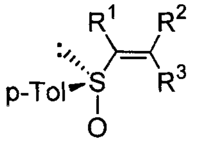
auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**11**	>5%		>90%	13,25
	**16**	90%		90%	13,25
	**17**	84%		94%	13,25

Chiral Vinylsulfoxides

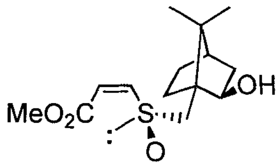
Thermal cycloadditions of chiral vinylsulfoxides **B** with cyclopentadiene, 1,3-cyclohexadiene and 1,3-butadiene have been examined in toluene at high temperature leading to the adducts in moderate selectivities. The electron-deficient sulfur residue activates the alkene unit and serves as a temporary substituent that can be easily removed by reduction or transformed into a variety of other functionalities. An increase in reactivity and excellent selectivities are observed in the presence of additional electron-withdrawing substituents at the alkene unit as shown for the examples **A**[26] and **C**[28,29] in the table below. At 20°C in dichloromethane the cycloadditions of **C** with cyclopentadiene proceed smoothly and highly stereoselective. In reactions of menthyl-3-(3-trifluoromethyl-2-pyridylsulfinyl)acrylate **A** with dienes, e.g. 2-methoxyfuran or cyclopentadiene, high diastereoselectivities (>98:2) were obtained, too.



A[26]



B[27]



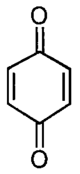
C[28,29]

sulfoxide	*endo* : *exo*	d.r. or *de*	*ee*	yield	ref.
A	>100:0	>98:2		72-100%	26
C	>100:0	>98%%		>90%	28,29

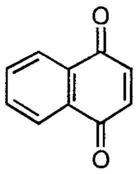
3.1.2 Reactions of Achiral Dienophiles with Chiral Dienes

Non-catalyzed Diels-Alder reactions of chiral dienes with the achiral dienophiles compiled below have been widely studied. As dienophiles especially quinones (1), maleic anhydride (2), nitro-substituted alkenes (5) and acrylates (4) have been examined.

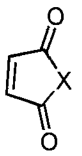
Types of Dienophiles



1

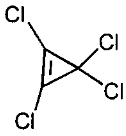


1



X = O, NH, NPh

2



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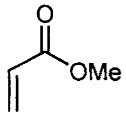

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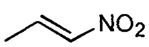

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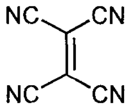

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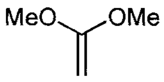

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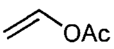
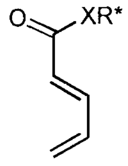


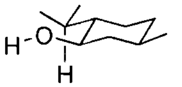
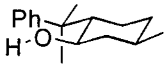
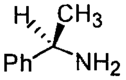
8

Chiral Esters and Amides of Pentadienoic Acid

Moderate selectivities were observed in non-catalyzed cycloaddition reactions of chiral pentadienoic acid esters and amides with e.g. benzoquinone even at higher temperature and at high pressure ($1\cdot10^7$ torr).

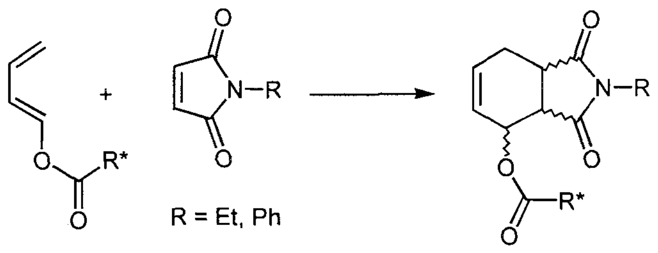


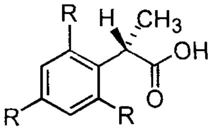
X = O, NR

auxiliary	no.	dienophile	d.r. or *de*	yield	ref.
ester derivatives					
	**10**	1	68 : 32	58%	30
	**11**	1	75 : 25	62%	30
amide derivatives					
	**31**	1	57.5 : 42.5	92%	30

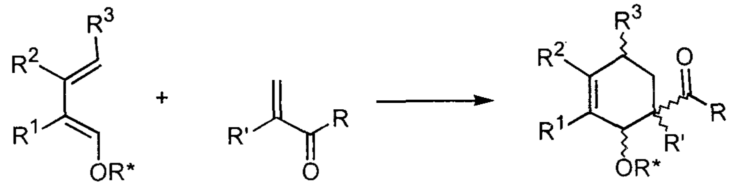
Chiral Acyloxydienes

Thermal cycloaddition reactions of chiral 1-acyloxy-1,3-butadienes derived from chiral carboxylic acids with electron-deficient alkenes, e.g. *N*-ethylmaleimide or quinones, were found to be highly *endo* selective. Moderate to high diastereoselectivities were obtained (>96:4).



auxiliary	no.	*endo* : *exo*	d.r. or *de*	yield	ref.
 R = H, Me	**51**	> 100:0	55:45 – 96:4	49-88%	31,32

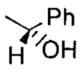
Chiral Alkoxydienes



R^1, R^2 = H, Et, Me
CO_2Me, OTMS, ^{t}Bu
R^3 = H, OTMS

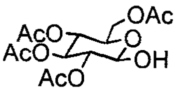
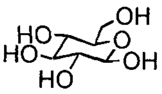
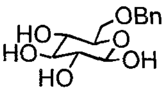
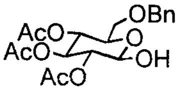
R = H, Alkyl, OMe
R' = H, Me

Asymmetric thermal cycloadditions of alkoxydienes with a variety of dienophiles (1,2,3,6), e.g. benzoquinone (1), tetracyanoethylene or maleic anhydride, lead very selectively to the cycloadducts.[33,34]

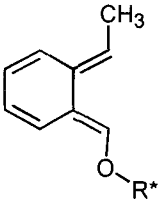
auxiliary	no.	dienophile	d.r. or *de*	ref.
		1	50 : 50 -> 97 : 3	33
		3	> 97:3	34

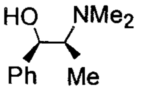
Carbohydrate-derived Auxiliaries

Chiral carbohydrate-derived 1-alkoxy-1,3-dienes have been intensively examined in asymmetric Diels-Alder reactions with quinones. Moderate selectivities were observed. However, in water as solvent high *endo* selectivities were obtained at room temperature.[35-37]

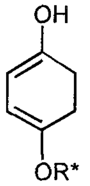
auxiliary	no.	*endo* : *exo*	d.r. or *de*	*ee*	yield	ref.
			4:1 - 7:1		32-74%	35
		100:0	60:40		90%	36
		95:5	69:31		86%	36
			>95:5		73%	37

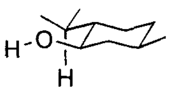
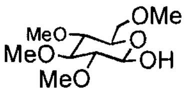
Reactions of chiral 2-quinodimethanes with alkyl acrylates, fumarates or maleic anhydride lead to tetralines. Moderate selectivities (d.r. 83:17) were obtained.

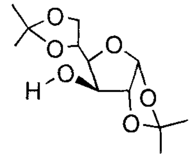


auxiliary	no.	dienophile	d.r. or *de*	yield	ref.
		4	83 : 17	75%	38

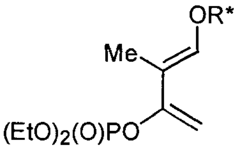
In asymmetric thermal [4+2] cycloaddition reactions of 1-alkoxy-4-hydroxy-cyclohexa-1,3-dienes with 1,4-naphthoquinone moderate diastereoselectivities were observed. Upon treatment with aqueous acid benzonaphthofuranes were obtained.



auxiliary	no.	d.r. or *de*	yield	ref.
	**11**	53 : 47	46%	39
	**23**	58 : 42	58%	39

auxiliary	no.	d.r. or *de*	yield	ref.
	**20**	>97 : 3	97%	39

In thermal cycloaddition reactions of chiral 1-alkoxy-1,3-dienes of type **A** with maleic anhydride at 20°C moderate to high stereoselectivities were observed.

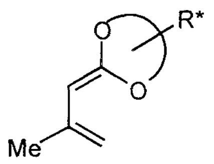


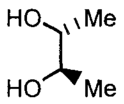
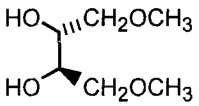
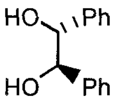
A

auxiliary	no.	dienophile	*endo : exo*	d.r. or *de*	*ee*	yield	ref.
 R = *cyclo*-C_6H_{11}		3	16 : 1	91 : 9		74%	40

Chiral 2-Allylidene-1,3-dioxolanes

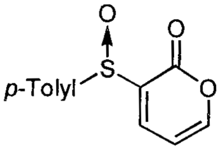
Excellent stereoselectivities were observed in reactions of chiral 2-allylidene-1,3-dioxolanes derived from C-2-symmetric dioles with electron-deficient alkenes, such as α,β-unsaturated carboxylic esters or *N*-methylmaleimide, in dichloromethane at room temperature.



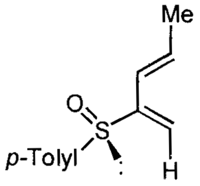
auxiliary	no.	d.r. or *de*	yield	ref.
	**53**	58 : 42	40%	[41]
	**59**	54 : 44	55%	[41]
	**54**	55 : 45 – 98 : 2	55 – 96%	[41]

Chiral 1,3-Butandienyl Sulfoxides

In reactions of the chiral 3-tosyl-2*H*-pyran-2-one **A** with ketene acetals (7) moderate selectivities were observed. 2-Substituted 1,3-butadienes with a chiral sulfoxide group have been studied in asymmetric Diels-Alder reactions with maleimide. These reactions have been found to proceed smoothly and highly stereoselective at 25°C.



A

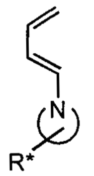


B

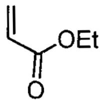
sulfoxides	dienophile	d.r. or *de*	yield	ref.
A	7	88 : 12 – 97 : 3	49%	42
B	2	> 100 : 0	66-96%	43

Chiral 1,3-Butadienyl Pyrrolidinones

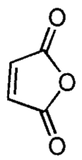
Moderate to high selectivities were observed in non-catalyzed reactions of chiral 1-amino-1,3-butadienes derived from the chiral auxiliary **36** with electron-poor alkenes.



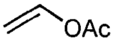
Type of Dienophile



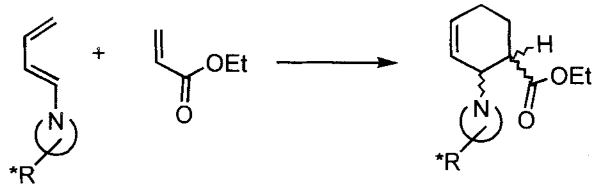
4

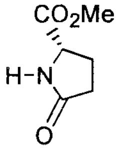


2



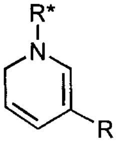
8



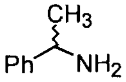
auxiliary	no.	dienophile	*cis: trans*	d.r. or *de*	*ee*	yield	ref.
	**36**	2,4,8					
		2	>99:1	>99%		73-76%	44
		4	82:18-100:0	2:1-18:1		77-91%	45

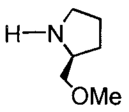
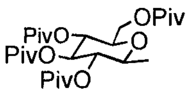
Chiral 1,2-Dihydropyridines

[4+2] Cycloaddition reactions of chiral dihydropyridines with acrylates proceed with high to complete *endo/exo* selectivity and moderate diastereoselectivity.



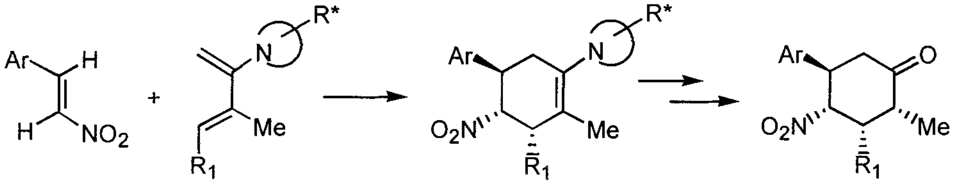
R = H, Et

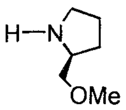
auxiliary	no.	*endo* : *exo*	d.r. or *de*	yield	ref.
	31	77:23-100:0	< 66:34	28%	46

auxiliary	no.	*endo : exo*	d.r. or *de*	yield	ref.
	**40**	97:13	66:34	68%	46
		100:0	92:8	30%	47

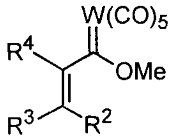
Non-catalyzed reactions of electron-rich, chiral 2-amino-1,3-butadienes with nitroalkenes stereoselectively furnish nitrocyclohexanones after acidic work-up in moderate yield.

Activation of the diene can be achieved by the introduction of an electron-donating nitrogen substituent. In nitroalkenes the nitro-group serves as an activating and regiocontrolling functionality, that can be readily removed or further functionalized after the cycloaddition reaction.

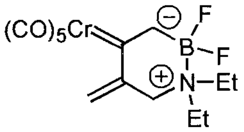


auxiliary	no.	*cis : trans*	d.r. or *de*	yield	ref.
	**40**	82:18-100:1	87:13-97:3	26-60%	48-50

The cycloaddition reactions of chiral 2-amino-1,3-dienes with Fischer-type carbene complexes have been examined by Barluenga et al.[51] Reactions with tungsten vinyl carbene complexes **A** and with boron-nitrogen-chelated chromium complexes **B** lead very selectively to cyclohexanone derivatives. However, when employing chromium vinyl carbene complexes in acetonitrile at room temperature in these reactions, cycloheptadienes were obtained selectively by cyclopropanation and subsequent Cope rearrangement.



A



B

3.2 Lewis Acid-Catalyzed Reactions

3.2.1 Reactions of Chiral Dienophiles

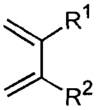
In a Diels-Alder reaction an electron-rich diene reacts with an electron-poor dienophile. By coordination of a Lewis acid the frontier orbital energies of the dienophile are lowered. Thus, the energy difference between the dienophile-LUMO and the diene-HOMO is decreased and the reaction rate accelerated. Most reactions are catalyzed by Lewis acids like $BF_3{\bullet}OEt_2$, $EtAlCl_2$, Et_2AlCl, $TiCl_4$ or for example $SnCl_4$, and thus can be carried out even at low temperature (-70°C).

Types of Dienes

Excellent selectivities were observed in Lewis acid-promoted Diels-Alder reactions. In general, cyclopentadiene or 1,3-butadiene were chosen as dienes (see, table column 4). Anthracene and other dienes, as for example (5) or (6), were examined in isolated cases as indicated in the following table. 1-Acetoxy-1,3-butadienes (5) and diene (6) were employed in natural product syntheses furnishing the desired cycloadducts as single diastereomers.

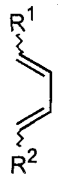
$X = (CH_2)_n$, n = 1, 2

1



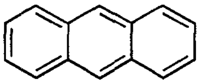
R^1 = H, Me
R^2 = H, Me

2

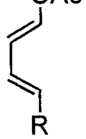


R^1, R^2 = H, Me

3

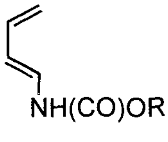


4



R = H, OAc

5

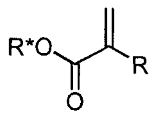


6

Lewis acids: $ZnCl_2$, $EtAlCl_2$, BF_3OEt_2, $TiCl_2(O^iPr)_2$, $TiCl_4$, $SnCl_4$, $LiClO_4$

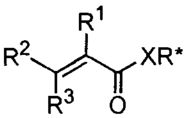
Types of Dienophiles

Excellent selectivities were observed in Lewis acid-promoted Diels-Alder reactions of chiral alkylidene malonates (**D**), fumarates (**C**) and allenic esters (**G**) with cyclopentadiene (see, column 3 in the table below).
In reactions of the electron-deficient alkene (**F**) with cyclopentadiene high *exo* stereoselectivity and diastereoselectivity (>98:2) is observed in the presence of Lewis acids, e.g. $TiCl_4$, $ZnCl_2$ or $AlCl_3$.



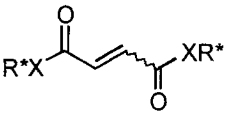
R = H, Alkyl

A



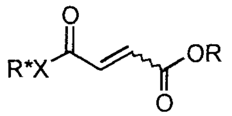
X = O, NR

B



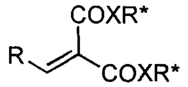
X = O, NR

C



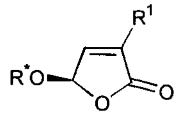
X = O, R = Me, ^tBu

C'

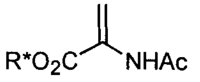


X = O, NR

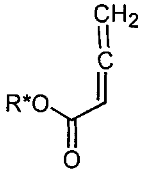
D



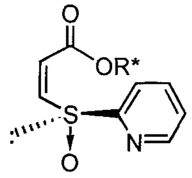
E



F



G

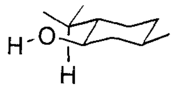
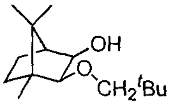


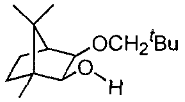
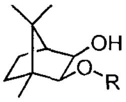
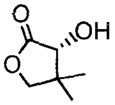
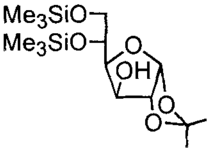
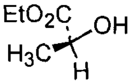
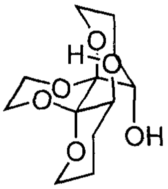
H

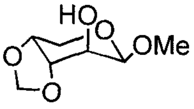
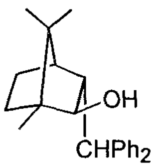
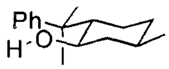
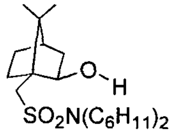
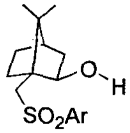
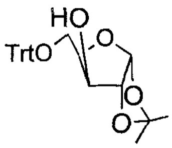
In the past Lewis acid-catalyzed [4+2] cycloaddition reactions of chiral alkyl acrylates have been systematically studied. Chiral auxiliaries derived from camphor, menthol and amino acids or from carbohydrates have been developed. Stereochemical and theoretical aspects of these chiral inductors have been intensively reviewed (see, Chapter 6). Asymmetric Diels-Alder reactions of chiral acrylamides derived from C_2-symmetrical secondary amines lead selectively to the cycloadducts in the presence of Lewis acids such as $AlCl_3$. In reactions of chiral auxiliaries derived from (*S*)-proline and (*S*)-prolinol excellent *endo*/*exo* selectivities and diastereoselectivities were obtained in the presence of catalytic amounts of Et_2AlCl or $TiCl_4$. Cycloadducts of chiral crotonoyl derivatives derived from oxazolidinones **62**, sultam **63** or for example (*S*)-lactate **15** were obtained with high selectivities in the presence of Lewis acids such as Et_2AlCl.

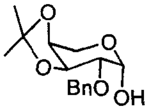
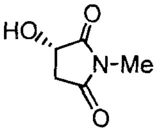
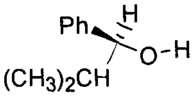
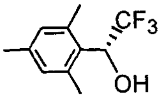
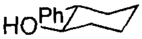
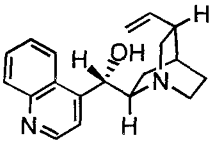
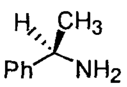
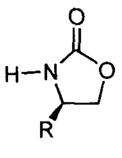
The [4+2] cycloaddition of chiral α,β-unsaturated ketones, derived from optically pure 2-hydroxy-3,3-dimethylbutyric acid, proceed with high selectivities and in excellent yield at low temperature in the presence of a Lewis acid, e.g. $ZnCl_2$ or $BF_3{\cdot}OEt_2$.[95,96] Cycloaddition reactions of chiral at iron acryloyl complexes with cyclopentadiene in the presence of $ZnCl_2$ have been studied by Davies et al.[97]

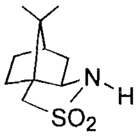
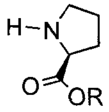
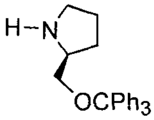
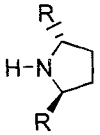
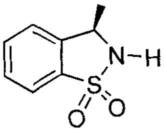
Cleavage of the chiral auxiliaries **5**, **6**, **9**, **10**, **63** and **64** was accomplished by treatment with $LiAlH_4$. Removal of the chiral inductors **19**, **36**, **62** and **63** can be achieved by applying LiOH or $LiOH/H_2O_2$.

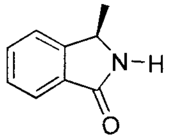
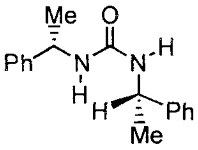
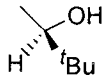
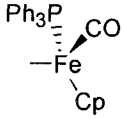
auxiliary	no.	type	diene	*endo:exo*	d.r. or *de*	yield	ref.
alcohol derivatives							
	**10**	A,B	1,2	92:8-100:0	77:23 – > 97:3	56-99%	10,53, 26,17 9,58,59
		C	1-4		97:3- >99:1	39-92%	57,56, 60
		I			> 90:10	>93%	56
		D		3:1	95:5	40-90%	56
		F			98:2	>43%	62
		H		50:50- 100:0	92:8-100:0	79-98%	63
		A	1,2	>90:10	72:28- >99:1	39-93%	64
	7	A	1,2	>20:1	>96%	>95%	65,66
		B				<10%	
		G	1	98:2	>98%	98%	

auxiliary	no.	type	diene	*endo : exo*	d.r. or *de*	yield	ref.
	**6**	A	1,2	96:4	> 98:2	95%	66
 R = Bn R = CONHPh		C	1,4		96:4- >99:1	>96%	17
	**19**	A	1,2,3	97:3-99:1	93:7 - >97:3	61-81%	67-70
		B		> 85:15	99:1	47%	68,70
		A	1,4	> 100:0	70:30 - 93:7	30-73%	71
	**15**	A		76:24-97:3	58:42-97:3	>88%	14,15
		B		89:11	>96:4	>45%	70
		C			78:22 - 95:5	88-99%	70
		A	1	1.5:1-23:1		12-99%	72

auxiliary	no.	type	diene	*endo : exo*	d.r. or *de*	yield	ref.
		A	1,2	>99:1	92:8-99:1	87-92%	73
	**5**	A			81%	>80%	65
	**11**	A,C, D	1,4	84:16-91:9	77:23-95:5	73-83%	58,65, 74,75
	**9**	A,C	1,4	>94%	89:11->94:6	52-99%	65,76
		A	1	95:5	66%	97%	77
	**21**	A,C		>100:1	>98:2	73%	71,78

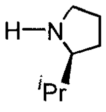
auxiliary	no.	type	diene	*endo : exo*	d.r. or *de*	yield	ref.
		A	2,3		55:45-85:15	37-68%	79
	**18**	A,C		13:1-82:1	97:3 - 99:1	62-89%	68,90
	**17**	D			84%	94%	13,25
		A		> 90:1	> 97:3	96%	81
	**12**	C	1	> 100:0	> 98:2	98%	9
	**1**	A	1,2	84:16- >97:3	69:31-96:4	35-70%	82
		C			97:3-99:1	44-96%	
amide derivatives							
	**31**	A,B		97:3	78:22		83
	**62**	A	1,2	48:1 - >100:1	93:7 - 98:2	81-88%	84,85
		B		> 98:2	79:21- >99:1	> 83%	

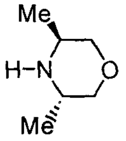
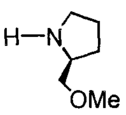
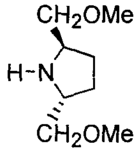
auxiliary	no.	type	diene	*endo : exo*	d.r. or *de*	yield	ref.
	**63**	A	1,2	97:3- 100:1	83:17- >99:1	57-98%	86
		A	5	>99:1	>20:1	83%	65,87, 88
		B		79:21	76:24-99:1	57-98%	
		C			> 98:2	80-95%	89
 R = Bzl		A,C	1,2	>98:2	90:10 - 96:4	41–96%	90
		A	1,2	93:7- >99:1	93:7-99:1	52-95%	91
 R = CO_2Me R = CH_2OMe R = CH_2OMOM	**42**	A		69:31–95:5	97:3-99:1	71-85%	19
	43	A		99:1	86:14-69:31	73-76%	
	**64**	A,C	1,2	93:7 - >99:1	51-93%	30-99%	92-94
		B		97:3	59-74%	74-86%	

auxiliary	no.	type	diene	*endo : exo*	d.r. or *de*	yield	ref.
	**34**	A		>98:2	66-72%	57-62%	92,93
		A,B		97:3	78:22	60-92%	9
Miscellaneous Compounds							
		A	1,2, 5,6	83:17 - 94:6	>98:2	84-95%	95,96
		A		> 86%	84:16- >93:7	88%	97

TfOTMS, $Et_3O^+BF_4^-$-catalyzed Reactions of Acrylates

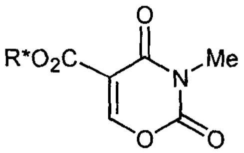
When using iminium salts derived from chiral acrylamides and trialkylsilyl triflate at low temperature, moderate to high stereoselectivities were observed.

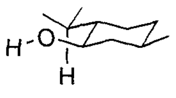
auxiliary	no.	*endo : exo*	d.r. or *de*	yield	ref.
	**39**	91:9	92:8	84-95%	77

auxiliary	no.	*endo : exo*	d.r. or *de*	yield	ref.
	**45**	>93:7	88:12-98:2	>95%	77
	**40**	84:16	>88:12	98%	19,76
	**42**	83:17-99:1	70:30-88:12	75-96%	19,76

Chiral Cyclic α,β-Unsaturated Compounds

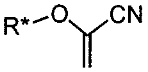
Moderate to high selectivities were obtained in Lewis acid-catalyzed cycloaddition reactions of the cyclic α,β-unsaturated compound **A**. However, high selectivities have been reported in catalyzed reactions of Meyers' bicyclic lactam with acyclic dienes.[22]

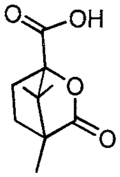


auxiliary	no.	*endo : exo*	d.r. or *de*	*ee*	yield	ref.
	**10**		97.5 : 2.5		53%	98

Chiral Vinyl Esters

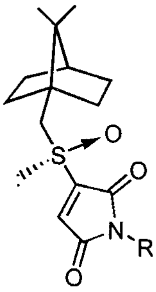
In reactions of chiral 1-cyanovinyl esters with dienes, e.g. furan, moderate stereoselectivities were obtained in the presence of ZnI_2 in dichloromethane at room temperature.



auxiliary	no.	*endo : exo*	d.r. *or de*	yield	ref.
	**52**	2:1		92%	99,100

Chiral Vinyl Sulfines

The cycloaddition reactions of the chiral sulfinyl maleimide with cyclopentadiene, 1,3-cyclohexadiene or anthracene proceed *endo* selective in the presence of $ZnCl_2$ with high diastereoselectivities.

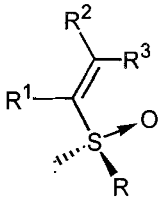


R = H, Bn

endo : exo	d.r. or *de*	yield	ref.
>100:0	97:3->99:1	72-100%	[101]

Chiral Vinylsulfoxides

Optically pure vinylsulfoxides have been employed in asymmetric Lewis acid-catalyzed Diels-Alder reactions with 1,3-butadiene and cyclopentadiene in the presence of $TiCl_4$, $AlCl_3$ or $EtAlCl_2$. Moderate to high *endo/exo* selectivities and stereoselectivities were reported.



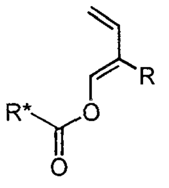
R^1 = H, COOH, COOBn
R^2 = H, COOH, COOMe
R^3 = H, COOH, COO^{t}Bu
R = Ph, *p*-Tol

endo : exo	d.r. or *de*	*ee*	yield	ref.
<97:3	86:14->98:2		66-96%	[102-106]

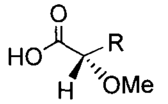
3.2.2 Reactions of Achiral Dienophiles with Chiral Dienes

Reactions of Chiral Carboxylic Acid Derivatives

Lewis acid-catalyzed reactions of chiral 1-acyloxy-1,3-butadienes with acrolein, methacrolein or quinones proceed *endo* selective at low temperature in the presence of $BF_3 \cdot OEt_2$ or $B(OAc)_3$ with moderate to high diastereoselectivities.

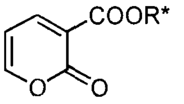


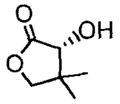
R=H, Me

auxiliary	no.	*endo* : *exo*	d.r. or *de*	*ee*	yield	ref.
 R= Ph, *cyclo*-C_6H_{11}	**50**	>99:1	80:20 – 99.2:0.8		46-94%	32,107-111

Reactions of Chiral Pyrones

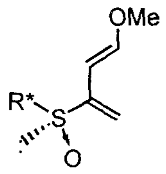
In [4+2] cycloaddition reactions of chiral 2-pyrones derived from chiral auxiliary **19** high *endo*/*exo* selectivities and diastereoselectivities were obtained with vinylethers in the presence of a catalytic amount of $Pr(hfc)_3$ or $Eu(hfc)_3$.



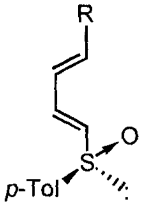
auxiliary	no.	*endo : exo*	d.r. or *de*	*ee*	yield	ref.
	**19**	100:0	>97:38		>94%	112,113

Reactions of Chiral 1,3-Butadienyl Sulfoxides

Excellent selectivities were observed in reactions of the chiral 1,3-butadienyl sulfoxides **A** with methyl acrylate in the presence of $LiClO_4$ or $ZnCl_2$ in dichloromethane at room temperature. Diene **B** has been employed in cycloaddition reactions with *N*-methyl maleimide in the presence of Lewis acids, e.g. $ZnBr_2$ or $SnCl_4$, in dichloromethane. The cycloadducts were obtained with high selectivity.

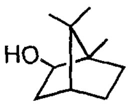
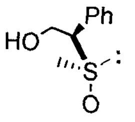


A



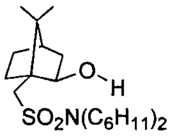
R=H, Me

B

sulfoxide	auxiliary	*endo : exo*	d.r. or *de*	*ee*	yield	ref.
A		100:0	96:4		70%	114
A		>99:1	74-92%		39%	114, 117
B	-		>99:1		66-96%	115

Miscellaneous Applications

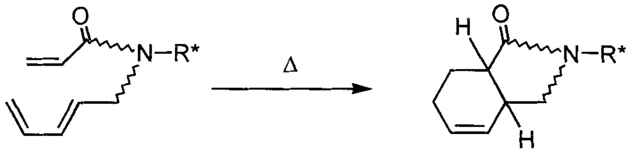
By asymmetric Diels-Alder reaction of optically pure 1,3-butadiene-2-carboxylates mikanecic acid was prepared. Moderate to high stereoselectivities were observed.

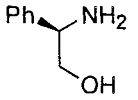
auxiliary	no.	*endo* : *exo*	d.r. or *de*	*ee*	yield	ref.
	**9**	>99:1	25-74%		51%	116

3.3 Intramolecular [4+2] Cycloadditions

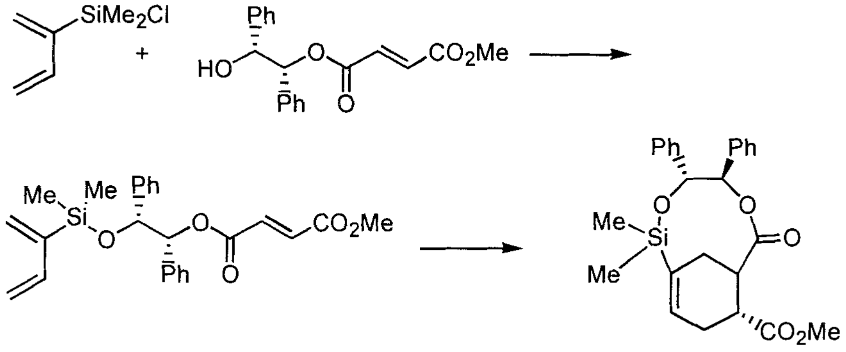
3.3.1 Thermal Reactions

Intramolecular cycloaddition reactions of chiral tertiary amides derived from auxiliary 27 have been studied by Mukaiyama et al.[118] In thermal reactions moderate results were observed. However, useful results were obtained by treatment with *n*BuMgBr via the magnesium alkoxide formed as an intermediate.



auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	27	88:12		77%	[118]

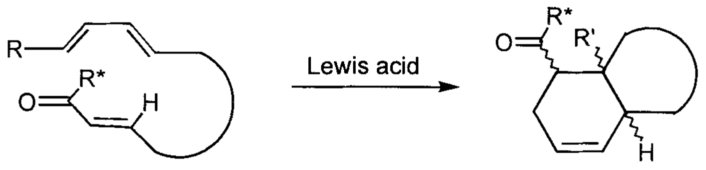
Asymmetric intramolecular Diels-Alder reactions have been accomplished selectively using a chiral diol (**54**) as disposable tether as shown in the scheme given below.[119]

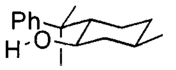
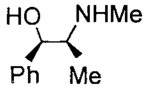


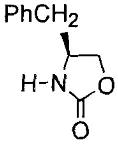
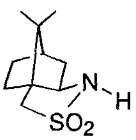
Mixtures of regioisomers were obtained (2-5:1). However, high diastereoselectivities were observed (d.r. 7:1 - 20:1). Enantiomerically pure cyclohexanes and decalins were isolated by separation of the diastereomers and removal of the tether.

3.3.2 Lewis Acid-Catalyzed Reactions

Lewis acid-catalyzed intramolecular Diels-Alder reactions of trienes, bearing an inducing moiety, e.g. oxazolidinones **62** or sultam **63**, have been widely examined and employed in natural product synthesis. The cycloadducts were obtained in high yield with excellent stereoselectivities. Among the Lewis acids studied in asymmetric intramolecular Diels-Alder reactions with auxiliary **11**, a chiral catalyst [(Bornyl)AlCl$_2$] proved to be highly efficient (72% *de*, 25-75%).



auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
ester derivatives					
	**11**	67:33-86:14		61-82%	120, 74
	**26**	> 93%		78%	121

auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
amide derivatives					
	**62**	66-94%		66-88%	85
	**63**	94:6-97:3		53-75%	86b

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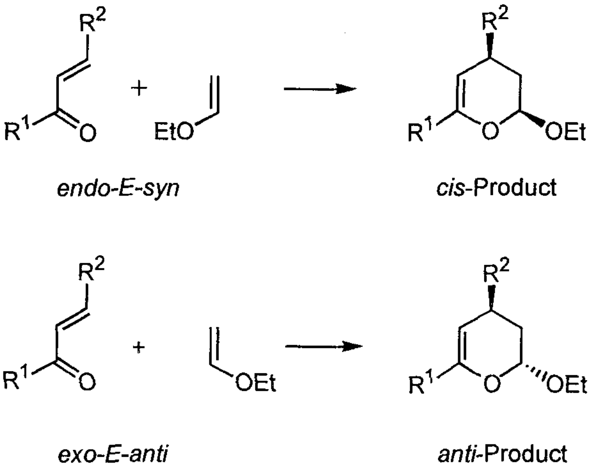
Chiral Auxiliaries in Cycloadditions
Karola Rück-Braun, Horst Kunz

4 Hetero [4+2] Cycloadditions

Hetero Diels-Alder cycloaddition reactions are of great importance in organic chemistry for the synthesis of six-membered heterocyclic ring systems.[1-3] In the past heterodienophiles and -dienes with one or more oxygen, nitrogen or sulfur atoms have been examined in thermal and Lewis acid-catalyzed reactions.[1-15]
Regarding selectivity, steric and electronic factors controlling regioselectivity, *endo/exo* approach as well as *Re/Si* side discrimination have to be discussed.[1-3,7,15] The formation of either *cis*- or *trans*-adduct in the [4+2] cycloaddition of an (*E*)-configurated 1-oxa-1,3-butadiene with a vinylether is outlined below. For example, by adapting an *endo-E-syn* orientation the *cis*-product is obtained.



Stereochemical and theoretical aspects of hetero Diels-Alder reactions have been intensively studied and recently reviewed. A clear definition for the *endo*- and *exo*-orientation regarding intermolecular all-carbon and hetero Diels-Alder reactions was recently suggested by Tietze in a review covering the literature of the last decade.[15] The reaction mechanisms of several hetero Diels-Alder reactions have been investigated and calculated and concerted processes as well as stepwise reaction pathways have been proposed depending on the compounds employed and the reaction conditions.

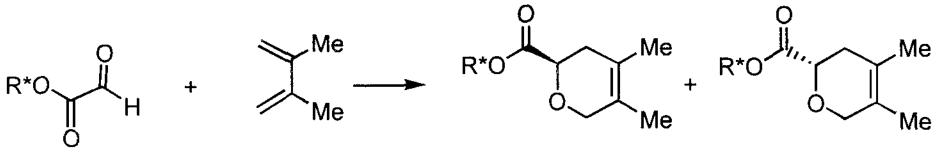
4.1 Reactions of Hetero-Dienophiles with Dienes

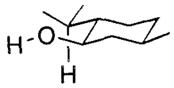
The cycloadditions of carbonyl compounds with dienes lead to 5,6-dihydro-2*H*-pyrans. Electron-deficient aldehydes have to be employed in combination with butadienes bearing electron-donating groups. However, using non-activated dienes rate acceleration can be achieved by applying high temperatures, high pressure or Lewis acids.

4.1.1 Reactions of Activated Carbonyl Dienophiles/Aldehydes

4.1.1.1 Reactions of Chiral Carbonyl Dienophiles with Achiral Dienes

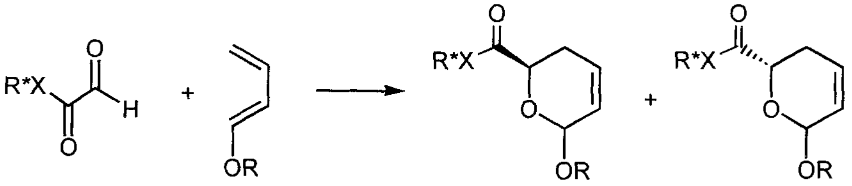
Reactions of chiral glyoxylates with non-activated dienes such as 2,3-dimethyl-1,3-butadiene or cyclohexadiene have been carried out at high pressure to increase yield and stereoselectivity.



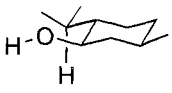
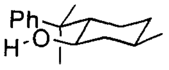
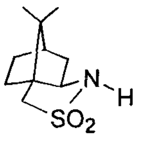
auxiliary	no.	*endo* : *exo*	d.r. or *de*	yield	ref.
ester derivatives					
	**10**	> 95 : 5	58 : 42 – 66 : 35	32 – 37%	16

Lewis Acid-catalyzed Reactions

Among the Lewis acids studied in asymmetric hetero Diels-Alder reactions of carbonyl compounds rare earth cations proved to be mild and efficient catalysts. This is demonstrated by the results observed in reactions of camphor sultam (**63**) derivatives with achiral 1-methoxy-1,3-butadiene.



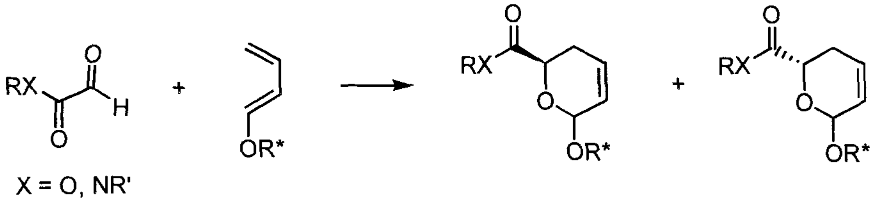
R = CH_3, TMS

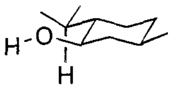
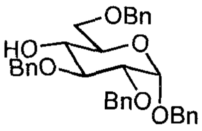
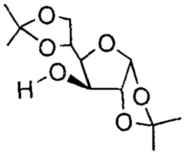
auxiliary	no.	conditions	*syn : anti*	d.r. or *de*	yield	ref.
ester derivatives						
	**10**	thermal	2:1	3-6%	55-90%	17,18
		$MgBr_2$		54.5 : 45.5	14%	19
	**11**	$MgBr_2$		91 : 9	5%	18
amide derivatives						
	**63**	$Eu(fod)_3$	95:5	94:6	81%	17

In reactions of phenylmenthyl glyoxylate with 2-trimethylsilyl-oxy-1,3-pentadiene in the presence of a catalytic amount of anhydrous $MgBr_2$ high diastereoselectivities were obtained (>98:2).[20]

4.1.1.2 Reactions of Achiral Carbonyl Dienophiles with Chiral Heteroatom-substituted Dienes

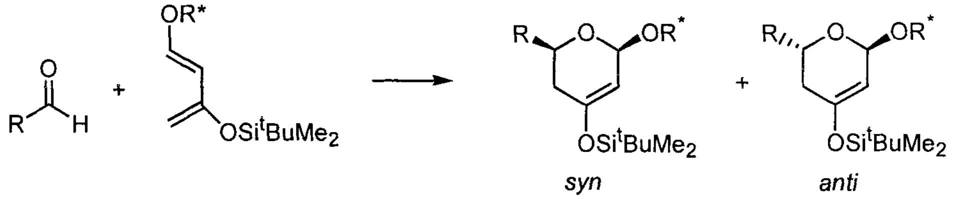
Thermal cycloaddition reactions of chiral 1-alkoxy-1,3-dienes derived from carbohydrates with glyoxylates have been widely studied delivering useful results.

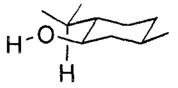
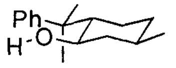
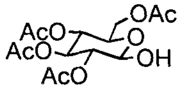


auxiliary	no.	*exo:endo*	d.r. or *de*	*ee*	yield	ref.
	**10**	52 : 48 - 78 : 22	5.6 : 1 -25 : 1		75 - 100%	21
		56%	96 : 4		52%	22
	**20**	78%	73 : 27		60%	22

Reactions of Non-activated Aldehydes with Chiral Heteroatom-substituted Dienes

The application of Lewis acids, such as the europium salt Eu(fod)$_3$, in [4+2] cycloadditions of carbonyl compounds (e.g. glyoxylates and aldehydes) with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) has been intensively examined by Danishefsky et al. and employed in natural product synthesis.[23]
Recently excellent diastereoselectivities were observed in reactions of the latter with chiral sulfinyl-substituted furfurylaldehydes in the presence of Sm(OTf)$_3$.[24]



auxiliary	no.	conditions	*exo:endo*	d.r. or *de*	*ee*	yield	ref.
	**10**	Eu(hfc)$_3$		5.6:1 - 25:1		75%	25
	**11**	Eu(hfc)$_3$		75:25 - 93:7		61-84%	25
		Eu(fod)$_3$ Eu(hfc)$_3$	90:10	*endo*: 79% 62:28:10 80:10:10		34-80%	26

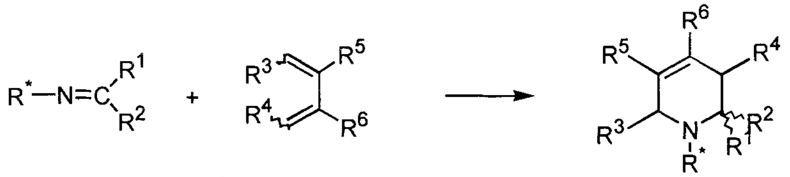
The cycloadditions of aldehydes with chiral siloxydienes, bearing the chiral substituent at the 1-position, proceed with moderate selectivities in the presence of Eu(fod)$_3$ or Eu(hfc)$_3$ at low temperature. Asymmetric thermal hetero Diels-Alder reaction of triketones with 2-methyl-1-(1-phenylalkoxy)-1,3-butadienes bearing the chiral alcohols **16** or **17** (Chapter 6) as auxiliaries lead highly selective to the cycloadducts.[27]

4.1.2 Reactions of Imines

Reactions of imino dienophiles with appropriate dienes lead to tetrahydropyridines. In general, activation of the C=N group is achieved by electron-withdrawing substituents and application of acids, such as trifluoroacetic acid or Lewis acids as catalysts, to take advantage of the higher reactivity of the protonated or complexed imine functionality.

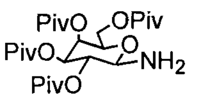
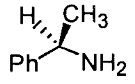
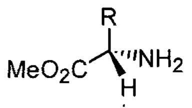
4.1.2.1 Reactions of Chiral Imines with Dienes

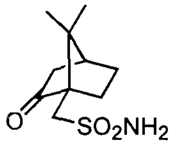
Moderate selectivities were observed in non-catalyzed and Lewis acid-promoted aza Diels-Alder reactions of non-activated imines with cyclopentadiene and 1,3-butadienes.



R^2 = H, Alkyl, Aryl
R^1 = H, Alkyl, Aryl

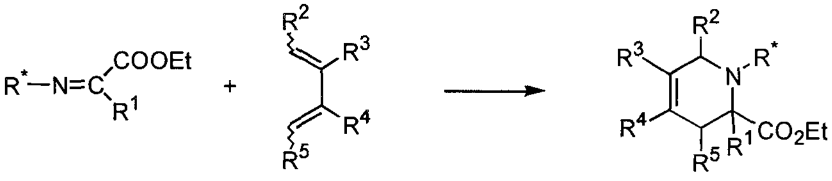
R^3, R^4 = H;
R^3 = R^4 = $(CH_2)_n$ n = 1,2;
R^5, R^6 = H, CH_3

auxiliary	no.	conditions	d.r. or *de*	yield	ref.
	**33**	$ZnCl_2$	70:30 - 90:10	90-95%	28
	**31**	H_2O/THF	50:12 - 90:10	62%	29,30
 R = Ph, ^iBu		H_2O/THF	63:37 - 93:7	22-90%	31,32

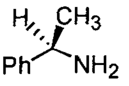
auxiliary	no.	conditions	d.r. or *de*	yield	ref.
	**65**	$ZnCl_2$, Et_2AlCl	50:50 – 70:30	45-58%	33

Reactions of C-Acylimines with a Chiral Nitrogen-Substituent

Reactions of C-acylimines derived from phenylethylamine and glyoxylate proceed highly stereoselective in the presence of trifluoroacetic acid.

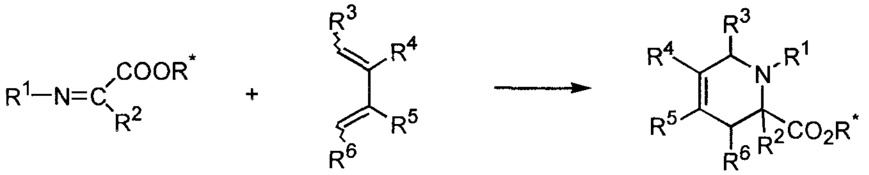


R^3, R^4 = H, Alkyl;
R^2, R^5 = H, Alkyl or
$R^2 = R^5 = (CH_2)_n$ n = 1,2

auxiliary	no.	*exo:endo*	d.r. or *de*	yield	ref.
	**31**	97:3- 98:2	exo: 84 -89% endo: >99%	31 - 82%	34,35

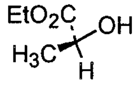
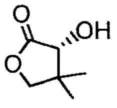
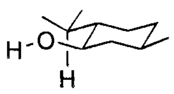
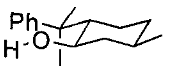
Reactions of C-Acylimines with a Chiral Carbon-Substituent

Stereoselective aza Diels-Alder reactions of *N*-acyliminium species derived from chiral glyoxylates have been intensively studied. The highest selectivities are obtained with 8-phenylmenthyl glyoxylate derivatives.

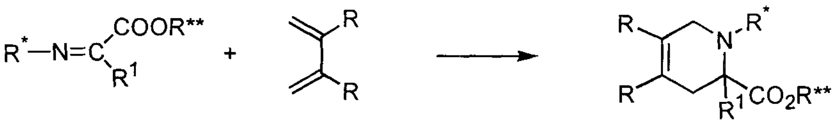


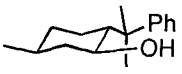
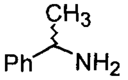
R^1 = Tos, Aryl

R^3, R^4 = H, Alkyl;
R^2, R^5 = H, Alkyl or
$R^2 = R^5 = (CH_2)_n$ n = 1,2

auxiliary	no.	conditions	d.r. or *de*	*ee*	yield	ref.
	15	Et_2AlCl	88 : 12		50-60%	36
	19	Et_2AlCl	85 : 15		50-60%	36
	10		56 : 44		84%	36,37
	11	$TiCl_4$	60 : 40 - > 95 : 5		60 -80%	38

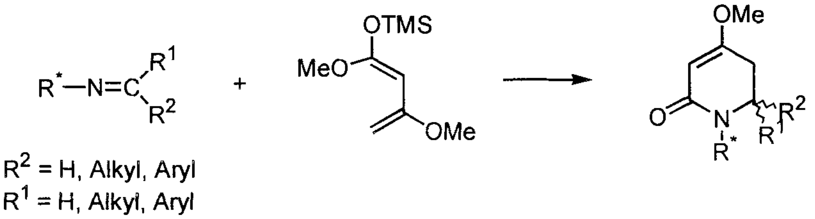
Highly stereoselective aza Diels-Alder cycloadditions have been observed in reactions of chiral *N*-acylimines bearing two chiral moieties with cyclopentadiene (matched pair) and 1,3-butadienes in the presence of trifluoroacetic acid.

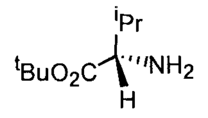


auxiliaries	no.	comments	d.r. or *de*	*ee*	yield	ref.
R^{**}: 	**11**	matched: $R^{*} = (R)$ $R^{**} = (R)$	>95%		40-69%	39
R^{*}: 	**31**	mismatched: $R^{*} = (S)$ $R^{**} = (R)$	38-61%			

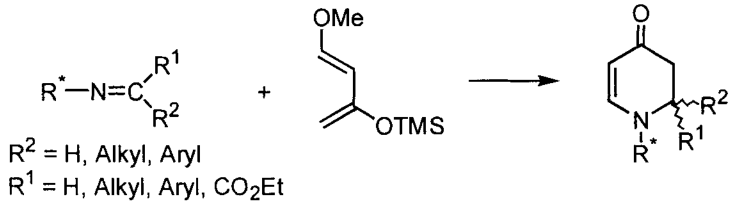
4.1.2.2 Reactions of Chiral Imines with Heteroatom-substituted Dienes

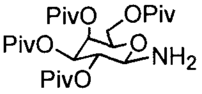
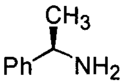
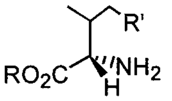
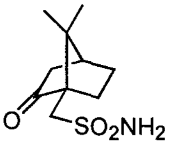
Reactions of imines derived from valine *tert*-butyl ester with Brassard's diene proceed highly stereoselective in the presence of Lewis acids, such as $EtAlCl_2$, at low temperature. Removal of the chiral auxiliary is achieved via a Curtius rearrangement.



auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
		92:8 - 97.5:2.5		57-84%	40

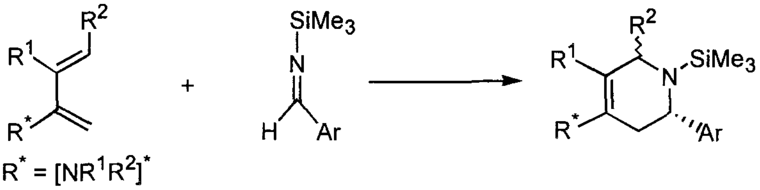
Lewis acid-catalyzed ($EtAlCl_2$, $ZnCl_2$) aza Diels-Alder reaction of imines derived from amino acid esters or carbohydrates with Danishefsky's diene provide precursors of chiral piperidine alkaloids. When using imines derived from O-pivaloylated glycosylamines and $ZnCl_2$ as Lewis acid, highly diastereoselective tandem-Mannich-Michael reactions are observed. The carbohydrate moiety is easily removed by treatment with HCl/MeOH. By employing galactopyranosylamine or arabinosylamine derivatives both enantiomeric series are readily available.

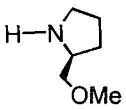


auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**33**	96:4 - 98:2		90-96%	41
	**31**	75:25 - 81:19		44-69%	42
 R' = H,Me		90:10 –97:3		45-80%	40a,43
	**65**	2:1		58–76%	44

4.1.2.3 Reactions of Achiral Imines with Chiral Heteroatom-substituted Dienes

Chiral 2-amino-1,3-butadienes derived from 2-(methoxymethyl)pyrrolidine and α-oxo enamines undergo cycloadditions with *N*-silylimines in the presence of $ZnCl_2$ to yield 4-piperidinones stereoselectively upon subsequent hydrolysis with aqueous $NaHCO_3$.

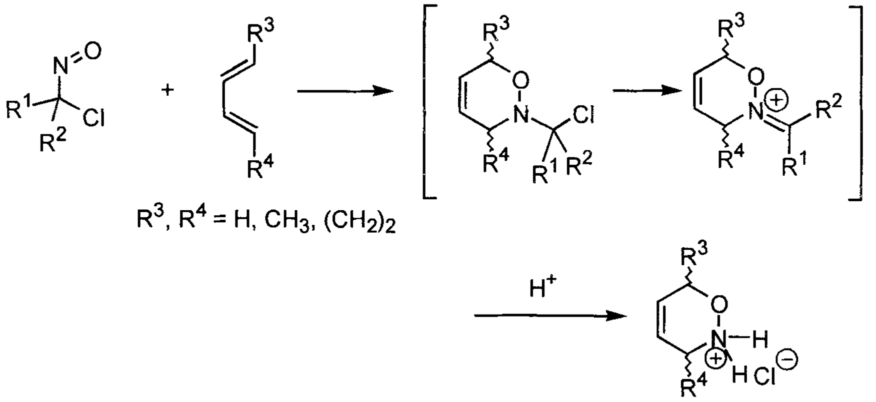


auxiliary	no.	conditions	*ee*	yield	ref.
	**40**	$ZnCl_2$	86-95%	63-76%	45

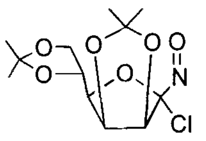
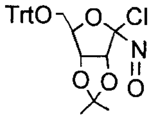
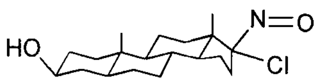
4.1.3 Reactions of Nitroso Compounds

4.1.3.1 Reactions of Chloronitroso Compounds

α-Chloronitroso compounds undergo hetero Diels-Alder cycloadditions with various dienes at low temperature. Carbohydrate-derived compounds have been intensively studied leading to dihydrooxazines enantioselectively.



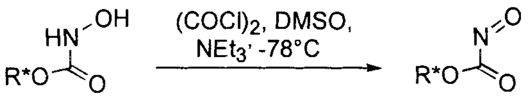
Reactions of Chiral α-Halonitroso Compounds

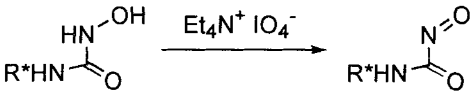
auxiliary	*ee*	yield	ref.
	>96%	70-89%	46
	>96%	68-96%	48
	>95%	79-89%	49

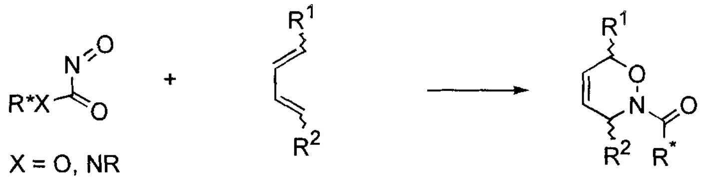
4.1.4 Reactions of *N*-Acylnitroso Compounds

4.1.4.1 Reactions of Chiral *N*-Acylnitroso Compounds with Dienes

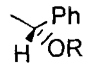
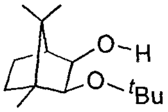
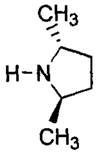
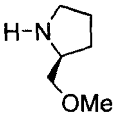
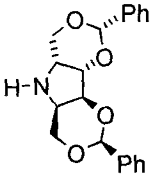
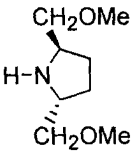
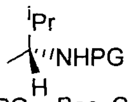
[4+2] Cycloadditions of chiral *N*-acylnitroso compounds have been widely studied.[50] These heterodienophiles are accessible e.g. by oxidation of hydroxamic acid derivatives with periodate.[51] C_2-symmetric pyrrolidines lead to high selectivities. 1,2-Oxazines are useful precursors of amino alcohols and aza sugars.

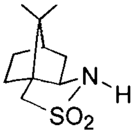






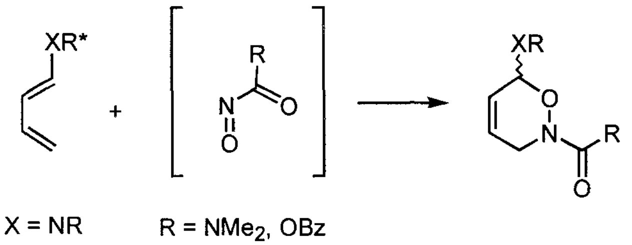
$R^1 = R^2 = H$; $R^1 = R^2 = (CH_2)_n$ n = 2, 3;
$R^1 = [NR^3R^4]^*$, $R^2 = H$;
$R^1 = SiMe_2{}^tBu$; $R^2 = H$.

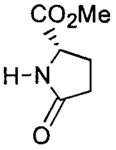
auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
 R= H, Me		3:1		41-80%	52,53
ester derivatives					
		91-96%		62-94%	54
amide derivatives					
	**41**	>98%		50-99%	52
	**40**	98:2		45%	52
	**44**	>99%		90%	52b
	**42**	87 - >99%		70-88%	55,56
 PG = Boc, Cbz		1 : 1.5 - 1 : 4			57

auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**63**	>98%		91-94%	56

4.1.4.2 Reactions of Achiral *N*-Acylnitroso Compounds with Achiral Dienes

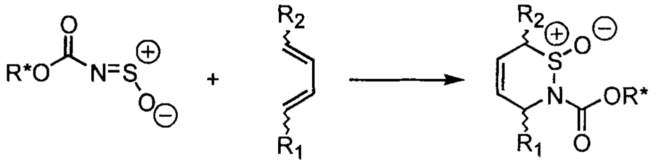
Encouraging results were obtained in asymmetric cycloadditions of chiral dienes, which react readily with achiral nitroso compounds as outlined below.



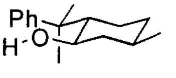
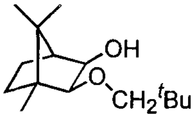
auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**36**	73 : 27 – 92 : 8		70-80%	58

4.1.5 Reactions of *N*-Sulfinyl Dienophiles

The cycloaddition of *N*-sulfinyl compounds with dienes gives dihydrothiazine oxides, which are precursors of homoallyl amines or pyrroles. Reactions of these reactive dienophiles in the presence of $SnCl_4$ or $TiCl_4$ yield the adducts diastereoselectively under mild reaction conditions.

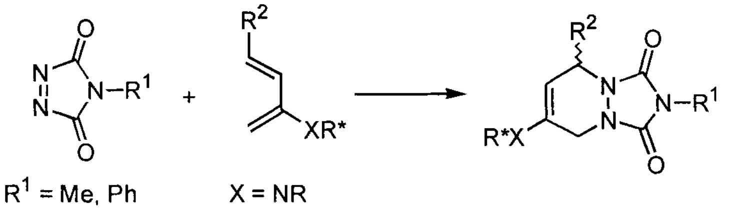


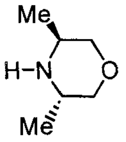
$R^1 = R^2 = Me$;
$R^1 = R^2 = (CH_2)_2$

auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	11	> 98 : 2		42-77%	59
	7	> 98 : 2		75%	60

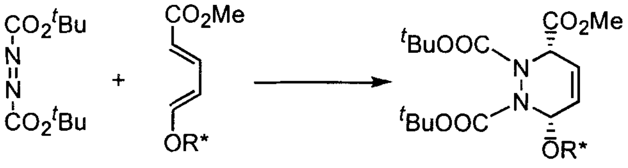
4.1.6 Reactions of N=N Dienophiles

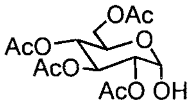
Azo compounds, such as *N*-phenyl- or *N*-methyltriazoline-dione, have been applied as dienophiles in thermal asymmetric hetero Diels-Alder reactions with heteroatom-substituted dienes, leading to cycloadducts with excellent diastereoselectivities.



auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**45**	87–97%		63-100%	61,62

Chiral 1-alkoxy-1,3-dienes derived from carbohydrates have been examined in cycloadditions with azo dienophiles by Stoodley et al. Thereby, reactions with acyclic azo dienophiles were found to be highly selective, leading to optically pure pyridazine derivatives.



auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	22	>99:1		77%	63

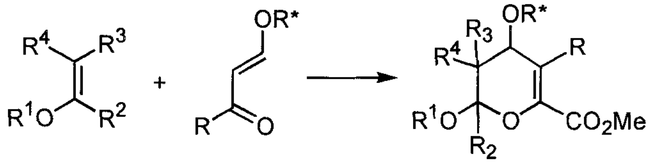
4.2 Reactions of Hetero-Dienes with Dienophiles

4.2.1 Reactions of Oxabutadienes

1-Oxa-1,3-butadienes have been applied in hetero Diels-Alder reactions with electron-rich alkenes as dienophiles, such as enolethers, ketene acetals or enamines, leading to 2-substituted 3,4-dihydro-2*H*-pyrans. These thermal cycloadditions with inverse electron-demand usually proceed at high temperature. The reactivity of 1-oxa-1,3-dienes can be enhanced by electron-withdrawing substituents. In the presence of Lewis acids a rate acceleration of the reaction is observed and higher regioselectivities are accessible.

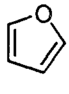
4.2.1.1 Reactions of Chiral Oxabutadienes with Achiral Vinylethers

1-Oxa-1,3-dienes with acyloxy functions at the C-4 position react with enolethers at room temperature, furnishing the cycloadducts with moderate selectivities. After removal of (*R*)-*O*-methyl mandelic acid by treatment with MeOH/K_2CO_3 the major isomer was transformed into (-)-*L*-olivose.

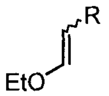


R = H, Me, CH_2OR'
R' = CO_2Me, SPh
R^1 = Et, Bn

Type of Enolether

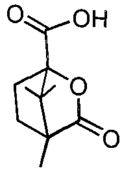
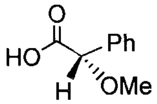


A

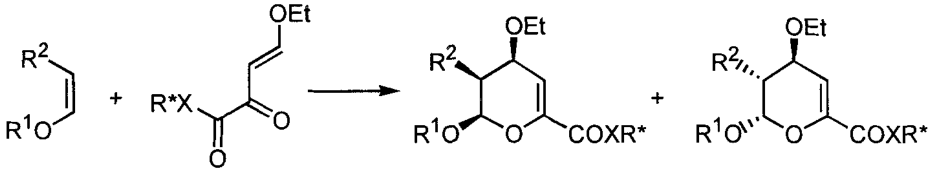


R = H, Me

B

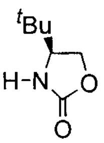
auxiliary	no.	type	*endo:exo*	d.r. or *de*	*ee*	yield	ref.
	**52**	**A**	1:2	52%		86%	64
	**50**	**B**	100:0	2:1		60%	65

Dihydropyrans are obtained with excellent selectivities starting from oxabutadienes with an acyloxy function at the C-2 position bearing a chiral oxazolidinone. A reversal of the *endo/exo* selectivity is achieved by appropriate choice of the Lewis acid.

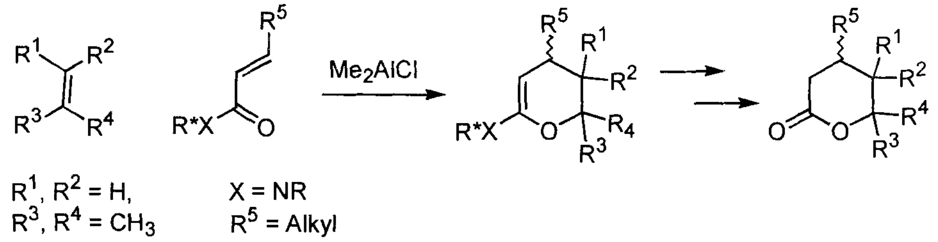


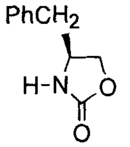
R^2 = Alkyl, OAc X = O, NR
R^1 = Et, Bn

Lewis acids: Me_2AlCl, TMSOTf, $SnCl_4$

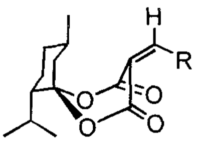
auxiliary	no.	*endo:exo*	d.r. or *de*	*ee*	yield	ref.
	**62**	24 : 1 - > 50 : 1	*endo*: 6 : 1 – 50 : 1		78-94%	66

The [4+2] cycloaddition of *N*-crotonyl oxazolidinones with alkenes at low temperature in the presence of Me_2AlCl as Lewis acid leads to δ-lactones stereoselectively.

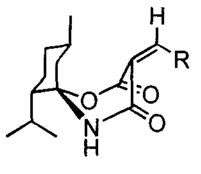


auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**62**	> 99 : 1			67

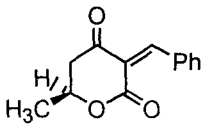
Cycloaddition reactions of the chiral exocyclic methylene compounds **A** and **B** derived from menthone and of related chiral 1-oxa-1,3-dienes (**C**) with alkenes as dienophiles, e.g. ketene acetals, proceed smoothly and are highly stereoselective.[68,69]



A



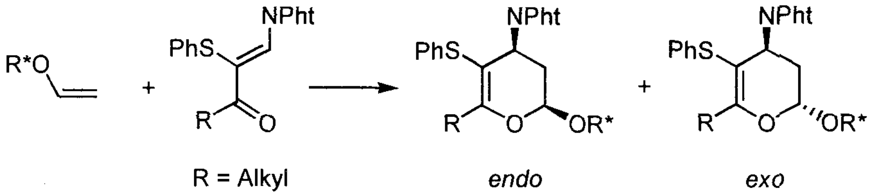
B

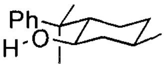


C

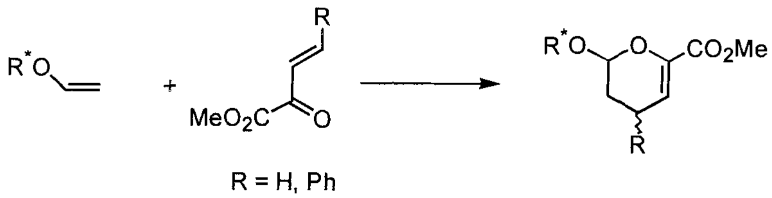
4.2.1.2 Reactions of Achiral Oxabutadienes with Chiral Vinylethers

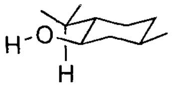
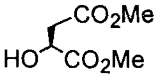
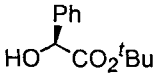
Reactions of chiral vinylethers with achiral heteroatom-substituted 1-oxa-1,3-dienes displaying moderate selectivities.



auxiliary	no.	endo:exo	d.r. or *de*	*ee*	yield	ref.
	11	3 : 1	1.5:1–3:1		74%	15

The hetero Diels-Alder reaction of chiral enolethers with achiral 1-oxa-1,3-dienes bearing an acyloxy function at the C-2 position in the presence of $Eu(fod)_3$, $Eu(hfc)_3$ or $Yb(fod)_3$ lead to dihydropyrones with high *endo*-selectivity but moderate diastereoselectivity.

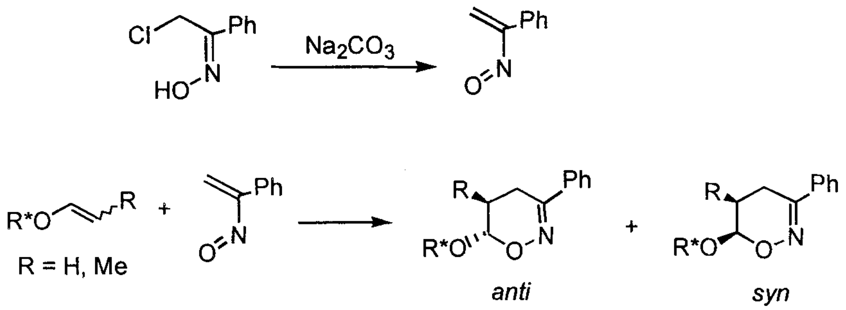


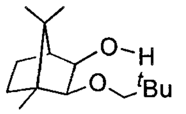
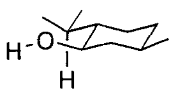
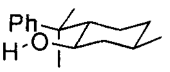
auxiliary	no.	*endo:exo*	d.r. or *de*	*ee*	yield	ref.
	**10**	>93:3	3 :1		>91%	70
		97:3	80 : 20		83%	70
		>97:3	78 : 22 - 92 : 8		>90%	70

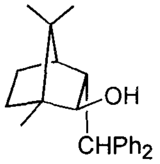
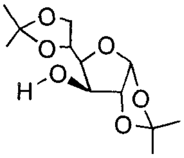
4.2.2 Reactions of Achiral Nitroso Compounds

Hetero Diels-Alder reactions of nitrosoalkenes, e.g. α-nitrosostyrene, with electron-rich alkenes lead to 5,6-dihydro-4H-1,2-oxazines. The cycloadducts are obtained with excellent selectivities. These reactions proceed smoothly under mild reaction conditions at room temperature in the absence of Lewis acids. Oxazines are useful precursors for the synthesis of pyrroles and γ-lactams.

Reactions of Achiral Nitroso Compounds as Dienes with Chiral Vinylethers as Dienophiles



auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	7		>98%	94%	71
	10	6%		75%	71
	11	34-48%		79%	71

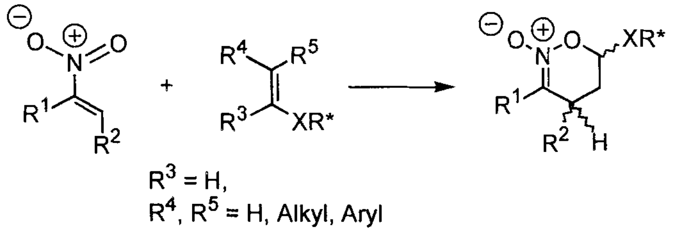
auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**5**	88:12 - 94:6		38-65%	71
	**20**	79:21 - >95:5		52-72%	71
	**12**		>97%	76%	71

4.2.3 Reactions of Nitroalkenes

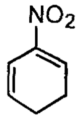
Reactions of Achiral Nitroalkenes as Dienes

Reactions of nitroalkenes with electron-rich alkenes lead to cyclic nitrones stereoselectively. Besides thermal reactions Lewis acid-catalyzed additions employing $SnCl_4$, $TiCl_2(^iPr)_2$ or bulky aluminum Lewis acids[73] have been described.

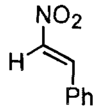
The cycloadducts have been transformed into pyrrolidines by reductive ring contraction. However, cycloadducts bearing a suitable alkene functionality in the side chain usually undergo [3+2] cycloaddition upon warming to room temperature. Inter- and intramolecular combinations of hetero Diels-Alder reactions with 1,3-dipolar cycloadditions of the resulting nitrone have been intensively studied, developed and have been recently reviewed by Denmark et al.[72]



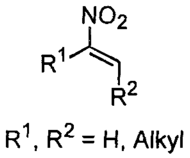
Type of Nitroalkene



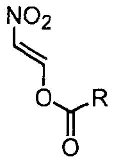
A



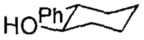
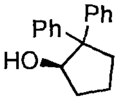
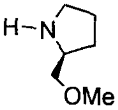
B



C



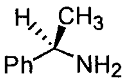
D

auxiliary	no.	conditions	nitroalkene	d.r. or *de*	yield	ref.
alcohol derivatives						
	**12**	Lewis acid[73]	B, C	87 : 10 : 3	96%	73
	**14**	Lewis acid[74]		25 : 1	96%	74
amine derivatives						
	**40**		A	99%	72%	75

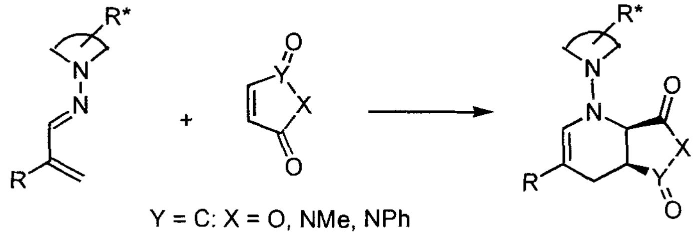
4.2.4 Reactions of 1-Aza-1,3-dienes

Reactions of Achiral 1-Aza-1,3-dienes with Chiral Dienophiles

High to complete stereoselectivities were observed in the reactions of 1-aza-1,3-dienes with appropriate alkenes. Concerted as well as two-step mechanisms have been suggested.

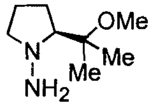
auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**31**	> 99 : 1		85%	76

Reactions of Chiral 1-Aza-1,3-dienes with Achiral Dienophiles



Y = C: X = O, NMe, NPh
Y = S=O: X = N^tBu

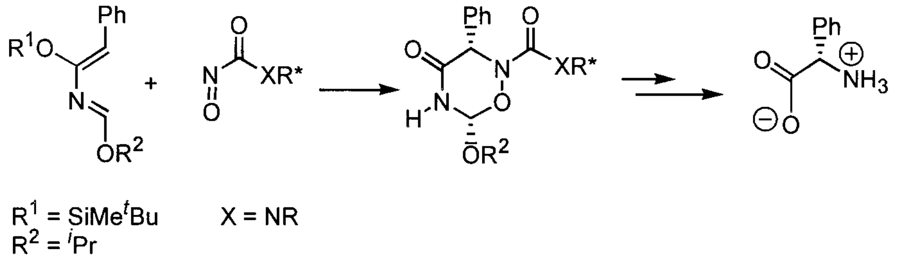
Thermal reactions of α,β-unsaturated SAMP hydrazones with reactive, electron-deficient alkenes, e.g. *N*-methylmaleimide, proceed highly stereoselective.

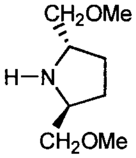
auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**66**	90 : 10 - > 99 : 1		51-81%	[77]

4.2.5 Reactions of 2-Aza-1,3-dienes

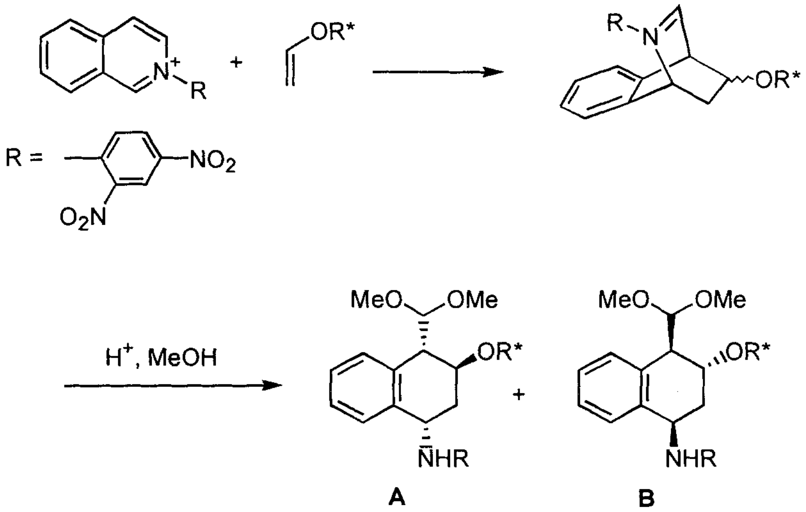
Asymmetric Lewis acid-catalyzed hetero Diels-Alder reactions of 2-aza-1,3-dienes have been studied for isolated cases. Highly selective thermal cycloadditions have been observed in the reactions of chiral, halogenated 2-aza-1,3-dienes with acyclic diazo compounds conducted at 80°C.[78]

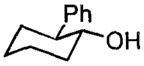
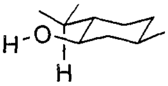
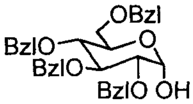
Reactions of 2-aza-1,3-butadienes with electron-donating substituents and chiral nitroso compounds take place selectively in the absence of Lewis acids at low temperature. The cycloadducts are useful precursors of α-amino acids.



auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**42**	94%		62%	79

Isoquinolinium salts represent 2-aza-1,3-butadienes activated by *N*-arylation. Highly stereoselective cycloadditions with chiral enolethers have been reported leading to enantiomerically pure functionalized tetralines in high yields.

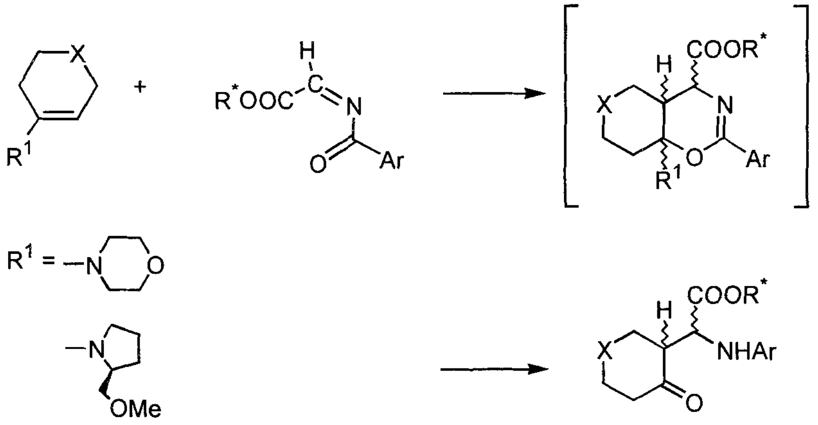


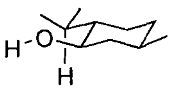
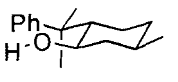
auxiliary	no.	d.r. (A : B)	*ee*	yield	ref.
	**12**	<95 : 5		91%	80
	**10**	36%		57%	80
	**24**	>95 : 5		70%	80

4.2.6 Reactions of Chiral *N*-Acyl-Imines

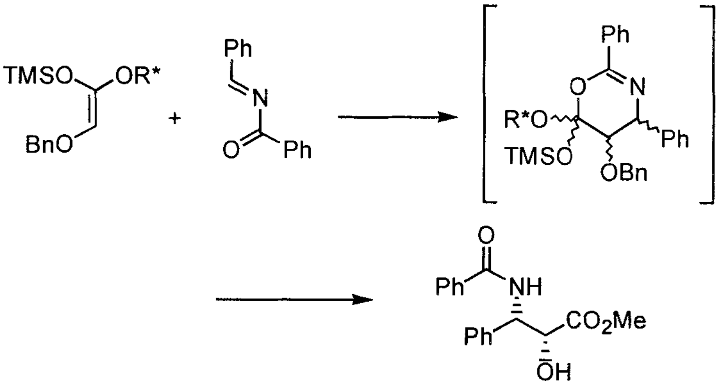
Reactions of Chiral N-Acyl-Imines as Dienes with Achiral Enamines or Alkenes

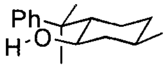
Reactions of *N*-acylimines with electron-rich alkenes furnish 5,6-dihydro-1,3-oxazines. Low to moderate diastereoselectivities were observed for the combination of chiral *N*-acylimines and achiral enamines. Highly selective reactions are observed in cycloadditions of chiral enamines with achiral dienes as well as with chiral dienes in the case of a matched pair.



auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**10**	62:38-99:1		quant.	81
	**11**	73:27->99:1		quant.	81

A highly stereoselective hetero Diels-Alder reaction of achiral N-acylimines with chiral enolethers derived from 8-phenylmenthol has been applied to the synthesis of the taxol side chain as outlined below.

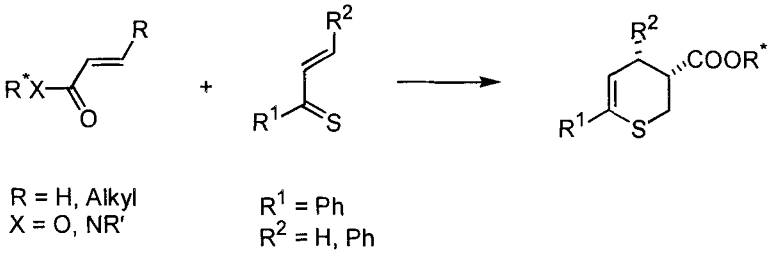


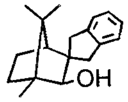
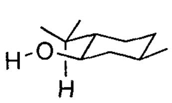
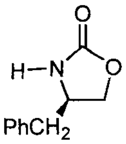
auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	11	86%		75%	82

4.2.7 Reactions of Thiabutadienes

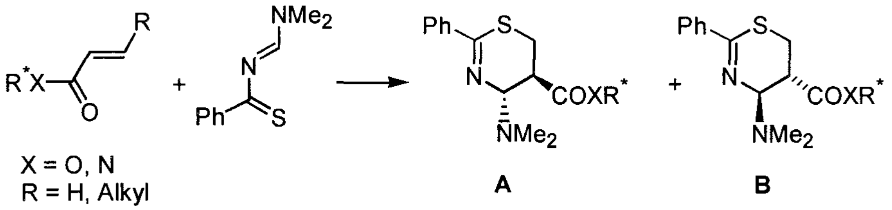
Reactions of Achiral Thiabutadienes with Chiral Dienophiles

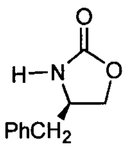
Thermal and Lewis acid-catalyzed reactions of 1-thia-1,3-dienes with chiral α,β-unsaturated carboxylic acid derivatives lead to thiopyrans. The cycloadditions of chiral α,β-unsaturated oxazolidinones in the presence of aluminum Lewis acids lead to encouraging stereoselectivities. Cleavage of the chiral auxiliaries was achieved by treatment with $LiAlH_4$.



auxiliary	no.	*endo*:*exo*	d.r. or *de*	*ee*	yield	ref.
alcohol derivatives						
	**8**	27:73 - 37:63	*exo*: 72-80% *endo*: 13.48%		75-99%	83
	**10**	89:11 - 95:5	*exo*: 8-31% *endo*: 24-48%		91-98%	83
amide derivatives						
	**62**	72:28 - 93:7	*exo*: 37-98% *endo*: 73-92%		>96%	83,84

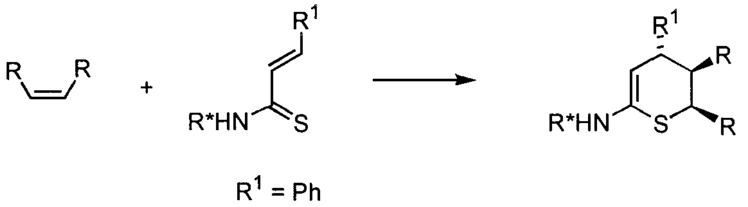
Hetero Diels-Alder reactions of 1-thia-3-aza-1,3-butadienes with chiral α,β-unsaturated oxazolidinones in the presence of $MgBr_2$ at 0°C yield 1,3-thiazines diastereoselectively in high yield.

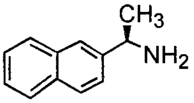


auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**62**	80:20- 100:0		72%	85

Reactions of Chiral Thiabutadienes with Achiral Dienophiles

Thermal [4+2] cycloadditions of chiral 1-thia-1,3-butadienes, bearing a chiral nitrogen substituent at the C-2 position, proceed with complete *exo*-selectivity and excellent *Re*/*Si*-side discrimination.

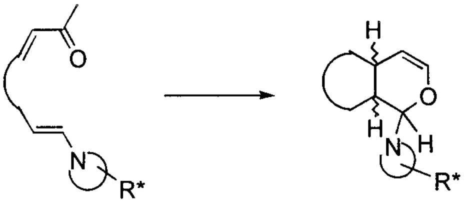


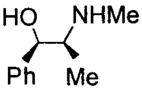
auxiliary	no.	*endo:exo*	d.r. or *de*	*ee*	yield	ref.
	**32**	0:100	72:28:1:1 - 98:<1:<1:<1		>90%	86

4.2.8 Intramolecular Hetero [4+2] Cycloadditions

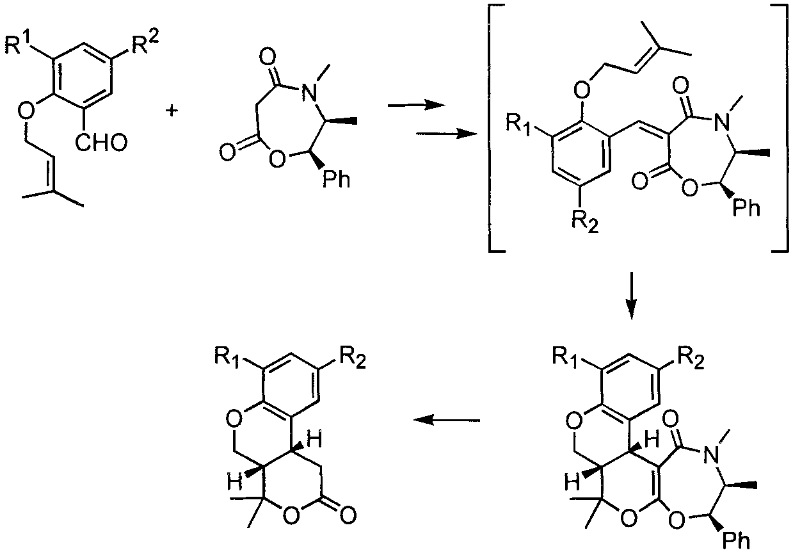
Asymmetric intramolecular hetero Diels-Alder reactions have been recently reviewed, thus only selected examples are shown below.[15]

Intramolecular thermal hetero Diels-Alder reactions of α,β-unsaturated aldehydes bearing a chiral enamine side chain have been reported to proceed highly stereoselective at room temperature. The cycloadduct was applied as useful precursor for the synthesis of natural products.

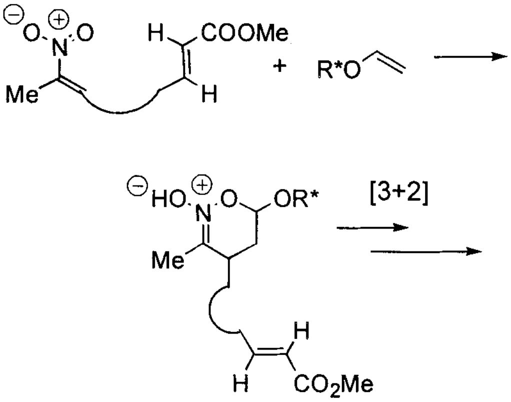


auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**26**	94%		75%	87

Excellent diastereoselectivities have been observed in intramolecular asymmetric cycloadditions of chiral benzylidene compounds derived from (-)-ephedrine, methyl malonate and benzaldehyde derivatives in the presence of Et_2AlCl in 1,2-dichloroethane at higher temperature.[88,89]



Highly stereoselective inter [4+2]/intra [3+2] cycloadditions of nitroalkenes as heterodienes have been developed by Denmark et al.[90] Applications in the synthesis of alkaloids have been reviewed.[72]



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[89] a) K. Hiroi, M. Umemura, Y. Tomikawa, Heterocycles 35 (1993) 73; b) K. Hiroi, M. Umemura, A. Fujisawa, Tetrahedron Lett. 33 (1992) 7161.

[90] a) S. E. Denmark, C. B. W. Senanyake, G.-D. Ho, Tetrahedron 46 (1990) 4857; b) S. E. Denmark, M. E. Schnute, C. B. W. Senanyake, J. Org. Chem. 58 (1993) 1859.

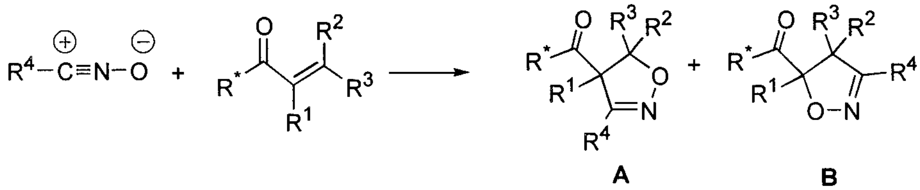
Chiral Auxiliaries in Cycloadditions
Karola Rück-Braun, Horst Kunz

5 [3+2] Cycloadditions

According to the Woodward-Hoffmann notation [3+2]-cycloaddition reactions are $\pi^4_s + \pi^2_s$ pericyclic reactions. They enable, usually under thermal reaction conditions, the selective construction of carbo- and heterocyclic ring systems. Secondary orbital interactions as well as other factors controlling diastereofacial discrimination, regiochemistry or *endo/exo* selectivity have been discussed in detail in the literature.[1-5] For many [3+2] cycloadditions it is not easy to predict, whether the 1,3-dipole functions as the donor or the acceptor component in these HOMO/LUMO-controlled conversions.[6-8]

5.1 Chiral Dipolarophiles

5.1.1 Reactions of Nitrile Oxides



The addition of nitrile oxides to α,β-unsaturated carboxylic acid derivatives opens up a route to chiral, substituted isoxazoline derivatives. The nitrile oxides are generated *in situ* via deprotonation with a base (e.g. triethylamine) starting from the chlorinated aldoxime as the precursor (solvents: $CHCl_3$, CH_2Cl_2, ether, benzene, toluene; temperature: -78°C up to 110°C). In most cases only one of two possible regioisomeric adducts is formed.

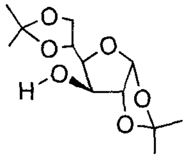
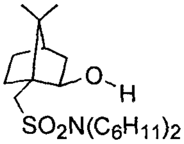
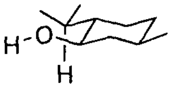
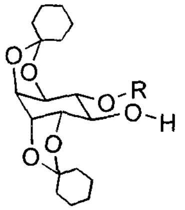
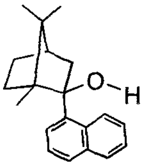
In general, lower regioselectivities were observed with chiral β-substituted α,β-unsaturated carbonyl compounds compared to reactions involving acrylic derivatives.

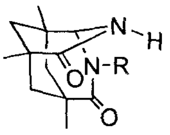
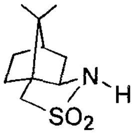
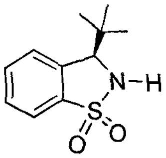
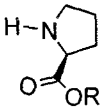
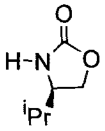
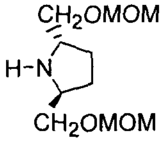
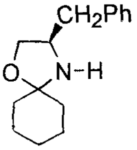
α,β-Unsaturated amides proved to be most effective.

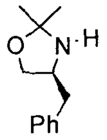
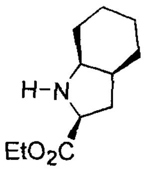
Experiences reported so far show that Lewis-acid catalysis can influence and even decrease the diastereoselectivity of these processes.[9,10] As a rule, dipolarophiles containing an electron-withdrawing substituent smoothly undergo cycloadditions with nitrile oxides, while electron-rich olefins, e.g. enolethers, do not. Furthermore, the diastereoselectivity varies in a broad range. However, an efficient stereoselection is only accomplished with rigid auxiliaries whose differentiating group is located in close vicinity to the reacting double bond. 2-Isoxazoline derivatives are readily converted into 3-hydroxycarbonyl compounds by reduction.

The chiral auxiliaries **9**, **13**, **63** and **65** are easily removed with L-Selectride.

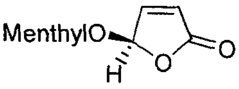
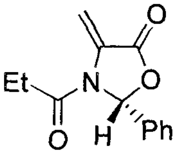
α,β-Unsaturated Carboxylic Acid Derivatives as Dipolarophiles

auxiliary	no.	product	*d.r.* or *de*	yield	ref.
ester derivatives					
	**20**	B	60 : 40 - 66.6 : 33.3	60-70%	11
	**9**	B	78 : 22	56%	9
	**10**	A	100 : 0	92-99%	9,12,13
 R = TBDMS TBDPS	**13**	B	84 : 16 - 95 : 5	54-95%	14
	**4**	A, B	A: 5-47% B: 68-80%	A + B: 91-100%	15,16

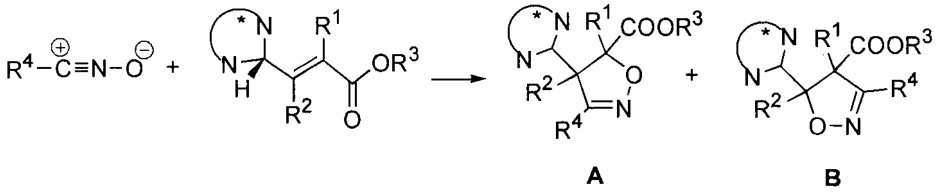
auxiliary	no.	product	*d.r.* or *de*	yield	ref.
amide derivatives					
 R=(*S*)-CH(CH$_3$)Ph		B	99 : 1	93-98%	9,17
	**63**	B	85 : 15 - 95 : 5	59-85%	18
	**64**	B	98 : 2	79%	18
 R = Bzl		B	53 : 47 - 78 : 22	82-98%	19
	**62**	B	73%	94%	10,20
	**43**	B	70%	78%	10,20
	**46**	B	> 99 : 1	> 90%	21

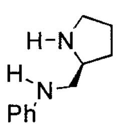
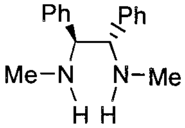
auxiliary	no.	product	d.r. or *de*	yield	ref.
	**47**	B	86%		10,21
	**35**	B	88 : 12 - 95 : 5	69-75%	22

Miscellaneous α,β-Unsaturated Carboxylic Acid Derivatives

compound	product	*d.r.* or *de*	yield	ref.
	A : B 100:0	> 99%	92%	12,23
	A: > 99%	> 99%	72%	24

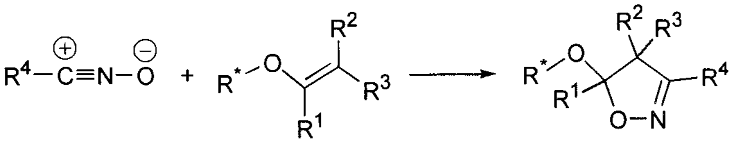
α,β-Unsaturated Carboxylic Acid Derivatives as Dipolarophiles with a Chiral Aminale Functionality in β-Position

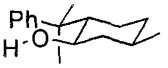
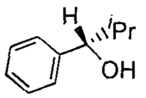


auxiliary	no.	product	*d.r.* or *de*	*ee*	yield	ref.
	**48**	A, B	A: 100 : 0 B: 70 : 30		A: 14% B: 38%	25
	**49**	A, B	100%		A: 10-16% B. 29-34%	25

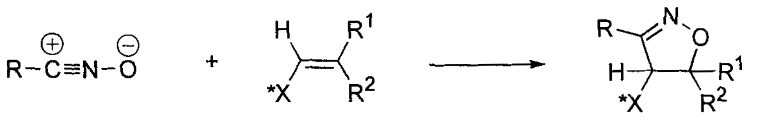
Vinylethers as Dipolarophiles

In reactions of nitrile oxides with chiral electron-rich alkenes, e.g. vinylethers, only moderate diastereoselectivities were obtained.



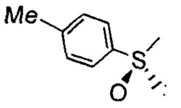
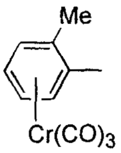
auxiliary	no.	*d.r.* or *de*	yield	ref.
	**11**	1.9 : 1	51%	26,27
	**17**	66%	59%	26,27

Miscellaneous Chiral Alkenes



Asymmetric 1,3-dipolar cycloaddition of chiral vinylsulfoxides proceed regio- and stereoselectively.

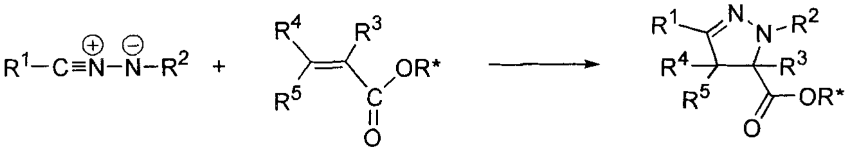
Optically pure tricarbonylchromium(0) complexes were applied in 1,3-dipolar cycloaddition reactions with nitrile oxides to give isoxazolidines in 70% yield with optical purities of up to 98% ee.

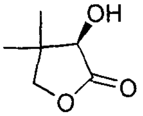
auxiliary	no.	*d.r.* or *de*	*ee*	yield	ref.
		100%			28,29
			98%	70%	30

Recently highly diastereoselective reactions of chiral vinyl phosphinoxides have been described.[31,32]

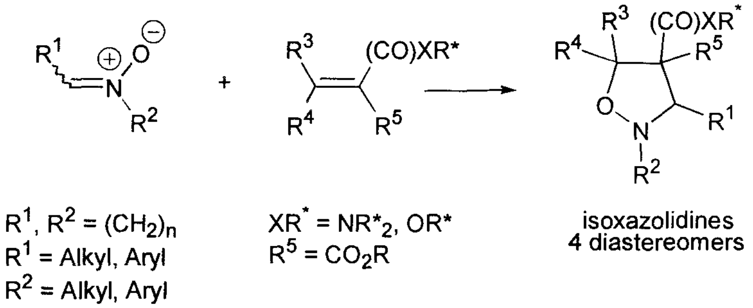
5.1.2 Reactions of Nitrile Imines

1,3-Dipolar cycloadditions of nitrile imines with alkenes lead to 2-pyrazolines. Moderate selectivities are observed in reactions with the acrylate of (*R*)-pantolactone.

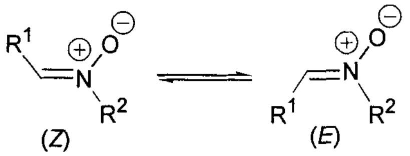


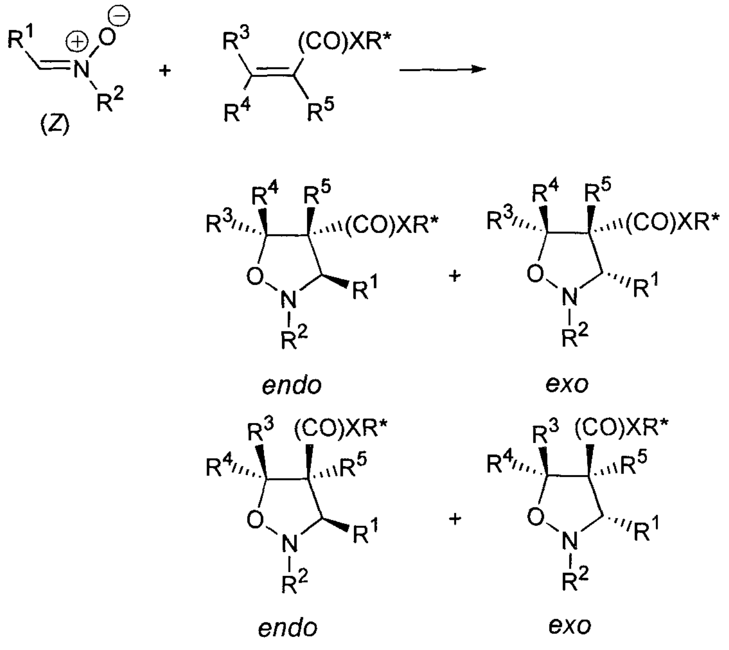
auxiliary	no.	*d.r.* or *de*	*ee*	yield	ref.
	**19**	50%		60%	33

5.1.3 Reactions of Nitrones



According to the concerted reaction pathway, in most cases the dipolarophile stereochemistry ((*E*)/(*Z*)-configuration) is preserved during the cycloaddition. For cycloaddition reactions of nitrones to olefins both *Re*/*Si*-discrimination as well as *endo*/*exo* selectivity have to be discussed.[4]

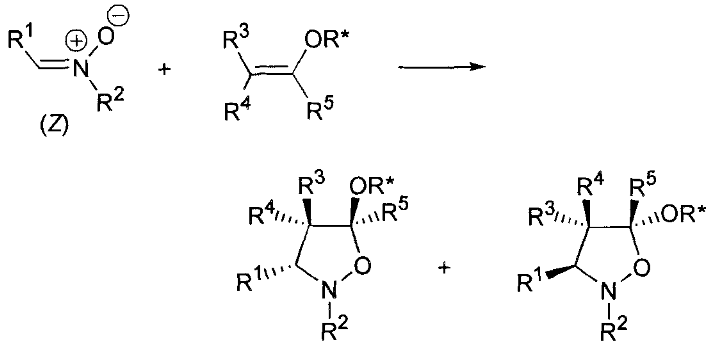




The reactions are carried out in toluene, $CHCl_3$ or CH_2Cl_2 at room temperature or under reflux and in some cases under high pressure.

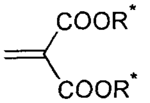
Rate accelerations in 1,3-dipolar cycloaddition reactions between alkenes and nitrones as well as improvements in *endo/exo* selectivity were achieved with certain Lewis acids, such as $ZnCl_2$, $TiCl(OiPr)_3$, $TiCl_2(OiPr)_2$, Mg(II) salts or $BF_3{\cdot}OEt_2$.[34]

ZnI_2 was applied successfully as Lewis-acid in order to increase the diastereoselectivity of the reaction of a cyclic nitrone with α,β-unsaturated imide derivatives.[35-37] It is noteworthy that chiral auxiliaries efficient in numerous other transformations, exhibit only low stereoselection in cycloadditions of nitrones.[35-37]

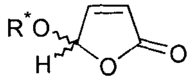


β-Amino alcohols are obtained upon reductive ring opening of the isoxazolidines by catalytic hydrogenation (Pd or Raney-Ni).

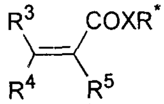
Type of Dipolarophile



A

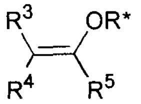


B

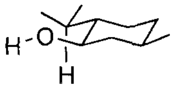
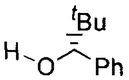
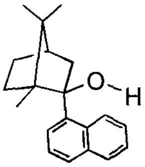
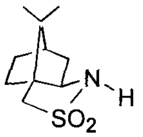
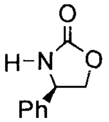
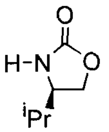


X = O, NR

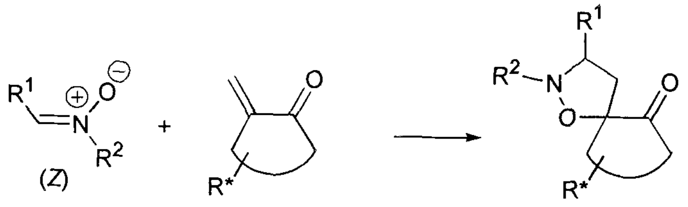
C



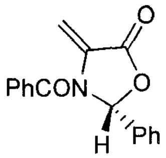
D

auxiliary	no.	type	*endo : exo*	*d.r.* or *de*	yield	ref.
alcohol derivatives						
	**10**	A,C		76 : 15 : 6 : 3	52-95%	12,23, 39
		B	65 : 35		95%	12,23
		D		15%	52%	38
	**16**	D		> 95%	89%	40
	**4**		2 : 1 – 100 : 0	30-68%	25-94%	15,41
amide derivatives						
	**63**	C	82 : 18 - 90 : 10	*endo*: 81-96% *exo*: 12-99%	20-90% 12-99%	42-44
	**62**	C		8 - 92%	53-99%	42
	**62**	C	100:0	> 99%	99%	42

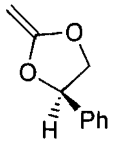
Chiral exo-cyclic Alkenes



Chiral *exo*-cyclic alkenes have been applied with moderate success, such as the chiral oxazolidinone **A**.[45,46]



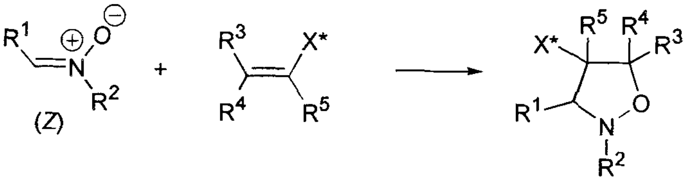
A

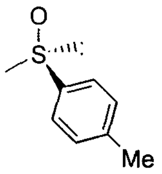


B

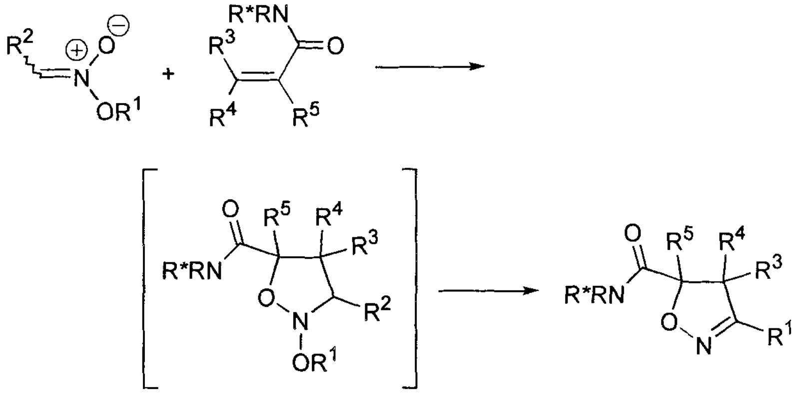
Chiral Vinyl Compounds

In reactions of chiral vinylsulfoxides,[47-51] absolute *exo* selectivity and high diastereoselectivities were obtained using cyclic nitrones. The cycloaddition of nitrones to chiral vinylphosphine oxides was found to proceed with high *endo/exo* selectivities and moderate diastereoselectivities.[52,53]



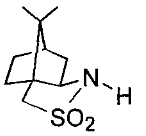
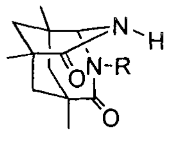
auxiliary	no.	*endo : exo*	*d.r.* or *de*	yield	ref.
		0 : 100	82-96%	85-95%	47-51

5.1.4 Reactions of Nitronates



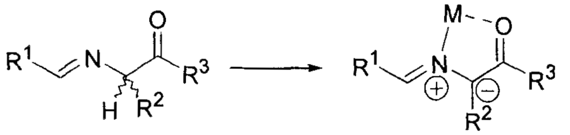
The addition of nitronates to alkenes opens up a route to isoxazolidines, useful precursors for the synthesis of 2-isoxazolines.[54] Tandem [4+2]/[3+2] cycloaddition reactions of nitroalkanes involving cyclic alkyl nitronates have been reported by Denmark et al.[55]

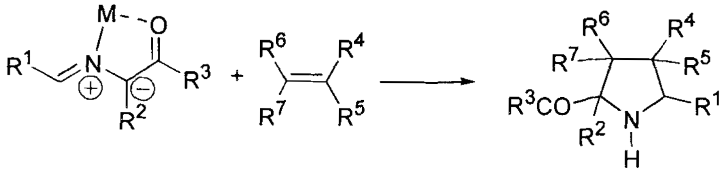
The camphor sultam auxiliary **63** was removed with L-Selectride.

auxiliary	no.	*d.r.* or *de*	yield	ref.
	**63**	82 : 18-90 : 10	85-96%	43,56
 R=(*S*)-CH(CH$_3$)Ph		86%	>98%	57,58

5.1.5 Reactions of Azomethine Ylides

5.1.5.1 Reactions of Azomethine Ylides Derived from Aldimines





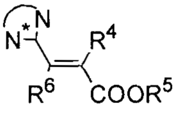
Cycloaddition reactions of azomethine ylides with electron-deficient alkenes furnish pyrrolidine derivatives, whereby up to four stereocenters are formed. Besides *Re/Si* discrimination *endo/exo* stereoselection has to be rationalized in these HOMO/LUMO controlled 1,3-dipolar cycloadditions.

Azomethine ylides are generated e.g. *in situ* starting from the corresponding Schiff bases of α-amino acids by deprotonation with an amine base (DBU or triethylamine) in the presence of metal salts such as LiBr or AgOAc, or by treatment of the starting materials with titanium salts. In general, the ylides are prepared in THF at –78°C/room temperature or in acetonitrile at higher temperature in the presence of the dipolarophile.[59,60]

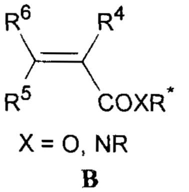
The obtained azomethine ylides (M = Ag(I), Li(I), Tl(I), Ti(IV)) have been reacted with electron-deficient alkenes. Reversal of regioselectivity was demonstrated by appropriate choice of the Lewis acid. Rate acceleration was achieved by addition of strong bases.[61]

Alternatively azomethine ylides are obtained from aziridines by thermolysis or photolysis.[62-66]

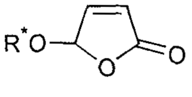
Type of Dipolarophile



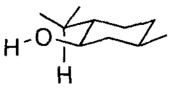
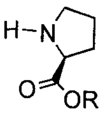
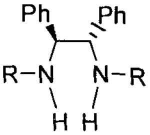
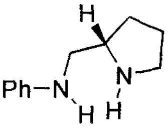
A



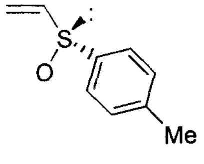
B



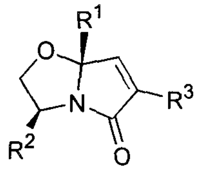
C

auxiliary	no.	type	*endo*:*exo*	*d.r.* or *de*	yield	ref.
ester derivatives						
	**10**	B	>99 : 1	10 : 1 - 99 : 1	70-90%	59, 67-72
		C	100 : 0	> 95%	65-91%	73,60, 67-70
amide derivatives						
 R = Bzl		B	93 : 7 – 99 : 1	91 : 9 – > 99 : 1	30-67%	74
miscellaneous derivatives						
 R = Me, Ph	**49**	A		45 : 55 – > 99 : 1	20-98%	63-65
	**48**	A	> 99 : 1	> 99%	82-96%	64,75

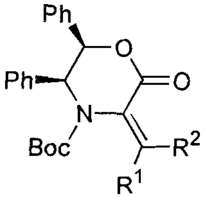
Besides the dipolarophiles discussed above, chiral unsaturated (R)$_s$-p-tolyl vinylsulfoxides **A** have been studied, too.[76] In addition, chiral unsaturated bicyclic lactams **B** have been applied successfully by Meyers et al. as dipolarophiles in cycloadditions with azomethine ylides.[77-80]



A[76]

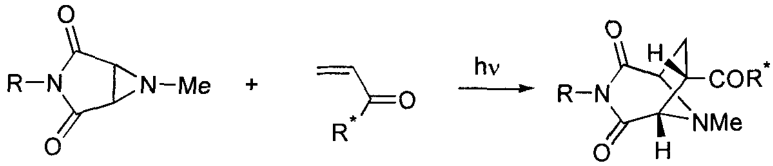


B[77-80]



C[81]

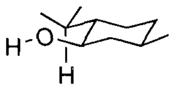
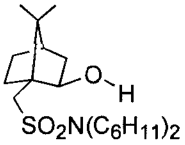
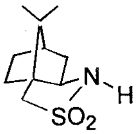
5.1.5.2 Reactions of Azomethine Ylides Derived from Aziridines



$R = CHR^1CO_2R^2$
$= CH_2Ph$
$= (R)\text{-}CH(R)Ph$

$R^* = OR^*, NRR^*$

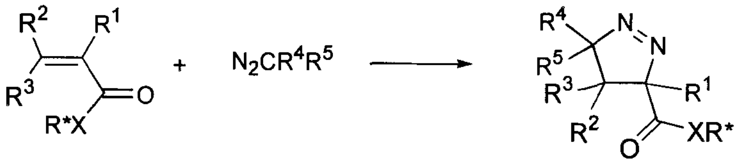
For the examples reported so far, usually in the presence of the alkene the azomethine ylide is generated *in situ* by photochemical disrotatory ring-opening of the aziridine (254 nm) in dioxane yielding pyrrolidines. (Obviously, thermal conrotatory ring-opening of aziridines demands conditions, which oppose an efficient stereocontrol of the subsequent cycloaddition with α,β-unsaturated carboxylic ester derivatives.)

auxiliary	no.	*d.r.* or *de*	*ee*	yield	ref.
alcohol derivatives					
	**10**	1 : 1		64%	82
	**9**	1 : 1-99 : 1		57-61%	82
amide derivatives					
	**63**	>25 : 1		39-61%	82-84

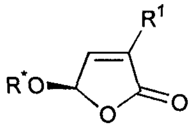
5.1.6 Reactions of Diazoalkanes

1,3-Dipolar cycloadditions of diazoalkanes with alkenes lead to pyrazolines, which are easily transformed into cyclopropanes.

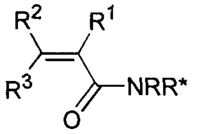
For compounds of type **A** reactions with ethyl diazoacetate were found to take place selectively. 1-Pyrazolines were obtained as cycloadducts in reactions of (trimethylsilyl)diazomethane with camphor sultam (**63**) derivatives. Upon treatment with acid the heterocycles rearrange to form 2-pyrrazolines diastereoselectively.



Type of Dipolarophile

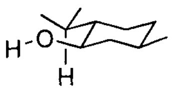
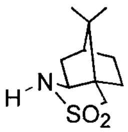


A



B

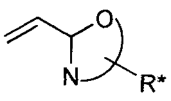
α,β-Unsaturated Carboxylic Acid Derivatives

auxiliary	no.	type	*d.r.* or *de*	*ee*	yield	ref.
	**10**	A	60 : 40 – > 99 : 1		67-69%	12,85
	**63**	B	90 : 10 – 94 : 6%		65-78%	86

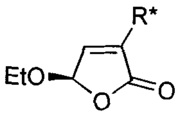
Astonishingly, stereoselective cycloadditions of diazomethane have been reported only for a few isolated cases. The reactions were carried out in dioxane at 95°C or in ether at room temperature.

Miscellaneous Vinyl Compounds

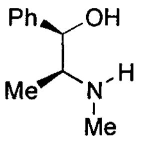
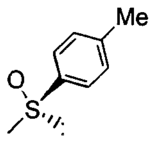
Type of Dipolarophile



A

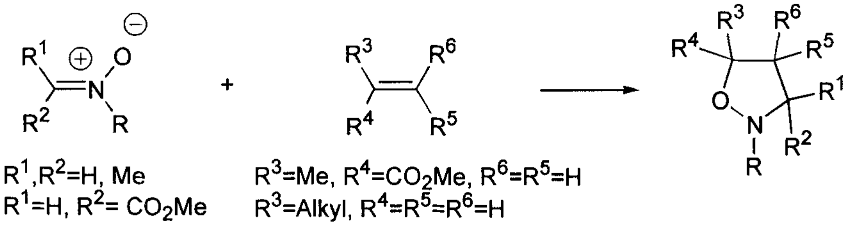


B

auxiliary	no.	type	*d.r.* or *de*	*ee*	yield	ref.
	**26**	A	90%		>90%	87
		**B**	>99 : 1		>98%	88

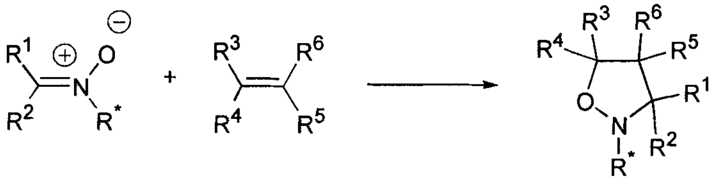
5.2 Chiral Dipolars

5.2.1 Reactions of Chiral Nitrones

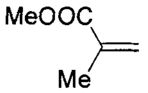


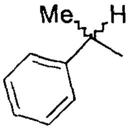
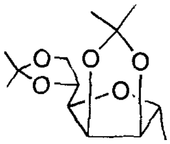
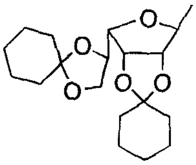
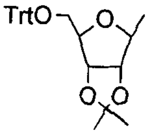
The stereofacial differentiation of the diastereotopic sides of nitrones by removable auxiliaries demands the positioning of the chiral group to be within the *N*-substituent. In order to exhibit a spatial differentiation, a preferred conformation of this substituent is crucial. Carbohydrates, due to their *exo*-anomeric effect revealed to be efficient auxiliaries for these transformations.[89,90] So far the reactivity and efficiency of more than 40 carbohydrate compounds have been examined. When optically active nitrones from inexpensive carbohydrates are applied, generally the optically purities of the *N*-substituted isoxazolidines are determined after removal of the chiral auxiliary.

5.2.1.1 Reactions of Nitrones with Chiral Nitrogen-Substituents

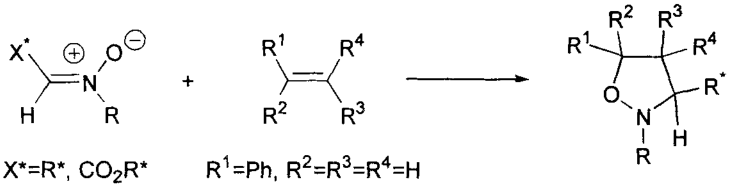


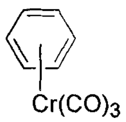
Dipolarophiles



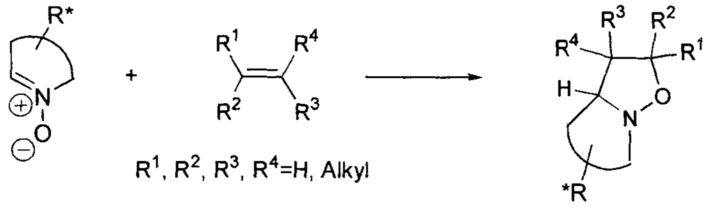
auxiliary	*exo : endo*	*d.r.* or *de*	*ee*	yield	ref.
	68 : 32 – 87 : 13	100%		45-89%	91-96
	1.7 : 1 - 87.5 : 12.5		79-90%	38-97%	97-99
	3 : 2		94%		100
		71 : 19 - 83 : 17		51 - 98%	98,99

5.2.1.2 Reactions of Nitrones with Chiral Carbon-Substituents

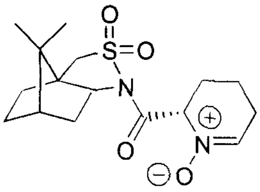
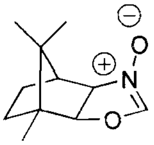
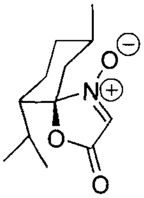
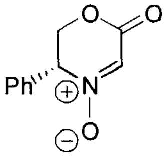


auxiliary	*endo : exo*	*d.r.* or *de*	*ee*	yield	ref.
	70 : 30 <2 : >98	96-98%		15-85%	100, 101

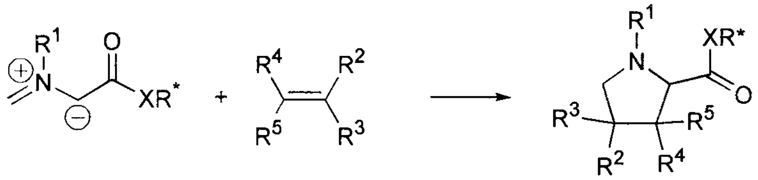
5.2.1.3 Reactions of Chiral Cyclic Nitrones



Chiral cyclic nitrones that have been obtained from recoverable chiral sources (e.g. camphor, *L*-menthone) did provide excellent selectivities in 1,3-dipolar cycloaddition reactions with alkenes.

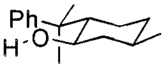
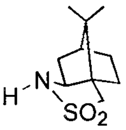
nitrones	*exo : endo*	*d.r.* or *de*	*ee*	yield	ref.
	100 : 0	93%			5
		86 : 14 – 100 : 0		49-80%	102-104
		100:0		>98%	35,36
		100%		87%	105

5.2.2 Reactions of Chiral Azomethine Ylides

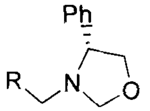
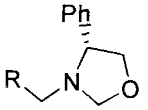


R^3 = H, Alkyl R^6= R^4=CO_2Et, R_7=R^5=H
X = O, NR

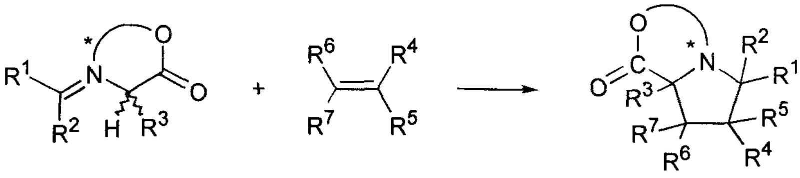
Reactions of chiral azomethine ylides usually derived from imines of α-amino acids have been achieved with electron-deficient alkenes and α,β-unsaturated carboxylic acid derivatives furnishing pyrrolidines.

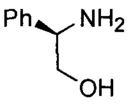
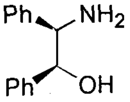
auxiliary	no.	*endo* : *exo*	*d.r.* or *de*	*ee*	yield	ref.
ester derivatives						
	**11**	100 : 0	> 95%		86%	106
amide derivatives						
	**63**		5 : 1 - 11 : 1		53-92%	107

Cyclic Five-membered Chiral Azomethine Ylide Precursors

precursors	*endo* : *exo*	*d.r.* or *de*	*ee*	yield	ref.
 R= CN, CO_2Et R= R*= CO_2Menthyl	55 : 45-93 : 7	60-80%		52-83%	106
 R= CN, CO_2Et R= R*= CO_2-(8)-Phenyl-menthyl	100 : 0	>95%%		86%	106

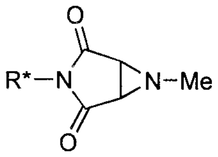
Cyclic Six-membered Chiral Azomethine Ylide Precursors



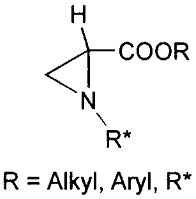
auxiliary	no.	*endo* : *exo*	*d.r.* or *de*	yield	ref.
	**27**	20 : 6 - 54 : 14	*endo*: 54%	26-72%	108
	**28**	> 95 : 5	*endo*: 4 : 1 - > 99 : 1	32-71%	109

Chiral Aziridines as Precursors for Azomethine Ylides

Type of Aziridine

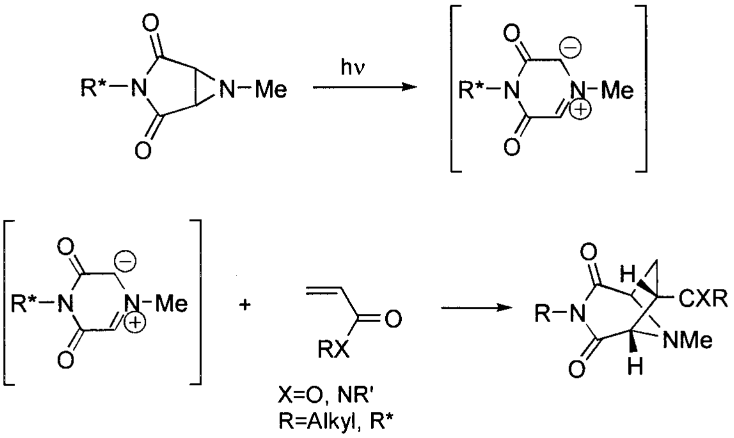


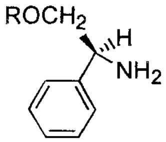
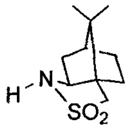
A



B

Aziridines of type **A**, with a chiral substituent located at the nitrogen atom have been applied successfully in asymmetric syntheses with α,β-unsaturated carboxylic acid derivatives derived from Oppolzer's chiral camphor sultam.[84,107,110]



auxiliary	no.	type	*d.r.* or *de*	yield	ref.
nitrogen-substituent					
		A B	>25 : 1	39-61%	110
carbon-substituent					
	**63**		>100 : 1	55-58%	110

In addition chiral tertiary amine N-oxides have been applied as precursors for azomethine ylides.[111-114]

5.3 References

[1] R. Huisgen in *1,3 Dipolar Cycloaddition Chemistry*, (Ed.: A. Padwa), General Heterocyclic Chemistry Series Vol. 1, John Wiley & Sons, New York (1984).

[2] P. Caramella in *1,3 Dipolar Cycloaddition Chemistry*, (Ed.: A. Padwa), General Heterocyclic Chemistry Series Vol. 2, John Wiley & Sons, New York (1984).

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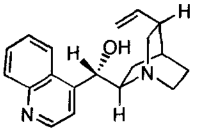
Chiral Auxiliaries in Cycloadditions
Karola Rück-Braun, Horst Kunz

6 Chiral Auxiliaries

6.1 Alcohols

6.1.1 Cinchona Alkaloid Derivatives

Cinchonine and **Cinchonidine** are Cinchona Alkaloids lacking the 6'-methoxy group.



1
Cinchonine

Application:
[4+2] Cycloaddition, p. 55.

Synthesis:
M. R. Uskovic, T. Henderson, C. Reese, H. L. Lee, G. Grethe, J. Gutzwiller, J. Am. Chem. Soc. 100 (1978) 571.
J. Gutzwiller, M. R. Uskovic, J. Am. Chem. Soc. 100 (1978) 576.
G. Grethe, H. L. Lee, T. Mitt, M. R. Uskovic, J. Am. Chem. Soc. 100 (1978) 581.
G. Grethe, H. L. Lee, T. Mitt, M. R. Uskovic, J. Am. Chem. Soc. 100 (1978) 589.

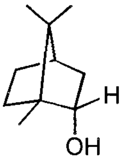
Preparation of Derivatives:
H. Suzuki, K. Mochizuki, T. Hattori, N. Takahasi, O. Tajima, T. Takiguchi, Bull. Chem. Soc. Jpn. 61 (1988) 1999.

6.1.2 Camphor-based Alcohols

Naturally occurring compounds containing the bicyclo[2.2.1]heptane skeleton:

Reviews:
W. Oppolzer, Tetrahedron 43 (1987) 1969.
M. E. C. Polywka, Chim. Oggi 10 (1992) 33.

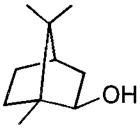
(+)-Borneol, (-)-Borneol



2
(+)-Borneol

Application:
[2+2] Cycloaddition, p. 24.
[4+2] Cycloaddition, p. 65.

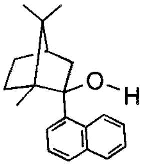
(+)-Isoborneol, (-)-Isoborneol



3
(-)-Isoborneol

Application:
[2+2] Cycloaddition, p. 22.
[4+2] Cycloaddition, p. 62.

(1*R*,2*R*,4*R*)-2-(1-Naphthyl)-isoborneol

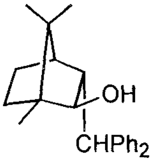


4

Application:
[3+2] Cycloaddition, p. 114, 122.

Synthesis:
P. Somfai, D. Tanner, T. Olson, Tetrahedron 41 (1985) 5973.

3-Benzhydryl-1,7,7-trimethyl-bicyclo[2.2.1]heptan-1-ol



5

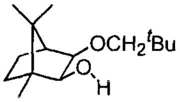
Application:

[4+2] Cycloaddition, p. 54.
Hetero [4+2] Cycloaddition, p. 96.

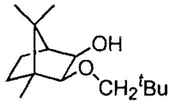
Synthesis:

W. Oppolzer, C. Chapuis, Tetrahedron Lett. 40 (1984) 5383.
W. Oppolzer, M. Kurth, D. Reichlin, C. Chapuis, M. Mohnhaupt, F. Moffat, Helv. Chim. Acta 64 (1981) 2802.
K. Hakam, M. Thielmann, T. Thielmann, E. Winterfeldt, Tetrahedron 43 (1987) 2035.

Monoethers of 3-*exo*-Hydroxy-isoborneol



6



7

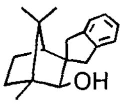
Application:

[2+2] Cycloaddition, p. 18, 25.
[4+2] Cycloaddition, p. 52, 53.
Hetero [4+2] Cycloaddition, p. 88, 95.

Synthesis:

W. Oppolzer, C. Chapuis, G. M. Dao, D. Reichlin, T. Godel, Tetrahedron Lett. 23 (1982) 4781.

1,7,7-Trimethylspiro{bicyclo[2.2.1]heptane-3,2'-indan}-2-ol



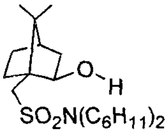
8

Application:
Hetero [4+2] Cycloaddition, p. 105.

Synthesis:
G. Helmchen, A. Selim, D. Dorsch, I. Taufer, Tetrahedron Lett. 24 (1983) 3213.

***N,N*-Dicyclohexyl-2-*exo*-hydroxy-10-bornane-sulfonamide**

(*1S,2R*)-N,N-Dicyclohexyl-2-*exo*-hydroxy-10-bornane-sulfonamide (**9**) and
(*1R,2S*)-N,N-Dicyclohexyl-2-*exo*-hydroxy-10-bornane-sulfonamide


9

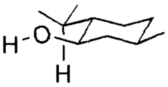
Application:
[2+2] Cycloaddition, p. 18.
[4+2] Cycloaddition, p. 34, 54, 63.
[3+2] Cycloaddition, p. 114, 128.

Synthesis:
W. Oppolzer, C. Chapuis, G. Bernardinelli, Tetrahedron Lett. 25 (1984) 5885.

6.1.3 Cyclohexyl-based Alcohols

Review:
J. K. Whitesell, Chem. Rev. 92 (1992) 953.

(-)-Menthol = (-)-(1*R*,2*S*,5*R*)-2-Isopropyl-5-methyl-cyclohexanol
(+)-Menthol = (+)-(1*S*,2*R*,5*S*)-2-Isopropyl-5-methyl-cyclohexanol


10
(-)-Menthol

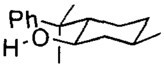
Application:
[2+1] Cycloaddition, p. 5.

[2+2] Cycloaddition, p. 18, 19, 20, 21, 22, 25.
[4+2] Cycloaddition, p. 33, 34, 38, 40, 52, 58.
Hetero [4+2] Cycloaddition, p. 73, 74, 75, 76, 79, 94, 95, 102, 103, 105.
[3+2] Cycloaddition, p. 114, 116, 122, 126, 128, 129, 136.

Synthesis:
G. Posner, D. G. Wettlaufer, Tetrahedron Lett. 27 (1986) 667.

8-Phenylmenthol

(-)-8-Phenylmenthol [=(*1R,2S,5R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanol]
(+)-8-Phenylmenthol



11
(-)-8-Phenylmenthol

Application:
[2+1] Cycloaddition, p. 9.
[2+2] Cycloaddition, p. 18, 21, 22, 25.
[4+2] Cycloaddition, p. 34, 37, 38, 40, 43, 54, 65.
Hetero [4+2] Cycloaddition, p. 74, 76, 79, 80, 88, 93, 95, 103, 104.
[3+2] Cycloaddition, p. 118, 135, 136.

Synthesis:
H. Buschmann, H.-D. Scharf, Synthesis (1988) 827.
H. Herzog, H.-D. Scharf, Synthesis (1986) 420.
O. Ort, Org. Synth. 65 (1987) 203.

trans-2-Phenyl-cyclohexanol

(-)-*trans*-2-Phenyl-cyclohexanol and (+)-*trans*-2-Phenyl-cyclohexanol

12

Application:
[2+2] Cycloaddition, p. 18.
[4+2] Cycloaddition, p. 44, 55.
Hetero [4+2] Cycloaddition, p. 96, 98, 102.

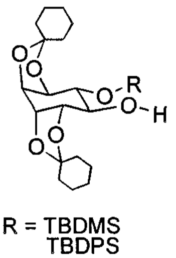
Synthesis:

J. K. Whitesell, H.-H. Chen, R. M. Lawrence, J. Org. Chem. 50 (1986) 4663.

K. Laumen, D. Breitgoff, R. Seemayer, M. P. Schneider, J. Chem. Soc. Chem. Commun. (1989) 148.

K. Laumen, R. Seemayer, M. P. Schneider, J. Chem. Soc. Chem. Commun. (1990) 49.

(1*L*)-1,2:5,6-Biscyclohexylidene-3-*tert*-butyldimethylsilyl-chiro-inositol



13

Application:

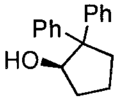
[3+2] Cycloaddition, p. 114.

Synthesis:

T. Akiyama, H. Nishimoto, S. Ozaki, Tetrahedron Lett. 32 (1991) 1335.

R. Plourde, M. d'Alarcao, Tetrahedron Lett. 31 (1990) 2693.

(*R*)-(-)-2,2-Diphenylcyclopentanol



14

Application:

Hetero [4+2] Cycloaddition, p. 98.

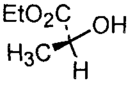
Synthesis:

D. Potin, F. Dumas, J. d'Angelo, J. Am. Chem. Soc. 112 (1990) 3483.

S. E. Denmark, M. E. Schnute, L. R. Marcin, A. Thorarensen, J. Org. Chem. 60 (1995) 3205.

6.1.4 Miscellaneous Alcohols

Ethyl-(*S*)-lactate

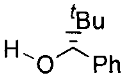


15

Application:
[4+2] Cycloaddition, p. 33, 34, 53.
Hetero [4+2] Cycloaddition, p. 79.

Synthesis:
T. Poll, G. Helmchen, B. Bauer, Tetrahedron Lett. 25 (1984) 2191.

(*R*)-2,2-Dimethyl-1-phenyl-propan-1-ol

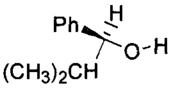


16

Application:
[4+2] Cycloaddition, p. 38.
[3+2] Cycloaddition, p. 122.

Synthesis:
M. Knollmueller, C. R. Noe, G. Steinbauer, K. Dungler, Synthesis (1986) 501.
(S)-2,2-Dimethyl-1-phenyl-propan-1-ol
S. Julia, A. Ginebreda, J. Guixer, J. Masana, A. Tomas, S. Colonna, J. Chem. Soc. Perkin Trans. I (1981) 574.

(*S*)-2-Methyl-1-phenyl-propan-1-ol

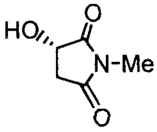


17

Application:
[4+2] Cycloaddition, p. 34, 38, 55.
[3+2] Cycloaddition, p. 118.

Synthesis:
K. Soai, S. Yokoyama, T. Hayasaka, J. Org. Chem. 56 (1991) 4264.
J. C. Ruble, H. A. Latham, G. C. Fu, J. Am. Chem. Soc. 119 (1997) 1492.

(*S*)-*N*-Methyl-2-hydroxysuccinimide
(*S*)-3-hydroxy-1-methyl-pyrrolidine-2,5-dione



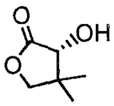
18

Application:
[4+2] Cycloaddition, p. 55.

Synthesis:
T. Poll, A. F. A. Hady, R. Karge, G. Linz, J. Weetman, G. Helmchen, Tetrahedron Lett. 30 (1989) 5595.
M. C. Sleevi, A. D. Cale, T. W. Gero, L. W. Jaques, W. J. Welstead, J. Med. Chem. 34 (1991) 1314.

Pantolactone

***D*-Pantolactone**



19

Application:
[2+1] Cycloaddition, p. 10.
[4+2] Cycloaddition, p. 53, 61, 62.
Hetero [4+2] Cycloaddition, p. 79.
[3+2] Cycloaddition, p. 119.

Synthesis:
I. Ojima, T. Kogure, T. Terasaki, K. Achiwa, J. Org. Chem. 43 (1978) 3444.
R. P. Lanzilotta, D. G. Bradley, K. M. McDonal, Appl. Microbiol. 27 (1974) 130.

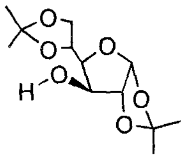
L-Pantolactone
E. J. Corey, H.-C. Huang, Tetrahedron Lett. 30 (1989) 5235.
T. Poll, A. Sobczak, H. Hartmann, G. Helmchen, Tetrahedron Lett. 26 (1985) 3095.

6.1.5 Carbohydrate-derived Alcohols

Reviews:
R. W. Franck, ACS Symp. Ser. 494 (1992) 24.
H. U. Reissig, Angew. Chem. 104 (1992) 295; Angew. Chem. Int. Ed. Engl. 31 (1992) 288.
H. Kunz, K. Rück, Angew. Chem. 105 (1993) 355; Angew. Chem. Int. Ed. Engl. 32 (1993) 336.
P. G. Hultin, M. A. Earle, M. Sudharshan, Tetrahedron 53 (1997) 14823.

1,2:5,6-Di-*O*-isopropylidene-α-*D*-glucofuranose

Diacetone glucose (DAG)

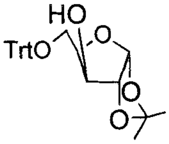


20

Application:
[2+2] Cycloaddition, p. 20.
[4+2] Cycloaddition, p. 44.
Hetero [4+2] Cycloaddition, p. 75, 96.
[3+2] Cycloaddition, p. 114.

Synthesis:
O. T. Schmidt, Methods Carbohydr. Chem. 2 (1968) 318.
1,2:5,6-Di-O-cyclohexylidene-α-D-glucofuranose
R. C. Hockett, R. E. Miller, A. Scattergood, J. Am. Chem. Soc. 71 (1949) 3072.

1,2-*O*-Isopropylidene-5-*O*-triphenylmethyl-α-D-ribofuranose

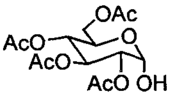


21

Application:
[4+2] Cycloaddition, p. 54.

Synthesis:
E. Chelain, O. Floch, S. Czernecki, J. Carbohydr. Chem. 14 (1995) 1251.

2,3,4,6-Tetra-*O*-acetyl-α-*D*-glucopyranose

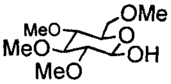


22

Application:
[4+2] Cycloaddition, p. 42.
Hetero [4+2] Cycloaddition, p. 89.

Synthesis:
C. C. McCloskey, G. H. Coleman, Org. Synth. Coll. Vol. 3 (1955) 434.
T. Utamura, K. Kuromatsu, K. Suwa, K. Koizumi, T. Shingu, Chem. Pharm. Bull. 34 (1986) 2341.

2,3,4,6-Tetra-*O*-methyl-β-D-glucose

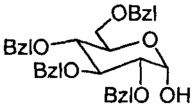


23

Application:
[4+2] Cycloaddition, p. 43.

Synthesis:
G. O. Aspinall, H. K. Fanous, N. S. Kumar, V. Puvanesarajah, Can. J. Chem. 61 (1983) 1858.

2,3,4,6-Tetra-*O*-benzyl-α-*D*-glucopyranose



24

Application:
Hetero [4+2] Cycloaddition, p. 102.

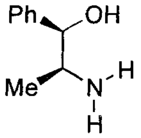
Synthesis:
C. P. J. Claudemans, H. G. Fletcher, Jr., Methods Carbohydr. Chem. 6 (1972) 374.
T. D. Perrine, C. P. J. Claudemans, R. K. Ness, J. Kyle, H. G. Fletcher Jr., J. Org. Chem. 32 (1967) 664.

6.2 1,2 Amino Alcohols

Reviews:
D. J. Ager, I. Prakash, D. R. Schaad, Chem. Rev. 96 (1996) 835.

6.2.1 Ephedrine and Norephedrine Derivatives

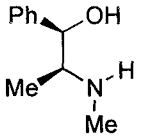
L(-)-Norephedrine = (1*R*,2*S*)-2-Amino-1-phenyl-1-propanol



25

Application:
Hetero [4+2] Cycloaddition, p. 108.

(-)-Ephedrine = (1*R*,2*S*)-2-Methylamino-1-phenyl-1-propanol



26

Application:
[2+1] Cycloaddition, p. 9.
[4+2] Cycloaddition, p. 43, 65.
Hetero [4+2] Cycloaddition, p. 107.
[3+2] Cycloaddition, p. 130.

Synthesis of Alkylated Derivatives:
E. L. Engelhardt, F. S. Crossley, J. M. Sprague, J. Am. Chem. Soc. 72 (1950) 2718.

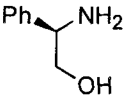
6.2.2 Amino Acids and Derivatives

Reviews:
A. Studer, Synthesis (1996) 793.
H. Waldmann, Synlett (1995) 133.

Synthesis of Amino Acid Derivatives:
T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 2nd ed., John Wiley & Sons, New York (1991).
P. J. Kocienski, *Protecting Groups*, Thieme, Stuttgart (1994).
(see, Chapter 6.5, p. 167)

Application of Amino Acid Esters and other Amino Acid Derivatives:
[2+1] Cycloaddition, p. 1, 8.
[2+2] Cycloaddition, p. 15, 16, 23.
[4+2] Cycloaddition, p. 35, 56.
Hetero [4+2] Cycloaddition, p. 77, 81, 82, 86.
[3+2] Cycloaddition, p. 115, 126, 135.

(-)-(*R*)-2-Amino-2-phenylethanol

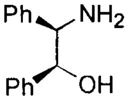


27

Application:
[4+2] Cycloaddition, p. 64.
[3+2] Cycloaddition, p. 127, 134, 136.

Synthesis:
P. C. Kamer, M. C. Cleij, R. J. M. Nolte, T. Harada, A. M. F. Alphons, W. Drenth, J. Am. Chem. Soc. 110 (1988) 1581.
H. Vorbrueggen, K. Krolikiewicz, Tetrahedron 49 (1993) 9353.
(+)-(S)-2-Amino-2-phenyl-ethanol
E. Nicolas, K. C. Russell, V. J. Hruby, J. Org. Chem. 58 (1993) 766.
J.-N. Denis, A. Correa, A. E. Greene, J. Org. Chem. 56 (1991) 6939.
Z.-Y. Chang, R. M. Coates, J. Org. Chem. 55 (1990) 3475.
A. Correa, J.-N. Denis, A. E. Greene, Synth. Commun. 21 (1991) 1.

(1*S*,2*R*)-2-Amino-1,2-diphenyl-ethanol



28

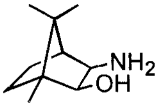
Application:
[3+2] Cycloaddition, p. 127, 136.

Synthesis:
F. Effenberger, B. Gutterer, T. Ziegler, Liebigs Ann. Chem. 3 (1991) 269.
F. A. Davies, M. S. Haque, R. M. Przeslawski, J. Org. Chem. 54 (1989) 2021.
(1R,2S)-2-Amino-1,2-diphenyl-ethanol
J. Brussee, F. Dofferhoff, C. G. Kruse, A. van der Gen, Tetrahedron 46 (1990) 1653.

(*S*)-Prolinol
G. H. Smith, R. E. Gawley, Org. Synth. 63 (1985) 136.
D. Enders, H. Fey, H. Kipphardt, Org. Synth. 65 (1987) 173.
(*R*)-Prolinol
D. Enders, H. Eichenauer, R. Pieter, Chem. Ber. 112 (1979) 3703.
U. Schmidt, R. Schölm, Synthesis (1978) 752.
D. Enders, Asymmetric Synthesis 3 (1984) 275.

6.2.3 Aminoalcohols with Bicyclo[2.2.1]heptane Skeleton

(1*R*,4*S*)-3-*exo*-Amino-isoborneol



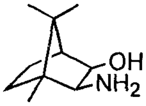
29

Application:
[2+1] Cycloaddition, p. 6.
[4+2] Cycloaddition, p. 36.

Synthesis:
R. A. Chittenden, G. H. Cooper, J. Chem. Soc. C (1970) 49.
H. Beckett, N. T. Lan, G. R. McDonough, Tetrahedron 25 (1969) 5689.
H. Beckett, N. T. Lan, G. R. McDonough, Tetrahedron 25 (1969) 5693.

M. T. Reetz, T. Zierke, Chem. Ind. (London) 20 (1988) 663.
C. Kouklovsky, A. Pouilhès, Y. Langlois, J. Am. Chem. Soc. 112 (1990) 6672.
(1R,4S)-3-endo-Aminoborneol
R. A. Chittenden, G. H. Cooper, J. Chem. Soc. C (1970) 49.
H. Pauling, Helv. Chim. Acta 58 (1975) 1781.

(1*R*,4*S*)-3-*exo*-2-Amino-3-bornanol



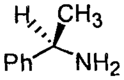
30

Application:
[4+2] Cycloaddition, p. 36.

Synthesis:
A. Pouilhes, E. Uriarte, C. Kouklovsky, N. Langlois, Y. Langlois, A. Chiaroni, C. Riche, Tetrahedron Lett. 30 (1989) 1395.
C. Kouklovsky, A. Pouilhès, Y. Langlois, J. Am. Chem. Soc. 112 (1990) 6672.

6.3 Primary Amines

Phenylethylamine
(*S*)-(-)-1-Phenylethylamine and (*R*)-(+)-1-Phenylethylamine (**31**)



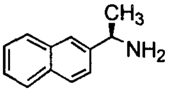
31

Application:
[2+2] Cycloaddition, p. 15.
[4+2] Cycloaddition, p. 40, 47, 55.
Hetero [4+2] Cycloaddition, p. 77, 78, 80, 82, 99.

Synthesis:
W. Ingersoll, Org. Synth. Coll. Vol. 2 (1943) 503.

1-Naphthalen-2-yl-ethylamine

(*S*)-1-Naphthalen-2-yl-ethylamine and (*R*)-(1)-Naphthalen-2-yl-ethylamine (**32**)



32

Application:

Hetero [4+2] Cycloaddition, p. 107.

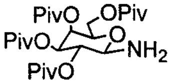
Synthesis:

R. Menicagli, O. Piccolo, L. Lardicci, M. L. Wis, Tetrahedron 35 (1979) 1301.

(S)-1-Naphthalen-2-yl-ethylamine

M. Pallavicini, E. Valoti, L. Villa, O. Piccolo, Tetrahedron: Asymmetry 7 (1996) 1117.

2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosylamine



33

Application:

[2+2] Cycloaddition, p. 16.

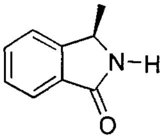
Hetero [4+2] Cycloaddition, p. 77, 82.

Synthesis:

H. Kunz, W. Sager, Angew. Chem. 99 (1987) 595; Angew. Chem. Int. Ed. Engl. 26 (1987) 557.

6.4 Secondary Amines

(*R*)-3-Methyl-2,3-dihydro-isoindol-1-one

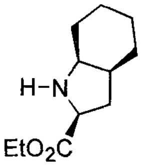


34

Application:
[4+2] Cycloaddition, p. 57.

Synthesis:
W. Oppolzer, M. Wills, M.-J. Kelly, M. Signer, J. Blagg, Tetrahedron Lett. 31 (1990) 5015.
J. P. Murphy, M. Nieuwenhuyzen, K. Reynolds, P. Sarma, P. J. Stevenson, Tetrahedron Lett. 36 (1995) 9533

(2*S*,3a*S*,7a*S*)-Octahydro-indole-2-carboxylic acid ethyl ester



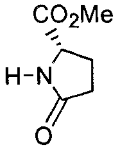
35

Application:
[3+2] Cycloaddition, p. 116.

Synthesis:
D. H. R. Barton, J. Guilhem, Y. Herve, P. Potier, J. Thierry, Tetrahedron Lett. 28 (1987) 1413.

6.4.1 Pyrrolidines

5-Oxo-pyrrolidine-2-carboxylic acid methyl ester

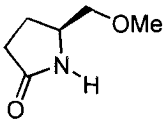


36

Application:
[4+2] Cycloaddition, p. 47.
Hetero [4+2] Cycloaddition, p. 87.

Synthesis:
H. Fritschi, U. Leutenegger, A. Pfaltz, Angew. Chem. 98 (1986) 1028; Angew. Chem. Int. Ed. Engl. 25 (1986) 1005.
E. Cesarotti, L. Prati, A. Sironi, G. Ciani, C. White, J. Chem. Soc. Dalton Trans. I (1987) 1149.
K. Drauz, A. Kleemann, J. Martens, P. Scherberich, F. Effenberger, J. Org. Chem. 51 (1986) 3494.
B. Rigo, S. E. Ghammarti, P. Gautret, D. Couturier, Synth. Commun. 24 (1994) 2597.
S. Saijo, M. Wada, J. Himizu, A. Ishida, Chem. Pharm. Bull. 28 (1980) 1449.
J. Ackermann, M. Matthes, C. Tamm, Helv. Chim. Acta 73 (1990) 122.

(*S*)-5-Methoxymethyl-pyrrolidin-2-one

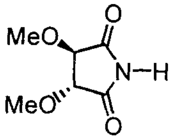


37

Application:
[2+2] Cycloaddition, p. 14.

Synthesis:
K. Yakushijin, R. Suzuki, N. Kawaguchi, Y. Tsuboi, H. Furukawa, Chem. Pharm. Bull. 34 (1986) 2049.

(3*R*,4*R*)-*trans*-3,4-Dimethoxy-pyrrolidine-2,5-dione

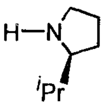


38

Application:
[2+2] Cycloaddition, p. 14.

Synthesis:
C. R. Young, J. Chem. Soc. 105 (1914) 1228.

(*S*)-(-)-2-(1-Methylethyl)-pyrrolidine



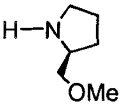
39

Application:
[4+2] Cycloaddition, p. 57.

Synthesis:
D. Enders, H. Kipphardt, P. Gerdes, L. J. Brena-Valle, V. Bhushan, Bull. Soc. Chim. Belg. 97 (1988) 691.

(*S*)-(+)-2-Methoxymethylpyrrolidine

Review:
D. Enders, M. Klatt, Synthesis (1996) 1403.



40

Application:
[2+2] Cycloaddition, p. 17.
[4+2] Cycloaddition, p. 37, 48, 58.

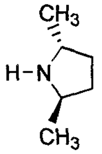
Hetero [4+2] Cycloaddition, p. 83, 86, 98, 103.

Synthesis:
D. Enders, H. Fey, H. Kipphardt, Org. Synth. 65 (1987) 173.
D. Enders, H. Fey, H. Kipphardt, Org. Prep. Proc. Int. 17 (1985) 1.
H. Ahlbrecht, D. Enders, L. Santowski, G. Zimmermann, Chem. Ber. 122 (1989) 1995.

6.4.2 C_2-Symmetric Pyrrolidines

Reviews:
J. K. Whitesell, Chem. Rev. 89 (1989) 1581.
H. Waldmann in *Organic Synthesis Highlights II* (Ed.: H. Waldmann), VCH, Weinheim (1995) 49.

(*2R,5R*)-2,5-Dimethylpyrrolidine

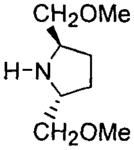


41

Application:
[2+2] Cycloaddition, p. 17.
Hetero [4+2] Cycloaddition, p. 86.

Synthesis:
R. H. Schlessinger, E. J. Iwanowicz, Tetrahedron Lett. 28 (1987) 2083.
(2R,5R)-2,5-Dimethylpyrrolidine
J. K. Lieser, Synth. Commun. 13 (1983) 765.

(2*R*,5*R*)-2,5-*trans*-Dimethoxymethylpyrrolidine

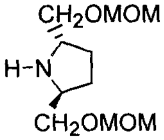


42

Application:
[4+2] Cycloaddition, p. 56, 58.
Hetero [4+2] Cycloaddition, p. 86, 101.

Synthesis:
J. Ahman, P. Somfai, Tetrahedron 48 (1992) 9537.
Y. Yamamoto, J. Hoshino, Y. Fujimoto, J. Ohmoto, S. Sawada, Synthesis (1993) 298.

(*S,S*)-2,5-Bis[(methoxymethoxy)methyl]pyrrolidine

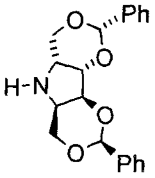


43

Application:
[4+2] Cycloaddition, p. 33, 35, 56.
[3+2] Cycloaddition, p. 115.

Synthesis:
Y. Yamamoto, H. Ohmori, S. Sawada, Synlett (1991) 319.
Y. Kawanama, T. Katsuki, M. Yamaguchi, Bull. Chem. Soc. Jpn. 60 (1987) 4190.

3,6-Diphenyl-hexahydro-2,4,5,7-tetraoxa-9-aza-fluorene

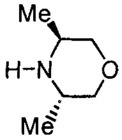


44

Application:
Hetero [4+2] Cycloaddition, p. 86.

Synthesis:
A. Defoin, A. Brouillard-Piochet, J. Streith, Helv. Chim. Acta 74 (1991) 103.
T. K. M. Shing, Tetrahedron 44 (1988) 7261.

(+)-(*S*,*S*)-3,5-Dimethylmorpholine

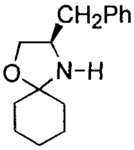


45

Application:
[4+2] Cycloaddition, p. 58.
Hetero [4+2] Cycloaddition, p. 89.

Synthesis:
D. Enders, O. Meyer, G. Raabe, J. Runsink, Synthesis (1994) 66.

(*R*)-3-Benzyl-1-oxa-4-aza-spiro[4.5]decane

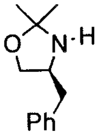


46

Application:
[3+2] Cycloaddition, p. 115.

Synthesis:
C. Stetin, B. De Jeso, J.-C. Pommier, J. Org. Chem. 50 (1985) 3863.

(*S*)-4-Benzyl-2,2-dimethyloxazolidine



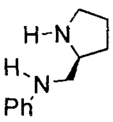
47

Application:
[2+2] Cycloaddition, p. 27.
[3+2] Cycloaddition, p. 116.

Synthesis:
S. Kanemasa, K. Onimura, Tetrahedron 48 (1992) 8631.

6.4.3 1,2 Diamines

(*S*)-2-Anilinomethylpyrrolidine

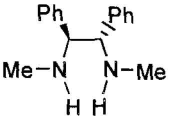


48

Application:
[3+2] Cycloaddition, p. 117, 126.

Synthesis:
T. Mukaiyama, Tetrahedron 37 (1981) 4111.

(*S*,*S*)-(+)-1,2-Bis-*N*-methylamino-1,2-diphenyl-ethane



49

Application:
[3+2] Cycloaddition, p. 117, 126.

Synthesis:
S. Kanemasa, T. Hayashi, J. Tanaka, H. Yamamoto, T. Sakurai, J. Org. Chem. 56 (1991) 4473.
P. Mangeney, F. Grojean, A. Alexakis, J. F. Normant, Tetrahedron Lett. 29 (1988) 2675.

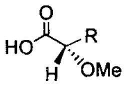
6.5 Carboxylic Acids

D-Amino Acids and Derivatives

Reviews:

R. M. Williams, *Synthesis of Optically Active α-Amino acids*, Organic Chemistry Series Vol. 7, Pergamon, Oxford (1989).
A. Studer, Synthesis (1996) 793.
H. Waldmann, Synlett (1995) 133.
(see, Chapter 6.2.2, p. 156)

O-Methylmandelic acid and Derivatives



R= Ph, *cyclo*-C_6H_{11}

50

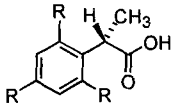
Application:

[4+2] Cycloaddition, p. 61.
Hetero [4+2] Cycloaddition, p. 91.

Synthesis:

M. Oshima, T. Mukaiyama, Chem. Lett. (1987) 377.
T. Raznikiewicz, Acta Chem. Scand. 16 (1962) 1097.
J. Jacobus, M. Raban, K. Mislow, J. Org. Chem. 33 (1968) 1142.
(R)-2-Cyclohexyl-2-hydroxyacetic acid
H. Lettré, H. Barnbeck, H. Staunau, Chem. Ber. 69 (1936) 1594.
K. Freudenberg, F. Brauns, H. Siegel, Chem. Ber. 56 (1923) 193.

2-(2,4,6-Trimethyl-phenyl)-propionic acid



R = H, Me

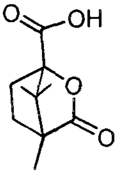
51

Application:

[4+2] Cycloaddition, p. 41.

Synthesis:
F. C. Fuson, D. J. Byers, N. Rabjohn, J. Am. Chem. Soc. 63 (1941) 2639.

(-)-Camphanic acid
4,7,7-Trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxylic acid
[(-)-1-(1*S*,4*R*)-camphanic acid]



52

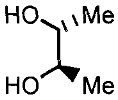
Application:
[4+2] Cycloaddition, p. 59.
Hetero [4+2] Cycloaddition, p. 91.

Synthesis:
D. Kappes, H. Gerlach, Synth. Commun. 20 (1990) 581.
E. Becher, R. Albrecht, K. Bernhard, H. G. W. Leuenberger, H. Mayer, R. K. Müller, W. Schuep, H. P. Wagner, Helv. Chim. Acta 64 (1981) 2419.
J. Golé, Bull. Soc. Chim. Fr. 16 (1949) 894.

6.6 Diols

Reviews:
H. J. Altenbach, *Organic Synthesis Highlights*, VCH, Weinheim (1991) 19.
J. K. Whitesell, Chem. Rev. 89 (1989) 1581.

(*R*,*R*)-2,3-Butanediol

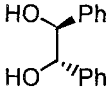


53

Application:
[4+2] Cycloaddition, p. 45.

Synthesis:
K. A. Thaker, N. S. Dave, J. Sci. Ind. Res. B 20 (1961) 329.
(S,S)-2,3-Butandiol
A. Holý, Collect. Czech. Chem. Commun. 47 (1982) 173.
M. Carmack, C. J. Kelly, J. Org. Chem. 33 (1968) 2171.
P. W. Feit, J. Med. Chem. 7 (1964) 14.

1,2-Diphenyl-1,2-dihydroxyethane

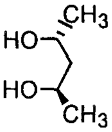


54

Application:
[2+1] Cycloaddition, p. 3.
[4+2] Cycloaddition, p. 45, 64.

Synthesis:
E. N. Jakobsen, I. Markó, W. S. Mungall, G. Schroeder, K. B. Sharpless, J. Am. Chem. Soc. 110 (1988) 1968.
J. S. M. Wai, I. Markó, J. S. Svendsen, M. G. Finn, E. N. Jakobsen, K. B. Sharpless, J. Am. Chem. Soc. 111 (1989) 1123.
B. H. McKee, D. G. Giheany, K. B. Sharpless, Org. Synth. 70 (1992) 47.

(*R*,*R*)-2,4-Pentanediol

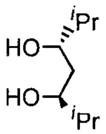


55

Application:
[2+1] Cycloaddition, p. 4.

Synthesis:
Z.-W. Guo, S.-H. Wu, C.-S. Chen, G. Girdaukas, C. J. Sih, J. Am. Chem. Soc. 112 (1990) 4942.
K. Ito, T. Harada, A. Tai, Y. Izumi, Chem. Lett. (1979) 1049.

(*R*,*R*)-2,6-Dimethyl-3,5-heptanediol



56

Application:
[2+1] Cycloaddition, p. 4.

Synthesis:
T. Sugimura, M. Yoshikawa. T. Yoneda, A. Tai, Bull. Chem. Soc. Jpn. 63 (1990) 1080.

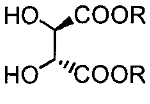
(*R*,*R*)-*trans*-1,2-Cyclohexanediol

57

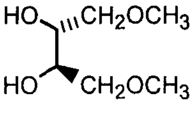
Application:
[2+1] Cycloaddition, p. 4.

Synthesis:
M. Kawashima, A. Hirayama, Chem. Lett. (1991) 763.
R. Seemayer, M. P. Schneider, J. Chem. Soc. Chem. Commun. (1991) 49.
N. Iranpoor, F. S. Zardaloo, Synth. Commun. 24 (1994) 1959.
(S,S)-trans-Cyclohexane-1,2-diol
D. H. G. Crout, V. S. B. Gaudet, K. Laumen, M. P. Schneider, J. Chem. Soc. Chem. Commun. (1986) 808.

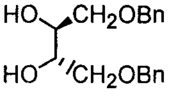
Dialkyl-tartrates (58)
1,4-Dialkoxy-2,3-butanediols (59) and (60)
N,*N*,*N'*,*N'*-Tetramethyl-tartramide (61)



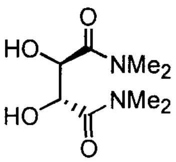
58



59



60



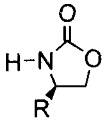
61

Application:
[2+1] Cycloaddition, p. 2, 3, 5.
[2+2] Cycloaddition, p. 23.
[4+2] Cycloaddition, p. 45.

Synthesis:
D. Seebach, H.-O. Kalinowski, B. Bastani, G. Crass, H. Daum, H. Dörr, N. P. DuPreez, V. Ehrig, W. Langer, C. Nüssler, H.-A. Oei, M. Schmidt, Helv. Chim. Acta 60 (1977) 301.
M. Schmidt, R. Amstutz, G. Crass, D. Seebach, Chem. Ber. 113 (1980) 1691.
N. Ando, Y. Yamamoto, J. Oda, Y. Inouye, Synthesis (1978) 688.

6.7 Oxazolidinones

4-Substituted 2-Oxazolidinones (62)



62

Reviews:
D. J. Ager, I. Prakash, D. R. Schaad, Aldrichimica Acta 30 (1997) 3.
J. I. G. Cadogan, A. A. Doyle, I. Gosney, P. K. G. Hodgson, P. Thorburn, Enantiomer 2 (1997) 81.

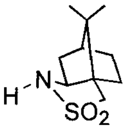
Application:
[2+2] Cycloaddition, p. 14, 26, 27.
[4+2] Cycloaddition, p. 55, 65, 66.
Hetero [4+2] Cycloaddition, p. 91, 92, 105, 106.
[3+2] Cycloaddition, p. 115, 122.

Synthesis:
Oxazolidinones are readily prepared from amino alcohols ((1*R*,2*S*)-norephedrine, (*S*)-valinol, (*S*)-phenylalaninol) and a carbondioxide equivalent, such as phosgene or diethylcarbonate.
D. A. Evans, K. T. Chapman, J. Bisha, J. Am. Chem. Soc. 110 (1988) 1238 and references cited.
D. A. Evans, A. E. Weber, J. Am. Chem. Soc. 108 (1986) 6757.
W. H. Pirkle, K. A. Simmons, J. Org. Chem. 48 (1983) 2520.

6.8 Sultams

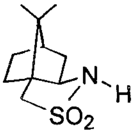
Camphorsultam (63)

(1*R*,2*S*)-(+)-Camphorsultam



(+)-Camphorsultam

(1*S*,2*R*)-(-)-Camphorsultam

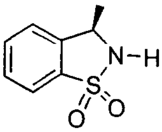


(-)-Camphorsultam

Application:
[2+1] Cycloaddition, p. 10.
[4+2] Cycloaddition, p. 56, 65, 66.
Hetero [4+2] Cycloaddition, p. 74, 87.
[3+2] Cycloaddition, p. 115, 122, 124, 128, 129, 135, 138.

Synthesis:
M. Vanderwalle, J. Van der Eycken, W. Oppolzer, C. Vullioud, Tetrahedron 42 (1986) 4035.
M. C. Weismiller, J. C. Towson, F. A. Davis, Org. Synth. 69 (1990) 154.
J. C. Towson, M. C. Weismiller, G. S. Lal, A. C. Sheppard, F. A. Davis, Org. Synth. 69 (1990) 158.

(*R*)-2,3-Dihydro-3-methylbenzoisothiazole-1,1-dioxide



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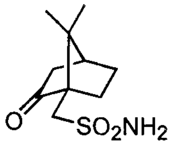
Application:
[4+2] Cycloaddition, p. 56.
[3+2] Cycloaddition, p. 115.

Synthesis:
W. Oppolzer, M. Wills, C. Starkemann, G. Bernardinelli, Tetrahedron Lett. 31 (1990) 4117.
F. A. Davis, J. C. Towson, D. B. Vashi, R. Thimma-Reddy, J. P. McCauley Jr., M. E. Harakal, D. J. Gosciniak, J. Org. Chem. 55 (1990) 1254.

Camphor-10-sulfonamide

(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide



65

Application:
Hetero [4+2] Cycloaddition, p. 78, 82.

Synthesis:
R. Cremlyn, M. Bartlett, J. Lloyd, Phosphorus Sulfur 40 (1988) 91.
M. Vanderwalle, J. Van der Eycken, W. Oppolzer, C. Vullioud, Tetrahedron 42 (1986) 4035.
F. A. Davis, J. C. Towson, M. C. Weismiller, S. Lal, P. J. Carroll, J. Am. Chem. Soc. 110 (1988) 8477.
F. A. Davis, R. H. Jenkins, S. B. Awad, O. D. Stringer, W. H. Watson, J. Galloy, J. Am. Chem. Soc. 104 (1982) 5412.

6.9 Miscellaneous Compounds

6.9.1 Sulfinates and Sulfoxides

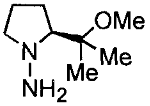
Application:
[2+1] Cycloaddition, p. 8.
[4+2] Cycloaddition, p. 37, 38, 45, 46, 51, 59, 60, 62.
Hetero [4+2] Cycloaddition, p. 88.
[3+2] Cycloaddition, p. 118, 123, 127, 130.

Synthesis:
J. E. Mulvaney, R. A. Ottaviani, J. Polym. Sci. 8 (1970) 2293.
D. J. Abbot, S. Colonna, C. J. M. Stirling, J. Chem. Soc. Perkin Trans 1 (1976) 492.
M. A. Brimble, B. R. Davis, Tetrahedron 41 (1985) 4965.
M. C. Carreño, J. L. G. Ruano, A. Urbano, Tetrahedron Lett. 30 (1989) 4003.
Y. Arai, Y. Hayashi, M. Yamamoto, H. Takeyama, T. Koizumi, J. Chem. Soc. Perkin Trans. 1 (1988) 3133.
C. R. Johnson, C. W. Schroeck, J. Am. Chem. Soc. 95 (1973) 7418.

4-Methylbenzenesulfinic acid
M. Hulce, J. P. Mallamo, L. L. Frye, T. P. Kogan, G. H. Posner, Org. Synth. 64 (1985) 196.
M. Mikolajczik, J. Drabowicz, B. Bujnicki, J. Chem. Soc. Chem. Commun. (1976) 568.
K. Hiroi, R. Kitayama, S. Sato, Synthesis (1983) 1040.

6.9.2 Hydrazines

2-(1-Methoxy-1-methylethyl)-1-pyrrolidinamine



66

Application:
Hetero [4+2] Cycloaddition, p. 100.

Synthesis:
D. Enders, H. Eichenauer, R. Pieter, Chem. Ber. 112 (1979) 3703.

Chiral Auxiliaries in Cycloadditions
Karola Rück-Braun, Horst Kunz

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Karola Rück-Braun, Horst Kunz

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ISBN 3-527-29386-8

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