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Recent developments in chiral non-racemic sulfinyl-group chemistry in asymmetric synthesis

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Dedicated to Prof. A. McKervey on the occasion of his retirement from the Queen’s University Belfast
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Abstract
Chiral sulfinyl groups have been widely used in organic synthesis as a stereo- and enantiodirecting functionality and the high efficiency of the selectivity has received much attention in recent years. In this review we wish to cover the work published in the literature since 1996. The participation of a chiral sulfinyl function in a wide range of reactions as well as the application of these methodologies to the synthesis of natural products are reported.

Keywords: Sulfoxide, Sulfinyl group, asymmetric synthesis, chiral auxiliary, chiral ligand

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1. Introduction

Over the two last decades, chiral three coordinate sulfur compounds have received considerable attention as key intermediates in asymmetric synthesis\(^4\) or as pharmaceutical goals.\(^2\) Among them, sulfoxides have been employed for a wide range of stereoselective carbon-carbon or carbon-heteroatom bond forming reactions.\(^3,6\) The use of optically active sulfoxides as chiral controllers in highly selective asymmetric synthesis is now a reliable method as their synthetic versatility is continuously demonstrated. Some excellent reviews by Drabowicz,\(^4\) Walker,\(^5\) and Carreño\(^6\) from 1988, 1992 and 1995 illustrate this expansion. Developments in the use of chiral non-racemic sulfoxides up to 2002 will be covered in this review with a particular attention to
the use of sulfoxides in homogeneous catalysis. Moreover, we will focus on the general applicability of methods from a synthetic organic chemist's point of view.

This review is divided into three sections. The first one deals with the stereoselective generation of new stereogenic centres using a chiral sulfinyl group as auxiliary. The second one will focus on homogeneous asymmetric transition metal catalysis using sulfoxides as source of chirality. Finally, the asymmetric transformation of the chiral sulfinyl group leading to new stereogenic centres will be described in the last section.

The chemistry of C$_2$ symmetric sulfoxides will not be mentioned in this paper since they have been reviewed very recently.$^7$

2. Use of the sulfinyl group as chiral auxiliary in stoichiometric stereoselective reactions

This area has lately received a lot of attention in asymmetric synthesis as a great number of stereoselective transformations involving sulfoxides have been described in the chemical literature. Although few conceptually new methods have been developed, we have selected in this section only recent insights of generally well-established methodologies.

This part is divided in several sections related to the sulfinyl-containing reactive species involved in stoichiometric diastereoselectives transformations.

2.1. Reactions involving keto sulfoxides

2.1.1. Nucleophilic additions to $\beta$-keto sulfoxides

Nucleophilic additions to enantiomerically pure $\beta$-keto sulfoxides have been widely used in asymmetric synthesis of carbinols. Alkylation and hydrocyanation reactions of these compounds with aluminium reagents have been reported to stereoselectively produce tertiary alcohols or cyanohydrins respectively, but the most used reaction has been the stereoselective synthesis of secondary alcohols using Dibal-H and Dibal-H/ZnX$_2$. These reagents can also be used with $\beta$-iminosulfoxides affording enantiomerically pure amines.

2.1.1.1. Reductions

One of the most versatile methods to obtain enantiomerically pure secondary carbinols involves the reduction of the corresponding enantiomerically pure $\beta$-keto sulfoxides with Dibal-H or Dibal-H/ZnX$_2$ followed by either hydrogenolysis of the carbon-sulfur bond or reductive Pummerer rearrangement of the resulting $\beta$-hydroxysulfoxides. The diastereoselective outcome in the reduction with Dibal-H is derived from intramolecular hydride transfer through a six-membered cyclic transition state, whereas the Dibal-H reduction in the presence of a Lewis acid gives the epimer at the hydroxylic centre, which is rationalised by a conformationally rigid six-
membered cyclic intermediate involving chelation of the Lewis acid to the sulfinyl and carbonyl oxygen. Application of this methodology in enantioselective synthesis of diols and total synthesis of natural products has been reviewed recently.\(^8\) Natural products such as (+) isobretonin A\(^9\) 1, (+) virol C\(^10\) 2 or (-) macrolactin A\(^11\) 3 have been prepared using this methodology as one of the key steps (Figure 1).

![Figure 1](image_url)

**Figure 1**

An efficient stereoselective synthesis of (-)-(R,R)-muricatacin has been recently reported.\(^12\) The enantiomerically pure γ,δ-unsaturated β-hydroxysulfoxide 4 is regio- and diastereoselectively transformed to the corresponding bromohydrin 5 via the cyclic sulfoxonium salt\(^12b\) intermediate 6 (Scheme 1).

![Scheme 1](image_url)

**Scheme 1**

Chiral α-acetylenic epoxides 7 and 8, which are versatile building blocks in natural products synthesis, have been prepared from propargylic esters by a three-step sequence with enantiomeric excesses that are higher using Dibal-H/ZnBr\(_2\) than Dibal-H alone (Scheme 2).\(^13\) The authors explain the lower observed de values compared to reduction of alkyl keto sulfoxides by a lower ability of the conjugated carbonyl group in compounds 10 to become chelated.
Scheme 2

The presence of an alkyl substituent in the α-position maintains the high level of diastereoselectivity in the Dibal-H/ZnBr₂ reduction when appropriate conditions are used.¹⁴ Generally, stereocontrol is modest in absence of the chelating agent and treatment of α-alkylated β-ketosulfoxides with Dibal-H produces diastereoisomeric mixtures. Later on, Bravo et al. obtained similar results with fluoro-substituted α-alkylated β-ketosulfoxides in the course of the synthesis of (R)-Sulcatol and its fluoro analogues.¹⁵

This methodology has been expanded to highly functionalised substrates. Dibal-H reduction of β-ketosulfoxides bearing additional alkoxy, keto, ester, amide, acetal or amine functionalities has been studied, and a predominant role of the sulfinyl group in the stereoselectivity is generally observed.⁸,¹⁶ By contrast in the presence of ZnX₂, when the additional function is able to compete with the sulfinyl group to chelate the metal, the reduction is less stereoselective, yielding a mixture of epimers at the β-hydroxylic centre. For example, Dibal-H/ZnX₂ reduction of β-ketosulfoxides 13 and 14 bearing an ester or an amide in γ position produces the same epimer at β position as major diastereoisomer as with Dibal-H reduction (Scheme 3).¹⁶
Scheme 3

β,δ-diketosulfoxides $17$, which are excellent intermediates for the enantio- and diastereoselective synthesis of $\text{syn}$ and $\text{anti}$ 1,3-diols, give with Dibal-H chemo- and diastereoselectively the corresponding β-hydroxy-δ-keto-sulfoxides $19$ with $de$ up to 95% but with moderate yields (30 to 50%).\(^8,18,19\) We showed recently\(^18\) without any ambiguity using NMR experiments, that the carbonyl group in β-position is totally enolised. This result is inconsistent with the previous hypothesis, which supposed the other tautomer (enolisation at δ−position) as the major one.\(^8,19\) This enolisation induces side-reactions during the reduction of unprotected β,δ-diketo-sulfoxides $17$ leading to $p$-tolyl disulfide and the corresponding ketones $18$ in an equimolecular ratio (Scheme 4). The Dibal-H/ZnX\(_2\) system is unadapted for the reduction of β,δ-diketosulfoxides reduction as it gives only degradation products.\(^17\)

Scheme 4

Protection of the δ-ketone as dioxolane allows the reduction using either Dibal-H alone or Dibal-H/ZnI\(_2\) to produce, after deprotection, both epimers at β position of β-hydroxy-δ-keto-sulfoxides $19$ with high overall yields and high $de$ (>95%).\(^18,20\)

Alternatively, Garcia Ruano et al. showed recently that syn and anti 1,3 diols could be prepared stereoselectively from Dibal-H or Dibal-H/ZnBr\(_2\) (used in large excess) reduction of bis-sulfinylhydroxyketones $20$ (Scheme 5). They demonstrate that the presence of the sulfinyl group completely controls the 1,3 induction.\(^21\)
Scheme 5

2.1.1.2. Alkylations and hydrocyanations

The main contribution to the synthesis of optically active secondary or tertiary cyanohydrins and alcohols from β-ketosulfoxides is due to Garcia Ruano et al. He recently achieved the synthesis of optically active tertiary β-hydroxysulfoxides 24 using different organometallics as nucleophiles leading to the bicyclic precursors of anthracycinones after asymmetric Pummerer reaction (see last section) (Scheme 6). 22

Scheme 6

The hydrocyanation reaction is highly stereoselective and treatment of β-ketosulfoxides with Et$_2$AlCN affords the corresponding sulfinyl cyanohydrins with high yield and de (>96%). The chirality induced at the hydroxylc centre is controlled only by the sulfoxide configuration, which is explained by assuming an intramolecular transfer of the CN group from a pentacoordinate aluminium intermediate. 23a For α-substituted β-ketosulfoxides, the configuration of C-α has no influence on the stereochemical course of the reaction, which is an asymmetric 1,3 induction. In contrast with the reduction of β-ketosulfoxides with Dibal-H, the addition of Lewis acids has little or no influence on the stereoselectivity of the reaction, affording the same diastereoisomer as major product in the same yields than using Et$_2$AlCN alone. The reaction has been successfully applied to the synthesis of enantiomerically pure 2-alkylglycidic acid derivatives 23b and 2,3-disubstituted oxirane-2-carboxamides. 22c Very mild conditions for the reductive
hydrolysis of β-cyanosulfoxides explained by the anchimeric assistance of the sulfinyl oxygen, have broadened the potential of hydrocyanations in asymmetric synthesis.\(^{23d}\)

Secondary cyanohydrins \(^{25}\) leading to the corresponding α-hydroxyamides \(^{26}\) have been prepared with high \(de>90\%)\) from optically pure α-hydroxyaldehydes.\(^{24}\) By contrast with α-keto analogues, the presence of ZnBr\(_2\) is required to obtain good conversions (Scheme 7).

\[\text{Scheme 7}\]

The diastereoselective reduction of β-iminosulfoxides does not behave as in the case of ketones. This was probably due to the lack of efficient methods to prepare enantiomerically pure acyclic α-sulfinyl ketimine since Garcia Ruano \(\text{et al}\) described in 1998 a general one based on α–sulfinylation of ketimine with \((R)\) or \((S)\) menthyl sulfinate.\(^{25}\)

Furthermore, the reduction with Dibal-H gives only poor diastereoselectivity of the resulting β-aminosulfoxide.\(^{26}\) The presence of ZnX\(_2\) is necessary to promote a diastereoselective reduction controlled by the chirality on sulfur (Scheme 8). It shifts the enamine-imine equilibrium towards the reactive imine tautomter. This procedure generally yields β-aminosulfoxides in optical purity higher than 94\% \(de\). The mechanism proposed was very similar to the one used to explain the stereoselectivity of the zinc halide assisted reduction of β-ketosulfoxides. The reagent approach is under steric control that only allows hydride attack from the bottom face of the twisted chair intermediate.

\[\text{Scheme 8}\]

Nucleophilic additions to enantiomerically pure fluorine containing β-iminosulfoxides have been reported by Bravo \(\text{et al}\). as key steps in the preparation of analogues of biologically active molecules such as optically active amines,\(^{27}\) amino alcohols,\(^{27}\) amino acids,\(^{27}\) and alkaloid precursors.\(^{28}\) Such compounds can be easily obtained from fluorinated \(N\)-substituted imidoyl chlorides with lithium derivatives of enantiomerically pure methyl \(p\)-Tolyl sulfoxide or by aza-Wittig reaction of γ-fluoro-β-keto sulfoxides and \(N\) aryliminophosphoranes (Scheme 9).\(^{29}\)
Their reactivity towards reducing reagents is rather different from that of the known unfluorinated analogues. Classical electrophilic reducing reagents such as Dibal-H (even with zinc halide) are inactive and the best conversions and diastereoselectivity are obtained using K and L-selectrides (50 to 75% yield and de>80%). The best method to obtain α-fluoroalkyl β-sulfinylamines is the asymmetric addition reaction of α-sulfinyl carbanions on fluoroalkylaldimines (see next section).

Scheme 9

Nevertheless, Fustero and Bravo recently developed a highly efficient hydride reduction of γ-fluoro-β-N-arylimino sulfoxides 27 using Bu₄NBH₄ affording the corresponding syn α-fluoroalkyl β-sulfinylamines 28 with high yield and de (>90%) (Scheme 10). The best de values are obtained using the 1-naphthylsulfinyl group suggesting intramolecular π-stacking interactions with N-aryl groups leading to one diastereotopic face being efficiently shielded (Figure 2) and a Si-selective attack of the nucleophile.

Scheme 10
Figure 2

1-Trifluoromethyl-tetrahydroisoquinoline alkaloid analogues have been synthesised with good stereoselectivity $({1S,R_S})/({1R,R_S})= 6/1$ and chemical yields.\textsuperscript{28} The key step is a stereoselective intramolecular Pictet-Spengler reaction of the $N$-arylthethyl $\gamma$-trifluoromethyl-$\beta$-iminosulfoxide $(R)$-$29$ (Scheme 11).

Scheme 11

The good diastereoselectivity is explained by an interaction between the electron-rich 3,4 dimethoxyphenyl group and the stereogenic $p$-tolylsulfynl group increased by the $cis$ geometry of the $C=\text{N}$ double bond. Then the sulfynyl group exerts a strong stereodirecting effect with a minimisation of the dipole-dipole interactions between the S=O and the C=\text{N} bonds during the ring closure.

2.1.2. Nucleophilic additions to $\gamma$-keto sulfoxides

Until 1996, only few reports were known concerning the nucleophilic additions to ketosulfoxides in which the sulfoxide group is in a remote position from the carbonyl: Iwata\textsuperscript{32} reported an 1,6-asymmetric induction in the Dibal-H reduction of the $\epsilon$-ketosulfoxide $33$ and more recently Arai\textsuperscript{33} a case of 1,4-asymmetric induction during the allylation of the $\gamma$-ketosulfoxide $34$ (Scheme 12).
Since 1996, Arai et al.\textsuperscript{34} observed 1,4 induction with rather good diastereoselectivities during several nucleophilic additions on thienyl 34 and furyl or 1'-methyl ketone analogues. The most significant example\textsuperscript{34b} is a lanthanide triflate catalysed Mukaiyama aldol condensation of silyl ketene acetal on furfural 36. The reaction proceeds with high diastereoselectivity (de>92%) and high isolated yield (>90%) (Scheme 13) using 5% of catalyst. In the case of silyl ketene acetal derived from propanoates, the anti-product is the major isomer resulting from a strong diastereoface selectivity (>90% de) and modest anti/syn selectivity (75/25).

**Scheme 13**

The results are consistent with a cyclic transition state model depicted in Figure 3, which involves an approach on the least hindered face of the silyl ketene acetal.

**Figure 3**
This reaction has been applied to the preparation of the chiral pyranone moiety of (+)-Dihydrokawain-5-ol by oxidative degradation of the furan ring in the furyl alcohol.\textsuperscript{34c}

Toru \textit{et al.} have reported a new diastereoselective reaction of 1-(arylsulfinyl)-2-naphtaldehydes and 2-Acyl-1-arylsulfynlnaphtalenes with various nucleophiles such as Grignard reagents, silyl ketene acetals and hydrides.\textsuperscript{35} In these reactions, the best diastereoselectivity is observed with (2,4,6-triisopropylphenyl)sulfinyl group as chiral auxiliary and the stereochemistry of the major products changes depending on the Lewis acids used and on the reducing agents used for hydride transfer reactions. For example, $\gamma$-hydroxysulfoxide 37 can be prepared with very high selectivity either by addition of phenylmagnesium bromide on the 1-(arylsulfinyl)-2-naphtaldehyde 38 or by Dibal-H reduction of the $\gamma$-ketosulfoxide 39 (Scheme 14). The high stereoselectivities of these reactions are due to a predominant rotamer around the C\textsubscript{napht}-S axis and the steric effect of the bulky 2,4,6-triisopropylphenylsulfinyl group.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme14}
\caption{Scheme 14}
\end{figure}

In the case of non conformationally restricted $\gamma$-ketosulfoxides high stereoselectivity is difficult to obtain,\textsuperscript{36} probably as a consequence of the relative unstability of seven-membered cyclic chelated intermediates. Nevertheless Toru \textit{et al.} observed very high de (>90\%) in the Dibal-H reduction of $\gamma$-ketosulfoxides 40 bearing the bulky 2,4,6-triisopropylphenyl group as sulfoxide substituent (Scheme 15).\textsuperscript{37}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme15}
\caption{Scheme 15}
\end{figure}
Diastereoselectivity is obtained in the reaction of all γ-ketosulfoxides 40 irrespective of the substituent (R) attached to the carbonyl group. The authors assume a twisted chair transition state involving a trigonal bipyramidal structure (Figure 4).

Figure 4

The use of an additive such as ZnCl₂ or Yb(OTf)₃ has only a weak effect on the stereoselectivity of the reduction leading to the same diastereoisomer as major product with lower de. The bulky substituent on the sulfinyl group probably destabilises a chelated intermediate, which would give the opposite configuration at the γ-position.³⁶

We have recently described a highly stereoselective reduction of γ-keto-β-silyloxy-αTolylsulfoxides¹⁷ using Dibal-H in THF alone or with ZnI₂ or Yb(OTf)₃. Dibal-H alone and Dibal-H/Yb(OTf)₃ lead to the same diastereoisomer (anti-1,2-diol). Addition of Yb(OTf)₃ generally increases both yields and diastereoselectivity (Scheme 16) during the total synthesis of (S,R)-epimuricatacin 43 from γ-keto-β-silyloxy-αTolylsulfoxide 4.

Scheme 16
Reduction of 42 in the presence of ZnI2 allowed the preparation of (R,R)-muricatacin 45 by stereoselectively affording the epimer at the γ-position (syn-diol 44). No rationale has been proposed for this 1,2 and/or 1,4-induction but the study of the influence of the relative configuration between the sulfinyl group and the silyloxy at the β-position is now under investigation. The different selectivity and the lower de observed for each reduction system on α-silyloxy-ketones and γ-ketosulfoxides36 suggest that both sulfinyl and silyloxy groups are implicated in the diastereoselectivity of the reduction.

2.2. Reactions involving sulfinyl-stabilised carbanions

The sulfoxide anion has been extensively investigated and described as a near planar four-centre chelate structure of the metalated species.38 This can explain the great configurational stability of α–sulfinyl carbanions, since the chelate favours one of the two diastereoisomeric carbanions.

2.2.1. Reactions of α-sulfinyl carbanions with 1,2-induction

The lithium carbanion of 4-(tert-butylsulfinylmethyl)-2-phenyl-2-oxazoline (46) can be alkylated under chelate control between the oxygen of the sulfinyl group and the nitrogen of the oxazoline with high diastereoselectivity and good yields which decrease as the alkylating reagent becomes bulkier (Scheme 17).39 A second highly diastereoselective alkylation is also possible but in low yields due to steric crowding limiting the scope of this reaction.

\[
\text{\chem{\begin{array}{c}
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\text{S} \\
\text{N} \\
\text{Ph}
\end{array}}\text{\chem{\begin{array}{c}
\text{O} \\
\text{S} \\
\text{N} \\
\text{Ph}
\end{array}}}} \xrightarrow{\text{LDA, RX}} \text{\chem{\begin{array}{c}
\text{O} \\
\text{S} \\
\text{N} \\
\text{Ph}
\end{array}}}
\]

\((S_R,R)-46 (S_R,R,R)-47\)

\(R=\text{Me, Et, Allyl}\)

Scheme 17

Reaction of saturated α-sulfinyl carbanions with carbonyl compounds proceeds also with low stereoselectivity.40,41 Nevertheless, when a trimethylsilyl group is in the β-position, the diastereoselectivity of this condensation is very high41 and has been extended to various nucleophiles. Toru et al. assumed a novel silicon-carbonyl oxygen interaction in the condensation transition state of the β-silyl-α-sulfinyl carbanion 48 with acetone as depicted in Scheme 18 to explain this remarkable 1,2 induction.

This Si-O interaction is postulated on the basis of stereochemical results from the reaction of several p-Tolyl-sulfoxides and is supported by MO calculations which confirm that the six-membered transition structures bearing the silylmethyl group at the axial position are more stable than the equatorial transition structures.
Scheme 18

Alkylation of a β-sulfinyl-thioacetamide enolate 50 with allyl halides possessing an electron-withdrawing group at the vinylic position has been performed recently (Scheme 19). The reaction proceeds via a conjugate addition of the carbon centre of the enethiolate followed by halide elimination.

Scheme 19

The efficient 1,2-induction is explained by an electronic control. The anti orientation of the lone pair of the sulfinyl moiety and the inside allylic position of the sulfinyl-oxygen atom maximises the energy level of the alkene HOMO. The electronic transfer is optimised by an antiperiplanar approach of the electrophile to the lone pair leading to the diastereoisomer (S,S,2S).
2.2.2. Reactions of α-sulfinyl carbanions with 1,3-induction

Intramolecular alkylation of an α-sulfinyl vinylc carbanion has been investigated by Tanaka et al.\textsuperscript{43} Cyclisation occurs at the α-position of β-(ω-haloalkyl) substituted vinylc sulfoxides affording 1-cycloalkenyl sulfoxides with a five to seven-membered ring. The thermodynamically stable (E)-isomer but also the (Z)-isomer cyclises via rapid inversion of the olefin geometry. The scope of this reaction is restricted by the moderate yield obtained when the cyclisation is performed with ω-secondary iodides.

In sharp contrast, α-lithiated vinylc sulfoxide as an intramolecular Michael donor to (Z)-enoates, cyclises with very high 1,3 induction.\textsuperscript{44} The diastereoselectivity of the reaction is strongly affected by the geometry of the enoate. The intramolecular Michael addition to (E)-enoates proceeds swiftly with high yield but without any selectivity (Scheme 20).

Scheme 20

Cyclohexene ring formation also proceeds in a similar fashion but with lower yield and completely reversed selectivity.\textsuperscript{44}

The reaction of the vinylc anion α to the chiral sulfinyl group with aldehydes gives α-alkenyl-β-hydroxysulfoxides with moderate selectivity. Despite the low 1,3-induction generally observed, the diastereoisomers are readily separated by chromatography and open the route to enantiopure propargylic and allylic alcohols\textsuperscript{45} after selective elimination of the sulfoxide or to enantiopure allenes after acetylation and sulfoxide-metal exchange reaction.\textsuperscript{46}

The conjugate addition of sulfoxide anions followed by ring-closure proceeds generally with good selectivity, as illustrated by the three examples depicted in Scheme 21.

For each example, the sulfinyl adduct is obtained in good yield and high optical purity at the β-stereogenic centre.
Scheme 21

Ghosez's cyclocondensation of sulfone-\(\gamma\)-orthoesters with carbonyl derivatives has been extended to an asymmetric version.\(^{50}\) Enantiomerically pure lithiated sulfoxide \(59\) adds to aldehydes to provide \(\gamma\)-butenolides \(60\) of high enantiomeric purities in a one pot three-step sequence (Scheme 22). The cyclocondensation with ketones is less stereoselective.

Scheme 22
The nucleophilic addition of enantiomerically pure \( \alpha \)-sulfinyl carbanions to the diasterotopic C=N double bond of imines allows the asymmetric synthesis of \( \beta \)-amino-sulfoxides with generally moderate diastereomeric excess. Since 1996 several groups have studied this reaction in order to improve the 1,3 induction and open an efficient route to \( \alpha \)-aminoacids. Bravo et al. have first established that the addition of chiral sulfoxide-stabilised carbanion on \( N \)-(p-methoxyphenyl)aldimines bearing trifluromethyl, pentafluoroethyl and \( \omega \)-hydrotetrafluoroethyl groups affords the corresponding \( \alpha \)-fluoroalkyl-\( \beta \)-sulfinyl amines in excellent yields and diastereoselectivity (Scheme 23).\(^{51}\)

![Scheme 23](image)

The authors assume a kinetic control and an enantiodirecting effect of the fluoroalkyl group to explain the stereochemical outcomes of these reactions. The reaction has been extended to \( N \)-(PMP)-arylimines as an excellent way to prepare enantiopure \( \alpha \)-arylglycinols.\(^{52}\)

The kinetic control of such reactions was confirmed by the addition of the lithium enolate of tert-butyl (\( R \))-p-tolylsulfinylacetate to several substituted \( N \)-(benzylidene)toluene-4-sulfonamides.\(^{53}\)

The selectivities observed when the reaction is performed at \(-60^\circ C\) are very high (>88\% de) and afforded after further transformations the corresponding \( \beta \)-amino acids with good overall yield and optical purity.

The behaviour of enantiomerically pure sulfinyl imines with non racemic chiral \( \alpha \)-sulfinyl carbanions has been reported by Bravo et al.\(^{54}\) The highest stereoselectivity is achieved when the configuration at the sulfur atoms of the two reagents are opposite (matched pair), affording only one diastereoisomer (Scheme 24). For each pair, the major diastereoisomer has identical configuration at the new stereogenic carbon (\( R \) in both case), despite the opposite configuration of the sulfoxide used as nucleophile in each case. This suggests that the stereoselectivity of the
reaction is primarily controlled by the sulfur configuration of the starting electrophilic sulfinamide 64.

Scheme 24

2.2.3 Reactions of α-sulfinyl carbanions with 1,2- and 1,3-induction

The conjugate addition of an α-sulfinyl-stabilised carbanion to α,β-unsaturated carbonyl compounds generally gives moderate stereoselection and the selectivity is dependant on the substituent of the sulfoxide moiety. Recently Casey et al. reported a complete selectivity using a pyridyl group as coordinating substituent of the sulfoxide in racemic series. Recently Casey et al. reported a complete selectivity using a pyridyl group as coordinating substituent of the sulfoxide in racemic series.55

As already mentioned in the preceding paragraph, β-silyl-α-sulfinyl carbanion 45 reacts smoothly with α,β-unsaturated carbonyl compounds with very high 1,2 induction. The high stereochemical outcome is ascribed to the presence of the trimethylsilyl group with a silicon-carbonyl oxygen interaction in the transition state (Scheme 18). Furthermore, only a single diastereoisomer is obtained when the 1,4 addition is performed on β-substituted α,β-unsaturated esters with 1,2 syn, 2,3 anti selectivity.56 Subsequent electrophilic trapping of the enolate intermediate adduct leads to 1,2 syn, 2,3 anti, 3,4 syn product with good yield and high selectivity (>96% de). When ω-halo-α,β-unsaturated esters are used, completely diastereoselective intramolecular trapping occurs, leading to enantiopure cyclopropanes, cyclopentenes and cyclohexenes. The model proposed for this tandem reaction is depicted in Scheme 25.
1,4-Addition to α,β-unsaturated ketones gives poor yields and lower selectivity due to the competitive 1,2 addition, except in the case of 2-cyclopentenone.

Aldonitrones react smoothly with α-stabilised carbanions of homoallylic sulfoxides 68 to give largely a single diastereoisomer of the unsaturated hydroxylamines 69 (Scheme 24). Subsequent reverse-Cope cyclisation of compound 69 affords the highly substituted pyrrolidine-N-oxides 70 with a high level of stereocontrol.

Scheme 26

The reaction has been applied to the preparation of chiral non-racemic products using enantiomerically pure homoallylic sulfoxide 68. Only one single diastereoisomer 70 is obtained with good overall yields but attempts to determine the absolute configuration of the adduct 70 failed.

Aldol-type condensation of enantiomerically pure tert-butyl sulfinyl acetate 71 on carbonyl compounds using tert-butylMgBr as base usually gives mainly one diastereoisomer with a predictable configuration. Surprisingly, when α,β unsaturated aldehyde 72 is used as electrophile, the opposite configuration at the stereogenic hydroxylic centre is observed in the adduct 75 (Scheme 27).
2.2.4. Reactions of β and γ-sulfinyl carbanions with 1,4-induction

The metalation and reaction with aldehydes of 4-(p-Tolylsulfinyl)-3,6-dimethoxypyridazine have been investigated recently.\textsuperscript{59} The remarkable diastereoselectivity observed is explained by the approach of the aldehyde on the less-hindered convex face of the metalated pyridazine leading to the formation of the $S_C,R_S$ diastereoisomer (Scheme 28).

Scheme 28

Stereocontrolled cyclisation of enantiomerically pure ($R$)-sulfoxide 76 provides the benzothiepine-oxide 77 with the $cis$ configuration (Scheme 29).\textsuperscript{60}
Scheme 29

The sulfoxide configuration determines the formation of the two stereogenic centres under thermodynamic control.

Sulfinyl-directed Barbier type allylation of aldehydes using zinc as promoter affords $\alpha$-vinyl-$\gamma$-hydroxysulfoxides with very good 1,4 induction (Scheme 30). \(^{61}\)

\[
\begin{align*}
\text{(S$_S$)-78} & \quad + \quad \text{RCHO} \quad \longrightarrow \quad \text{(S$_S$, 4R)-79} \\
\text{Zn dust 2 eq.} & \quad \text{NaI 3 eq.} \quad \text{aqueous NH$_4$I/THF} \\
\text{R= Ph, cyclohexyl} & \quad 60 \text{ to } 80\% \text{ yields and } 65 \text{ to } 72\% \text{ de}
\end{align*}
\]

Scheme 30

An open antiperiplanar transition state model is preferred over a six-membered cyclic transition state involving a 1,3-diaxial interaction between R and the sulfoxide moiety. The open-chain transition-state model is consistent with empirical results observed when enantiomerically pure $\alpha$-amino aldehydes are used.\(^{61b}\) In this case, a "matched" stereoinduction is observed with aldehydes derived from natural $\alpha$-amino acids.

Nucleophilic reactions of enantiomerically pure stabilised ortho-sulfinyl benzyl lithium carbanion occurs diastereoselectively by a 1,4-induction process.\(^{62}\) Regioselective deprotonation of ortho-sulfinyl derivatives 80a and 80b followed by the reaction of the lithiated intermediate with various electrophiles affords benzylic stereocentres in a highly diastereoselective manner and with the same asymmetric induction, independent of the electrophile (Scheme 31).
Very recently, we described an efficient access to anti- and syn-2-methyl-1,3-diol moieties bearing a linear aliphatic substituent.\textsuperscript{63} The key-step of this method is a stereoselective samarium-promoted Reformatsky reaction with linear aliphatic aldehydes. When the sulfur atom is substituted by a tert-butyl group high 1,4 induction with a strong syn-selectivity is observed (\textit{de}>90\%) (Scheme 32).

\textbf{Scheme 32}

2.3. Reactions involving chiral $\alpha$-sulfinyl acetals

Chemical asymmetric desymmetrisation of prochiral diols using chiral sulfoxides has been studied extensively over the last decade by Iwata \textit{et al.} They first established that synthetically useful chiral building blocks such as enantiomerically pure 1,2 or 1,3-diols can be obtained via diastereoselective $\beta$-elimination of chiral $\alpha$-sulfinyl acetals.\textsuperscript{64} Prochiral 1,3-diols 82 are transformed into the $\alpha$-sulfinyl bicyclic acetal 83, which interestingly gives the two diastereoisomers of the dihydropyran derivative 84 depending on the conditions used for the diastereoselective C-O bond fission. Treatment of 83 with titanium tetrachloride affords mainly 84b via an oxonium intermediate, while with LDA 84a is selectively obtained via diastereoselective $\beta$-elimination followed by an olefin isomerisation. Later on, an extension of this method gave an efficient route to chiral 2,2,5-trisubstituted tetrahydropyran 85\textsuperscript{65} from
bicyclic acetal 83. Group and facial nucleophilic cleavage reaction affords the simultaneous installation of two stereogenic centres with high 1,3- and 1,6-asymmetric induction from the sulfinyl chirality (Scheme 33).

Scheme 33

2.4. Reactions involving polymer-supported sulfoxides

Owing to both its chemical stability and chemical versatility, the sulfinyl group is a potentially useful linker for solid-phase chemistry. As solid-phase asymmetric reactions are of great importance in the pharmaceutical industry, some reports describing the use of the sulfoxide functionality as a new linker and as chiral auxiliary have appeared in the literature over the last two years. Thus, we recently described the stereoselective reduction of β-ketosulfoxides on Wang resin and the electrophilic reaction of their enolates.\textsuperscript{66} The cleavage of the product from the resin is quantitative using modified Pummerer conditions. The route to asymmetric solid-phase synthesis using optically active sulfoxides is opened since enantiomerically enriched polymer-bound β-ketosulfoxides are available from enantiomerically pure Wang-supported ρ-alkoxyphenylmenthyl-sulfinate.\textsuperscript{67}

Toru et al. have also used optically active sulfoxides as linkers and chiral auxiliaries in an asymmetric conjugate addition of polymer-supported enantiomerically enriched β-(trimethylsilyl)ethyl sulfoxide to cinnamate derivatives. Thermal treatment or reaction with TBAF liberates chiral non-racemic 3-phenyl-5-trimethylsilylpent-4-enoates or 3-phenylpent-4-enoates respectively with high enantioselectivity (ee 90%).\textsuperscript{68}
2.5. Reactions involving vinyl sulfoxides

Vinyl sulfoxides are among the most widely used sulfinyl compounds in asymmetric synthesis. The sulfinyl group is responsible for strong stereodifferentiation leading to highly stereoselective reactions on the double bond, but it is also in many cases at the origin of the synthetic versatility of these compounds as it can undergo a variety of useful transformations.

2.5.1. Cycloaddition reactions

One useful and widespread application of vinyl sulfoxides are cycloaddition reactions, which provide easy access to highly functionalised and complex targets.

2.5.1.1 1,3-Dipolar cycloadditions

Hootelé et al. had already described the 1,3-dipolar cycloaddition reaction of a 6-membered cyclic nitrone 86 with acetylenic sulfoxides which proceeds readily but with low diastereoselectivities and gives access to enantiomerically pure aminoketones. They subsequently investigated the reactions of the same cyclic nitrone with (Z)-vinylc sulfoxides 87. Excellent diastereoselectivities and yields were observed in that case. Subsequent ring cleavage and desulfinylation provided enantiomerically pure aminoalcohols and an efficient access to the piperidine alkaloid (+)-sedridine 88 (Scheme 34).

Simultaneously, a report by Viehe et al. showed the reactivity of α-trifluoromethyl vinyl sulfoxides with various 1,3-dipoles, including diazo compounds and azomethine ylides. However, there is no account of any observed diastereoselectivities in this report.

Hootelé later showed that the stereoselectivities dropped considerably with (E)-vinyl sulfoxides whereas the previously used (Z) isomer proved to be an efficient dipolarophile for 5-membered cyclic nitrones 89 as well. The described cycloaddition adducts provide an efficient access to natural products (-)-hygroline 90 and (-)-(2S)-N-carbomethoxypelletierine 91 (Scheme 35).
Scheme 35

Bravo et al. studied the cycloaddition reactions of nitrones as well as nitrile oxides with chiral fluorinated sulfinyl enol ethers \(^{92,73}\). The dipoles afforded sulfinylisoxazolines \(^{93}\) regio- and stereoselectively in modest to good yields depending on the substituents, along with minor amounts of sulfinylisoxazoles \(^{94}\). The cycloaddition of nitrones with the same alkenes afforded isoxazolidines \(^{95}\) in the same range of yields and again as single regio- and diastereoisomers (Scheme 36).

Scheme 36

Garcia Ruano studied the 1,3-dipolar cycloaddition of nitrile oxides with butenoic acid derivatives \(^{96}\) bearing a sulfinyl group in the 2-position.\(^ {74}\) In addition to the high regioselectivities, the labile sulfoxide group provides an access to substituted isoxazoles \(^{97a}\) and \(^{97b}\) as the intermediate sulfinylisoxazolines undergo in situ desulfinylation. The intermediate sulfinylated isoxazoles \(^{98a}\) and \(^{98b}\) could however be isolated in the case of bicyclic adducts and the diastereoselectivity could thus be deduced and explained by a transition state model (Scheme 37).
The cycloaddition of diazoalkanes to vinyl sulfoxides has also been investigated. Garcia Ruano has studied the reaction of diazomethane with sulfinyl furanones 99. The resulting pyrazolines 100 were obtained as single diastereomers in quantitative yield. These compounds were stable and fully characterised and could be pyrolysed by heating in toluene to afford the corresponding methyl-substituted furanones 101 (Scheme 38). Midura and Mikolajczyk reported the reactions of α-phosphoryl vinyl sulfoxides 102 with different diazoalkanes. Depending on the dipole used, one obtains either phosphorylpyrazoles 103 and 104 which are formed in good yield by elimination of the sulfinyl group from the first cycloadduct, whereas in the case of diazopropane the sulfinyl group is maintained to form the primary cycloadduct 105 in quantitative yield. In the case of diphenyldiazomethane however, a cyclopropane derivative 106 is obtained by elimination of nitrogen from the primary cycloadduct (Scheme 39).

Scheme 37

Scheme 38
Scheme 39

Garcia Ruano et al. have also investigated the reactions of N-metalated azomethine ylides with 2-sulfinylacrylates 107. Cycloadditions proceed with complete regio- and endo-selectivity but afford nevertheless a mixture of two diastereomers in useful yield. Their ratio can however be inverted in different solvents and the cycloadducts can be separated to give access to enantiomerically pure sulfanylpyrrolidines 108a and 108b, or 2,5-dihydro-1H-pyrroles 109a and 109b by pyrolytic elimination of the sulfanyl group (Scheme 40).

Scheme 40
The 1,3-dipolar cycloaddition of vinyl p-tolyl sulfoxide with oxidopyridinium betaines provides an interesting access to different tropane derivatives.\textsuperscript{78} These reactions display complete regioselectivity and useful levels of stereocontrol.

Previously unpublished results concerning the reactions of various vinyl sulfoxides with different dipoles (diazooalkanes, azomethine ylides and nitrones) are briefly presented in a review on Diels-Alder reactions by Garcia Ruano.\textsuperscript{79,80}

2.5.1.2. [4+2]-Cycloadditions

Sulfinyl dienophiles
Diels-Alder type cycloadditions of vinyl sulfoxides are by far the most studied cycloaddition reactions of this type of compounds. In this case, the vinylsulfinyl moiety can either act as dienophile, or be a part of the diene, the former being the most popular approach. The subject has been extensively covered in different reviews.\textsuperscript{6,79,80,81} Some new and remarkable results will be presented in this paragraph.

The stereochemical and mechanistic models used to predict the outcome of the asymmetric Diels-Alder reactions of vinyl sulfoxides have been revised in view of the results obtained in thermal and Lewis acid catalysed cycloadditions of ester-substituted vinylic sulfoxides.\textsuperscript{81}

One recent development concerns the use of 2-sulfinylacrylonitriles 110 as dienophiles.\textsuperscript{82} The authors describe the Diels-Alder reactions of the substrates with cyclopentadiene and two substituted butadienes (Scheme 41). Whereas the bicyclic cycloadducts were generally obtained in good yield and with useful endo-selectivity, the six-membered cycloadducts were not stable and afforded products resulting from the pyrolytic elimination of the sulfoxide. In the case of Danishefsky's diene, the reaction was no longer regiospecific, and a mixture of two isomeric products was obtained. The authors have also observed that racemisation of the sulfinyl group in the preparation of the starting dienophile takes place very easily and this is ascribed to the strong electron-withdrawing environment of the sulfur centre. The inversion equilibrium was studied by \textsuperscript{1}H-NMR.

![Scheme 41](image-url)
An \(\alpha\)-sulfinylacrylate derived from enantiomerically pure \((1R,2S,3R)-3\text{-mercaptocamphan-2-ol}\) undergoes cycloaddition with cyclopentadiene under thermal and \(\text{ZnCl}_2\)-catalysed conditions.\(^{83}\) The Lewis acid greatly improved the diastereoselectivity and at low temperatures the \textit{endo} product was obtained with good selectivity.

The use of sulfinyl benzoquinones as dienophiles has known a considerable growth in recent years. The Diels-Alder reactivity of \((S)-2-(p\text{-tolylsulfinyl})-1,4\text{-benzoquinone 111}\) has been extensively studied.\(^{84}\) Interestingly, this compound reacts with cyclopentadiene under thermal conditions to afford a mixture of two adducts 112 and 113, both arising from \textit{endo} approach of the diene on the two diastereotopic faces of the unsubstituted double bond (Scheme 42). The stereoselectivity of the reaction can be controlled by careful choice of the solvent and reaction conditions. Lewis acids accelerate the reaction rate as well as the diastereoselectivity. On the other hand, the presence of \(\text{ZnBr}_2\) in the reaction mixture results in formation of a single diastereoisomer 114 arising from \textit{endo} approach of the diene on the substituted double bond, thus inverting the regioselectivity. The same selectivities are obtained for cyclohexadiene, albeit with longer reaction times due to the lower reactivity of the diene. In contrast, acyclic dienes undergo cycloaddition on the substituted double bond selectively, and the resulting intermediates can not be isolated, as they undergo a pyrolytic sulfoxide elimination spontaneously, even at low temperatures. Reaction with \textit{trans}-piperylene afforded the corresponding dihydronaphtoquinone 115 in optically pure form, whereas the cycloadduct with \(1\text{-[(trimethylsilyl)oxy]-1,3\text{-butadiene}}\) underwent aromatisation into 1,4-naphthoquinone 116 at temperatures higher than -20°C (Scheme 43). Sulfinylbenzoquinones also react with Dane's diene under thermal and Lewis acid conditions with reversal of the regiochemistry but similar \(\pi\)-facial selectivity.\(^{85}\) Spontaneous elimination of the sulfinyl group thus provides an easy access to tetracyclic systems.

![Scheme 42](image-url)
Scheme 43

The sulfinylbenzoquinone Diels-Alder strategy provides an enantioselective approach to both enantiomers of helical bisquinones. The sulfinylbenzoquinone Diels-Alder strategy provides an enantioselective approach to both enantiomers of helical bisquinones.\(^{86}\)

Methylene-bridged sulfinyl-1,4-naphthoquinones 117 were also shown to undergo Diels-Alder cycloaddition with cyclopentadiene.\(^{87}\) The thermal and Lewis acid-catalysed reactions show the directing influence of the sulfoxide moiety and provide an easy access to both endo-anti-endo 118 and exo-anti-endo 119 bisadducts (Scheme 44). If sulfinylnorborneno-p-benzoquinones 120 are used, the stereochemical outcome of the reaction is solely controlled by the sulfoxide group, and depending on whether the reaction is run under thermal or Lewis acid conditions, the \(\pi\)-facial diastereoselection can be completely inverted (Scheme 45).\(^{88}\)

Scheme 44
Scheme 45

The previously described methodologies found their first synthetic application in the enantioselective synthesis of Angucyclinones. The asymmetric Diels-Alder reaction of an enantiomerically pure sulfinyl naphthoquinone 121 and a vinylcyclohexenol 122 derivative was used as the key step to establish the tetracyclic angucyclinone skeleton 123 (Scheme 46). The sulfinyl group proved to achieve a double induction in the Diels-Alder reaction which led to an efficient kinetic resolution of the racemic diene.

Scheme 46

The same naphthoquinones react with chiral racemic acyclic dienes in a tandem cycloaddition/pyrolytic sulfoxide elimination sequence to afford enantiomerically enriched adducts which arise from a partial kinetic resolution of the racemic dienes. When chiral racemic vinylcyclohexenes bearing allylic and nonallylic oxygenated substituents were used, the same reaction sequence took place to produce enantiomerically enriched tetracyclic quinones arising again from an efficient kinetic resolution of the dienes.

The same Diels-Alder/kinetic resolution strategy was applied in the synthesis of the angucyclicone antibiotics (+)-ochromycinone 124a and (+)-rubiginone B2 124b where this highly efficient process accounts for the construction of the tetracyclic framework (Figure 5). Similarly, an access to a C3-oxygenated angucyclinone-type skeleton was devised and allowed the synthesis of enantiomerically enriched (-)-8-deoxytetrangomycin 125. Finally, the more oxygenated angucyclinone antibiotics rubiginones A2 126a and C2 126b as well as (+)-royleanone could be obtained in an analogous fashion.
Figure 5

**Sulfinyl dienes**

The use of sulfinyl-containing dienes in asymmetric Diels-Alder reactions has emerged more recently, but has nevertheless known a considerable growth over the last few years. However, this subject has been extensively and recently reviewed. Some developments in this field are not covered by these reviews and will be presented here.

Some new methods for the synthesis of sulfinyl dienes and their derivatives have been published. Sulfinyl dienes can be prepared by Horner-Wadsworth-Emmons type chemistry. Similar compounds have also been synthesised via Stille coupling of halovinyl sulfoxides, partial hydrogenation of sulfinyl enynes or vinylcupration of sulfinyl alkynes. The formation of the corresponding iron(0) tricarbonyl complexes is also described. Enantiomerically pure hydroxy sulfinyl dienes were prepared from base-induced rearrangement of epoxy vinyl sulfoxides, the E-Z-stereoselectivity being controlled by the chiral sulfur auxiliary. These compounds were used in a Diels-Alder reaction with N-phenylmaleimide and phenyltriazolinedione and were found to react with high face selectivity (Scheme 47). Interestingly, the sulfinyl group managed to override the intrinsic allyl stereocontrol of the substrates.

Scheme 47

Racemic and enantiomerically pure exocyclic sulfinyl 1,3-dienes can be prepared by an intramolecular Heck reaction (Scheme 48). Five- and six-membered mono- and bicyclic
Dienes have been obtained by the use of an intramolecular palladium-catalysed coupling of vinyl sulfoxides with a distant vinyl iodide.

\[
\text{SO}_2\text{-Tol} \rightarrow \text{Pd(OAc)}_2 \text{PPh}_3 \xrightarrow{\text{Ag}_2\text{CO}_3, \text{CH}_3\text{CN}} \text{SO}_2\text{-Tol}
\]

**Scheme 48**

An interesting route to 2-sulfinylbuta-1,3-dienes would be the deoxygenation reaction of the corresponding allylic epoxides 128 in the presence of P₂I₄. However, in any case, the sulfur centre was reduced at the same time. On the other hand, β-hydroxyselenides 129, prepared from reaction of lithiated vinylsulfoxide with α-selenyl carbonyl compounds, were subjected to a Krief-Reich elimination to obtain the desired dienes 130 (Scheme 49).

\[
\begin{align*}
\text{SO}_2\text{-Tol} & \rightarrow \text{Pd(OAc)}_2 \text{PPh}_3 \xrightarrow{\text{Ag}_2\text{CO}_3, \text{CH}_3\text{CN}} \text{SO}_2\text{-Tol} \\
128 & \rightarrow \text{P}_2\text{I}_4, \text{Et}_2\text{O}, \text{r.t.}, 30 \text{ min.} \\
129 & \rightarrow \text{SOCl}_2/\text{Et}_3\text{N} \text{ or MsCl}/\text{Et}_3\text{N} \\
129 & \rightarrow \text{SO}_2\text{-Tol} \xrightarrow{\text{P}_2\text{I}_4, \text{Et}_2\text{O}, \text{r.t.}, 30 \text{ min.}} \text{R}_1\text{R}_2
\end{align*}
\]

**Scheme 49**

Sulfinyl dienes 131 react in an interesting way with maleic anhydride. Indeed, the expected cycloadducts 132 are only obtained under high pressure conditions, whereas the reactions that are run at normal pressure afford unsaturated lactones 133a and 133b that arise from S_N2' substitution of the sulfinyl group or from sulfoxide-sulfenate rearrangement followed again by S_N2' substitution (Scheme 50).

\[
\begin{align*}
\text{SO}_2\text{-Tol} & \rightarrow \text{Pd(OAc)}_2 \text{PPh}_3 \xrightarrow{\text{Ag}_2\text{CO}_3, \text{CH}_3\text{CN}} \text{SO}_2\text{-Tol} \\
131 & \rightarrow \text{P}_2\text{I}_4, \text{Et}_2\text{O}, \text{r.t.}, 30 \text{ min.} \\
132 & \rightarrow \text{SOCl}_2/\text{Et}_3\text{N} \text{ or MsCl}/\text{Et}_3\text{N} \\
132 & \rightarrow \text{SO}_2\text{-Tol} \xrightarrow{\text{P}_2\text{I}_4, \text{Et}_2\text{O}, \text{r.t.}, 30 \text{ min.}} \text{R}_1\text{R}_2
\end{align*}
\]

**Scheme 50**
On the other hand, reaction of enantiomerically pure 1-sulfinyl-1,3-pentadiene with 1-pyrrolidinylcyclohex-1-ene and methyl acrylate evidences a low reactivity of the diene, and needs thus to be run under high pressure conditions.\textsuperscript{103} Whereas the sulfoxide-controlled regio- and endo-selectivities are high for the enamine, the $\pi$-facial selectivity is low. For methyl acrylate, the diastereoselectivities are different for the two observed regiosomeric approaches.

1-methoxy-3-sulfinylbutadienes have been synthesised using the addition of sulfenic acids to enynes affording the $E$ and $Z$ isomers.\textsuperscript{104} The $E$ isomer \textbf{134} reacts with activated dienophiles in lithium perchlorate catalysed Diels-Alder reactions with complete control of regioselectivity and, in some cases, complete endo-selectivity (Scheme 51).

\begin{center}
\textbf{Scheme 51}
\end{center}

The reaction of amino-substituted sulfinyl dienes \textbf{135} with N-methyl maleimide proceeds with complete endo-selectivity and a 3:1 diastereoselectivity.\textsuperscript{105} This reaction gives access to oxazoloisoindoles \textbf{136} by a short sequence featuring a 2,3-sigmatropic rearrangement and intramolecular cyclisation (Scheme 52).

\begin{center}
\textbf{Scheme 52}
\end{center}
Yang et al. have investigated the interesting behaviour of sulfinylsulfolenes. These compounds can be desulfonylated by refluxing in toluene and are thus precursors of enantiomerically pure sulfinyldienes. The sulfinylsulfolenes can also be regioselectively alkylated in the 2-position and may thus give access to substituted dienes. The Diels-Alder reaction of such dienes with N-phenylmaleimide and methyl propiolate is described (Scheme 53). These reactions display good yields and are regio- and diastereoselective. Yields and selectivities are improved by Lewis acid catalysis. When an unsaturated side-chain is introduced in the sulfolene, thermal desulfonylation is followed by intramolecular Diels-Alder reaction to afford bicyclic adducts.

\[ \text{Scheme 53} \]

The asymmetric Diels-Alder reaction of 2-sulfinyl dienes has been used in the total synthesis of (-)-(1S,5R)-Karahana ether (138) (Scheme 54). The key step involves the cycloaddition of maleic anhydride with 2-sulfinylpentadiene proceeds with good yield to afford 4:1 mixture of diastereomeric cycloadducts, which could be converted in 5 steps into the desired monoterpenoid, using, among others an intramolecular conjugate addition of an alkoxide onto a vinyl sulfoxide.

The use of sulfinyl-containing \( \alpha,\beta \)-unsaturated ketones in hetero-Diels-Alder reactions has emerged recently. 3-p-tolylsulfinylbut-3-en-2-one has thus proved to be particularly reactive in inverse electron demand heterocycloaddition reactions. However, the stereoselectivity of the process is highly dependent on the dienophile that is used. Thus, styrenic compounds lead to the highest diastereoselectivities. Although their reactivity is much lower, the resulting dihydropyran derivatives could be isolated in good yield.
A similar methodology was used for the synthesis of both enantiomers of 1,7-dioxaspiro[5.5]undecane 140, which is a pheromone component of the olive fruit-fly Dacus Olæ (Scheme 55). The previously described 2-(p-tolylsulfinyl)acrolein 141 underwent a cycloaddition reaction with 2-methylenetetrahydropyran to afford a 1:1 mixture of diastereoisomers in 60% total yield. These could be separated and converted, by hydrogenolytic sulfinyl-group cleavage followed by double bond hydrogenation, to the two enantiomers of the spiroketal. Different hydrogenation conditions afford the unsaturated spiroketal.

Heterocycloaddition of 3-p-tolylsulfinylbut-3-en-2-one 141 with a vinylsulfide affords a separable mixture of diastereoisomers of which only one cyclised under acidic conditions to form a spiroketal that was converted in two steps into the Mus musculus pheromone 143 (Scheme 56).
Scheme 56

1-p-tolylsulfinyl-1,3-pentadiene 131 reacts with 4-methyl-1,2,4-triazoline-3,5-dione in the presence of P(OMe)₃ to afford an enantiomerically pure hydroxy substituted triazolopyridazine 144 (Scheme 57). This process involves a tandem Diels-Alder cycloaddition/sulfoxide-sulfenate rearrangement and trapping of the intermediate sulfenate.

Scheme 57

Similarly, hetero-Diels-Alder reaction of the same diene with benzyl nitrosoformate takes place at low temperature to afford the cycloaddition product in 54% yield as a single diastereoisomer (Scheme 58). This adduct was transformed into enantiomerically pure 1,4,5-trideoxy-1,4-imino-L-ribitol 145.

Scheme 58
Finally, the intramolecular hetero-Diels-Alder cycloaddition of an unsaturated ketone 146 derived from 3-methylcitronellal proceeds under Lewis acid catalysis to afford a mixture of the two diastereomeric adducts 147a and 147b (Scheme 59) in good to excellent yields (42 - 100%) but with low to moderate diastereoselectivities (3 – 60.6 % de).\textsuperscript{116}

\[
\begin{array}{c}
\text{146} \\
\text{147a} + \text{147b}
\end{array}
\]

Scheme 59

A chiral sulfoxide group can also be used as stereochemical controller for the Diels-Alder reaction on more distant double bonds. Thus, the $\alpha,\beta$-unsaturated ketones 148 derived from 3-sulfinylfuran undergo cycloaddition with cyclopentadiene under Lewis acid catalysis to afford the endo adduct as major product with good de (up to 97 %) (Scheme 60).\textsuperscript{117} Enantiomerically pure bicyclic systems may be obtained by oxidative degradation of the furan moiety. Similar results are obtained for the corresponding thienyl derivatives.\textsuperscript{118}

\[
\begin{array}{c}
\text{148} \quad \text{R} = \text{Me, Ph} \\
\text{R' = H, Me}
\end{array}
\]

Scheme 60

In a very similar fashion, 2-sulfinylpyrrole-derived enones 149 react with cyclopentadiene under Lewis acid catalysed conditions with good to excellent endo-selectivity (92 to 99 % de) (Scheme 61).\textsuperscript{119} However, the bicyclic adducts feature an amide linkage which can easily be hydrolysed. The bicyclic esters are produced readily and the sulfinylpyrrole auxiliary 150 can thus be recovered without loss of optical activity.

\[
\begin{array}{c}
\text{149} \quad \text{R} = \text{Me, Ph} \\
\text{150}
\end{array}
\]

Scheme 61
2.5.1.3. [4+3] Cycloadditions

[4+3]-cycloaddition reactions are a very attractive class of reactions in that they provide access to very difficult to synthesise 7-membered carbocycles.

The cycloaddition of furans with oxyallyl cations is particularly interesting as it affords conformationally restrained bicyclic adducts that can undergo further functionalisation. In an effort to effect these cycloadditions in asymmetric fashion, Montañá et al. examined the influence of various chiral auxiliaries in the 2-position of the furan ring. They found that the best results were obtained for 2-\textit{p}-tolylsulfinylfuran 151 (Scheme 62). Indeed, the authors obtained complete \textit{cis}- and \textit{endo}-selectivity in the process, and, depending on the reaction conditions could achieve promising \(\pi\)-facial diastereoselectivities (up to 54 \% de.).

![Scheme 62](image)

2.5.1.4. [5+2]-Cycloadditions

[5+2]-Cycloadditions, like their [4+3] analogues, give access to the highly desirable 7-membered carbocycles. Again, it is possible to obtain synthetically useful oxygenated or nitrogenated bicyclic systems. In the case of intramolecular reactions, tricyclic systems are obtained.

An asymmetric intramolecular version of such a reaction using a sulfinyl tether was first proposed by Mascareñas \textit{et al.} Intramolecular reaction of a vinylsulfoxide with a silyloxypyrone leads to a tricyclic system 152 in a highly diastereoselective fashion, the sulfinyl group being responsible as well for a significant acceleration of the reaction (Scheme 63). The chiral auxiliary can subsequently be removed with Raney Ni. This strategy was successfully applied to the total synthesis of (+)-nemorensic acid 153 (Scheme 64). Interestingly, switching from a sulf oxide to a sulf oximine auxiliary, allowed a complete inversion of the stereoselectivity. Furthermore, this methodology was extended to the intramolecular acetoxypyranone-vinylsulfoxide cycloadition. Good yields and excellent diastereoselectivities were obtained in this case as well and desulfynylation affords enantiomerically pure tricyclic compounds (Scheme 65).

![Scheme 63](image)
2.5.2. Addition reactions

This paragraph focuses on reactions in which nucleophiles are added to the double bond of vinylic sulfoxides.

β-Sulfinylenamines 153 react readily with O, N, C and S-centred nucleophiles to afford diastereomeric mixtures of the corresponding adducts (Scheme 66). On the other hand, hydride reduction of the enamine with L- and K-Selectride displayed higher diastereoselectivities (up to 95:5). The described compounds could all be desulfinylated under reducing or Pummerer conditions to afford enantiomerically pure amines, aminoalcohols or aminoacids.
Takeda et al. have described a reductive cyclisation to form functionalised cyclohexane derivatives that involves an intramolecular Michael addition.\textsuperscript{127} Indeed, hydride reduction of an enoate affords an ester enolate, which can undergo intramolecular conjugate addition to a vinylsulfoxide moiety (Scheme 67). The optimised protocol yields trans cyclisation product 154 exclusively with 50% yield when a (Z)-vinylsulfoxide is used, the major side-reactions being reductive dimerisation and 1,4-reduction of the enoate. On the other hand, the (E) isomer shows poor stereoselectivity. A five-membered cycle (155) was obtained by the same methodology.

\begin{equation}
\text{Scheme 67}
\end{equation}

The group of Marino showed that allylic mesyloxy sulfinyl steroids 156 undergo S\textsubscript{N}2' displacements with cyanocuprates in a highly stereoselective fashion.\textsuperscript{128} This was used to achieve formal syntheses of Brassinolide (157) and the naturally occurring (24R)-epibrassinolide (Scheme 68). Similarly, epoxy vinyl sulfoxides 158\textsubscript{a} and 158\textsubscript{b} were shown to react with cyanocuprates in S\textsubscript{N}2' fashion with high regio- and stereoselectivity and moderate to good yields (Scheme 69).\textsuperscript{129} The displacements can either take place in syn or anti fashion, in which the sulfoxide is the predominant element of stereocontrol. This is an interesting illustration of the strong stereocontrolling character of the sulfinyl group which, in a nonreinforcing scenario,\textsuperscript{130} overrides the intrinsic anti tendency of the vinyl oxirane.

\begin{equation}
\text{Scheme 68}
\end{equation}
Scheme 69

While 1-halovinyl sulfoxides were first studied for their ability to undergo sulfinyl-metal exchange and produce magnesium alkylidene carbenoids (see last section), an interesting reaction pathway was discovered with carbanions derived from acetonitrile. Indeed, \( \alpha \)-chlorovinyl \( p \)-tolyl sulfoxides 159 react with an excess of cyanomethyllithium to afford cyclopentadienyl enaminonitriles 160, in a cascade sequence that involves formation of three consecutive carbon-carbon bonds (Scheme 70).

Scheme 70

The use of a single equivalent of the anion produces the 1,4-addition product, whereas the presence of a hydrogen atom on the double bonds considerably lowers the yields. The latter effect should be due to the lability of the vinylic protons. Cyanomethylmagnesium bromide and other cyanoalkyllithium compounds afforded only the corresponding single addition products, without formation of the cyclic adduct. Mechanistic insight into the reaction was gained by isolation of different intermediates and by deuteration studies.

The obtained cyclic enaminonitriles could also be converted to different cyclopentanone derivatives (e.g. 161) by acidic hydrolysis. Similarly, reaction of optically active 1-chlorovinyl \( p \)-tolyl sulfoxides with cyanomethyllithium affords disubstituted cyclopentenones with stereocontrolled formation of a quaternary chiral center. The compounds can be hydrolysed and decyanated by heating in an acidic medium to obtain the corresponding cyclopentenone. The configuration of the quaternary chiral centre depends upon the stereochemistry of the double
bond in the vinylsulfoxide. This technique has very recently permitted the asymmetric total synthesis of (+)-α-cuparenone (162) (Scheme 71).^134

![Scheme 71](image)

Vinylsulfoxides can be stereoselectively hydrocyanated to obtain enantiomerically pure compounds containing tertiary or quaternary chiral centers.\(^135\) Indeed, vinylsulfoxides react with Et\(_2\)AlCN in THF with complete diastereoselectivity to afford β-cyanosulfoxides (Scheme 72). Due to the chemical versatility of both the sulfinyl and cyano groups, these compounds can be used as precursors to a variety of optically pure compounds; as an example the cyano group can be hydrolysed to afford amides, which, after desulfinylation, are obtained in enantiomerically pure form. This methodology has been applied to the asymmetric total synthesis of the fungicide Systhane (163) (Scheme 73).\(^136\) The synthetic sequence involves six steps from commercially available 1-hexyne via the described hydrocyanation and affords (R)-systhane in 35% yield and 92% e.e.

![Scheme 72](image)

![Scheme 73](image)

We showed that a flavanone precursor comprising an α-sulfinyenone 164 undergoes conjugate addition with phenyl magnesium bromide in the presence of dilithium tetrachlorocuprate to afford the desired diastereoisomer 165 in 45% yield (Scheme 74).\(^137\) This compound was rapidly desulfinylated and converted to the flavanone structure 166 that had been erroneously assigned to the natural product leridol.
During their studies on estradiol derivatives, researchers at Schering described the diastereoselective cyclopropanation of estradiol-derived vinyl sulfoxides. The steroid featuring the \((R)\)-phenylsulfinyl group was cyclopropanated with trimethylsulfoxonium iodide and sodium hydride in DMSO to afford a separable mixture of diastereomers 168a and 168b with a 12:1 selectivity (Scheme 75). The epimer at sulfur reacted with an inverse and lower 1:3 selectivity. Desulfinylation yielded the corresponding methylene-bridged estradiol analogues.

Vinyl sulfoxides 169 bearing an \(\alpha\)-phosporyl group can be cyclopropanated diastereoselectively. The reaction of enantiomERICALLY pure vinyl sulfoxide with deuterated dimethyl(oxo)sulfonium methylide and diphenylsulfonium isopropylide affords the corresponding cyclopropanes 170 as single diastereoisomers in good yield (Scheme 76). As mentioned previously, reaction with diazomethane gives the cycloaddition product, whereas the use of diphenyl diazomethane gives the cyclopropane adduct. The authors present experimental evidence for a two-step mechanism in the case of diphenyldiazomethane and propose a model for the stereochemical outcome of the cyclopropanation reaction, based on the crystal structure of the adducts.
A vinyl sulfoxide cyclopropanation provided an access to a conformationally constrained analogue 171 of the GABA_B antagonist phaclofen (Scheme 77). Reaction of (1-dimethoxysulfonyl-2-phenyl)vinyl p-tolyl sulfoxide 172 with different sulfur ylides affords the cyclopropanated products with moderate to high diastereoselectivity. Importantly, reaction with EDSA (ethyl (dimethylsulfuranylidene)acetate) takes place with an 8:1 selectivity and the major diastereoisomer 173 could be converted to the target compound by simple functional group transformations.

Scheme 77

Vinyl sulfoxides can also undergo conjugate addition reactions with nitrogen nucleophiles. The reaction of a chiral sulfinylcinnamate 174 with pyrazolidine in the presence of t-BuOK and in situ desulfinylation with SmI2 affords a bicyclic adduct 175, which arises from a tandem conjugate addition-cyclisation sequence (Scheme 78). Reductive N-N bond cleavage by sodium in liquid ammonia affords an 8-membered heterocycle 176, in which the amine nitrogen can be reductively methylated and the resulting cyclic product can be converted to the natural product Homaline (177) in the presence KOH and 1,4-dibromobutane. The dimerisation reaction can also be run before methylation of the amine functionality, but in any case, the natural product is obtained with moderate diastereomeric excesses.

Scheme 78
Acyclic nitrogen nucleophiles, such as ammonia, benzylamine, 1,3-diaminopropane, 1,4-diaminobutane do also perform conjugate addition to 2-(p-tolylsulfinyl)cinnamate 174 in good yield (Scheme 79). Subsequent desulfinylation with samarium iodide affords enantiomerically enriched β-amino esters with low to good enantiomeric excesses (17 to 89 % ee).142

Scheme 79

The same strategy has been applied to the synthesis of celacinnine 178.143 This time, the conjugate addition-cyclisation sequence was achieved with piperidazine, and thus, after desulfinylation and N-N bond reduction, a nine-membered macrocycle 179 was obtained with high stereoselectivity (Scheme 80). This intermediate can be converted to the macrocyclic lactam celacinnine by two different routes, involving ring enlargement to the 13-membered ring system. Depending on the configuration of the sulfoxide auxiliary, both enantiomers of the natural product can be synthesised.

Scheme 80

Although vinyl sulfoxides are only moderately electron-deficient, they react under nucleophilic epoxidation conditions to form epoxy sulfoxides in good yield.144 In most cases, overoxidation to sulfones can be avoided or limited, and the diastereoselectivities are good to excellent which are only governed by the configuration at sulfur and the geometry of the double bond. The authors also showed that a change in the alkali metal counterion may improve the diastereoselectivity considerably. Sulfinyl dienes were found to be reactive in the same conditions with a generally lower stereoselectivity. Cyclic substrates proved to be less reactive:
the presence of an activating ketone group proved necessary, and the stereoselectivities were again lower as for the open-chain analogues.\textsuperscript{145}

The nucleophilic epoxidation of vinyl sulfoxides bearing an additional stereogenic centre adjacent to the double bond with alkali metal alkyl peroxides proceeds stereoselectively to afford enantiopure sulfinyl and sulfonyl oxiranes.\textsuperscript{146} The stereochemical outcome may in some cases be controlled by changing the reaction conditions and the outcome is primarily directed by the chiral sulfur atom. This methodology was successfully applied to the formal synthesis of (+)-\textit{trans}-Kumausyne \textsuperscript{180} and (+)-Kumausallene \textsuperscript{181} (Scheme 81).\textsuperscript{147}

![Scheme 81](image)

2-(Arylsulfinyl)-2-cycloalkenones undergo $\beta$-addition of alkyl radicals in a highly stereoselective fashion.\textsuperscript{148} The addition of Lewis acids gives rise to chelated intermediates and reverses the stereoselectivity. Additionally, addition of alkyl radicals to diastereomeric mixtures of 4- or 5-methyl substituted 2-(Arylsulfinyl)-2-cyclopentenones leads to a kinetic resolution of the two diastereoisomers.\textsuperscript{149}

The sulfinyl group has been used to successfully control the stereochemistry of conjugate additions of arylcopper reagents to distant enones.\textsuperscript{150} 2-sulfinylpyrrole-derived cinnamides \textsuperscript{182} undergo conjugate addition with aryl Grignard reagents in the presence of copper(I) iodide with high 1,6-induction (Scheme 82). The reactions of the cinnamide with alkyl cuprates or of the analogous crotonamide with aryl cuprates gave rise to lesser stereoselectivity. The chiral sulfinylpyrrole \textsuperscript{150} could be recovered by hydrolysis without loss of optical purity.
Sulfoxides can also bring about stereoselective addition reactions to distant double bonds. Thus, organoaluminium reagents can be used to desymmetrise sulfanylquinols by a diastereoselective conjugate addition to the enone fragment of the quinol 183 (Scheme 83). A variety of alanes can be used and in all the cases described, only one single diastereoisomer is obtained.

Non-symmetric sulfanyl quinines and quinamines 184 were converted to heterocyclic cage compounds 185 by reaction 2-(trimethylsilyloxy)furan a process which involves three consecutive conjugate addition reactions (Scheme 84). Whereas unsubstituted quinols afford a 1:1 mixture of diastereoisomers, a methyl substituent on the double bond enables a complete diastereoselection. The resulting adducts were desulfanylated to produce enantiomerically pure cage compounds.
Finally, the sulfinyl group can be used as an internal nucleophile for the stereoselective synthesis of bromohydrins from distant double bonds in the presence of NBS. The neighbouring group participation of the sulfoxide is evidenced by the inversion the configuration at sulfur that takes place during the reaction.

2.5.3. Rearrangements

Until very recently, no accounts were known of sigmatropic rearrangements involving the double bond of vinylic sulfoxides. Metzner et al. pioneered in this area and published the first Claisen rearrangement that was stereocontrolled by the sulfinyl group. The authors prepared α-sulfinyl dithioesters by addition of lithiated alkyl methyl sulfoxides to 4-fluorophenyltrithiocarbonate. These were then deprotonated with LDA and the resulting enethiolates were S-allylated to afford ketene dithioacetals (Scheme 85). The latter compounds rearrange readily at room temperature into γ-unsaturated α-sulfinyl dithioesters. The crude yields of the process are excellent (>90%), although purification of the compounds gives rise to partial decomposition on silica gel. The diastereoselectivity is excellent as well (93:7 to >99:1 d.r.). A stereochemical model is proposed to explain the high level of induction exerted by the sulfinyl group.
This methodology was extended to the rearrangements of ketene aminothioacetals 189, which proceeds with good yields and high stereoselectivities as well (Scheme 86). An interesting effect of the substituents of the allyl bromides used to prepare the starting material: when electron-withdrawing substituents were present in the allyl bromide, C-allylation occurred exclusively.

Scheme 86

Another example of Claisen rearrangements involving chirality transfer from a sulfoxide group at C-5 has been reported recently: up to 2 stereogenic centres could be created and the products maintain the useful vinylsulfoxide functionality which may account for subsequent stereoselective transformations.

3. Sulfoxide groups in asymmetric transition metal-catalysed reactions

Transition-metal-catalysed reactions have received much attention in recent years for achieving carbon-carbon bond forming reactions with high stereoselectivity. In this context, a number of methods using a chiral organosulfur functionality have been developed. To the best of our knowledge, this area has not been reviewed so far.

3.1. Use of sulfoxides as chiral auxiliaries in transition metal-catalysed reactions

Although sulfoxides have proved to be efficient chiral auxiliaries in asymmetric synthesis, few examples are known in asymmetric transition metal-catalysed reactions.

The first examples of asymmetric intermolecular Heck reactions using sulfoxides as chiral auxiliaries were reported by Carretero and he demonstrated how the sense of the enantioselection can be controlled by the appropriate choice of the substitution at the sulfinyl moiety (Scheme 87).
Scheme 87

The best results have been obtained with $\alpha$-($N,N$-dimethylamino)phenyl sulfoxides, in which the presumed co-ordination of the Pd atom with the nitrogen determines a high asymmetric induction in the key insertion step.

Furthermore intramolecular Heck reaction of (Z)-2-iodo-1,6-diene 190 bearing a 2-($N,N$-dimethylamino)-phenylsulfinyl group as a chiral auxiliary occurred stereoselectively (Scheme 88). 158

Scheme 88

In asymmetric Pauson-Khand reactions the tert-butylsulfinyl group has emerged as the most efficient chiral auxiliary. 159 Synthesis of enantiopure bicyclo[3.3.0]oct-1-en-3-ones 191 has been achieved with high enantioselectivity (Scheme 89).

Scheme 89
A plausible explanation of the high diastereoselectivity observed in the Pauson-Khand reaction of tert-butylsulfinyl enynes could rely on the conformational preferences around the C-S bond (dihedral angle C=C-S-O of approximately 0°) with complexation of the cobalt atom on the less hindered side of the double bond.

The stereodirecting ability of the chiral sulfoxide in combination with organotransition metal chemistry was also illustrated in the diastereoselective allylation of an \( \eta^4-(1Z,3E)-(1\text{-sulfinyldiene})\text{iron(0)tricarbonyl complex 192} \) (Scheme 90).

\[
\text{Scheme 90}
\]

The aldehyde predominantly reacts through the s-cis conformation.

Palladium catalysed allylations of nucleophiles with the sulfinyl group as chiral director have been carried out.\(^{161,162}\) Llebaria\(^{161}\) reported the cyclisation of the sodium salts of \( N\)-Boc or \( N\)-trifluoroacetyl substituted 4-acetoxy-5-(p-tolylsulfinyl)-5-hexenylamines 193 giving the corresponding pyrrolidines 194 in 50-88% yield and up to 80% diastereomeric excess (Scheme 91).

\[
\text{Scheme 91}
\]

The major cycloadducts obtained in the trifluoroacetamide and NHBoc series were epimeric at the \( \alpha \)-nitrogen stereogenic carbon, thus indicating a dependence of the stereoselectivity on the anionic nitrogen nucleophile.

Asymmetric synthesis of cyclopentane derivatives using a chiral sulfinyl group as the source of chirality has been successfully executed by a transition metal-catalysed asymmetric cycloaddition reaction of a chiral (\( \beta \)-sulfinyl)vinylcyclopropane derivative 195 with acrylonitrile (Scheme 92).\(^{163}\)
Scheme 92

An intermediate π-allylpalladium complex is presumably formed by the effect of the chiral sulfinyl group without steric control by the racemic carbon center. The palladium catalyst would react from the sterically less crowded downward direction on the same side as the sterically less demanding lone pair of the sulfinyl group. In the same way, chiral cyclopentenes were synthesised starting from [4-chiral arylsulfinyl-1,3-(E or Z)-butadienyl]cyclopropanes.  

Hiroi also reported intramolecular allyl transfer in chiral α-sulfinyl allylic esters. The participation of the catalyst and the chiral sulfinyl functionality, presumably by the coordination of the sulfinyl group to the catalyst is proposed (Scheme 93).

Scheme 93

Ester enolates containing an allyl functionality undergo intramolecular allylation via π-allyl-metal complexes.

The efficiency of the sulfoxide group was also demonstrated in alkylation of aldehydes with enantiopure 2-sulfinylallyl building blocks (Scheme 94).
Scheme 94

In the field of stereoselective hydrogenation of functionalised ketones in the presence of a chiral metal catalyst, the hydrogenation of β-keto sulfoxides catalysed by ruthenium complexes was investigated by Genêt. Starting from either optically pure or racemic β-keto sulfoxides, the diastereoselectivity of the hydrogenation was controlled by the chiral ruthenium complexes (Scheme 95).

Scheme 95

3.1.1. Catalysts bearing chiral sulfinyl functionality as ligands in asymmetric transition metal-catalysed reactions

In recent years the synthesis of chiral catalysts carrying bidentate phosphine ligands or a combination of heteroatoms such as phosphorus, oxygen, nitrogen or sulfur has been extensively developed. The design of new chiral ligands that allow bond formation in a highly enantioselective fashion has remained an important challenge in modern asymmetric synthesis. The use of chiral non-racemic sulfoxides as ligands in coordination and in transition metal-catalysed reactions has been introduced a few years ago.

We focus in this review our attention on asymmetric synthesis with ligands bearing chiral organosulfur groups such as sulfinyl functions as the sole source of chirality. A chiral sulfinyl group forms a chiral chelate of palladium by coordination of the sulfinyl sulfur atom. The design and development of chiral efficient ligands along this line provided new ligands bearing chiral sulfinyl groups as sole source of chirality and other coordinable heteroatoms such as nitrogen and phosphorus.

Hiroi reported asymmetric syntheses with new chiral sulfoxide ligands possessing amino, acetamido, phosphano or phosphanoamino functionality as an alternative coordinating
element.\textsuperscript{169} He first described the use of chiral nonracemic \(\alpha\)-sulfinylacetamides and \(\beta\) or \(\gamma\) aminosulfoxides in the palladium-catalysed asymmetric allylic alkylations (Scheme 96).\textsuperscript{169a}

\[
\begin{align*}
\text{Me} & \quad \text{Ot-Bu} \\
\text{Me} & \quad \text{Ot-Bu}
\end{align*}
\]

\[
\text{NaH, 1.0 equiv.} \quad \text{allylacetate, 1.5 equiv.} \quad [\text{Pd}(\eta^3-C_3H_5)\text{Cl}]_2 \quad 0.03 \text{ equiv.}
\]

\[
\text{Me} \quad \text{Ot-Bu}
\]

197 \((-\)-(S))

\[
\begin{align*}
\text{chiral ligands, 0.12 equiv.} & \quad \text{solvent} & \quad \text{yield\%} & \quad \text{ee\% of (-)-(S)} \\
\text{DME} & \quad 18 & \quad 50 \\
\text{Et}_2\text{O} & \quad 17 & \quad 29 \\
\text{DME} & \quad 39 & \quad 48
\end{align*}
\]

\textbf{Scheme 96}

Much higher enantioselectivities were obtained with \(\beta\)-phosphinosulfoxides 198 as chiral ligands in palladium catalysed asymmetric allylic alkylation and amination (Scheme 97).\textsuperscript{169b,c}

\[
\begin{align*}
\text{Ph} & \quad \text{OAc} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\[
[\text{Pd}(\eta^3-C_3H_5)\text{Cl}]_2 \ or \ \text{PdCl}_2(\text{CH}_3\text{CN})_2 \ 0.03\text{equiv.}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{X} \quad \text{H} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\[
\begin{align*}
\text{X} = \text{CH(\text{CO}_2\text{Me})}_2 & \quad \text{82\% ee. 71\% yield} \\
\text{X} = \text{NHCH}_2\text{Ph} & \quad \text{85\% ee. 51\% yield}
\end{align*}
\]

\textbf{Scheme 97}

Another family of chiral ligands such as oxazolines tethered to sulfoxides 199 has been examined for their ability to provide asymmetric induction in palladium catalysed allylic substitution reactions.\textsuperscript{170} The enantioselectivity obtained is highly dependent upon the stereochemistry of the sulfur atom (Scheme 98).
More recently, new ruthenium bis(pyridine) sulfoxide complexes 200 were demonstrated as efficient catalysts for asymmetric alkene epoxidation.\textsuperscript{171} Asymmetric induction up to 94\% was observed for $\beta$-methylstyrene (Scheme 99).

\[
\begin{align*}
\text{R}^1 \quad \text{R}^2 & \quad \text{PhI(OAc)}_2, \text{CH}_2\text{Cl}_2, \text{r.t.} & \quad \text{R}^1 \quad \text{R}^2 \\
& \quad \text{yield 97\%, ee. 33\%} & \quad \text{R}^1 = \text{R}^2 = \text{Ph}, \text{yield 97\%, ee. 33\%} \\
R^1 = \text{Ph}, R^2 = H & \quad \text{yield 85\%, ee. 66\%} & \quad R^1 = \text{Ph}, R^2 = \text{H}, \text{yield 85\%, ee. 66\%} \\
R^1 = \text{Ph}, R^2 = \text{Me} & \quad \text{yield 92\%, ee. 94\%} & \quad R^1 = \text{Ph}, R^2 = \text{Me}, \text{yield 92\%, ee. 94\%}
\end{align*}
\]

Scheme 99

C\textsubscript{2}-symmetric bis-sulfoxide ligands\textsuperscript{172} have been studied in coordination with transition metals in different transition states. Synthetic applications in asymmetric transition metal-catalysed reactions have been developed.

For example Shibasaki\textsuperscript{173} studied the $(S,S)$-1,2-bis(p-tolylsulfinyl)benzene in coordination with Pd, Rh and Ru. Moderate asymmetric induction was observed in the Pd-catalysed allylic substitution using this C\textsubscript{2}-symmetric bis-sulfoxide ligand 201 (Scheme 100).
Scheme 100

3.1.2. Catalysts bearing chiral sulfinyl functionality as ligands in other reaction types

Inter- and intramolecular asymmetric radical carbon-carbon bond-forming reactions of sulfonamides were successfully achieved by Hiroi\textsuperscript{174} using chiral sulfoxides 202, 203 and 204 as ligands in presence of a Lewis acid (Scheme 101).

Scheme 101

Recently Carretero\textsuperscript{175} investigated a new family of aminosubstituted tert-butylsulfinylferrocenes 205 and 206 and enantioselectivities of up to 96% were obtained in the addition of Et\textsubscript{2}Zn to aromatic aldehydes (Scheme 102).

Scheme 102
4. Asymmetric transformations of chiral non-racemic sulfoxides

4.1. Asymmetric transformations of sulfoxides

In addition to the high stereochemical inductions that are observed when chiral sulfoxides are used as auxiliaries, the chemical versatility of the sulfinyl functionality adds to the attractiveness of this class of compounds. Besides the classical sulfoxide transformations, the commonly called ligand exchange reaction of sulfoxides, which has been used essentially to generate structurally modified sulfoxides so far, has been developed to generate chiral organometallic species during the last decade. The substitution by alkylmetals of readily available enantiopure α-heterosubstituted sulfoxides or (axially or planar) chiral arylsulfoxides provides chiral d-synthons in high stereochemical purity. The metalated species generated by this transformation are configurationally stable at -78°C for extended periods of time and can be used in subsequent stereoselective reactions. Highly enantiomerically enriched aziridinyl-, oxiranyl-, α-haloalkyl, and ferrocenyl lithium and Grignard reagents have been prepared and used in the synthesis of several useful chiral synthons. As the sulfoxide chirality is not directly implicated in these transformations, they will not be developed in this paper.

In this section we will focus only the synthetically useful and stereoselective transformations of sulfoxides.

4.1.1. Asymmetric Pummerer rearrangements

The Pummerer rearrangement is a well-known and useful transformation of a sulfoxide to the corresponding α-acetoxysulfide. The classical reaction conditions involve refluxing of the sulfoxide in acetic anhydride in the presence of sodium acetate. Thermally labile sulfoxides can undergo a Pummerer rearrangement under milder conditions using trifluoroacetic anhydride as activating agent.

The asymmetric Pummerer reaction involving the chirality transfer from sulfur to the adjacent α-carbon has been known for over 30 years now. Induction can take place for cyclic and acyclic substrates. However, in all the early examples, the yields as well as the enantioselectivities were low. Protocols that achieve synthetically useful yields and enantioselectivities have only been described more recently.

4.1.1.1. Pummerer rearrangement induced by O-silylated ketene acetalts

The use of an O-silylated ketene acetal as activating agent has been introduced in 1984. This area has received a lot of attention in the last 20 years, and only the most recent developments will be covered here. The main advances in this area have been made by the group of Kita, and their most notable results have been reviewed in 1996.

These reagents have been shown to be exceedingly efficient in the case of chiral non-racemic α-substituted sulfoxides. Thus syn- and anti-2-alkylsulfoxides 207a and 207b react in the
presence of silylated ketene acetal 208 and zinc iodide to afford enantiomERICally pure $\alpha$-alkyl-$\alpha$-silyloxsulfides 209a and 209b (> 99% ee). In the absence of the $\alpha$-alkyl substituents, the enantioselectivity is lower (79 – 83% ee). The 2-pyridyl substituent seems to play a crucial role in the high extent of chirality transfer, whereas the stereochemistry of the sulfoxide has no effect on the configuration of the product (Scheme 103).

Scheme 103

4.1.1.2. Pummerer cyclisations

Pummerer-type conditions have been used successfully for the stereoselective synthesis of cyclic compounds by an intramolecular attack of a nucleophile on the sulfinium intermediate formed under the reaction conditions.

By analogy with the vinylogous Pummerer reaction first reported by Marino and applied in numerous other cases, the reaction of a fluorinated vinyl sulfoxide (210) with dichloroketene affords enantiomERICally pure, trans-substituted $\beta$-fluoroalkyl $\gamma$-tolylthio $\gamma$-butyrolactones 211 which can be desulfurised and dechlorinated to obtain the enantiomERICally pure fluorinated lactones 212 (Scheme 104).

Scheme 104

We have observed that enantiomERICally pure $\tau$-butyl 4-sulfinyl-3-silyloxybutanoate (213) can be converted under Pummerer conditions, giving either the usual aldehyde 214 or, when sodium trifluoroacetate is used as a base, enantiomERICally pure cis $\beta$-hydroxy-$\gamma$-sulfenyl-$\gamma$-butyrolactone (215) (Scheme 105).
The Pummerer sulfonium intermediates have also been captured intramolecularly by an electrophilic aromatic ring. This reaction has been used as a key step in the synthesis of bicyclic precursors of anthracyclinones.\textsuperscript{196} Thus, enantiomerically pure $\beta$-hydroxysulfoxides \textsuperscript{216} have been cyclised to afford bicyclic structures \textsuperscript{217} with high to total diastereoselectivity (Scheme 106). However, bulky substituents on the carbinol carbon atom were shown to be detrimental for the cyclisation step.

4.1.1.3. The “non-oxidative” Pummerer rearrangement

In 1995, Bravo \textit{et al.} reported an unusual Pummerer rearrangement of $\gamma$-trifluoro-$\beta$-aminosulfoxides.\textsuperscript{197} They found that, surprisingly, treatment of a $\beta$-aminosulfoxide (\textsuperscript{218}) with TFAA and \textit{sym}-collidine produced a sulfenamide (\textsuperscript{219}) in good yield as the only product (Scheme 107). The formation of this product was interpreted by an abnormal Pummerer rearrangement in which deprotonation took place on the nitrogen atom in \textsuperscript{220} instead of the carbon atom adjacent to the sulfinyl group. Nucleophilic attack of the nitrogen atom on sulfur would form a 4-membered cyclic intermediate (\textsuperscript{221}) which can be opened by a nucleophilic attack of trifluoroacetate. It was shown by deuteration experiments that indeed deprotonation did
not take place on the carbon atoms. The “abnormal” rearrangement product was successfully converted to the corresponding β-fluoro-α-aminoalcohol.

Scheme 107

This methodology, together with the addition of lithiated sulfoxide anions to imines or sulfinimines (vide supra), was successfully applied to the synthesis of trifluoronorephedrine and other fluorinated analogues,\(^{198}\) (+)- and (-)-γ-trifluoromethyl-GABOB\(^{199}\) and other stereochemically defined α-fluoroalkyl amino compounds,\(^{200}\) L-α-trifluoromethylthreoninate and D-α-trifluoromethyl-\(\text{allo}\)-threoninate\(^{201}\) as well as simple β-amino alcohols.\(^{202}\)

The non-oxidative chloro-Pummerer reaction is a variant of the previous methodology in which β-sulfinyl amines 222 are treated with oxalyl chloride to afford the corresponding β-chloro sulfenamides (Scheme 108).\(^{203}\) The mechanism of this reaction is likely to be analogous to the non-oxidative Pummerer reaction and consistent with that of the Swern reaction. The new C-Cl bond is formed with inversion of the configuration, while the sulfinyl group undergoes deoxygenation and migration to the neighbouring nitrogen atom. The resulting vicinal chloramines 223 can be converted to the corresponding aziridines 224 in good yield by treatment with NaH.

Scheme 108
4.1.1.4. Titanium-catalised enyne cyclisation

Sulfinyl enynes 225 react in the presence of titanium alkoxides without affording the expected cyclisation product 226 (Scheme 109).\(^{204}\) Instead, a cyclic aldehyde 227 is obtained. This result can be explained by a Pummerer-type mechanism induced by the highly Lewis acidic titanium centre that takes place even at low temperature. This cyclisation takes advantage of the chirality of the sulfoxide group and shows high asymmetric induction.

![Scheme 109](image)

5. Miscellaneous

5.1. Asymmetric protonation of enolates using 1,2 sulfinyl alcohols and thiols.

Enantiomerically pure β-hydroxysulfoxides can serve as chiral proton source for the enantioselective protonation of prochiral enolates with a tertiary stereogenic carbon at the α-position. Trifluoromethyl-β-hydroxy-p-tolylsulfoxide (\(S,R_s\)) acts as highly enantioselective chiral protonating agent of lithium enolates of cyclohexanone derivatives.\(^{205}\) This asymmetric protonation has been used as the key step in the total synthesis of (-) epibatidine.\(^{206}\)

Asensio et al. showed later that the stereoselectivity of this reaction was closely related with the experimental conditions. Stereoselectivity is generally enhanced when lithium bromide is
present in the medium during enolisation and when the reaction is performed in methylene chloride. Furthermore, optimum enantioselective protonation of 2-alkylcycloalkanones is reached when the α-sulfinyl alcohol/enolate ratio is 3:1. This ratio can be lowered to 1:1 if an achiral proton source such as trifluormethanol is present in the medium to regenerate the α-sulfinyl alcohol. The enantioselectivity drops dramatically when a substoichiometric amount of chiral proton source is used. α-sulfinyl thiols can also be used as chiral proton source but moderate selectivity is generally observed.

6. Conclusions

Since 1995 the use of sulfoxides in asymmetric synthesis has been extended as they offer opportunities for shortening asymmetric syntheses for many examples. Recent new applications have focused on (hetero)-cycloaddition reactions using enantiopure sulfinyl dienes as well as enantiopure vinylsulfoxides derivatives. The field of asymmetric catalysis using sulfoxides as chiral ligands has been developed also this last decade. The key to the success is related to the possibility of the sulfinyl functionality to co-ordinate both with its oxygen or sulfur atom extending the scope of metals used as catalysts. This field will probably be of growing interest in the future.

7. References

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