Organic Synthesis Highlights IV

Edited by
Hans-Günther Schmalz

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Preface

During the past century, the world has changed to an unprecedented extent, and the development of the chemical sciences has greatly contributed to this change. The ability of chemists to synthesize complex organic molecules such as dyes, drugs, fragrances and crop protection agents is largely responsible for the high standard of living we enjoy today. Moreover, synthesis as a key discipline is contributing to the development of modern life sciences and materials technology. However, while the power of synthesis has led to remarkable achievements, the technology and art of organic synthesis is still far from being fully developed. Many problems remain unsolved concerning, for instance, the efficiency and atom-economy of syntheses. Organic synthesis continues to offer multifarious academic and technological challenges, and a tremendous amount of research is carried out worlwide in this field.

This fourth volume of Organic Synthesis Highlights (OSH) comprises a collection of more than 40 articles reflecting some more recent developments and achievements of organic synthesis. About half of the contributions have their origin in the review section "Synthese im Blickpunkt" in *Nachrichten aus Chemie, Technik und Laboratorium* (1994–1998), the members' journal of the GDCh; most of the others have been selected from the "Highlights" of *Angewandte Chemie* (1997–1998). The first half of the present volume concerns synthetic methodology, with emphasis on stereoselective synthesis, transition metal organometallic methods, and enantioselective catalysis. The second part focuses on applications in total synthesis of natural products and non-natural compounds and materials. In addition, a few articles reflect the recent renaissance of solid-phase synthesis and the growing importance of combinatorial chemistry.

The articles taken from "Synthese im Blickpunkt" have all been carefully updated and translated by the authors (U. Koert, O. Reiser, M. Reggelin, C. Rück-Braun). I would like to express special thanks to these colleagues and their co-workers. I am also grateful to all the other authors for their excellent and up-to-date contributions. I also have to thank the team at Wiley-VCH, especially Dr. A. Eckerle, Dr. G. Walter, Dr. A. Kessinger and P. Biel for their excellent, professional support and their patience with the editor.

I hope this new volume will find as much acceptance in the scientific community as the first three volumes of this series and will help to stimulate the interest of, in particular, young chemists in the field of synthesis.

Cologne, February 2000

Hans-Günther Schmalz

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Part I. Synthetic Methods

A. New Methods in Stereoselective Synthesis

Stereocontrolled Simmons-Smith Cyclopropanation

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The cyclopropyl subunit is a frequent structural element in natural and non-natural products. In FR-900848 (**1**) [1], a natural product with fungicide bioactivity even five cyclopropane rings are found, which make its structure remarkable and its synthesis a challenging issue. Other representatives of naturally occurring cyclopropanated compounds are *allo*-coronamic acid (**2**) [2] and *cis*-chrysanthemic acid (**3**) [3]. Among the non-natural products containing cyclopropane rings the perspirocyclopropanated [3]-rotaxane (**4**) [4] and the trifunctional fullerene (**5**) [5] are worth mentioning.

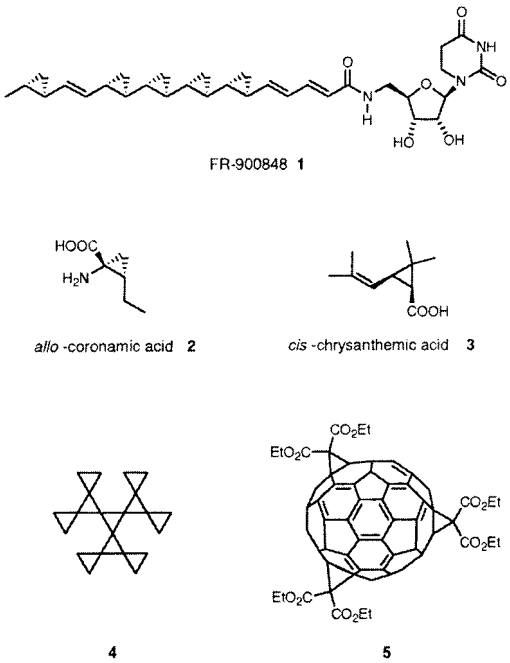
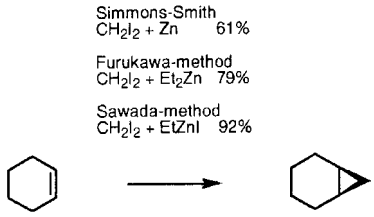


Figure 1

From the multitude of synthetic work in the field of cyclopropanation, we will focus on the asymmetric synthesis of cyclopropanes. Besides the known stereocontrolled addition of diazo-compounds to olefins (diazo-method) [6] the stereocontrolled Simmons-Smith cyclopropanation has received significant attention in the last ten years. The latter will be discussed further.

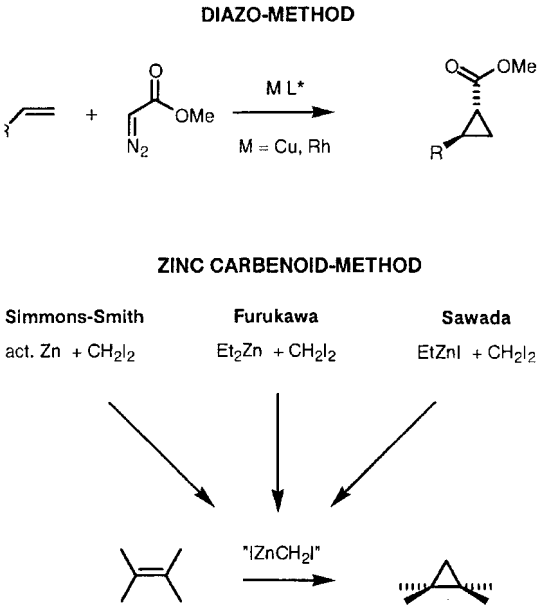
The reaction of activated zinc and CH_2I_2 results in the formation of a zinc carbenoid reagent "$IZnCH_2I$", which, originally introduced to literature by Simmons and Smith, converts alkenes into cyclopropanes [7]. For a successful reaction the activation of zinc metal is essential. Apart from the originally applied Cu [7] by Simmons and Smith the activation may be accomplished using Ag [8], $TiCl_4$ [9] or $TMSCl/BrCH_2$-CH_2Br (Knochel-zinc) [10]. Highly activated zinc can also be obtained by the reduction of zinc salts (Rieke-zinc [11], Fürstner-zinc [12]). Concerning commercially available zinc, the purity is of great importance. Electrolytically prepared zinc is highly pure, but pyrometallurgically made zinc, which is obtained by distillation, contains traces of lead, which can inhibit the cyclopropanation reaction [13].

Despite the various methods for activation of zinc metal, the Simmons-Smith reaction remains a heterogeneous reaction, holding all known preparative disadvantages. Hence, many efforts have been directed towards the development of homogeneous reaction conditions. Among others, two particularly successful methods will be highlighted here: the Furukawa-procedure ($Et_2Zn + CH_2I_2$) [14] and the Sawada-procedure ($EtZnI + CH_2I_2$) [15] [Eq. (1)].



(1)

Another approach in the preparation of zinc carbenoids has been developed by Wittig [16]. It involves the reaction of diazomethane with a Zn(II) salt, but the delicate preparation of diazo-compounds has hindered the wide spread preparative application so far (scheme 1).



Scheme 1. Diazo method and zinc carbenoid method for cyclopropanation

The advantages of the homogeneous procedure are evident: mild conditions and low temperatures cause increased compatibility with other functional groups. The control of stoichiometry is simplified compared to the heterogeneous case by the application of an organo-zinc solution of known molarity. Furthermore, the homogeneous reaction also proceeds in non-coordinating solvents, which is of great importance especially for asymmetric synthesis. Finally, compared to a heterogeneous reaction the homogeneous procedures afford higher yields in most cases.

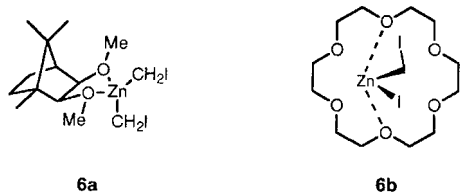
Although the Simmons-Smith cyclopropanation has attracted increased attention during recent years, the exact structure of the cyclopropanating reagent is still uncertain. NMR-spectroscopic investigations revealed a Schlenk equilibrium between $IZnCH_2I$ and ICH_2ZnCH_2I [Eq. (2)] [15].

$$2\ IZnCH_2I \rightleftharpoons ICH_2ZnCH_2I + ZnI_2 \quad (2)$$

Denmark et al. studied the effect of zinc iodide on the catalytic, enantioselective cyclopropanation of allylic alcohols with bis(iodomethyl)-zinc as the reagent and a bismethanesulfonamide as the catalyst [17]. They found significant rate enhancement and an increased enantiomeric excess of the product cyclopropane upon addition of 1 equivalent zinc iodide. Their studies and spectroscopic investigations showed that the Schlenk equilibrium appears to lie far on the left ($IZnCH_2I$). Charette et al. used low temperature ^{13}C-NMR spectroscopy to differentiate several zinc-carbenoid species [18]. They also found evidence that in the presence of zinc iodide, bis(iodomethyl)zinc is rapidly converted to (iodomethyl)zinc iodide. Solid-state structures of (halomethyl)zinc species have been described by Denmark for a bis(iodomethyl)zinc ether complex (**6a**) [19] and Charette for an (iodomethyl)zinc iodide as a complex with 18-crown-6 (**6b**) [20] (Fig. 2).

However, future work will show whether the cyclopropanating species actually is $IZnCH_2I$ or ICH_2ZnCH_2I.

Regarding the addition of a carbenoid **7** to an olefin **8**, resulting in the formation of cyclopropane **9**, theoretical calculations point towards a concerted mechanism involving a transition state **10** (Scheme 2) [21]. For a better understanding of the transition state of cyclopropanation with zinc carbenoids a reflection on the well-studied lithium carbenoids is profitable. Hoffmann et al.

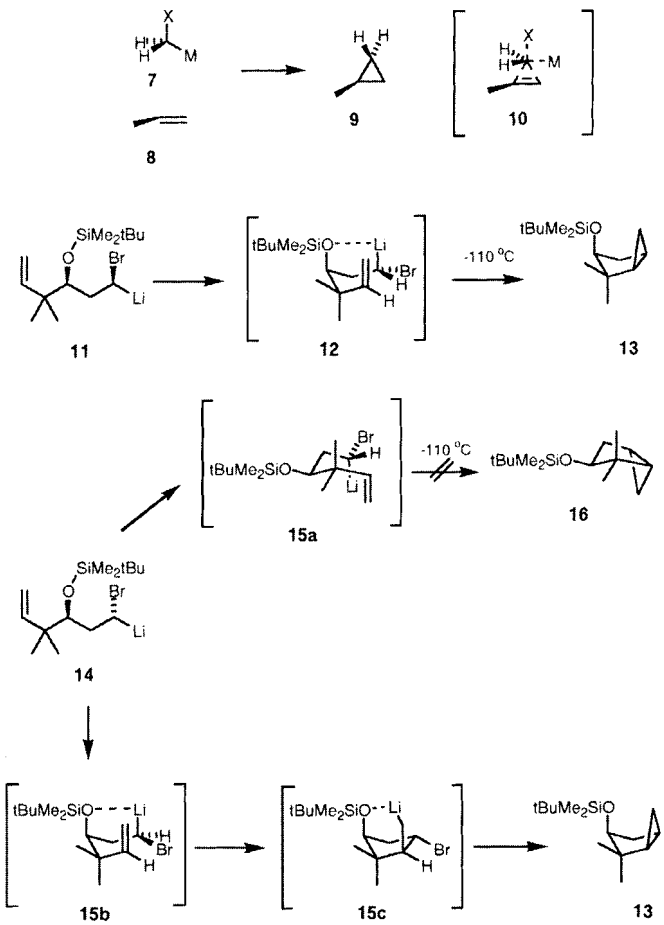


6a **6b**

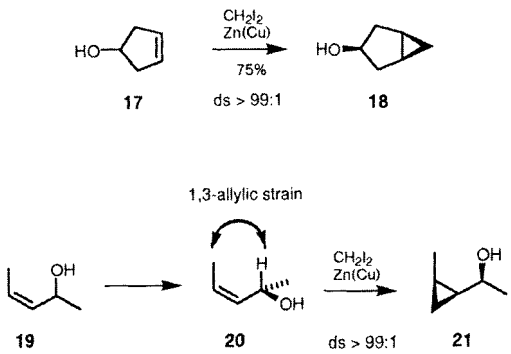
Figure 2

studied the stereochemical course of the intramolecular cyclopropanation for the carbenoids **11** and **12**, utilizing an internal stereocentre as a reference (Scheme 2) [23].

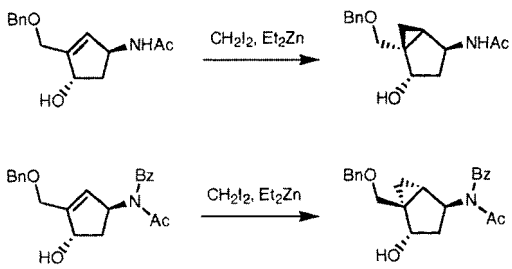
The stereochemically defined lithium carbenoid **11** forms the bicyclus **13** by intramolecular cyclopropanation even at −110 °C. In contrast, no conversion of the epimeric lithium carbenoid **14** into diastereomeric bicyclus **16** is observed under similar conditions. These results are explained on the basis of the transition state structures **12** and **15a/b**. Structure **12** allows complexation of the lithium atom by ether oxygen. This leads to activation of the carbenoid and accelerates the cyclopropanation (**11** → **12** → **13**) by a transition state choreography of type **10**. In structure **15a** the ether group is in equatorial position, which does not allow the complexation of the lithium atom. Accordingly, this carbenoid is less reactive and cyclopropanation does not proceed at −110 °C. Hoffmann et al. suggest that for this case (**14** → **15b** → **15c** → **13**) the carbolithiation competes with the concerted mechanism. In theoretical studies on the cyclopropanation of ethylene with lithium and zinc carbenoids Nakamura et al. found two competing pathways: methylene transfer and carbometallation [22]. For the lithium carbenoid, both pathways have similar activation energies and may compete in cyclopropanation, which is consistent with the results of Hoffmann's experiment [23]. However, for the zinc carbenoid, methylene transfer is found to be favored, because of a much lower activation energy compared to the carbometallation.



Scheme 2. Mechanistic studies on carbenoid mediated cyclopropanation



Scheme 3. The stereodirecting influence of OH-groups in cyclic and acyclic systems



Scheme 4. The stereodirecting influence of NH-groups

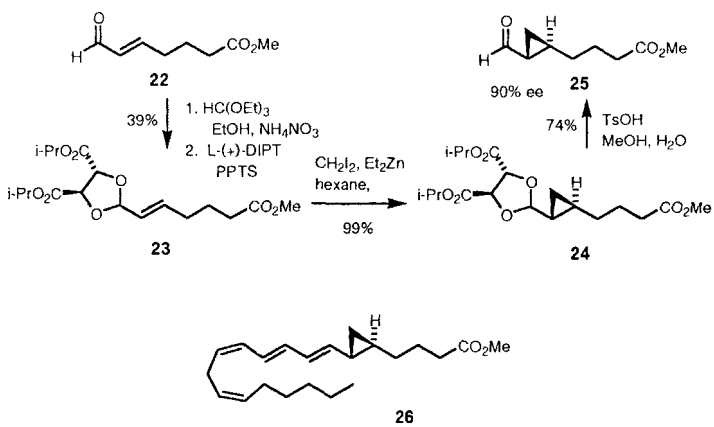
As found for lithium carbenoids, an activating and directing influence of intramolecular O-donators is also known for zinc carbenoids [21]. Alcohol-groups in cyclic systems seem to have a strong syn-directing influence (**17** → **18**) (Scheme 3) [24]. High stereocontrol in acyclic systems is achieved only if conformational control restricts the rotation of single bonds. This is found for example in the cyclopropanation reaction (**19** → **21**) (Scheme 3) [25]. Herein, due to 1,3-allylic strain, the three-dimensional arrangement of the directing OH-groups in relation to the double bond is fixed.

A directing effect has also been found for intramolecular NH groups. When an OH and an NH group are in competing allylic positions, the cyclopropanation is completely directed by the NH groups. The directing influence by the OH group only comes forward after protection of the amide hydrogen (Scheme 4) [26].

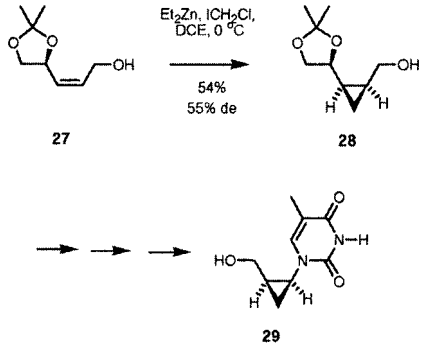
For the enantioselective synthesis of cyclopropanes using zinc carbenoids, two different approaches are possible: first, by using a covalent bound chiral auxiliary or, second, by application of a chiral catalyst.

Numerous chiral auxiliaries are known today. For instance, acetals derived from tartaric acid enable the preparation of enantiomerically pure cyclopropanated aldehydes (**22** → **23** → **24** → **25**) (Scheme 5). Aldehyde **25** is a key intermediate in the synthesis of leucotriene inhibitor **26** [27].

The chiral acetonide **27** has been stereoselectively transformed into **28** by cyclopropanation. This reaction serves as the key step in the synthesis of **29** (Scheme 6) [28]. Cyclopropanated nucleosides such as **29** are interesting drug candidates for HIV therapy.

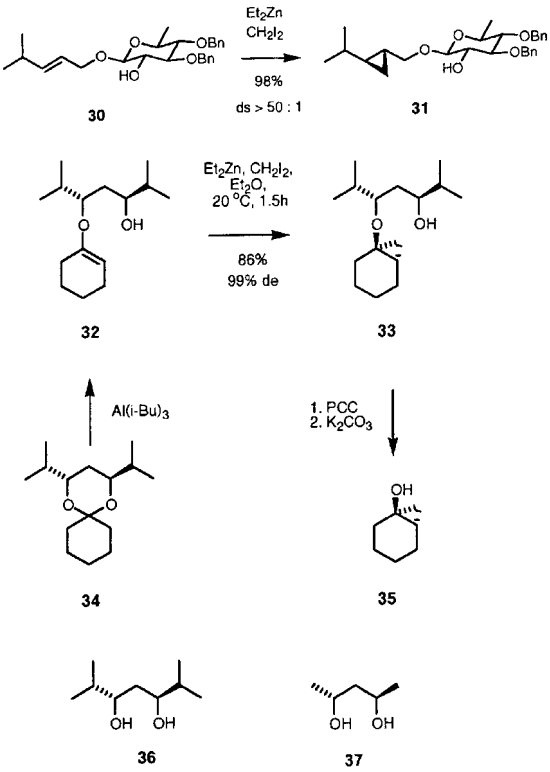


Scheme 5. Chiral acetals serving as covalent-bound auxiliaries



Scheme 6. Stereocontrolled cyclopropanation in the synthesis of cyclopropanated nucleosides

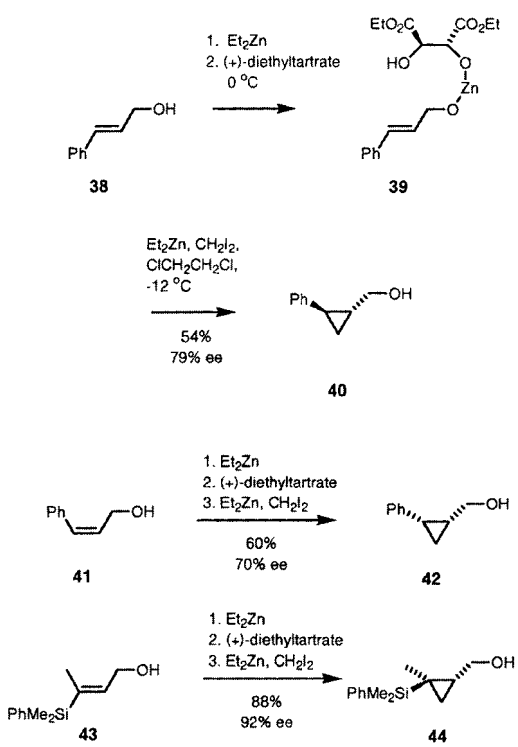
Carbohydrates have been used as chiral auxiliaries in cyclopropanation reactions using zinc carbenoids. The conversion of acetal **30** affords the cyclopropanated compound **31** with high diastereoselectivity [Eq. (3)] [29].



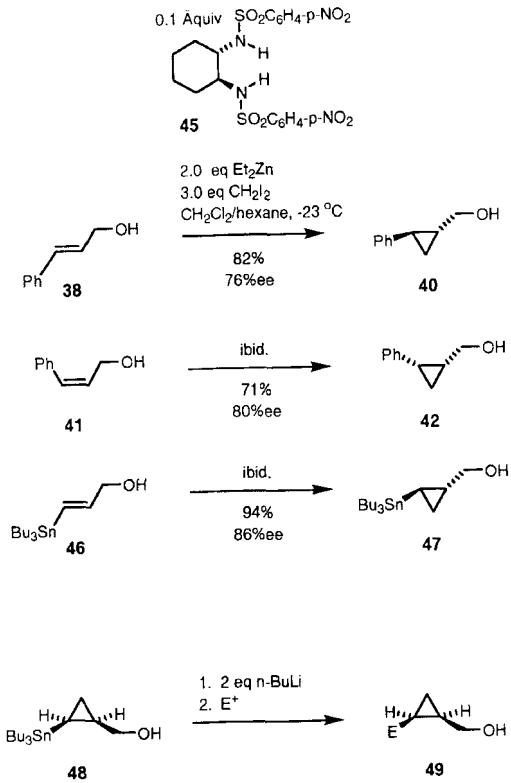
Scheme 7. Stereocontrolled cyclopropanation of enol ethers

Enol ethers may also be cyclopropanated using zinc carbenoids stereoselectively. Furukawa cyclopropanation of enol ether **32** proceeds with high stereoselection, and the obtained cyclopropyl ether **33** can be easily transformed into the enantiomerically pure cyclopropyl alcohol **35** [30]. In this case, high stereoselectivity is achieved by employing the chiral diol **36**, which is not commercially available. Using the commercially available enantiopure diol **37**, the level of stereoselectivity is significantly lower (Scheme 7).

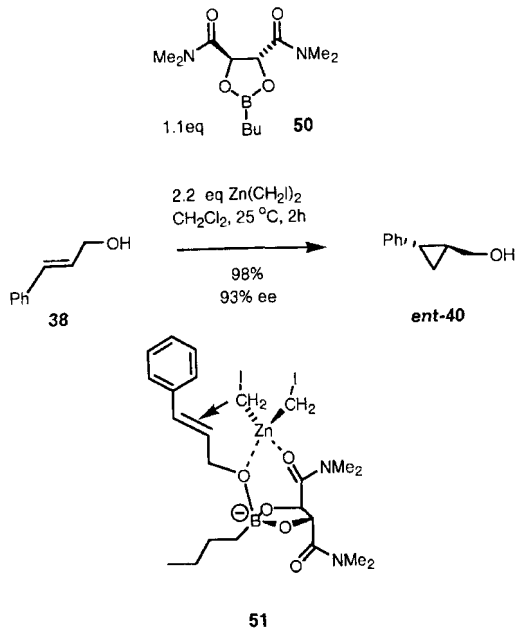
Asymmetric Simmons-Smith cyclopropanation using no covalent-bound auxiliary but a chiral catalyst have only been successful with allylic alcohols so far. Fujisawa had shown that allylic alcohols such as **38** are converted into the corresponding alcoholate by Et_2Zn (1.1 equivalents) first [31]. Addition of diethyltartrate (1.1 equivalents) results in the formation of an intermediate **39**, which is cyclopropanated under Furukawa conditions (Et_2Zn + CH_2I_2) to give compound



Scheme 8. Asymmetric cyclopropanation according to Fujisawa



Scheme 9. Asymmetric cyclopropanation according to Kobayashi



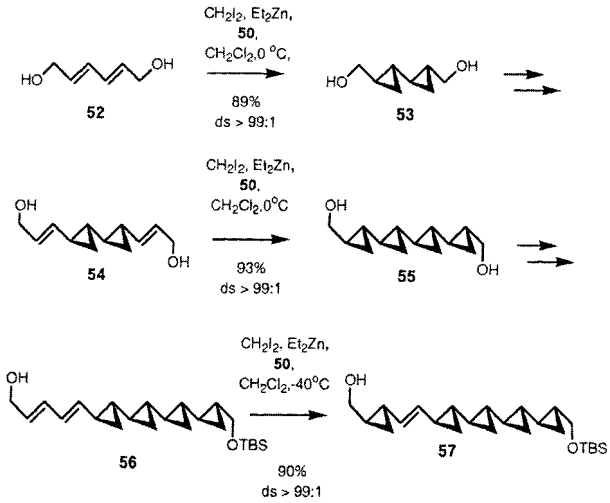
Scheme 10. Asymmetric cyclopropanation according to Charette

40. No significant influence of the double bond geometry on the stereoselectivity was found. Both stereoisomers the *E*-allylic alcohol **38** and the corresponding *Z*-configured compound **41** are converted with similar enantioselectivity (ee 70–80 %). Using silyl-substituted olefins an enantiomeric excess above 90 % has been reached (Scheme 8).

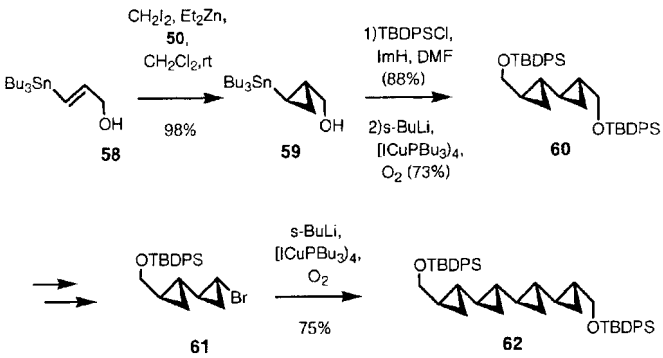
Kobayashi et al. successfully performed asymmetric cyclopropanation using substoichiometric amounts of catalyst **45** (Scheme 9). [32] The levels of enantioselectivity achieved are in the 70–90 % range. Both, *E*- and *Z*-allylic alcohols are readily converted. Vinylstannanes **46** are also appropriate substrates. The resulting enantiomerically pure cyclopropanated stannanes hold great synthetic potential [33]. Thus, the cyclopropanated stannane **48** can be converted into the substituted cyclopropane **49** after successful tin-lithium exchange and electrophilic substitution.

In an extensive study of the effect of experimental variables on the rate and selectivity of this reaction, Denmark et al. found the independent formation of ethylzinc alkoxide and bis(iodomethyl)zinc to be crucial for effective cyclopropanation [34]. They also detected an autocatalytic behavior of the reaction due to the generation of zinc iodide.

High enantioselectivity (> 90 %) and excellent yields are observed employing a method developed by Charette et al. (Scheme 10). [35] Herein, a chiral, amphoteric, bifunctional boron acid ester **50** serves as the catalyst. For example, allylic alcohol **38** can be efficiently transformed into compound **ent-40** with high enantioselectivity (ee 93 %). Unfortunately, stoichiometric amounts of **50** are necessary. With an acidic binding site at boron and a basic binding site at the carbonyl group, a transition state **51** may be reasonable. The alcoholate of the allylic alcohol and the boron acid ester form an ate-complex where the zinc carbenoid reagent now coordinates at the alcoholate-oxygen and at one of the carbonyl groups. Attack on the double bond proceeds from the direction indicated by the arrow (Scheme 10)



Scheme 11. Construction of the cyclopropane rings of FR-900848 (**1**) according to Barrett



Scheme 12. Construction of the cyclopropane rings of FR-900848 (**1**) according to Falck

[35]. The formation of ate-complexes by those tailor-made ligands of type **50** was proven by X-ray crystallographic investigations [36].

With regard to the synthesis of the oligo-cyclopropane natural product FR-900848 (**1**) multiple and consecutive cyclopropanation reactions using zinc carbenoids have been applied. Thus, in the total synthesis of **1** by Barrett et al. the Furukawa-procedure was used for the conversion of **52** into the biscyclopropane **53** (Scheme 11). [37] After bidirectional elongation of the molecule, another double cyclopropanation of diene **54** using Charette's catalyst gave tetracyclopropane **55** in 93 % yield as one stereoisomer only. Finally, the olefin **56** is cyclopropanated at −40 °C to yield the desired pentacyclopropane alcohol **57**. Thus, all five cyclopropane rings of FR-900848 (**1**) are introduced with Charette's modified Furukawa method.

In the total synthesis of FR-900848 (**1**) published by Falck et al. a cyclopropane coupling strategy was successfully applied for the preparation of the tetracyclopropane backbone (Scheme 12) [38].

Summary

The examples mentioned above illustrate the progress in the field of stereocontrolled cyclopropanation. Nowadays, the asymmetric Simmons Smith cyclopropanation may well be mentioned in the line with other asymmetric reactions like epoxidation or dihydroxylation. High enantioselectivity and diastereoselectivity can be

achieved applying chiral catalysts. Unfortunately, in most cases only allylic alcohols are successfully cyclopropanated using a chiral catalyst in equimolar amounts. Further work upon these problems has to be done and newly developed methods regarding the usage of substoichiometric amounts of the chiral catalyst and the application to other systems than allylic alcohols is to be expected soon. Still, great progress has been achieved so far, which is nicely represented in the recently published total syntheses of FR-900848 (**1**).

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Oppolzer Sultams

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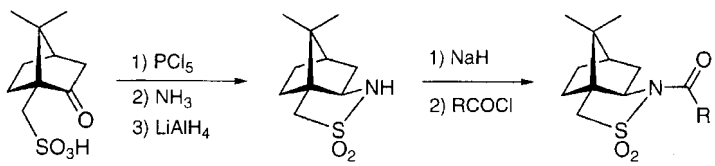
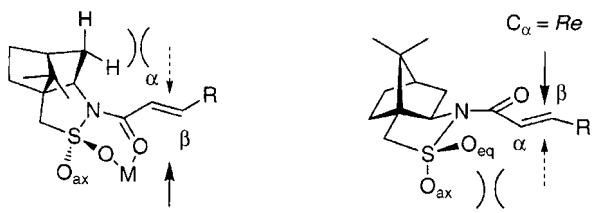
On March 15, 1996, Wolfgang Oppolzer, Professor at the University of Geneva, Switzerland, died. Of his numerous important contributions to organic synthesis, the sultams, derived from campher sulfonic acid, have found widespread application especially as chiral auxiliaries.

Camphor-10-sulfonic acid (**1**) is available in large quantities in both enantiomeric forms. In only 3 steps the cyclic sulfonamide **2** (sultam) can be synthesized, which can be acylated with acid chlorides after deprotonation with sodium hydride (Scheme 1) [1, 2]. The resulting amides **3** are considerable more reactive towards nucleophiles than the corresponding carboxylic esters and the α,β-unsaturated derivatives undergo, with excellent selectivities, Diels-Alder reactions or Michael additions under mild conditions. Almost all resulting *N*-acyl derivatives are stable and can be purified by crystallization. Moreover, diastereomeric mixtures can be enriched this way. The chiral auxiliary can be cleaved under mild conditions, without erosion of the induced chirality, by saponification or reduction and subsequently reisolated in high yields and purity [3, 4].

One of the most notable properties of sultam-modified substrates is that they undergo highly selective reactions in Lewis-acid-catalyzed as well as in thermal processes. There are a number of investigations into the basic selection mechanisms of the sultam auxiliary [5], which were carried out mainly by the groups of W. Oppolzer and D. Curran. In summary, the following model has arisen, which is described here giving the



(*R*)-**1** (*R*)-**2** (*R*)-**3**



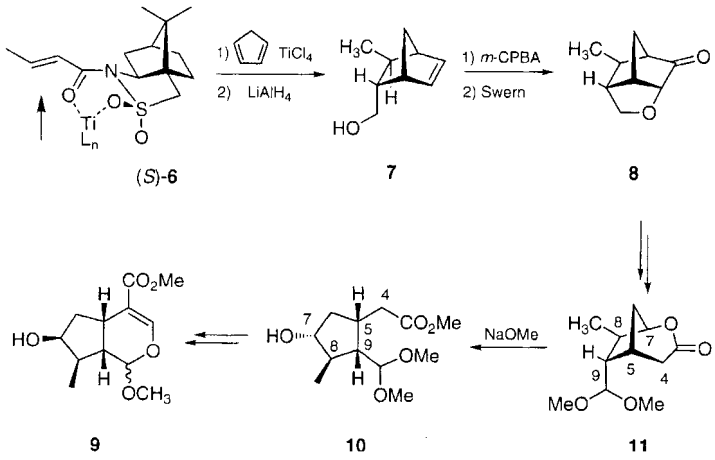
4 **5**

Scheme 1

example of the acryl sultams **4** and **5**. It has to be noted that the following discussion relies on the assumption that the conformations of the ground states are similar to the conformations of the transition states. For a side-selective reaction with the C-C double bond three conditions have to be fulfilled:

- The reactive conformation of the possible rotamers (rotation around the OC–CC bond) has to be unambiguous. Of the two possible planar conformations, which allow conjugation with the π-systems, the *s-cis*-orientation of C=O/C_α=C_β is favored based on steric reasons (O < NR_2, analogously to the well-known fact that (*Z*)-enolates of amides are more stable than (*E*)-enolates).
- The orientation of the carbonyl group has to be unambiguous, which can be parallel or antiparallel to the nitrogen-sulfur bond. Other orientations are energetically less favored because of the missing mesomeric stabilization with the amide nitrogen.
- In the most favored conformation, one side of the double bond has to be effectively blocked by the chiral auxiliary to allow an unambiguous attack of the reagent. By choosing the reaction conditions appropriately, the orientation of the carbonyl group can be influenced. Addition of a Lewis acid with *two* open coordination sites (e.g. $TiCl_4$ or $EtAlCl_2$) results in the formation of a chelate **4**. It is important to note that the two oxygen atoms connected to sulfur are *not equivalent* but that one is positioned pseudo-axial and the other pseudo-equatorial in the five-membered ring. As X-ray structure analyses show [6], the Lewis acid coordinates selectively with the equatorial oxygen atom, since this way an almost planar chelate is formed allowing one to preserve the conjugation of the π-system. In **4**, the upper side of the double bond is blocked by the camphor structure, and the attack has consequently to take place from the lower side of the molecule (chelate model). In the absence of Lewis acids or with Lewis acids having only *one* free coordination site (e.g. BF_3) no chelation is possible. Therefore, the *anti*-position of C=O and NSO_2, as shown in **5**, is favored based on steric and in particular stereoelectronic reasons (minimization of the dipole moment). In this conformation the camphor structure is too far away from the double bond to shield it effectively. However, the axially positioned oxygen atom of the SO_2 group can now take over that role, so that attack occurs mainly from the top side. Therefore, in Lewis-acid-catalyzed as well as in thermal reactions the same stereoselectivity is induced according to that model.

The direction of the induction that is shown in the following examples can be understood in almost all cases with the model described above. Only typical examples of different reaction types can be given; to comprehensively cover the vast number of applications of the sultams is beyond the scope of this article.



Scheme 2

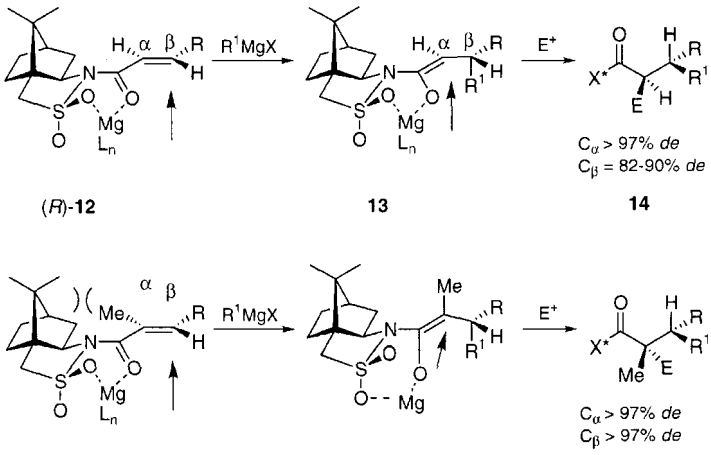
Diels-Alder Reactions

Sultam-modified acrylates undergo [4 + 2]-cycloadditions with 1,3-dienes with excellent *endo*- and side-selectivity in the presence of $EtAlCl_2$ or $TiCl_4$ [7–9]. This feature could be used for an effective synthesis of the loganin-aglycon **9** (Scheme 2) [10]:

The Diels-Alder reaction between cyclopentadiene and the crotylsultam (*S*)-**6** and the subsequent reductive cleavage of the auxiliary gave rise to **7** in diastereo- and enantiomerically pure form, in which already three stereocenters (C5, C8 and C9) have the right configuration for the final product. Especially elegant is the subsequent regioselective opening of the norbornene structure: epoxidation with concurrent intramolecular epoxide opening of **7** followed by oxidation leads to **8**. After reductive opening of the tetrahydrofuran ring and oxidation/ketalization of the resulting CH_2–OH group at C9, the breaking point into the norbornane structure is introduced by a regioselective Baeyer-Villiger oxidation of the more highly substituted C–C bond leading to **11**. Saponification of the lactone resulted in the highly functionalized cyclopentane derivative **10**, in which its "wrong" configuration at C7 is fixed by a Mitsunobu-Inversion. The dihydropyran **9** was finally formed by formylation at C4 and Lewis-acid-catalyzed ring closure.

1,4-Additions

Acryl sultams such as (*R*)-**12** and (*R*)-**15** are also excellently suited for stereoselective 1,4-additions of various nucleophiles (Scheme 3) [11–13]. Even simple Grignard reagents can be added with excellent 1,4-regio- and good diastereoselectivity according to the chelate model [14], which seems especially useful from a preparative point of view. The resulting (*Z*)-enolates **13** and **16** can be captured with electrophiles, which proceeds also with high stereocontrol. It should be noted, that **13** reacts with *opposite* selectivity to that of **16** in this second step. The additional methyl substituent in (*R*)-**15** is sterically repelled by the camphor structure. Nevertheless, coplanarity of the acryl amide is a necessary condition for the nucleophilic addition. Therefore, despite the unfavorable interactions in the reactive conformation, chelation occurs and attack of the nucleophile takes place from the side away from the auxiliary. For the trapping of the enolate, conjugation is not necessary any longer, resulting in the formation of the more favorable enolate **16**, which is attacked from the front.



Scheme 3

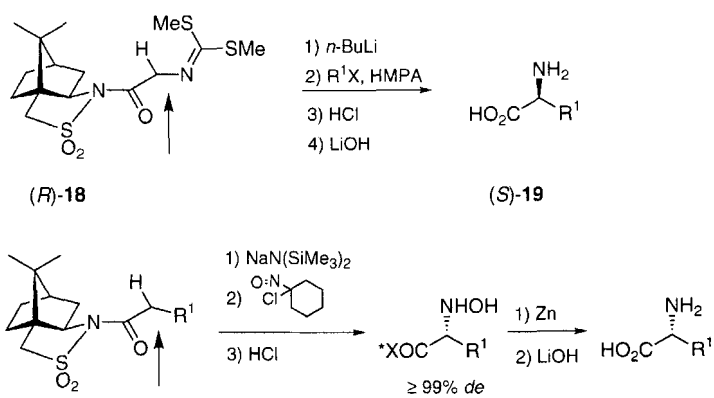
Enolate Reactions

It became apparent from the previous examples that sultam auxiliaries could be used in stereoselective enolate reactions. Indeed, acyl derivatives (*R*)-**18** or (*R*)-**20** can be alkylated in a highly diastereoselective manner [15], which was applied e.g. for the synthesis of α-amino acids (Scheme 4) [16–18]. After deprotonation of the glycinate (*R*)-**18** with *n*-butyllithium, the resulting (*Z*)-enolate can be trapped with alkyl-, allyl- or benzylhalides according to the chelate model with selectivities of > 90 % *de* (> 99 % *de* after recrystallization). After acidic hydrolysis and cleavage of the auxiliary, enantiomerically pure amino acids (*S*)-**19** are obtained. A complementary method is the highly selective electrophilic amination of (*R*)-**20** with 1-chloro-1-nitrosocyclohexane, which – again according to the chelate model – leads to (*R*)-**19** [19].

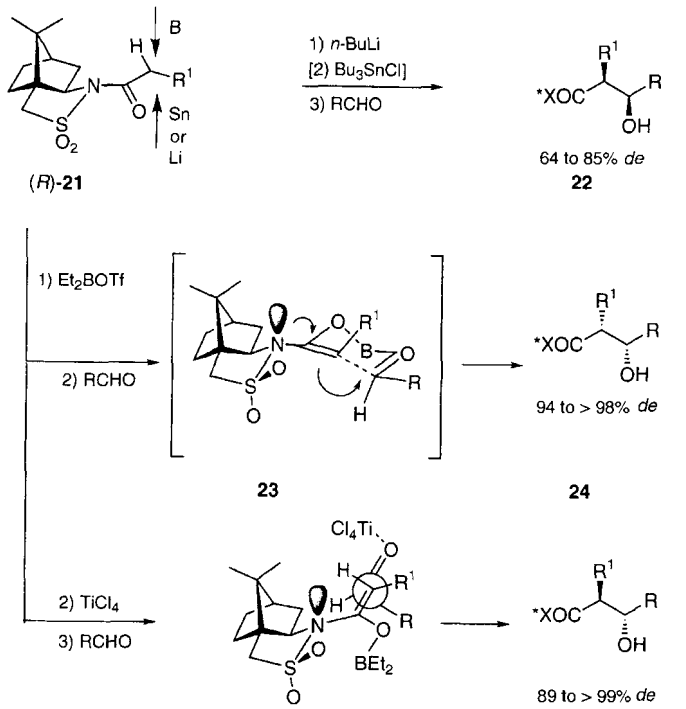
Syn-, *anti*- and acetate aldol derivatives can be synthesized by choosing appropriate enolization protocols (Scheme 5) [20]. With lithium, boron and tin Lewis acids, *syn*-aldols can be obtained *via* (*Z*)-enolates [21]. If enolization is carried out with lithium or tin, there are enough open coordination sites available to position the aldehyde and the enolate in accordance with the chelate model for the sultam auxiliary and with the Zimmermann-Traxler model. The combination of these models predicts the formation of **22**, which is indeed experimentally obtained. If Lewis acids with only two open coordination sites are used (e.g. Et_2BOTf), chelatization is only possible between the enolate oxygen and the aldehyde. Such reactions should therefore occur through a transition state which is analogous to **5** and should also lead to **22**. However, aldol reactions catalyzed by dialkylboron triflate lead with excellent selectivities to **24**. A plausible transition state that reflects this result is depicted in **23**, in which the aldehyde reacts with the enolate from the lower face being sterically disfavored. Stereoelectronic reasons (antiperiplanar position of l_{PN} to the aldehyde) could be decisive.

If another equivalent of titanium(IV) chloride is added to the boronenolates and only subsequently the aldehyde is introduced, the reaction proceeds *via* the open transition state **25** and leads to the *anti*-aldols **26** [22]. The aldehyde attacks the enolate from the sterically favored lower face, and the group R is oriented away from the auxiliary.

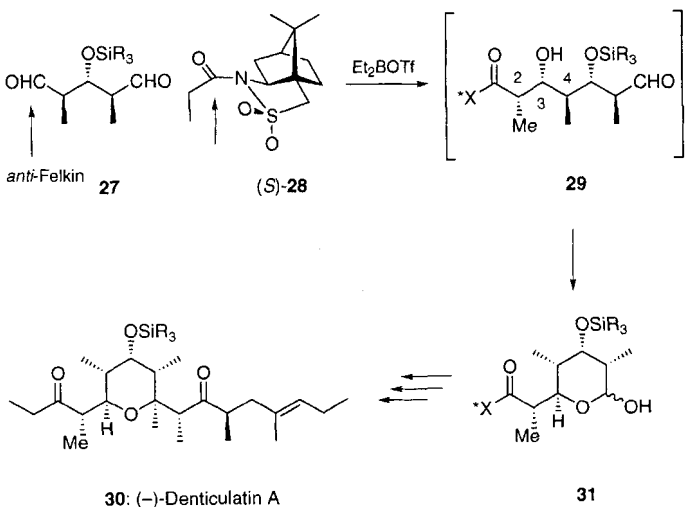
The asymmetric synthesis of (–)-denticulatin A (**30**) shows an interesting application of the boron aldol chemistry (Scheme 6) [23]. In a group-selective aldol reaction between the *meso*-aldehyde **27** and (*S*)-**28**, the hydroxyaldehyde **29** was formed with > 90 % *de*, which spontaneously cyclized to the lactol **31**. The configuration at the stereocenters of C-2 and C-3 in **29** is in accordance with the induction through the sultam auxiliary as well as with preference of an α-chiral aldehyde to react to the *anti*-Felkin diastereomer in an aldol reaction which is controlled by the Zimmermann-Traxler model [24, 25].



Scheme 4



Scheme 5

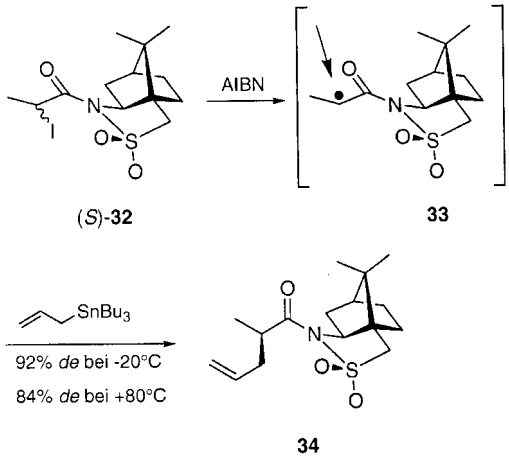


Scheme 6

The synthesis of heteroaromatic side-chain analogs masked as β-lactams of paclitaxel was efficiently accomplished by a cyclocondensation strategy between sultam-modified ester enolates and imines, demonstrating yet another strategy in sultam-enolate chemistry [26].

Radical Reactions

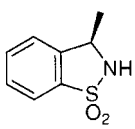
Also for stereoselective radical reactions such as radical additions or radical cyclizations, the camphor sultam **2** is suitable as an auxiliary (Scheme 7). The acyl radical which was gener-



Scheme 7

ated from the iodo compound (*S*)-**32** can be allylated even at +80 °C with remarkable selectivities [27]. Alkyl radicals also add highly selectively to camphor sultam derivatives of oxime ethers to provide a convenient method for the preparation of enantiomerically pure α,β-dialkyl-β-amino acids [28].

There are many more applications of the sultams of camphor-sulfonic acid that could have been described in this article. Finally, it should be noted that recently structurally simpler sultams **35**, which are available from saccharin, have also been successfully applied as a chiral auxiliary [29].



(*R*)-**35**

Figure 1

Without doubt, with the discovery of the sultam auxiliaries W. Oppolzer has earned himself a place in the hall of fame of chemistry. With this contribution he will never be forgotten, even by people who, like the author of this article, have never had the chance to meet him personally.

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Oxazolines: Chiral Building blocks, Auxiliaries and Ligands

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Do you need a chiral starting material which can be converted into a number of enantiopure products? Or a chiral auxiliary to perform an asymmetric transformation at a certain point of a complex molecule? Would you like to have a protecting group for an acid, which activates the *ortho*-position of an aromatic ring? Or do you need an easy-to-synthesize chiral catalyst? For all these problems oxazolines can be the solution.

Oxazolines [1] can be synthesized by several routes; two common methods are described below (Fig. 1). Readily available β-amino alcohols **1** can be coupled with an acid chloride to yield the amide **2** which is then cyclized to the oxazoline **3** in the presence of zinc(II) chloride. Alternatively a one step synthesis of **3** can be achieved by reacting **1** with nitriles. Both methods are reliable and give good yields. Twofold cyclization which leads to bis(oxazolines) **4** is also possible, giving access to a most important class of ligands for asymmetric catalysis. An obvious advantage of oxazolines is their simple synthesis; however, the synthesis of oxazolines depends on the availability of the corresponding amino alcohols, which are generally accessible from the *chiral pool* in only one enantiomeric form.

The recent development of the Sharpless aminohydroxylation [2] makes it possible to synthesize an amino alcohol in both optical antipodes (Fig. 2). For example, starting from 2-vinylnaphthalene (**5**), the amino alcohol **6** is readily synthesized by the aminohydroxylation protocol [3]. After deprotection, the free amino alcohol **8** was coupled with dimethylmalonic acid di-

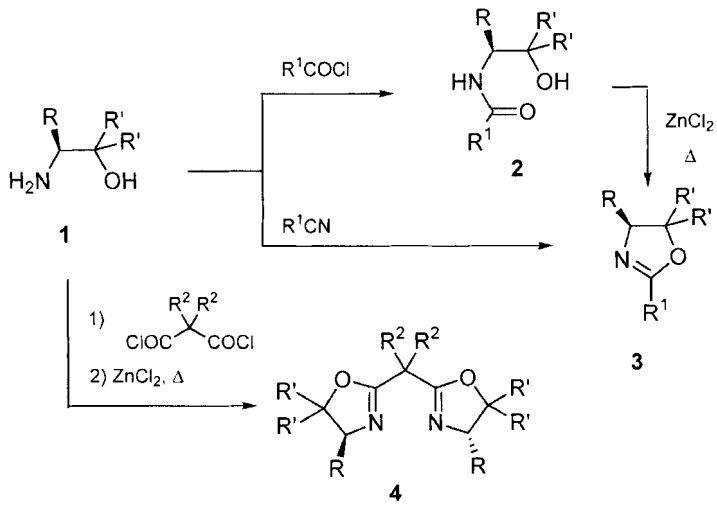

Figure 1. Synthesis of oxazolines from β-amino alcohols and carboxylic acid derivatives.

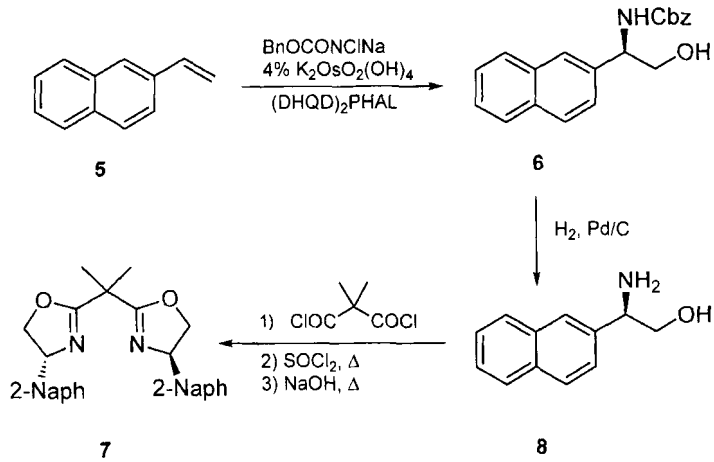

Figure 2. Use of the Sharpless aminohydroxylation to generate chiral amino alcohols.

chloride and subsequently cyclized to the corresponding bis(oxazoline) **7** which was used as chiral ligand for the Diels-Alder reaction of cyclopentadiene (**54**) with the acrylamide **55** yielding **56** in 94% *ee* (*cf.* Fig. 9).

Oxazolines as Chiral Auxiliaries

The oxazoline **11** developed by Meyers is a versatile building block for the synthesis of chiral carboxylic acids (Fig. 3). Its synthesis is based

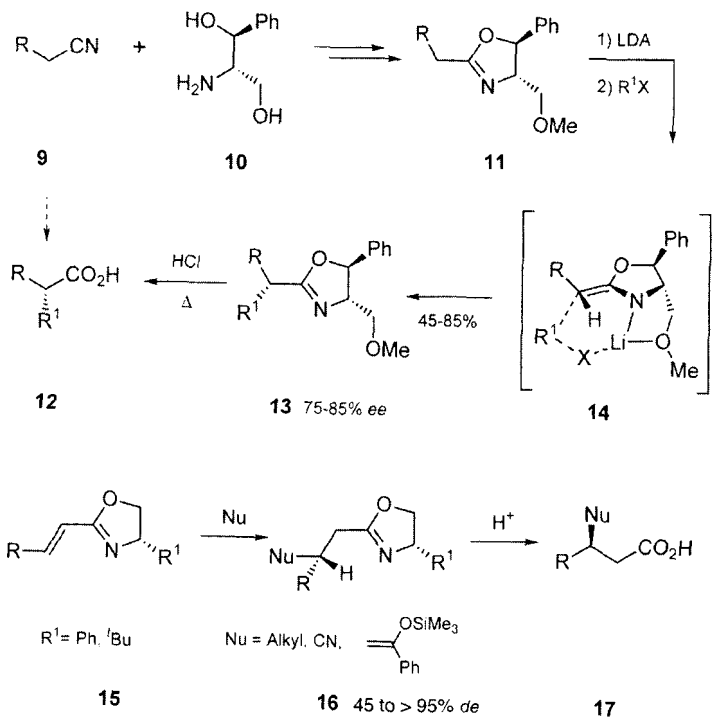

Figure 3. Asymmetric synthesis of carboxylic acids.

on the amino alcohol **10** which is accessible from serin [4]. Metallation of **11** followed by quenching with electrophiles was done in numerous variations. One example is the alkylation of **11** which leads to **13** in good optical yields. Probably the reaction proceeds through the highly ordered intermediate **14** in which a *Z*-enolate is formed and the 1,3-allylic strain (H/Li vs. R/Li) is minimized. Lithium is coordinated by oxygen and nitrogen and directs the electrophile R^1X to the lower side of the double bond. The phenyl group is shielding the upper side of the double bond from unwanted non-coordinated attacks of R^1X. The auxiliary is hydrolyzed to the carboxylic acid **12** by heating in dilute hydrochloric acid. When R and R^1 are introduced in the reverse order the enantiomer of **12** is also accessible.

Conversion of the auxiliary into other funcional groups is also possible. For example, **13** can be reacted with methyl triflate, reduced with sodium borohydride and then hydrolyzed with acids to yield the corresponding aldehydes [5].

1,4-Additions of nucleophiles to α,β-unsaturated oxazolines of the type **15** are generally conducted with high diastereoselectivity [6]. Good results are obtained with organolithium compounds [7] and silyl enol ethers [8a], while the addition of cyanide seems to be problematic [8b]. For these reactions it is not necessary to have a chelating moiety R^1 in the auxiliary in order to obtain good selectivities. However, there is a loss of activity, which can in some cases be compensated by activating the oxazoline with acetic anhydride [9].

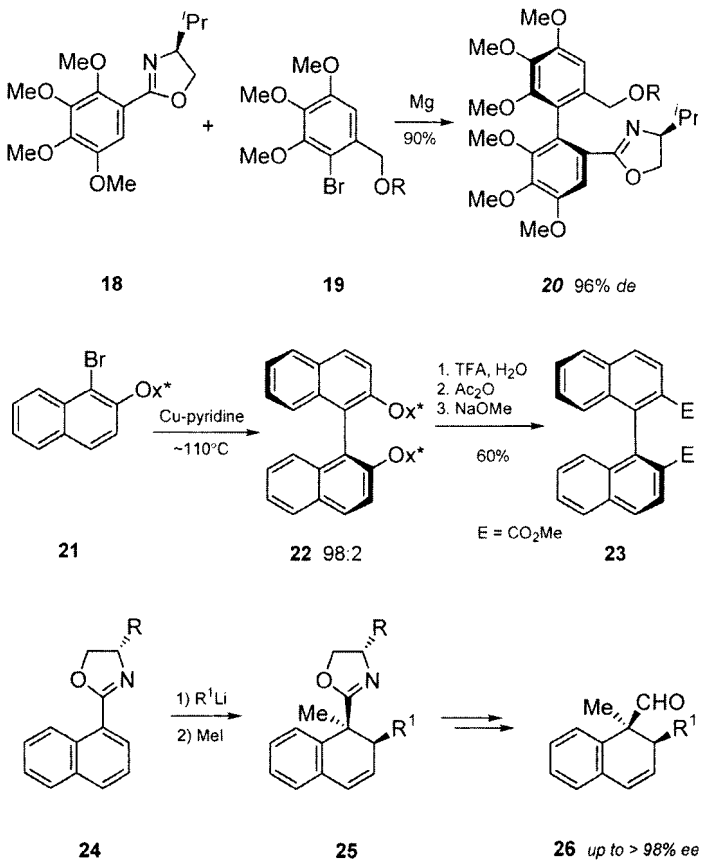

Figure 4. Reactions of aromatic systems involving chiral oxazolines.

In aromatic systems, oxazolines can have three different functions (Fig. 4). Firstly, they can be used as protecting groups for carboxylic acids. Secondly, they activate even electron-rich aromatic systems for nucleophilic substitution. Fluorine or alkoxy groups in the *ortho* position can be substituted by strong nucleophiles such as Grignard reagents. Thirdly, when biaryl compounds with axial chirality are synthesized in these reactions, oxazolines can induce the formation of only one atropisomer with excellent selectivity. These three qualities were all used in the synthesis of **20**, a precurser of the natural product isochizandrine [10].

It is also possible to conduct a diastereoselective Ullmann coupling using 1-bromo-2-oxazolylnaphthalene (**21**). Binaphthyloxazolines **22** are generated in up to 98 % *de* and can be further converted to chiral binaphthoic esters **23** [11].

Addition of alkyllithium compounds at the *ortho*-position of oxazolines is possible with heteroarenes as well as naphthalenes **24** (benzene derivatives usually tend to *ortho*-metallations) [12]. After reductive cleavage of the auxiliary, enantiopure aldehydes **26** are obtained, which have found wide application as versatile chiral precursers for complex polycyclic natural products.

Oxazolines as Ligands for Chiral Catalysts

Oxazolines are excellently suited for the complexation of metals. Based on this knowledge, a variety of metal-oxazoline complexes have been synthesized in recent years and used with outstanding results. In 1986 Pfaltz developed the semicorrin ligands **27** and thereby laid the foundation for future developments [13]. However, the more recently developed bis(oxazoline) ligands are more easily accessible and have therefore found wider application (Fig. 5).

In the beginning, the interest was focused on C_2-symmetric bis(oxazolines) such as for example **4** and **28–30** [14], and one of the first applications was the rhodium-catalyzed hydrosilylation of ketones. The generally successful concept of C_2-symmetry also proved to be advantageous here. The conversion of aromatic or aliphatic ketones **33** to the alcohols **34** was conducted with higher selectivities in the presence of ligand **30** [15] than with ligand **31** [16], although with the latter 86 % *ee* could be reached in the reduction of acetophenone (Fig. 6). Copper-bis(oxazoline)-complexes were used for cyclopropanations [17] and aziridinations [18] with great success. The latter reaction performs especially well

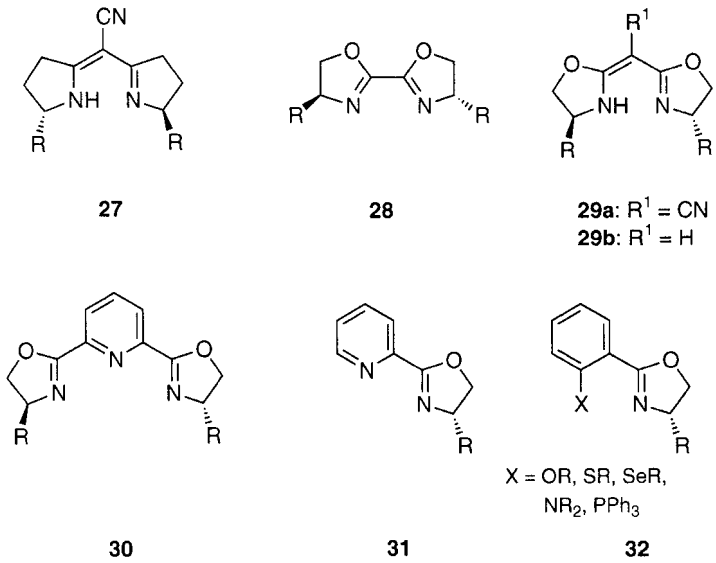

Figure 5. Semicorrin- and oxazoline-ligands for asymmetric catalysis.

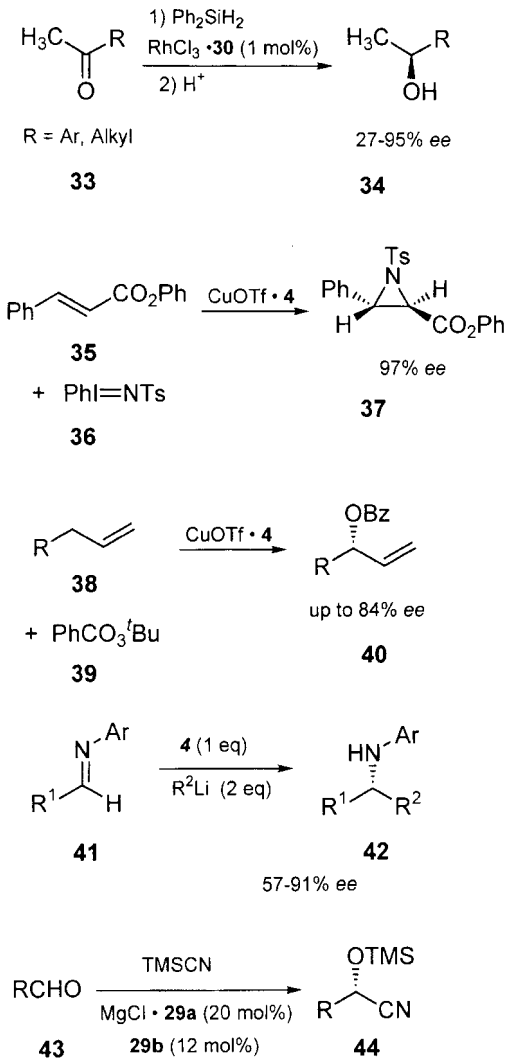

Figure 6. Application of bis(oxazolines) in asymmetric catalysis.

with cinnamic acid esters such as **35**. The aziridine **37** was obtained with excellent enantioselectivity and could be further converted to α-amino acid derivatives [19]. Oxidations are also possible with these complexes as two research groups [20] showed in recent developments. The copper(I)-catalyzed allylic oxyacylation (Kharasch reaction) of cyclic and acyclic olefines by peracid-esters was conducted in the presence of **4** with enantioselectivities up to 84 % *ee*. Another interesting application of the bis(oxazoline)-ligands was shown by Denmark. Alkyllithium compounds can be added enantioselectively to imines, but equimolar quantities of ligand **4** are necessary [21]. A catalytic system involving two bis(oxazolines) was developed by Corey and Wang [22] for the enantioselective conversion of aldehydes **43** to cyanhydrins **44**. One bis(oxazoline) (**29a**) served as ligand for magnesium which coordinates the aldehyde, while the second bis(oxazoline) (**29b**) together with TMSCN provided a source for a "chiral cyanide". The optical yields were modest for α,β-unsaturated and aromatic aldehydes (52 % *ee* for benzaldehyde) and high for aliphatic aldehydes (95 % *ee* for heptanal).

The Mukaiyama aldol reaction could be catalyzed by chiral bis(oxazoline) copper(II) complexes resulting in excellent enantioselectivities (Fig. 7) [23]. A wide range of silylketene acetals **46** and **49** were added to (benzyloxy)acetaldehyde **45** and pyruvate ester **48** in a highly stereoselective manner. The authors were also able to propose a model to predict the stereochemical outcome of these reactions.

Chiral bis(oxazolines) **51** with an oxalylic acid backbone were used for the Ru-catalyzed enantioselective epoxidation of *trans*-stilbene yielding *trans*-1,2-diphenyloxirane in up to 69 % *ee* [24]. The asymmetric addition of diethylzinc to several aldehydes has been examined with ferrocene-based oxazoline ligand **52** [25], resulting in optical yields from 78–93 % *ee*. The imide **53** derived from Kemp's triacid containing a chiral oxazoline moiety was used for the asymmetric protonation of prochiral enolates [26]. Starting from racemic cyclopentanone- and cyclohexanone derivatives, the enantioenriched isomers were obtained in 77–98 % *ee*.

Metal-bis(oxazoline) complexes were widely used as effective catalysts for enantioselective Diels-Alder reactions. Two research groups could achieve excellent diastereo- and enantioselectivity for the reaction of cyclopentadiene (**54**) and the acrylamide **55** (Fig. 9) [27]. Yet the decisive feature is only recognizable when both studies are analyzed together. In both cases the *endo* products are obtained in high selectivities using either the magnesium- or the copper-containing catalyst. However, despite the same

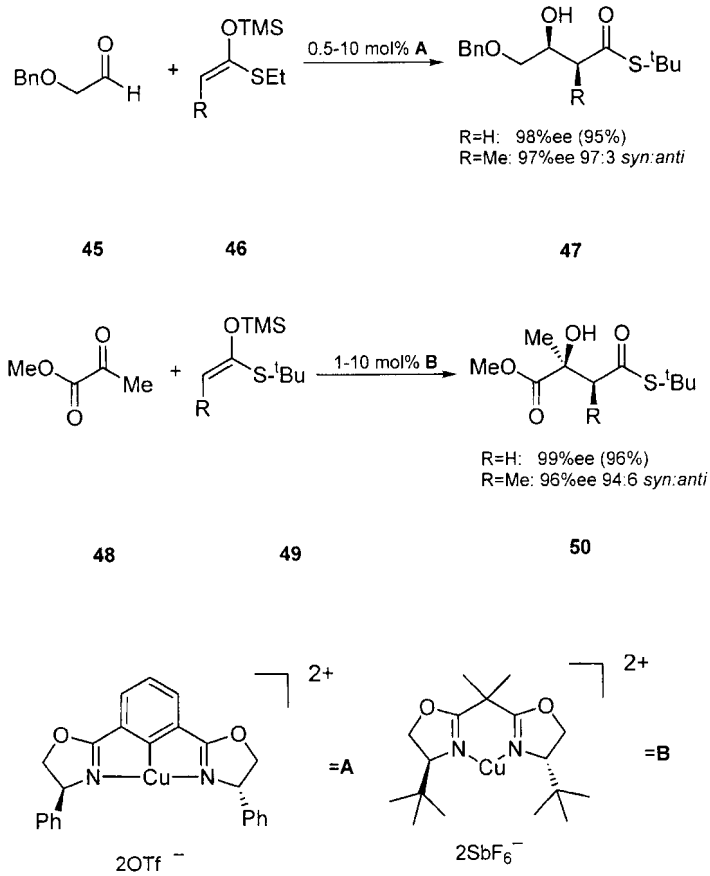

Figure 7. Enantioselective Mukaiyama aldol reaction.

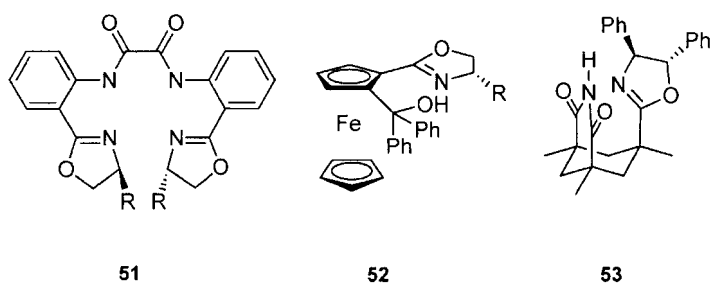

Figure 8. Oxazoline-ligands in asymmetric catalysis.

chirality of the ligands, products of opposite absolute configuration were obtained. These results can be explained assuming the dienophile being coordinated tetrahedrally in the magnesium complex and in square planar configuration in the copper complex. In **57** the acrylate is turned by 90° compared to the coordination in **58**. The attack of the diene at the dienophile, which reacts from an *s-cis* configuration, takes place from the less hindered side opposite the bulky groups (Ph and ^{t}Bu).

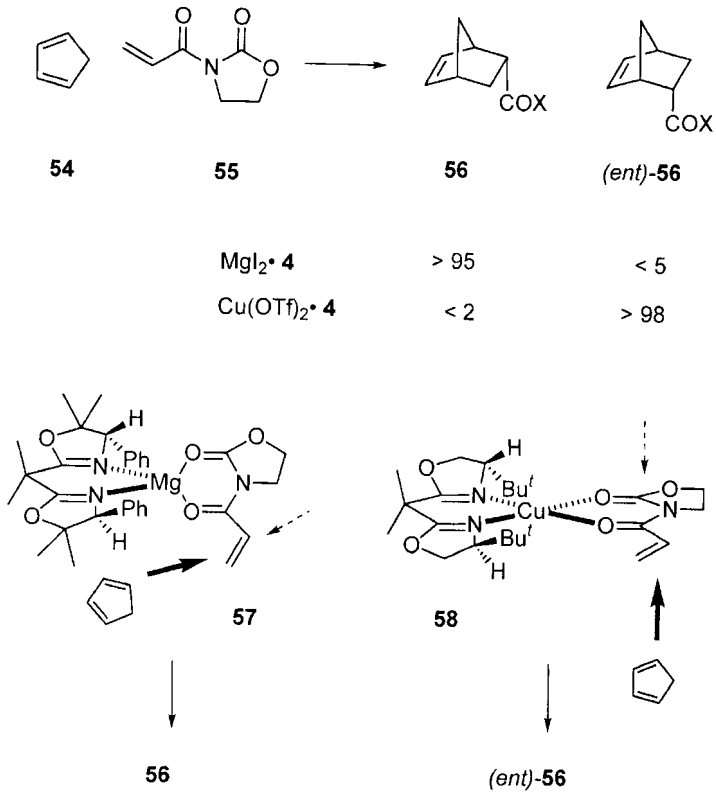

Figure 9. Asymmetric Diels-Alder reaction with metal-bis(oxazoline) complexes.

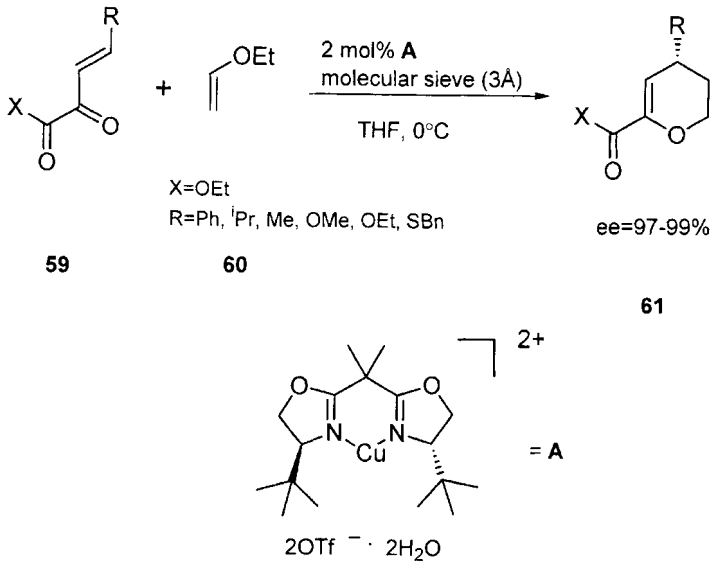

Figure 10. Hetero-Diels-Alder reaction catalyzed by chiral bis(oxazolines).