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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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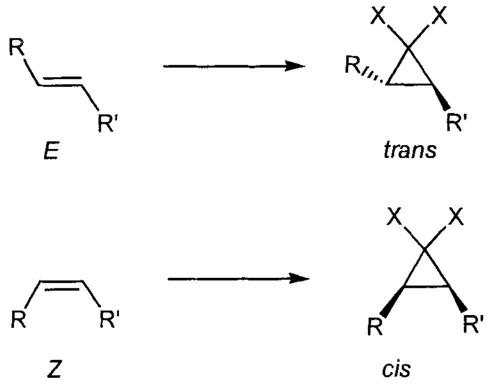
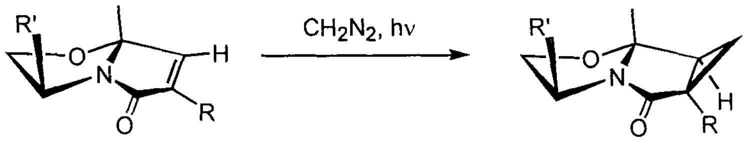
1 [2+1] Cycloadditions (Cyclopropanations)

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]

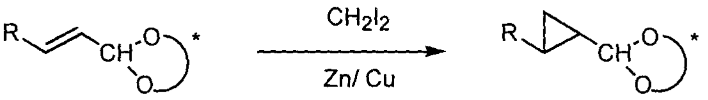


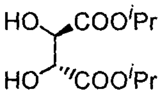
1.1 Simmons-Smith Reactions

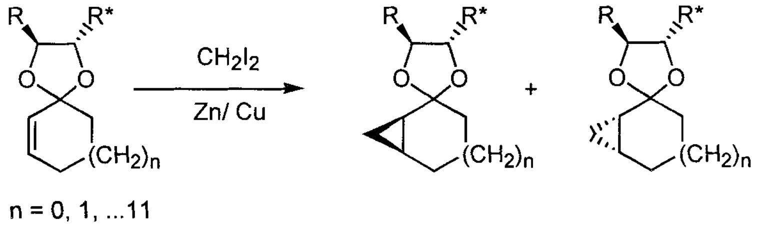
Cyclopropanes are efficiently obtained from alkenes by Simmons-Smith reaction applying CH_2I_2/Zn-Cu couple or CH_2I_2/Et_2Zn as reagents.[6,11] A variety of compounds bearing a chiral moiety have been studied, as for example α,β-unsaturated acetals and oxazolidines, enolethers, allylic alcohols, alkenylboronic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

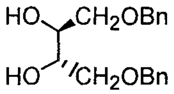
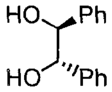
Chiral Acetals and Ketals

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.



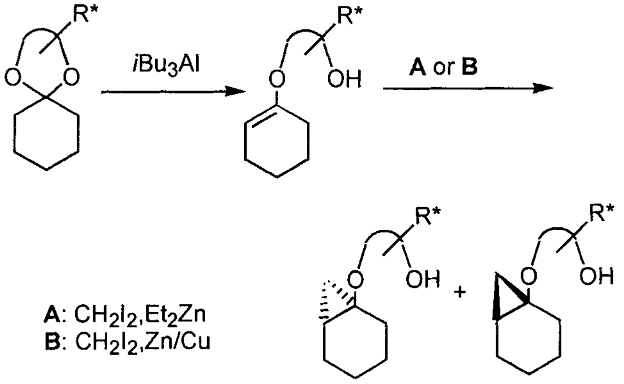
auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**58**	87-94%		80-95%%	13-15

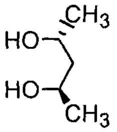
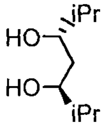


auxiliary	no.	d.r. or *de*	*ee*	yield	ref.
	**60**	67:33-95:5		37-98%	16,17
	**54**	> 93:7		66-90%	18

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]

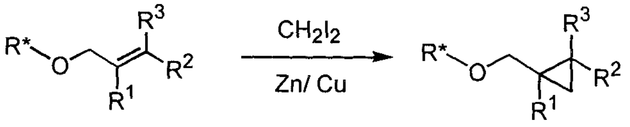


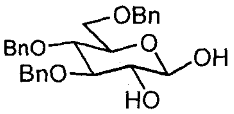
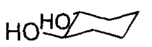
auxiliary	no.	method	d.r. or *de*	yield	ref.
	**55**		14-95%	56-70%	19
	**56**	**A**	95-99%	59-86%	19
		B	53-69%	81-94%	

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

Chiral Allylethers

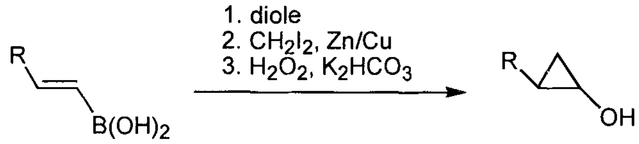
Besides monoallylethers of chiral alcohols, allylglycosides bearing a free alcohol functionality have been applied in asymmetric syntheses of enantiomerically pure cyclopropanemethanols with success.[11] The cleavage of the chiral carbohydrate-derived auxiliary was achieved by treatment of the cycloadducts with a. Tf$_2$O, pyridine; b. DMF/H$_2$O, pyridine, whereas for the compounds derived from **57** a. Tf$_2$O, Bu$_4$NI 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.



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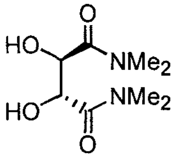
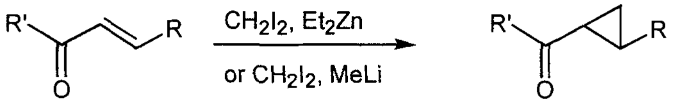
	**61**	89-94%	46-48%	21

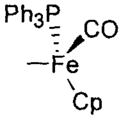
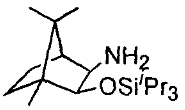
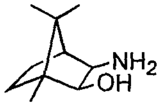
Chiral α,β-Unsaturated Carbonyl Compounds

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.

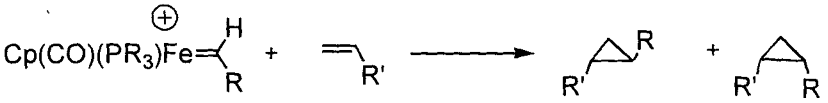


R' = R*, OR*, NRR*

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]

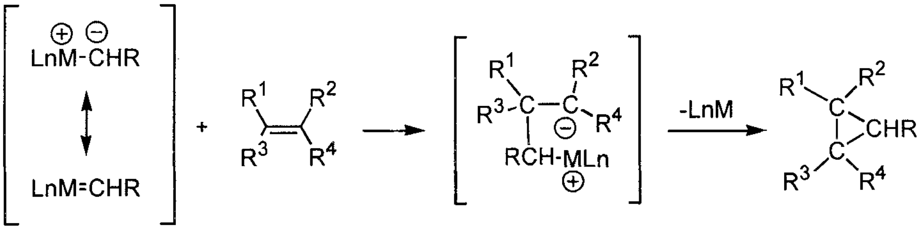


trans : *cis* = 3.5:1

83% *ee*, 75%

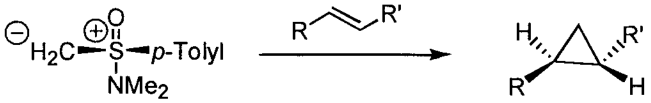
1.3 Cyclopropanations with Ylide Reagents

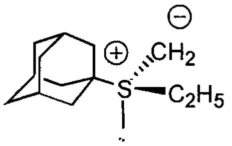
Asymmetric ylide cyclopropanations have been studied since 1960 and have been intensively discussed and documented in the literature.[26] Besides chiral aminosulfoxonium ylides, chiral sulfonium as well as chiral sulfoxonium ylides have been examined in reagent-controlled asymmetric cyclopropanations.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



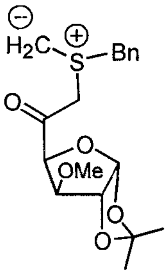
1.3.1 Chiral Ylide Reagents

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.

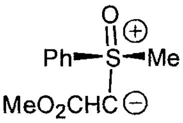




A



B



C