Chiral Auxiliaries – Principles and Recent Applications

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Dedicated to David A. Evans on the occasion of his 65th birthday

Abstract: With modern methods for asymmetric catalysis breaking ground, the use of chiral auxiliaries seems to be old-fashioned and rather inefficient. However, for many transformations, chiral auxiliaries often represent the only selective method available. In addition, high levels of selectivity and reliability are often attractive characteristics of chiral auxiliaries and allow for the efficient and rapid synthesis of desired chiral compounds. In addition, even in cases with imperfect selectivity, the use of an attached chiral auxiliary allows the enrichment of diastereoselectivity, and hence enantioselectivity after removal of the auxiliary, by many standard separation techniques. This article gives an overview on the most important classes of chiral auxiliaries, discussing the mode of action and highlighting some recent applications. It does not deal with the use of chiral catalysts, reagents or achiral auxiliaries.

1 Introduction

The increasing demand in the life sciences for enantiomerically pure compounds has led to a wealth of methods for asymmetric synthesis. Although asymmetric catalysis and biocatalytic methods increasingly allow for the efficient synthesis of many enantiomerically pure compounds,1 chiral auxiliaries remain to be the workhorses of asymmetric synthesis.2 Chiral auxiliaries (X) are enantiomerically pure compounds that are linked to a substrate and influence the stereochemical course of a reaction. A certain functional group is needed in the substrate to selectively bind the auxiliary. In most cases the auxiliary is introduced prior to the stereoselective reaction and removed afterwards. These additional synthetic steps and the cost of stoichiometric amounts of auxiliary seem to render this approach rather unattractive.

Can chiral auxiliaries compete with methods like asymmetric catalysis? For many applications, no enantioselective catalytic method exists, and chiral auxiliaries are the only available stereoselective method. Furthermore, auxiliaries are generally reliable and the great knowledge of chiral auxiliaries allows a high level of predictability, enabling the synthesis of a plethora of enantiomerically pure compounds in a time-efficient manner. Most importantly, even in cases with imperfect selectivity, the use of an attached chiral auxiliary allows the enrichment of diastereoselectivity, and hence enantioselectivity after removal of the auxiliary, by many standard separation techniques. As a consequence, chiral auxiliaries are often the method of choice in, for example, the early phases of drug development.3

With respect to the vast number and diverse nature of applications of chiral auxiliaries in asymmetric synthesis, this review cannot be a comprehensive treatment of chiral auxiliaries. Rather, it gives an update on some of the most important classes of chiral auxiliaries, discussing their mode of action and highlighting some recent applications. Each section begins with general information on the auxiliary itself and methods for its incorporation. After the discussion of a couple of insightful recent applications, each section ends with information about the cleavage of the particular auxiliary class. Chiral catalysts, chiral reagents or achiral auxiliaries are not included in this review.

2 Sulfinamides, Sulfoxides, Bis(sulfoxides)

2.1 Sulfinamides

Three different substituents and an additional lone pair render the sulfur atom of sulfinamides and sulfoxides chiral. Sulfinamides 1 are often employed in asymmetric synthesis in the form of their N-sulfinimines. They are versatile precursors for a variety of chiral nitrogen-containing molecules. Commonly used chiral auxiliaries like p-toluenesulfinyl imines 2a and N-tert-butanesulfinyl imines 2b can easily be derived by condensation of the enantiopure, commercially available (R)- or (S)-p-toluenesulfinimide or tert-butanesulfimide with an appropriate aldehyde or ketone, mediated by, for example, Ti(Oi-Pr)4 (Scheme 1).4

The most important applications of these chiral auxiliaries are the synthesis of α- and β-amino acids and 1,2- and 1,3-aminoalcohols.5 Typically, these chiral sulfinimines are employed in nucleophilic addition reactions of C- and P-
nucleophiles as well as [2+1] and [3+2] cycloadditions. In addition the C=N moiety is activated electronically by the N-sulfinyl group to such an extent that the addition of organometallic reagents becomes a facile process. Since the N-sulfinyl group stabilizes anions at nitrogen, epimerization of the newly formed carbon stereocenter in the resulting sulfinamide is prevented. Presumably, the stereochemistry is controlled by a cyclic transition state. In the presence of smaller and more covalently bound metals, higher diastereoselectivities are obtained.5

A recent example for the innovative application of sulfinimines was reported by Ellman and co-workers.6 Deprotonation (possibly followed by transmetallation) of the tert-butanesulfinyl ketimine 3 forms an N-sulfinyl metalloenamine 4. Addition of nitroalkenes or α,β-unsaturated ketones to the thus-formed electrophile led to Michael additions, wherein the additions to α,β-unsaturated ketones proceeded with very high diastereoselectivities (Scheme 2). The obtained N-sulfanylamino ketones 5 could be easily converted to piperidines 6 by stereoselective reduction of 5 and subsequent cyclization. This sequence represents the first asymmetric synthesis of 2,4,6-trialkyl-substituted piperidines.6 A similar example for stereoselective reduction of sulfinimides is given in Scheme 4.

The addition of N-sulfinyl metalloenamines 8 to aldehydes were reported by Ellman and co-workers resulting in the asymmetric synthesis of syn- and anti-1,3-amino alcohols.7 Deprotonation of the tert-butanesulfinyl ketimine 7 occurs with LDA and is followed by addition of an aldehyde resulting in the formation of 9 (Scheme 3). Addition of metal salts like MgBr2 or ZnBr2 gave higher diastereoselectivities which have been attributed to a six-membered transition state, depicted in 8a.

Furthermore, careful choice of the reducing agent allows for a highly diastereoselective syn or anti reduction of the β-hydroxy-N-sulfinyl imines 10 (Scheme 4).7

Scheme 1 Introduction of the chiral auxiliary.

Scheme 2 Diastereoselective addition of N-sulfinyl metalloenamines to α,β-unsaturated ketones.

Biographical Sketches

Yvonne Gnas was born in Marburg (Germany) in 1981. She studied chemistry at the Philipps-University in Marburg and obtained her diploma in 2005. She is currently working as a Ph.D. student in the group of Prof. Glorius on asymmetric hydrogenation reactions.

Frank Glorius was educated in chemistry at the Universität Hannover, Stanford University (Prof. Paul A. Wender), Max-Planck-Institut für Kohlenforschung and Universität Basel (Prof. Andreas Pfaltz), and Harvard University (Prof. David A. Evans). In 2001 he began his independent research career at the Max-Planck-Institut für Kohlenforschung in Mülheim/Ruhr (Germany). Since 2004 he is a Professor of Organic Chemistry at the Philipps-Universität Marburg. The purpose of his research program is to significantly facilitate organic synthesis by developing new concepts for catalysis. At present his group focuses on the design of new N-heterocyclic carbazenes, challenging cross-coupling reactions, asymmetric hydrogenations, and organocatalyzed umpolung reactions.
Scheme 1 Deprotection of the resulting sulfinamine and thus allows the optimization of the reaction conditions favors or disfavors a Cram-type chelate between the alcohol protecting group of sulfinimine and the enamine.\(^{8}\) The diastereofacial selectivity of the scheme favors the formation of the syn-products. Changing the alcohol protecting group of sulfinimine or the reaction conditions favors or disfavors a Cram-type chelate and thus allows the optimization of the synlant selectivity (Scheme 5). Deprotection of the resulting sulfinimine is carried out with HCl/MeOH or HF/piperidine, affording the N-sulfinyl metallo-enamines in high yields.\(^{9}\)

Scheme 2 Diastereoselective reduction of \(\beta\)-hydroxy-N-sulfinyl imines 9.

In the synthesis of amino alcohols, chiral sulfinimines can also act as electrophiles. A recent example for nucleophilic addition of Grignard reagents to sulfinimines is the synthesis of 1,2-disubstituted enamines.\(^{9}\) The diastereofacial selectivity of the \(N\)-sulfinyl group overrides the inherent preference of the \(\alpha\)-stereocenter of the imine 11, resulting in the highly selective formation of the syn and anti products. Changing the alcohol protecting group of sulfinimine or the reaction conditions favors or disfavors a Cram-type chelate and thus allows the optimization of the synlant selectivity (Scheme 5). Deprotection of the resulting sulfinimine is carried out with HCl/MeOH or HF/pyridine, affording the \(\beta\)-amino alcohol in high yields.

Scheme 3 Diastereoselective addition of \(N\)-sulfinyl metallo-enamines to some aldehydes.

Recently, Xu and co-workers reported the reductive homocoupling of \(N\)-tert-butanesulfinyl imines to \(C_2\)-symmetrical vicinal diamines.\(^{9}\) An extension of this work is the cross-coupling of \(N\)-tert-butanesulfinyl imines with nitrones or aldehydes affording unsymmetrical vicinal diamines and \(\alpha\)-\(\beta\)-amino alcohols 14 (Scheme 6).\(^{10}\) Due to competitive imine homocoupling and pinacol coupling of the aldehyde substrates, only aliphatic aldehydes can be successfully employed in this challenging SmI\(_2\) mediated reaction. Remarkably, the free \(\beta\)-amino alcohol was obtained after final acidic hydrolysis of 14 with enantiomeric excesses of greater than 94% for all substitution patterns shown in Scheme 6.

Scheme 4 Diastereoselective reduction of \(\beta\)-hydroxy-N-sulfinyl imines 9.

The cleavage of the auxiliaries under acidic conditions (HCl–MeOH or HCl–dioxane) generally provides the corresponding amines in high yields and high enantiomeric excess (>95%). This method provides a very efficient route to \(\beta\)-amino alcohols, as demonstrated by the rapid preparation of \(\alpha\)-erythro-sphinganine and (3R,4S)-statine (15) (Scheme 7).\(^{10b}\)

Scheme 5 Diastereoselective nucleophilic addition of Grignard reagents.

Viso et al. investigated a highly diastereoselective 1,3-dipolar cycloaddition of \(p\)-toluenesulfinyl imines with azomethine ylides yielding enantiopure imidazoline 18 (Scheme 8).\(^{11}\) Interestingly, only two out of eight possible 1,3-imidazoline diastereomers are formed, and in a 95:5 ratio. The [3+2] cycloaddition products can be opened to the corresponding vicinal diaminoalcohols by treatment of cycloadduct 18 with LiAlH\(_4\) and TFA/MeOH.\(^{11}\)
In general, the sulfinamide auxiliary can be removed easily. Typically, imine-type substrates like 9 can be converted to ketones 19 by hydrolysis with acetic acid in MeOH–H₂O.⁷ In the case of sulfinamides 12, cleavage by treatment with acid generates the corresponding amines 20 upon decomposition of the auxiliary (Scheme 9).⁴b,12

**Scheme 9** Typical conditions for cleavage of the sulfinamide auxiliary.

### 2.2 Sulfoxides

Enantiomerically pure sulfoxides can be efficient chiral controllers – cheap and easy to both introduce and functionalize. Therefore, they are versatile intermediates for a number of organic reactions. Introduction of the sulfinyl group mostly occurs by nucleophilic addition of the deprotonated sulfoxide 21 to an ester to form β-keto sulfoxides 22 (Scheme 10).¹³ Another entry to sulfoxides is the nucleophilic substitution of diastereomerically pure menthyl-p-toluenesulfonates 23 with Grignard reagents occurring with complete inversion of the configuration at sulfur. This method, forming alky1 or aryl sulfoxides 24, is also known as the Andersen synthesis (Scheme 10).¹⁴ Furthermore, the asymmetric oxidation of sulfides also provides easy access to the desired sulfoxides.⁵a In analogy to the sulfinamides, p-tolyl or tert-butyl groups are often the substituents of choice at sulfur.¹⁵

**Scheme 10** General methods for the introduction of a chiral sulfoxide auxiliary.

Sulfoxides have been mostly employed in asymmetric reductions of β-keto sulfoxides, carbon–carbon and carbon–heteroatom bond formation, cycloadditions and other metal-catalyzed reactions. Moreover, chiral sulfoxides have found numerous applications in natural product synthesis.¹⁵–¹⁷ The stereoinduction can be explained by the coordination of the auxiliary oxygen to a Lewis acid or transition metal, resulting in highly ordered transition states. As a consequence, the bulky substituents at sulfur are either placed in an equatorial position or shield one diastereotopic face of the substrate, allowing for highly stereoselective reactions.

A recent example for the well-known highly selective asymmetric reduction of β-keto sulfoxides 25 to give products 27 was reported by Carreno et al. (Scheme 11).¹⁸

**Scheme 11** Stereocomplementary diastereoselective reductions of β-keto sulfoxides 25.
In the cyclic transition state (26a) an intramolecular hydride transfer takes place. This reaction was used as a key step in the asymmetric synthesis of (+)-isolaurepan 28. If ZnBr₂ is added, a zinc chelate is formed and the hydride transfer proceeds in an intermolecular fashion (26b).²⁹ In addition, chiral sulfoxides are becoming ever more important in the area of transition-metal-catalyzed reactions, like Pauson–Khand (PKR)²⁰ and Heck reactions.²¹ Asymmetric intra- and intermolecular PKRs were reported by Carretero and co-workers.²²,²³ The more demanding intermolecular version of this cyclopentenone synthesis (30) proceeds completely regioselectively and with very high diastereoselectivities (93:7 to >98:2) obtained; with terminal alkynes the yields were low (0–33%).

\[ \text{Scheme 12: Diastereoselective Pauson–Khand reaction.} \]

Intriguingly, chiral sulfoxides can even be used as temporary chiral auxiliaries, as demonstrated by Malacria and co-workers in an intramolecular radical vinylation.²⁴,²⁵ Starting with auxiliary-substituted substrates 31, alkylidenecyclopentanes 32 were synthesized in a tandem reaction by a radical 5-exo-cyclization followed by β-elimination of the chiral auxiliary (Scheme 13).²⁴ Interestingly, in these cyclization reactions, the addition of several Lewis acids like methylaluminum bis(2,6-di-tert-butyl-4-methylphenoxide) (MAD) to 33 reversed the selectivity to preferentially give enantiomer 34 (Scheme 13).²⁴

\[ \text{Scheme 13: Asymmetric radical cyclization reactions.} \]

If cleavage of the auxiliary is not part of the reaction, several methods for desulfinylation exist. Traceless cleavage can be accomplished with Zn/NaH₂Cl in H₂O/THF,²³ or by generation of a double bond by sulfoxide pyrolysis in refluxing toluene.²² Cleavage of the auxiliary by a Pummerer reaction unveils an aldehyde group (e.g. 35) and allows for further functionalization (Scheme 14).²⁶,³⁶

\[ \text{Scheme 14: Representative methods for auxiliary cleavage.} \]

### 2.3 Bis(sulfoxides)

An important class of sulfoxide auxiliaries are C₂-symmetric bis(sulfoxides) with 1,1-bis-p-toluenesulfonfyl derivatives 36 and cyclic dithioacetal dioxides 37 being commonly used (Figure 1). These compounds can be synthesized following Andersen’s approach,³²,³³ asymmetric oxidation methods³⁴ or with the assistance of chiral auxiliaries.³²

\[ \text{Figure 1: C₂-symmetric bis(sulfoxides).} \]

Bis(sulfoxides) 36 and 37 have been used mainly as chiral ketene equivalents in epoxidation reactions or cycloadditions, extensively studied by Aggarwal et al.³⁵-³⁷ Examples are the asymmetric [3+2] cycloadditions of nitrones with thioacetal 38 that can be accomplished intra- or intermolecularly to give isoxazolidine 39 in good yield and high diastereoselectivity (Scheme 15).³⁵,³⁶,³⁸

Another recent application of chiral bis(sulfoxides) was reported by Fensterbank, Malacria and co-workers.³⁹ Using 40 as a Michael acceptor for a diastereoselective conjugate addition, only a single diastereomeric product, 42a, was obtained in near quantitative yield (Scheme 16). An
X-ray structural analysis of 40 (with $R = \text{Ph}$) revealed that the preferred conformation is the one shown in the transition state 41a.

Addition of Lewis acids can reverse the diastereoselection through a complexation of the two sulfoxide oxygen atoms. In a cyclic transition state (41b), attack of the nucleophile occurs from the opposite side and product 42b is formed in excellent yield and diastereoselectivity.

Podlech and Wedel used bis(sulfoxides) for the asymmetric addition of enolates to a bis(sulfoxide)-derived Michael acceptor (Scheme 17).\textsuperscript{40} Beside enolates prepared by deprotonation with $\text{BuLi}$ oder $\text{NaHMDS}$, silyl enolethers can also be added to bis(sulfoxides) 43. In general, yields and diastereoselectivities of these reactions lie between 66–94\% and 72–92\%, respectively.

Finally, cleavage of the auxiliary of 44 in two steps releases the original aldehyde or ketone functional group in good yield (Scheme 18).\textsuperscript{40} Alternatively, a Pummerer reaction can be used to remove or transform the auxiliary via intermediate 45 to an alcohol 46 (Scheme 18). Instead of a reduction with $\text{LiAlH}_4$, $\text{Hg(OAc)}_2$ in $\text{MeOH}$ can be employed to yield the corresponding ester.\textsuperscript{39,41}

## 3 Camphor-Derived Auxiliaries

Both enantiomeric forms of camphor are commercially available and inexpensive. Its rigid backbone is an attractive structural element for chiral auxiliaries. As a consequence, many structurally diverse camphor-derived auxiliaries (Figure 2) have been prepared in only a few steps as well as successfully employed in a variety of different reactions.\textsuperscript{42}

As shown in Scheme 19, the camphor-derived auxiliaries can often be readily incorporated into the substrate.\textsuperscript{42b,43}

The broad variety of organic reactions stereochemically controlled by camphor auxiliaries is impressive: among others are Michael additions,\textsuperscript{44} Baylis–Hillman reactions,\textsuperscript{45,46} Darzens reactions,\textsuperscript{43} cyclopropanations,\textsuperscript{47} Pauson–Khand reactions,\textsuperscript{48} cyclopentannelations,\textsuperscript{49,50} enantioselective epoxidations\textsuperscript{51} and reductions.\textsuperscript{52}

Arguably, the most prominent camphor-derived auxiliary is Oppolzer’s sultam (47).\textsuperscript{53} Very recently, an asymmetric [2,3] rearrangement of allyldimethyl ammonium sultam ylides 55 to allyl glycine derivatives 56 was reported by Sweeney and co-workers in good yield and excellent selectivities (Scheme 20).\textsuperscript{54}
Moreover, the auxiliary can also be attached to the other end of the substrate (57); this also results in high stereoselectivities (Scheme 21). To underline the versatility of this methodology, an efficient asymmetric synthesis of (R)-(+)−allylglycine was carried out with good overall yield (86%) and very high diastereoselectivity (>95:5 dr).54,55

Oppolzer’s sultam 47 is also known to be a powerful auxiliary in the asymmetric Baylis–Hillman reaction. The use of one equivalent of aldehyde leads to the formation of the expected chiral allylic alcohols. Intriguingly, Leahy and co-workers reported that the use of two equivalents of aldehyde results in the direct cleavage of the auxiliary and thus in the formation of the cyclic products 58 with excellent selectivities (Scheme 22).45 Aliphatic aldehydes can be employed in this reaction, however, aromatic aldehydes like benzaldehyde are not sufficiently reactive. The obtained 1,3-dioxan-4-ones 58 can be easily converted into versatile products such as α-methylene-β-hydroxy esters.45

More recently, Chen and Yang developed another bicyclic camphor-derived auxiliary 48 for the Baylis–Hillman reaction.46 Interestingly, the solvent severely influences the selectivity of this reaction. Whereas in DMSO diastereomer 59a is formed predominantly, in a THF–H2O solvent system the selectivity is completely reversed and 59b is formed selectively (Scheme 23). The stabilization of the zwitterion intermediate by intermolecular hydrogen bonding with the solvent might be important for the stereochemical outcome, but more information is needed for a definite analysis. It is also important to note that the reaction time for different substrates and solvents varies greatly. For example, the reaction of benzaldehyde in DMSO takes 7 days to reach completion, whereas in THF–H2O as the solvent, no isolable product formed even after 21 days.
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**REVIEW**

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Scheme 23  Asymmetric Baylis–Hillman reaction.

Substrate 60 can easily be prepared in multigram quantities from δ-lactol auxiliary 54, which is available in two steps from (+)-camphor. The Michael addition of the corresponding amide enolate to α,β-unsaturated esters, lactones or ketones (chalcone, 78% de) leads to the highly selective formation of a variety of amino acid derivatives 61 with two newly formed stereocenters (Scheme 24). Dixon et al. rationalize the stereochemical outcome in the following way. First, the lithium amide enolate of 60 forms, in which the inner si face is shielded by the auxiliary. As a consequence, the Michael acceptor attacks the less-shielded re face in a synclinal manner, resulting in the formation of the observed diastereomer 61.

Camphor-derived sulfides and sulfur ylides are also versatile chiral substrates, suitable for a number of asymmetric reactions. A recent example is the highly enantioselective Darzens reaction of sulfonium amide 62 (derived from 49) reported by Aggarwal et al. After deprotonation, the sulfur ylide adds to the aldehyde and the resulting betaine eliminates the auxiliary while closing the epoxide ring to give 63 (Scheme 25).

Notably, the auxiliary fulfills three different tasks in this sequence: it facilitates the formation of the nucleophile by means of acidification, efficiently controls the stereochemistry of the nucleophilic attack, and finally, acts as a leaving group. Many aromatic aldehydes lead to the formation of epoxides 63 in high yields and very good enantioselectivities. Aliphatic aldehydes like tridecanal and 2-methyl propanal gave much lower enantioselectivities (63% and 10%, respectively).

Even more impressively, the auxiliary can be successfully used *catalytically* in a related epoxidation reaction (Scheme 26). The phase-transfer catalyst (PTC) allows for the in situ formation of the diazo compound under mild conditions starting from tosyl hydrazone 64. This diazo compound reacts with the rhodium catalyst to give a metal carbenoid 67 that reacts subsequently with the auxiliary 52 to form the sulfur ylide 66 (Scheme 27). As in the non-catalytic variant, this ylide adds to the aldehyde and the successive formation of epoxide 65 liberates the auxiliary 52.

Scheme 25  Darzens reaction of sulfonium amide 62.

Scheme 24  Asymmetric Michael addition.

methyl propanal gave much lower enantioselectivities (63% and 10%, respectively).

In a process related to the aforementioned epoxidation of aldehydes, sulfur ylides can also be used for a cyclopropagation of terminal 1,2-disubstituted and 1,2,3-trisubstituted electron-deficient olefins. A representative
example is the cyclopropanation of electron-poor alkenes like vinylesters or acrylonitrile with the sulfonium salt 68 reported by Huang and Huang (Scheme 28). Again, the auxiliary is removed in the course of the reaction. Interestingly, the stereoselectivity of this reaction can be reversed by simply changing the base. Whereas KO\textsubscript{t}-Bu leads to the selective formation of cyclopropane 69, the use of NaH gives rise to \textit{ent}-69.61

A proposed transition state for the formation of 69 is shown in Figure 3.60 However, the impact of the base on the enantioselectivity cannot yet be sufficiently explained.

Camphor-derived thiols like 50 are used as chiral control-

lers in an asymmetric PKR reported by Riera and co-

workers.48 Alkynes 70 react with both norbornene and norbornadiene in moderate yields and good to excellent diastereoselectivities (30–96% de), forming bicyclic cyclopentenones 71 (Scheme 29).

A tandem Michael addition and Meerwein–Ponndorf–Verley (MPV) reduction of auxiliary 51 and the \(\alpha,\beta\)-unsaturated ketone 72 was reported by Node and co-workers.62 This sequence allows the impressive construction of three contiguous stereocenters in an acyclic compound (Scheme 30). The MPV reduction occurs intramolecularly between the alcohol group of the auxiliary and the ketone. The cyclic transition state leads to the predominant formation of diastereomer 73. Destructive cleavage of the auxiliary associated with transfer of the sulfur atom to the product results in the formation of product 74.

Another camphor-derived auxiliary was synthesized from camphoric acid and used in an asymmetric cyclopentan-

elation by Tius and co-workers (Scheme 31).49,50 Addition of substrate 75 (derived from 53) to \(\alpha,\beta\)-unsaturated amide 76 under acidic conditions led to the formation of 77 in good yields and enantioselectivities. In these trans-

formations, the chiral allene moiety is essential for high selectivities and ee values of up to 96% were obtained in the matched case.49a Cleavage of the auxiliary is carried out in situ to release the corresponding alcohol 77. This reaction sequence gives ready access to an important building block for the synthesis of roseophilin.63

Closely related to camphor, though much less commonly used, are derivatives of pinene or myrtenal.64 A recent ex-

ample for asymmetric aldol reactions with (-\(\beta\))-pinene auxiliaries was reported by Pinheiro et al.65 The reaction of pinene-substituted esters with aldehydes led to chiral

Figure 3  Reasonable transition state for cyclopropanation of acry-

lates.
alcohols in good yields (70–90%) and moderate selectivities (anti/syn = 64:36 to 80:20). Costa and co-workers used pinene-derived auxiliaries for asymmetric Friedel–Crafts reactions with greatly varying stereoselectivities.66,67

In some cases presented in this section, the auxiliary acts as a leaving group and is removed under the reaction conditions. On one hand, this is elegant and advantageous since no additional cleavage step is needed in these cases. On the other hand, the loss of an enantiopure chiral auxiliary also has undesirable consequences: the determination of the enantiomeric purity of the product and the purification of the stereoisomers (enantiomers vs. diastereomers) by crystallization or chromatography both become more difficult.

In the majority of cases, auxiliary-substituted products are isolated. The cleavage conditions for these compounds depend on the nature of the auxiliary attachment. In addition to the reductive elimination with SmI2,49,50 LiOH52 or LiAlH4,53 hydrolytic cleavage procedures are often the method of choice.44,68,69

4 Carbohydrate-Derived Auxiliaries

The attractiveness of carbohydrate-derived auxiliaries results from the fact that they bear many stereocenters and are often commercially available and reasonably priced. They have been successfully employed in numerous organic reactions, such as cycloadditions (Diels–Alder reactions70 [2+2] cycloadditions71), cyclopropanations,72 alkylations,73 and Mannich reactions.74–76

Pyranosides like 78 or 79 derived from α-D-glucos-, α-D-galacto-, or α-D-mannopyranosides are commonly used auxiliaries. The alcohol functionalities of the sugar serve two purposes: first, they are ideal anchoring groups for attachment of the auxiliary to the substrate, and second, they allow for the tuning of the steric bulk of the auxiliary by protection with a variety of groups with different steric demands.76a Furanosides like L-sorbide-derived 8077 or bicyclic sugars like isomannide (81) and isosorbide (82)78 are somewhat less popular than pyranoside auxiliaries (Figure 4).

Auxiliaries like 78 or 79 can easily react with nucleophilic substrates to form enamides 83 or esters 84 (Scheme 32).

A 6-deoxy-D-glucopyranoside derivative 85 can be used for several asymmetric reactions. Tadano et al. reported a highly diastereoselective α-alkylation of ester 85 that gave rise to products 87. Deprotonation with NaHMDS resulted in the formation of the metal-associated Z-enolate 86, which attacked the electrophile with its unhindered back face (Scheme 33).79–81 Interestingly, the use of other bases like LDA or n-BuLi resulted in a reversal of stereoselectivity and rather low selectivities (46–68% de).79 In order to explain these latter results, the authors proposed that as a consequence of the bulky substituents on Li, the 180° rotamer around the former ester C–O bond (curved arrow in 86) is more stable. Attack of the electrophile by this rotamer would then lead to formation of the opposite diastereomer.

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influences the stereoselectivity, since different conformations of the resulting crotyl ester moiety are preferred. Whereas organocopper reagents are capable of coordination with the crotyl carbonyl, the organolithium nucleophile is not.80

Scheme 34  Asymmetric 1,4-addition of cuprates and organolithium compounds to an $\alpha,\beta$-unsaturated ester.

O-Pivaloylated pyranosides like 78 are rather popular auxiliaries. Kunz and co-workers reported the synthesis of enantiomerically pure piperidines starting from N-galactosylated pyridones 83. In the key step, the silylated triflate salt of 83 was treated with a variety of Grignard reagents to give differently substituted dehydropiperidinones 93 (Scheme 36).82 It is reasonable to assume that the pivaloyl group next to the anomeric center shields the front of the heterocycle in 92. Consequently, the Grignard reagent attacks from the back to form stereoisomer 93 that can be used for the asymmetric synthesis of natural products such as coniine (94) (Scheme 36).82,83

The asymmetric Mannich reaction of O-pivaloylated galactosyl substituted imines 95 with bis-O-trimethylsilylketeneacetals 96 leads to the selective formation of $\beta$-amino acids 97 or esters 98. In general, of the four possible diastereomers only the two threo-isomers were observed (Scheme 37).74

The galactosyl auxiliaries can often be recovered as galactosylalcohols 99 in quantitative yields after cleavage by treatment with dilute HCl in methanol (Scheme 38).74 Cleavage of an ester-bound auxiliary under alkaline hydrolysis results in the formation of carboxylic acids like 101 and auxiliary 79 in high yields, allowing a recycling of the chiral auxiliary.84–86
First introduced by Enders and Eichenauer in 1976, (S)-1-amino-2-methoxymethylpyrrolidine (SAMP) and (R)-1-amino-2-methoxymethylpyrrolidine (RAMP) have become commonly used chiral auxiliaries for organic synthesis. The auxiliary SAMP is available in four steps starting from (S)-proline, RAMP can be synthesized in six steps from glutamic acid. Both enantiomeric forms of the auxiliary are also commercially available. Moreover, a number of related, albeit sterically more demanding, auxiliaries like SADP, SAEP, SAPP and RAMBO have been developed (Figure 5).

**5 RAMP, SAMP**

SAMP- or RAMP-containing hydrazone substrates like 104 are easily prepared by condensation of SAMP/RAMP with the appropriate aldehyde or ketone under rather mild reaction conditions (Scheme 39).

![Scheme 39](image)

**Scheme 39** Synthesis of RAMP-hydrazones.

α-Alkylation of chiral hydrazones still represent the most popular application of these auxiliaries. Deprotonation of the hydrazone substrates with lithium bases results in an enamine forming a six-membered chelate (e.g. 105). In this rigid structure, the auxiliary shields the enamine top face and as a consequence, alkylation from the bottom face is favored (Scheme 40). In addition, these hydrazone auxiliaries can be used in various organic reactions such as aldol reactions, Michael additions, rearrangements, nucleophilic addition reactions to the C=N double bond, Diels–Alder reactions and synthesis of organometallic substrates like substituted ferrocenes. Some important recent advances are presented in the following paragraphs.

![Scheme 40](image)

**Scheme 40** Proposed mechanism for α-alkylations of SAMP-hydrazones.

Ferrocenyl ligands are of increasing interest for asymmetric catalysis in academia and industry. Therefore, the asymmetric synthesis of planar- or central chiral ferrocenes with phosphorus, sulfur and nitrogen substituents is an important goal. Starting from SAMP-derived hydrazones, Enders et al. successfully used the auxiliary to control central as well as planar chirality in the synthesis of ferrocenes (Scheme 41).

![Scheme 41](image)

**Scheme 41** Synthesis of ferrocenes.

Subsequent functionalization of the side chain of 107 and of the ortho-position in 108 can be executed with several electrophiles. The first deprotonation is carried out with LDA, whereas a stronger lithium base has to be used for the directed ortho-metallation. High yields and stereose-
lectivities were obtained with nine different substrates. Finally, reductive cleavage of the auxiliary in two steps liberated the ferrocenyl ligand 109 in moderate yield and high enantioselectivity.

More recently, SAMP was employed by Enders et al. in the synthesis of the planar chiral 2-monosubstituted diferrocenyl ketones 110 (Scheme 42). For all reported electrophiles the alkylation step proceeds with 96% de. This sequence provides ready access to a novel class of planar chiral ferrocenyl ligands containing a diferrocenyl ketone backbone.

Dihydroxyacetone phosphates (DHAP) are used in nature as C2-building blocks for enzyme-catalyzed asymmetric aldol reactions leading to carbohydrates. Hydrazones like 111 are currently of interest as chiral dihydroxycetone synthons in organic synthesis. With the SAMP-hydrazone 111, high selectivities can be achieved in asymmetric α-alkylations forming 112 (Scheme 43). An aziridine, Michael acceptors, alkyl halides and a silyl triflate were successfully employed as electrophiles in these reactions. In addition, a bisalkylation using the same or different electrophiles proceeded with impressive selectivities to yield 113.

The versatility of these hydrazine auxiliaries is reflected in applications in the asymmetric synthesis of important building blocks such as aza- or deoxy sugars or the total synthesis of natural products like (+)-aspiricillin. The demand for enantiomerically pure fluorinated compounds for medicinal chemistry, crop science or materials science is constantly increasing. In 1998 the asymmetric induction reported for the synthesis of α-alkoxy-α-trifluoromethyl aldehydes using the RAMP/SAMP methodology was still low (51:49 to 81:19 dr). More recently, Enders and co-workers published an efficient synthesis of α-trifluoro methyl-substituted primary amines using a highly diastereoselective nucleophilic 1,2-addition of alkyl lithium reagents to SAMP-hydrazone 114. Under optimized reaction conditions, 115 was obtained in moderate yields but with very high diastereoselectivities (>96% de) (Scheme 44). Purification by column chromatography increased the diastereomeric purity even further (>98% de). Only the addition of phenyllithium remains unsatisfactory, giving the desired product in a disappointingly low yield of 15%. Benzoylation of 115 provided hydrazides 116, which could be converted to the corresponding enantiomerically pure α-trifluoromethyl substituted amides 117 by reductive cleavage with SmI2 in THF (Scheme 44).

In general, oxidative, hydrolytic and reductive cleavage conditions allow the synthesis of the corresponding ketones or aldehydes from the hydrazones 118. Oxidative cleavage is normally accomplished by ozonolysis, with singlet oxygen, aqueous sodium periodate, sodium perborate or other oxidizing agents releasing the ketone or aldehyde products. Often, the auxiliary can be isolated as the nitrosamine and easily transformed back to the hydrazine auxiliary. Oxidative cleavage with H2O2 or with per-
acids like m-chloroperoxybenzoic acid (MCPBA) or MeCO$_3$H, leads to the formation of the corresponding nitriles. Hydrolysis can be achieved with CuCl$_2$, Cu(OAc)$_2$, oxalic acid, methyl iodide/HCl (salt method) or (NH$_4$)H$_2$PO$_4$. Finally, the reductive cleavage with TiCl$_3$, SnCl$_2$ or Cr(OAc)$_2$ was reported in some cases (Scheme 45).$^{106}$

**Scheme 44** Stereoselective nucleophilic 1,2-addition to SAMP-hydrazones.

![Scheme 44](image1)

6 Alcohols, Amines, Amino Alcohols

Alcohols, amines and amino alcohols are versatile chiral auxiliaries that have been successfully applied in numerous reactions.$^{107-109}$ Although chiral alcohols can easily be attached to suitable substrates by esterification, their use as chiral auxiliaries is mainly limited to a few nucleophilic addition reactions.$^{110,111}$ cycloadditions$^{112}$ or radical reactions.$^{113}$ Typically, alcohols such as pantolactone 119a,$^{107}$ pantolactam 119b (Scheme 46),$^{114}$ cyclohexanols,$^{113}$ and diphenylethanedio$^{116}$ have been used successfully.

Much more frequently used auxiliaries are the readily available chiral amines such as phenylglycine amide or phenylethylamine 120.$^{108}$ Most often, they are introduced into the substrate as imines (Scheme 46). Chiral amine auxiliaries have been successfully applied in nucleophilic addition reactions to C=N double bonds,$^{115}$ hydrogenations$^{116,117}$ and Michael addition reactions.$^{118}$

In general, chelating auxiliaries allow the formation of highly ordered, cyclic transition states often resulting in high levels of stereocontrol. Therefore, it does not come as a surprise that chiral amino alcohols are especially useful auxiliaries.$^{109,119}$ In this respect, ephedrine is an especially important amino alcohol. Ephedrine and pseudoephedrine 121 are commercially available, cheap and no further modification is needed prior to their use. However, legislative restrictions may apply since they are possible drug precursors. Incorporation of the aminoalcohol into the substrate by imine or amide formation (Scheme 46) allows for an easy introduction, non-destructive cleavage, and reuse of the auxiliary. Successful applications of ephedrine auxiliaries$^{120}$ can be found in the areas of Mannich reactions,$^{121}$ alkylation$^{122}$ and aldol reactions.$^{123}$

**Scheme 45** Conditions for cleavage of the hydrazone auxiliaries.

![Scheme 45](image2)

6.1 Alcohols as Auxiliaries

Numerous applications of pantolactone (119a) in asymmetric synthesis have been reported.$^{107}$ An industrially relevant application is the highly selective Lewis acid catalyzed Diels–Alder reaction of D-pantolactone-substituted substrate 122 originally developed by Helmchen and co-workers.$^{124a}$ Treatment with cyclopentadiene and a catalytic amount of TiCl$_4$ in CH$_2$Cl$_2$–petroleum ether led to the highly stereoselective formation of the corresponding Diels–Alder product. The diastereomeric excess of the product was significantly increased to >99.8% by crystallization. For the scale-up to kilogram scale and in order to reduce the cost of this process, conditions were developed by Chang et al. to allow for the recovery of the chiral auxiliary. Successful applications of ephedrine auxiliaries$^{120}$ can be found in the areas of Mannich reactions,$^{121}$ alkylation$^{122}$ and aldol reactions.$^{123}$
filtrate resulted in lactonization and provided the enantiomerically pure D-pantolactone auxiliary in good yield, thus allowing for the recycling of the auxiliary. Overall, this represents a highly stereoselective, cost-efficient application of pantolactone.\textsuperscript{124}

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme47}
\caption{Asymmetric Diels–Alder reaction, product isolation by precipitation, and efficient recovery of the chiral auxiliary.}
\end{scheme}

An innovative application of a chiral $C_2$-symmetric diol for the asymmetric synthesis of amines was reported by Charette and co-workers.\textsuperscript{125} Starting from ($R,R$)-1,2-diphenylethylene-1,2-diol (123), orthoacylimines were prepared in two steps. Addition of organolithium reagents to 124 followed by removal of the auxiliary by acidic hydrolysis in a one-pot procedure revealed the chiral amine 125 and auxiliary diol 123 (Scheme 48).\textsuperscript{110,125} It was shown that an appropriately substituted 125 ($R_1 = t$-Bu, $R_2 = \text{Ph}$) can be transformed into precious enantiomerically pure tert-leucine in three simple steps. High selectivities, mild conditions for auxiliary cleavage, and recovery of the auxiliary render this method attractive.

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme48}
\caption{Nucleophilic addition to chiral orthoacylimines.}
\end{scheme}

An efficient application of a lactol as a chiral reagent has recently been reported by Dixon and co-workers.\textsuperscript{126,127} Therein, highly diastereoselective oxy-Michael additions are accomplished, resulting in chiral tetrahydropyranol ethers.\textsuperscript{128,129}

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme49}
\caption{Asymmetric Michael addition under high pressure.}
\end{scheme}

In a more recent publication, Sato and co-workers described a related carbon–carbon coupling reaction. Addition of a chiral ($\eta^2$-imine)Ti(Or-Pr)\textsubscript{2} complex 131 to terminal or substituted alkynes led to allyl- or $\alpha$-allenylamines (Scheme 51).\textsuperscript{138} $\beta$-Elimination of an intermediate

6.2 Amines as Auxiliaries

D’Angelo and co-workers developed a highly stereoactive Michael addition using ($R$)-phenylethylamine\textsuperscript{130} derived imine 126 (Scheme 49).\textsuperscript{131–133} Intriguingly, whereas thermal activation of these reactions fails, activation by high pressure overcomes the steric hindrance that arises in the course of the addition process. The high selectivities obtained are a result of an energetic preference for conformations with minimized 1,3-allylic strain in the intermediate enamine moiety. Interestingly, with phenylcrotonates, a product of type 127 is not observed; instead, the reaction affords bicyclic lactams by N-heterocyclization of the transient Michael adduct.\textsuperscript{134,135}

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme50}
\caption{Asymmetric synthesis of allenylamines.}
\end{scheme}
azatitanacyclopentene resulted in synthetically useful products 132 or 133. In these reactions, an amine auxiliary with a second coordination site (2-methoxy-1-phenylethylamine) was essential for obtaining high enantiomeric excess. The authors proposed that the reaction proceeds through the chelated, six-membered chair-like titanacycle 134 to result in the high selectivities (Scheme 52). 138

The asymmetric synthesis using (S)-valinol or (S)-tert-leucinol derived methyl- or TMS-protected amino ethers as chiral auxiliaries also profits from the capacity to form a chelate with zinc chloride (135 and 136, Scheme 53). 139 This reaction proceeded in high yields and selectivities with a series of cyclic imines. The use of a sterically more-demanding TBDMS protecting group on the alcohol moiety decreased both the yield (14%) and stereoselectivity (55% ee) significantly.

In addition to ethylene, other alkenes like propene and styrene can also be employed with good results. Furthermore, treatment of the γ-zincimine intermediates 136 with electrophiles other than H⁺ allowed for an interesting functionalization and resulted in products 137–139 (Figure 6). 140–143 Chelation also plays an important role in the mode of action of chiral amino acid amide auxiliaries. (R)-phenylglycine amide is an efficient auxiliary for the asymmetric allylation of amino-acid-derived imines 140 developed by Kellogg and co-workers (Scheme 54). 144 Many differently substituted imine substrates 140 result in highly selective transformations. In the proposed six-membered chair transition state 141, the organozinc reagent is chelated by the C=O function of the amide and the N-atom of the imine. This leads to the highly selective formation of the observed product. The diastereomeric chair transition state is less favorable, since the phenyl substituent of the auxiliary would interact unfavorably with the allyl group (Scheme 54). Related auxiliary-modified imines can be used in asymmetric Strecker reactions with good yields (76–93%) and excellent diastereoselectivities (de > 98%). 145

Scheme 53 Asymmetric alkylation of zinc enamides with ethylene.

Figure 6 Functionalized products.

Scheme 54 Asymmetric alkylation reaction.
More recently, an impressive asymmetric hydrogenation using (S)-phenylglycine amide as chiral auxiliary was reported by Ikemoto, Tellers, Rivera and co-workers.116,117 The substrates 142 can easily be prepared from the corresponding β-keto esters or amides. The amine of the resulting Z-enamine 142 acts as a hydrogen-bond donor and forms hydrogen bonds with both carbonyl groups, resulting in a rigid, mostly planar structure. As a consequence, the phenyl substituent of the auxiliary shields one of the two diastereomeric n-faces of the enamine (top face in Scheme 55). Diastereoselective hydrogenation of the double bond from the less-hindered face resulted in the formation of precious optically active β-amino acid derivatives 143 (Scheme 55).116,146

Scheme 55  Asymmetric hydrogenation of chiral enamines.

A further noteworthy application of chelating amine auxiliaries is the copper-catalyzed Michael addition of chiral enamines 144 to electron-deficient alkenes developed by Christoffers and Mann.147 In this highly asymmetric synthesis of chiral cyclohexanone derivatives 145, valine- or tert-leucine-derived amides were used as chiral auxiliaries (Scheme 56). Interestingly, the auxiliary is hydrolytically cleaved under the reaction conditions, making an additional cleavage step unnecessary. More recent reports from Christoffers and co-workers dealt with the synthesis and application of exocyclic enamines, resulting in a switch of configuration of the resulting product stereocenters.148,149 However, the yields and stereoselectivities obtained in this process were only moderate.

Scheme 56  Enantioselective synthesis of cyclohexanone derivatives.

6.3 Amino Alcohols as Auxiliaries

Another class of important chiral auxiliaries capable of forming chelates are the amino alcohols. Ephedrine derivatives are especially popular in this respect. The asymmetric alkylation of substrates attached to pseudoephedrine is a very efficient method for the synthesis of optically active carboxylic acids or amino acids. Myers developed a high-yielding and highly stereoselective alkylation of amides 146 with alkyl halides RX (Scheme 57). The broad scope renders this reaction to be of great synthetic interest. Of the examples given in Scheme 57, only the reaction with BOMCI results in a low diastereomeric excess (33%) of product 147.150 This method also gives ready access to D- and L-amino acids of high optical purity – up to >99% de (Scheme 57, b).151 Organofluorine compounds, especially those that are enantiomERICally pure, are increasingly important for many areas of chemistry and their synthesis using this auxiliary-based method was investigated. The use of pseudoephedrine-derived α-fluoroacetamides as starting materials resulted in the highly stereoselective formation of chiral organofluorine compounds (Scheme 57, c).152

Scheme 57  Asymmetric alkylation of various substrates 146.

An efficient asymmetric synthesis of α-methyl-β-amino esters by stereoselective Mannich reaction was reported by Badía and co-workers applying (S,S)-(−)-pseudoephedrine as the chiral auxiliary (Scheme 58).153 Non-enolizable as well as enolizable imines can be successfully employed in this transformation, and in all cases excellent stereoselectivities were obtained. A six-membered chelate transition state 148 formed by the amide enolate and the imine is proposed and, in addition, the alcohol of pseudoephedrine is thought to coordinate to the lithium reagent. Finally, the products 149a can be easily converted to α,β-disubstituted aminoesters or β-lactams in good yields and with enantiomeric excesses of >99% in all reported cases.

Whereas the auxiliary-bearing chiral amide enolate was used as the nucleophile, the pseudoephedrine-derived α,β-unsaturated amide 150 was employed as the electrophile in an aza-Michael reaction (Scheme 59). This aza-Michael reaction leads to the formation of β-amino amides 151.
 Rather reactive lithium benzylamides had to be used as nucleophiles since simple amines, like benzylamine, resulted in the recovery of starting material (Scheme 59).120,154 Some more recent examples for the use of ephedrine derivatives as chiral auxiliaries in asymmetric synthesis, for example in aldol reactions, have been reported.123,155,156

Another related class of chiral auxiliaries are amino acids and amino acid esters.119 Most often, however, cyclic derivatives of these compounds are used and these are discussed elsewhere in this review.

6.4 Cleavage

In most cases, the auxiliaries are attached to the product by an ether, amide or imine bond and hydrolysis under acidic conditions proceeds smoothly. For example, imine 152 or amide 147 can be converted into the corresponding ketone 153 or carboxylic acid 154 by hydrolysis (Scheme 60). Under these conditions, the auxiliaries can often be recovered. Alternatively, reductive cleavage of amides with borane–lithium pyrrolidide or LiAlH(OEt)3 yields the desired alcohol or aldehyde, respectively.122

7 Oxazolidinones, Oxazolines and Oxazolidines

Amino alcohol derived oxazolidinones 155, oxazolines 156 and oxazolidines 157 are members of arguably one of the most commonly used classes of chiral auxiliaries in organic synthesis (Figure 7).110,157–160 The popularity of these auxiliaries relies on their ready availability, the generally high diastereoselectivities obtained for many transformations and the rather facile introduction and cleavage of the auxiliary. Oxazolidinones are linked to the substrate through their N atom, most often by an N-acylation resulting in N-acyl oxazolidinone products 164.157,158 On the contrary, the oxazolines 165 are generally connected to the substrate by their 2-position (Rsubstrate in Figure 7). Meyers has popularized the use of oxazolines in organic synthesis and many routes for the synthesis of enantiomerically pure oxazolines exist.159 In general, they can be prepared from a carboxylic acid derivative of the substrate and the appropriate amino alcohol (route 1). Alternatively, a preformed oxazoline can be linked to the substrate (route 2). Oxazolidines 166 can be bound to the substrate at the N atom or at the 2-position. In the latter case, the oxazolidine ring is readily prepared by reaction of the substrate aldehyde with an appropriate amino alcohol (Scheme 61).160

7.1 Oxazolidinones

Oxazolidin-2-ones, first introduced by Evans et al. in 1981,161 have found widespread applications and a great wealth of structural modification of these auxiliaries has...
Representative oxazolidinones (also commonly called Evans auxiliary) are the very popular monosubstituted oxazolidinones 158 [for example (S)-4-benzyl-2-oxazolidinone 158a] and the more highly substituted oxazolidinones 159, 160, camphor-derived 161,166 carbohydrate-derived 162,167 or SuperQuats 163162,163 (Figure 8). Furthermore, related auxiliaries using other heteroatoms like imidazolidinones,168,169 thiazolidine thiones170–173 or oxazolidinethiones170,174,175 have also been successfully used.

Even though oxazolidinones are linked to the substrate via a single bond only, additional factors like chelation (167)176 or dipole-moment minimization (168, 169)161,177,178 often lead to preferred conformations (Scheme 62) in which the substituent R1 of the oxazolidinone efficiently shields one of the molecule’s diastereotopic faces. As a consequence of this type of energetic preference for certain rotamers, in many cases very high stereoselectivities are obtained. Asymmetric aldol reactions, alkylations and pericyclic reactions are traditionally the most important areas of usage for these auxiliaries.110,157–160

The versatility of oxazolidinone auxiliaries is nicely demonstrated by their numerous applications in aldol reactions (Scheme 63).110,157,158 Proper choice of reagents and reaction conditions allows access to all four diastereomers. In this respect, boron enolates are very popular since, as a result of short B–C and B–O bonds, they form tighter transition states, generally leading to higher selectivities. As a consequence, the reaction of Z-boron enolates of the acyl oxazolidinones with an aldehyde generally leads to the highly selective formation of syn products 170 (also called ‘Evans syn’ aldol product).178 Arguably, this represents one of the most popular applications of acyl oxazolidinones. In some cases, the additional use of a large Lewis acid like Et2AlCl allows the formation of anti products 172.176

Chelate-controlled methods usually result in the formation of ‘non-Evans’ products. The use of titanium enolates (also Li, Zn or Sn)136 gives rise to ‘non-Evans syn’ products 171.170b The synthesis of ‘non-Evans anti’ products 173 (Scheme 63) was recently reported in a MgCl2-catalyzed aldol reaction by Evans et al. (Scheme 64).179 The use of TMSCI allowed the turnover of the metal complex by silylation of the anti-aldol products. It appears that there is a delicate balance between silylation of the aldolate and the retro-aldol reaction and that the anti diastereomer is silylated in preference to the syn isomer. Cleavage of the silyl protection group results in the formation of the unprotected products 176. Instead of oxazolidinones, the reaction can also be run with related N-acetylthiazolidinethiones,177 the advantage of these sulfur-containing oxazolidinones being the milder cleavage conditions.176b

Modification of the acyl substituents of substrate 175 over a wide range does not result in a deterioration of yields and diastereoselectivities as long as no β-branched substituents are used. However, only non-enolizable aldehydes can be successfully used, whereas enolizable aldehydes result in their own undesired self-condensation. Mechanistic studies show that no enolsilane is formed and that the reaction does not proceed by a Mukaiyama aldol reaction.
Silylation of the metal aldolate is essential for the catalytic process, since the equilibrium of the reversible aldol reaction is shifted towards the silylated aldol products.\textsuperscript{173,179}

Scheme 64  Asymmetric magnesium halide catalyzed aldol reaction.

Optically active polyhydroxylated products can be obtained by an oxy-aldol reaction wherein the substituent R\textsuperscript{2} of the oxazolidinone substrate 164 contains an \(\alpha\)-alkoxy substituent.\textsuperscript{180–182} This oxo-aldol methodology has found many applications in the synthesis of natural products. For example, it allowed for the asymmetric synthesis of interesting seven-, eight- and nine-membered rings by Crimmins and co-workers.\textsuperscript{181,182} Originally, an auxiliary-controlled aldol reaction was used to build precursors for a metathesis reaction leading to up to nine-membered rings.\textsuperscript{182} Recently, the total syntheses of a number of natural products like (+)-prelaureatin, (+)-laurallene and (–)-isolaurallene were completed using this aldol technology.\textsuperscript{183,184}

It is important to note that the recent developments in the area of organocatalysis and especially enamine catalysis using proline have resulted in powerful methods for enantioselective aldol reactions for many different classes of substrates.\textsuperscript{185,186}

A recent example for an asymmetric alkylation utilizing an oxazolidinone auxiliary is part of the synthesis of bicyclooctanone 179, a useful building block for the synthesis of the diterpenoid vinigrol.\textsuperscript{187} Conversion of 177 with LDA and allylbromide leads to 178 in excellent yield and diastereoselectivity (Scheme 65).

The stereochemical outcome of pericyclic reactions can also be efficiently controlled by oxazolidinone auxiliaries. Diels–Alder reactions, especially those that are intramolecular, lead to a significant increase in structural complexity.\textsuperscript{188–190} Quite recently, Evans et al. reported on a useful aldol/Diels–Alder reaction sequence.\textsuperscript{188} Enantio-merically pure 180 was prepared by an Evans syn aldol reaction, followed by a Parikh–Doering oxidation. Intriguingly, the cycloaddition of oxazolidinone-substituted substrate 180 leads to the bicyclic product 181 in high diastereomeric excess. Subsequent conversion of the acyloxazolidinone to a thioester, followed by decarboxylation, removed the auxiliary and the initially created ring stereocenter. Finally, treatment with the Tebbe reagent gave rise to enantiomerically pure \(\alpha\)-himachalene (182) (Scheme 66).\textsuperscript{188,189}
An asymmetric samarium diiodide mediated Reformatsky reaction of α-bromoacetoxyazolidinones 183 was recently reported by Fukuzawa et al.191 A variety of differently substituted azolidinones lead to the desired products in good to excellent yields and high diastereoselectivities. The use of 5,5-disubstituted azolidinone 163 (Super-Quat, $R^2 = \text{Me or Ph}$) resulted in lower yields but slightly improved diastereoselectivities (Scheme 67).191,192

### Scheme 67 Oxazolidinone auxiliaries in asymmetric Reformatsky reactions.

Steric control of reactions with singlet oxygen is a challenging problem. Wirth, Adam, and co-workers reported on the successful use of oxazoline auxiliaries in diastereoselective [4+2] cycloadditions with singlet oxygen as dienophile in 1998.193 More recently, oxazolidinone-functionalized enecarbamates 184 were used in [2+2] cycloadditions with $1O_2$ by Bosio, Adam, and Turro (Scheme 68).194 The high levels of diastereoselectivity were explained to be a result of steric repulsion caused by the $R^1$ substituent of the auxiliary. The other stereocenter at C3 is without any significant influence, as can be seen by the fact that the use of an achiral oxazolidinone ($R^1 = \text{H}$) leads to an unselective formation of the two diastereomers of 185. In addition, switching from the $R$- to the $S$-configured auxiliary leads to the highly selective formation of the corresponding diastereomeric product.194,195

Although examples of selective free radical reactions have been reported in recent years,199 stereoselective radical reactions are still a great challenge in organic synthesis. Pioneering work by Sibi and co-workers dealt with the application of oxazolidinone auxiliaries in conjugate β-radical additions (Scheme 70).200,201 Rare-earth Lewis acids and especially Yb(OTf)$_3$ provided the best results in terms of diastereoselectivity. It turned out that a large substituent (i.e. diphenylmethyl) on the oxazolidinone of substrate 188 resulted in much higher diastereoselectivities than smaller substituents like phenyl, isopropyl or benzyl.202–208

Oxazolidinone-substituted substrates have also successfully been employed in heterogeneous catalysis. Prakash et al. developed a stereoselective synthesis of (2S,3R)-erythro-methyl phenidate 189, the key step being an oxazolidinone-controlled hydrogenation of a tetrasubstituted double bond.209 The excellent diastereoselectivity obtained in this reaction is a result of an energetically pre-

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**Scheme 66** Asymmetric Diels–Alder reaction; $X_c = 4-\text{4-(S)-benzyl-2-oxazolidinone.}$

**Scheme 67** Oxazolidinone auxiliaries in asymmetric Reformatsky reactions.

**Scheme 68** [2+2] cycloaddition of singlet oxygen and oxazolidinone-functionalized enecarbamates; TPFPP = 5,10,15,20-tetrakis(pentafluorophenyl)porphine (sensitizer).

The combination of multiple transformations in a single step is highly desirable, since it often rapidly increases the structural complexity of the substrate. This kind of tandem reaction can also benefit from oxazolidinone auxiliaries, as showcased by Hsung and co-workers. A tandem epoxidation, epoxide opening and [4+3] cycloaddition of chiral allenamide 186 led to product 187 with high diastereoselectivity (Scheme 69).196 The intermolecular variant of this reaction resulted in good stereoselectivities as well.197 This method might become an important tool for the synthesis of complex natural products.198
ferred conformation caused by a hydrogen bond and by a minimization of the molecule’s overall dipole moment. As a consequence, the benzyl substituent of the oxazolidinone moiety shields the bottom face of the molecule and hydrogenation takes place from the opposite top face (Scheme 71).

Another recent application of oxazolidinones in heterogeneous catalysis is instructive, too. A variety of 2-oxazolidinone-substituted pyridines was selectively hydrogenated to enantiomerically pure piperidines by Glorius et al. This method represents the first auxiliary-mediated asymmetric hydrogenation. Pyridines were selectively generated in a single step (Scheme 71).192

Scheme 71 Asymmetric hydrogenation of a highly substituted double bond.

2. minimization of dipole moment

Asymmetric hydrogenation catalyst and the successive hydrogenation takes place from the opposite top face of the molecule is available for attack by the heteroeneous catalysis is instructive, too. A variety of 2-oxazoline-substituted pyridines was selectively hydrogenated to enantiomerically pure piperidines by Glorius et al. This method represents the first auxiliary-mediated highly stereoselective pyridine hydrogenation. Pyridines 190 (4-, 5- or 6-substituted) as well as multiply substituted derivatives lead to products 193 in high yields and high enantiomeric excess. Up to three ring stereocenters of compound 193 and four ring stereocenters of compound 192 were selectively generated in a single step (Scheme 72).177 The proposed mechanism starts off with the protonation of 190. As a consequence of a hydrogen bond formed in pyridinium salt 191, the i-Pr group of the auxiliary shields the top face, whereas the unhindered bottom face of the molecule is available for attack by the heterogeneous hydrogenation catalyst and the successive hydrogenation. Cleavage of the resulting aminal 192 under slightly acidic conditions (AcOH) and hydrogenation of the imine/enamine intermediates gave product 193. Many attractive features, like high yields and selectivities, traceless cleavage of the oxazolidinone auxiliary under the reaction conditions, and facile separation and purification of the piperidine products, arguably render this reaction to be one of the most efficient applications of chiral auxiliaries.

Scheme 72 Plausible mechanism for the asymmetric heterogeneous hydrogenation of pyridines.

7.2 Oxazolines

2-Oxazolines (also called 4,5-dihydrooxazoles) have less often been used as chiral auxiliaries. Exciting recent applications can be found in the area of C–H bond activation, which is a powerful method for the functionalization of organic molecules. However, it is often limited by low tolerance for functional groups, restriction to aryl groups and other activated C–H bonds, and stereoselectivity is as yet an untackled problem. An important step towards this goal is an exciting asymmetric C–H bond activation with the help of an oxazoline auxiliary reported by Sames and co-workers. Preformed platinum complexes 194 allowed a stereoselective dehydrogenation, giving rise to products 195 (Scheme 73).211 A delicate temperature dependence of the diastereoselectivity of this C–H bond activation was observed. The highest stereoselectivity was obtained with the tert-butyl-substituted oxazoline (>90% de), however the product could not be isolated (conversion <10%). It has to be noted that, even though stoichiometric amounts of a noble metal had to be used for this step and only moderate selectivities and yields were obtained, this is a trendsetting transformation. Two more steps completed the short synthesis of the natural product (–)-rhazinilam.210

Another stereoselective C–H bond activation has very recently been reported by Yu and co-workers. The asymmetric palladium-catalyzed iodination of unactivated C–H bonds occurred with high diastereoselectivities and good yields, forming products 197 and 199 (Scheme 74).211 Both sp³ and sp²-hybridized carbons can be functionalized in this reaction. Interestingly, a secondary C–H bond of a cyclopropane can be iodinated in the presence of a methyl group in reasonable yield (65%) and very high diastereoselectivity (98% de).159,211,212
Oxazolidines have found a number of applications as chiral auxiliaries. Some impressive results have been obtained and should be highlighted. However, it is important to note that oxazolidines are rather acid-sensitive and in some cases exist in equilibrium with the open-chain imine alcohol.\textsuperscript{213} Clayden and co-workers showed that a chiral oxazolidine can influence the conformation of a long carbon chain and finally control the addition to an aldehyde group at the opposite end of the molecule (Scheme 75).\textsuperscript{214–216} Most impressively, the auxiliary and the electrophilic aldehyde can be separated by more than 20 C–C bonds, and nevertheless, the Grignard addition to 200 still is highly diastereoselective (\textgt;90\% de) (Scheme 75).\textsuperscript{214} Once again, minimization of the overall dipole moment is key to the success of this transformation. The auxiliary influences the amide next to it and leads to a preferred conformation. The following amides are alternatingly pointing to the back and to the front in order to minimize the dipole moment. Finally, the last one shields one of the aldehyde $\pi$-faces (see 200 and 201).

An insightful synthesis of 1,4-dihydropyridines by a face-selective addition to a cation-$\pi$ complex was reported by Yamada and Morita (Scheme 76).\textsuperscript{217} Addition of silyl ketene acetals to auxiliary-substituted pyridine 202 in the presence of methyl chloroformate resulted in the highly selective formation of 1,4-dihydropyridine adducts 203. By careful choice of the appropriate solvent, the formation of the undesired 1,6-adduct could be strongly suppressed (Scheme 76). X-ray analysis of 202 showed no intramolecular interaction of the two aromatic rings. However, X-ray analysis of the corresponding N-methylated pyridinium derivative of 202 unambiguously showed that a cation-$\pi$ interaction determines the conformation to be 204a (R = Me). The authors postulate that for R = CO$_2$Me, rotamer 204b is energetically favored over 204a, as indicated by $ab$ $initio$ calculations (Figure 9). Addition of the nucleophile to the less-shielded $st$ face of 204b would result in the observed highly selective formation of 203.\textsuperscript{217}
Another recent example for the use of oxazolidine auxiliaries is the asymmetric epoxidation of acetylated or carbamoyl-substituted oxazolidines 205 reported by Schambony and co-workers.218,219 A hydrogen bond between the urea functionality NH and the oxidant seems to be important for high stereoselectivities. This can be deduced from a reversal in stereoselectivity in the case where the substrate with \( R^1 = \text{Me} \) is employed (26:74 dr). The epoxidation reaction can be run with dimethyldioxirane (DMD) (Scheme 77) or alternatively with \( m \)-chloroperbenzoic acid, resulting in slightly lower yields and diastereoselectivities of products 206.219–223

Scheme 77 Asymmetric epoxidation of oxazolidine-substituted double bonds.

### 8 Conclusion

The recent applications of chiral auxiliaries presented in this review show a high level of sophistication. Low cost and ready availability, ease of introduction and cleavage of the auxiliaries, as well as high levels of predictability, reliability, time-efficiency and stereoinduction, often render auxiliaries an attractive method in asymmetric synthesis. In addition, and contrary to other methods of asymmetric synthesis, facile purification of the auxiliary-substituted product diastereomers allows for very high enantiomeric purities of the final products after removal of the auxiliary. Future research will most likely focus on the application of auxiliaries in challenging transformations and increasingly efficient methods. In this context, processes using temporary or catalytic auxiliaries might become role models for future developments.

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