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

Gilles Hanquet*, Françoise Colobert, Steve Lanners, and Guy Solladié

Laboratoire de Stéréochimie associé au CNRS, ECPM, Université Louis Pasteur 25 rue Becquerel, 67087 Strasbourg, France
E-mail: ghanquet@chimie.u-strasbg.fr

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

Table of contents

1. Introduction

Over the two last decades, chiral three coordinate sulfur compounds have received considerable attention as key intermediates in asymmetric synthesis[1] or as pharmaceutical goals.[2] Among them, sulfoxides have been employed for a wide range of stereoselective carbon-carbon or carbon-hetereoatom 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 β-keto sulfoxides

Nucleophilic additions to enantiomerically pure β-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 β-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 β-ketosulfoxides with Dibal-H or Dibal-H/ZnX_2 followed by either hydrogenolysis of the carbon-sulfur bond or reductive Pummerer rearrangement of the resulting β-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).

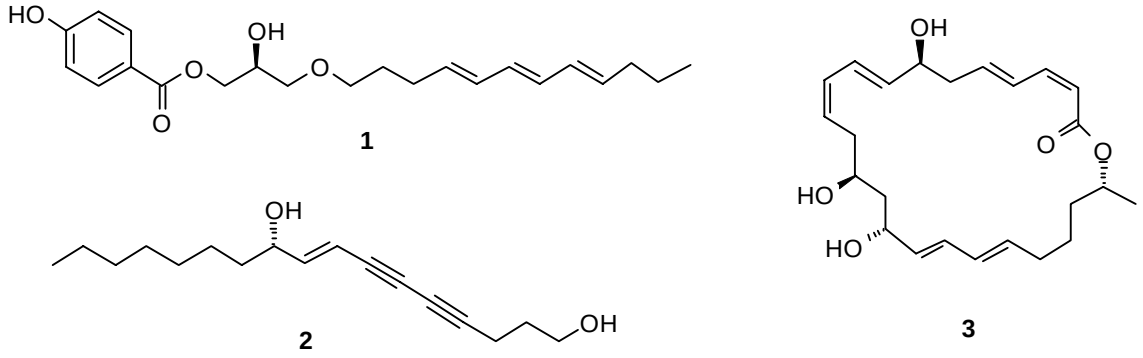
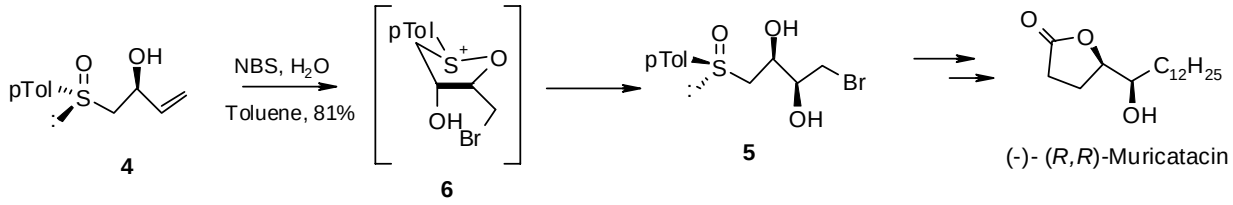


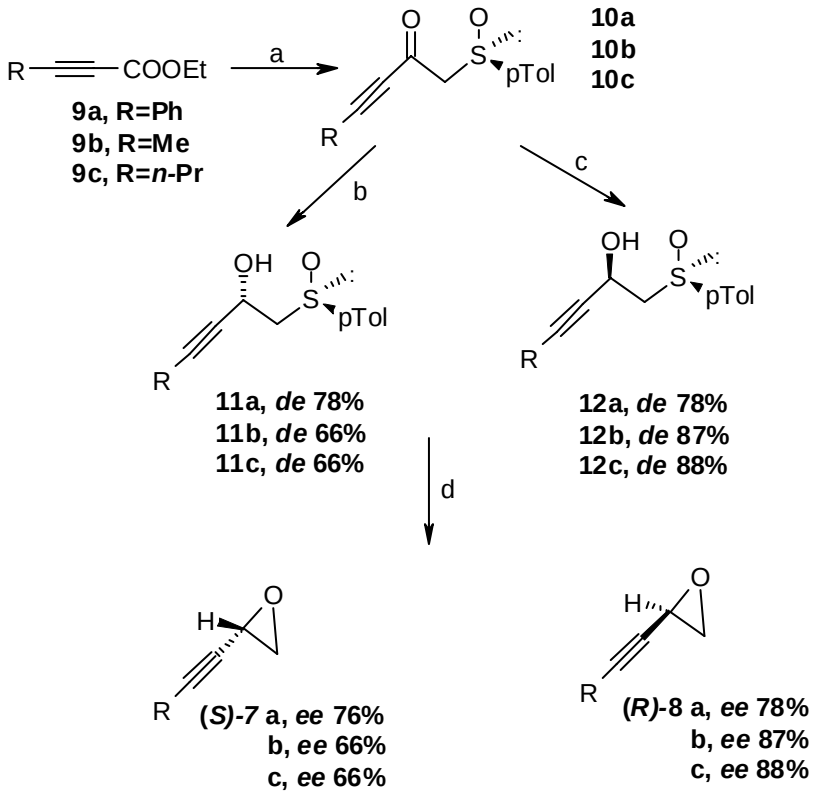
Figure 1

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

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.

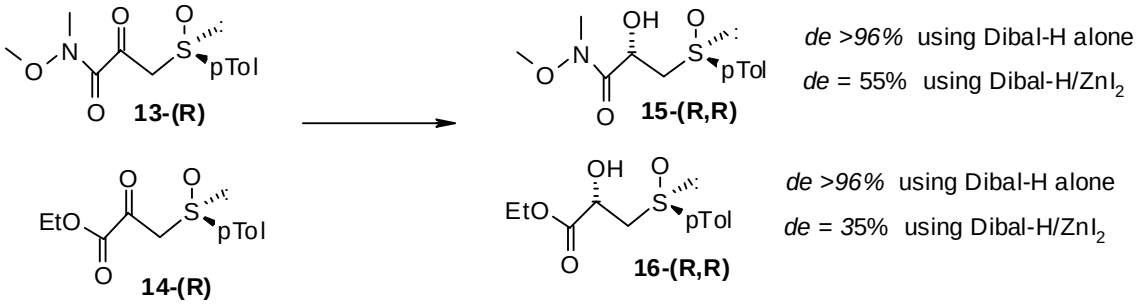


a) *(R)-p*Tol-SO-Me (2equiv.), LDA (2equiv.), THF, -78°C, 3h; b) Dibal-H, -78°C THF, 1h; c) Dibal-H/$ZnBr_2$, THF, -78°C, 0.5h; d)$TICl_3$, EtOH, rt, 15min; then Me_3OBF_4, Dichloromethane, rt, 3h; K_2CO_3 (2 equiv.), water, 30 h.

Scheme 2

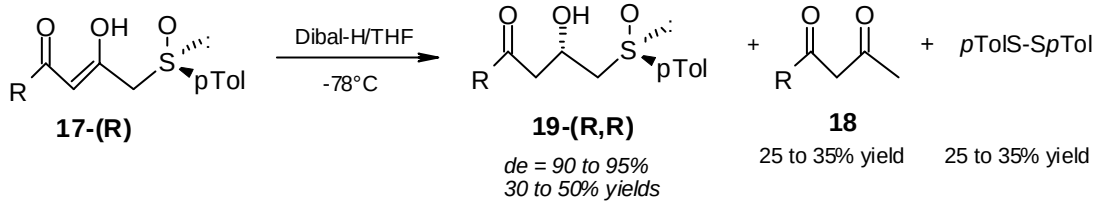
The presence of an alkyl substituent in the α-position maintains the high level of diastereoselectivity in the Dibal-H/$ZnBr_2$ reduction when appropriate conditions are used.[14] Generally, stereocontrol is modest in absence of the chelating agent and treatment of α-alkylated β-ketosulfoxides with Dibal-H 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 ZnX_2, 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/ZnX_2 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

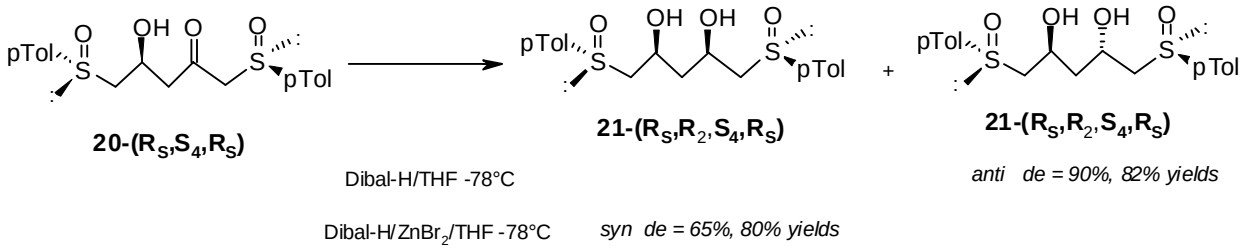
β,δ-diketosulfoxides **17**, which are excellent intermediates for the enantio- and diastereoselective synthesis of *syn* and *anti* 1,3-diols, give with Dibal-H chemo- and diastereoselectively the corresponding β-hydroxy-δ-keto-sulfoxides **19** with *de* up to 95% but with moderate yields (30 to 50%).[8, 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*-tolyldisulfide 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]

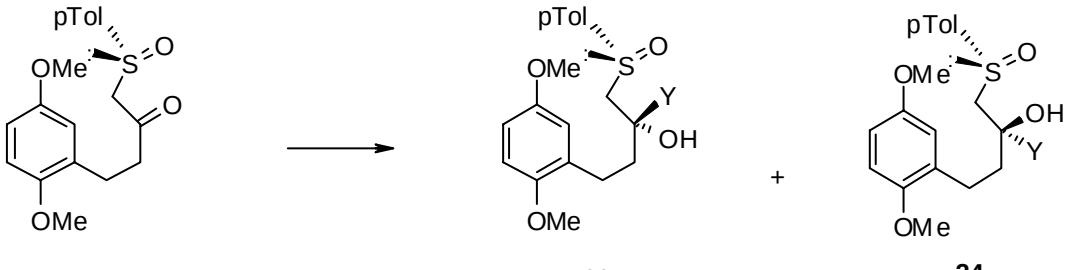
Alternatively, Garcia Ruano *et al.* showed recently that *syn* and *anti* 1,3 diols could be prepared stereoselectively from Dibal-H or Dibal-H/$ZnBr_2$ (used in large excess) reduction of bis-sulfinylhydroxyketones **20** (Scheme 5). They demonstrate that the presence of the sulfinyl group completely 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 anthracyclinones after asymmetric Pummerer reaction (see last section) (Scheme 6).[22]



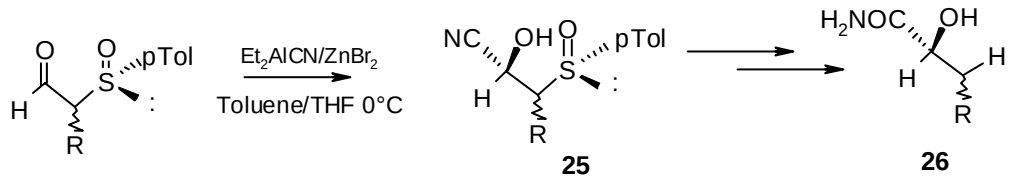
Reagent		23	24	
Et_2AlCN	Y= CN	98	2	97% yield
EthynylMgBr/$ZnBr_2$	Y= H—≡	90	10	60% yield
VinylMgBr/$ZnBr_2$	Y= H_2C=—	86	14	60% yield
$Me_3Al/ZnBr_2$	Y= Me	85	15	64% yield

Scheme 6

The hydrocyanation reaction is highly stereoselective and treatment of β-ketosulfoxides with Et_2AlCN affords the corresponding sulfinyl cyanohydrins with high yield and *de* (>96%). The chirality induced at the hydroxylic 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[8], 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_2AlCN 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]

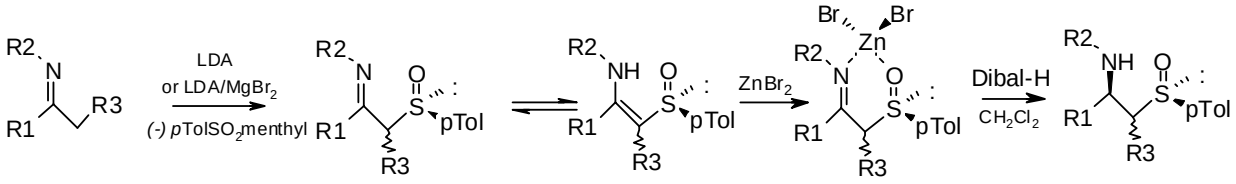
Secondary cyanohydrins **25** leading to the corresponding α-hydroxyamides **26** have been prepared with high *de* (>90%) from optically pure α-hydroxyaldehydes.[24] By contrast with α-keto analogues, the presence of $ZnBr_2$ is required to obtain good conversions (Scheme 7).



Scheme 7

The diasteroselective 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 *et al* described in 1998 a general one based on α–sulfinylation of ketimine with (*R*) or (*S*) menthyl sulfinate.[25]

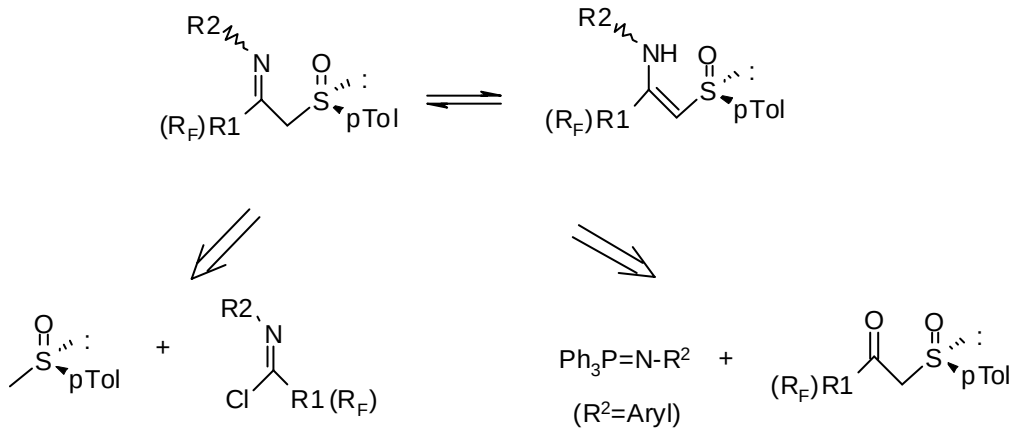
Furthermore, the reduction with Dibal-H gives only poor diastereoselectivity of the resulting β-aminosulfoxide.[26] The presence of ZnX_2 is necessary to promote a diastereoselective reduction controlled by the chirality on sulfur (Scheme 8). It shifts the enamine-imine equilibrium towards the reactive imine tautomer. 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.



Scheme 8

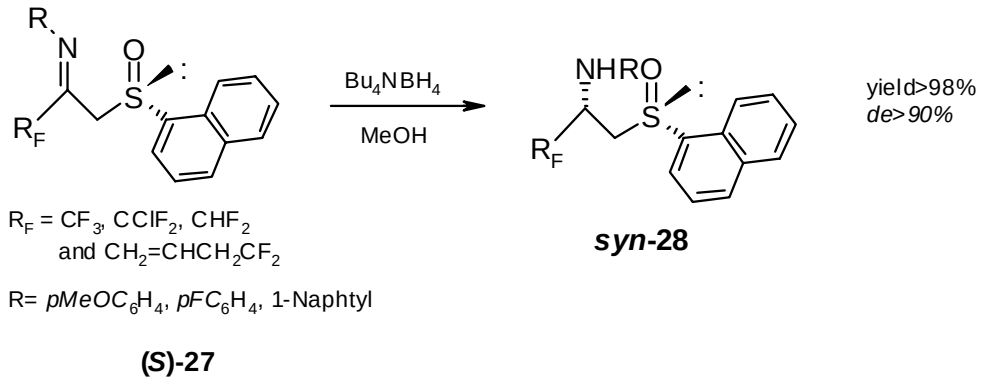
Nucleophilic additions to enantiomerically pure fluorine containing β-iminosulfoxides have been reported by Bravo *et al.* as key steps in the preparation of analogues of biologically active molecules such as optically active amines,[27] amino alcohols,[27] aminoacids[27] and alkaloid precursors.[28] 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 diasteroselectivity are obtained using K and L-selectrides (50 to 75% yield and *de*>80%).[27, 30] The best method to obtain α-fluoroalkyl β-sulfinylamines is the asymmetric addition reaction of α-sulfinyl carbanions on fluoroalkyl aldimines (see next section).

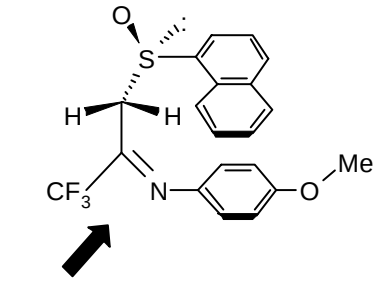


Scheme 9

Nevertheless, Fustero and Bravo recently developed a highly efficient hydride reduction of γ-fluoro-β-*N*-arylimino sulfoxides **27** using Bu_4NBH_4 affording the corresponding *syn* α-fluoroalkyl β-sulfinylamines **28** with high yield and *de* (>90%) (Scheme 10).[31] 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.



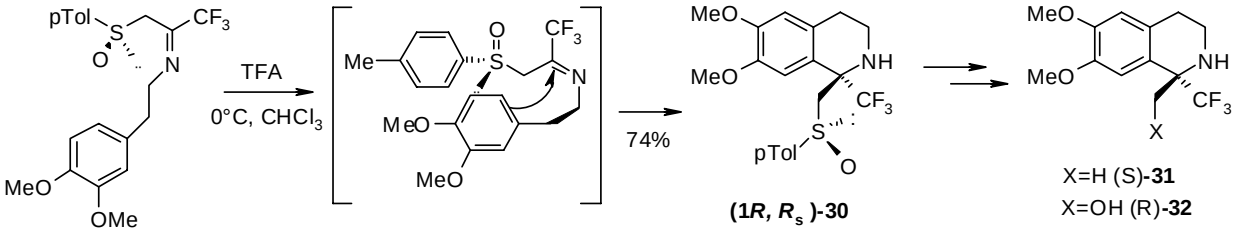
Scheme 10



(*R*)-27

Figure 2

1-Trifluoromethyl-tetrahydroisoquinoline alkaloid analogues have been synthesised with good stereoselectivity (1*S*,R_S)/(1*R*,R_S)= 6/1 and chemical yields.[28] The key step is a stereoselective intramolecular Pictet-Spengler reaction of the *N*-arylethyl γ-trifluoromethyl-β-iminosulfoxide (*R*)-**29** (Scheme 11).



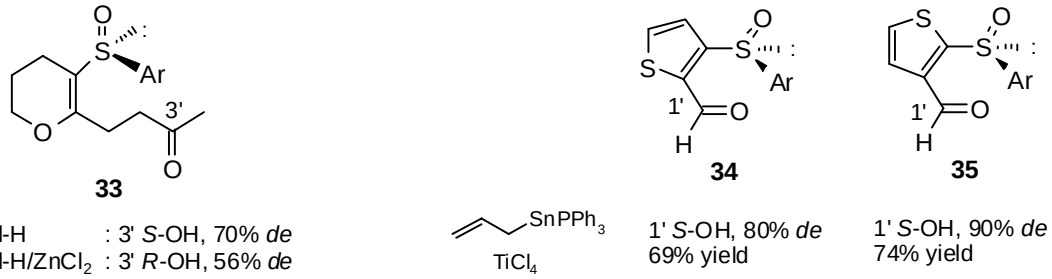
(*R*)-**29** **(1*R*, R_s)-30**

Scheme 11

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

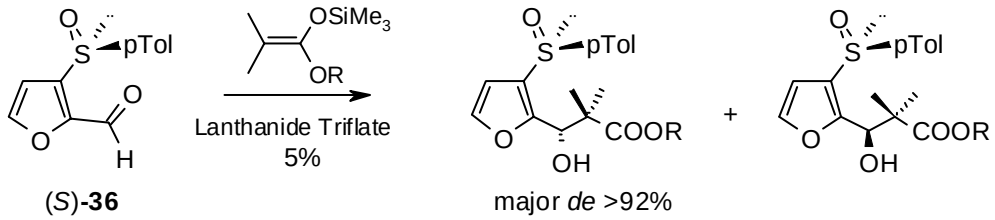
2.1.2. Nucleophilic additions to γ-keto sulfoxides

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[32] reported an 1,6-asymmetric induction in the Dibal-H reduction of the ε-ketosulfoxide **33** and more recently Arai[33] a case of 1,4-asymmetric induction during the allylation of the γ-ketosulfoxide **34** (Scheme 12).



Scheme 12

Since 1996, Arai *et al.*[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[34b] is a lanthanide triflate catalysed Mukaiyama aldol condensation of silyl ketene acetals 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 acetals 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.

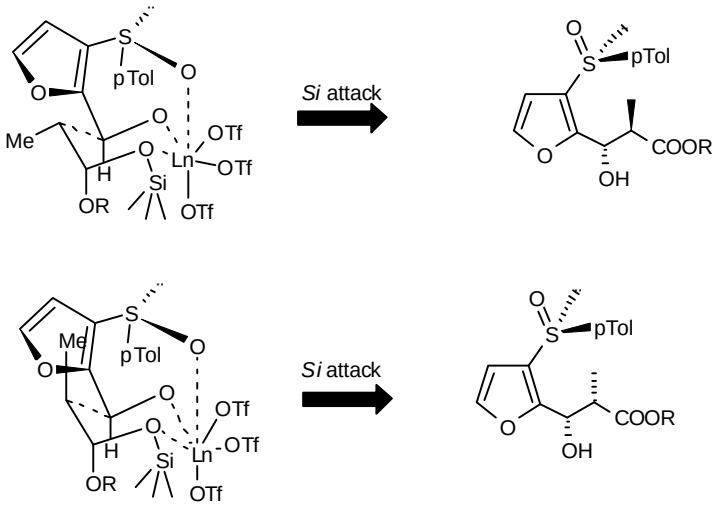
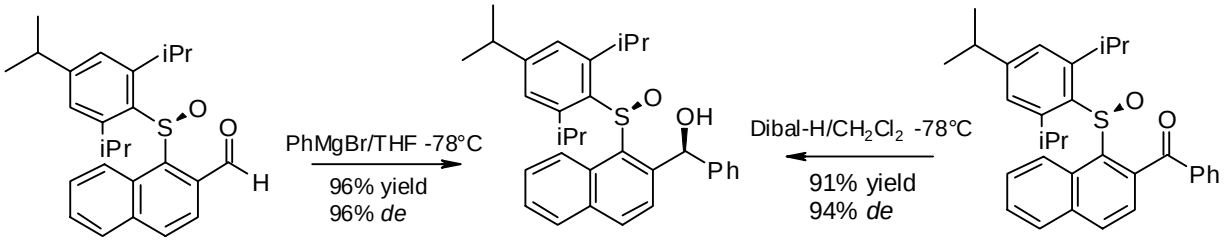


Figure 3

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.[34c]

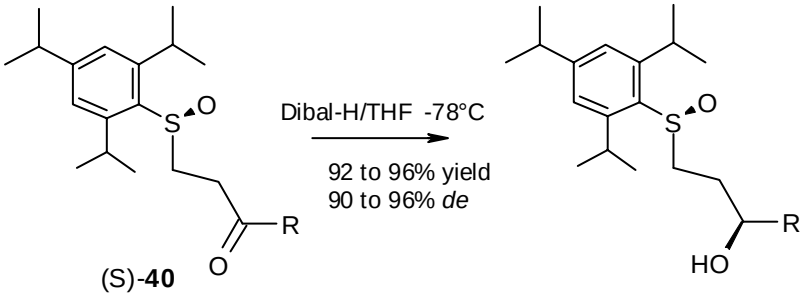
Toru *et al.* have reported a new diastereoselective reaction of 1-(arylsulfinyl)-2-naphtaldehydes and 2-Acyl-1-arylsulfinylnaphtalenes with various nucleophiles such as Grignard reagents, silyl ketene acetals and hydrides.[35] In these reactions, the best diastereoselectivity is observed with (2,4,6-triisopropylphenyl)sulfinyl 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, γ-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 γ-ketosulfoxide **39** (Scheme 14). The high stereoselectivities of these reactions are due to a predominant rotamer around the C_{napht}-S axis and the steric effect of the bulky 2,4,6-triisopropylphenylsulfinyl group.



(R_S)-**38** (*R*$_S$, *S*)-**37** (R_S)-**39**

Scheme 14

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



(S)-**40**
R= Ph, Me, Et

(*S*, *S*$_S$)- **41**

Scheme 15

Diastereoselectivity is obtained in the reaction of all γ-ketosulfoxides **40** irrespective of the substituant (R) attached to the carbonyl group. The authors assume a twisted chair transition state involving a trigonal bipyramidal structure (Figure 4).

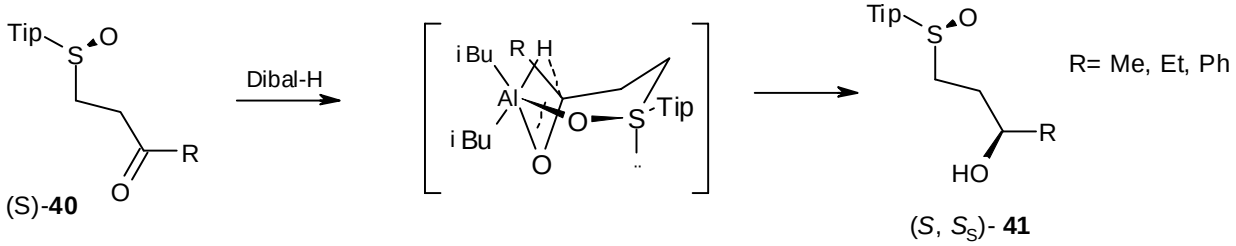
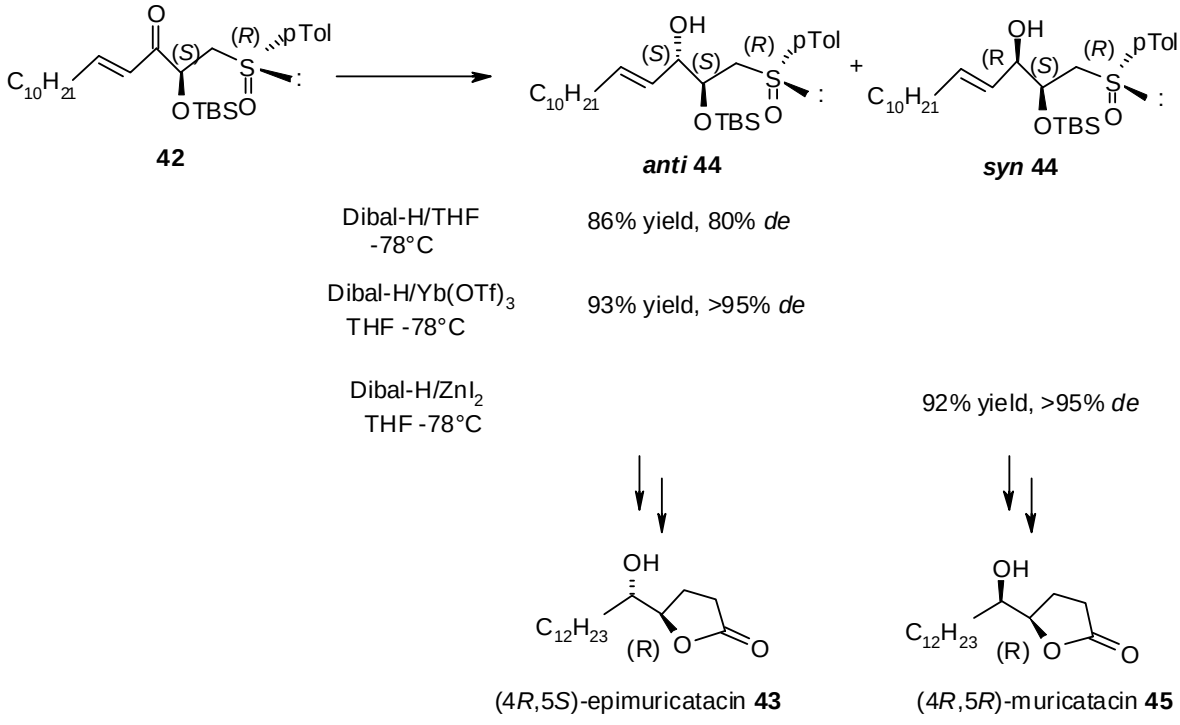


Figure 4

The use of an additive such as $ZnCl_2$ 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-*p*Tolylsulfoxides[17] using Dibal-H in THF alone or with ZnI_2 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-*p*Tolylsulfoxide **4**.



Scheme 16

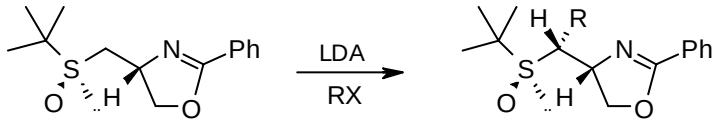
Reduction of **42** in the presence of ZnI_2 allowed the preparation of (*R*,*R*)-muricatacin **45** by stereoselectively affording the epimer at the γ-position (*syn*-diol **44**). No rationale has been proposed for this 1,2 and/or 1,4-induction but the study of the influence of the relative configuration 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-ketosulfoxides[36] 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 configurationnal 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.

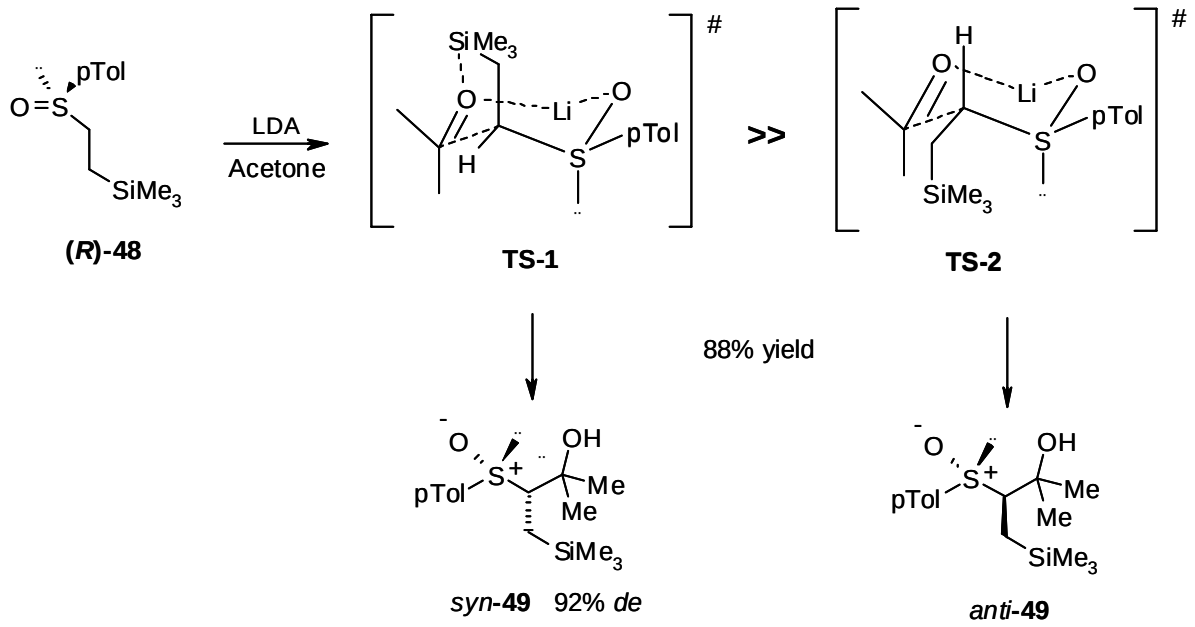


(S_R,*R*)-**46** (S_R,*R*,*R*)-**47**
R= Me, Et, Allyl

Scheme 17

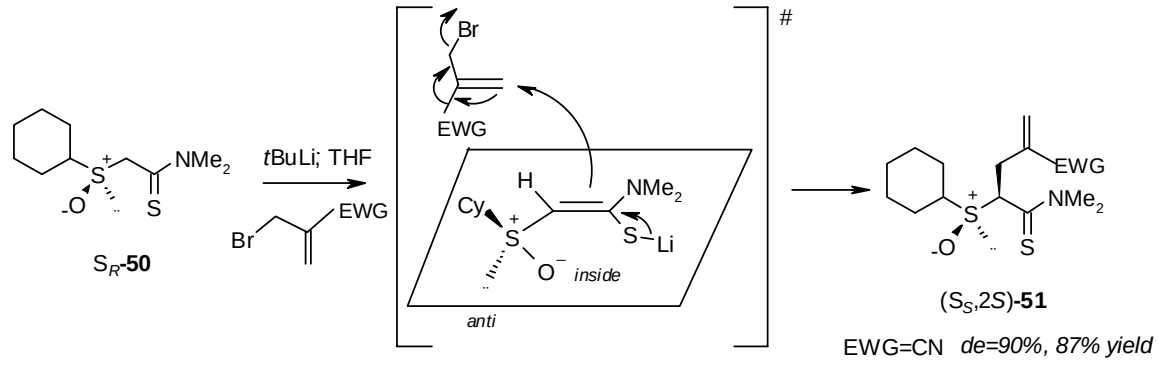
Reaction of saturated α-sulfinyl carbanions with carbonyl compounds proceeds also with low stereoselectivity.[40,41] Nevertheless, when a trimethylsilyl group is in the β-position, the diastereoselectivity of this condensation is very high[41] and has been extended to various nucleophiles. Toru *et al.* 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 (Scheme19).[42]
The reaction proceeds via a conjugate addition of the carbon centre of the enethiolate followed by halide elimination.



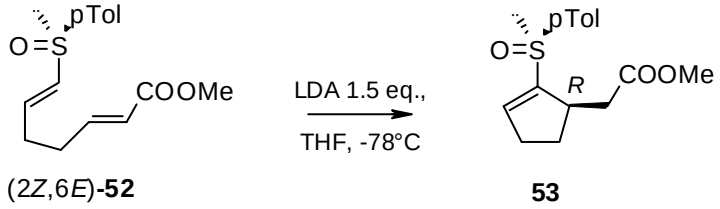
Scheme 19

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,2*S*).

2.2.2. Reactions of α-sulfinyl carbanions with 1,3-induction

Intramolecular alkylation of an α-sulfinyl vinylic carbanion has been investigated by Tanaka *et al.*[43] Cyclisation occurs at the α-position of β-(ω-haloalkyl) substituted vinylic 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 vinylic sulfoxide as an intramolecular Michael donor to (*Z*)-enoates, cyclises with very high 1,3 induction.[44] The diasteroselectivity 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).



(2*Z*,6*E*)-**52** **53**

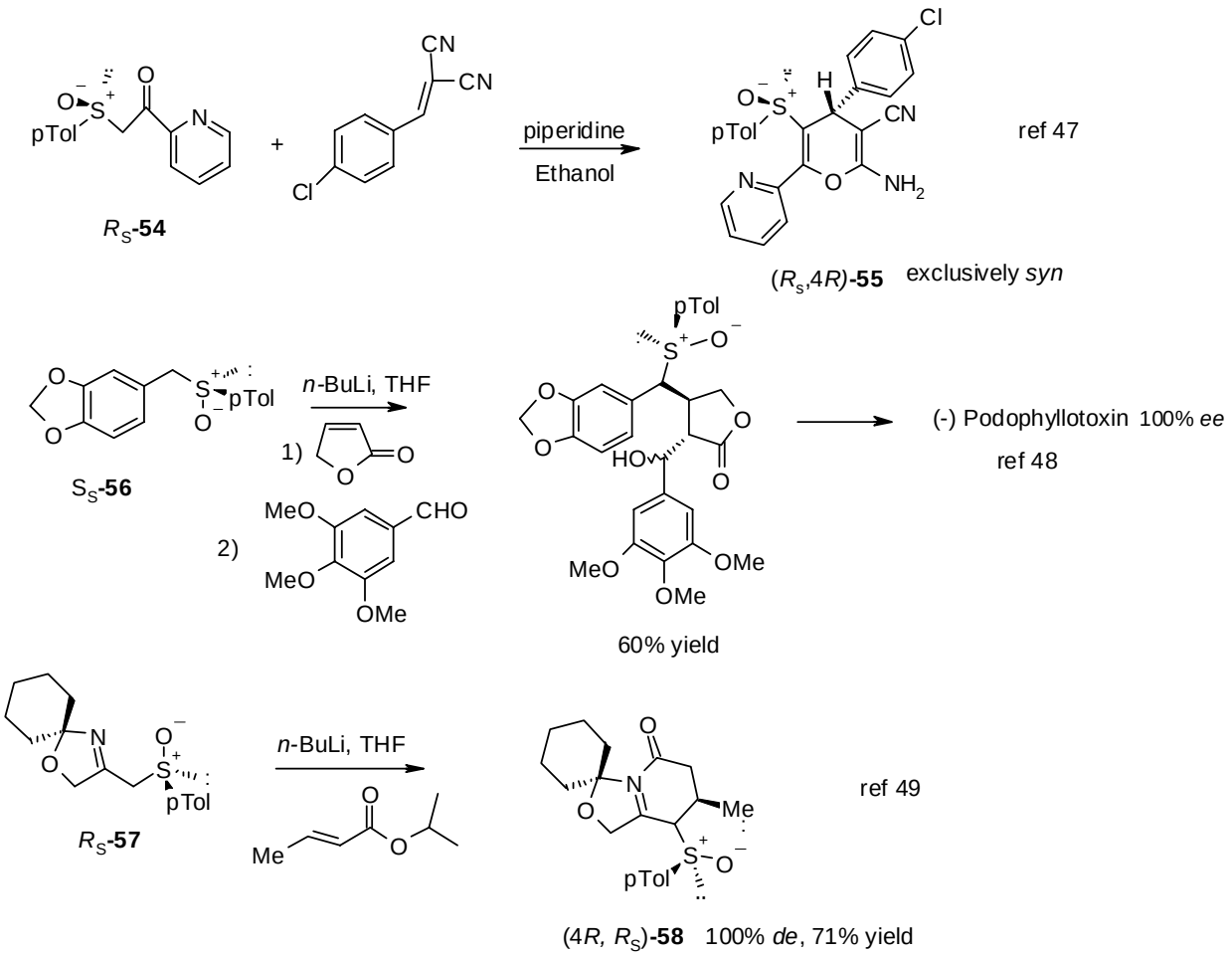
Scheme 20

Cyclohexene ring formation also proceeds in a similar fashion but with lower yield and completely reversed selectivity.[44]

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

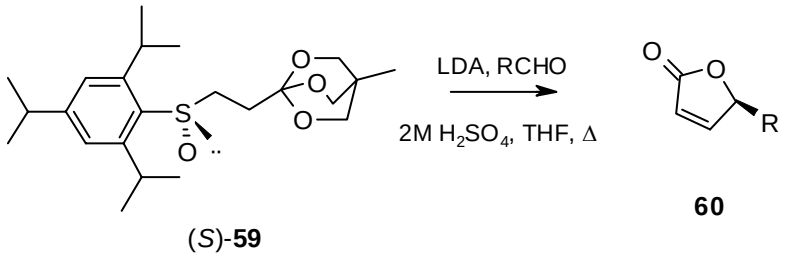
The conjugate addition of sulfoxide anions followed by ring-closure proceeds generally with good selectivity, as illustrated by the three examples depicted in Scheme 21.

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



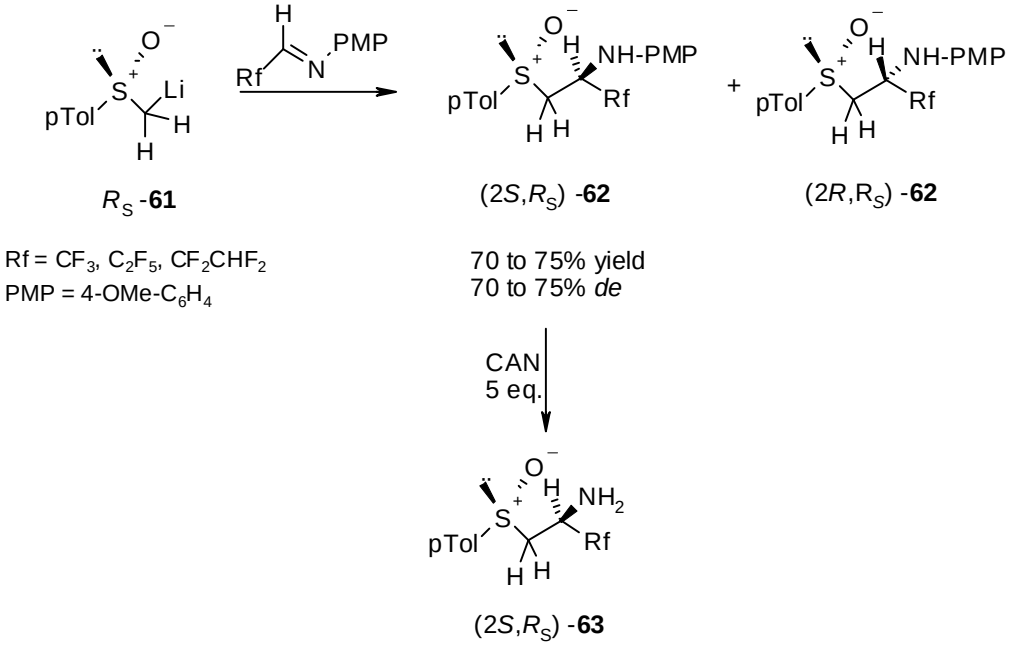
Scheme 21

Ghosez's cyclocondensation of sulfone-γ-orthoesters with carbonyl derivatives has been extended to an asymmetric version.[50] Enantiomerically pure lithiated sulfoxide **59** adds to aldehydes to provide γ-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 α-sulfinyl carbanions to the diasterotopic C=N double bond of imines allows the asymmetric synthesis of β-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 α-aminoacids. Bravo *et al.* have first established that the addition of chiral sulfoxide-stabilised carbanion on *N*-(*p*-methoxyphenyl)aldimines bearing trifluromethyl, pentafluoroethyl and ω-hydrotetrafluoroethyl groups affords the corresponding α-fluoroalkyl-β-sulfinyl amines in excellent yields and diastereoselectivity (Scheme 23).[51]

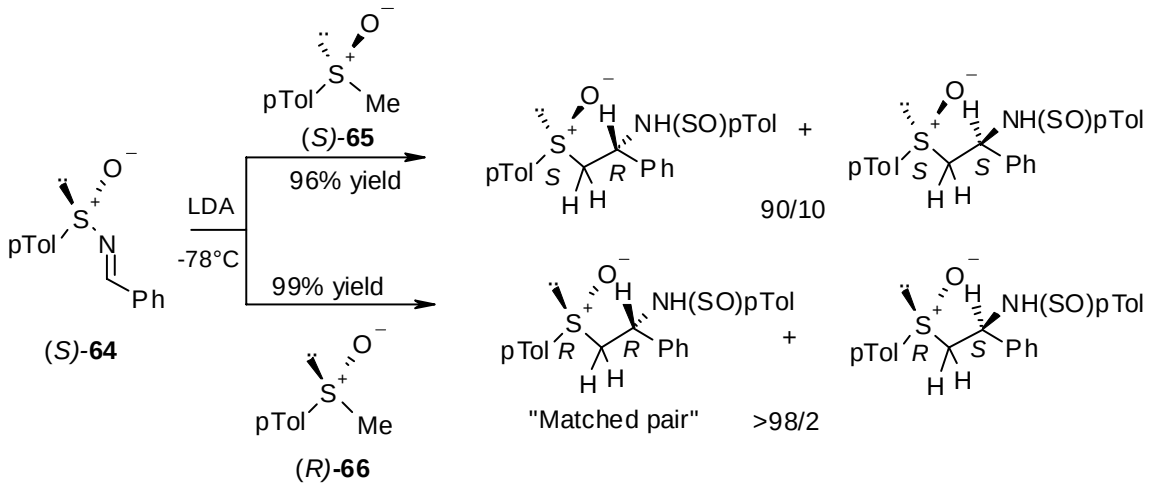


Scheme 23

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 α-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°C are very high (>88% *de*) and afforded after further transformations the corresponding β-amino acids with good overall yield and optical purity.

The behaviour of enantiomerically pure sulfinyl imines with non racemic chiral α-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**.

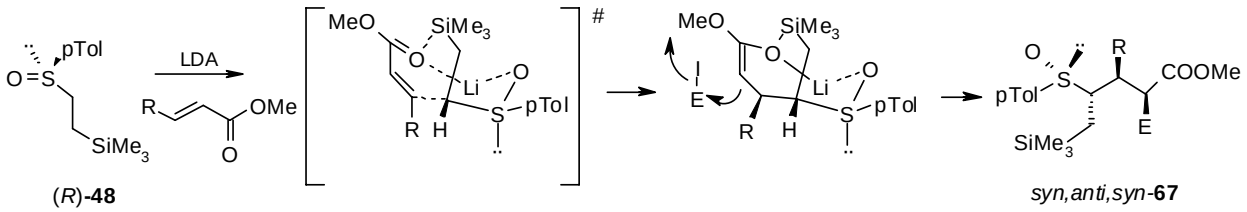


Scheme 24

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.[55]

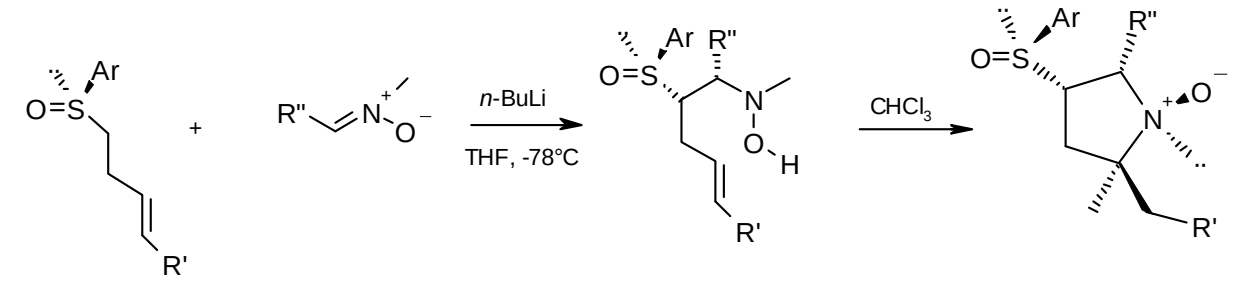
As already mentioned in the preceding paragraph, β-silyl-α-sulfinyl carbanion **45** reacts smoothly with α,β-unsaturated carbonyl compounds with very high 1,2 induction. The high stereochemical outcome is ascribed to the presence of the trimethylsilyl group with a silicon-carbonyl oxygen interaction 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.



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).[57] Subsequent reverse-Cope cyclisation of compound **69** affords the highly substituted pyrrolidine-*N*-oxides **70** with a high level of stereocontrol.

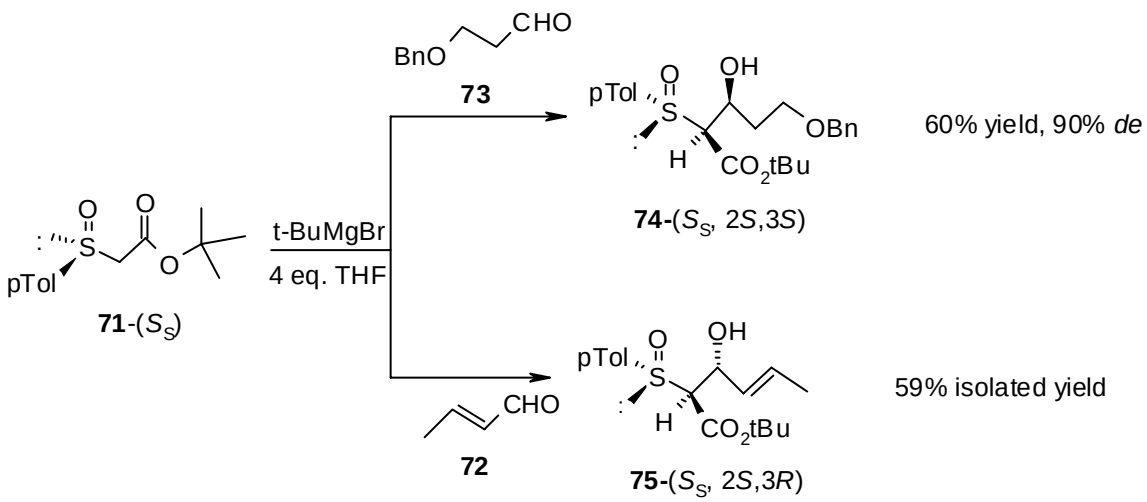


68 **69** **70**

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.

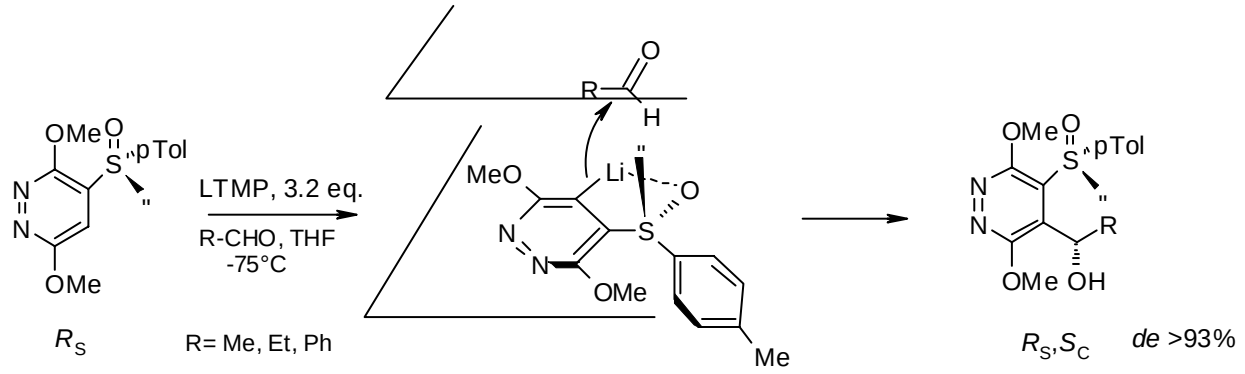
Aldol-type condensation of enantiomerically pure *tert*-butyl sulfinyl acetate **71** on carbonyl compounds using *tert*-butylMgBr as base usually gives mainly one diastereoisomer with a predictable configuration.[58] Surprisingly, when α,β unsaturated aldehyde **72** is used as electrophile, the opposite configuration at the stereogenic hydroxylic centre is observed in the adduct **75** (Scheme 27).



Scheme 27

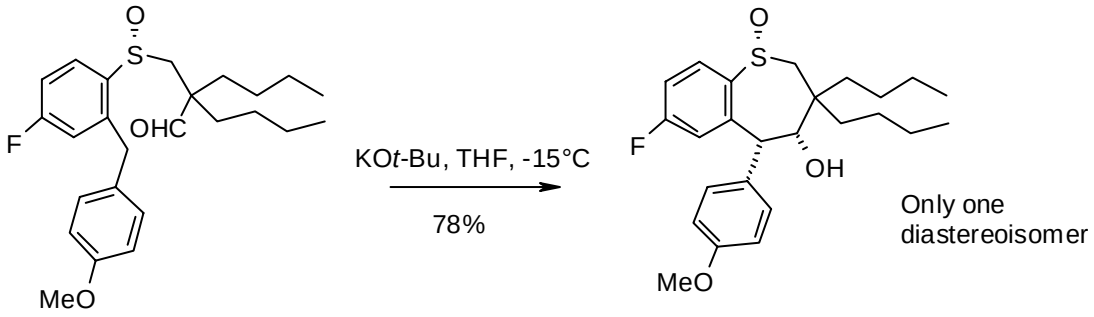
2.2.4. Reactions of β and γ-sulfinyl carbanions with 1,4-induction

The metalation and reaction with aldehydes of 4-(*p*-Tolylsulfinyl)-3,6-dimethoxypyridazine have been investigated recently.[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).[60]

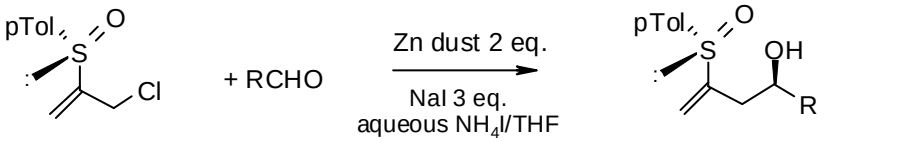


R_S-**76** (R_S, 4*R*, 5*R*)-**77**

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 promotor affords α-vinylic-γ-hydroxysulfoxides with very good 1,4 induction (Scheme 30).[61]



(S_S)-**78** (S_S, 4*R*)-**79**

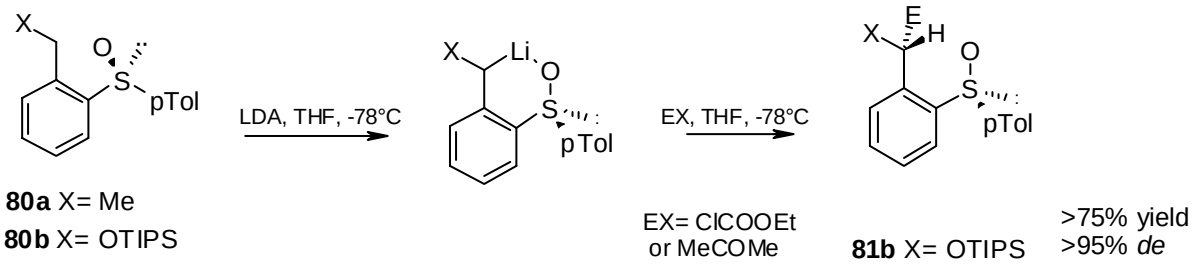
R= Ph, cyclohexyl 60 to 80% yields and 65 to 72% *de*

Scheme 30

An open antiperiplanar transition state model is preferred over a six-membered cyclic transition stateinvolving 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 α-amino aldehydes are used.[61b] In this case, a "matched" stereoinduction is observed with aldehydes derived from natural α-amino acids.

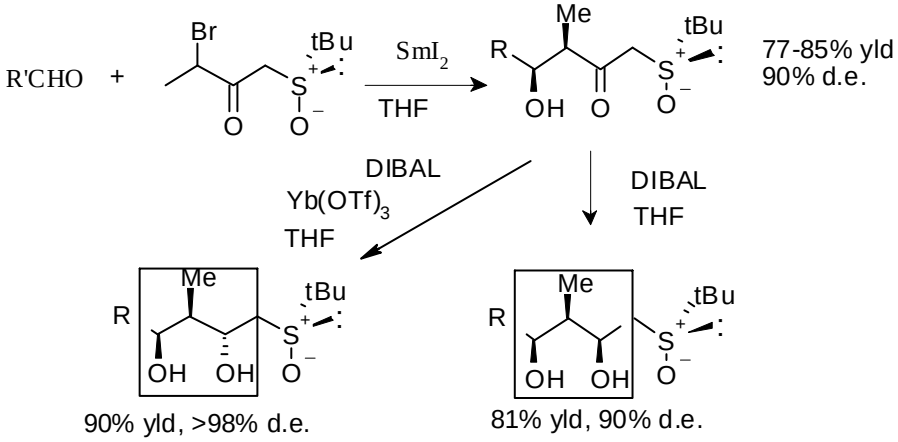
Nucleophilic reactions of enantiomerically pure stabilised *ortho*-sulfinyl benzyllithium carbanion occurs diastereoselectively by a 1,4-induction process.[62]

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).



Scheme 31

Very recently, we described an efficient access to *anti*- and *syn*-2-methyl-1,3-diol moieties bearing a linear aliphatic substituent.[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 (*de*>90%) (Scheme 32).

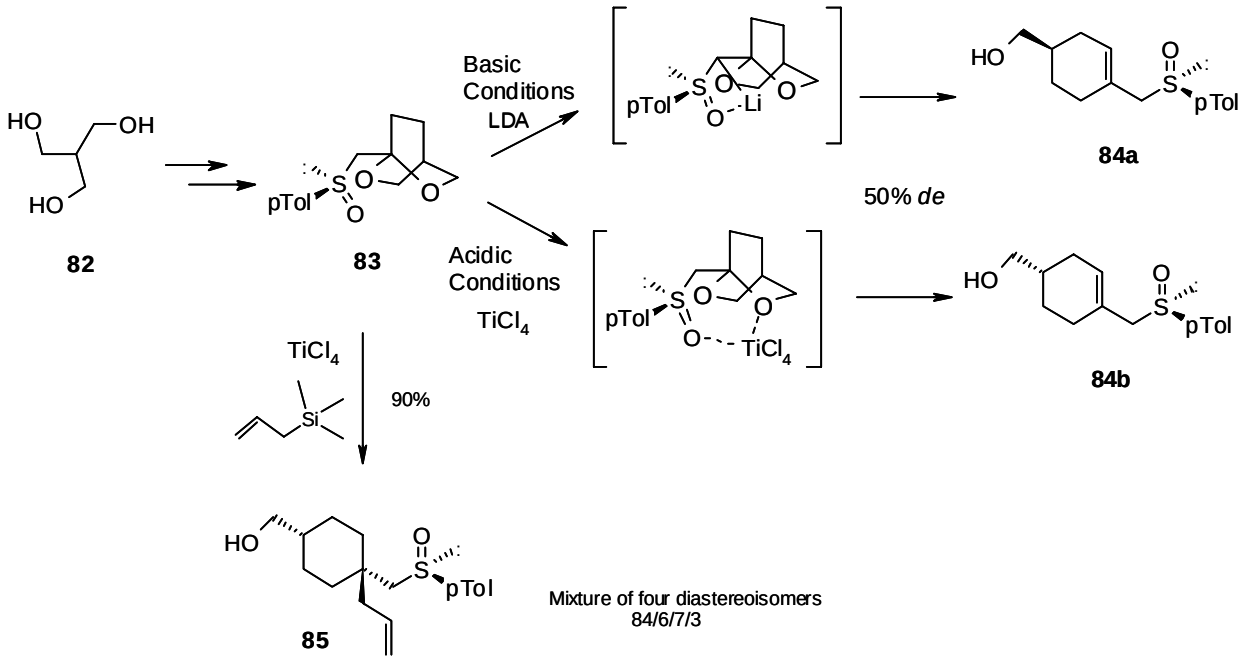


Scheme 32

2.3. Reactions involving chiral α-sulfinyl acetals

Chemical asymmetric desymmetrisation of prochiral diols using chiral sulfoxides has been studied extensively over tje last decade by Iwata *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 β-elimination of chiral α-sulfinyl acetals.[64] Prochiral 1,3-diols **82** are transformed into the α-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 β-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**[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 appeaedr 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.[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 *p*-alkoxyphenylmenthyl-sulfinate.[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%).[68]

2.5. Reactions involving vinyl sulfoxides

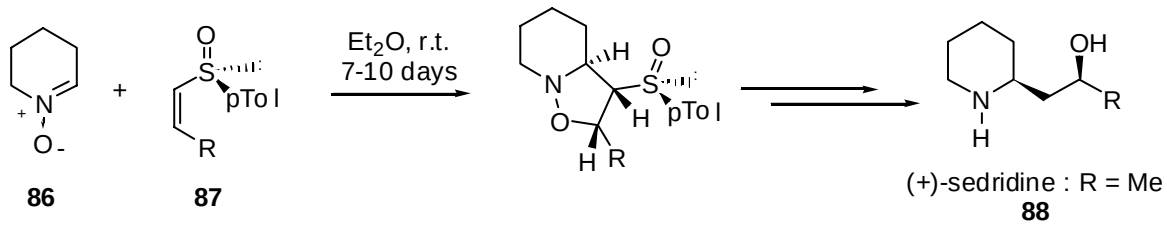
Vinyl sulfoxides are among the most widely used sulfinyl compounds in asymmetric synthesis. The sulfinyl group is responsible for a strong stereodifferentiation leading to highly stereoselective reactions on the double bond, but it is also in many cases at the origin of the synthetic versatility of these 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[69] 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*)-vinylic sulfoxides **87**.[70] 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).

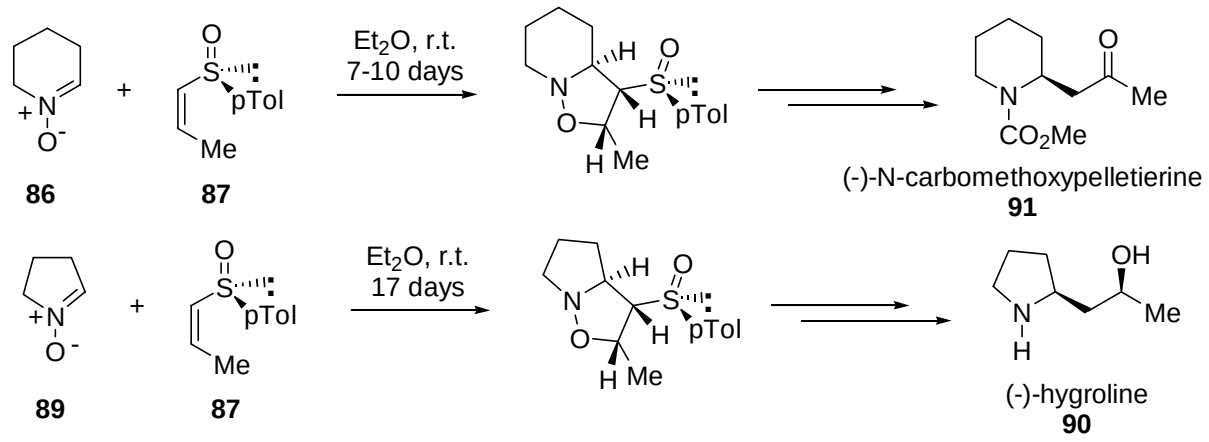


86 **87** **88**

Scheme 34

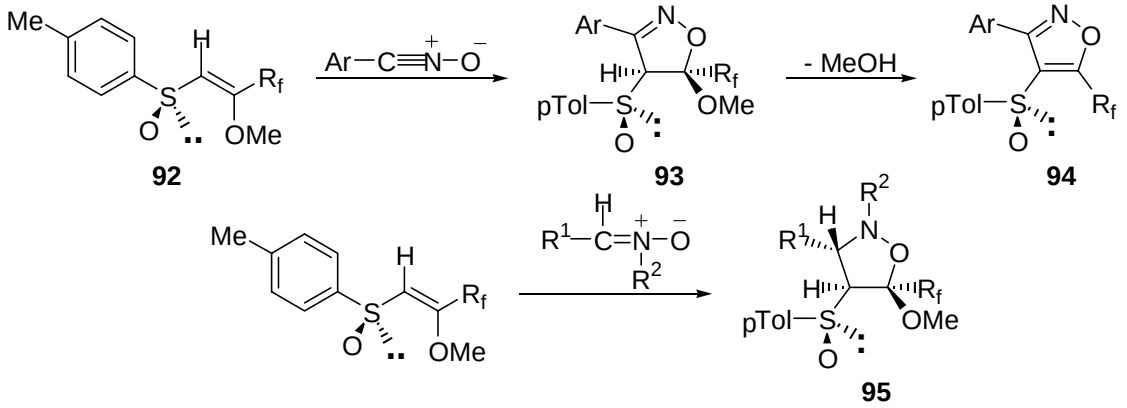
Simultaneously, a report by Viehe *et al.* showed the reactivity of α-trifuoromethyl vinyl sulfoxides with various 1,3-dipoles, including diazo compounds and azomethine ylides.[71] However, there is no account of any observed diastereoselectivities in this report.

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.[72] The described cycloaddition adducts provide an efficient access to natural products (-)-hygroline **90** and (-)-(2*S*)-*N*-carbomethoxypelletierine **91** (Scheme 35).



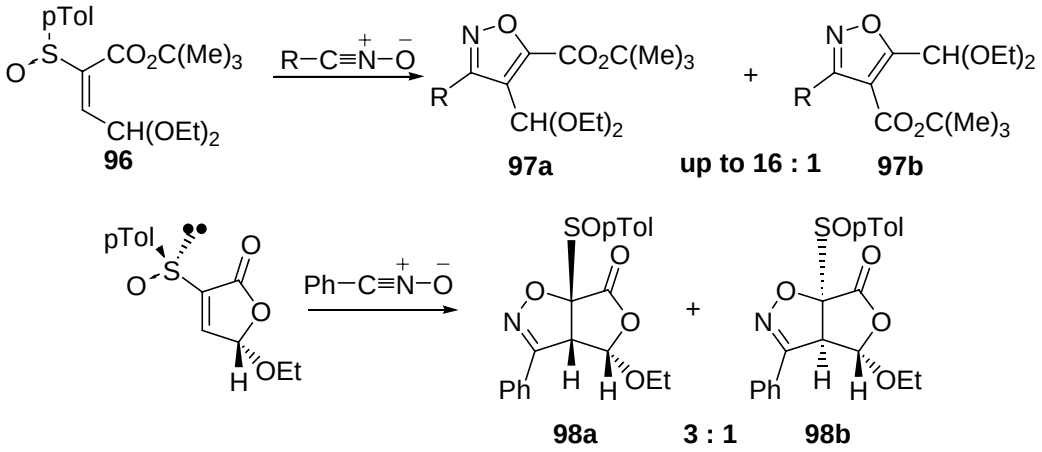
Scheme 35

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).



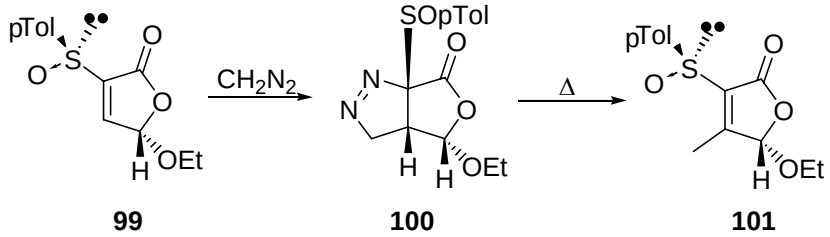
Scheme 36

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 isoxazolines **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).

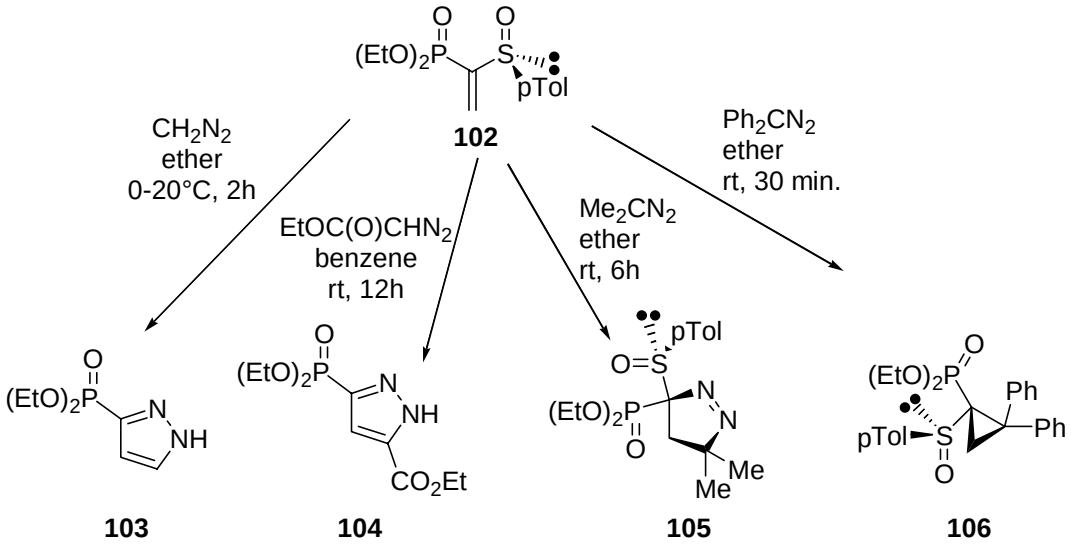


Scheme 37

The cycloaddition of diazoalkanes to vinylsulfoxides has also been investigated. Garcia Ruano has studied the reaction of diazomethane with sulfinylfuranones **99**.[75] 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.[76] 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).

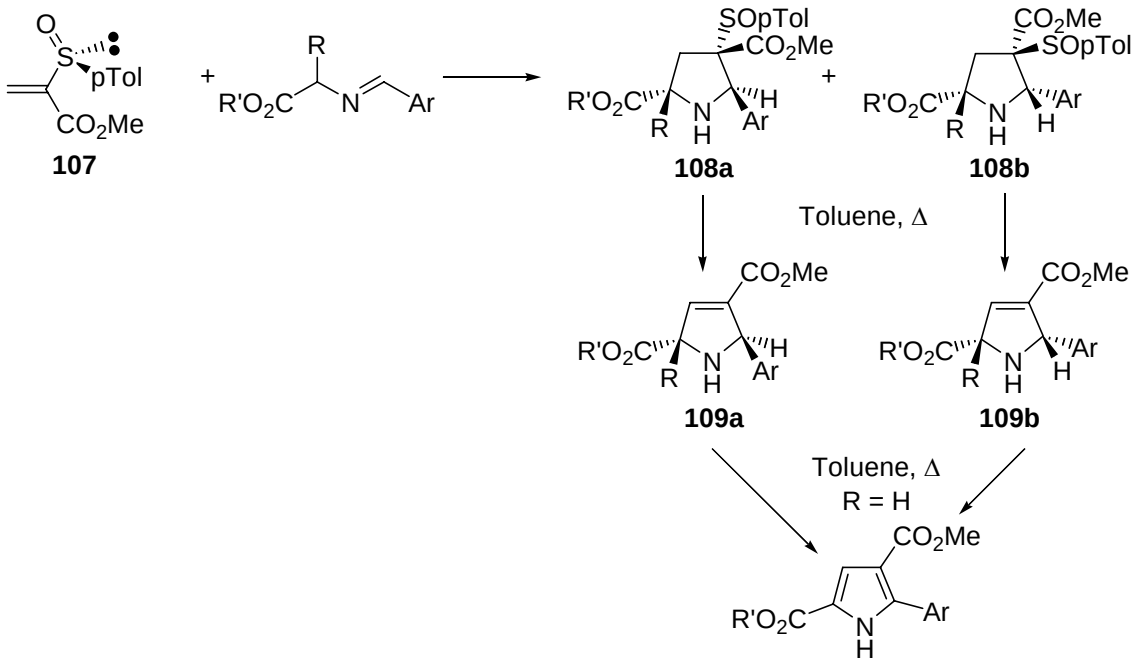


Scheme 38



Scheme 39

Garcia Ruano *et al.* have also investigated the reactions of N-metalated azomethine ylides with 2-sulfinylacrylates **107**.[77] 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 sulfinylpyrrolidines **108a** and **108b**, or 2,5-dihydro-1H-pyrroles **109a** and **109b** by pyrolytic elimination of the sulfinyl 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.[78] These reactions display complete regioselectivity and useful levels of stereocontrol.

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

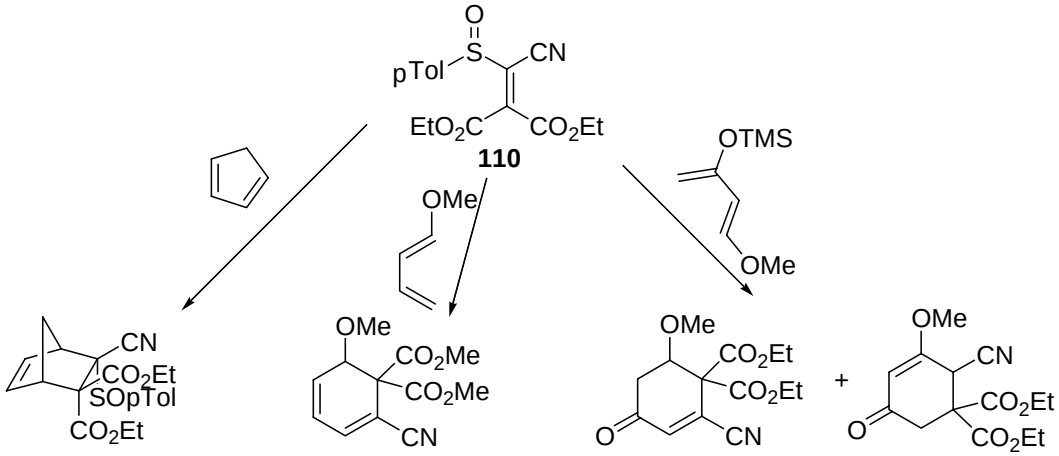
2.5.1.2. [4+2]-Cycloadditions

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.[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.[81]

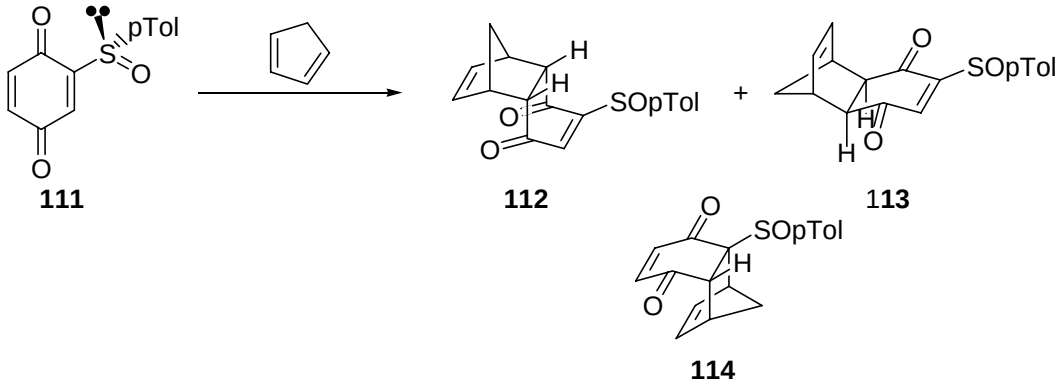
One recent development concerns the use of 2-sulfinylacrylonitriles **110** as dienophiles.[82] The authors describe the Diels-Alder reactions of the substrates with cyclopentadiene and two substituted butadienes (Scheme 41). Whereas the bicyclic cycloadducts were generally obtained in good yield and with useful *endo*-selectivity, the six-membered cycloadducts were not stable and afforded products resulting from the pyrolitic 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 ^{1}H-NMR.



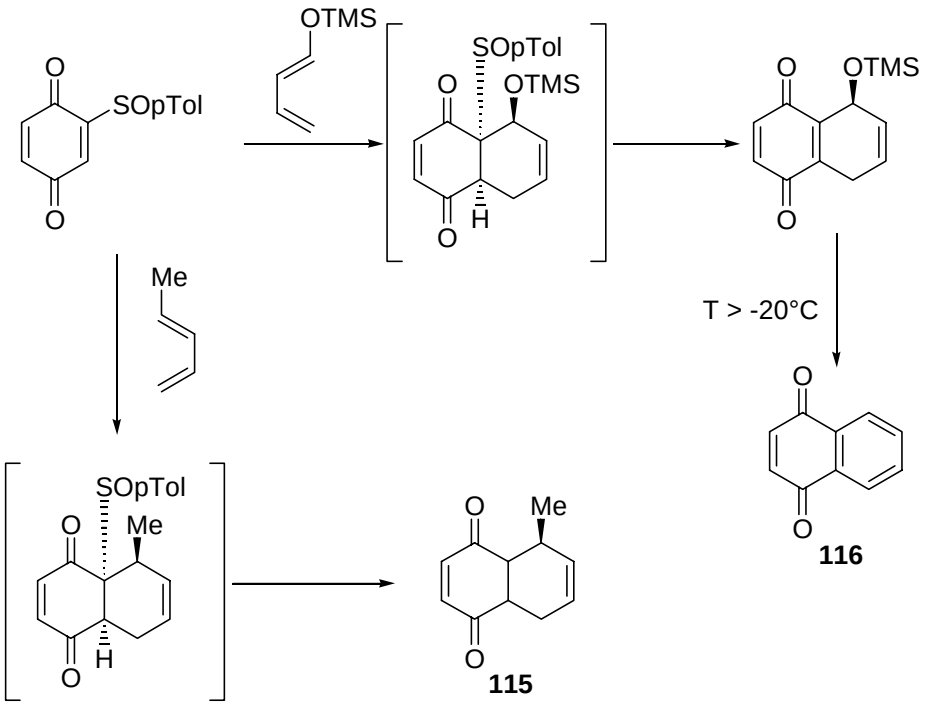
Scheme 41

An α-sulfinylacrylate derived from enantiomerically pure (1*R*,2*S*,3*R*)-3-mercaptocamphan-2-ol undergoes cycloaddition with cyclopentadiene under thermal and $ZnCl_2$-catalysed conditions.[83] The Lewis acid greatly improved the diastereoselectivity and at low temperatures the *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*-tolylsulfinyl)-1,4-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 *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 $ZnBr_2$ in the reaction mixture results in formation of a single diastereoisomer **114** arising from *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 *trans*-piperylene afforded the corresponding dihydronaphtoquinone **115** in optically pure form, whereas the cycloadduct with 1-[(trimethylsilyl)oxy]-1,3-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 π-facial selectivity.[85] Spontaneous elimination of the sulfinyl group thus provides an easy access to tetracyclic systems.



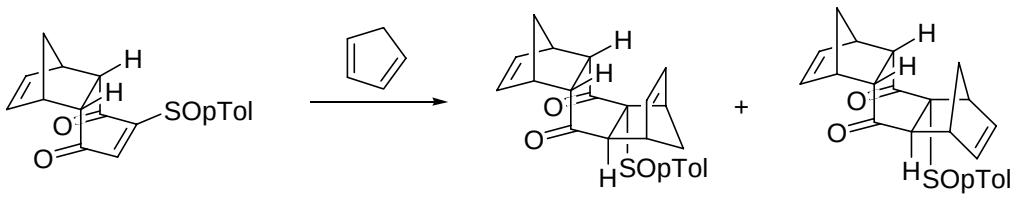
Scheme 42



Scheme 43

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 π-facial diastereoselection can be completely inverted (Scheme 45).[88]

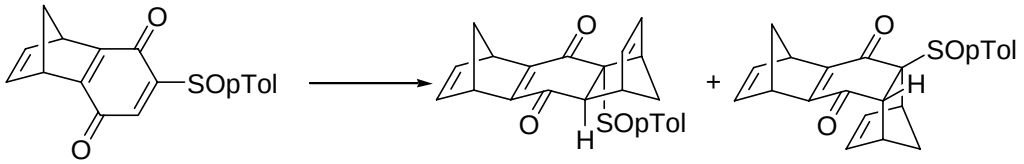


117

endo-anti-endo
118

exo-anti-endo
119

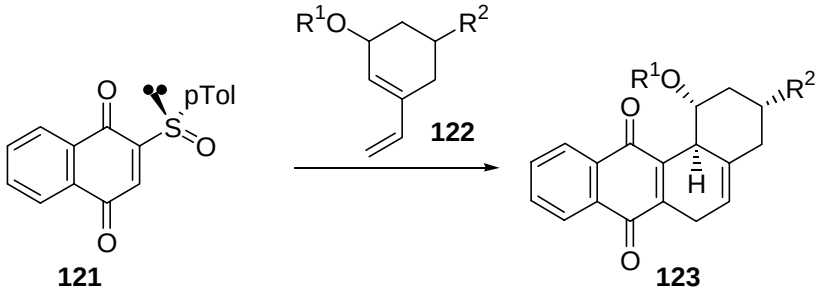
Scheme 44



120 *endo-anti* *endo-syn*

Scheme 45

The previously described methodologies found their first synthetic application in the enantioselective synthesis of Angucyclinones.[89] 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.

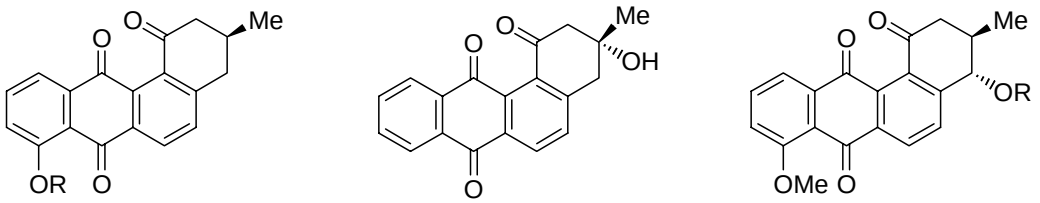


121 **123**

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.[90] 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.[91]

The same Diels-Alder/kinetic resolution strategy was applied in the synthesis of the angucyclicone antibiotics (+)-ochromycinone **124a** and (+)-rubiginone B_2 **124b** where this highly efficient process accounts for the construction of the tetracyclic framework (Figure 5).[92] Similarly, an access to a C3-oxygenated angucyclinone-type skeleton was devised and allowed the synthesis of enantiomerically enriched (-)-8-deoxytetrangomycin **125**.[93] Finally, the more oxygenated angucyclinone antibiotics rubiginones A2 **126a** and C2 **126b** as well as (+)-royleanone could be obtained in an analoguous fashion.[94]



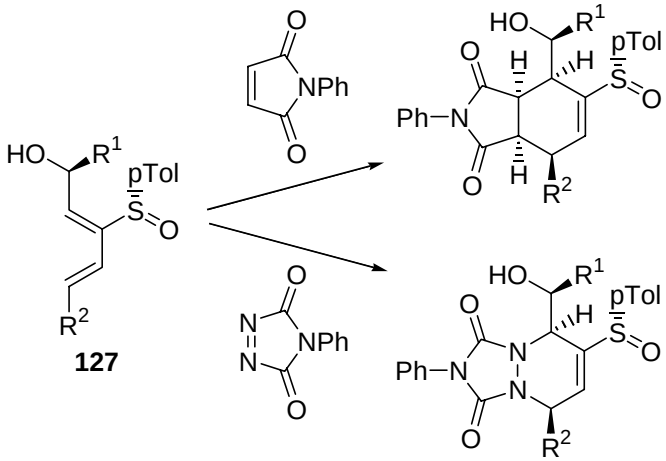
124a : (+)-Ochromycinone (R = H) **125** : (-)-8-deoxytetrangomycin **126a** : (+)-Rubiginone A_2 (R = H)
124b : (+)-Rubiginone B_2 (R = Me) **126b** : (+)-Rubiginone C_2 (R = CO*i*-Pr)

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.[95] 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. Sulfinyldienes can be prepared by Horner-Wadsworth-Emmons type chemistry.[96] Similar compounds have also been synthesised via Stille coupling of halovinyl sulfoxides, partial hydrogenation of sulfinyl enynes or vinylcupration of sulfinyl alkynes.[97] The formation of the corresponding iron(0) tricarbonyl complexes is also described. Enantiomerically pure hydroxy sulfinyl dienes **127** were prepared from base-induced rearrangement of epoxy vinyl sulfoxides, the *E*-*Z*-stereoselectivity being controlled by the chiral sulfur auxiliary.[98] 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).[99] Interestingly, the sulfinyl group managed to override the intrinsic allylic stereocontrol of the substrates.

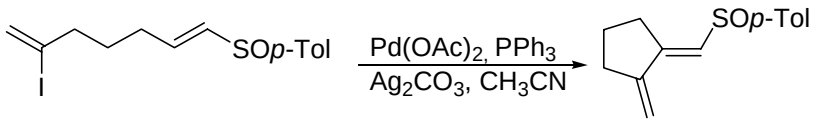


127

Scheme 47

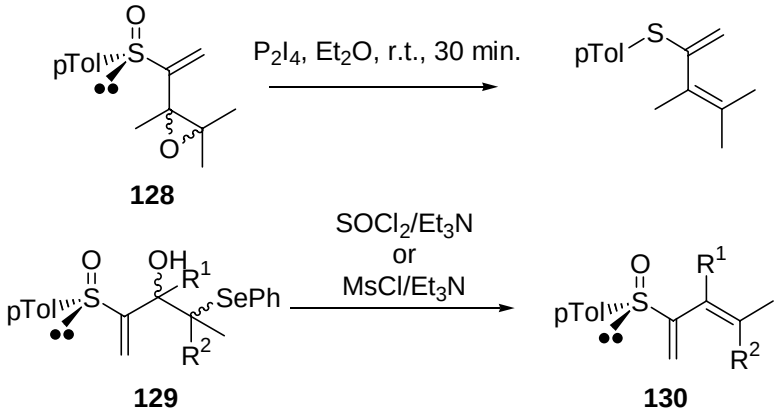
Racemic and enantiomerically pure exocyclic sulfinyl 1,3-dienes can be prepared by an intramolecular Heck reaction (Scheme 48).[100] Five- and six-membered mono- and bicyclic

dienes have been obtained by the use of an intramolecular palladium-catalysed coupling of vinyl sulfoxides with a distant vinyl iodide.



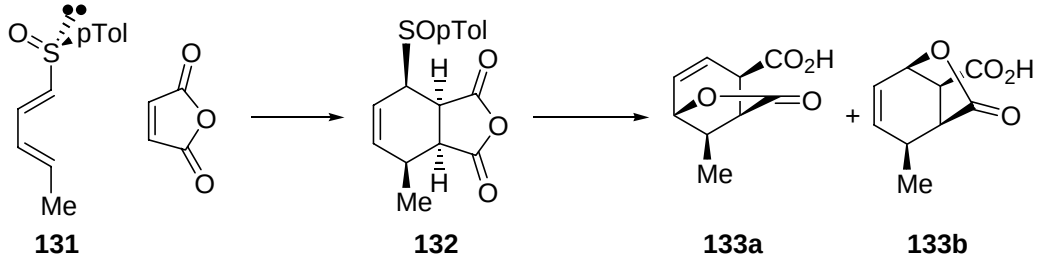
Scheme 48

An interesting route to 2-sulfinylbuta-1,3-dienes would be the deoxygenation reaction of the corresponding allylic epoxides **128** in the presence of P_2I_4.[101] 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).



Scheme 49

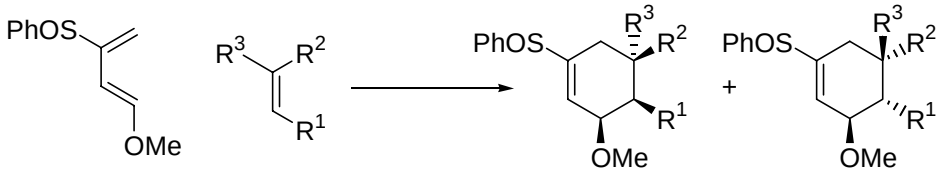
Sulfinyl dienes **131** react in an interesting way with maleic anhydride.[102] Indeed, the expected cycloadducts **132** are only obtained under high pressure conditions, whereas the reactions that are run at normal pressure afford unsaturated lactones **133a** and **133b** that arise from S_N2' substitution of the sulfinyl group or from sulfoxide-sulfenate rearrangement followed again by S_N2' substitution (Scheme 50).



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.[103] Whereas the sulfoxide-controlled regio- and *endo*-selectivites are high for the enamine, the π-facial selectivity is low. For methyl acrylate, the diastereoselectivities are different for the two observed regioisomeric approaches.

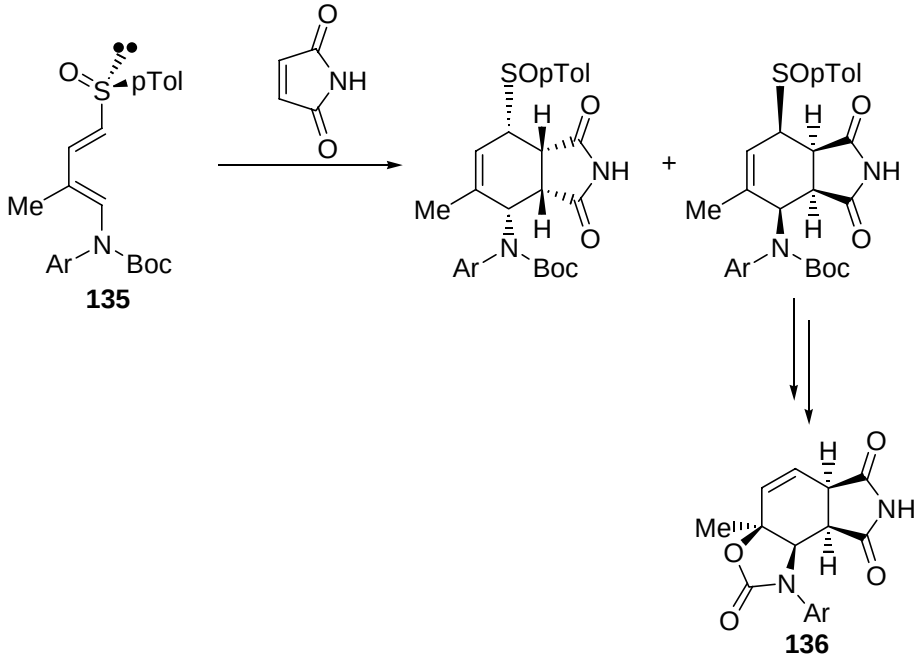
1-methoxy-3-sulfinylbutadienes have been synthesised using the addition of sulfenic acids to enynes affording the *E* and *Z* isomers.[104] The *E* isomer **134** reacts with activated dienophiles in lithium perchlorate catalysed Diels-Alder reactions with complete control of regioselectivity and, in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



134 *endo* *exo*

Scheme 51

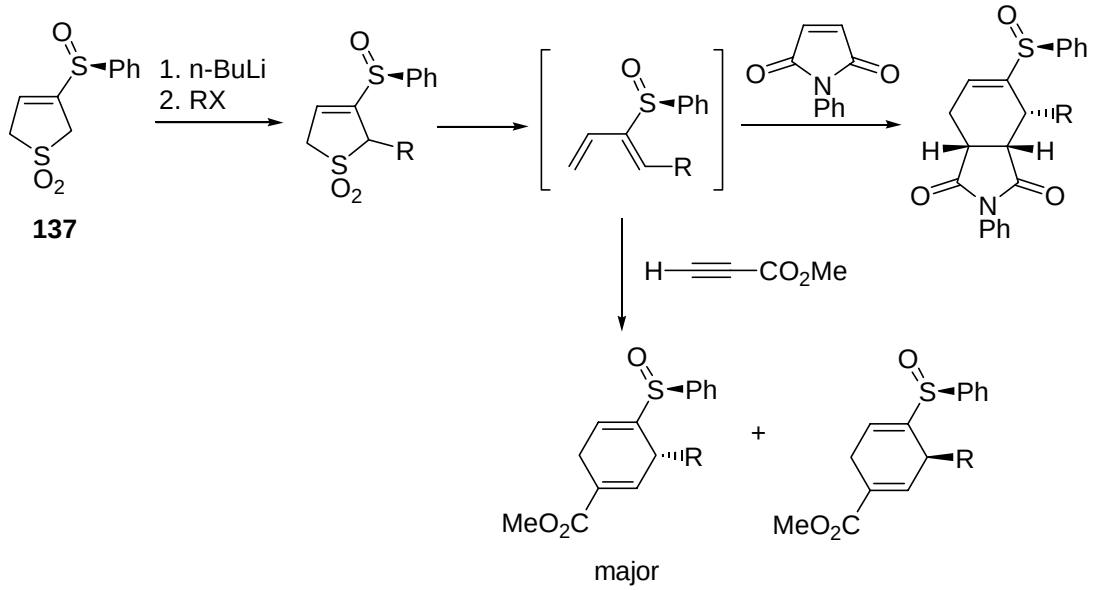
The reaction of amino-substituted sulfinyl dienes **135** with N-methyl maleimide proceeds with complete *endo*-selectivity and a 3:1 diastereoselectivity.[105] This reaction gives access to oxazoloisoindoles **136** by a short sequence featuring a 2,3-sigmatropic rearrangement and intramolecular cyclisation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



135 **136**

Scheme 52

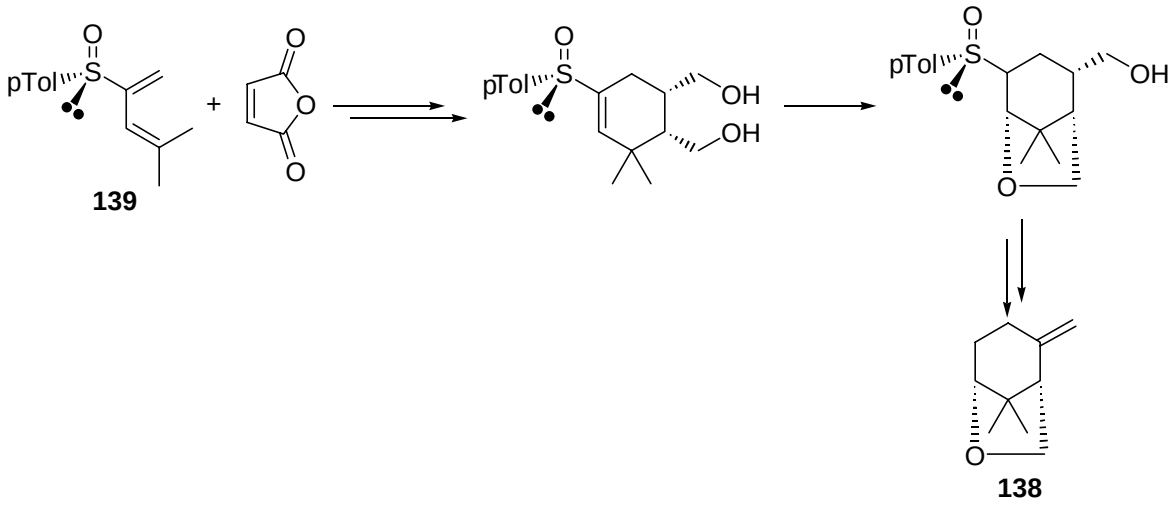
Yang *et al.* have investigated the interesting behaviour of sulfinylsulfolenes.[106] These compounds can be desulfonylated by refluxing in toluene and are thus precursors of enantiomerically pure sulfinyldienes. The sulfinylsulfolenes **137** can also be regioselectively alkylated in the 2-position 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).[107] 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.



Scheme 53

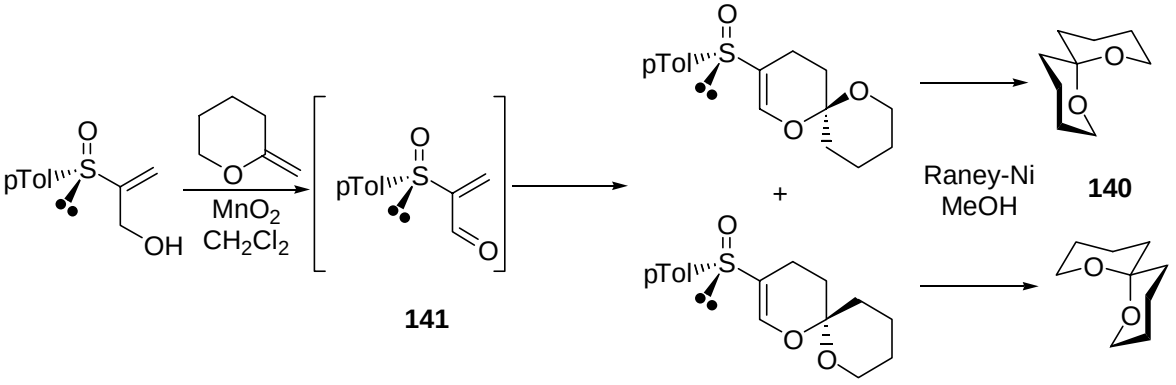
The asymmetric Diels-Alder reaction of 2-sulfinyl dienes has been used in the total synthesis of (-)-(1*S*,5*R*)-Karahana ether (**138**) (Scheme 54).[108] The key step involves the cycloaddition of maleic anhydride with 2-sulfinylpentadiene **139** proceeds with good yield to afford 4:1 mixture of diastereomeric 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 α,β-unsaturated ketones in hetero-Diels-Alder reactions has emerged recently.[109,110] 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.[110] Thus, styrenic compounds lead to the highest diastereoselectivities. Although their reactivity is much lower, the resulting dihydropyran derivatives could be isolated in good yield.



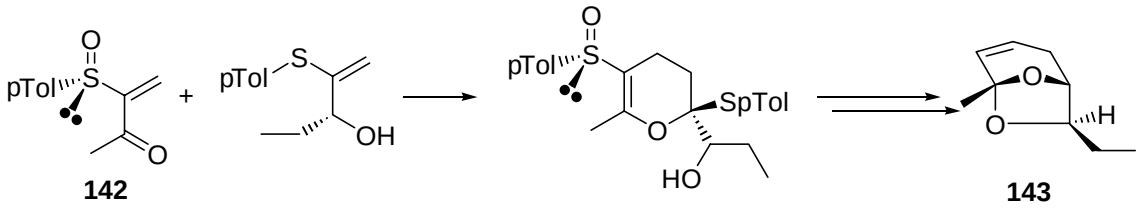
Scheme 54

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 Olae* (Scheme 55).[112] 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.



Scheme 55

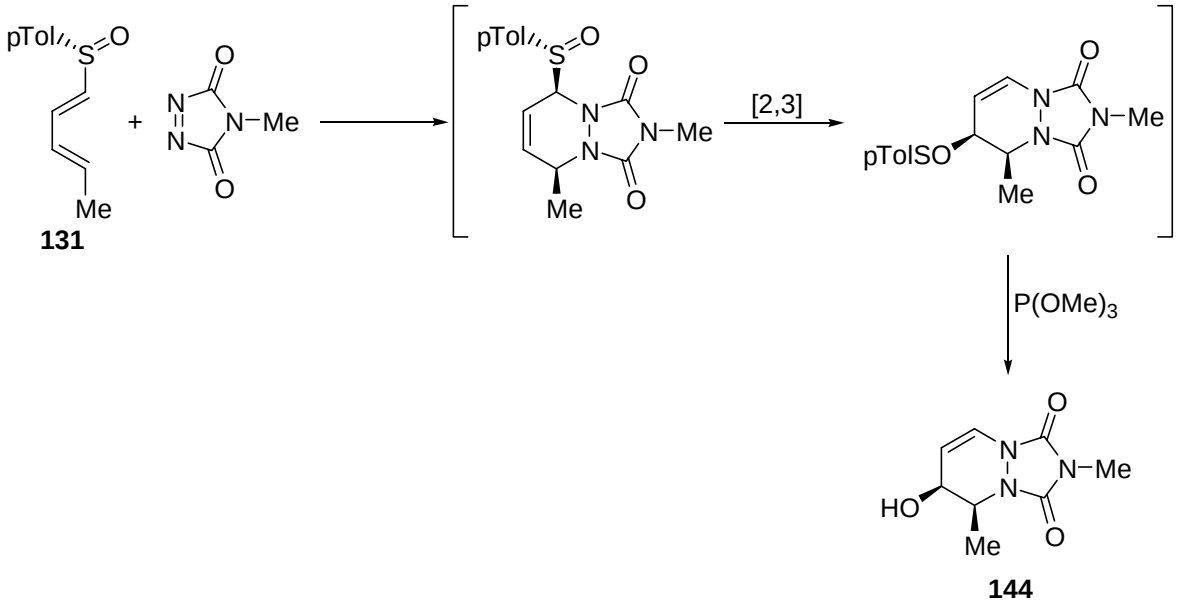
Heterocycloaddition of 3-*p*-tolylsulfinylbut-3-en-2-one **141** with a vinylsulfide affords a separable mixture of diastereoisomers of which only one cyclised under acidic conditions to form a spiroketal that was converted in two steps into the *Mus musculus* pheromone **143** (Scheme 56).[113]



142 **143**

Scheme 56

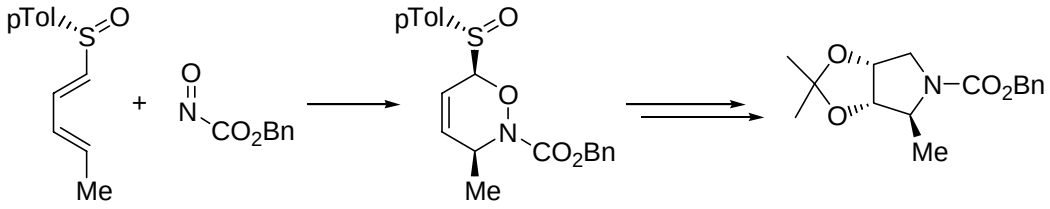
1-*p*-tolylsulfinyl-1,3-pentadiene **131** reacts with 4-methyl-1,2,4-triazoline-3,5-dione in the presence of $P(OMe)_3$ to afford an enantiomerically pure hydroxy substituted triazolopyridazine **144** (Scheme 57).[114] This process involves a tandem Diels-Alder cycloaddition/sulfoxide-sulfenate rearrangement and trapping of the intermediate sulfenate.



131 **144**

Scheme 57

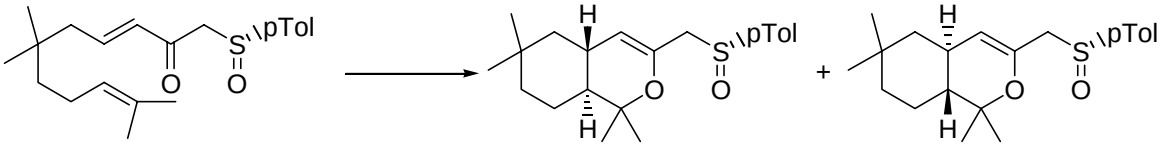
Similarly, hetero-Diels-Alder reaction of the same diene with benzyl nitrosoformate takes place at low temperature to afford the cycloaddition product in 54% yield as a single diastereoisomer (Scheme 58).[115] This adduct was transformed into enantiomerically pure 1,4,5-trideoxy-1,4-imino-L-ribitol **145**.



131 **145**

Scheme 58

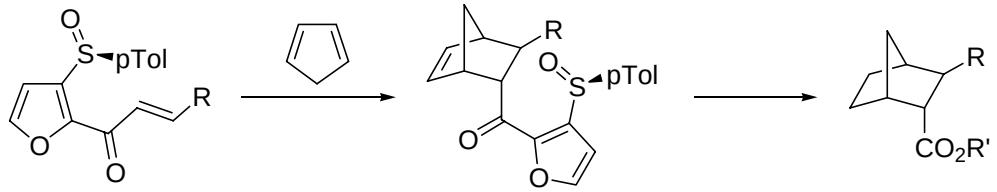
Finally, the intramolecular hetero-Diels-Alder cycloaddition of an unsaturated ketone **146** derived from 3-methylcitronellal proceeds under Lewis acid catalysis to afford a mixture of the two diastereomeric adducts **147a** and **147b** (Scheme 59) in good to excellent yields (42 - 100%) but with low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



146 **147a** **147b**

Scheme 59

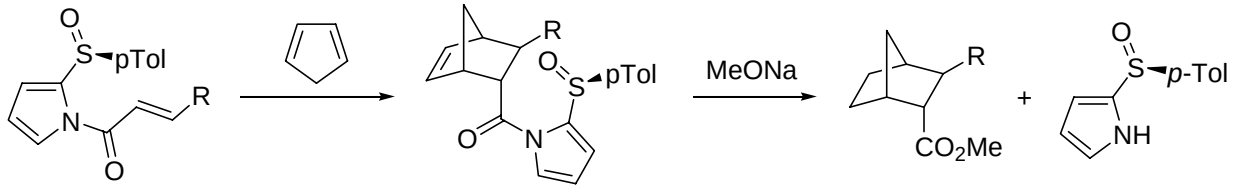
A chiral sulfoxide group can also be used as stereochemical controller for the Diels-Alder reaction on more distant double bonds. Thus, the α,β-unsaturated ketones **148** derived from 3-sulfinylfuran undergo cycloaddition with cyclopentadiene under Lewis acid catalysis to afford the endo adduct as major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



148, R = Me, Ph R' = H, Me

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).[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.



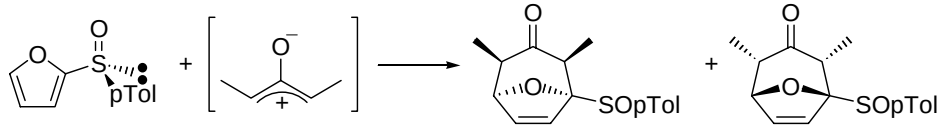
149, R = Me, Ph **150**

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, Montaña *et al.* examined the influence of various chiral auxiliaries in the 2-position of the furan ring.[120] They found that the best results were obtained for 2-*p*-tolylsulfinylfuran **151** (Scheme 62). Indeed, the authors obtained complete *cis*- and *endo*-selectivity in the process, and, depending on the reaction conditions could achieve promising π-facial diastereoselectivities (up to 54 % de.).



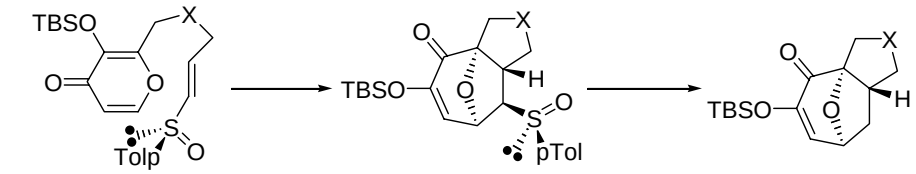
151

Scheme 62

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.

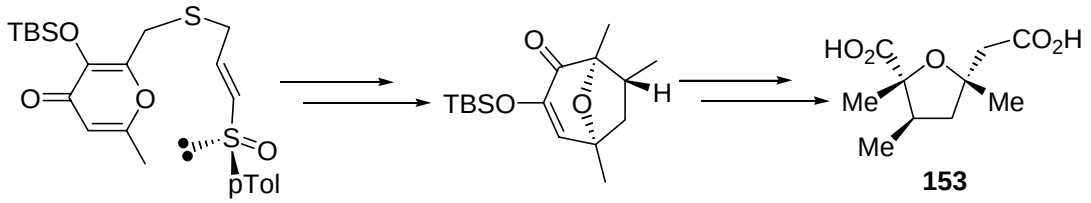
An asymmetric intramolecular version of such a reaction using a sulfinyl tether was first proposed by Mascareñas *et al.*[121] Intramolecular reaction of a vinylsulfoxide with a silyloxypyrone leads to a tricyclic system **152** in a highly diastereoselective fashion, the sulfinyl group being responsible as well for a significant acceleration of the reaction (Scheme 63).[122] 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).[123] Interestingly, switching from a sulfoxide to a sulfoximine auxiliary, allowed a complete inversion of the stereoselectivity.[124] Furthermore, this methodology was extended to the intramolecular acetoxypyranone-vinylsulfoxide cycloaddition.[125] Good yields and excellent diastereoselectivities were obtained in this case as well and desulfinylation affords enantiomerically pure tricyclic compounds (Scheme 65).



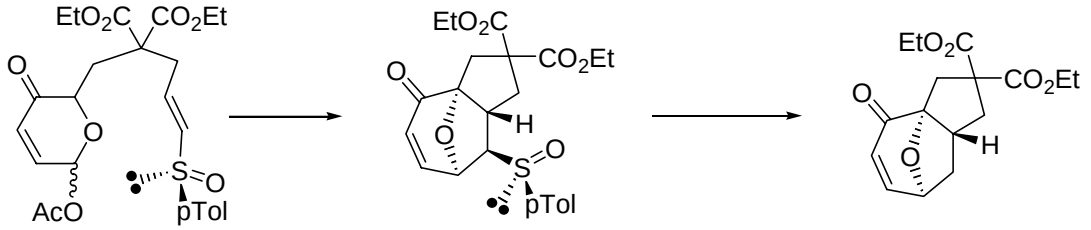
152

X = $C(CN)_2$, $C(CO_2Et)_2$, S.

Scheme 63



Scheme 64

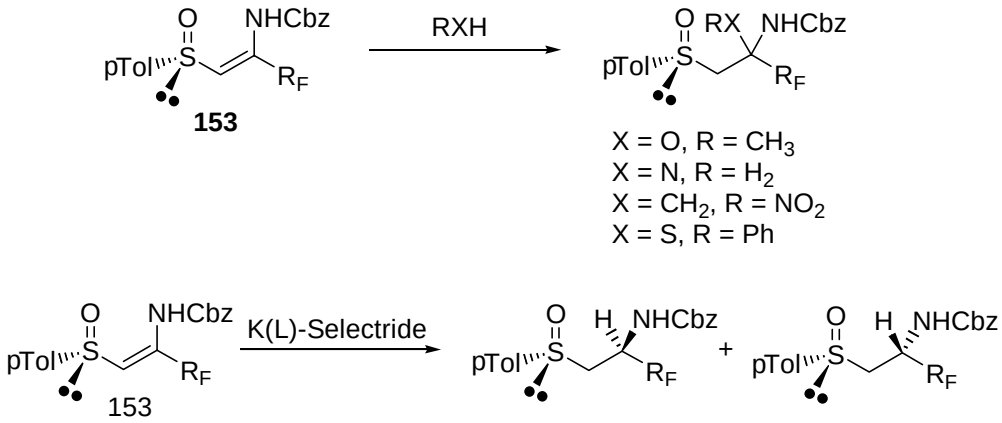


Scheme 65

2.5.2. Addition reactions

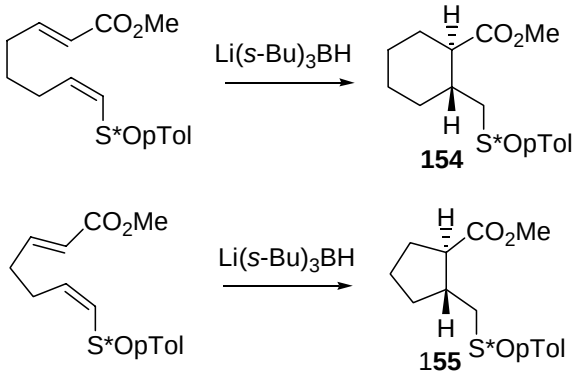
This paragraph focuses on reactions in which nucleophiles are added to the double bond of vinylic sulfoxides.

β-Sulfinylenamines **153** react readily with O, N, C and S-centred nucleophiles to afford diastereomeric mixtures of the corresponding adducts (Scheme 66).[126] 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.



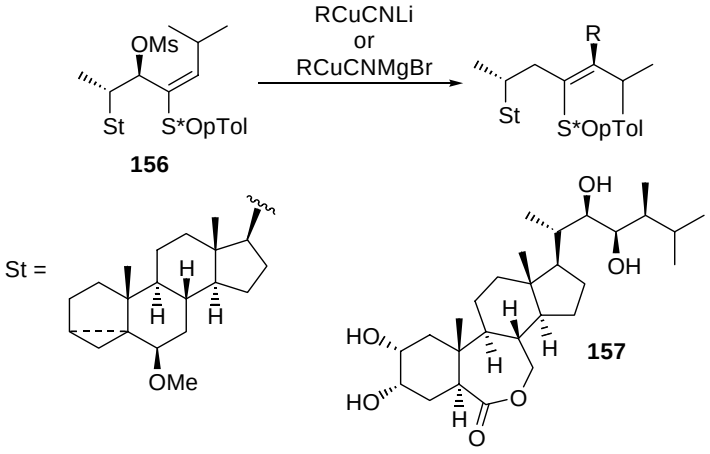
Scheme 66

Takeda *et al.* have described a reductive cyclisation to form functionalised cyclohexane derivatives that involves an intramolecular Michael addition.[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.

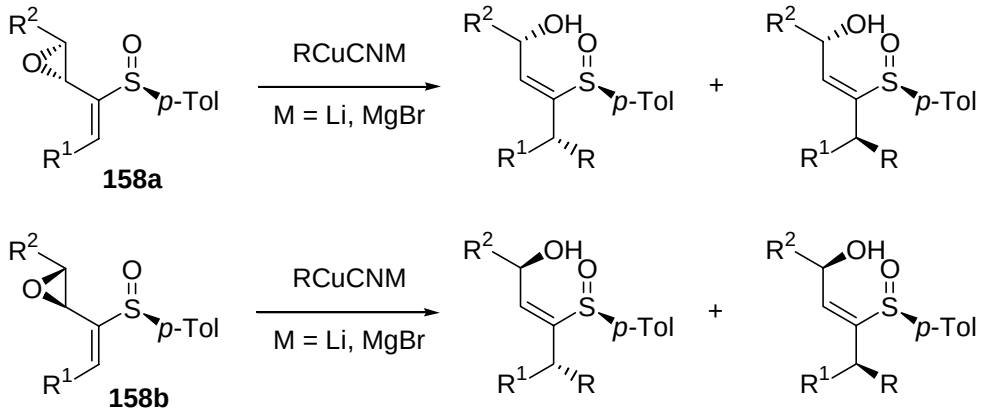


Scheme 67

The group of Marino showed that allylic mesyloxy sulfinyl steroids **156** undergo S_N2' displacements with cyanocuprates in a highly stereoselective fashion.[128] This was used to achieve formal syntheses of Brassinolide (**157)** and the naturally occurring (24*R*)-epibrassinolide (Scheme 68). Similarly, epoxy vinyl sulfoxides **158a** and **158b** were shown to react with cyanocuprates in S_N2' fashion with high regio- and stereoselectivity and moderate to good yields (Scheme 69).[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,[130] overrides the intrinsic *anti* tendency of the vinyl oxirane.

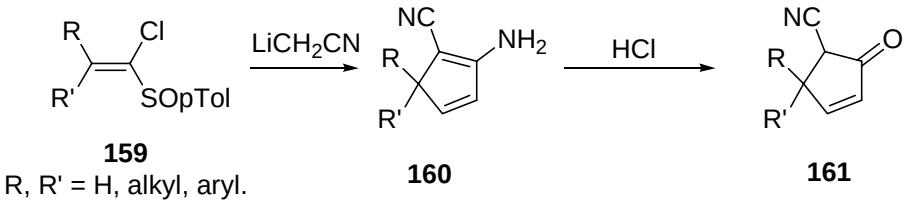


Scheme 68



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),[131] an interesting reaction pathway was discovered with carbanions derived from acetonitrile. Indeed, α-chlorovinyl *p*-tolyl sulfoxides **159** react with an excess of cyanomethyllithium to afford cyclopentadienyl enaminonitriles **160**, in a cascasde sequence that involves formation of three consecutive carbon-carbon bonds (Scheme 70).



159
R, R' = H, alkyl, aryl.

160

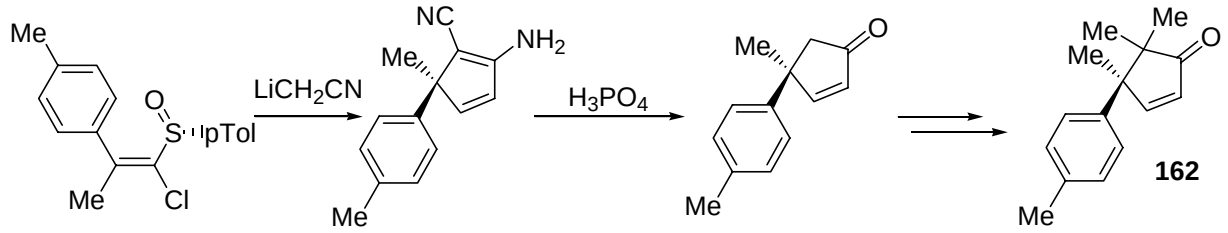
161

Scheme 70

The use of a single equivalent of the anion produces the 1,4-addition product,[132] 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.

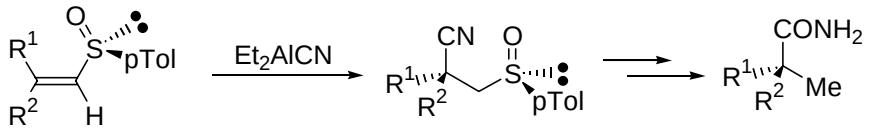
The obtained cyclic enaminonitriles could also be converted to different cyclopentanone derivatives (e.g. **161**) by acidic hydrolysis. Similarly, reaction of optically active 1-chlorovinyl *p*-tolyl sulfoxides with cyanomethyllithium affords disubstituted cyclopentenones with stereocontrolled formation of a quaternary chiral center.[133] 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]

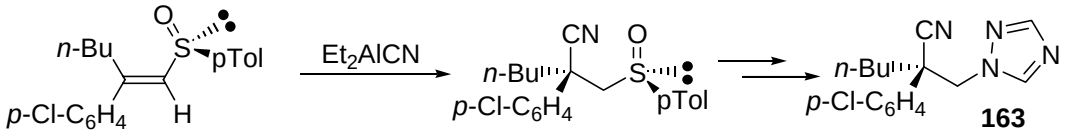


Scheme 71

Vinylsulfoxides can be stereoselectively hydrocyanated to obtain enantiomerically pure compounds containing tertiary or quaternary chiral centers.[135] Indeed, vinylsulfoxides react with Et_2AlCN 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 goup 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.

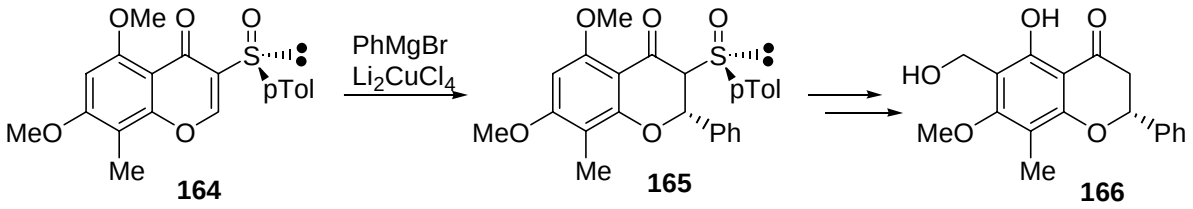


Scheme 72



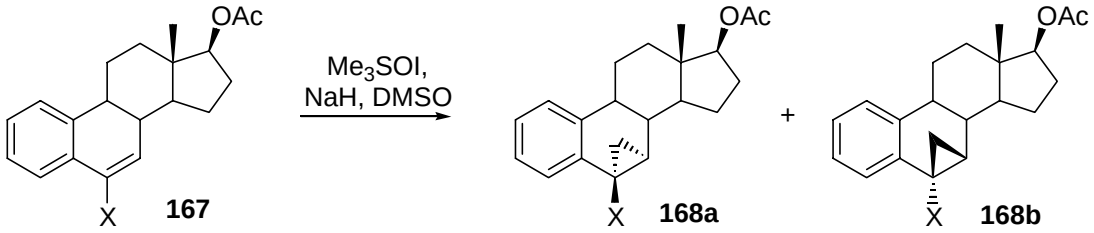
Scheme 73

We showed that a flavanone precursor comprising an α-sulfinylenone **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.



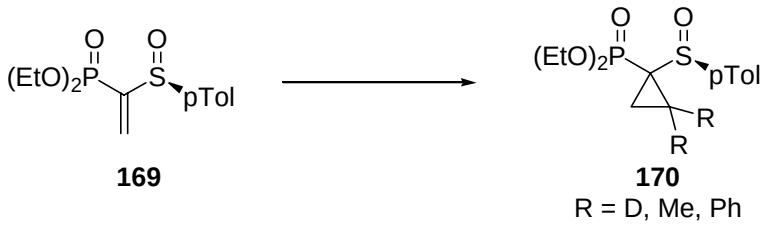
Scheme 74

During their studies on estradiol derivatives, researchers at Schering described the diastereoselective cyclopropanation of estradiol-derived vinyl sulfoxides.[138] The steroid **167** 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.



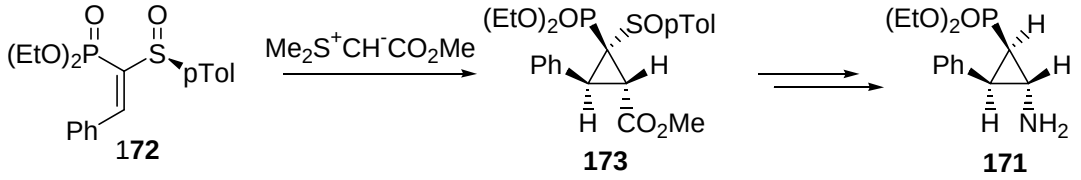
Scheme 75

Vinyl sulfoxides **169** bearing an α-phosporyl group can be cyclopropanated diastereoselectively.[139] 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,[76] reaction with diazomethane gives the cycloaddition product, whereas the use of diphenyldiazomethane 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.



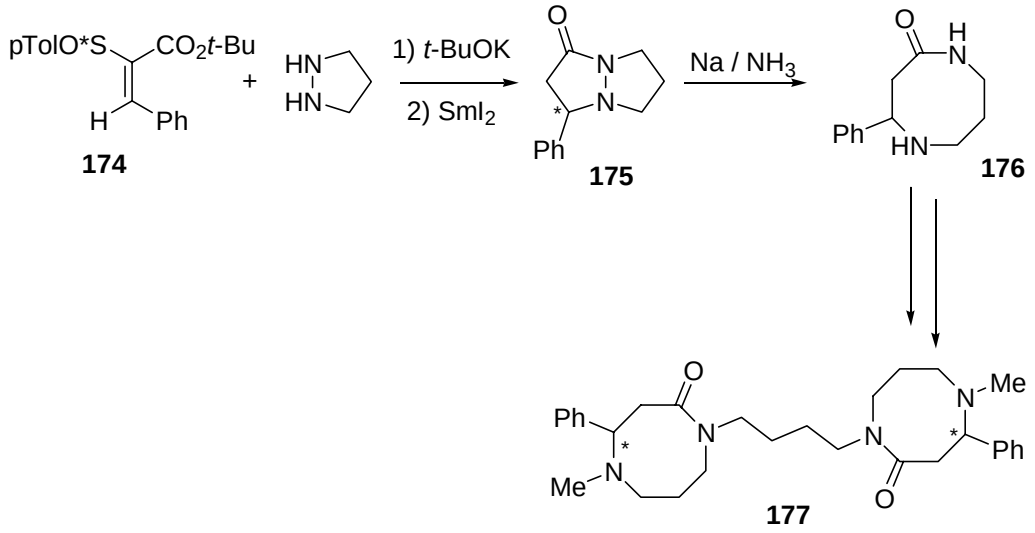
Scheme 76

A vinyl sulfoxide cyclopropanation provided an access to a conformationally constrained analogue **171** of the $GABA_B$ antagonist phaclofen (Scheme 77).[140] Reaction of (1-dimethoxyphosphoryl-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.



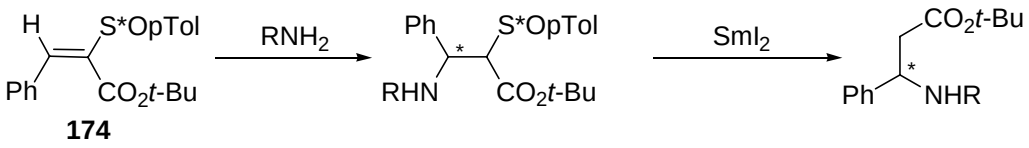
Scheme 77

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 SmI_2 affords a bicyclic adduct **175**, which arises from a tandem conjugate addition-cyclisation sequence (Scheme 78).[141] 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

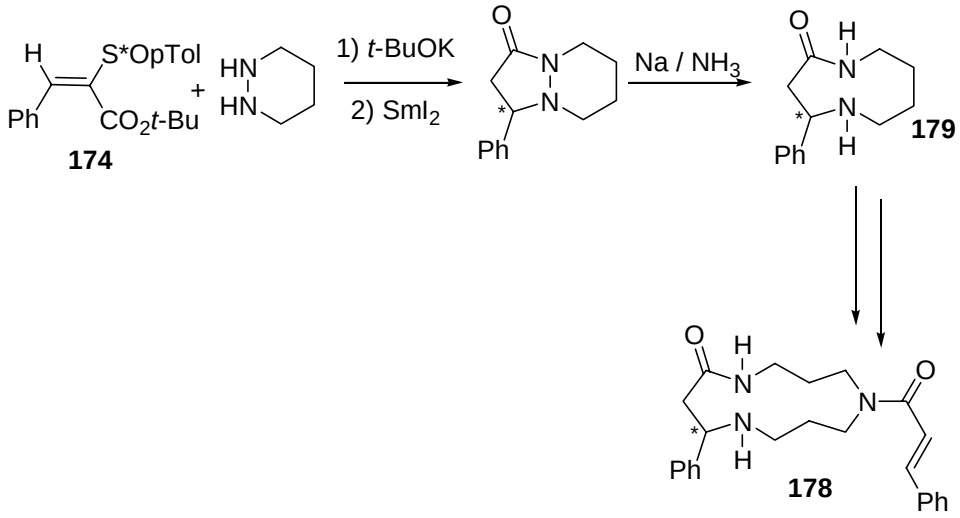
Acyclic nitrogen nucleophiles, such as ammonia, benzylamine, 1,3-diaminopropane, 1,4-diaminobutane do also perform conjugate addition to 2-(*p*-tolylsulfinyl)cinnamate **174** in good yield (Scheme 79). Subsequent desulfinylation with samarium iodide affords enantiomerically enriched β-amino esters with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



174

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.



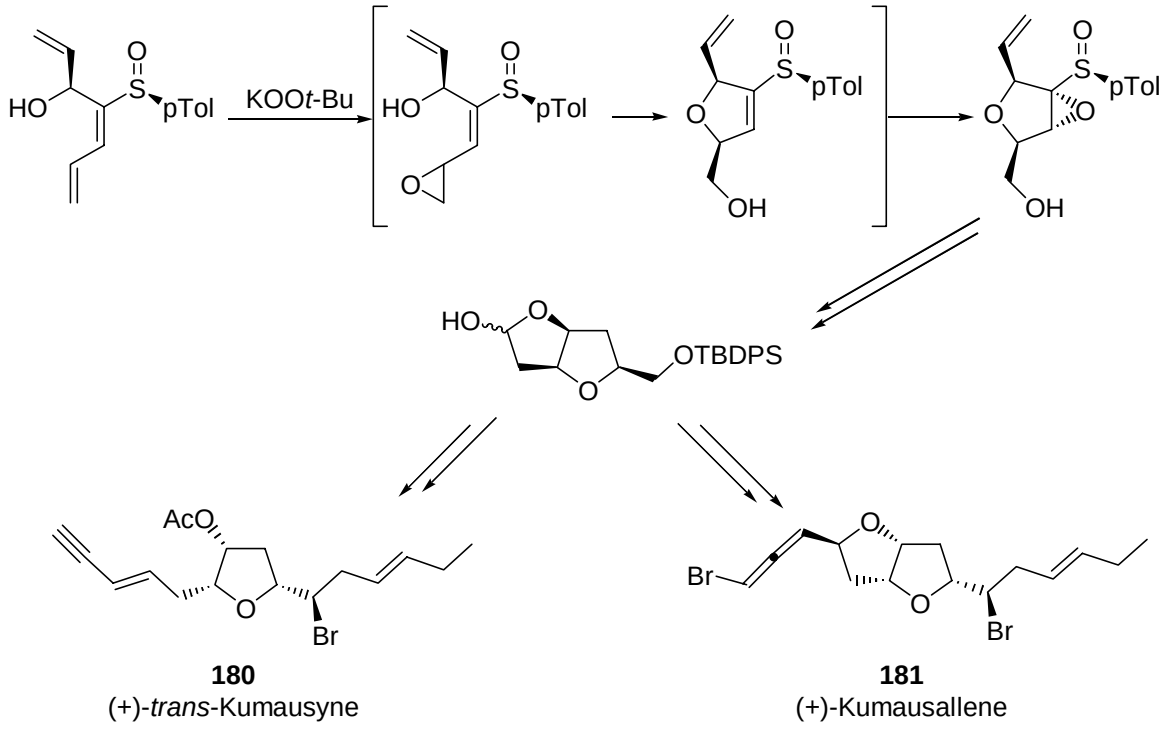
174

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.[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.[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 (+)-*trans*-Kumausyne **180** and (+)-Kumausallene **181** (Scheme 81).[147]



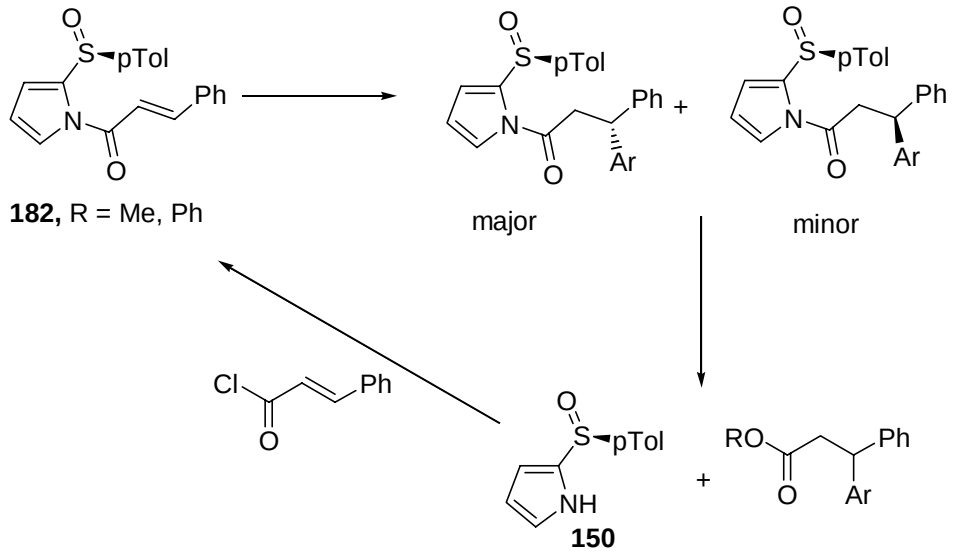
180
(+)-*trans*-Kumausyne

181
(+)-Kumausallene

Scheme 81

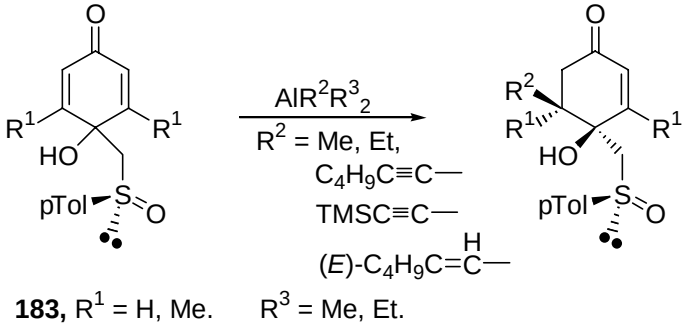
2-(Arylsulfinyl)-2-cycloalkenones undergo β-addition of alkyl radicals in a highly stereoselective fashion.[148] The addition of Lewis acids gives rise to chelated intermediates and reverses the stereoselectivity. Additionally, addition of alkyl radicals to diastereomeric mixtures of 4- or 5-methyl substituted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

The sulfinyl group has been used to successfully control the stereochemistry of conjugate additions of arylcopper reagents to distant enones.[150] 2-sulfinylpyrrole-derived cinnamides **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 **150** could be recovered by hydrolysis without loss of optical purity.



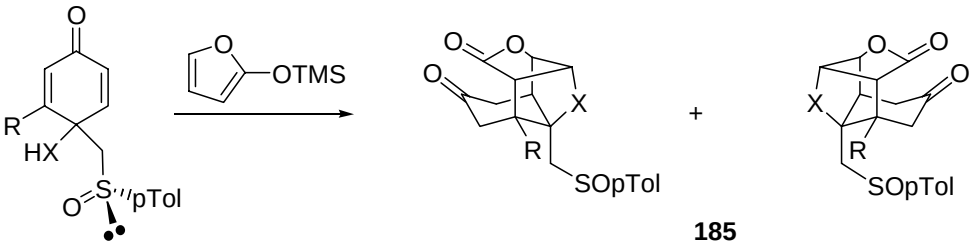
Scheme 82

Sulfoxides can also bring about stereoselective addition reactions to distant double bonds. Thus, organoaluminium reagents can be used to desymmetrise sulfinylquinols by a diastereoselective conjugate addition to the enone fragment of the quinol **183** (Scheme 83).[151] A variety of alanes can be used and in all the cases described, only one single diastereoisomer is obtained.



Scheme 83

Non-symmetric sulfinyl 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).[152] 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 desulfinylated to produce enantiomerically pure cage compounds.



184
R = H, Me.
X = O, N.

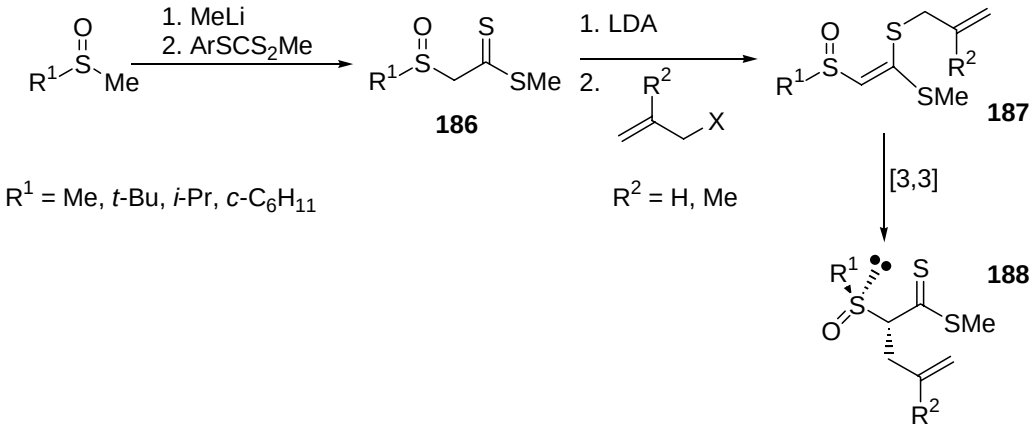
185

Scheme 84

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.[153] 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.[154] The authors prepared α-sulfinyl dithioesters **186** 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 **187** (Scheme 85). The latter compounds rearrange readily at room temperature into γ-unsaturated α-sulfinyl dithioesters **188**. 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.



186

187

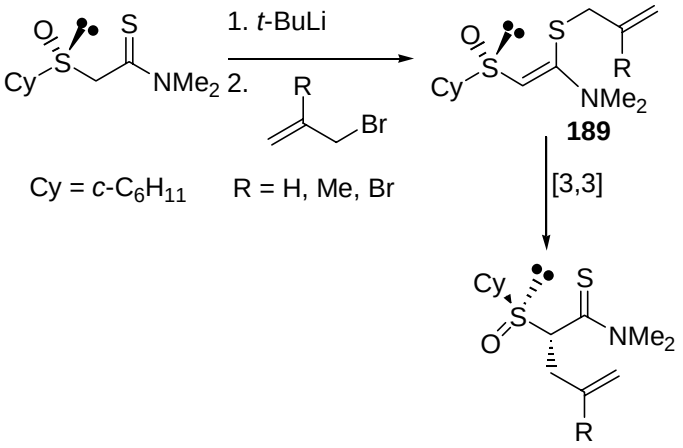
188

R^1 = Me, *t*-Bu, *i*-Pr, *c*-C_6H_{11}

R^2 = H, Me

Scheme 85

This methodology was extended to the rearrangements of ketene aminothioacetals **189**, which proceeds with good yields and high stereoselectivities as well (Scheme 86).[155] 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.[42]



Scheme 86

Another example of Claisen rearrangements involving chirality transfer from a sulfoxide group at C-5 has been reported recently[156]: up to 2 stereogenic centres could be created and the products maintain the useful vinylsulfoxide functionality which may account for subsequent stereoselective transformations.

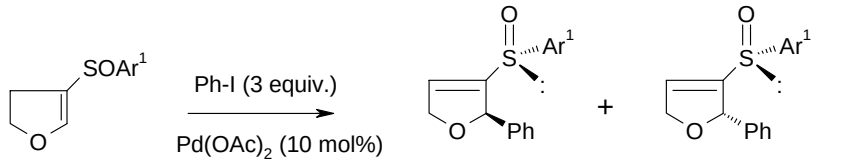
3. Sulfoxide groups in asymmetric transition metal-catalysed reactions

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 review 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).[157]

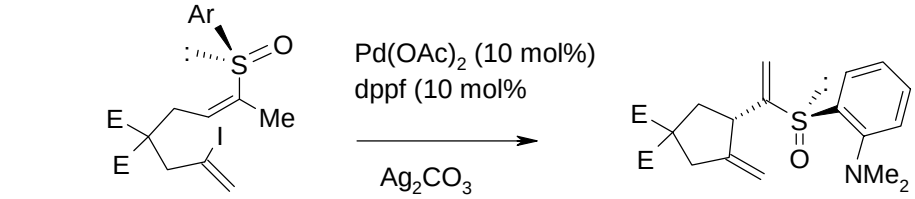


			yld%
Ar^1 : C_6H_5	77	23	68
2,4-$Me_2C_6H_3$	78	22	80
1-naphtyl	71	29	43
o-(MeO)C_6H_4	75	25	47
o-(Me_2N)C_6H_4	6	94	80

Scheme 87

The best results have been obtained with *o*-(*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.

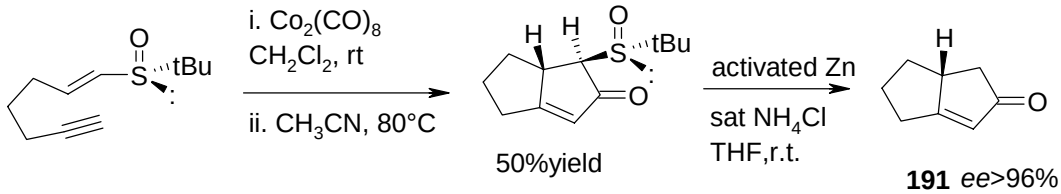
Furthermore intramolecular Heck reaction of (*Z*)-2-iodo-1,6-diene **190** bearing a 2-(*N*,*N*-dimethylamino)-phenylsulfinyl group as a chiral auxiliary occurred stereoselectively (Scheme 88).[158]



E = CO_2Et **190** *de* >96% yield 61%

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).



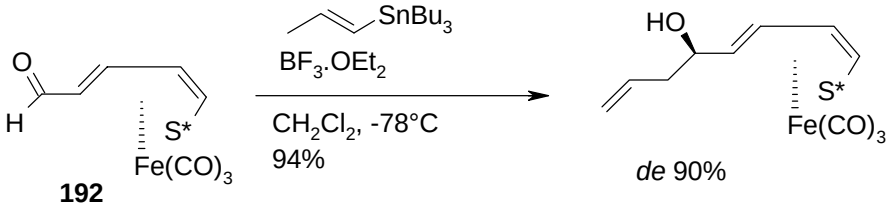
50%yield

191 *ee*>96%

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.

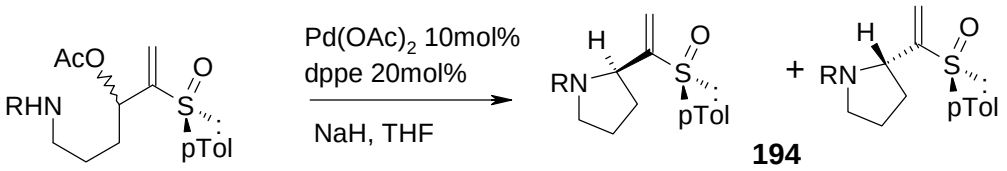
The stereodirecting ability of the chiral sulfoxide in combination with organotransition metal chemistry was also illustrated in the diastereoselective allylation of an η^4-(1Z,3E)-(1-sulfinyldiene)iron(0)tricarbonyl complex **192** (Scheme 90).[160]



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).

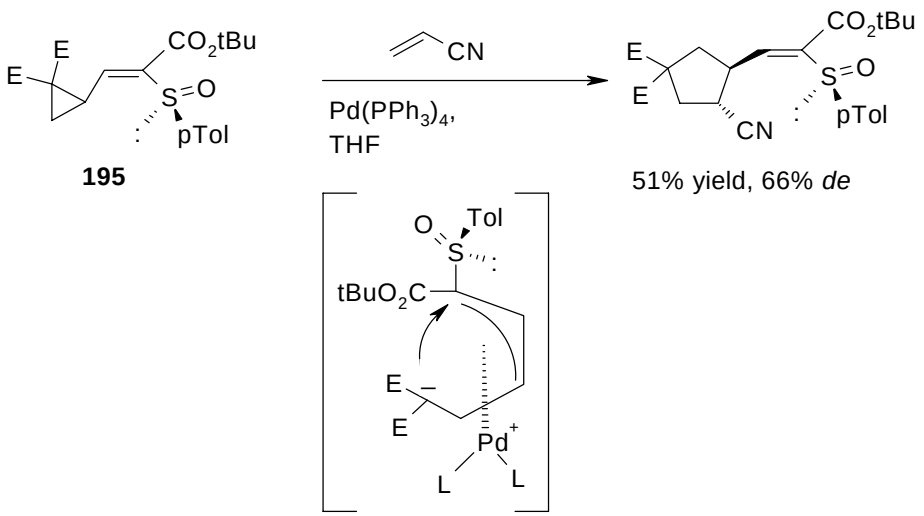


R = Boc	90	10
R = $COCF_3$	10	90

Scheme 91

The major cycloadducts obtained in the trifluoroacetamide and NHBoc series were epimeric at the α-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 (β-sulfinyl)vinylcyclopropane derivative **195** with acrylonitrile (Scheme 92).[163]

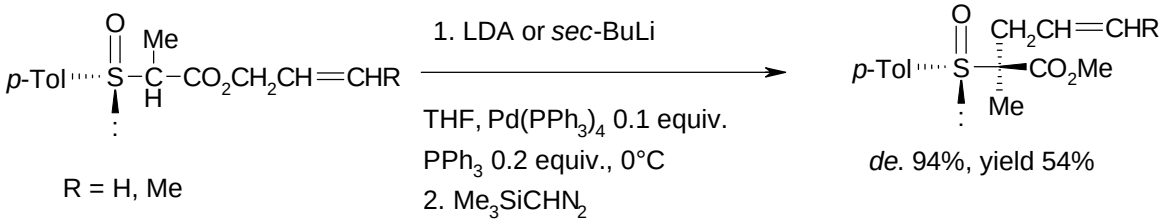


Scheme 92

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.[164]

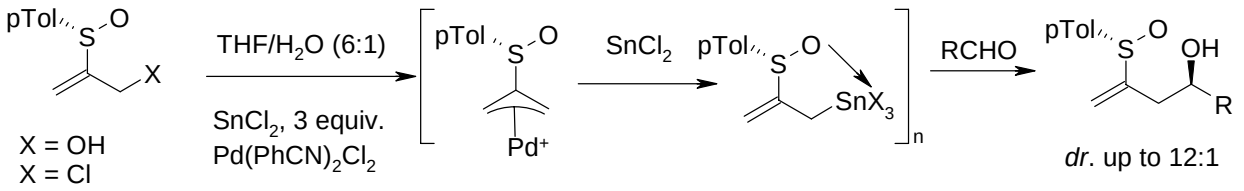
Hiroi also reported intramolecular allyl transfer in chiral α-sulfinyl allylic esters.[165] The participation of the catalyst and the chiral sulfinyl functionality, presumably by the coordination of the sulfinyl group to the catalyst is proposed (Scheme 93).



Scheme 93

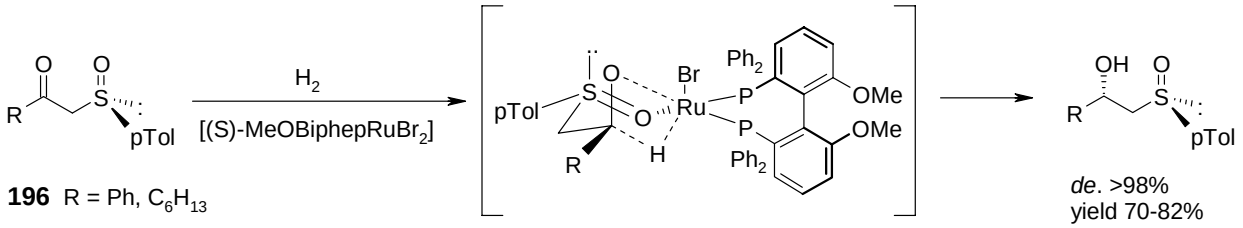
Ester enolates containing an allyl functionality undergo intramolecular allylation via π-allyl-metal complexes.

The efficiency of the sulfoxide group was also demonstrated in allylation of aldehydes with enantiopure 2-sulfinylallyl building blocks (Scheme 94). [166]



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[167]. Starting from either optically pure or racemic β-keto sulfoxides **196**, the diastereoselectivity of the hydrogenation was controlled by the chiral ruthenium complexes (Scheme 95).



196 R = Ph, C_6H_{13}

Scheme 95

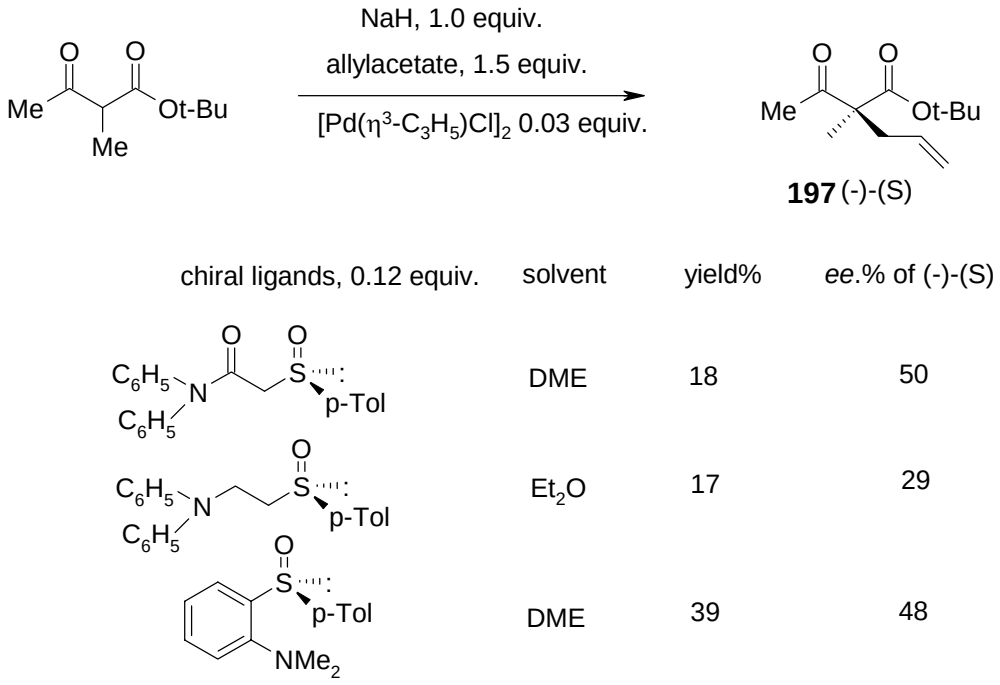
3.1.1. Catalysts bearing chiral sulfinyl functionality as ligands in asymmetric transition metal-catalysed reactions

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.[168]

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.

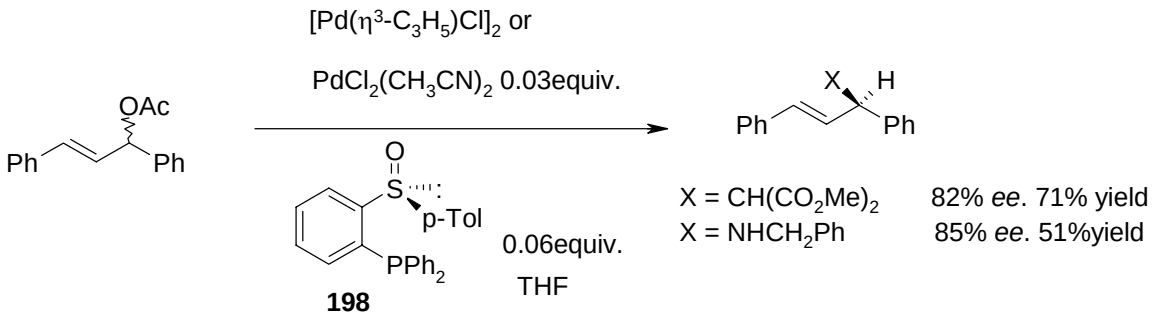
Hiroi reported asymmetric syntheses with new chiral sulfoxide ligands possessing amino, acetamido, phosphano or phosphanoamino functionality as an alternative coordinating

element.[169] He first described the use of chiral nonracemic α-sulfinylacetamides and β or γ aminosulfoxides in the palladium-catalysed asymmetric allylic alkylations (Scheme 96).[169a]



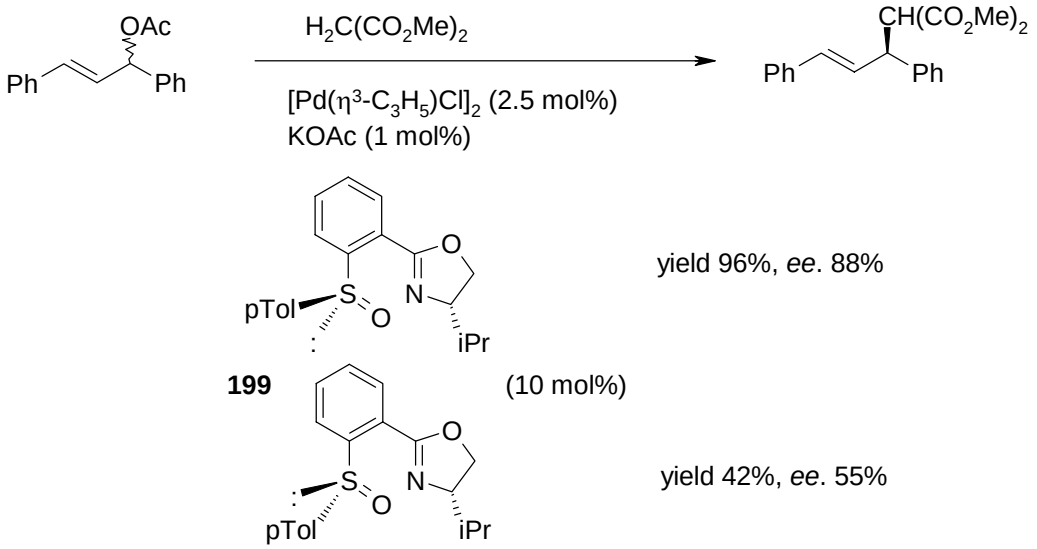
Scheme 96

Much higher enantioselectivities were obtained with β-phosphinosulfoxides **198** as chiral ligands in palladium catalysed asymmetric allylic alkylation and amination (Scheme 97).[169b,c]



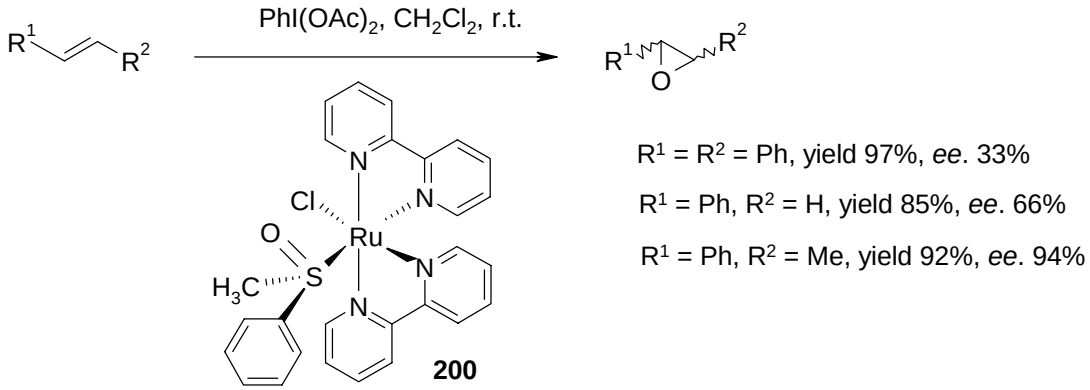
Scheme 97

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.[170] The enantioselectivity obtained is highly dependent upon the stereochemistry of the sulfur atom (Scheme 98).



Scheme 98

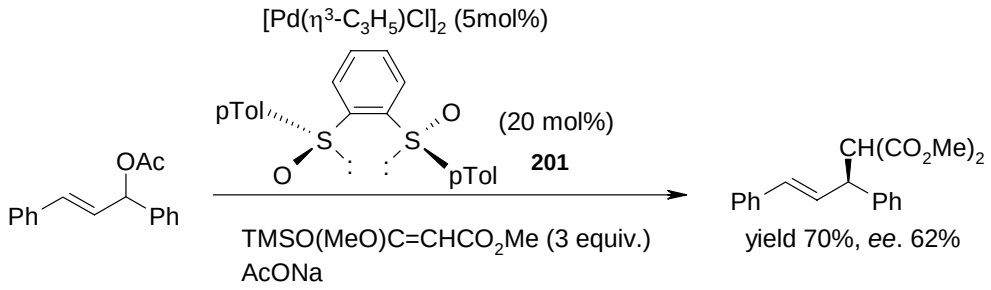
More recently, new ruthenium bis(pyridine) sulfoxide complexes **200** were demonstrated as efficient catalysts for asymmetric alkene epoxidation.[171] Asymmetric induction up to 94% was observed for β-methylstyrene (Scheme 99).



Scheme 99

C_2-symmetric bis-sulfoxide ligands[172] have been studied in coordination with transition metals in different transition states. Synthetic applications in asymmetric transition metal-catalysed reactions have been developed.

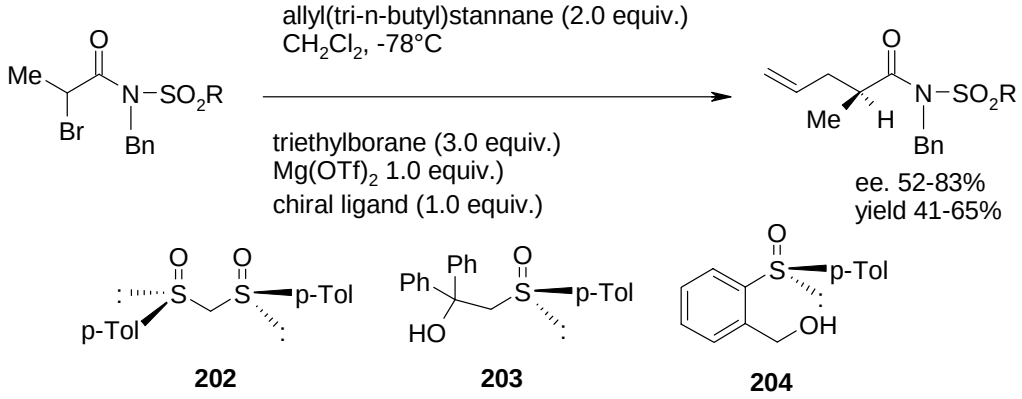
For example Shibasaki[173] studied the (*S*,*S*)-1,2-bis(p-tolylsulfinyl)benzene in coordination with Pd, Rh and Ru. Moderate asymmetric induction was observed in the Pd-catalysed allylic substitution using this C_2-symmetric bis-sulfoxide ligand **201** (Scheme 100).



Scheme 100

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

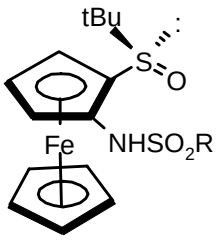
Inter- and intramolecular asymmetric radical carbon-carbon bond-forming reactions of sulfonamides were successfully achieved by Hiroi[174] using chiral sulfoxides **202**, **203** and **204** as ligands in presence of a Lewis acid (Scheme 101).



202 **203** **204**

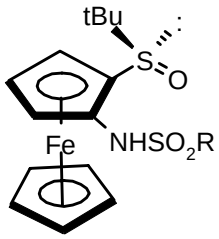
Scheme 101

Recently Carretero[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_2Zn to aromatic aldehydes (Scheme 102).



R = CH_3, *p*-Tol, *p*-MeO(C_6H_4), *p*-NO_2(C_6H_4), mesityl, α-naphtyl

205



R = CH_3, CF_3, *t*-Bu, Ph

206

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 attractivity 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[176] so far, has been developed to generate chiral organometallic species[177] during the last decade. The substitution by alkylmetals of readily available enantiopure α-heterosubstituted sulfoxides or (axially or planar) chiral arylsulfoxides provides chiral d^1-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-,[178] oxiranyl-,[179] α-haloalkyl[180] , and ferrocenyl[181] 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.[182,183] 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.[184]

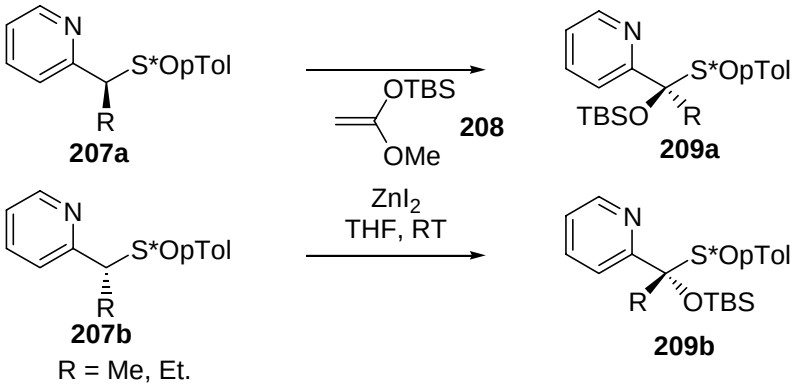
The asymmetric Pummerer reaction involving the chirality transfer from sulfur to the adjacent α-carbon has been known for over 30 years now.[185] Induction can take place for cyclic[186] and acyclic[187] substrates. However, in all the early examples, the yields as well as the enantioselectivities were low. Protocols that achieve synthetically useful yields and enantioselectivities have only been described more recently.[188]

4.1.1.1. Pummerer rearrangement induced by O-silylated ketene acetals

The use of an O-silylated ketene acetal as activating agent has been introduced in 1984.[189] This area has received a lot of attention in the last 20 years,[190] 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.[191]

These reagents have been shown to be exceedingly efficient in the case of chiral non-racemic α-substituted sulfoxides.[192] 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 α-alkyl-α-silyloxysulfides **209a** and **209b** (> 99% ee). In the absence of the α-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).

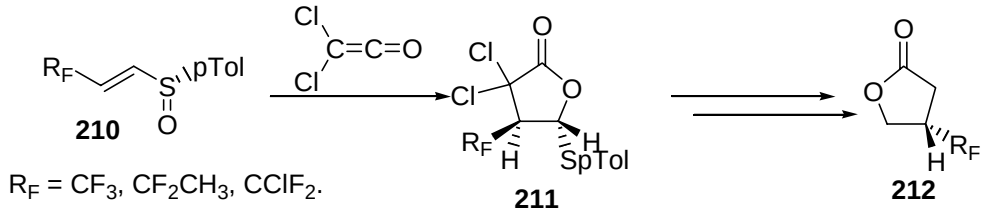


Scheme 103

4.1.1.2. Pummerer cyclisations

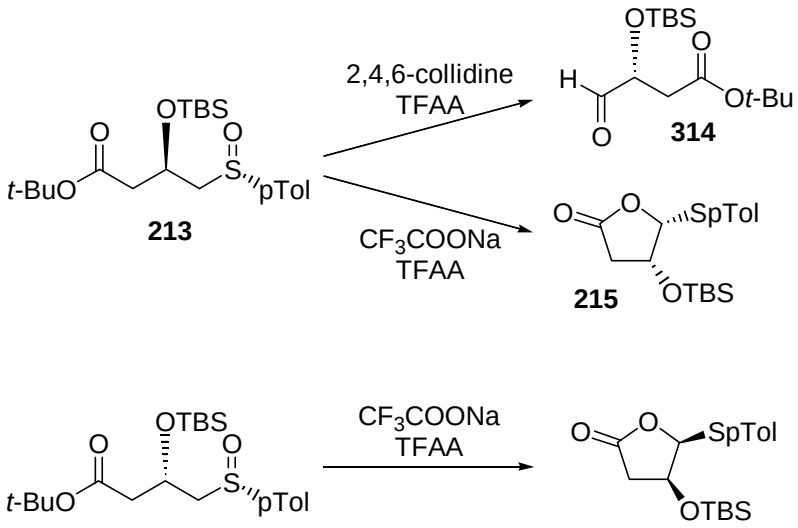
Pummerer-type conditions have been used successfully for the stereoselective synthesis of cyclic compounds by an intramolecular attack of a nucleophile on the sulfenium intermediate formed under the reaction conditions.

By analogy with the vinylogous Pummerer reaction first reported by Marino and applied in numerous other cases,[184,193] the reaction of a fluorinated vinyl sulfoxide (**210**) with dichloroketene affords enantiomerically pure, *trans*-substituted β-fluoroalkyl γ-tolylthio γ-butyrolactones **211** which can be desulfurised and dechlorinated to obtain the enantiomerically pure fluorinated lactones **212** (Scheme 104).[194]



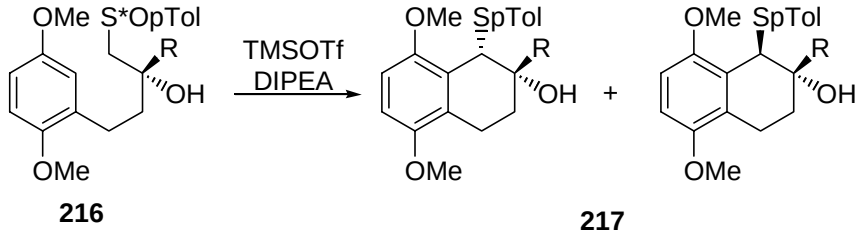
Scheme 104

We have observed that enantiomerically pure *t*-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* β-hydroxy-γ-sulfenyl-γ-butyrolactone (**215**) (Scheme 105).[195]



Scheme 105

The Pummerer sulfenium 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.[196] Thus, enantiomerically pure β-hydroxysulfoxides **216** have been cyclised to afford bicyclic structures **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.

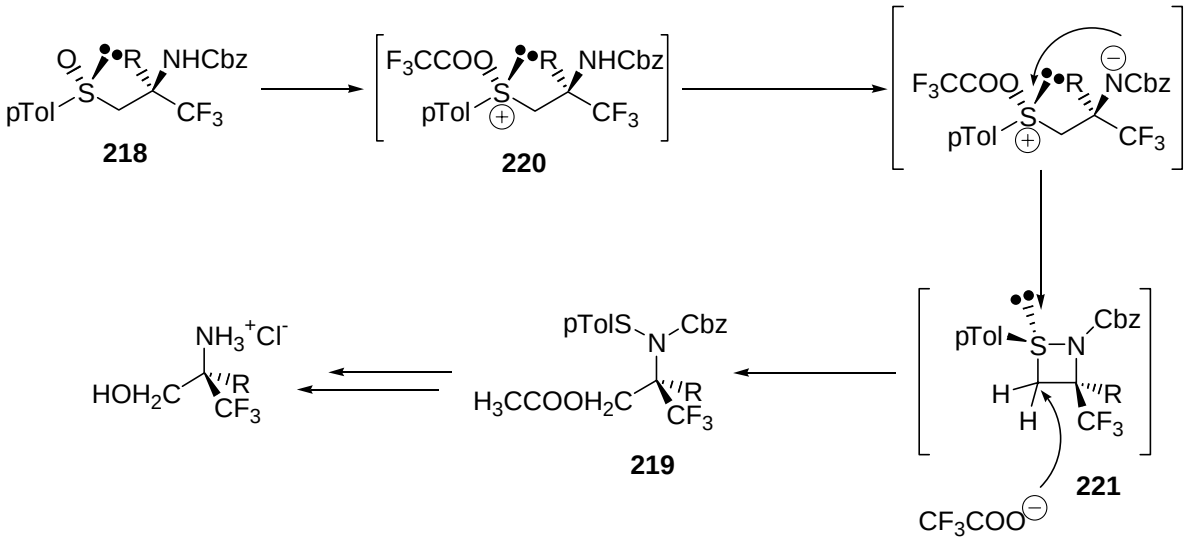


Scheme 106

4.1.1.3. The "non-oxidative" Pummerer rearrangement

In 1995, Bravo *et al.* reported an unusual Pummerer rearrangement of γ-trifluoro-β-aminosulfoxides.[197] They found that, surprisingly, treatment of a β-aminosulfoxide (**218**) with TFAA and *sym*-collidine produced a sulfenamide (**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 **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 (**221**) which can be opened by a nucleophilic attack of trifluoroacetate. It was shown by deuteration experiments that indeed deprotonation did

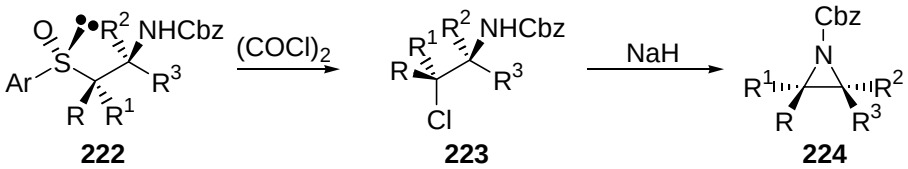
not take place on the carbon atoms. The "abnormal" rearrangement product was successfully converted to the corresponding β-fluoro-α-aminoalcohol.



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-*allo*-threoninate[201] as well as simple β-amino alcohols.[202]

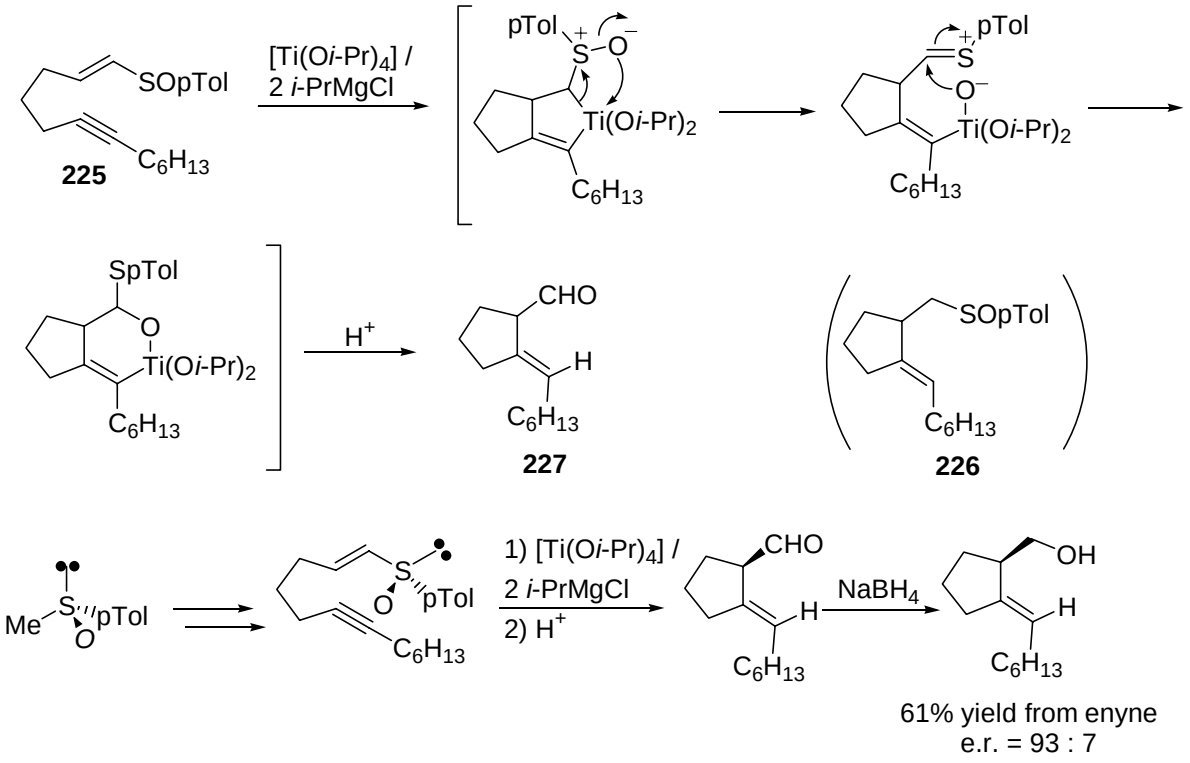
The non-oxidative chloro-Pummerer reaction is a variant of the previous methodology in which β-sulfinyl amines **222** are treated with oxalyl chloride to afford the corresponding β-chloro sulfenamides (Scheme 108).[203] The mechanism of this reaction is likely to be analogous to the non-oxidative Pummerer 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

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.[207] Furthermore, optimum enantioselective protonation of 2-alkylcycloalkanones is reached when the α-sulfinyl alcohol/enolate ratio is 3:1.[208] 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.[209] α-sulfinyl thiols can also be used as chiral proton source but moderate selectivity is generally observed.[210]

6. Conclusions

Since 1995[6] 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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