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Use of chiral sulfoxides in asymmetric synthesis

Hélène Pellissier*

UMR n° 6180, Faculté des Sciences de Saint-Jérôme, Avenue Esc. Normandie-Niemen, 13397 Marseille Cedex 20, France

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1. Introduction

Although the first chiral organosulfur compounds were obtained at the beginning of this century, they have received more attention since the early 1960s. Initially, chiral sulfur compounds served as model compounds in studies on the mechanism and stereochemistry of nucleophilic substitution at sulfur. Quite soon, however, it was recognised

Abbreviations list: Ac, acetyl; Acac, acetylacetone; AIBN, 2,2′-azobisisobutyronitrile; Ar, aryl; $BF_3 \cdot Et_2O$, boron trifluoride etherate; BINAP, 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; Bn, benzyl; Boc, *tert*-butoxycarbonyl; Born, borneol; Bu, butyl; Cbz, benzyloxycarbonyl; Cod, 1,5-cyclooctadiene; Cy, cyclohexyl; dba, (*E*,*E*)-dibenzylideneacetone; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; de, diastereomeric excess; DIBAL, diisobutylaluminium hydride; DIPEA, diisopropylethylamine; DMAD, dimethyl acetylenedicarboxylate; DMF, dimethylformamide; Dodec, dodecyl; dppf, 1,1′-bis(diphenylphosphanyl)ferrocene; dr, diastereomeric ratio; E, electrophile; ee, enantiomeric excess; Et, ethyl; Hex, hexyl; HMDS, hexamethyldisilazide; isoB, isoborneol; LDA, lithium diisopropylamide; LHMDS, lithium hexamethyldisilazide; LICA, lithium dicyclohexylamine; M, metal; MA, maleic anhydride; *m*-CPBA, 3-chloroperoxybenzoic acid; Me, methyl; Ment, menthyl; Mes, mesyl; MOM, methoxymethyl; Naph, naphthyl; NMM, *N*-methylmaleimide; NMO, *N*-methylmorpholine *N*-oxide; NPM, *N*-phenylmaleimide; Pent, pentyl; Ph, phenyl; Piv, pivaloyl; PMB, *p*-methoxybenzoyl; PMP, *p*-methoxyphenyl; Pr, propyl; PTAD, phenyltriazolinedione; Py, pyridine; TBAF, tetra-*n*-butylammonium fluoride; TBDMS, *tert*-butyldimethylsilyl; Tf, trifluoromethanesulphonyl; TFAA, trifluoroacetic anhydride; THF, tetrahydrofuran; THP, tetrahydropyranyl; TIP, triisopropylphenyl; TIPS, triisopropylsilyl; TMS, trimethylsilyl; TMSOTf, trimethylsilyl trifluoromethanesulphonate; Tol, tolyl; Ts, 4-toluenesulphonyl (tosyl).

* Tel.: +33 4 91 28 27 65; e-mail: h.pellissier@univ.u-3mrs.fr

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that chiral sulfur compounds are of great value in asymmetric synthesis, since many reactions may be efficiently stereocontrolled by chiral sulfur auxiliaries, which, later, are easily removable under mild conditions by reductive or eliminative methods. As a result, there has been a literature explosion in this field. On the other hand, over the last three decades, more than 40 different classes of chiral sulfur compounds have been described in the chemical literature and a large number of useful procedures for the synthesis of enantiomerically pure sulfur compounds have been developed, especially of tri- and tetracoordinated sulfur structures. Every year, the literature records dozens and dozens of diverse sulfur-mediated asymmetric syntheses applied in both academic and industrial laboratories for obtaining desirable chiral materials like natural products, drugs or agrochemicals. A book that covers a wide range of chiral organosulfur compounds has been published.[1] Several other excellent reviews pertinent to this area are available.[2]

Chiral sulfoxides belong to the class of chiral organosulfur compounds which are most widely used in asymmetric synthesis. Their application as chiral synthons has now become a well-established and reliable strategy. This is mainly due to their ready availability and high asymmetric induction exerted by the chiral sulfinyl group. Moreover, the chiral sulfur groupings that induce optical activity can be removed from the molecule easily, under fairly mild conditions, thus presenting an additional advantage in the asymmetric synthesis of chiral compounds. The main advantage of sulfoxides over other sulfur functions such as sulfides and sulfones is indeed their chirality. The efficacy of a sulfoxide in diastereoselective auxiliary-induced reactions is mainly due to the steric and stereoelectronic differences existing between the substituents of the stereogenic sulfur atom, a lone electron pair, an oxygen, and two different carbon ligands, which are able to differentiate the diastereotopic faces of a proximal or even of a remote reaction centre. Sulfoxides are chiral groups, which are easy to introduce and easy to remove and which give high asymmetric induction in many reactions. The oxygen atom of a sulfoxide can be coordinated to a metal ion or a proton, and electronic and steric repulsions between nucleophiles and the substituents of a sulfoxide are also expected. The sulfinyl group acts as an electron-withdrawing group and activates a carbon–carbon double bond for conjugate addition and stabilises the corresponding α-carbanion. The stable pyramidal structure of a chiral sulfoxide allows a diastereoselective reaction to occur at a nearby or distant reaction centre. Complexation of the sulfoxide group with a suitable metal ion forms a rigid diastereomeric intermediate, which can undergo subsequent reactions stereoselectively.

To date, a large number of asymmetric syntheses using chiral sulfoxides[3] have been investigated in a wide range of reactions such as the reduction of β-ketosulfoxides,[3e] the Michael addition of nucleophiles to activated α,β-unsaturated sulfoxides, C–C bond formation using sulfoxide-stabilised carbanions,[3b,4] or the Diels–Alder reaction of vinyl sulfoxides.[3e] Enantiopure sulfoxides have become one of the most important classes of chiral auxiliaries as a result of their ease of preparation, remarkable synthetic versatility, and straightforward removal.[5]

The synthesis of chiral sulfoxides has been the subject of constant interest over the past two decades.[3b,c,6] A real breakthrough occurred in the synthesis of chiral sulfoxides at the beginning of the 1990s, when various new methodologies appeared. Several methods are presently available to obtain optically active sulfoxides: optical resolution,[7] asymmetric oxidation of nonsymmetric sulfides,[8] asymmetric biological oxidation,[8] and nucleophilic addition of alkyl or aryl ligands to diastereochemically pure chiral sulfinates[9] such as the Andersen procedure, which is still the most important and generally used method.[10] The Andersen method consists of a substitution at the sulfur atom of commercially available (*S*)-menthyl *p*-toluenesulfinate with an appropriate organometallic reagent, which is favoured since it has the advantage that the substitution takes place with 100% inversion of configuration.[10,11] This classical method has been extensively used to prepare *p*-tolyl alkyl or aryl sulfoxides, and the use of various organometallic nucleophiles has allowed the synthesis of a wide variety of enantiomerically pure sulfoxides. The usefulness of this method is mainly due to the accessibility of the sulfinylating agent, obtained as a mixture of sulfur epimers, which are separated by repeated recrystallisations. The enantiomerically pure sulfinate is then displaced by an organomagnesium halide with complete inversion of stereochemistry at the sulfur, as first demonstrated by Mislow et al.[12] The separation of alkyl menthylsulfinate diastereomers appears to be tricky, however, and Andersen's synthesis is not efficient enough to access enantiomerically pure dialkyl sulfoxides. Other authors have developed synthetic schemes that established the enantiomeric purity at sulfur prior to addition to the organometallic reagent.[13]

Other techniques have been developed for the preparation of optically active sulfoxides such as classical resolution of racemic sulfoxides containing a resolving handle, formation and separation of optically active diastereomeric transition metal complexes, direct resolution of racemic sulfoxides by chromatography over optically activated stationary phases, optical enrichment by incorporation into inclusion compounds with a chiral host molecule, kinetic resolution by partial oxidation or reduction with chiral reagents.

Chiral sulfoxides are important intermediates in asymmetric synthesis and bioactive ingredients in the pharmaceutical industry, as demonstrated in this review. A recent industrial application of the enantioselective oxidations of sulfides using chiral metal catalysts was the development of two syntheses of sulindac, an efficient non-steroidal anti-inflammatory drug (NSAID). The first synthesis was based on an iron-catalysed sulfoxidation,[14] whereas the second involved an asymmetric Kagan sulfoxidation as the key step.[15] In addition, Matsugi et al. reported a practical synthesis of the platelet adhesion inhibitor, OPC-29030, via a catalytic asymmetric oxidation of sulfide with a titanium–mandelic acid complex.[16]

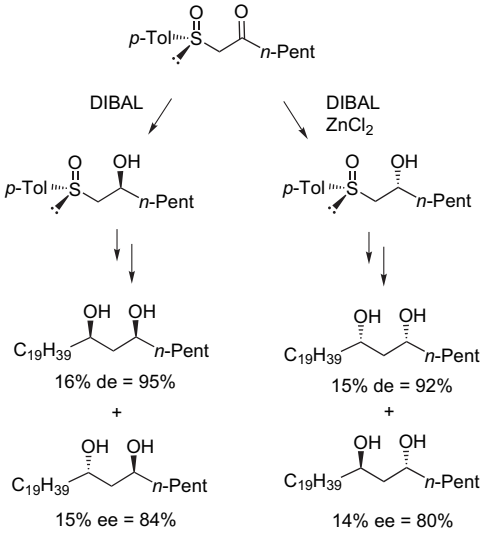
The goal of the present review is to examine recent advances in the use of chiral sulfoxides as chiral auxiliaries in asymmetric synthesis, focusing on those which have been published since 2000, the most recent review covering the literature until this latter year.[17] This review is divided into

seven sections corresponding to the different types of reactions making possible the stereoselective generation of new stereogenic centres by means of sulfoxides.

Since a recent review has focused on the preparation of chiral sulfoxides,[18] the present review only deals with the use of chiral sulfoxides as chiral auxiliaries, focusing on their applications in the synthesis of biologically active products. It is important to note that the chemistry of chiral sulfinimines[19] has recently been reported in excellent reviews by Davis et al.,[20] as well as that of chiral sulfoximines.[21,2e]

2. Reduction reactions

The reduction of chiral β-ketosulfoxides has been the most extensively investigated and used reaction involving the asymmetric induction of chiral sulfoxides. The stereochemical outcome in the reduction of either isomer of the β-ketosulfoxide can be controlled by the configuration of the sulfoxide, the reducing reagent, and the absence or presence of a Lewis acid. As an example, both diastereomers of β-hydroxysulfoxides, precursors of biologically active heptacosane-6,8-diols, could be prepared by reduction of the corresponding β-ketosulfoxide by treatment with DIBAL in the presence or absence of $ZnCl_2$ (Scheme 1).[22]



Scheme 1. Synthesis of heptacosane-6,8-diols induced by chiral sulfoxides.

This methodology was successfully applied by Stefani et al. in order to develop a total synthesis of a natural polyacetylenic product, (+)-virol C (Fig. 1).[23] Similarly, Solladié et al. have prepared the C8–C18 subunit of pamamycin 607, which has a remarkable range of biological activities, via stereoselective reduction of a chiral β,δ-diketosulfoxide (Fig. 1).[24]

In 2002, Carreno et al. described the first enantioselective total synthesis of (−)-centrolobine, based on the stereoselective reduction of a chiral β-ketosulfoxide bearing an ester as the source of chirality (Scheme 2).[25]

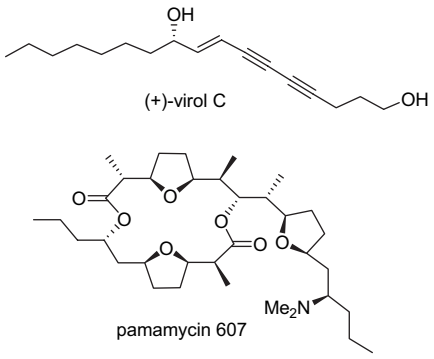
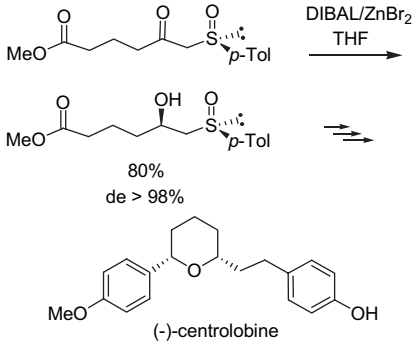
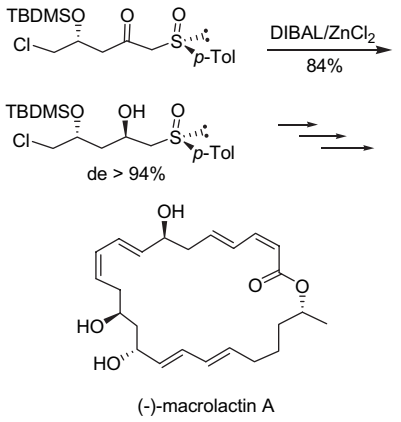


Figure 1. Structures of natural products prepared via chiral sulfoxide methodology.



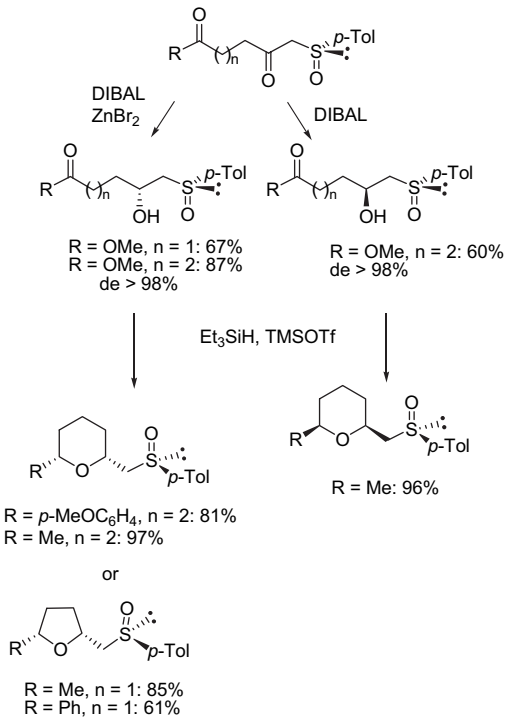
Scheme 2. Synthesis of (−)-centrolobine.

The chiral sulfoxide methodology was applied by the same group to the preparation of the C12–C24 fragment of macrolactin A, a 24-membered polyene macrolide possessing powerful antiviral activities.[26] This latter product was also prepared by Marino et al., starting from a functionalised chiral sulfoxide (Scheme 3).[27]



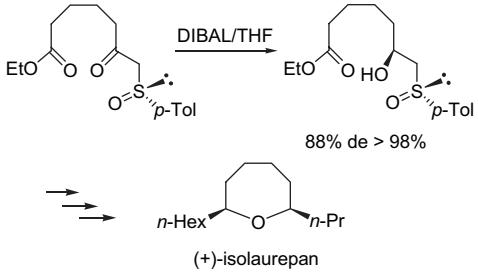
Scheme 3. Synthesis of (−)-macrolactin A.

In 2003, Carreno et al. reported the stereocontrolled formation of *cis*-2,5-disubstituted tetrahydrofurans and *cis*-2,6-disubstituted tetrahydropyrans from enantiopure ketosulfinyl esters by reduction (Scheme 4).[28] The sulfoxide bearing heterocycles were further converted into natural products.



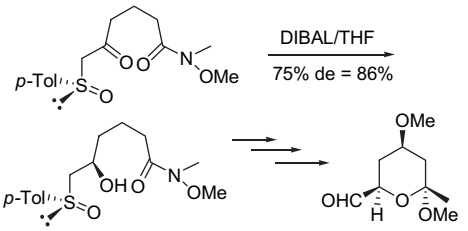
Scheme 4. Enantioselective access to tetrahydropyran and tetrahydrofuran derivatives.

In 2004, an extension of this methodology allowed a formal synthesis of (+)-isolaurepan and, more generally, an easy access to chiral 2,7-*cis*-disubstituted oxepanes (Scheme 5).[29]



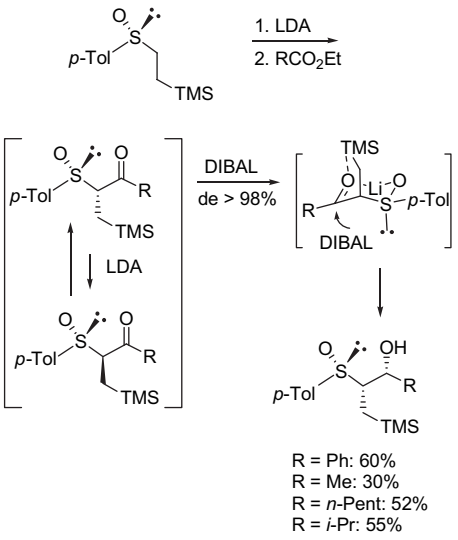
Scheme 5. Synthesis of (+)-isolaurepan.

In addition, the enantioselective construction of the tetrahydropyran ring, the C32–C38 fragment of phorboxazoles, was based on a stereoselective reduction of a chiral sulfoxide bearing a Weinreb amide (Scheme 6).[30]



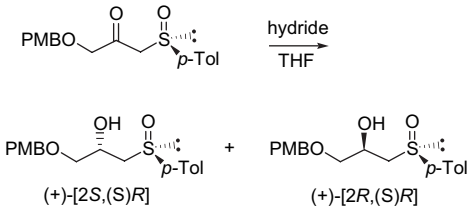
Scheme 6. Synthesis of C32–C38 THP fragment of phorboxazoles.

In 2003, Toru et al. reported an asymmetric reduction of α-(trimethylsilyl)methyl-β-ketosulfoxide with DIBAL under basic conditions (Scheme 7). The stereoselective reaction was demonstrated to proceed through a dynamic kinetic resolution pathway via a six-membered cyclic transition state involving Si–O interaction.[31]



Scheme 7. Asymmetric reduction of α-(trimethylsilyl)methyl-β-ketosulfoxide.

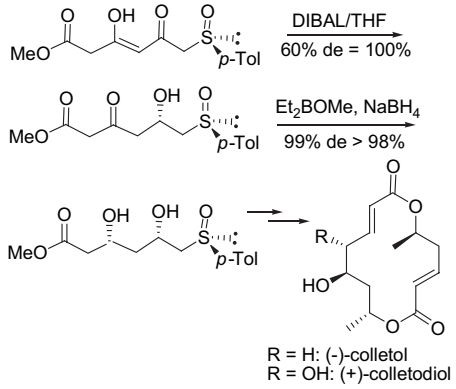
In 2004, Colobert et al. studied the use of various hydrides for the reduction of a β-ketosulfoxide bearing an oxygenated function at C1 of the β-ketosulfoxide.[32] As expected, when the reduction was carried out in the presence of DIBAL, the [2*S*,(S)*R*]-product was obtained as a single diastereomer, whereas the DIBAL/ZnX_2 (X=Cl, Br, I) reduction was poorly stereoselective and led to an almost equimolecular mixture of the two diastereomers. The presence of an oxygenated function at C1 of the β-ketosulfoxide, which could compete with the sulfinyl oxygen for chelation with the Zn atom, could be the origin of the lack of selectivity. Other hydrides such as $LiAlH_4$, $NaBH_4$, and Bu_4NBH_4 gave diastereomeric ratios that were not in the range of utility. On the other hand, the use of $Yb(OTf)_3$ and DIBAL afforded a mixture of the [2*R*,(S)*R*]-product and its epimer in a 92:8 ratio (Scheme 8).



Hydride	(+)-[2*S*,(S)*R*]/(+)-[2*R*,(S)*R*]	Yield (%)
DIBAL	100/0	98
$ZnCl_2$/DIBAL	50/50	62
$ZnBr_2$/DIBAL	67/33	65
ZnI_2/DIBAL	50/50	60
$LiAlH_4$	24/76	41
$NaBH_4$	36/64	99
Bu_4NBH_4	38/72	99
$Yb(OTf)_3$/DIBAL	8/92	96

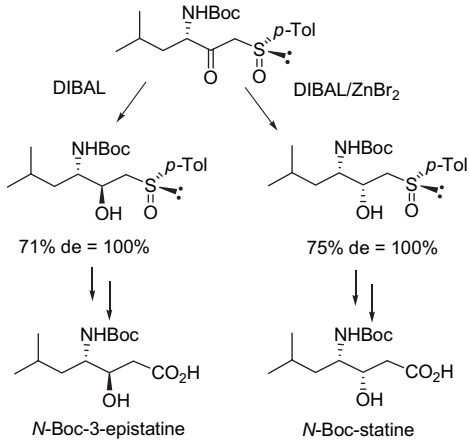
Scheme 8. Stereoselective reduction of a δ-alkoxy-β-ketosulfoxide.

In 2000, Solladié et al. reported a general synthetic strategy towards the two bis(lactones), (−)-colletol and (+)-colletodiol, based on two successive stereoselective reduction reactions induced by a chiral β,δ-diketosulfoxide.[33] Since the δ carbonyl was entirely enolised, the first reduction carried out in the presence of DIBAL yielded the corresponding β-hydroxysulfoxide as a single isomer. In the next step, the δ carbonyl group was reduced with $Et_2BOMe/NaBH_4$ to give the corresponding *syn*-diol in quantitative yield and with de>98% (Scheme 9).



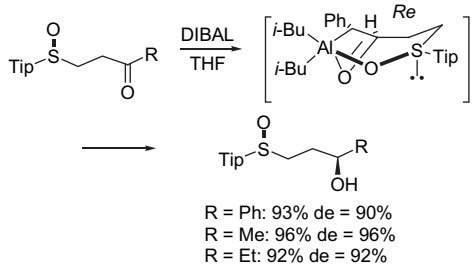
Scheme 9. Synthesis of (−)-colletol and (+)-colletodiol.

β-Hydroxy-γ-amino acids have received considerable attention, notably those acting as key components of peptidomimetic protease inhibitors such as statine. In 2003, Garcia Ruano et al. developed a unique approach to the *syn*- and *anti*-stereoisomers of *N*-Boc statine, based on the stereodivergent reduction of a chiral β-ketosulfoxide derived from *N*-Boc-L-leucine methyl ester.[34] Since *N*-Boc-D-leucine was also commercially available, the synthesis of the four stereoisomers of statine could be performed using this methodology (Scheme 10).



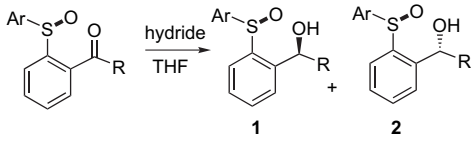
Scheme 10. Synthesis of *N*-Boc-statine and *N*-Boc-3-epistatine mediated by sulfoxides.

In 2000, Toru et al. reported a highly diastereoselective reduction of γ-ketosulfoxides having a sterically bulky aryl group such as 2,4,6-triisopropylphenyl (Scheme 11).[35] In comparison with the lower stereoselectivities obtained in the reaction of γ-ketosulfoxides bearing *p*-tolyl or 2,4,6-trimethylphenyl groups, the sterically bulky (2,4,6-triisopropylphenyl)sulfinyl group was extremely efficient in effecting high 1,4-remote asymmetric induction, irrespective of the substituent R attached to the carbonyl group, showing very weak steric or electronic effects of these substituents on the stereoselectivity. The high stereoselectivity could be ascribed to a cyclic twisted-chair transition state involving a trigonal bipyramidal structure, as depicted in Scheme 11. The bulky group was placed at the pseudoequatorial position and might constrain the cyclic transition state more efficiently than the *p*-tolyl and mesityl groups. The reduction would preferably occur from the *re* face of the carbonyl.



Scheme 11. Asymmetric reduction of γ-ketosulfoxides bearing a 2,4,6-triisopropylphenyl group.

The same authors have reported a 1,4-asymmetric induction in the stereoselective reduction of enantiomerically enriched γ-ketosulfoxides where the sulfinyl and carbonyl groups were separated by a phenyl ring (Scheme 12).[36] Thus, these authors have studied the reactions of *p*-tolylsulfinyl, (2,4,6-trimethylphenyl)sulfinyl and [(2,4,6-triisopropylphenyl)-sulfinyl]phenyl ketones with various reducing reagents, without, or in the presence of Lewis acids. Reduction with



Ar	R	Hydride	Yield (%)	Ratio **1**:**2**
Tol	Ph	$LiAlH_4$	80	47:53
Tol	Ph	DIBAL	80	15:85
Tol	Me	$LiAlH_4$	84	51:49
Tol	Me	DIBAL	85	37:63
Mes	Ph	$LiAlH_4$	82	21:79
Mes	Ph	DIBAL	92	2:98
Mes	Me	$LiAlH_4$	94	56:44
Mes	Me	DIBAL	94	16:84
Tip	Ph	$LiAlH_4$	81	35:65
Tip	Ph	DIBAL	96	2:98
Tip	Ph	L-selectride	86	11:89
Tip	Ph	Superhydride	86	11:89
Tip	Ph	DIBAL/LiBr	88	16:84
Tip	Ph	$DIBAL/Yb(OTf)_3$	81	19:81
Tip	Ph	$DIBAL/ZnCl_2$	92	85:15
Tip	Me	DIBAL	96	3:97
Tip	Allyl	DIBAL	94	2:98

Scheme 12. Stereoselective reduction of 2-(arylsulfinyl)phenyl ketones.

$LiAlH_4$ proceeded with low diastereoselectivity, irrespective of the bulkiness of the substituent on the sulfur. The diastereoselectivity of the products in the DIBAL reduction depended upon the substituent on the sulfur. (*p*-Tolylsulfinyl)phenyl ketones with DIBAL afforded the products with low stereoselectivity, whereas [(2,4,6-triisopropylphenyl)-sulfinyl]phenyl ketones gave the corresponding alcohols with high stereoselectivity, favouring isomer **2**. Other reducing agents such as L-Selectride and Superhydride gave slightly lower stereoselectivity. Solladié et al. have previously reported that the reduction of γ-ketosulfoxides with DIBAL proceeded with moderate diastereoselectivity without Lewis acids and the stereochemistry of the product was reversed in the presence of $Yb(OTf)_3$.[37] In the DIBAL reduction of [(2,4,6-triisopropylphenyl)-sulfinyl]phenyl ketones, the stereoselectivity was lowered in the presence of $Yb(OTf)_3$ or LiBr, but not reversed. On the other hand, $ZnCl_2$ significantly reversed the diastereoselectivity in favour of isomer **1**.

The stereochemical outcome in the reduction of 2-(arylsulfinyl)phenyl ketones with DIBAL was ascribed to a seven-membered cyclic transition state, as shown in Figure 2. The bulky 2,4,6-triisopropylphenyl group was placed away from the neighbouring acyl substituent in a preferred transition state, and intramolecular reduction occurred from the *si* face of the carbonyl to give isomer **2**. High stereoselectivity could be achieved through the cyclic transition state constrained preferably by the 2,4,6-triisopropylphenyl group rather than by the mesityl and *p*-tolyl groups. Addition of $ZnCl_2$ reversed the stereochemistry of the product, indicating that $ZnCl_2$ would form a chelate in place of DIBAL, and reduction occurred from the outside of the chelate.

In the course of developing a new access to chiral benzothiepines, which are potent apical sodium co-dependent bile acid transporter inhibitors, Lee et al. have studied the reduction of a polyfunctionalised chiral γ-ketosulfoxide carried out in the presence of $NaBH_4$, providing a 27:73 mixture of both corresponding alcohols favouring the trans-isomer (Scheme 13).[38]

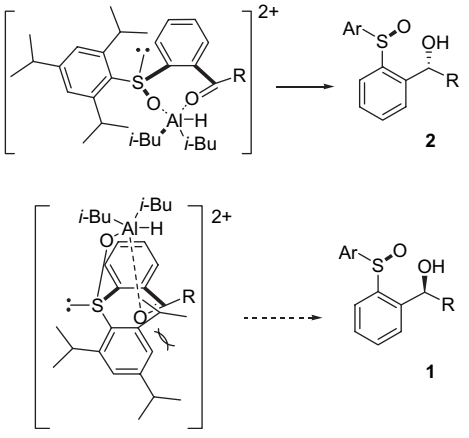
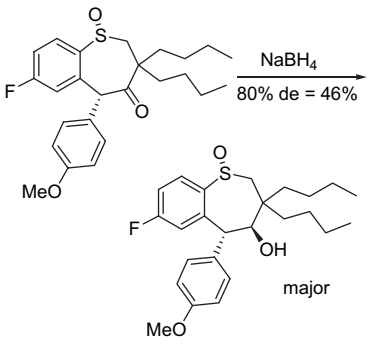
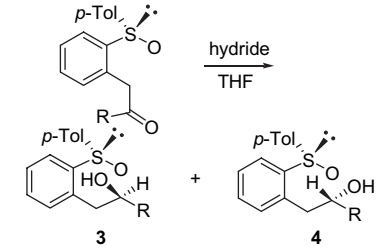


Figure 2. Assumed transition states in DIBAL reduction of 2-(arylsulfinyl)-phenyl ketones.

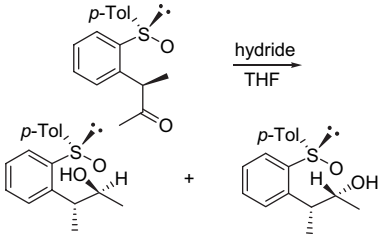


Scheme 13. Asymmetric reduction of a polyfunctionalised γ-ketosulfoxide.

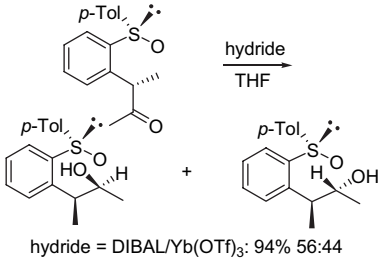
Very recently, Garcia Ruano et al. demonstrated that the reduction of δ-ketosulfoxides constituted the first evidence of the efficiency of the sulfinyl group to control the stereoselectivity of 1,5-asymmetric induction processes.[39] The use of DIBAL/$Yb(OTf)_3$ or L-Selectride as the reducing agents provided the corresponding δ-hydroxysulfoxides **3** and **4** with the opposite configuration at the hydroxylic carbon in a highly stereoselective manner (Scheme 14).



R	Hydride	3:4	Yield (%)
Me	DIBAL/$Yb(OTf)_3$	97:3	96
Me	L-Selectride	5:95	75
Ph	DIBAL/$Yb(OTf)_3$	89:11	95
Ph	L-Selectride	40:60	55
n-Pr	DIBAL/$Yb(OTf)_3$	92:8	95
n-Pr	L-Selectride	2:98	65
i-Pr	DIBAL/$Yb(OTf)_3$	92:8	97
i-Pr	L-Selectride	2:98	60



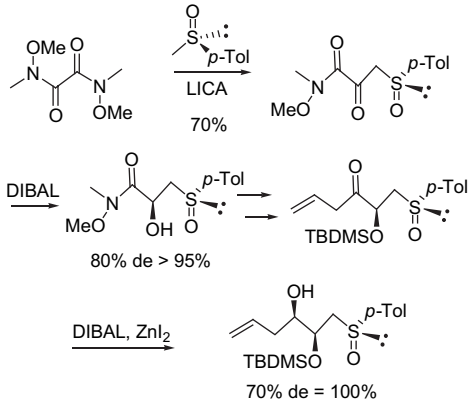
hydride = DIBAL/$Yb(OTf)_3$: 70% 100:0
hydride = L-Selectride: 65% 86:14



hydride = DIBAL/$Yb(OTf)_3$: 94% 56:44
hydride = L-Selectride: 60% 53:47

Scheme 14. Asymmetric reduction of δ-ketosulfoxides.

Solladié has considerably extended the sulfoxide-mediated enantioselective reduction of carbonyl compounds to the synthesis of enantiomerically pure diols, including C_2 symmetric diols from the corresponding diketodisulfoxides.[40] This methodology could be successfully applied to the synthesis of many biologically important compounds such as (−)-tarchonanthuslactone,[41] cladospolide,[42] solenopsins,[43] compactin analogues,[44] insect pheromones[45] and descarestrictine.[46] More recently, a formal synthesis of the 10-membered lactone core of ascidiatrienolides and didemnilactones was developed on the basis of two successive highly diastereoselective sulfoxide-directed reductions of an oxalic diamide (Scheme 15).[47]

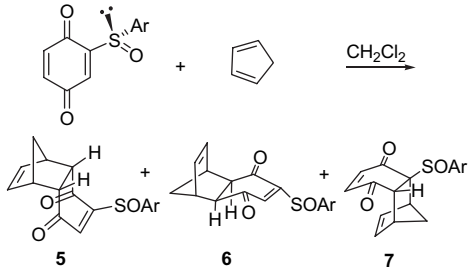


Scheme 15. Sequential DIBAL sulfoxide-directed reduction of an oxalic diamide derivative.

3. Cycloaddition reactions

3.1. Diels–Alder reactions

3.1.1. Sulfinyl dienophiles. The combination of a Diels–Alder reaction with asymmetric induction exerted by sulfoxides represents a very powerful method for C–C bond formation in a stereocontrolled manner.[48] The sulfinyl group has, equally, become one of the most interesting chiral inductors in asymmetric Diels–Alder reactions, due to: (a) its ability to differentiate between diastereotopic faces of neighbouring double bonds, (b) the ease of chemical transformations into different functional groups including its clean removal under mild conditions and (c) the existence of several efficient methods that allow the preparation of enantiomerically pure sulfoxides. The poor results obtained in the Diels–Alder reaction using unsubstituted vinylic sulfoxides (low reactivity and only moderate stereoselectivity)[49] were substantially improved by attaching additional groups to the double bond, which increased the reactivity and simultaneously restricted the conformational mobility around the C–S bond, hence improving the stereoselectivity of the dienophile. In this sense, several electron-withdrawing groups have been incorporated to vinylic sulfoxides such as carbonyl,[50] nitro,[51] sulfonyl,[52] sulfinyl[53] and cyano.[54] Nevertheless, the most widely studied is doubtlessly the ester group, the contributions by Koizumi in this field clearly being the most significant.[55] Application of optically active vinyl sulfoxides as dienophiles is a fascinating strategy, since the chiral sulfinyl auxiliary is known to exert a high asymmetric induction in the carbon–carbon bond formation. Such a strategy creates the possibility of an easy synthesis of complex products possessing several chiral centres of desired stereochemistry. This approach has been the subject of a great number of publications.[55–57] It should be emphasised that, while the *endo*/*exo* stereoselection, consisting of a different orientation of the diene with respect to the sulfoxide substituents in a dienophile is rather a consequence of steric and/or electronic interaction, the π-facial stereoselectivity arising from the approach of the diene to a different face of the dienophile is only a result of the influence of the sulfinyl group chirality.[58] Thus, the π-facial stereoselectivity can be considered as a measure of the asymmetric induction exerted by the sulfinyl group. Diels–Alder reactions of enantiomerically enriched dienophiles and dienes are highly stereoselective and efficient for the asymmetric construction of cyclic or bicyclic skeletons. In recent years, a number of examples of Diels–Alder reactions of optically active sulfinyl dienophiles have been reported.[59] Subsequent efforts focused on the design of sulfinyl dienophiles bearing additional electron-withdrawing groups on the double bond such as ketones, esters and sulfones, which allowed a serious improvement of the facial selectivity in both cases. Although quinones are among the best dienophiles traditionally used in Diels–Alder reactions, relatively few examples of chiral derivatives for use in asymmetric synthesis are known, despite their potential to construct structurally complex molecules in enantiomerically pure form. Carreno et al. have extensively studied the use of 2-(arylsulfinyl)-1,4-benzoquinones as chiral dienophiles in Diels–Alder reactions. They have shown that reactions with acyclic dienes took place through a sequential Diels–Alder cycloaddition/pyrolytic sulfoxide elimination, giving rise to chiral polycyclic dihydroquinones.[60] This process, coupled with the kinetic resolution of a chiral racemic vinylcyclohexene, which occurred simultaneously, was further applied to the enantioselective synthesis of several angucyclinones.[61] In 2000, these authors extended the same methodology to cyclic dienes such as, for the first time, cyclopentadiene (Scheme 16 and Table 1).[62] They demonstrated that the reactivity, chemoselectivity and π-facial diastereoselectivity of Diels–Alder reactions of 2-(arylsulfinyl)-1,4-benzoquinones and cyclopentadiene were related to the electron-donating or withdrawing character of the substituent at the aromatic sulfoxide, as well as the Lewis acid employed. In the presence of $BF_3\cdot Et_2O$, the cycloadditions occurred exclusively on the unsubstituted double bond C5–C6, affording the diastereoisomers **6** as the major isomers, whereas $Eu(fod)_3$ directed the attack mainly on C5–C6 with the opposite π-facial diastereoselectivity, affording predominantly the diastereoisomers **5**. The opposite chemoselectivity (90% of the cycloaddition from the sulfinyl-substituted



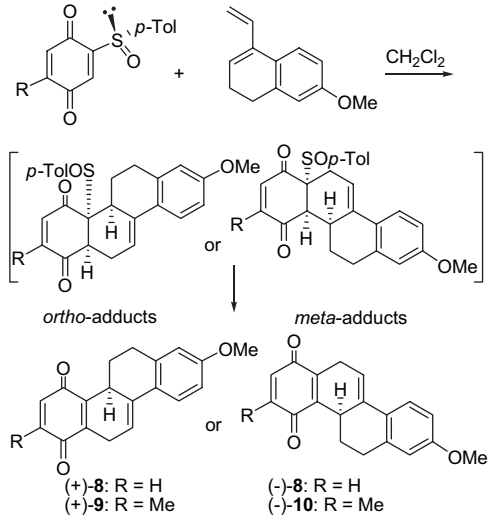
Scheme 16. Diels–Alder reaction of 2-(arylsulfinyl)-1,4-benzoquinones with cyclopentadiene.

Table 1

Ar	Lewis acid	**5**:**6** (% de)	**7** (% de)	Yield (%)
p-Tol	—	71:29 (42)	—	95
2-MeONaph	—	63:37 (26)	—	98
p-MeOPh	—	68:32 (36)	—	98
p-NO_2Ph	—	66:34 (32)	—	95
p-Tol	Eu(fod)$_3$	80:10 (70)	10 (100)	80
2-MeONaph	Eu(fod)$_3$	82:18 (64)	—	90
p-MeOPh	Eu(fod)$_3$	78:8 (70)	14 (100)	87
p-NO_2Ph	Eu(fod)$_3$	58:19 (39)	23 (100)	87
p-Tol	$BF_3{\cdot}Et_2O$	10:90 (80)	—	90
2-MeONaph	$BF_3{\cdot}Et_2O$	5:95 (90)	—	92
p-MeOPh	$BF_3{\cdot}Et_2O$	5:95 (90)	—	92
p-NO_2Ph	$BF_3{\cdot}Et_2O$	19:81 (62)	—	65
p-Tol	$ZnBr_2$	20:20 (0)	60 (100)	83
2-MeONaph	$ZnBr_2$	42:58 (16)	—	60
p-MeOPh	$ZnBr_2$	32:32 (0)	36 (100)	75
p-NO_2Ph	$ZnBr_2$	6:4 (20)	90 (100)	70

double bond C2–C3) was achieved from benzoquinone substituted by a *p*-nitrophenyl group in the presence of $ZnBr_2$, yielding exclusively the diastereoisomer **7** (de=100%).

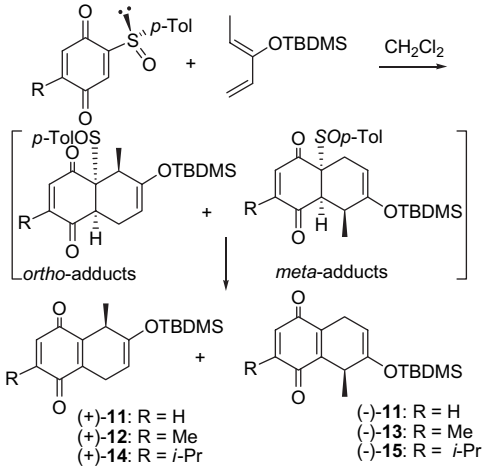
This group has reported the extension of this reaction to various 1,2-disubstituted dienes such as Dane's diene (Scheme 17) and differently substituted enantiopure (*p*-tolylsulfinyl)-1,4-benzoquinones.[63] Similar π-facial diastereoselectivities, but reversed regiochemistry under thermal conditions and in the presence of $ZnBr_2$, were observed in all dienes. After spontaneous elimination of the sulfoxide, optically active polycyclic dihydroquinones were formed with ees ranging from 36 to >97%. It was demonstrated that the regiochemistry of the process was controlled by the alkyl substituent at C1 in thermal reactions, whereas, in the presence of $ZnBr_2$, the oxygenated function at C2 became the main controller.



R	Lewis acid	Products (% Yield)	Products (% ee)
H	-	(+)-**8** (23)	(+)-**8** (80)
H	$ZnBr_2$	(-)-**8** (20)	(-)-**8** (36)
Me	-	(+)-**9** (43)	(+)-**9** (80)
Me	$ZnBr_2$	(-)-**10** (38)	(-)-**10** (> 97)

Scheme 17. Diels–Alder reaction of 2-(*p*-tolylsulfinyl)-1,4-benzoquinones with Dane's diene.

All cases of cycloadditions carried out with 3-(*tert*-butyldimethylsilyloxy)-1,3-pentadiene occurred through the sulfinyl-substituted C2–C3 double bond of the sulfinyl-quinones, affording the corresponding 5,8-dihydronaphthoquinones, which partially aromatised to the corresponding naphthoquinones during the isolation process (Scheme 18).

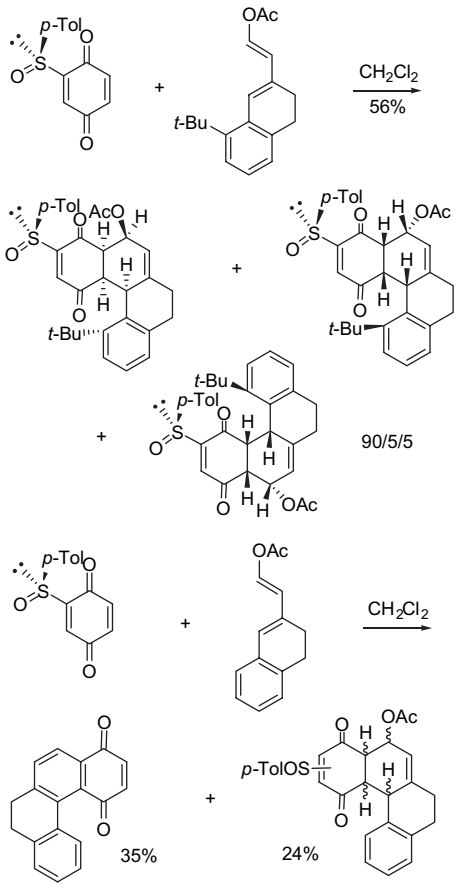


R	Lewis acid	Products (% Yield)	Products (% ee)
H	-	**11** (32)	**11** (0)
H	$ZnBr_2$	(-)-**11** (36)	(-)-**11** (36)
Me	-	(+)-**12** (25) + (-)-**13** (22)	**12** (78) + **13** (72)
Me	$ZnBr_2$	(+)-**12** (0) + (-)-**13** (100)	**13** (72)
i-Pr	-	(+)-**14** (40) + (-)-**15** (10)	**14** (>97) + **15** (74)
i-Pr	$ZnBr_2$	(-)-**15** (62)	**15** (74)

Scheme 18. Diels–Alder reaction of 3-(*tert*-butyldimethylsilyloxy)-1,3-pentadiene.

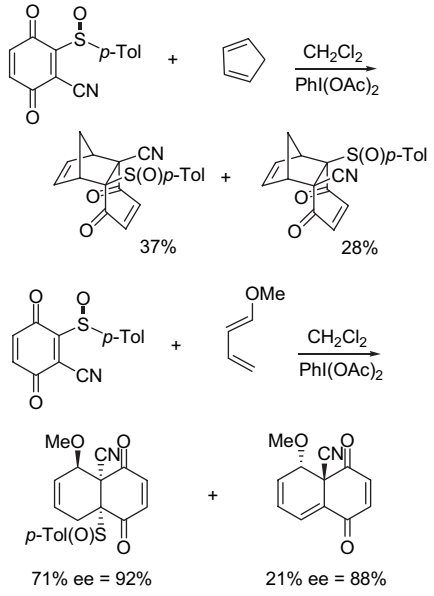
In addition, 1-methyl-2-(*tert*-butyldimethylsilyloxy)-1,3-cyclohexadiene was investigated using the same conditions as before, giving reactions, which took place chemoselectively on the sulfinyl-substituted double bond of the quinones in all cases of benzoquinones. The influence of diene substitution on Diels–Alder reactions between vinyl dihydronaphthalenes and 2-(*p*-tolylsulfinyl)-1,4-benzoquinone was studied in 2003 (Scheme 19).[64] It was shown that the reaction carried out with 2-(*E*-2-acetoxyvinyl)-8-*tert*-butyl-3,4-dihydronaphthalene took place exclusively on the unsubstituted C5–C6 double bond of the benzoquinone with a very high control of the chemo-, regio- and diastereoselectivities of the process, affording the corresponding tetracyclic sulfinyl derivative possessing five stereogenic centres. On the other hand, the analogue diene lacking the *tert*-butyl group gave a less chemoselective reaction (C2–C3/C5–C6=60:40) in favour of reaction through the sulfoxide-substituted double bond C2–C3 of benzoquinone. A balance between steric effects of a remote *tert*-butyl group and electronic factors in the diene partner was the origin of the observed chemo- and regioselectivities of the cycloadditions that occurred from the C5–C6 unsubstituted double bond of the dienophile.

In order to increase the reactivity of the C2–C3 double bond of the dienophile, thus inverting the chemoselectivity, and to avoid desulfinylation by subsequent aromatisation, Garcia Ruano et al. introduced a cyano group at C3 of the benzoquinone.[65] Thus, (*S*)-2-cyano-3-(*p*-tolylsulfinyl)-1,4-benzoquinone was submitted to cycloaddition in the presence of



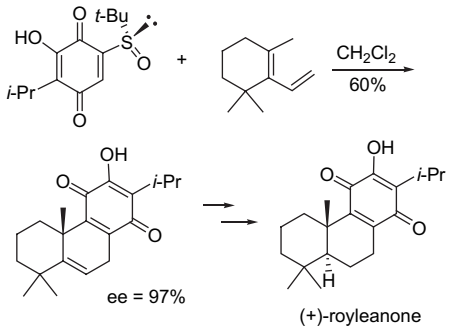
Scheme 19. Diels–Alder reaction of vinyl dihydronaphthalenes.

cyclic and acyclic dienes, affording the Diels–Alder adducts with a complete chemo- (only reaction with the sulfinyl-substituted double bond took place), regio- (controlled by the cyano group) and *endo* selectivities (with respect to the quinone moiety), whereas the π-facial selectivity was dependent on the structure of the diene (Scheme 20).



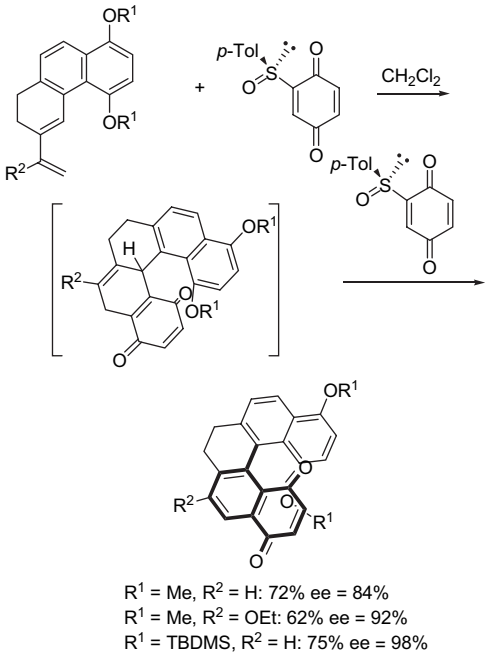
Scheme 20. Diels–Alder reaction of (*S*)-2-cyano-3-(*p*-tolylsulfinyl)-1,4-benzoquinone.

An enantioselective synthesis of (+)-royleanone, an insecticide and disinfectant agent, could be developed using the sulfinylquinone methodology.[66] The key step was a tandem asymmetric Diels–Alder reaction/pyrolytic sulfoxide elimination process involving (*S*)-3-hydroxy-2-isopropyl-5-*tert*-butylsulfinyl-*p*-benzoquinone as chiral auxiliary (Scheme 21).



Scheme 21. Synthesis of (+)-royleanone.

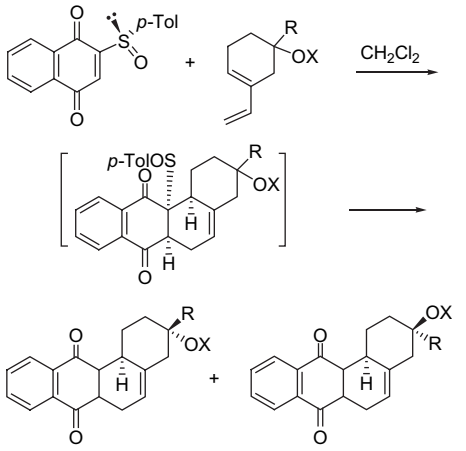
This powerful methodology was also applied to the first synthesis of chiral dihydro[5]helicenequinones and bisquinones, by reaction of 1,4-divinyl-1,3-cyclohexadiene, 5,8-dimethoxy- or *tert*-butyldimethylsilyloxy-3-vinyl-1,2-dihydrophenanthrene or 6-vinyl-7,8-dihydro-1,4-phenanthrenequinone with (*S*,*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone.[67] A domino Diels–Alder cycloaddition/sulfoxide elimination/partial aromatisation process occurred, the absolute configuration of the final helicene being defined in the aromatisation step (Scheme 22).



Scheme 22. Enantioselective synthesis of (*P*)-dihydro[5]helicenequinones and bisquinones.

In the same way, enantiomerically enriched 1,4-dihydro-9,10-anthraquinone derivatives have been prepared by reaction between (*S*,*S*)-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone and racemic acyclic dienes bearing a substituted allylic centre through a tandem cycloaddition/pyrolytic sulfoxide

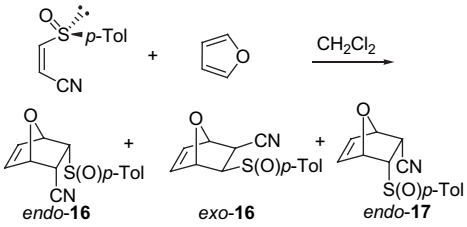
elimination.[68] When vinylcyclohexenes, bearing oxygenated substituents and/or a methyl group at the C5 position of the cyclohexene ring, were used as dienes, the asymmetric domino process led to the formation of chiral C3-oxygenated angucyclinones, which are a large group of naturally occurring quinones that display a broad range of biological properties such as antiviral, antifungal and antitumour effects, as well as enzyme-inhibitory activity (Scheme 23).[69] The process took place through a domino Diels–Alder reaction/pyrolytic sulfoxide elimination with simultaneous kinetic resolution of the racemic diene.



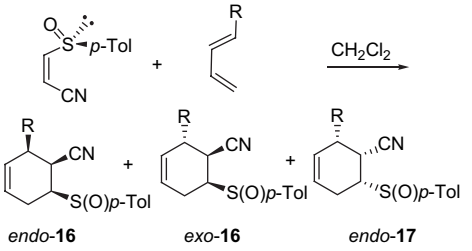
Scheme 23. Asymmetric synthesis of C3-oxygenated angucyclinones.

On the other hand, the behaviour of (*Z*)-3-*p*-tolylsulfinylacrylonitrile as a chiral dienophile has been evaluated by Garcia Ruano et al. from its reaction with furan and acyclic dienes.[54a] Electrostatic interactions of the cyano group with the sulfinyl moiety restricted the conformational mobility around the C–S bond, thus controlling the π-facial selectivity, which was almost complete in all cases, the approach of the diene from the less hindered face of the dienophile (that bearing the lone electron pair) in the predominant rotamer being favoured. The regioselectivity was also completely controlled by the cyano group. Additionally, the reactivity of (*Z*)-3-*p*-tolylsulfinylacrylonitrile, as well as its *endo* selectivity, was both higher than those observed for the corresponding (*Z*)-3-sulfinylacrylates, thus proving the potential of sulfinylnitriles as chiral dienophiles (Scheme 24). The same group has also outlined the Diels–Alder reactions of the corresponding chiral (*E*)-3-formyl-2-sulfinylacrylonitrile and its diethyl acetal derivative with cyclopentadiene.[70]

In the course of studying the stereoselectivity control in Diels–Alder reactions of 4-thiosubstituted 5-alkoxyfuranones, Martin et al. have developed the cycloaddition of (*S*)-4-phenylsulfinyl-(5*S*)-5-(*l*-menthyloxy)furan-2(5*H*)-one with cyclopentadiene.[71] They have demonstrated that the sulfur substituents at C4 inverted the trend imposed by C5 on the π-facial selectivity and the *syn*-adducts became favoured. Indeed, Scheme 25 shows that the major adduct resulted from the *exo* approach of the diene to the *syn* face bearing the menthyloxy moiety. Moreover, the π-facial selectivity,



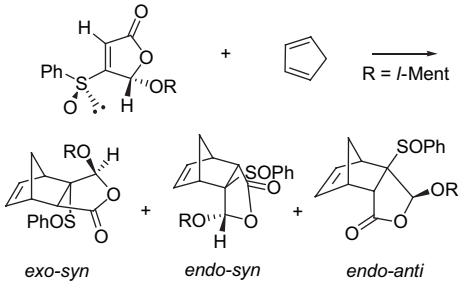
Catalyst	*endo*-**16** (%)	*exo*-**16** (%)	*endo*-**17** (%)	*endo*/*exo*	**16**/**17**
-	51	11	0	84/16	> 33
$ZnBr_2$	42	13	0	86/14	> 33
Me_2AlCl	53	10	0	87/13	> 33



Catalyst	R	*endo*-**16** (%)	*exo*-**16** (%)	*endo*-**17** (%)
-	OMe	70	12	0
$ZnBr_2$	OMe	63	13	16
-	Me	70	5	0
$ZnBr_2$	Me	57	4	13

Scheme 24. Diels–Alder reaction of (*Z*)-3-*p*-tolylsulfinylacrylonitriles.

measured as the *syn*/*anti* adduct ratio (≥3:1), indicated that the approach of the diene from the same face of the alkoxy group was favoured, and the *exo*/*endo* ratio (>1) revealed that the *exo* addition mode was slightly preferred.

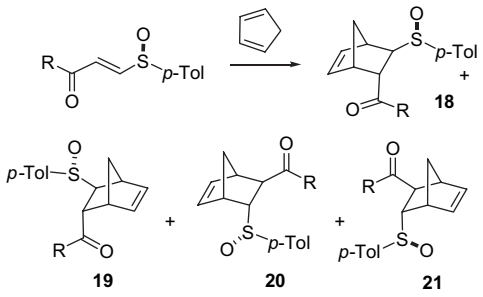


Catalyst	Yield (%)	Adduct ratio *exo-syn*	*endo-syn*	*endo-anti*
-	88	53	21	26
$ZnBr_2$	76	60	20	20

Scheme 25. Diels–Alder reaction of (*S*)-4-phenylsulfinyl-(5*S*)-5-(*l*-menthyloxy)furan-2(5*H*)-one.

In 2004, Ordonez et al. reported the Diels–Alder reaction of chiral (*E*)-γ-keto-α,β-unsaturated *p*-tolyl sulfoxides with cyclopentadiene (Scheme 26).[72] The effect of several Lewis acids on the reaction was studied, revealing a high *endo* selectivity with respect to the carbonyl group and a moderate π-diastereoselectivity using $BF_3 \cdot Et_2O$ as catalyst. The

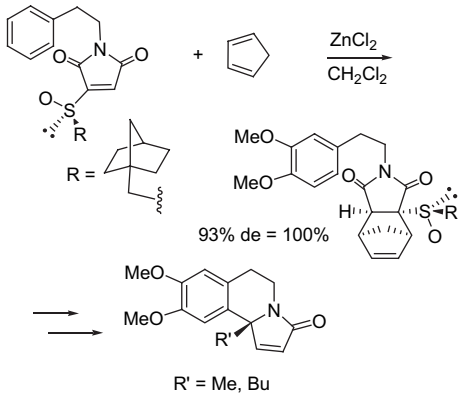
reactivity, as well as the *endo* selectivity, was both higher than those observed for the corresponding (*E*)-3-sulfinylacrylates.



Catalyst	R	Yield (%)	18/19/20/21	*endo*/*exo*	% de *endo*	% de *exo*
-	*n*-Pr	90	21/33/17/29	54/46	22	26
-	*i*-Pr	95	15/36/17/32	51/49	41	31
SiO_2	*n*-Pr	99	19/36/16/29	55/45	31	29
$LiClO_4$	*n*-Pr	95	20/35/16/29	55/45	27	29
$ZnBr_2$	*n*-Pr	97	32/45/09/14	77/23	17	23
$SnCl_4$	*n*-Pr	80	35/54/05/06	89/11	21	9
$SnCl_4$	*i*-Pr	82	37/52/06/05	89/11	17	9
$TiCl_4$	*n*-Pr	85	53/31/07/09	84/16	26	13
Et_2AlCl	*n*-Pr	86	60/25/11/04	85/15	41	47
$BF_3.Et_2O$	*n*-Pr	97	71/22/05/02	93/7	53	43
$BF_3.Et_2O$	*i*-Pr	98	60/24/10/06	86/14	42	25

Scheme 26. Diels–Alder reaction of (*E*)-γ-keto-α,β-unsaturated *p*-tolyl sulfoxides.

A stereoselective Diels–Alder reaction of a chiral sulfinylmaleimide with cyclopentadiene was one of the key steps in the enantioselective synthesis of dihydropyrrolo[2,1-*a*]isoquinolones.[73] The reaction, in the presence of $ZnCl_2$, afforded the corresponding sulfinylnorbornenimide in excellent yield and as a single diastereoisomer (Scheme 27).

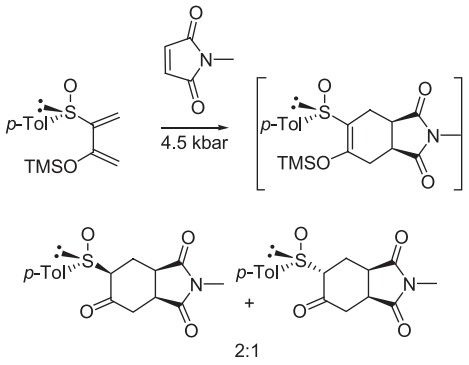


Scheme 27. Diels–Alder reaction of a chiral sulfinylmaleimide.

In addition, Aversa et al. have investigated the Diels–Alder reactivity of chiral sulfinyl dienophiles with a carbohydrate attached to the sulfoxide moiety. Unfortunately, their reactivity was very low (about 14 days were required for the reaction to be completed) and the cycloadducts spontaneously underwent regioselective elimination of sulfenic acid.[74]

Finally, among the large number of synthetic applications of chiral C_2-symmetric bis(sulfoxides) are their involvement in asymmetric Diels–Alder reactions.[75]

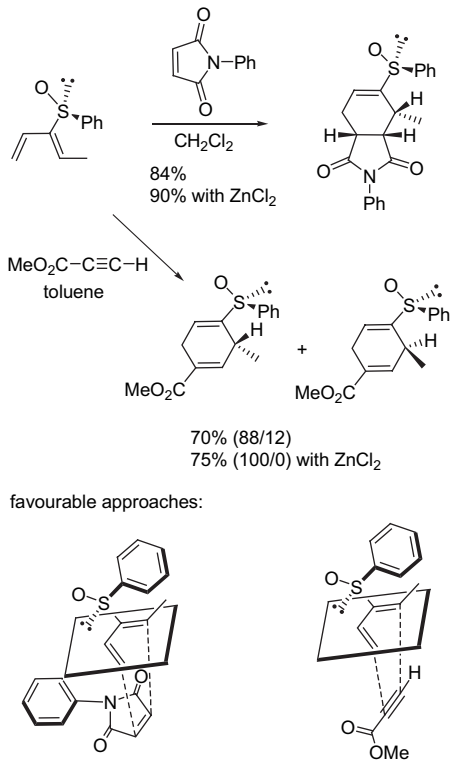
3.1.2. Sulfinyl dienes. Diels–Alder reactions of enantiomerically enriched sulfinyl dienes are less well documented in the literature, presumably due to the synthetic difficulties in preparing such molecules. Nevertheless, enantiomerically enriched sulfinyl 1,3-butadienes are frequently used to react with a variety of dienophiles that undergo Diels–Alder cycloaddition.[76] The use of a Lewis acid to restrict the rotation around the C–S bond has been used to improve the stereoselectivities. In 2000, Garcia Ruano et al. studied the behaviour of chiral 2-(*p*-tolylsulfinyl)-3-trimethylsilyloxybuta-1,3-diene in Diels–Alder reactions with cyclic dienophiles such as *N*-methylmaleimide.[77] The reaction provided a 2:1 diastereomeric mixture of cycloadducts (Scheme 28), from which the major stereoisomer was isolated in enantiomerically pure form by crystallisation. The results supported a cycloaddition occurring in a completely stereoselective manner, followed by a less diastereoselective Si–O bond cleavage.



Scheme 28. Diels–Alder reaction of (*S*)-2-(*p*-tolylsulfinyl)-3-trimethylsilyloxybuta-1,3-diene.

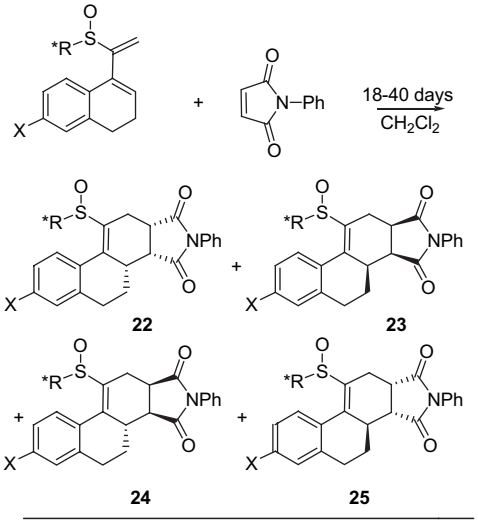
Similarly, chiral (*Z*)-1-methyl-2-(*p*-toluenesulfinyl)-1,3-butadiene has been condensed on *N*-phenylmaleimide and methyl propiolate, providing the expected corresponding cycloadducts with good to excellent regio-, stereo- and enantioselectivities, either under thermolysis or Lewis acid catalysis.[78] The stereospecific formation of a single stereoisomer from *N*-phenylmaleimide could be rationalised as shown in Scheme 29. The chiral dienyl sulfoxide preferred to adopt a conformation in which the S–O bond was parallel to the C=C bond, and *endo* addition of *N*-phenylmaleimide from the less hindered side of the diene (below the plane) would give the observed product. Since the Lewis acid-catalysed reaction gave the same product, it was assumed that similar steric arrangements were involved. The formation of two diastereoisomers from the thermal reaction with methyl propiolate indicated that the regioselectivity of the cycloaddition was dominated by the phenylsulfinyl group at C2 over the methyl group at C1. Preferential approach of methyl propiolate from the bottom face of the diene would give the major product. In the presence of the Lewis acid, this reaction led to only one stereoisomer, presumably by lowering the energy difference of HOMO (diene)−LUMO (dienophile) and thus making this reaction more stereoselective.

The use of enantiopure 2-sulfinylbuta-1,3-dienes in Diels–Alder reactions has allowed the development of a stereoselective approach to an azasteroidal skeleton.[79] Thus, Diels–Alder reactions of several chiral dihydro(vinyl)naphthalenes with *N*-phenylmaleimide occurred under thermal



Scheme 29. Diels–Alder reaction of chiral (*Z*)-1-methyl-2-(*p*-toluenesulfinyl)-1,3-butadiene.

conditions very slowly, but with notable stereoselectivity, giving, in each case, just one of the two *endo* adducts in high yield (Scheme 30). These results have opened the way for the setting up of stereocontrolled syntheses of further estrone-like compounds.

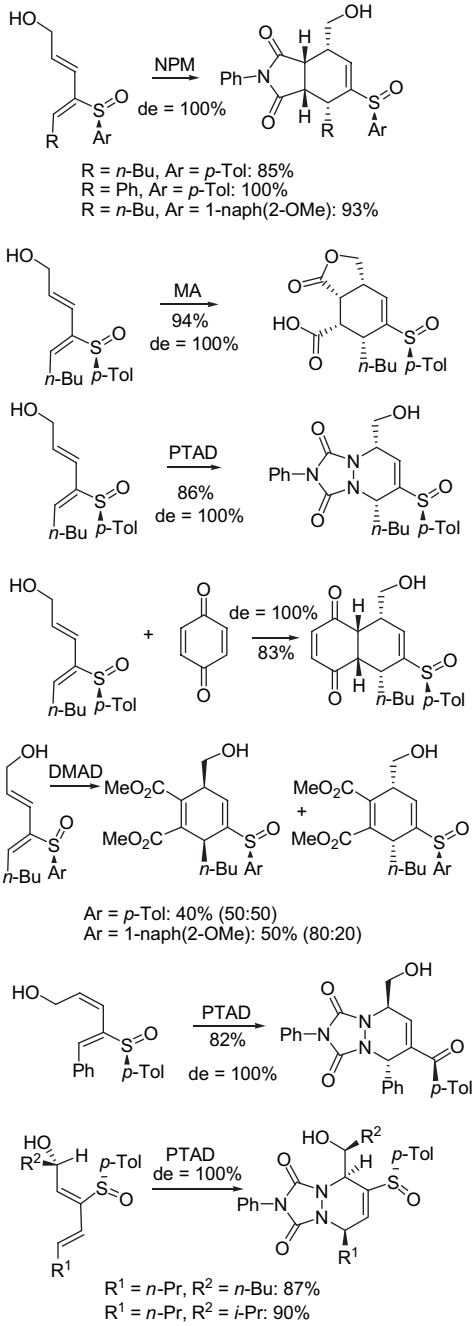


S*	R*	X	Yield (%)	*endo*	*exo*	Ratio
R	isoB	H	95	**22**	**24** + **25**	42:29:29
R	isoB	OMe	93	**22** + **23**	**24** + **25**	52:5:23:20
S	Born	OMe	95	**23**	**24** + **25**	67:19:14

S* : configuration at sulfur

Scheme 30. Synthesis of an azasteroidal skeleton via Diels–Alder reaction of chiral 2-sulfinylbuta-1,3-dienes.

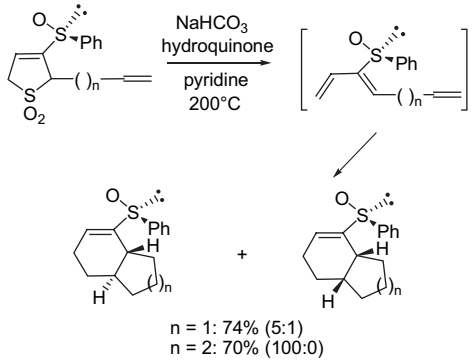
In 2005, de la Pradilla et al. reported highly diastereoselective Diels–Alder reactions of enantiopure sulfinyl-substituted 1-hydroxymethyldienes with various dienophiles.[80] Both hydroxy-2- and -3-sulfinyl dienes displayed highly π-face-selective Diels–Alder cycloadditions with dienophiles such as maleic anhydride (MA), phenyltriazolinedione (PTAD), *N*-phenylmaleimide (NPM), dimethyl acetylenedicarboxylate (DMAD) or *p*-benzoquinone, generating densely functionalised cycloadducts (Scheme 31).



Scheme 31. Diels–Alder reactions of chiral sulfinyl-substituted 1-hydroxymethyldienes.

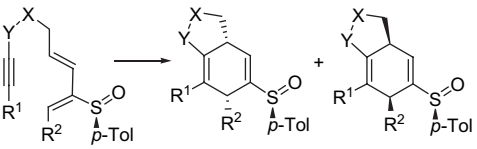
Both intermolecular and intramolecular Diels–Alder reactions involving chiral sulfoxides have been reported. As an example, Chou et al. have reported the intramolecular Diels–Alder reaction of a chiral sulfinyltriene intermediate, which

was generated in situ, providing the corresponding bicyclic products (Scheme 32).[78]



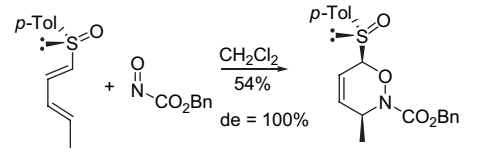
Scheme 32. Intramolecular Diels–Alder reaction of in situ-generated chiral sulfinyltrienes.

Dienynes generally require harsh thermal conditions to cycloadduct, which limit their applications in synthesis. De la Pradilla et al. have shown, however, that 2-sulfinylbutadienes tethered to unactivated alkynes underwent a facile thermal intramolecular Diels–Alder cycloaddition, often at room temperature, to produce cyclohexa-1,4-dienes with good selectivities (Scheme 33).[81] This strategy allowed the highly diastereoselective construction of a broad range of carbo- and heterocycles under exceptionally mild conditions, whilst preserving the valuable vinyl sulfoxide functionality.



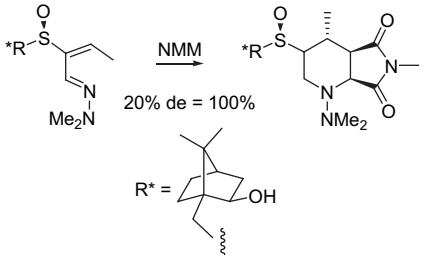
Scheme 33. Intramolecular Diels–Alder reaction of 2-sulfinylbutadienes.

Relatively few intermolecular and intramolecular hetero Diels–Alder reactions involving chiral sulfoxides give generally high stereoselectivities. Complete regioselectivity and stereoselectivity were, however, observed for the first asymmetric hetero Diels–Alder reaction of 1-sulfinyl dienes with acylnitroso derivatives such as benzyl nitrosoformate (Scheme 34).[82] The stereochemical course of the reaction could be explained by considering that the heterodienophile approached the less hindered face of diene that which supported the lone electron pair at sulfur, with the sulfinyl group in an *s*-trans arrangement with respect to C1═C2.



Scheme 34. Hetero Diels–Alder reaction of a 1-sulfinyldiene with a nitroso derivative.

In addition, a new approach towards chiral six-membered nitrogen heterocycles was developed by Aversa et al., on the basis of a hetero Diels–Alder reaction occurring between chiral (*E*,*E*)-2-[(1*S*)-isoborneol-10-sulfinyl]-2-butenal dimethylhydrazone and *N*-methylmaleimide (NMM).[83] This latter sulfoxide behaved as a 1-azabuta-1,3-diene, providing a unique cycloadduct with complete *endo* and facial selectivities (Scheme 35).

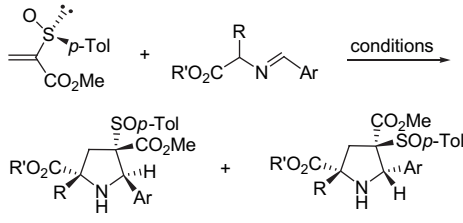


Scheme 35. Hetero Diels–Alder reaction of chiral (*E*,*E*)-2-[(1*S*)-isoborneol-10-sulfinyl]-2-butenal dimethylhydrazone.

Aversa et al. have also tested phenyl vinyl sulfide and ethyl vinyl ether as electron-rich dienophiles towards chiral (*E*)-3-[(1*S*)-isoborneol-10-sulfinyl]-1-phenyl-2-propen-1-one.[84] The reaction led to (4*S*,6*R*)-4-[(1*S*)-isoborneol-10-sulfinyl]-5,6-dihydro-2-phenyl-6-phenylthio-4*H*-pyran as the only cycloadduct among four possible diastereomers.

3.2. 1,3-Dipolar cycloaddition reactions

1,3-Dipolar cycloaddition involving a stereogenic centre or a chiral auxiliary on the dipole or the dipolarophile moiety is a useful tool for the regio- and stereoselective construction of five-membered heterocycles.[85] Most of the reported studies concern the use of acrylates as chiral dipolarophiles. Chiral vinyl sulfoxides, widely used as dienophiles, have been much less investigated as homochiral dipolarophiles.[59c] Several years ago, Garcia Ruano et al. initiated a research programme to explore the scope and limitations of vinyl sulfoxides in asymmetric 1,3-dipolar cycloadditions.[86] As an example, in 2002, this group reported the first 1,3-dipolar cycloaddition of azomethine ylides to vinyl sulfoxides such as methyl (*S*)-2-(*p*-tolylsulfinyl)acrylate (Scheme 36).[87] The

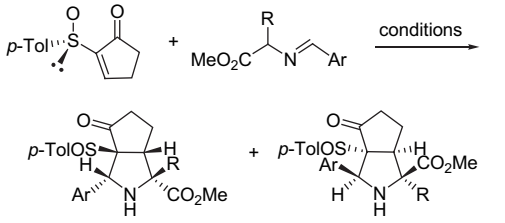


Ar	R	R'	Conditions	Yield (%)
Ph	H	Me	AgOAc/DBU/MeCN	13% + 36%
Ph	H	Me	AgOAc/DBU/THF	32% + 13%
Naph	H	Me	AgOAc/DBU/THF	50% + 8%
Naph	H	Me	AgOAc/DBU/MeCN	12% + 51%
Naph	Me	Me	AgOAc/DBU/MeCN	51% + 6%
Naph	Me	Et	AgOAc/DBU/MeCN	50% + 3%
Naph	Me	Et	AgOAc/DBU/THF	44% + 9%
Naph	Me	Et	AgOAc/NEt3/MeCN	11% + 48%

Scheme 36. Cycloaddition of azomethine ylides to sulfinylacrylates.

reaction evolved with complete regio- and *endo* selectivities, but, nevertheless, mixtures of two diastereoisomers (de 75–88%) resulting from the *anti* dipole/*s*-cis dipolarophile and *syn* dipole/*s*-trans dipolarophile approaches, respectively, were obtained. The stereoselectivity could, however, be controlled by using THF or MeCN as solvents. This new methodology represented a new entry into the synthesis of highly substituted pyrrolidines, which constitute the main building blocks of many alkaloids and pharmacologically active compounds.

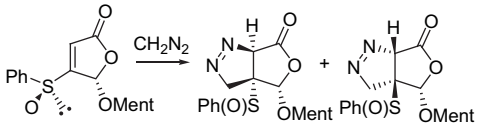
Similarly, azomethine ylides generated from imino esters could be condensed on (*S*)-2-*p*-tolylsulfinyl-2-cyclopentenone in a completely regio- and *endo* selective manner, but with a low facial selectivity, affording a mixture of two cycloadducts (Scheme 37).[88] When the ylides were prepared with LHMDS, only one diastereoisomer was obtained in almost quantitative yield. A nucleophilic addition/ring-closure process easily accounted for the stereochemical results.



Ar	R	Conditions	Yield (%)
Ph	H	AgOAc/DBU/MeCN	42% + 38%
2-Naph	H	AgOAc/DBU/MeCN	42% + 31%
2-Naph	Me	AgOAc/DBU/MeCN	34% + 33%
2-Naph	H	AgOAc/DBU/THF	19% + 19%
2-Naph	H	AgOAc/NEt_3/MeCN	20% + 18%
2-Naph	Me	LHMDS/THF	91% + < 2%
Ph	H	LHMDS/THF	89% + < 2%
Ph	Me	LHMDS/THF	91% + < 2%
2-Naph	H	LHMDS/THF	93% + < 2%

Scheme 37. Cycloaddition of azomethine ylides to (*S*)-2-*p*-tolylsulfinyl-2-cyclopentenone.

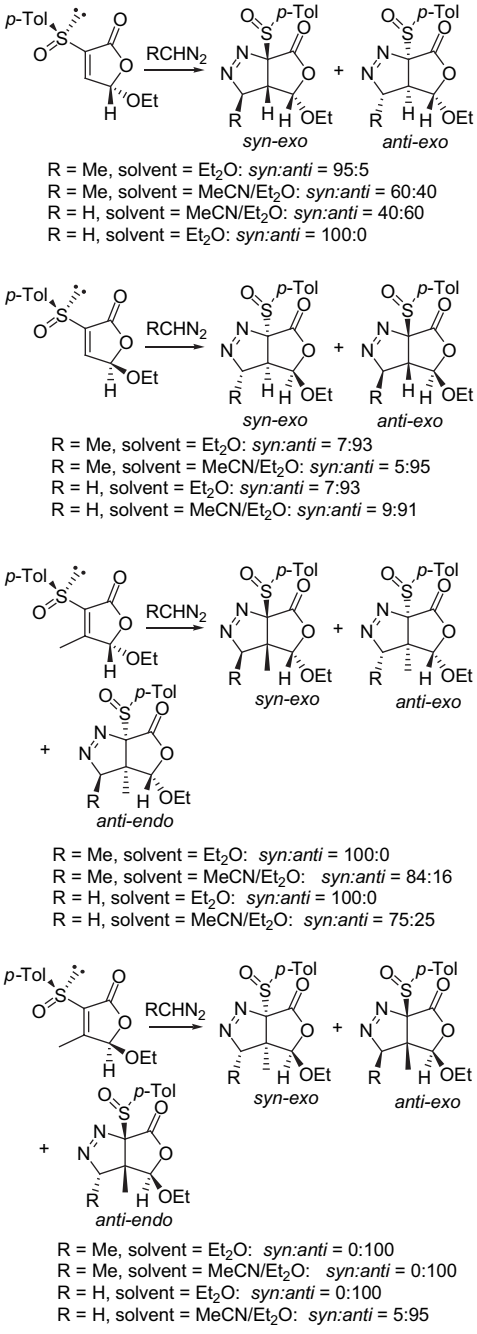
Diazoalkanes have also been submitted to asymmetric 1,3-dipolar cycloaddition in the presence of ($5S,S_S$)-5-[(1*R*)-menthyloxy]-4-phenylsulfinylfuran-2(5*H*)-ones, providing the corresponding pyrazolines resulting from the approach of the dipole to both diastereotopic faces of the dipolarophile (Scheme 38).[89] The reactions were completely regioselective, yielding only the adduct resulting from formation of the N_{dipole}–$C(3)_{furanone}$ bond.



80% de = 70%
with $ZnBr_2$: 79% de = 100%

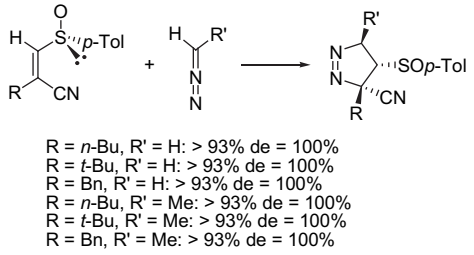
Scheme 38. Cycloaddition of ($5S,S_S$)-5-[(1*R*)-menthyloxy]-4-phenylsulfinylfuran-2(5*H*)-one to diazomethane.

The role of steric and electronic interactions in the stereocontrol of the asymmetric 1,3-dipolar reactions of 5-alkoxy-3-*p*-(*S*)-tolylsulfinylfuran-2(5*H*)-ones with diazoalkanes was studied in 2003 (Scheme 39).[90] It was demonstrated that these reactions evolved in high yields under mild conditions, affording bicyclic pyrazolines with complete regioselectivity, which could be modulated, becoming almost complete, with the solvent polarity. Electrostatic interactions between dipoles and the alkoxy group at C5 were, however, also significant in apolar solvents. The steric interactions between the substituents at diazoethane and at C4 of the furanone rings were the main reasons for the observed *exo* selectivity.



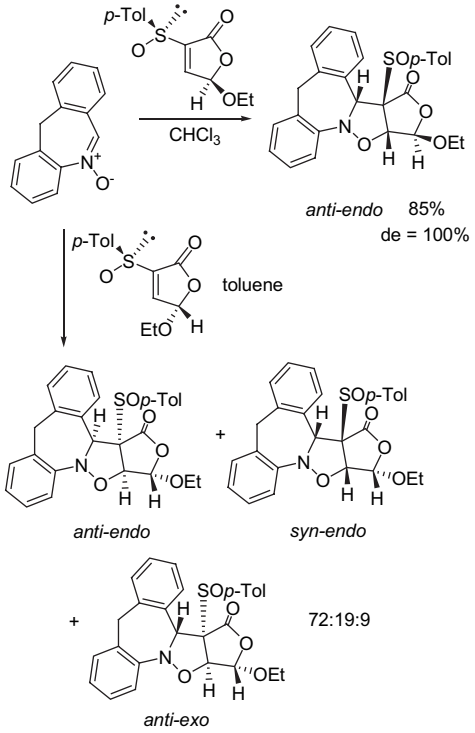
Scheme 39. Cycloaddition of chiral 5-alkoxy-3-*p*-(*S*)-tolylsulfinylfuran-2(5*H*)-ones to diazoalkanes.

In addition, the dipolarophilic reactivity of chiral (*Z*)-3-*p*-tolylsulfinylacrylonitriles has been evaluated with diazoalkanes, providing a new entry into chiral Δ^1-cyanopyrazolines, the structures of which are much less frequently reported in the literature than those of their corresponding Δ^2-analogues (Scheme 40).[91] Moreover, the asymmetric synthesis of pyrazolines has been studied mainly from cyclic and much less from acyclic alkenes. In each case, only one cycloadduct was formed in high yield under mild conditions, therefore evidencing a complete control of the regioselectivity and the *endo*/*exo* and π-facial selectivities.



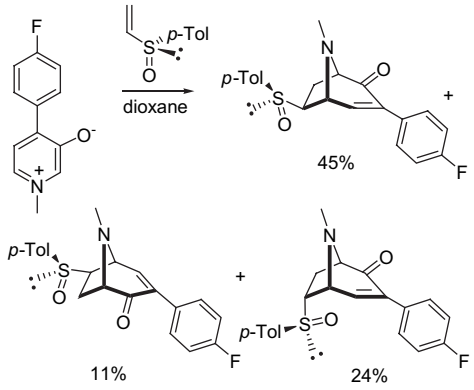
Scheme 40. Cycloaddition of chiral (*Z*)-3-*p*-tolylsulfinylacrylonitriles to diazoalkanes.

The biological activity of molecules containing a modified azepine ring has been intensively tested against various diseases. In the course of preparing new chiral pyrroloazepines and isoxazoloazepines, Rosario Martin et al. have developed asymmetric 1,3-dipolar reactions of 3-sulfinylfuran-2(5*H*)-ones with 11*H*-dibenzo[*b*,*e*]azepine 5-oxide, affording the corresponding furoisoxazoloazepines (Scheme 41).[92] In one case, the regio-, π-facial and *endo* selectivities were complete, yielding only one diastereoisomer.



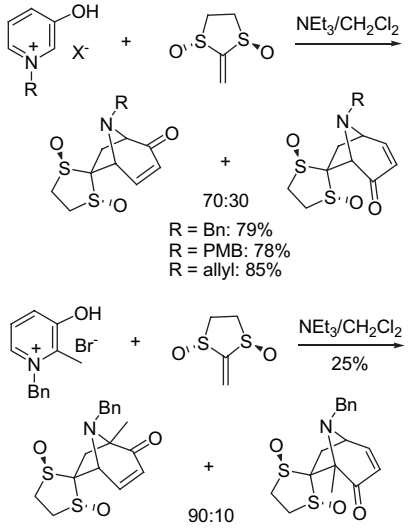
Scheme 41. Cycloaddition of 3-sulfinylfuran-2(5*H*)-ones to 11*H*-dibenzo[*b*,*e*]-azepine 5-oxide.

In 2000, the 1,3-dipolar cycloaddition methodology was applied to the synthesis of chiral 7-fluorotropanes as structural probes of the dopamine transporter.[93] The synthesis of these cocaine analogues was accomplished with complete regioselectivity through the reaction of an oxidopyridinium betaine with the chiral dipolarophile, (*R*)-*p*-tolyl vinyl sulfoxide (Scheme 42).



Scheme 42. Cycloaddition of an oxidopyridinium betaine to (*R*)-*p*-tolyl vinyl sulfoxide.

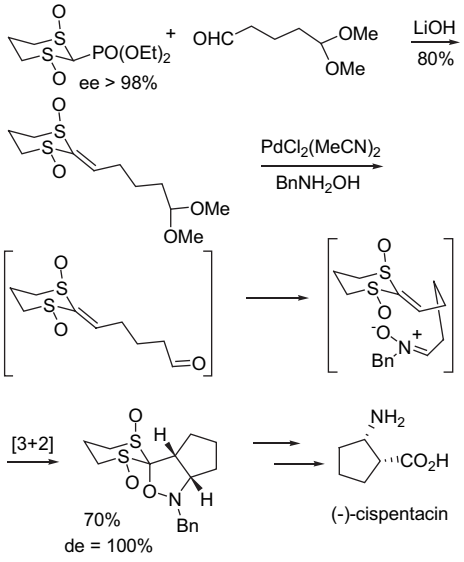
A range of 3-oxidopyridinium betaines bearing various substituents on nitrogen was found to react with the C2-symmetric vinyl sulfoxide, *trans*-2-methylene-1,3-dithiolane 1,3-dioxide, with total diastereoselectivity in the case of simple 3-oxidopyridinium betaines (Scheme 43).[94] These reactions were under kinetic control, although, over longer periods of time, the ratio of regioisomers changed, on account of the reversibility of the reaction. The regioselectivity in these reactions was moderate, although this could be improved by placing an additional substituent at the 2-position of the betaine.



Scheme 43. Cycloaddition of 3-oxidopyridinium betaines to chiral *trans*-2-methylene-1,3-dithiolane 1,3-dioxide.

In 2003, Aggarwal et al. reported the intramolecular 1,3-dipolar nitrone cycloaddition onto an enantiomerically pure ketene dithioacetal dioxide using a three-carbon tether, providing the corresponding 5,5-disubstituted isoxazolidine as a single diastereomer (Scheme 44).[95] In fact, such a process

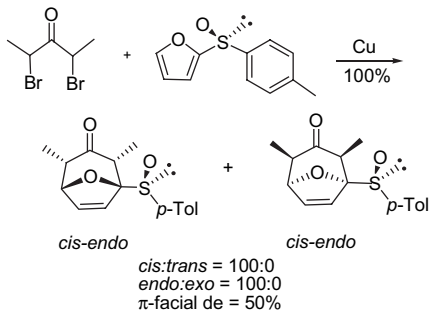
was the first example of an intramolecular cycloaddition in which a chiral ketene equivalent was employed. This reaction has been used as the key step in an asymmetric synthesis of the naturally occurring antibiotic, (−)-cispentacin. In addition, a first asymmetric synthesis of 4-amino-pyrrolidine-3-carboxylic acid has also been carried out using the intramolecular nitrone cycloaddition as the stereocontrolling step.



Scheme 44. Intramolecular nitrone cycloaddition of chiral ketene dithioacetal bis(sulfoxides).

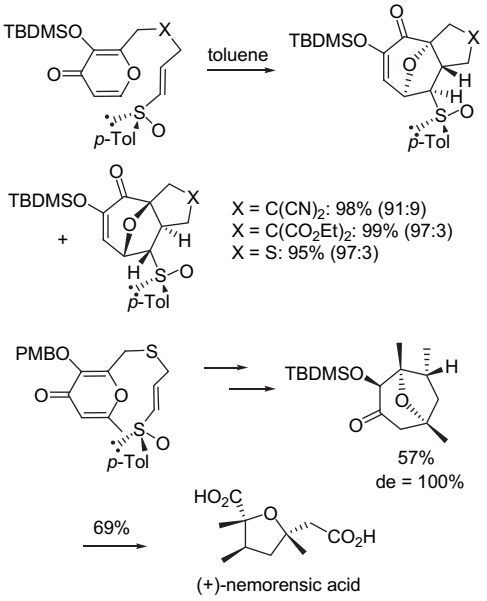
3.3. Other cycloaddition reactions

The [4+3] cycloaddition reaction between C2-functionalised furans and oxyallyl cations is an elegant and efficient method to synthesise polyfunctionalised cycloheptenes; these synthons facilitate the straightforward synthesis of molecules having a seven-membered ring. In 2002, Montana et al. reported [4+3] cycloaddition reactions of chiral C2-functionalised furans with a 2-oxyallyl cation in which the asymmetry was introduced by a chiral auxiliary such as a chiral sulfoxide on C2 of the furan (Scheme 45).[96] The process gave almost stereospecifically the cis-*endo* diastereoisomeric cycloadducts. The exclusive formation of the *endo* isomers could be due to the fact that the extended approach leading to the formation of the *exo* products was destabilised in favour of the compact approach, due to the presence of a bulky group on C2 of the diene.



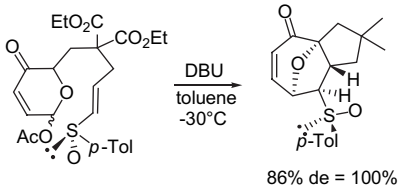
Scheme 45. [4+3] Cycloaddition of a chiral furyl sulfoxide to 2-oxyallyl cation.

A practical route to enantiopure 8-oxabicyclo[3.2.1]octane derivatives has been developed by Mascarenas et al. on the basis of a sulfinyl-directed diastereoselective [5+2] pyrone–alkene cycloaddition.[97] Thus, these authors have shown that the introduction of a homochiral *p*-tolylsulfinyl group at the trans-terminal position of an alkene accelerated its thermal [5C+2C] intramolecular cycloaddition to β-silyloxy-γ-pyrones and led to excellent levels of diastereodifferentiation (Scheme 46). The stereochemical outcome of the reaction could be rationalised by assuming that the alkenyl sulfoxide unit adopted an *s*-trans conformation in order to avoid repulsive dipole–dipole interactions with the pyrone, disfavouring the approach from the face of the sulfoxide displaying the *p*-tolyl group. In addition, these authors have shown that switching from a sulfinyl to a sulfonimidoyl group allowed the reversal of the sense of asymmetric induction.[97b] The utility of this methodology was demonstrated by its application to a concise synthesis of the naturally occurring pyrrolizidine alkaloid, (+)-nemorensic acid.[98]



Scheme 46. Sulfinyl-directed diastereoselective [5+2] pyrone-alkene cycloaddition.

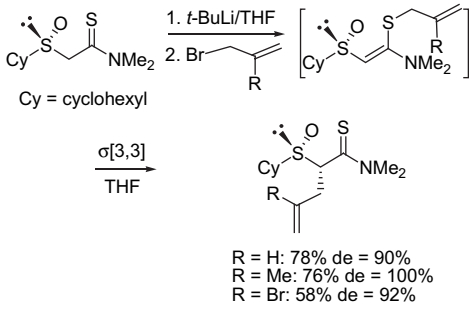
Another version of this reaction could be developed starting from the more classical oxidopyrilium-alkenes.[97c] A mild and fully diastereoselective intramolecular cycloaddition led to the formation of 6-acetoxy-3-pyranones (Scheme 47).



Scheme 47. Diastereoselective [5+2] acetoxypyrone-alkene cycloaddition.

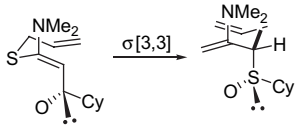
The Claisen rearrangement is a powerful reaction for the construction of complex molecules including natural products and biologically active molecules.[99] Metzner et al. have developed a new version of this reaction, in which the absolute and relative stereochemistries were directed

by a sulfinyl group, located in an adjacent position to the pericyclic [3,3] sigmatropic nucleus.[100] Thus, ketene aminothioacetals bearing an enantiopure vinylic alkylsulfinyl substituent underwent a Claisen rearrangement upon heating at THF reflux to afford α-sulfinyl γ-unsaturated thioamides (Scheme 48). In this transposition, which needed heating to be accomplished, an unexpected facile sulfenic acid elimination was often observed. In order to avoid this problem, Metzner et al. replaced the oxygen atom of the Claisen pericyclic nucleus by a sulfur atom, leading to an acceleration of the rearrangement.[100] A second way to modulate this elimination was to use a cyclohexyl group linked to sulfur. With all substrates, the asymmetric induction of the sulfinyl group was excellent (de≥90%).



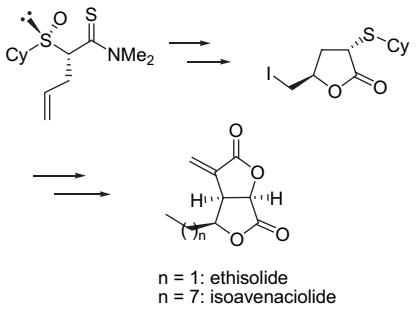
Scheme 48. Thio-Claisen rearrangement of chiral allyl ketene aminothioacetals.

In order to explain the stereochemical course of the [3,3] sigmatropic transposition, an electronic model was proposed as an extension of the Felkin Anh model (Scheme 49). The allyl moiety (electrophilic) approached the keteneaminothioacetal bond (nucleophilic) with substituents oriented on the chiral sulfur atom so that placing the most electron-donating group in an antiperiplanar position maximised the orbital overlap. The oxygen atom (linked to sulfur) occupied the inside allylic position, and the large cyclohexyl moiety the outside position.



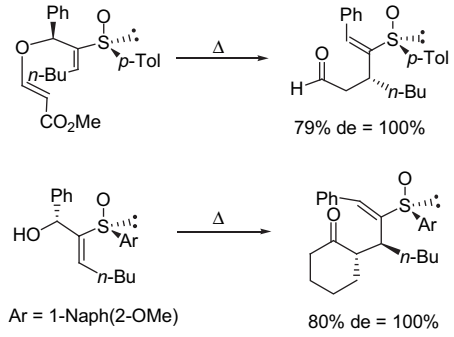
Scheme 49. Stereochemical course of the Claisen rearrangement.

The easy access to this attractive, small, functionalised chiral synthon was applied to the synthesis of natural bis(lactones) such as ethisolide and isoavenaciolide (Scheme 50).



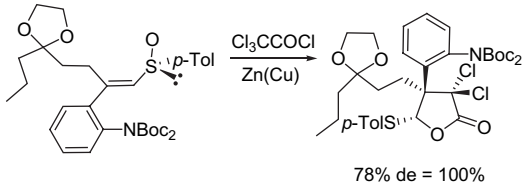
Scheme 50. Synthesis of ethisolide and isoavenaciolide.

In 2002, the first examples of Claisen rearrangements of substrates bearing a sulfinyl functionality at C5 were described, allowing for the creation of up to two asymmetric centres (Scheme 51).[101]



Scheme 51. Claisen rearrangements of substrates bearing sulfinyl functionality at C5.

A [3,3]-sigmatropic rearrangement of a chiral vinyl sulfoxide with in situ-generated dichloroketene was the key step of a total synthesis of (+)-aspidospermidine.[102] This ketene lactonisation reaction afforded the corresponding chiral dichlorolactone as a single diastereoisomer (Scheme 52).



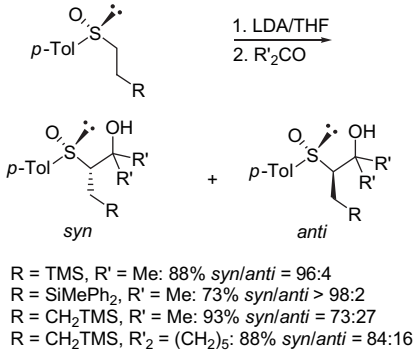
Scheme 52. Asymmetric ketene lactonisation reaction.

4. Reactions of sulfoxide-stabilised carbanions

4.1. Unconjugated addition reactions

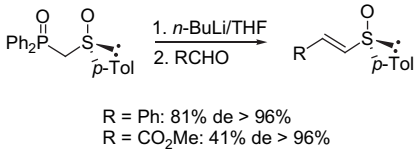
The ability of sulfoxides to stabilise a negative charge on an adjacent carbon atom has prompted the development of synthetic procedures based on optically active α-sulfinyl carbanions.[103] The use of chiral sulfoxide-stabilised carbanions for asymmetric carbon–carbon bond formation via alkylation, or addition to carbonyl and activated C=C double bonds, has been extensively studied over the past two decades. Deprotonation of the α-carbon of the sulfoxide requires a strong base such as $LiNH_2$, LDA, *n*-BuLi, LiHMDS or a Grignard reagent. High stereoselectivity usually requires steric hindrance in the vicinity of the α-carbon of the sulfoxide and the use of an electrophile with a bulky group. Condensations of α-sulfinyl carbanions with aldehydes provide a useful method for generating 1,2-asymmetry, as well as for the construction of 1,3-asymmetric relationships in acyclic systems. If optically active sulfoxides such as methyl *p*-tolyl sulfoxide give a poor diastereoselectivity when such an α-sulfinyl carbanion is added to a carbonyl, the presence of another function such as an ester, sulfide or amide, which has a chelating effect in the transition state, makes optically active α-sulfinyl esters, sulfides or amides very useful in asymmetric aldol-type condensations. In 2000, Toru et al. demonstrated the stereoselectivity of the reaction of α-sulfinyl carbanions derived from chiral 2-(trialkylsilyl)ethyl sulfoxides with ketones (Scheme 53).[104]

Interaction between the silicon in the trialkylsilyl group and the carbonyl oxygen in the nucleophiles was postulated to stabilise the transition state, leading preferably to the *syn* diastereoisomers. This novel silicon–oxygen interaction was supported by an MO calculation study.



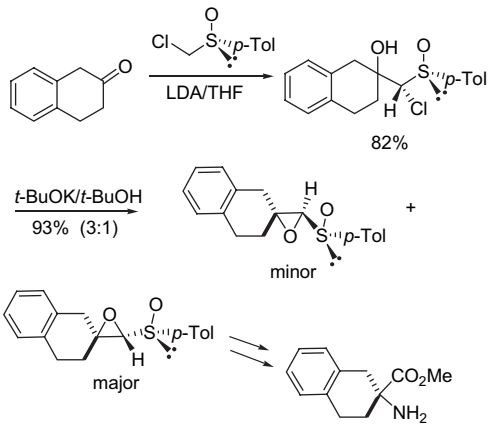
Scheme 53. Reaction of chiral 2-(trialkylsilyl)ethyl sulfoxides with ketones.

In the course of preparing new (*E*)-vinyl sulfoxides by the Horner–Wittig reaction, van der Gen et al. have shown that the use of (*S*)-diphenyl(*p*-tolylsulfinylmethyl)phosphane oxide allowed the synthesis of chiral (*E*)-vinyl sulfoxides (Scheme 54).[105]



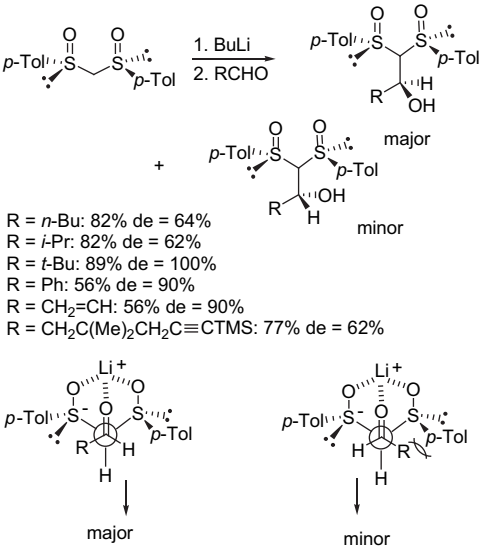
Scheme 54. Horner–Wittig synthesis of (*S*)-(*E*)-vinyl tolyl sulfoxides.

In 2005, Satoh et al. developed a novel synthesis of α-quaternary α-amino acid methyl esters from ketones via sulfinyloxiranes. Starting from β-tetralone and (*R*)-chloromethyl *p*-tolyl sulfoxide, an asymmetric synthesis of optically pure (*R*)-methyl 2-aminotetraline-2-carboxylate was performed in good overall yields.[106] As depicted in Scheme 55, the reaction of β-tetralone with the lithium α-sulfinyl carbanion generated from (*R*)-chloromethyl *p*-tolyl sulfoxide and LDA in THF gave the intermediate chloride as a mixture of two diastereomers. Without separation, this mixture was treated with *t*-BuOK to afford a 3:1 mixture of sulfinyloxiranes. The separated major product was further converted into the expected (*R*)-methyl 2-aminotetraline-2-carboxylate.



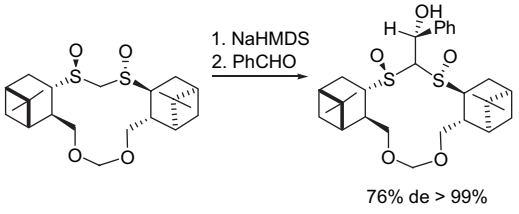
Scheme 55. Synthesis of (*R*)-methyl 2-aminotetraline-2-carboxylate.

The chemistry of C_2-symmetric bis(sulfoxides) has been widely studied by Malacria et al. and, in particular, their condensation onto carbonyl derivatives.[75] Thus, the diastereoselectivity of the alkylation of the lithium anion of (*S*,*S*)-bis-*p*-tolylsulfinylmethane with aldehydes was examined.[107] The reaction proved to be fairly diastereoselective, even for simple alkyl aldehydes, and not only for aromatic aldehydes, as found for cyclic disulfoxides.[108] Scheme 56 depicts the most favourable approach involving a chelated transition state in which nonbonding interactions between the *p*-tolyl group of the anion and the R group of the aldehyde are minimised.



Scheme 56. Reaction of anion of (*S*,*S*)-bis-*p*-tolylsulfinylmethane with acyclic aldehydes.

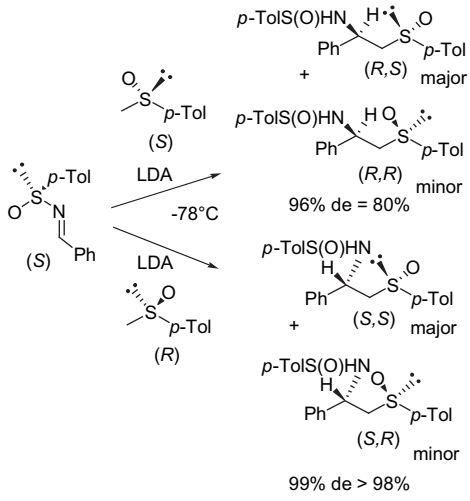
An efficient preparation of a myrtenal-derived bis-sulfoxide was reported in 2005 by Zepeda et al.[109] The utility of this *trans* bis-sulfoxide as a chiral acyl donor was explored by condensing its derived anion with benzaldehyde in THF, giving the corresponding carbinol with complete diastereoselectivity (Scheme 57). The stereochemical outcome of the reaction was explained by a reasonable chair-like six-membered transition state, in which the axial-like arrangement of the phenyl group, which minimised steric interactions with the β-oxygen of the nonchelated sulfoxide, could be appreciated. Accordingly, it could be inferred that nucleophilic addition by the *si* face was disfavoured.



Scheme 57. Reaction of anion of a myrtenal-derived bis-sulfoxide with benzaldehyde.

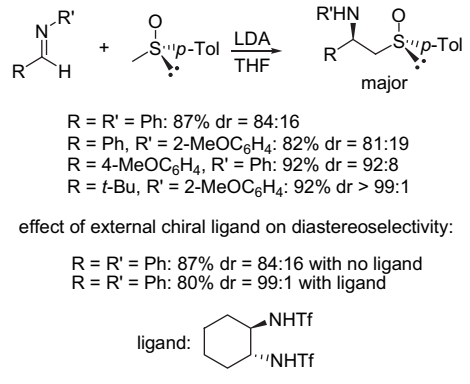
There are few reports on chiral sulfoxide anion addition to imines. The reaction of chiral α-sulfinyl anions with imines has been reported to proceed with better diastereoselectivity for simple systems than the analogous reactions

on aldehydes.[110] In 2000, Garcia Ruano et al. reported the addition of the lithium anions derived from (*R*)- and (*S*)-methyl and -ethyl *p*-tolyl sulfoxides to (*S*)-*N*-benzylidene-*p*-toluenesulfinamide, providing an easy access route to enantiomerically pure β-(*N*-sulfinyl)amino sulfoxides (Scheme 58).[111] Stereoselectivity could be achieved when the configurations at the sulfur atoms of the two reagents were opposite, thus resulting in only one diastereoisomer, even for the case in which two new chiral centres were created. The *N*-sulfinyl group primarily controlled the configuration of the carbon bonded to the nitrogen, whereas the configuration of the α-sulfinyl carbanion seemed to be responsible for the level of asymmetry induction, as well as for the configuration of the new stereogenic C–SO carbon, in the reactions with ethyl *p*-tolyl sulfoxides. This methodology constituted one of the best methods for obtaining enantiomerically pure β-amino sulfoxides.



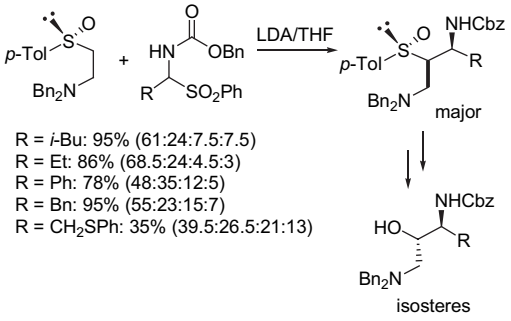
Scheme 58. Reaction of α-sulfinyl carbanions with (*S*)-*N*-sulfinimines.

In 2003, Tanner et al. revisited the diastereoselective addition of α-metallated methyl tolyl sulfoxides to imines recently studied by several groups,[112] showing that up to >98% des could be obtained under conditions of kinetic control (short reaction time, low temperature).[113] Moreover, these authors demonstrated that the use of external chiral ligands such as C_2-symmetric bis(sulfonamide) ligands enhanced the diastereoselectivity of otherwise moderately selective reactions (Scheme 59).



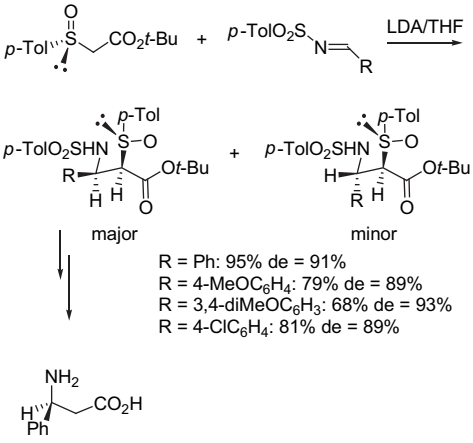
Scheme 59. Reaction of α-metallated methyl tolyl sulfoxides with imines.

In 2004, Zanda et al. reported a novel synthesis of chiral hydroxyethylamine dipeptide isosteres on the basis of the Mannich-type reaction of a lithiated β-sulfinylethylamine with *N*-Cbz-imines generated in situ from α-amino-sulfones (Scheme 60).[114] The 2-sulfinyl-1,3-diamines thus formed could be converted into an epimer of saquinavir, an inhibitor of HIV protease. In that context, a similar methodology was also applied to the synthesis of both enantiomers of natural statine, exploiting an α-lithiated alkylsulfoxide as a chiral α-hydroxyalkyl carbanion equivalent.[115]



Scheme 60. Synthesis of hydroxyethylamine isosteres.

In 2001, Bhat et al. developed an elegant synthesis of β-aminophenylpropionic acid, based on the stereoselective condensation of *tert*-butyl (*R*)-*p*-tolylsulfinylacetate with *N*-(benzylidene)toluene-4-sulfonamides in the presence of LDA (Scheme 61).[116]

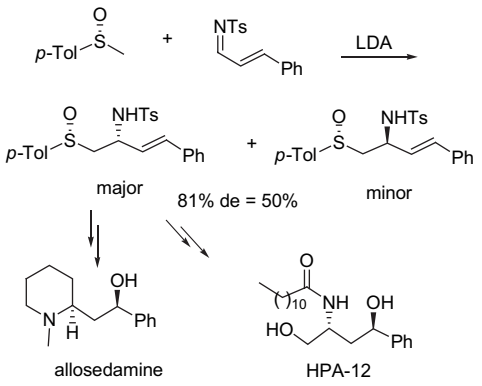


Scheme 61. Synthesis of chiral β-aminophenylpropionic acid.

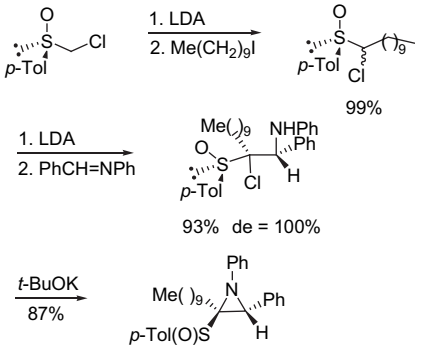
The diastereoselective addition of the carbanion derived from (*S*)-*tert*-butyl phenylmethylsulfoxide to imines derived from α,β-unsaturated aldehydes such as cinnamaldehyde was the key step of a total synthesis of biologically active (−)-allosedamine and HPA-12 (Scheme 62).[117]

In addition, Satoh et al. have prepared various chiral sulfinylaziridines by condensation of the anion of *p*-tolyl sulfoxides onto imines, followed by treatment with potassium *tert*-butoxide, as depicted in Scheme 63.[118]

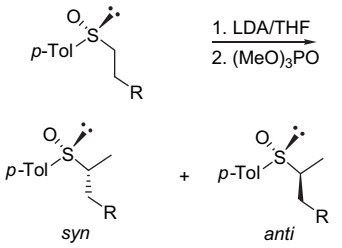
α-Sulfinyl carbanions have been condensed onto various other electrophiles such as trimethyl phosphate, which gave excellent diastereoselectivities in the case of carbanions derived from chiral 2-(trialkylsilyl)ethyl sulfoxides (Scheme 64).[104]



Scheme 62. Reaction of anion of (*S*)-*tert*-butyl phenylmethylsulfoxide with unsaturated imine.



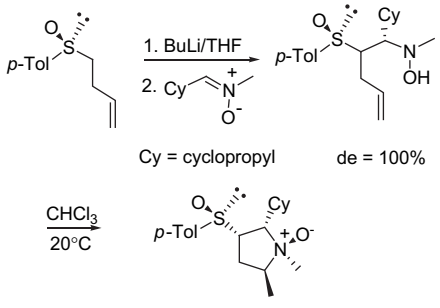
Scheme 63. Synthesis of a chiral sulfinylaziridine.



R = TMS: 94% *syn*/*anti* = 96:4
R = $SiMePh_2$: 69% *syn*/*anti* = 94:6
R = $SiMePh_2$: 69% *syn*/*anti* = 94:6
R = Me: 64% *syn*/*anti* = 88:12
R = CH_2TMS: 80% *syn*/*anti* = 83:17
R = *t*-Bu: 68% *syn*/*anti* = 19:81

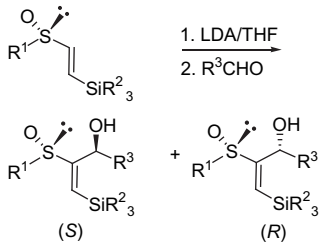
Scheme 64. Methylation reaction of chiral *p*-tolyl sulfoxides.

Knight et al. have shown that the chiral lithiated homoallylic sulfoxide depicted in Scheme 65 added smoothly to an aldonitrone to give a single diastereoisomer of the corresponding unsaturated hydroxylamine, which then underwent a reverse Cope cyclisation to give the corresponding highly substituted pyrrolidine-*N*-oxide in a stereocontrolled manner.[119]



Scheme 65. Synthesis of a chiral pyrrolidine-*N*-oxide.

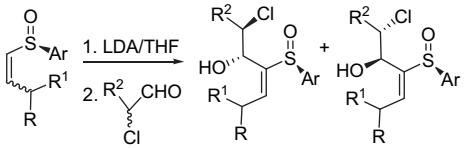
Nucleophilic addition of α-carbanions of enantiomerically enriched vinyl sulfoxides is also useful in the construction of new stereogenic centres. Several authors have studied the reaction of the α-vinyl anions derived from chiral vinyl sulfoxides with aldehydes. As an example, Toru et al. have prepared chiral alcohols by condensation of lithiated silylvinyl sulfoxides onto aldehydes (Scheme 66).[120]



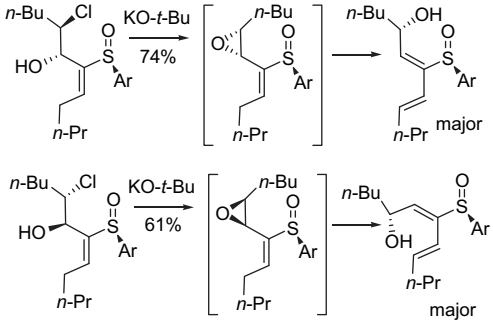
R^1 = *p*-Tol, SiR^2_3 = TMS, R^3 = Ph: 88% (*S*):(*R*) = 45:55
R^1 = *p*-Tol, SiR^2_3 = TMS, R^3 = Me: 82% (*S*):(*R*) = 68:32
R^1 = *p*-Tol, SiR^2_3 = TMS, R^3 = n-C_5H_{11}: 93% (*S*):(*R*) = 73:27
R^1 = *p*-Tol, SiR^2_3 = TMS, R^3 = *i*-Pr: 92% (*S*):(*R*) = 68:32
R^1 = *p*-Tol, SiR^2_3 = TMS, R^3 = *t*-Bu: 71% (*S*):(*R*) = 76:24
R^1 = *p*-Tol, SiR^2_3 = $SiPh_2Me$, R^3 = n-C_5H_{11}: 77% (*S*):(*R*) = 69:31
R^1 = *p*-Tol, SiR^2_3 = $SiPh_3$, R^3 = n-C_5H_{11}: 70% (*S*):(*R*) = 66:34
R^1 = *p*-Tol, SiR^2_3 = $SiPh_3$, R^3 = *t*-Bu: 74% (*S*):(*R*) = 67:33
R^1 = *t*-Bu, SiR^2_3 = TMS, R^3 = Ph: 88% (*S*):(*R*) = 34:66
R^1 = *t*-Bu, SiR^2_3 = TMS, R^3 = n-C_5H_{11}: 82% (*S*):(*R*) = 29:71
R^1 = *p*-Tol, SiR^2_3 = TMS, R^3 = n-C_5H_{11}: 70% (*S*):(*R*) = 37:63
R^1 = *p*-Tol, SiR^2_3 = $SiPh_2Me$, R^3 = n-C_5H_{11}: 65% (*S*):(*R*) = 32:68

Scheme 66. Reaction of chiral silylvinyl sulfoxides with aldehydes.

Similar stereoselectivities were observed for the preparation of chiral α′-hydroxy vinyl sulfoxides through lithiation followed by addition to aldehydes of various alkylvinyl sulfoxides.[121] In the same context, sulfur-directed synthesis of enantiopure hydroxy 2-sulfinylbutadienes was reported in 2004.[122] It was shown that the treatment of sulfinyl



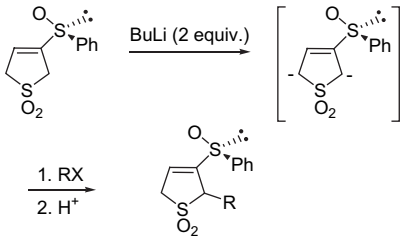
Ar = *p*-Tol, R = *n*-Pr, R^1 = H, R^2 = *n*-Bu: 74% (46:54)
Ar = *p*-Tol, R = Me, R^1 = H, R^2 = Bn: 58% (48:52)
Ar = *p*-Tol, R = *i*-Pr, R^1 = H, R^2 = Bn: 58% (58:42)
Ar = *p*-Tol, R = Me, R^1 = Me, R^2 = *n*-Bu: 73% (52:48)
Ar = *p*-Tol, R = *n*-Pr, R^1 = H, R^2 = *i*-Pr: 75% (56:44)



Scheme 67. Sulfur-directed synthesis of chiral hydroxy 2-sulfinylbutadienes.

chlorohydrins with KO-*t*-Bu in THF generated epoxy vinyl sulfoxides that underwent an efficient base-induced rearrangement to generate chiral hydroxy 2-sulfinyl dienes (Scheme 67). This novel process took place with high chemo- and stereoselectivity. The chirality at sulfur effectively controlled the geometry of the trisubstituted alkene.

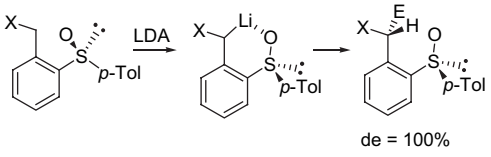
On the other hand, the deprotonation of the cyclic chiral 3-phenylsulfinyl-3-sulfolene depicted in Scheme 68 and its subsequent reaction with alkyl halides gave regiospecifically the C2-alkylated products.[78] The regiospecific alkylation could be explained by a first deprotonation at the most acidic C5 position, followed by a second deprotonation at C2. The reaction with allyl bromide yielded only one enantiomer, whereas the reactions with other electrophiles gave a mixture of two diastereomers.



RX = MeI: 88% (*S*,*S*)/(*S*,*R*) = 6:1
RX = allylBr: 84% (*S*,*S*)/(*S*,*R*) = 100:0
RX = BnBr: 75% (*S*,*S*)/(*S*,*R*) = 5:1
RX = CH_2=$CH(CH_2)_3$I: 80% (*S*,*S*)/(*S*,*R*) = 4:1
RX = CH_2=$CH(CH_2)_4$I: 82% (*S*,*S*)/(*S*,*R*) = 4:1

Scheme 68. Reaction of a chiral 3-phenylsulfinyl-3-sulfolene with alkyl halides.

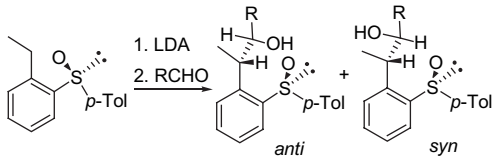
Garcia Ruano et al. have demonstrated that enantiopure *ortho*-sulfinyl groups could stabilise benzyllithium carbanions and promote diastereoselective reactions with electrophiles by a 1,4-induction.[123] This possibility was firstly evaluated for (*S*)-2-ethylphenyl *p*-tolyl sulfoxide and (*S*)-2-(triisopropylsiloxymethyl)phenyl *p*-tolyl sulfoxide, the corresponding carbanions of which were alkylated with various electrophiles (Scheme 69). With simple electrophiles such as ethyl chloroformate or acetone, the new benzylic stereogenic centres were always generated in a highly diastereoselective manner and with the same induction, independent of the electrophile.



Electrophile = $ClCO_2Et$, E = CO_2Et, X = Me: 75%
Electrophile = $ClCO_2Et$, E = CO_2Et, X = OTIPS: 75%
Electrophile = MeCOMe, E = CO_2Et, X = Me: 81%
Electrophile = MeCOMe, E = CO_2Et, X = OTIPS: 78%

Scheme 69. Enantioselective generation of benzylic stereocentres mediated by a remote sulfoxide.

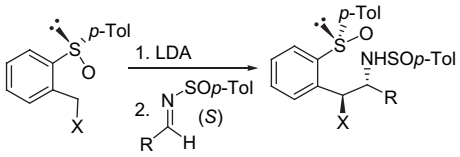
In contrast, when additional stereogenic centres were created, the stereoselectivity of the latter process was electrophile dependent. Thus, when aldehydes were used as electrophiles, the diastereoselectivity of the reaction was dependent upon the nature of the aldehyde.[124] Reactions from aliphatic and aromatic aldehydes containing electron-donating groups were completely stereoselective at C2, but exhibited a moderate stereoselectivity at C1, which was mainly related to the aliphatic or aromatic character of the aldehydes (Scheme 70). After separation by chromatography, a further desulfinylation allowed the obtention of enantiomerically pure 1-alkyl (or aryl)-2-phenyl-1-propanols.



R = Ph: 65% *anti*:*syn* = 85:15
R = (p-$OMeC_6H_4$): 80% *anti*:*syn* = 84:16
R = (2-Naph): 62% *anti*:*syn* = 85:15
R = (1-Naph): 73% *anti*:*syn* = 88:12
R = (2,6-$Me_2C_6H_3$): 70% *anti*:*syn* = 67:33
R = *n*-Bu: 87% *anti*:*syn* = 37:63
R = *i*-Pr: 75% *anti*:*syn* = 29:71
R = *t*-Bu: 58% *anti*:*syn* = 24:76

Scheme 70. Reaction of chiral *ortho*-sulfinyl benzyl carbanions with aldehydes.

The scope of this reaction could be extended to other electrophiles such as *N*-*p*-toluenesulfinylimines. Addition of lithium (*R*)-*ortho*-(*p*-toluenesulfinyl)benzylic carbanions took place with complete stereoselectivity, yielding useful chiral 1,2-diaryl (and 1-alkyl-2-aryl) ethyl and propylamines (Scheme 71).[125] Similarly, enantiomerically pure *anti*-1,2-amino alcohol derivatives could be achieved by the reaction of prochiral oxygenated 2-*p*-tolylsulfinylbenzyl carbanions with *N*-sulfinylimines bearing the same configuration at sulfur (Scheme 71).[126]

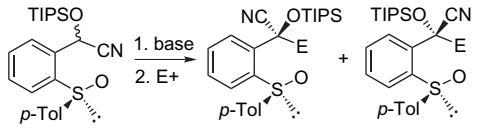


X = OTIPS, R = Ph: 81% de > 98%
X = OTIPS, R = *o*-BrC_6H_4: 71% de > 98%
X = OTIPS, R = *p*-$MeOC_6H_4$: 78% de > 98%
X = OTIPS, R = *p*-CNC_6H_4: 74% de > 98%
X = OTIPS, R = *p*-ClC_6H_4: 76% de > 98%
X = OTIPS, R = 2-py: 77% de > 98%
X = OTIPS, R = 2-Naph: 68% de > 98%
X = OTIPS, R = *n*-Bu: 74% de > 98%
X = OTIPS, R = *i*-Pr: 72% de > 98%
X = Me, R = Ph: 82% de > 98%
X = Me, R = *o*-BrC_6H_4: 87% de > 98%
X = Me, R = *p*-$MeOC_6H_4$: 84% de > 98%
X = Me, R = *p*-CNC_6H_4: 60% de > 98%
X = Me, R = 2-Naph: 75% de = 78%
X = Me, R = *n*-Bu: 85% de > 98%
X = Me, R = *i*-Pr: 88% de > 98%
X = Me, R = *t*-Bu: 89% de > 98%
X = Me, R = Bn: 88% de > 98%

Scheme 71. Reaction of chiral *ortho*-sulfinyl benzyl carbanions with *N*-sulfinylimines.

Finally, optically pure functionalised cyanohydrins derived from 1-[2-(*p*-tolylsulfinyl)phenyl] ethanone could be obtained by the reaction of 2-*p*-tolylsulfinylbenzaldehyde-derived cyanohydrins with bases and further treatment with suitable electrophiles.[127] Thus, this remote 1,4-asymmetric

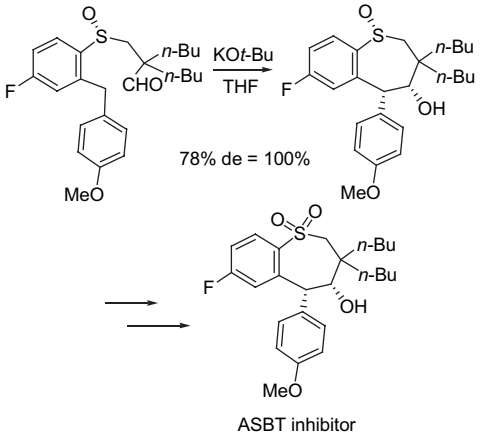
induction process constituted a new strategy for preparing chiral ketone-derived cyanohydrins, starting from the much more readily available aldehyde-derived cyanohydrins (Scheme 72).



Base	Electrophile	dr (Yield %)
KHMDS	$ClCO_2Me$	> 98:2 (85)
KHMDS	ClCOMe	> 98:2 (83)
KHMDS	allylBr	> 98:2
LiHMDS	$ClCO_2Me$	> 98:2
LiHMDS	ClCOMe	> 98:2
LiHMDS	$CH_2=N^+Me_2\ I^-$	> 98:2 (74)
LiHMDS	BnBr	> 98:2 (77)
LiHMDS	allylBr	> 98:2 (89)
K/18-crown-6	MeI	88:12 (76)
K/18-crown-6	EtOTf	87:13 (73)

Scheme 72. Quaternisation of cyanohydrins derived from 2-*p*-tolylsulfinylbenzaldehyde.

Stereoselective intramolecular additions of α-sulfinyl carbanions are also present in the literature such as intramolecular aldol condensation involved in the formation of a benzothiepine ring, in which the chirality of the sulfoxide controlled the configurations of two new stereogenic centres.[38] This strategy was applied to the synthesis of the apical sodium co-dependent bile acid transporter (ASBT) inhibitor depicted in Scheme 73. The cyclisation providing a single diastereomer was shown to be thermodynamically controlled. A metal chelate between the sulfoxide oxygen and the alkoxide oxygen was proposed to rationalise the configuration of the newly formed stereogenic centre at C4. The cis configuration was lower in energy, due to unfavourable steric interactions berween the C5-aryl and C3-butyl groups in the trans configuration. Thus, the configuration of the chiral sulfoxide determined the absolute configuration at both of the newly formed stereogenic centres.

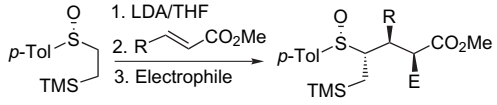


Scheme 73. Synthesis of an ASBT inhibitor via intramolecular aldol reaction.

Other intramolecular reactions of α-sulfinyl vinylic carbanions have also been reported such as those described by Tanaka et al., allowing a novel route to chiral 1-cycloalkenyl sulfoxides.[128]

4.2. Conjugated addition reactions

Michael addition of enantiomerically enriched sulfinyl carbanions to α,β-unsaturated carbonyl compounds is a very useful method for stereoselective C–C bond formation. Toru et al. have discovered that the reaction of chiral *p*-tolyl 2-(trimethylsilyl)ethyl sulfoxide with LDA and acetone gave the *syn*-isomer in high yield and 92% de.[104] It was postulated that a novel Si–O interaction between the trimethylsilyl and the carbonyl group, which stabilised the transition state of the nucleophilic addition, accounted for the *syn*-isomer formation. Conjugated addition reactions of the carbanion of a chiral β-silylethyl sulfoxide with α,β-unsaturated esters afforded the conjugate addition products as a single diastereoisomer. Moreover, high diastereoselectivities were also observed for the Michael addition reactions of the same carbanion with α,β-unsaturated esters, where the enolate intermediates were subsequently trapped with alkyl halides or aldehydes (Scheme 74).[129] In general, the trapping reactions took place in good yields, except for the reaction involving methyl acrylate, because of polymerisation.

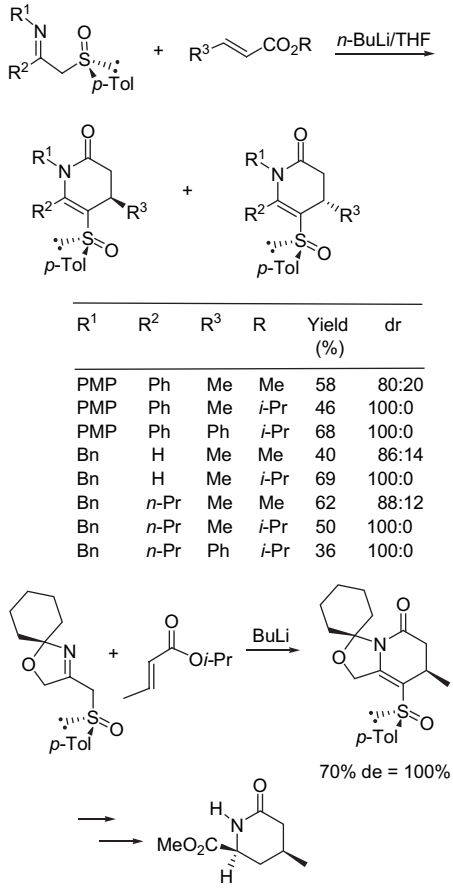


R	Electrophile	Yield (%)	de (%)
H	MeI	21	> 96
Me	MeI	59	> 96
Ph	MeI	75	> 96
Ph	BnBr	74	> 96
Ph	*i*-PrCHO	90	> 96
Ph	PhCHO	98	> 96

Scheme 74. Conjugate addition and subsequent trapping reactions of a chiral β-silylethyl sulfoxide.

As an extension of this work, the asymmetric conjugate addition reactions of polymer-supported highly enantioenriched β-(trimethylsilyl)ethyl sulfoxides were reported. Thus, chiral β-(trimethylsilyl)ethyl sulfoxides supported on Merrifield resin could be treated with LDA and subsequently with methyl cinnamate.[130] Thermal treatment or reaction with TBAF liberated the optically active methyl 3-phenyl-5-trimethylsilylpent-4-enoate or methyl 3-phenylpent-4-enoate, respectively, in good yields with high enantioselectivity.

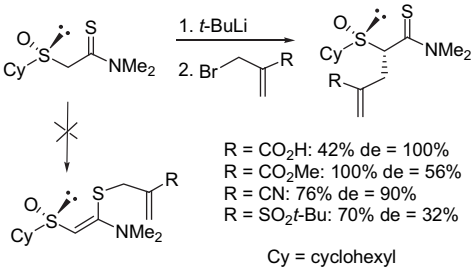
Alvarez-Ibarra et al. have explored the sulfoxide-mediated diastereoselective Michael reaction of chiral α-sulfinylketimines and β-substituted ene esters (Scheme 75).[131] Straightforward cyclisation of the open-chain adducts took place under the reaction conditions, to provide the corresponding 4-substituted 5-(*p*-tolylsulfinyl)-5,6-dehydropiperidin-2-ones, the stereochemistry of which was formed in the prior step. Furthermore, the role of the metal ion of the aza-enolate reagents, and the steric demands of the *O*-alkyl ester group have been examined. It appeared that the *anti*-diastereoselectivity depended upon metal chelation by the oxygen of the ester, as well as the oxygen of the sulfinyl group and the nitrogen in the aza-enolate ((*Z*)-configuration). These results could be applied to the synthesis of methyl L-(2*S*,4*S*)-4-methyl-6-oxopipecolate.



R^1	R^2	R^3	R	Yield (%)	dr
PMP	Ph	Me	Me	58	80:20
PMP	Ph	Me	*i*-Pr	46	100:0
PMP	Ph	Ph	*i*-Pr	68	100:0
Bn	H	Me	Me	40	86:14
Bn	H	Me	*i*-Pr	69	100:0
Bn	*n*-Pr	Me	Me	62	88:12
Bn	*n*-Pr	Me	*i*-Pr	50	100:0
Bn	*n*-Pr	Ph	*i*-Pr	36	100:0

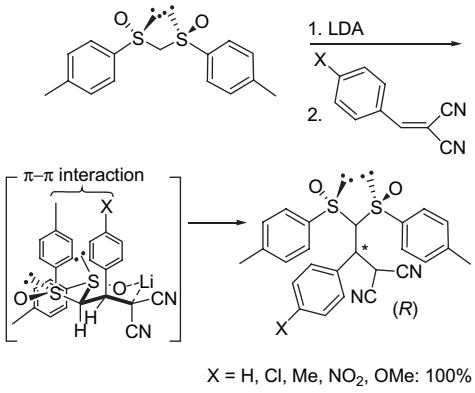
Scheme 75. Michael reaction of chiral α-sulfinylketimines with β-substituted ene esters.

In 2002, Metzner et al. showed that the alkylation of the lithium enolate of a chiral α-cyclohexylsulfinyl thioacetamide with allyl bromides possessing an electron-withdrawing group at the vinyl position did not occur at the sulfur centre, as expected in the sulfur series, but at the carbon centre through conjugate addition, followed by bromide elimination (Scheme 76).[132]



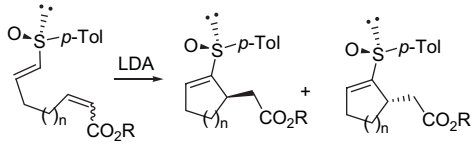
Scheme 76. C-allylation of a chiral α-sulfinyl thioacetamide.

Highly diastereoselective 1,4-additions to stabilised Michael acceptors have also been carried out by Fernandez et al. with carbanions of C_2-symmetric bis-sulfoxides such as (*S*,*S*)-bis-*p*-tolylsulfinylmethane (Scheme 77).[133] These authors claimed thermodynamic control and proposed a Zimmerman–Traxler-type model, which disclosed a favourable π–π interaction between the two aromatic rings, one belonging to the Michael acceptor, and the other to the anion.



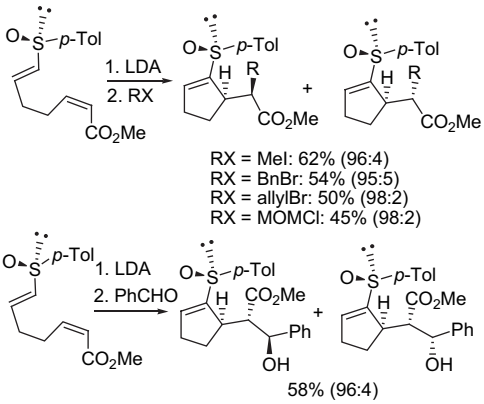
Scheme 77. Reaction of a C_2-symmetric bis-sulfoxide with stabilised Michael acceptors.

The first example of an asymmetric intramolecular Michael addition reaction using an α-lithiated vinylic sulfoxide as a Michael donor was reported by Tanaka et al.[134] Michael addition of the α-lithiated vinylic sulfoxide to (*Z*)-enoates proceeded with high diastereoselectivity to give the adducts having a stereogenic centre with (*R*)-configuration at the β-position of the ester in the cyclopentene ring formation (Scheme 78). The diastereoselectivity was dependent upon the geometry of the enoate, since low des were systematically obtained with the corresponding (*E*)-enoates. Moreover, the selectivity was reversed in the six-membered ring formation.



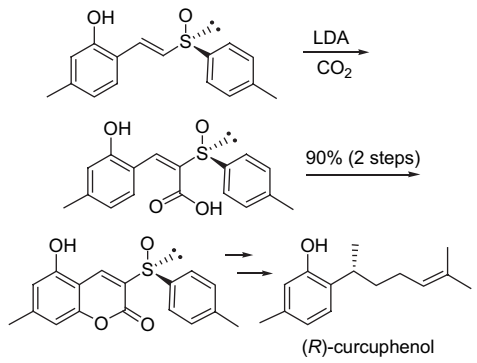
Scheme 78. Intramolecular Michael addition of α-sulfinyl vinylic carbanion to enoates.

The intramolecular Michael addition of the α-sulfinyl vinyl carbanion generated a new anion species, which was expected to react diastereoselectively with electrophiles such as alkyl halides or benzaldehyde, providing two stereocentres in a one-pot operation reaction (Scheme 79).



Scheme 79. Intramolecular Michael addition followed by alkylation or aldol reaction.

In 2005, Pan et al. reported an enantioselective synthesis of (*S*)- and (*R*)-curcuphenol, showing, respectively, potent antifungal and antitumour activity, and antibacterial activity. The key step was an asymmetric conjugate addition using a chiral sulfoxide (Scheme 80).[135]



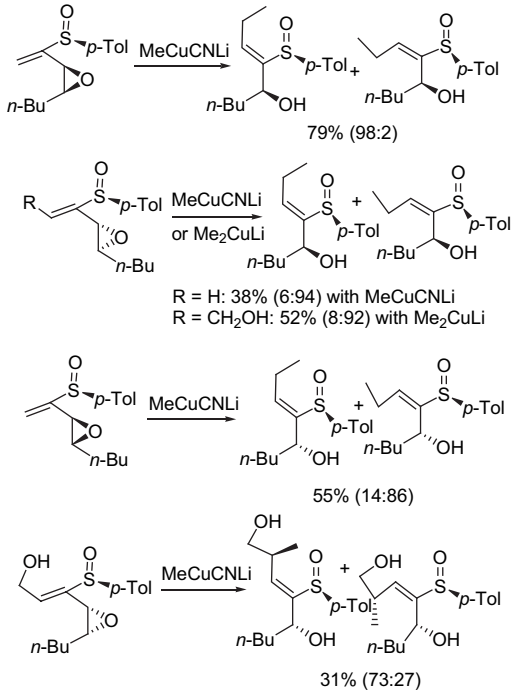
Scheme 80. Synthesis of (*R*)-curcuphenol.

5. Conjugated additions to α,β-unsaturated sulfoxides

α,β-Unsaturated sulfoxides have been extensively used in asymmetric synthesis as versatile chiral reagents with the sulfinyl group playing the role of chiral auxiliary.[136]

5.1. C–C bond formation

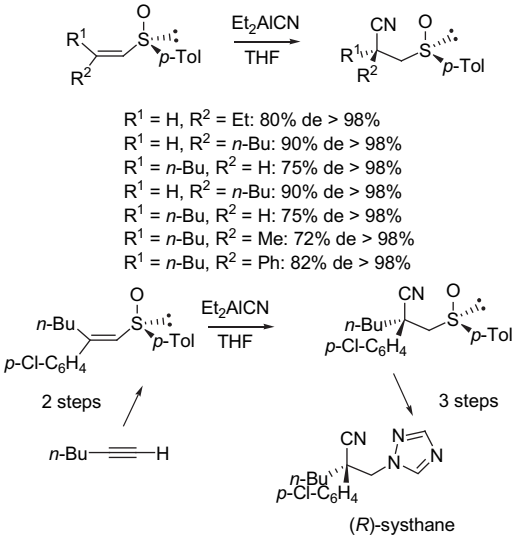
The conjugate addition of carbon nucleophiles to chiral α,β-unsaturated α-arylsulfinyl carbonyl compounds was studied by Posner et al., giving the best results in the case of cyclic systems.[137] In 2000, Marino et al. demonstrated that chiral acyclic epoxy vinyl sulfoxides underwent highly regio- and stereoselective S_N2' displacements with lithium cyanocuprates to give the corresponding α′-alkylated, γ-oxygenated



Scheme 81. S_N2' displacements between cyanocuprates and vinyl and alkynyl epoxy sulfoxides.

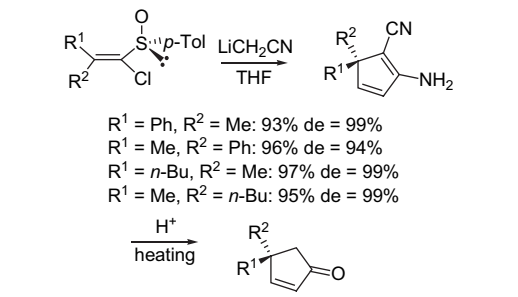
Z α,β-unsaturated sulfoxides in good yields and with good to excellent diastereoselectivities.[138] In order to extend this study, the readily available vinyl epoxy sulfoxides depicted in Scheme 81 were submitted to S_N2' displacement with organocopper reagents, producing the corresponding chiral α-hydroxy vinyl sulfoxides with high *anti* selectivity and a good degree of *E*/*Z* stereocontrol.

In 2001, Garcia Ruano et al. showed that the hydrocyanation of alkenyl sulfoxides with Et_2AlCN took place in a completely stereoselective manner (Scheme 82).[139] This methodology was applied for the synthesis of the fungicide, systhane, in which the sulfinyl group controlled the two key steps of the synthetic sequence, the highly stereoselective hydrocyanation of vinyl sulfoxides and the further introduction of the proper functionality into the molecule (Scheme 82).[140]



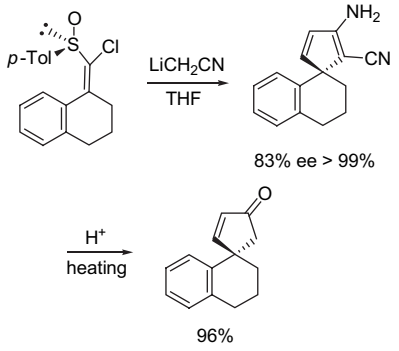
Scheme 82. Stereoselective hydrocyanation of alkenyl sulfoxides.

Treatment of optically active 1-chlorovinyl *p*-tolyl sulfoxides having two different substituents at the 2-position, which were synthesised from unsymmetrical ketones and (*R*)-chloromethyl *p*-tolyl sulfoxide, with cyanomethyllithium was shown to give chiral 2-amino-1-cyano-5,5-disubstituted-1,3-cyclopentadienes with very high asymmetric induction.[141] The products were further converted into the corresponding chiral 4,4-disubstituted 2-cyclopentenones by heating with phosphoric acid (Scheme 83). This novel reaction was successfully applied to the total synthesis of (+)-α-cuparenone,[142] and 2,4,4-trisubstituted cyclopent-2-enones.[143]



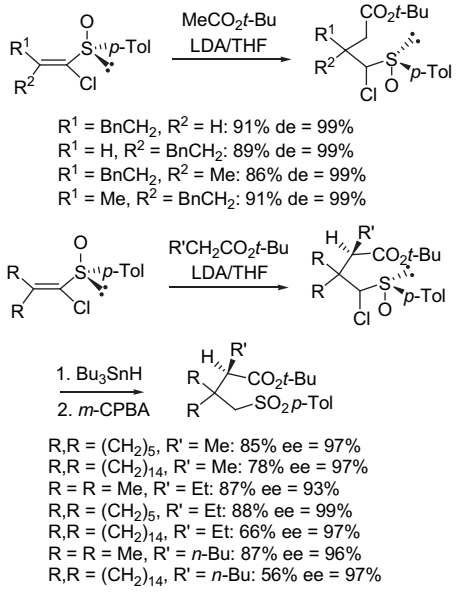
Scheme 83. Reaction of cyanomethyllithium with 1-chlorovinyl *p*-tolyl sulfoxides.

This methodology was extended to cyclic 1-chlorovinyl *p*-tolyl sulfoxides, providing under the same conditions the corresponding spirocyclic enaminonitriles, the acidic treatment of which afforded the corresponding chiral spiro[4,*n*]alkenones (Scheme 84).[144] By using an unsymmetrical cyclic ketone such as α-tetralone and chiral chloromethyl *p*-tolyl sulfoxide, this procedure afforded chiral spiro[4,5]decenone with excellent induction. This method was applied to a formal synthesis of a spirocyclic sesquiterpene, acorone.



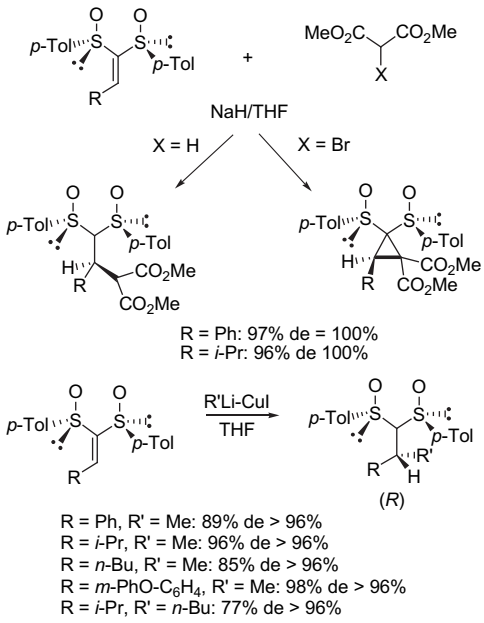
Scheme 84. Synthesis of chiral spiro[4,5]decenone.

Similarly, lithium ester enolates were condensed onto chiral 1-chlorovinyl *p*-tolyl sulfoxides, leading to the formation of chiral esters and lactones having a tertiary or a quaternary stereogenic centre at the γ-position (Scheme 85).[145]



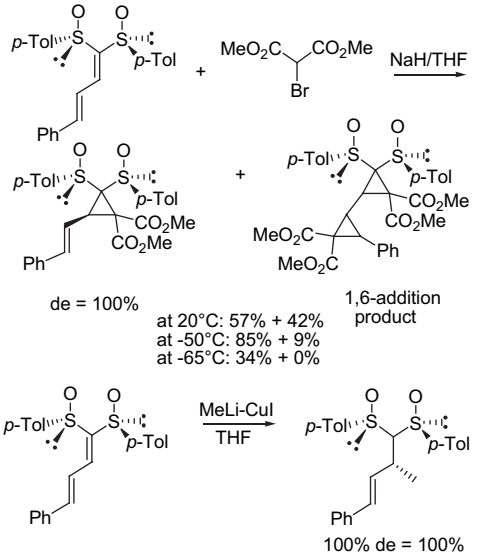
Scheme 85. Reaction of lithium ester enolates with 1-chlorovinyl *p*-tolyl sulfoxides.

Malacria et al. have shown that alkylidene bis(sulfoxides) were exceptional partners in high yielding and totally diastereoselective Michael additions, as well as with heteronucleophiles (Section 5.2) or carbon nucleophiles such as sodium dimethylmalonate or copper reagents, which both gave complete stereoselectivity when reacting with alkylidene bis(sulfoxides) (Scheme 86).[146]



Scheme 86. Reaction of carbon nucleophiles with chiral alkylidene bis(sulfoxides).

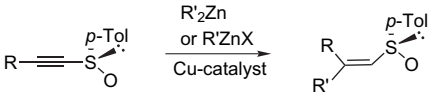
In 2005, this methodology was extended to a dienyl bis-sulfoxide derived from cinnamaldehyde, which gave stereoselective conjugate additions with the same carbon nucleophiles, providing the corresponding 1,4-addition products (Scheme 87).[147] When the reaction was carried out at low temperature, the formation of the 1,6-addition products could be avoided. The use of this outstanding Michael acceptor with a methylcopper reagent gave an access to an enantiopure precursor of cryptophycin.



Scheme 87. Michael additions onto dienyl bis-sulfoxides.

A new synthetic method for chiral β,β-disubstituted vinylic sulfoxides bearing various functionalities has been developed by employing Cu-catalysed conjugate addition of an organozinc reagent to a chiral 1-alkynyl sulfoxide.[148] Since the reaction proceeded with very high *syn*-selectivity, both geometric β,β-disubstituted vinylic sulfoxides were

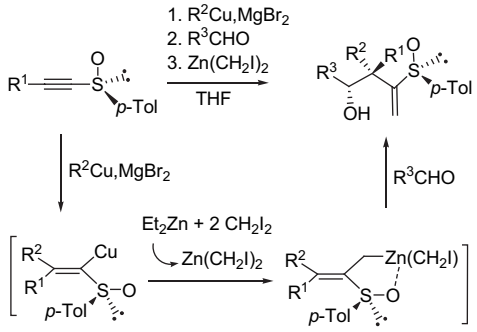
stereoselectively synthesised by changing the combination of the 1-alkynyl sulfoxide and the organozinc reagent (Scheme 88). The scope of the reaction could be extended to the synthesis of trisubstituted vinylic sulfoxides by trapping the resulting intermediate α-sulfinyl vinylic carbanion with electrophiles such as alkyl halides. Moreover, highly diastereoselective THF and THP ring formations were accomplished by means of this methodology, followed by an intramolecular Michael addition.[149]



R	R'_2Zn or R'ZnX	Cu-cat.	Yield (%)
n-Bu	Et_2Zn	CuI	97%
$TBDMSO(CH_2)_2$	Et_2Zn	CuI	78%
$AcO(CH_2)_2$	Et_2Zn	CuI	84%
$I(CH_2)_4$	Et_2Zn	CuI	84%
H	Et_2Zn	CuI	24%
n-Bu	Me_2Zn	CuI	67%
H	Et_2Zn	CuI	24%
n-Bu	allylZnBr	CuI	72%
n-Bu	allylZnBr	$Cu(OTf)_2$	81%
n-Bu	$PivOCH_2ZnI$	$Cu(OTf)_2$	75%

Scheme 88. Addition of organozinc reagents to 1-alkynyl sulfoxides.

On the other hand, chiral alkynyl sulfoxides were involved in a new four-component reaction, leading to the creation of three new carbon–carbon bonds and two new chiral centres, including a quaternary centre.[150] First, the regio- and stereospecific carbocupration reactions of the alkynyl sulfoxide with an organocopper derivative, easily prepared from the corresponding alkylmagnesium halide and CuBr, provided the corresponding metallated β,β-dialkylated α,β-ethylenic sulfoxide in quantitative yield. The reaction mixture was then treated with an aldehyde or an imine, followed by bis(iodomethyl)zinc carbenoid (Scheme 89).

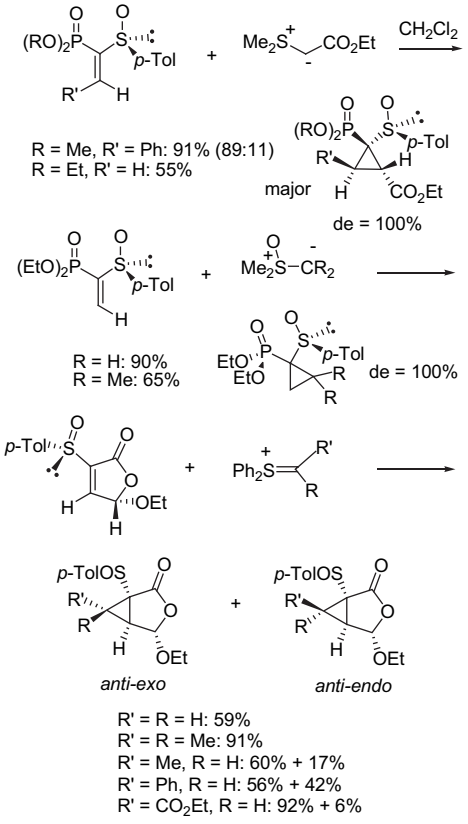


R^1 = *n*-Bu, R^2 = Et, R^3 = Ph: 78% de > 98%
R^1 = Et, R^2 = *n*-Bu, R^3 = Ph: 68% de > 98%
R^1 = *n*-Bu, R^2 = Me, R^3 = Ph: 66% de > 98%
R^1 = Et, R^2 = Me, R^3 = Ph: 66% de > 98%
R^1 = H, R^2 = Et, R^3 = Ph: 78% de = 60%

Scheme 89. Four-component reactions with chiral alkynyl sulfoxides.

In 2004, Midura et al. showed that chiral α-phosphorylvinyl sulfoxides were effective acceptors in conjugate additions of various nucleophiles such as alkoxides, amines or malonates. In all cases, a 2:1 mixture of two (from four possible) diastereoisomers was obtained.[151]

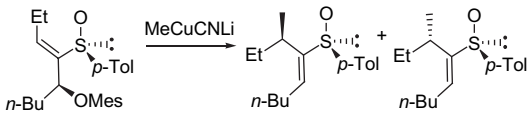
Enantiomerically enriched cyclopropanes are widely used as building blocks for the synthesis of complex molecules. In this context, Mikolajczyk et al. have studied the asymmetric cyclopropanation of chiral (1-dialkoxyphosphoryl)vinyl *p*-tolyl sulfoxides with sulfur ylides, opening a new access to chiral 2-amino-1-cyclopropane-phosphonic acid derivatives (Scheme 90).[152] A constrained analogue of the GABA antagonist, phaclofen and cyclopropylphosphonate analogues of nucleotides could be synthesised using this methodology. The extension of this method to (5*S*,*S*)-3-*p*-tolylsulfinyl-5-ethoxyfuran-2(5*H*)-one led to a very high π-facial selectivity.



R' = R = H: 59%
R' = R = Me: 91%
R' = Me, R = H: 60% + 17%
R' = Ph, R = H: 56% + 42%
R' = CO_2Et, R = H: 92% + 6%

Scheme 90. Cyclopropanation of (1-dialkoxyphosphoryl)vinyl *p*-tolyl sulfoxides.

De la Pradilla et al. have reported that an α′-alkylated γ-mesyloxy-(*Z*)-α,β-unsaturated sulfoxide depicted in Scheme 91 could readily undergo stereoselective S_N2' displacement with lithium methyl cyanocuprate to yield the corresponding vinyl sulfoxide with high diastereoselectivity.[153]

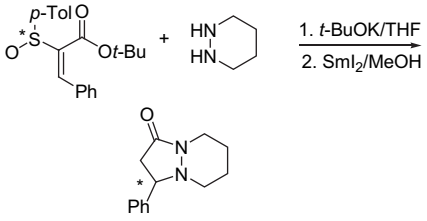


Scheme 91. Reaction of an α′-alkylated γ-mesyloxy-(*Z*)-α,β-unsaturated sulfoxide with MeCuCNLi.

5.2. C–N, C–O and C–S bond formations

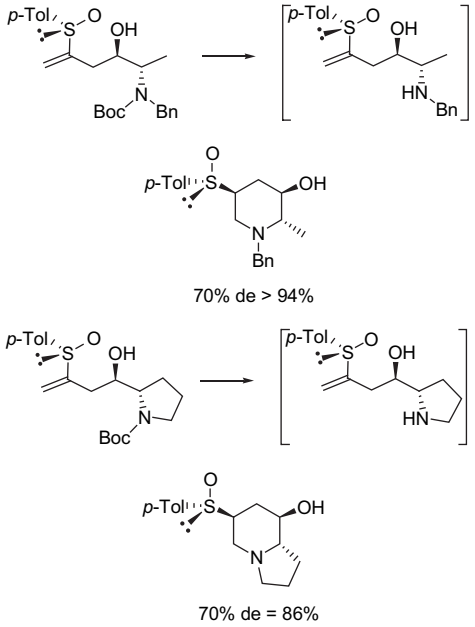
Asymmetric induction in the conjugate addition of nitrogen nucleophiles to chiral vinyl sulfoxides has proved to be a useful methodology for the synthesis of chiral compounds.[2c]

The intermolecular conjugate addition of nitrogen nucleophiles to chiral α,β-unsaturated-sulfoxides has not been widely applied in synthesis, probably due to the low reactivity of these simple Michael acceptors. Matsuyama et al. have, however, developed the conjugate addition of a six-membered hydrazine to chiral *tert*-butyl (*E*)-2-(*p*-tolylsulfinyl)cinnamates.[154] The asymmetric conjugate addition–cyclisation of piperidazine with *tert*-butyl (*E*)-2-[(*R*)- or (*S*)-*p*-tolylsulfinyl]cinnamate gave diastereoselectively the corresponding bicyclic lactam after the subsequent removal of the *p*-tolylsulfinyl group with SmI_2 (Scheme 92). Next, the reductive cleavage of the N–N bond of the bicyclic lactam gave rise to the corresponding nine-membered azalactam, (*S*)- or (*R*)-4-phenyl-1,5-diazacyclononan-2-one, which was a potent precursor for the synthesis of the natural 13-membered alkaloid, celacinnine.



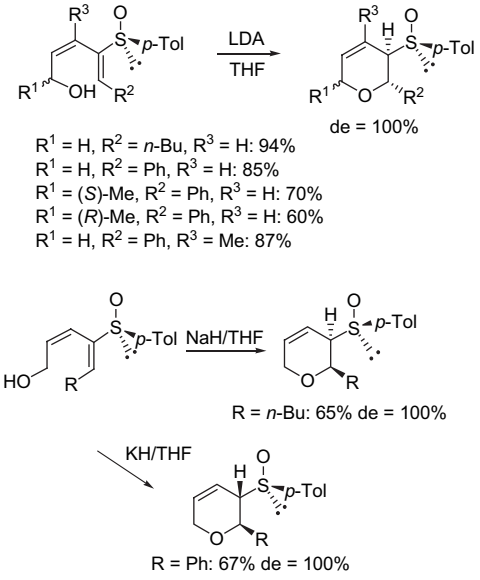
Scheme 92. Conjugate addition of piperidazine to *tert*-butyl (*E*)-2-(*p*-tolylsulfinyl)cinnamate.

On the other hand, the intramolecular version of the Michael addition of nitrogen nucleophiles, which took place at a lower temperature, was used in the development of a new diastereoselective route to piperidine and indolizidine scaffolds from chiral vinylsulfinyl-containing amino alcohols (Scheme 93).[155] In addition, pyrolytic elimination of the resulting cycloadducts resulted in the regioselective formation of the corresponding tetrahydropyridines and indolizidines.



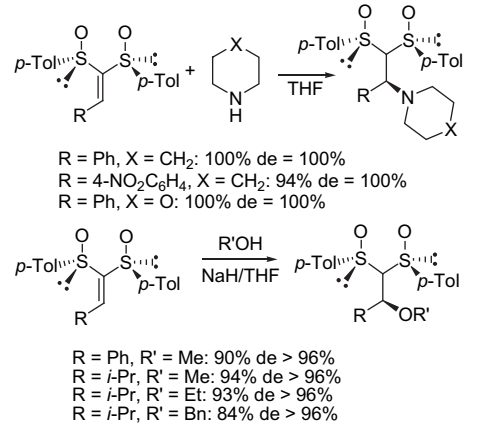
Scheme 93. Intramolecular addition–cyclisation of vinylsulfinyl-containing amino alcohols.

It is known that alcohols add to α,β-unsaturated sulfoxides in the presence of bases in a reversible, thermodynamically controlled process.[156] In some cases, however, particularly when the conjugate addition proceeds in an intramolecular fashion, it is possible to isolate the kinetically controlled product usually formed with a very high stereoselectivity. Thus, the first examples of base-promoted intramolecular cyclisation of 2-sulfinyl dienols affording sulfinyl dihydropyrans have been reported (Scheme 94).[157] This new strategy allowed the creation of two asymmetric centres within a synthetically useful dihydropyran framework in an expedient manner.



Scheme 94. Intramolecular addition–cyclisation of 2-sulfinyl dienols.

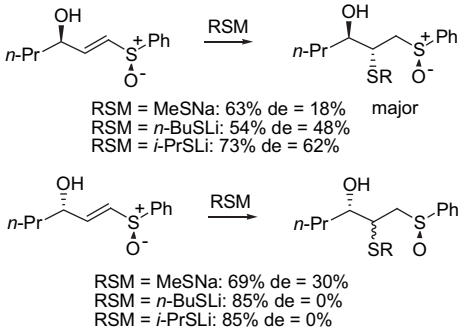
In Section 5.1, it was shown that alkylidene bis(sulfoxides) were appealing candidates for asymmetric conjugate additions to carbon nucleophiles. In addition, Malacria et al. were able to extend their methodology to amines, the reaction of which gave the corresponding amino adducts in a completely diastereoselective manner.[146] Moreover, oxygenated nucleophiles such as sodium alkoxides also gave the conjugate addition in high yields and with total stereoselectivity (Scheme 95).



Scheme 95. Addition of amines and alkoxides to alkylidene bis(sulfoxides).

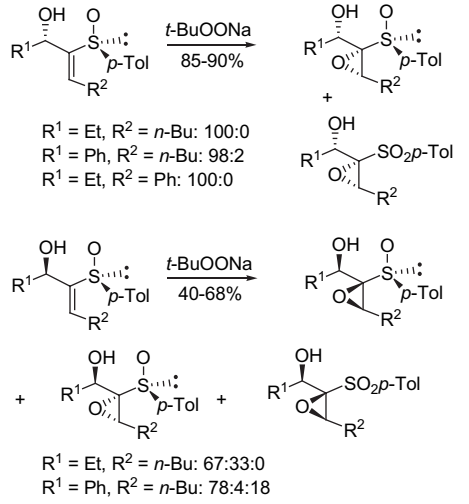
Other heteronucleophiles such as dimethylamine, ethyl mercaptan in the presence of Et_3N, and methanol in the presence of KOH could also form adducts with α-phosphorylvinyl sulfoxides, affording the desired products as a mixture of diastereomers in around a 2:1 ratio.[151] In addition, Ma et al. have reported a short synthesis of the HIV protease inhibitor, nelfinavir, via a diastereoselective 1,4-addition of ammonia to an α,β-unsaturated sulfoxide derived from (*R*)-glyceraldehyde acetonide.[158]

There has been considerable interest in the development of novel methodologies for the 1,4-additions of other heteroatom nucleophiles to vinyl sulfoxides. With this aim in view, Forristal et al. have reported the first stereoselective conjugate addition of thiolate nucleophiles to chiral (*E*)-γ-hydroxy α,β-unsaturated sulfoxides, as depicted in Scheme 96.[159] Moderate levels of diastereoselectivity were observed, with the two stereocontrolling elements, the hydroxyl group and the sulfoxide moiety, showing reinforcing and nonreinforcing control of stereoselectivity, depending upon their relative configuration.



Scheme 96. Reaction of (*E*)-γ-hydroxy α,β-unsaturated sulfoxides with thiolates.

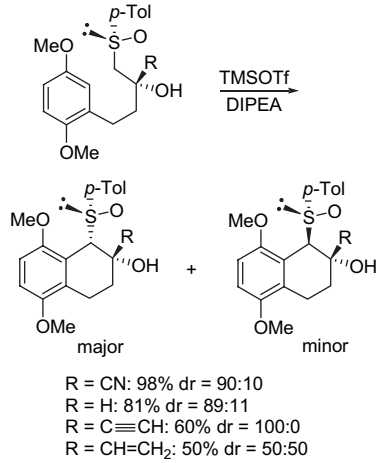
There continues to be considerable interest in the stereoselective preparation of heterosubstituted oxiranes using the nucleophilic epoxidation of vinyl sulfoxides. Diastereoselective nucleophilic epoxidation takes place when enantiomerically enriched sulfoxides are treated with MOO*t*-Bu (M: Li, Na, K) in ether or THF at 0 °C, to afford α,β-epoxy sulfoxides in good yield. As an example, de la Pradilla et al. have studied the epoxidation of a variety of α′-(1-hydroxyalkyl)vinyl sulfoxides.[121] As shown in Scheme 97, a highly *syn*-selective epoxidation–oxidation was observed with the (S,S_S)-sulfoxide, whereas the (R,S_S)-diastereoisomer showed diminished reactivities and a very substrate-dependent stereochemical outcome. The same group also reported that the nucleophilic epoxidation of simple (γ-silyloxy)vinyl sulfoxides took place with complete stereocontrol in high yields.[160] For substrates bearing an additional substituent at the γ-position, once again a reinforcing/nonreinforcing scenario was operative.



Scheme 97. Nucleophilic epoxidation of α′-(1-hydroxyalkyl)vinyl sulfoxides.

6. Pummerer reactions

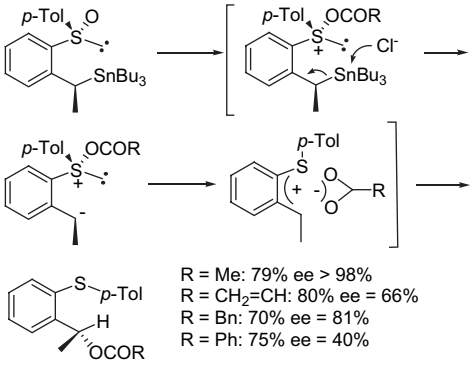
The reaction discovered by Pummerer consists of the transformation of sulfoxides bearing α-hydrogens in α-acyloxy sulfides by treatment with acid anhydrides and has been widely used in synthesis.[161] From a stereochemical point of view, this is a self-immolative asymmetric process where the chirality at sulfur is transferred to the α-carbon. The asymmetric Pummerer reaction of chiral, nonracemic sulfoxides[162] is of significant interest, since it allows the synthesis of enantiomerically pure α-substituted sulfides.[163] Intramolecular Pummerer cyclisation is especially useful for building chiral heterocyclic compounds.[164] As an example, highly stereoselective Pummerer reactions were observed on reaction of the β-hydroxysulfoxides depicted in Scheme 98 with TMSOTf.[165] Sulfenium intermediates were captured intramolecularly by the electrophilic aromatic ring, thus yielding bicyclic structures with a *p*-tolylsulfenyl group at the benzylic position in a cis arrangement with respect to the hydroxyl group. The stereogenicity transfer seemed to be mainly controlled by the hydroxylated chiral carbon. The resulting compounds could be used as bicyclic precursors of different anthracyclinones.



Scheme 98. Intramolecular Pummerer reaction of β-hydroxysulfoxides.

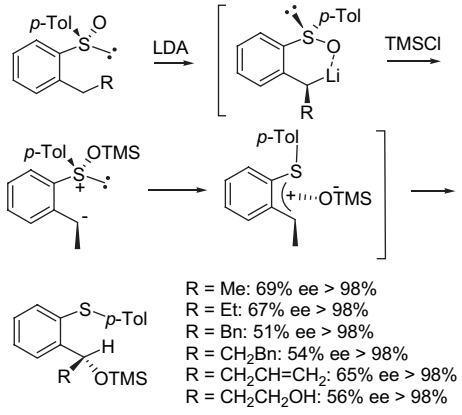
In general, better results are obtained for the additive Pummerer-type reaction, which occurs on vinylic sulfoxides. In 2004, Garcia Ruano et al. reported a new type of vinylogous

tin-Pummerer rearrangement reaction, which was observed when benzyltin derivatives containing a sulfinyl group at the *ortho* position were allowed to react with acyl chlorides (Scheme 99).[166] The reaction was thought to proceed by nucleophilic attack of the leaving carboxylate at the γ-position of the conjugated thionium ion and gave ees of up to 98%, constituting a new route to chiral benzyl alcohols.



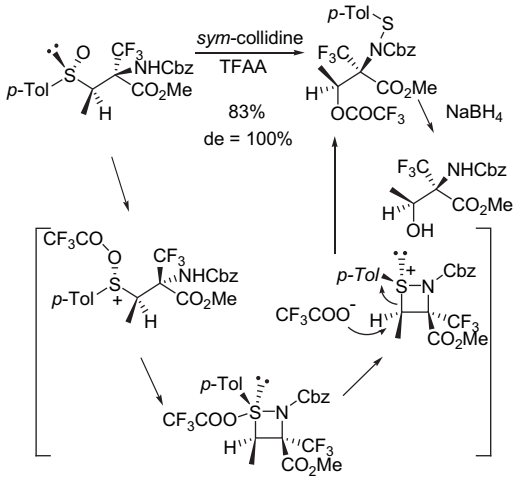
Scheme 99. Vinylogous tin-Pummerer rearrangement reaction.

Another highly stereoselective vinylogous Pummerer reaction mediated by Me_3SiX was developed by the same group in 2005.[167] This reaction involving 1,4-migration of the sulfinyl oxygen atom occurred when *ortho*-sulfinyl benzyl carbanions were treated with trimethylsilyl halides with good yield and high enantioselectivity (Scheme 100).



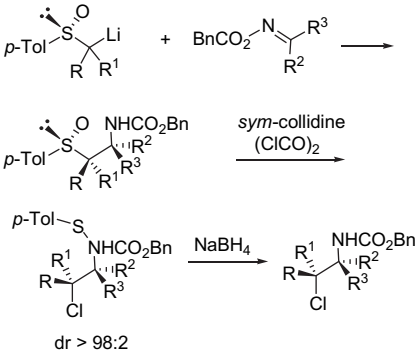
Scheme 100. Sila-Pummerer reaction.

In the course of investigating the synthesis of a new statine dipeptide isostere, Zanda et al. have discovered the non-oxidative Pummerer reaction.[168] When the chiral sulfoxide depicted in Scheme 101 was treated with 5 equiv of trifluoroacetic anhydride (TFAA) and 3 equiv of *sym*-collidine in acetonitrile, the normal Pummerer rearrangement did not take place. Instead, the trifluoroacetoxy group displaced the sulfinyl group in an S_N2 manner to afford a sulfenamide intermediate, treatment of which with aqueous K_2CO_3 and $NaBH_4$ provided the corresponding β-amino alcohol in high yield and with high diastereoselectivity. The authors have proposed an explanation for this transformation that involves the formation of an intermediate acylated sulfoxide, followed by a cyclisation to give the corresponding σ-sulfurane. The dissociation of the trifluoroacetoxy group and the subsequent S_N2 displacement gave the final sulfenamide with inversion of configuration at the α-sulfinyl carbon.



Scheme 101. Non-oxidative Pummerer reaction.

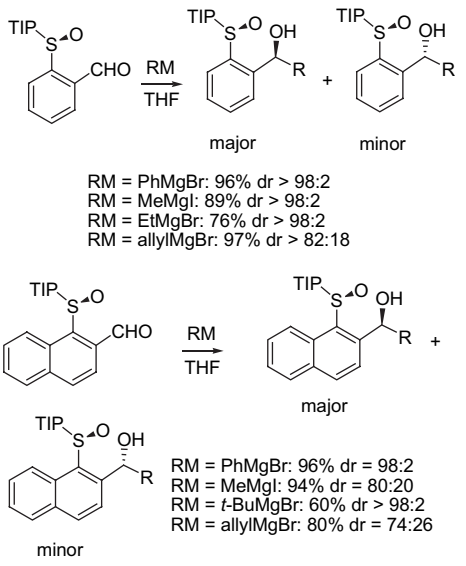
An extension of this methodology was the non-oxidative chloro-Pummerer reaction, providing a highly stereoselective entry into β-chloro amines and aziridines.[169] Thus, chiral α-Li alkyl sulfoxides could be used as chiral α-chloroalkyl carbanions with *N*-protected imines by means of the non-oxidative chloro-Pummerer reaction (Scheme 102). This methodology allowed a one-pot displacement of a sulfinyl group by chlorine from *N*-alkoxycarbonyl β-sulfinylamines derived from aryl, fluoroalkyl and alkyl imines, with clean stereoinversion at carbon. In addition, several 1,2-chloroamines produced by this method could be converted into the corresponding aziridines.



Scheme 102. Non-oxidative chloro-Pummerer reaction.

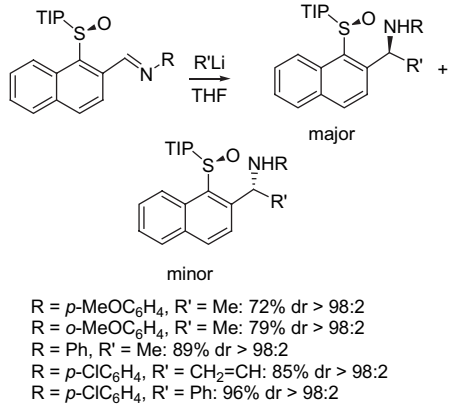
7. Miscellaneous reactions

The asymmetric approach to enantiopure carbinols based on the simplest addition of the widely used Grignard reagents or other organometallic compounds to benzaldehydes bearing a chiral auxiliary has been studied only recently. In 2001, Toru reported the Grignard reaction of benzaldehydes bearing a bulky (2,4,6-triisopropylphenyl)-sulfinyl group at the 2-position occurring with high 1,4-remote asymmetric induction (Scheme 103).[36] As an extension, this methodology could be applied to naphthalenic systems (Scheme 103).



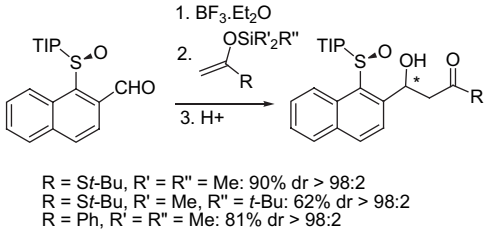
Scheme 103. Addition of Grignard reagents to bulky 2-(arylsulfinyl)benzaldehydes.

Another extension of this work was the reaction of alkyllithium reagents with (1-sulfinyl-2-naphthyl)methanimines bearing a 2,4,6-triisopropylphenylsulfinyl group, leading to the corresponding products as a single diastereomer (Scheme 104).[170] It was demonstrated that the high diastereoselectivity was due to the restricted rotation about the C_{naphth}–S bond having the bulky 2,4,6-triisopropylphenylsulfinyl group. The subsequent elimination of the sulfinyl group allowed an easy access to chiral 1-(2-naphthyl)ethylamines.



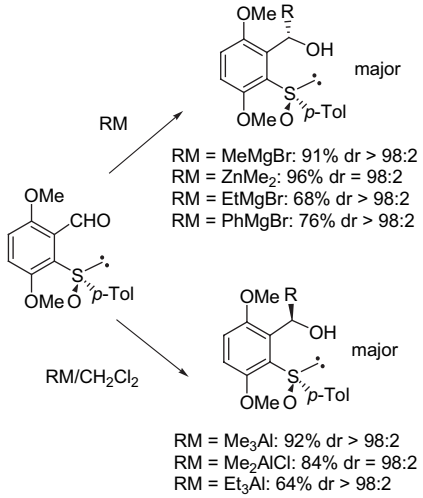
Scheme 104. Addition of alkyllithium reagents to 1-sulfinyl-2-naphthylmethanimines.

High stereoselectivity was also observed during the Mukaiyama aldol reactions of naphthaldehydes having a 2,4,6-triisopropylphenylsulfinyl group (Scheme 105).[171] In addition, the aldol reaction of a chiral sulfinyl furaldehyde with 1-phenoxy-1-trimethylsilyloxyethene was the basis of an asymmetric synthesis of (+)-dihydrokawain-5-ol, having anxiolytic and analgesic properties. The Mukaiyama reaction provided the expected chiral functionalised furylpropanoate with 91% yield and 90% diastereoisomeric excess.[112a]



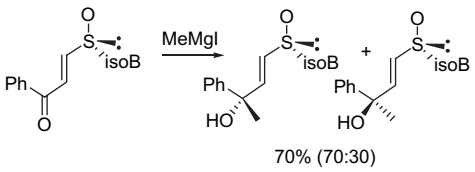
Scheme 105. Mukaiyama aldol reactions of a 1-sulfinyl-2-naphthaldehyde.

In 2003, Carreno et al. demonstrated that it was not necessary to use a bulky group such as (2,4,6-triisopropylphenyl)-sulfinyl to obtain good results.[172] Thus, the common *p*-tolylsulfinyl group proved to be very efficient in directing the nucleophilic addition of different organometallic derivatives onto the carbonyl group of [(S)*S*]-3,6-dimethoxy-2-(*p*-tolylsulfinyl)-benzaldehyde, allowing the diastereodivergent synthesis of the corresponding sulfinyl-substituted (*S*) or (*R*) alkyl aryl or diaryl carbinols, by simply choosing the appropriate organometallic reagent (Scheme 106).



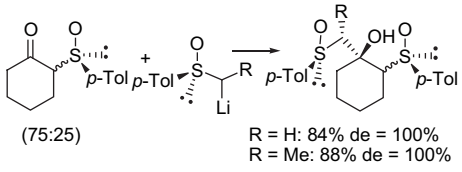
Scheme 106. Addition of organometallic reagents to 3,6-dimethoxy-2-(*p*-tolylsulfinyl)-benzaldehyde.

Moreover, an unsaturated sulfoxide such as chiral (*E*)-3-[(1*S*)-isoborneol-10-sulfinyl]-1-phenyl-2-propen-1-one has confirmed its expected value as a nucleophile acceptor, giving useful stereochemical results in 1,2-additions of Grignard reagents (Scheme 107).[84] It was demonstrated that the chiral sulfur atom exerted a remote stereocontrol if assisted by the hydroxyl group being part of the isoborneol substituent.



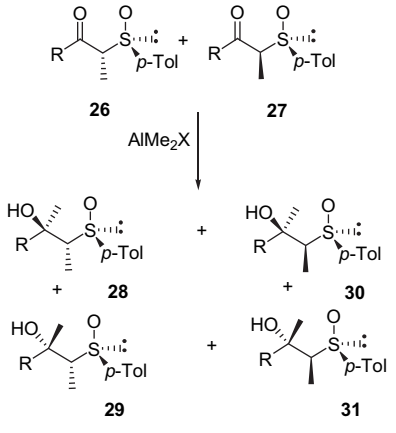
Scheme 107. Addition of MeMgI to (*E*)-3-[(1*S*)-isoborneol-10-sulfinyl]-1-phenyl-2-propen-1-one.

In 2000, Garcia Ruano et al. described the addition reaction of α-thiocarbanions derived from sulfoxides to 2-(*p*-tolylsulfinyl)cyclohexanone, which occurred with a total control of the stereoselectivity at the hydroxylic carbon (Scheme 108).[173]



Scheme 108. Reaction of α-thiocarbanions with 2-(*p*-tolylsulfinyl)cyclohexanone.

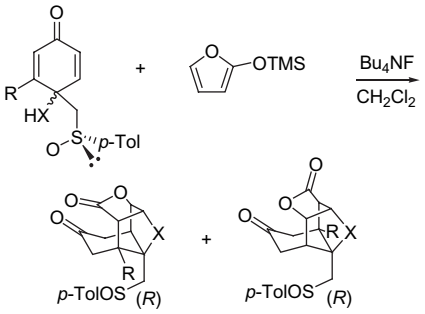
In order to stereoselectively methylate α-methyl-β-ketosulfoxides, other nucleophiles such as aluminium reagents could be successfully employed (Scheme 109).[174] The induced configuration at the hydroxylic carbon was mainly controlled by the configuration at C-α. The resulting hydroxysulfoxides could be used in the synthesis of optically pure tertiary methyl carbinols.



X	R (**26**:**27**)	Yield	**28**:**29**:**30**:**31**
Me	*n*-Pr (39:61)	72%	13:10:67:10
Me	*i*-Pr (36:64)	58%	29:0:71:0
Me	Ph (44:56)	89%	33:10:38:19
Me	*t*-Bu (100:0)	40%	70:30:0:0
Me	*t*-Bu (0:100)	43%	0:0:100:0
Me	*n*-Pr (40:60)	90%	18:9:69:4
Me	*i*-Pr (36:64)	98%	35:0:65:0
Me	Ph (44:56)	77%	23:3:74:0
Me	*t*-Bu (100:0)	0%	-
Me	*t*-Bu (0:100)	0%	-

Scheme 109. Reaction of Me_2AlX with α-methyl-β-ketosulfoxides.

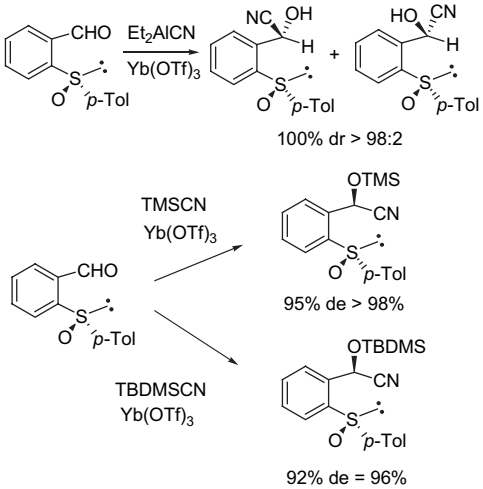
With the aim of preparing new chiral tetracyclic cage compounds, Carreno et al. have developed new domino conjugate additions of 2-(trimethylsilyloxy)furan with enantiopure 4-amino- or 4-hydroxy-3-methyl-4-[(*p*-tolylsulfinyl)-methyl]cyclohexa-2,5-dienones in the presence of Bu_4NF (Scheme 110).[175] The method was particularly valuable, not only because of the stereochemical control, but also because the reactions occurred in an experimentally simple one-pot procedure through a domino sequence of three consecutive conjugate additions.



Starting material	R	X	Ratio (products)	Yield (%)
[(S)*R*]	H	NH	50:50	67
[4*R*(S)*R*]	Me	NH	100:0	56
[4*S*(S)*R*]	Me	NH	0:100	70
[(S)*R*]	H	O	50:50	67
[4*S*(S)*R*]	Me	O	100:0	67

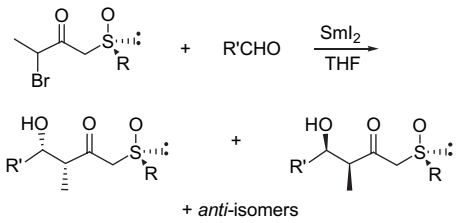
Scheme 110. Synthesis of chiral cage compounds via domino conjugate additions.

The hydrocyanation of (*S*)-2-*p*-tolylsulfinylbenzaldehyde with Et_2AlCN and R_3SiCN was reported in 2005 (Scheme 111).[176] A high stereoselectivity was observed in the presence of Lewis acids such as $Yb(OTf)_3$ as a consequence of cyanide attack on a chelate involving aldehyde and sulfoxide coordination with the metal.



Scheme 111. Hydrocyanation of 2-*p*-tolylsulfinylbenzaldehyde.

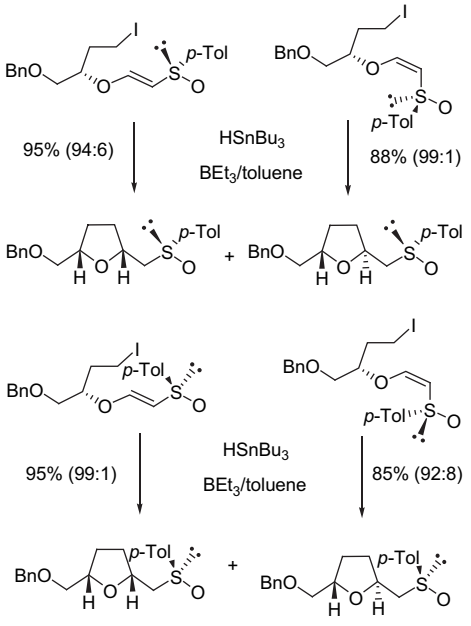
In 2003, Colobert et al. reported a highly stereoselective Reformatsky addition of chiral α-bromo-α′-sulfinyl ketones with various linear aliphatic aldehydes promoted by samarium(II) diiodide (Scheme 112).[177] The corresponding adduct was obtained with excellent *syn* diastereoselectivity and could be converted by further reduction into the corresponding *anti*- and *syn*-2-methyl-1,3-diol moieties.



R = *p*-Tol, R' = Ph: 47% 80:20 *syn:anti* = 75:25
R = *t*-Bu, R' = Ph: 61% 96:4 *syn:anti* = 96:4
R = *t*-Bu, R' = Et: 85% 95:5 *syn:anti* = 98:2
R = *t*-Bu, R' = *n*-Pr: 85% 95:5 *syn:anti* = 98:2
R = *t*-Bu, R' = *n*-Pent: 75% 92:8 *syn:anti* = 98:2
R = *t*-Bu, R' = *n*-C_7H_{15}: 77% 95:5 *syn:anti* = 98:2

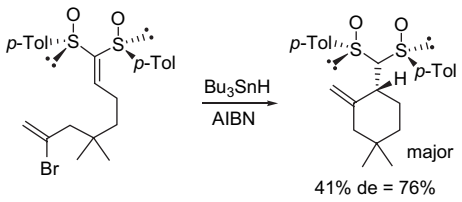
Scheme 112. Reformatsky-type reaction of α-bromo-α′-sulfinyl ketones with aldehydes.

Radical-mediated asymmetric reactions have been extensively studied.[178] This is due, in part, to the high compatibility of radical reactions with a large number of interesting functionalities, notably present on chiral auxiliaries. Chiral sulfoxides have been used to control the configuration of newly formed stereogenic centres in free radical reactions. The addition of radicals to prochiral alkenes bearing a chiral centre is an important radical-mediated asymmetric process.[179–182] High diastereoselectivities were obtained by Malacria et al. for the Michael addition of a vinyl radical onto β-alkoxy vinyl sulfoxides.[183] This radical cyclisation was more recently revisited by Lee et al. and applied to the stereoselective synthesis of chiral tetrahydrofuranyl allyl carbinols after subsequent Pummerer rearrangement and allylstannane reaction (Scheme 113).[184]



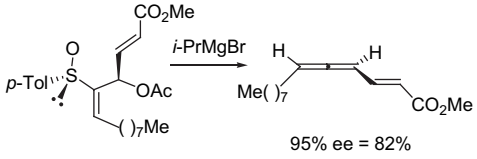
Scheme 113. Radical cyclisation of β-alkoxy vinyl sulfoxides.

In 2003, Malacria et al. introduced enantiopure alkylidene-1,1-bis-*p*-tolyl sulfoxides as new partners in diastereoselective radical cyclisations.[185] In particular, good diastereoselectivities could be observed for the 6-*exo-trig* precursor, as depicted in Scheme 114, whereas, in the 5-*exo* precursor case, rather frustrating results were obtained (de≤15%).



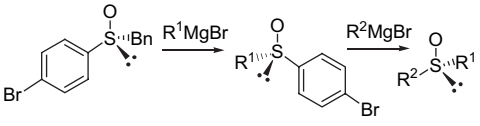
Scheme 114. Radical cyclisation of alkylidene-1,1-bis-*p*-tolyl sulfoxides.

The sulfoxide–metal exchange reaction of β-acetoxy or β-mesyloxy sulfoxides with a Grignard or alkyllithium reagent at low temperature gave allenes in good yields. Enantiomerically pure allenes were synthesised from enantiopure 2-substituted ethenyl *p*-tolyl sulfoxides. A short asymmetric synthesis of (*R*)-(−)-methyl tetradeca-2,4,5-trienoate, depicted in Scheme 115, a male bean weevil sex attractant, from an enantiopure alkenyl sulfoxide was developed by using this method.[186]



Scheme 115. Synthesis of (*R*)-(−)-methyl tetradeca-2,4,5-trienoate.

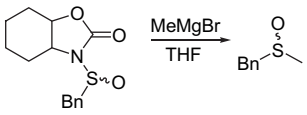
In 2000, Naso et al. demonstrated that displacement of leaving groups by Grignard reagents on sulfinyl compounds constituted an efficient route to chiral dialkyl sulfoxides.[187] An extension of this work was the development of a sequence of two stereocontrolled carbon-for-carbon substitution reactions (Scheme 116).[188]



R^1 = *n*-Pent, R^2 = *n*-dodec: 62% ee > 98%
R^1 = *n*-dodec, R^2 = *n*-Pent: 69% ee > 98%
R^1 = *n*-dodec, R^2 = *i*-Pr: 91% ee > 98%

Scheme 116. Two carbon-for-carbon substitution sequences.

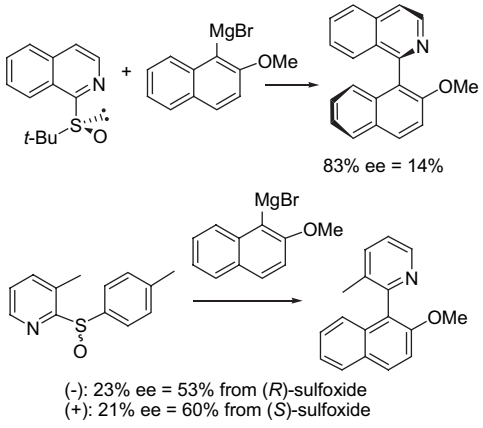
Other enantioselective chiral sulfinyl-transfer reactions have been performed by Juaristi et al., using *N*-(thiobenzylsulfinyl)hexahydrobenzoxazolidin-2-ones as recoverable chiral auxiliaries (Scheme 117).[189]



Substrate configuration	Yield (%)	Product configuration	ee (%)
(4*S*,5*S*,R_S)	70	(R_S)	> 98
(4*R*,5*R*,S_S)	70	(S_S)	> 98
(4*S*,5*R*,S_S)	75	(S_S)	> 98
(4*R*,5*S*,R_S)	75	(R_S)	> 99

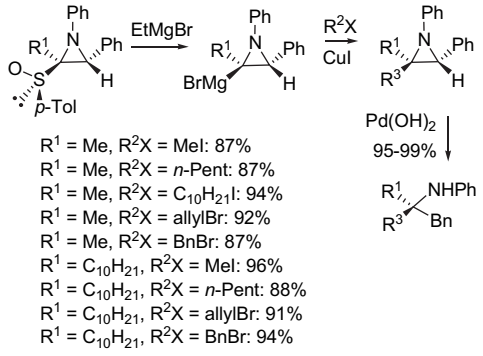
Scheme 117. *N*-(Thiobenzylsulfinyl)hexahydrobenzoxazolidin-2-ones as chiral sulfinyl-transfer reagents.

In 2005, Baker et al. reported an enantioselective synthesis of axially chiral 1-(1-naphthyl)isoquinolines and 2-(1-naphthyl)pyridines through sulfoxide ligand coupling reactions.[190] Good selectivities were obtained for the coupling between 2-methoxy-1-naphthylmagnesium bromide and (*R*)- and (*S*)-2-[(4′-methylphenyl)sulfinyl]-3-methylpyridines, whereas the same Grignard reagent gave low ees when reacting with (*S*)-1-(*tert*-butyl-sulfinyl)isoquinoline, because of partial racemisation of the starting material (Scheme 118).



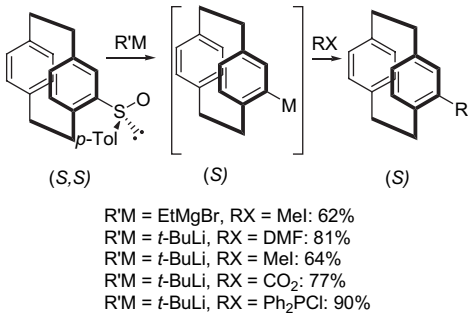
Scheme 118. Sulfoxide ligand coupling reactions.

On the other hand, Satoh et al. have reported a new synthesis of chiral amines bearing a quaternary chiral centre on the basis of a sulfoxide–magnesium exchange reaction.[191,118] Treatment of sulfinylaziridines with ethylmagnesium bromide gave the corresponding nonstabilised aziridinylmagnesium derivatives by sulfoxide–magnesium exchange reactions, and the organomagnesium compounds were then cross-coupled with various alkyl halides (Scheme 119). The resulting alkylated aziridines were further converted into amines bearing a quaternary chiral centre by hydrogenation.



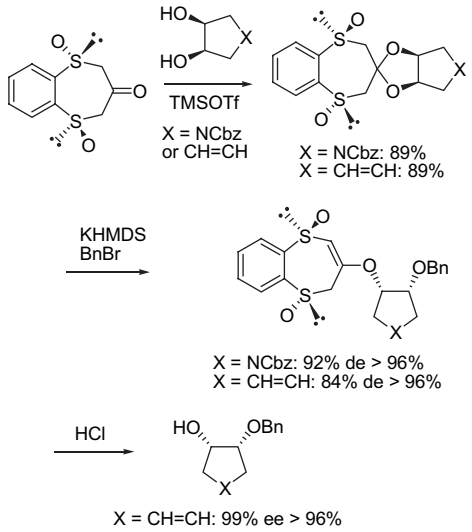
Scheme 119. Sulfoxide–magnesium exchange from sulfinylaziridines.

In 2005, the sulfoxide–metal exchange methodology was applied to the development of a general strategy for the synthesis of chiral 4-substituted [2.2]paracyclophane derivatives.[192] The sulfoxide moiety was able to both resolve planar chirality and act as a precursor to the formation of 4-metallo[2.2]paracyclophanes (Scheme 120).



Scheme 120. Synthesis of 4-substituted [2.2]paracyclophanes.

C_2-symmetric bis-sulfoxides have proved to be efficient chiral auxiliaries for asymmetric desymmetrisation of various diols such as *meso*-erythritol derivatives,[193] or cyclic *meso*-1,2-diols (Scheme 121).[194] These reactions were applied to the synthesis of two natural biologically active products, (+)-aspicilin and mosin B.[195]



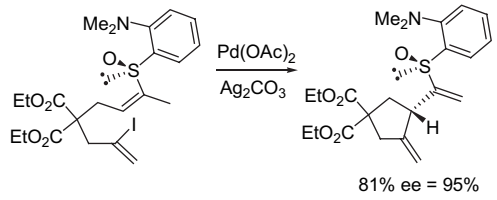
Scheme 121. Desymmetrisation of cyclic *meso*-1,2-diols.

8. Diastereoselective processes promoted by transition metals

Significant advances have been made in the use of chiral sulfoxides in processes catalysed by transition metals.[18] In order to combine the stereodirecting effect of the sulfinyl group with the chemistry of transition metals,[196] various groups started programmes in the mid-1990s directed towards this end. The contributions in this specific area can be divided into two approaches, those using the transition metal as a part of the molecule, and those using the metal as a reagent in a key asymmetric bond event. Only the second approach will be developed in this report.

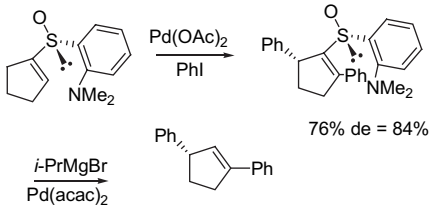
The Heck reaction is widely used for C–C bond formation that couples a vinyl or aryl halide (or anhydride) with an alkene in the presence of an appropriate palladium catalyst. Stereoselective Heck reactions usually involve the use of palladium complexes with chiral ligands. Carretero et al. successfully used chiral 2-iodo-1,6- and 1,7-dienes bearing an (*N*,*N*-dimethylamino)phenylsulfinyl group as chiral

auxiliaries in intramolecular Heck reactions to construct five-membered rings (Scheme 122).[197]



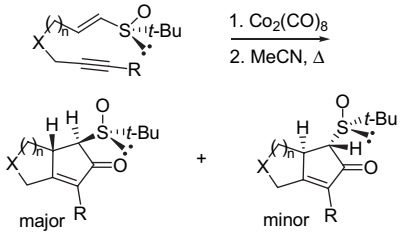
Scheme 122. Intramolecular Heck reaction of a 2-(*N*,*N*-dimethylamino)-phenylsulfinyl derivative.

These authors have reported the asymmetric synthesis of tetrahydrofurans from the Heck reaction of chiral 3-arylsulfinyl-2,3-dihydrofurans with aryl iodides.[198] An application of this methodology was the asymmetric synthesis of (*S*)-1,3-diphenylcyclopentene, depicted in Scheme 123, via a double Heck reaction of the corresponding chiral 1-sulfinylcyclopentene with iodobenzene, followed by palladium-catalysed reductive desulfurisation of the corresponding sulfoxide.[199] This work illustrated that sulfoxides were excellent stereochemical controllers in intermolecular Heck reactions. It should be noted that the 2-(*N*,*N*-dimethylamino)phenyl substituent was necessary in order to obtain high stereoselectivity, presumably via coordination of the Pd atom with the nitrogen.



Scheme 123. Double Heck reaction of a chiral 1-sulfinylcyclopentene.

Over the past few decades, the Pauson–Khand reaction, in which a cyclopentenone framework is constructed, has received great attention, due to its potential application in complex-molecule synthesis.[200] In 2001, Carretero reported an intramolecular version of the Pauson–Khand reaction involving enantiopure 1-sulfinyl-1,6-enynes (Scheme 124).[201]

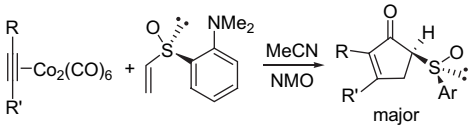


X = CH_2, n = 1, R = H: 50% de > 96%
X = CMe_2, n = 1, R = H: 65% de > 96%
X = $C(CO_2Et)_2$, n = 1, R = H: 60% de > 96%
X = $C(CO_2Et)_2$, n = 2, R = H: 60% de > 96%
X = NBoc, n = 1, R = H: 30% de > 96%

Scheme 124. Intramolecular Pauson–Khand reaction of 1-sulfinyl-1,6-enynes.

As the final desulfinylation step was high yielding, this procedure constituted an efficient alternative to the synthesis of chiral bicyclo[3.3.0]oct-1-en-3-ones. Complete diastereoselectivities were obtained using the *tert*-butylsulfinyl group as a chiral auxiliary.

The same group has also explored the capability of sulfoxide-based chiral auxiliaries in the much less thermodynamically favourable intermolecular processes. These workers reported the first asymmetric version of intermolecular Pauson–Khand reactions of acyclic alkenes.[202] Thus, chiral vinyl sulfoxides, depicted in Scheme 125, reacted under very mild conditions with terminal alkynes to yield the corresponding 5-sulfinylcyclopente-2-enones with complete regioselectivity and high stereoselectivity. A recent application of this methodology allowed the enantioselective synthesis of natural cyclopentanoids such as (−)-pentenomycin I and the (−)-aminocyclopentitol moiety of a hopane triterpenoid.[203]

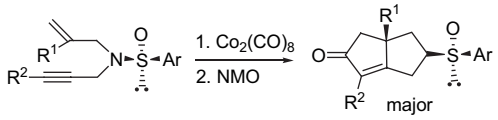


R = *n*-Bu, R' = H: 74% de = 86%
R = *t*-Bu, R' = H: 55% de > 96%
R = Bn, R' = H: 58% de = 86%
R = *p*-Tol, R' = H: 49% de = 86%
R = TMS, R' = H: 59% de > 96%
R = $(CH_2)_3Br$, R' = H: 68% de > 96%
R = $(CH_2)_2OTIPS$, R' = H: 66% de > 96%
R = R' = Me: 33% de = 84%

NMO = *N*-methylmorpholine *N*-oxide

Scheme 125. Pauson–Khand reaction of chiral acyclic vinyl sulfoxides with terminal alkynes.

In 2001, Hiroi et al. reported the first example of the use of a chiral sulfinamide functionality in Pauson–Khand reactions.[204] The cobalt-catalysed reaction of chiral *N*-allyl-*N*-propargyl-*N*-arylsulfinamide derivatives, however, gave the corresponding chiral 3-azabicyclo[3.3.0]oct-5-en-7-ones with only moderate or low enantioselectivity (Scheme 126).

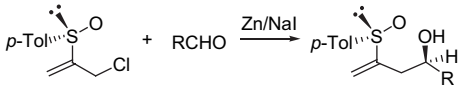


Ar = *p*-Tol, $R^1 = R^2$ = H: 79% de = 38%
Ar = *p*-Tol, R^1 = H, R^2 = Me: 87% de = 10%
Ar = *p*-Tol, R^1 = H, R^2 = TMS: 81% de = 18%
Ar = *p*-Tol, R^1 = Me, R^2 = TMS: 42% de = 10%
Ar = *p*-Tol, R^1 = Me, R^2 = H: 55% de = 11%
Ar = 2-MeOnaph, $R^1 = R^2$ = H: 13% de = 15%

Scheme 126. Pauson–Khand reaction of chiral sulfinamide derivatives.

The allylation of carbonyl derivatives to afford homoallylic alcohols is a useful synthetic transformation that has attracted considerable attention over the past few years. In this context, Delgado et al. have described a simple, efficient and diastereoselective zinc-promoted allylation of aldehydes with enantiopure 3-chloro-2-(*p*-tolylsulfinyl)-1-propene

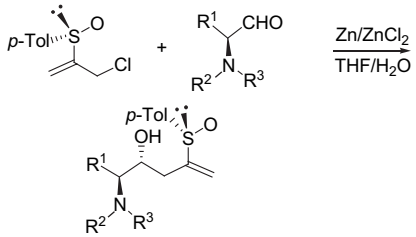
under aqueous Barbier conditions (Scheme 127).[205] Tin-promoted, palladium-catalysed carbonyl allylation was also studied as a suitable alternative to this Barbier-type process.[206] Although, in general, Barbier-type Zn-promoted allylations afforded the expected sulfinyl alcohols in higher yields at lower temperatures and with shorter reaction times than the Sn/Pd system, the Sn/Pd methodology proved to be superior in terms of diastereoselectivity. The sense of diastereoselectivity was identical in both allylation systems. A total synthesis of natural (*S*)-nicotine was elaborated using this methodology.



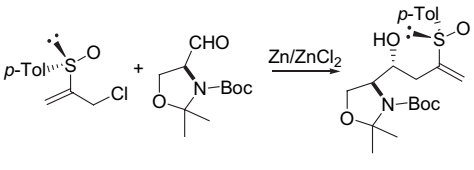
R = Ph: 80% de = 72%
R = Cy: 60% de = 66%
R = *n*-Bu: 67% de = 50%
R = *t*-Bu: 60% de = 66%
R = *p*-(OCH_3)Ph: 70% de = 66%
R = 2-furyl: 60% de = 60%
R = $BnOCH_2$: 75% de = 44%

Scheme 127. Zinc-promoted allylation of aldehydes with a 2-sulfinylallyl halide.

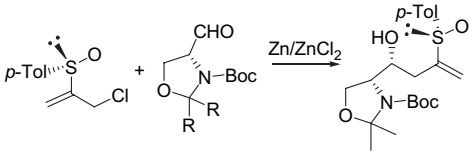
A similar methodology was applied to the use of a series of α-amino aldehydes, providing the corresponding chiral sulfinylamino alcohols in good yields and diastereoselectivities.[207] Particularly high levels of diastereoselectivity could be achieved from α-amino aldehydes configurationally related to natural α-amino acids such as serine, glycine or alanine (Scheme 128).



R^1 = H, R^2 = Boc, R^3 = Bn: 90% de = 50%
R^1 = Me, R^2 = H, R^3 = Boc: 82% de = 50%
R^1 = Me, R^2 = Bn, R^3 = Boc: 70% de = 86%
R^1 = *i*-Pr, R^2 = Bn, R^3 = Boc: 75% de = 76%
R^1 = R^2 = Bn, R^3 = Boc: 75% de = 86%



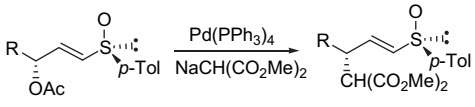
75% de = 76%



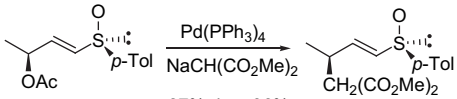
R = Me: 75% de = 20%
R = H: 79% de = 82%

Scheme 128. Allylation of α-amino aldehydes.

In 2001, Llera et al. reported the first example of palladium-mediated allylic substitution on chiral γ-oxygenated α,β-unsaturated sulfoxides.[208] Excellent regio- and stereoselectivities were observed using sodium dimethylmalonate. The reactivity of these substrates was controlled by both the chiral sulfinyl group and the size of the alkyl group attached to the terminus of the allylic system (Scheme 129). This process constituted an example of palladium-mediated resolution of a 50:50 mixture of the two starting acetates.



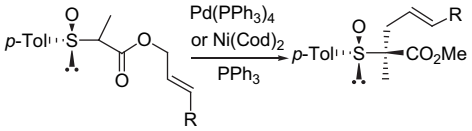
R = Me: 93% de > 96%
R = Et: 89% de > 96%
R = *n*-Pr: 86% de > 96%
R = *n*-Pent: 78% de > 96%
R = *i*-Pr: 71% de > 96%



87% de > 96%

Scheme 129. Palladium-mediated allylic substitution of chiral γ-oxygenated α,β-unsaturated sulfoxides.

The stereochemistry of palladium- or nickel-catalysed asymmetric intramolecular allyl transfer in chiral α-sulfinyl allylic esters has been studied by Hiroi et al.[209] Participation of the catalyst and the chiral sulfinyl functionality in these reactions, presumably by the coordination of the sulfinyl group to the catalyst, allowed the achievement of good diastereoselectivities (Scheme 130).

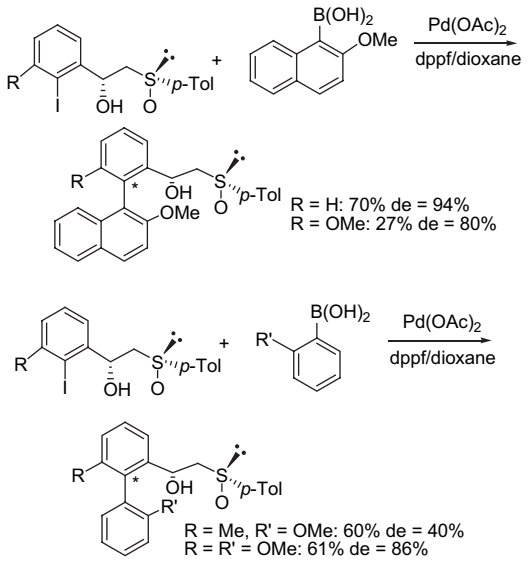


R = H, with $Pd(PPh_3)_4$: 54% de = 94%
R = H, with $Ni(Cod)_2$: 18% de = 87%
R = Me, with $Pd(PPh_3)_4$: 73% de = 98%

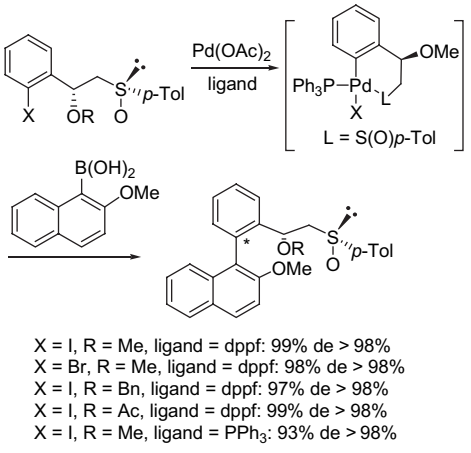
Scheme 130. Transition metal-catalysed intramolecular allyl transfer in α-sulfinyl allylic esters.

Axially chiral biaryls are of importance, not only as chiral ligands in asymmetric reactions, but also as biologically active natural products. Among the few successful methods allowing the asymmetric synthesis of this biaryl subunit are the asymmetric Suzuki reactions, which have been reported only in the past few years. Thus, Colobert et al. have involved enantiopure β-hydroxysulfoxide derivatives as novel chiral auxiliaries in asymmetric biaryl Suzuki reactions in the presence of aryl- or naphthylboronic acids (or esters).[210] High yields were obtained associated with an excellent control of the axial chirality (Scheme 131).

In 2005, the best results were obtained when the chiral sulfoxide was bearing an alkoxy group in the β-position.[211] A plausible mechanism responsible for the high selectivity might reasonably invoke the formation of a palladacycle during the oxidative addition, in which the palladium was coordinated to the internal chelating ligand such as the *p*-tolyl sulfoxide group (Scheme 132).

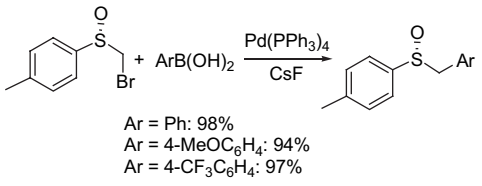


Scheme 131. Biaryl Suzuki coupling reactions of β-hydroxysulfoxide derivatives with aryl- or naphthylboronic acids.



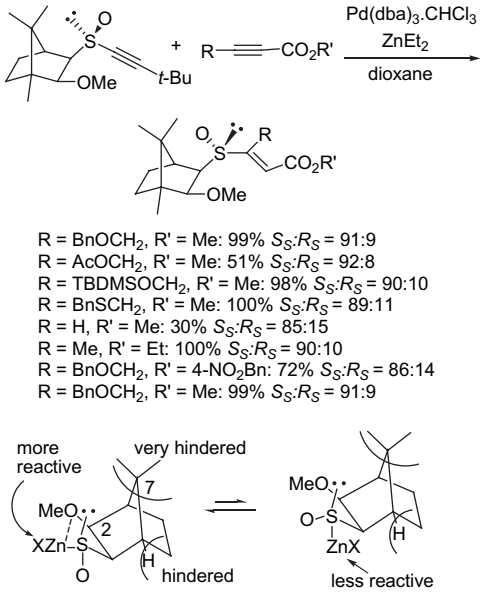
Scheme 132. Suzuki reactions of phenyl halide-containing protected β-hydroxysulfoxide derivatives with 2-methoxynaphthylboronic acid.

On the other hand, palladium-catalysed cross-coupling reactions of chiral α-bromo sulfoxides with arylboronic acids were reported in 2004 allowing the formation of a new C sp^3–sp^2 bond (Scheme 133).[212] The corresponding chiral aryl benzyl sulfoxides were isolated in high yields despite the previously reported racemisation of the chiral sulfur centre in chiral α-sulfinyl–palladium(II) complexes.[213]



Scheme 133. Palladium-catalysed reaction of boronic acids with α-bromo sulfoxides.

In 2003, Tanaka et al. accomplished a novel asymmetric sulfinylzincation of alkynoates via a palladium-catalysed sulfinylzincation using 1-alkynyl sulfoxides bearing chiral auxiliaries such as isoborneol as a sulfinylating reagent.[214] The reaction proceeded in a highly *syn*-selective fashion, giving the (*E*)-β-sulfinyl α,β-unsaturated ester exclusively (Scheme 134). The diastereoselectivity of the reaction could be interpreted (Scheme 134) by postulating that, in the preferred conformer of the sulfinylzinc species, the smallest lone pair electron would situate at the most crowded space near one of the C_7–Me and C_2–MeO groups.

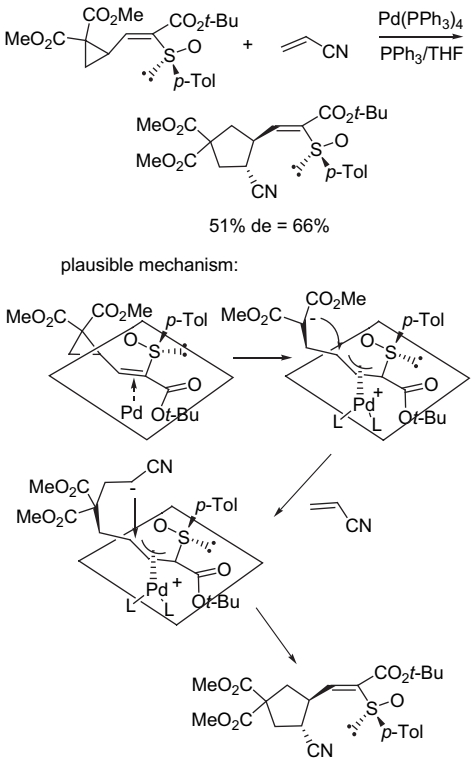


Scheme 134. Asymmetric sulfinylzincation of 1-alkynoates with chiral 1-alkynyl sulfoxides.

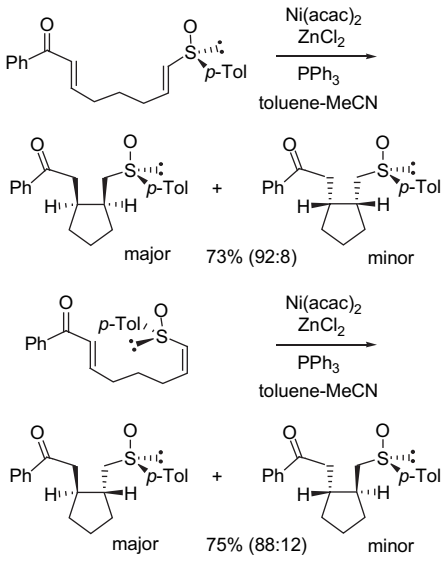
Asymmetric synthesis of a cyclopentane derivative using a chiral sulfinyl functionality as the chiral source has been successfully executed by a transition metal-catalysed asymmetric cycloaddition reaction of a chiral (β-sulfinyl) vinylcyclopropane derivative to acrylonitrile.[215] A plausible mechanism is depicted in Scheme 135, involving an intermediary π-allylpalladium complex formed by the effect of the chiral sulfinyl group, without steric control by the racemic carbon centre. The palladium catalyst would react from the sterically less crowded downward direction on the same side as the sterically smallest lone pair side of the chiral sulfinyl group in the conformationally most stable conformer having coplanarity between the olefinic bond and the sulfur–oxygen bond of the sulfinyl group, affording a chiral π-allylpalladium complex possessing a chiral sulfinyl group at the α-site. The carbanion formed would undergo a conjugate addition to acrylonitrile. The thus-formed α-carbanion to the cyano group would react from the back side of the palladium catalyst at the sterically less crowded γ-site in the π-allylpalladium system, to afford the final product.

In 2005, Tanaka et al. reported the diastereoselective Ni(0)-catalysed carbocyclisation of enone to chiral vinylic sulfoxide, in which two stereogenic centres were constructed simultaneously to give cis- and trans-disubstituted cyclopentanes from (*E*)- and (*Z*)-vinylic sulfoxides, respectively (Scheme 136).[216]

Sato et al. have developed a new tandem asymmetric reaction constituted by a titanium-promoted cyclisation and a Pummerer reaction involving a chiral enyne bearing a vinylic sulfoxide moiety as chiral starting material (Scheme 137).[217]

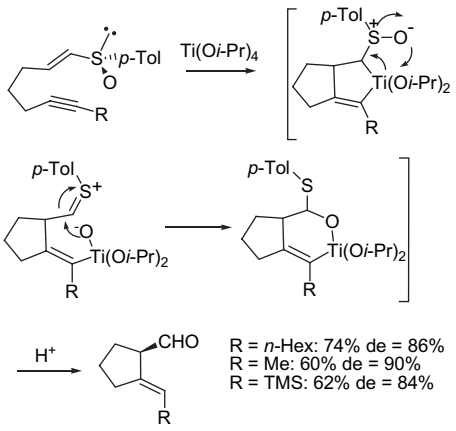


Scheme 135. Palladium-catalysed asymmetric cycloaddition.

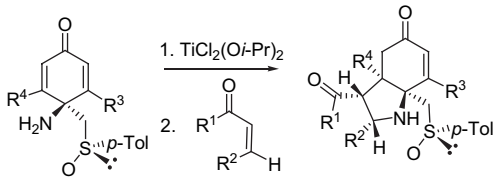


Scheme 136. Ni(0)-catalysed carbocyclisation to chiral vinylic sulfoxide.

In addition, a titanium-promoted stereoselective synthesis of hydroindolones, commonly found in alkaloids, from *p*-quinamines bearing a chiral sulfoxide was accomplished by Carreno et al. on the basis of a domino conjugate reaction.[218] Thus, the reaction of chiral 4-[(*p*-tolylsulfinyl)methyl]-*p*-quinamines with α,β-unsaturated ketones in the presence of $TiCl_2(O\textit{i}\text{-}Pr)_2$ yielded stereoselectively the corresponding hydroindolones as a single diastereoisomer (Scheme 138). The method allowed quaternary centres to be created efficiently with a single configuration through consistent asymmetric induction.



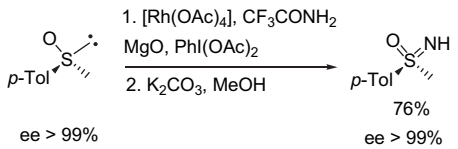
Scheme 137. Asymmetric tandem titanium-promoted cyclisation/Pummerer reactions.



$R^1,R^2 = (CH_2)_2$, $R^3 = R^4 = H$: 60%
$R^1,R^2 = (CH_2)_3$, $R^3 = R^4 = H$: 60%
R^1 = Et, $R^2 = R^3 = R^4 = H$: 51%
R^1 = Et, $R^2 = H$, R^3 = Me, $R^4 = H$: 54%
$R^1,R^2 = (CH_2)_2$, R^3 = Me, $R^4 = H$: 50%
$R^1,R^2 = (CH_2)_3$, R^3 = Me, $R^4 = H$: 54%
R^1 = Me, $R^2 = R^3 = H$, R^4 = Me: 68%
R^1 = Et, $R^2 = R^3 = H$, R^4 = Me: 62%

Scheme 138. Asymmetric domino titanium-promoted conjugate reactions.

Various sulfoxides have been converted into their corresponding sulfoximines using $[Rh(OAc)_4]$ as a catalyst with trifluoroacetamide in combination with iodobenzene diacetate and magnesium oxide.[219] Synthetically valuable *NH*-sulfoximines could easily be obtained by cleavage of the *N*-acyl bond of the resulting *N*-trifluoroacetyl-protected derivatives. The imination reaction was stereospecific and proceeded with retention of configuration at the stereogenic centre. Consequently, enantiomerically pure sulfoximines were accessible by starting from chiral sulfoxides (Scheme 139).



Scheme 139. Rhodium-catalysed imination of chiral sulfoxides.

9. Conclusions

The main purpose of this review has been to demonstrate the growing potential of enantiomerically pure sulfur reagents in transmitting chirality to other centres, establishing the sulfinyl group as an excellent stereocontrolling element in various asymmetric reactions.

The chiral sulfinyl group clearly appears to be one of the most efficient and versatile chiral controllers in C–C and C–X bond formations.

The key to success is related to the steric and electronic differences between the substituents at sulfur, as well as to the conformational behaviour of the sulfinyl group, which is able to react in a rigid conformation. The presence in the reaction medium of metal atoms in the reagents or in an added catalyst, which may undergo a bonding interaction with the sulfinyl oxygen, can dramatically modify the nature of the reactive conformation, in many cases being able to achieve products of opposite configuration from a common starting material by changing the reaction conditions.

An advantage of using chiral sulfinyl auxiliaries is that they can be readily introduced to effect the diastereomeric induction and subsequently can be removed to afford the molecule of interest. Moreover, the stereochemical course can be successfully navigated by the configuration of the sulfoxide and the reaction conditions.

This review amply demonstrates that new examples and methodologies using chiral sulfoxides for asymmetric syntheses continue to emerge in the literature. In particular, the utility of chiral sulfoxides in asymmetric syntheses of biologically interesting compounds is well documented.

References and notes

1. Mikolajczk, M.; Drabowicz, J.; Kielbasinski, P. *Chiral Sulfur Reagents*; CRC: Boca Raton, New York, NY, 1997.
2. (a) Mikolajczyk, M.; Drabowicz, J. *Top. Curr. Chem.* **1982**, *13*, 333–468; (b) Barbachyn, M. R.; Johnson, C. R. *Asymmetric Synthesis* **1984**, *4*, 227–261; (c) Carreno, M. C. *Chem. Rev.* **1995**, *95*, 1717–1760; (d) Matsuyama, H. *Sulfur Rep.* **1999**, *22*, 85–121; (e) Pyne, S. G. *Sulfur Rep.* **1999**, *21*, 281–334; (f) Taylor, P. C. *Sulfur Rep.* **1999**, *21*, 241–280; (g) Masdeu-Bultó, A. M.; Diéguez, M.; Martin, E.; Gómez, M. *Coord. Chem. Rev.* **2003**, *242*, 159–201; (h) Bayón, J. C.; Claver, C.; Masdeu-Bultó. *Coord. Chem. Rev.* **1999**, *193–195*, 73–145; (i) Solladié, G. *Enantiomer* **1999**, *4*, 183–193; (j) Blake, A. J.; Cooke, P. A.; Kendall, J. D.; Simpkins, N. S.; Westaway, S. M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 153–163.
3. (a) Andersen, K. K. *The Chemistry of Sulfones and Sulfoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; Wiley: New York, NY, 1988; Chapter 3, pp 56–94; (b) Walker, A. J. *Tetrahedron: Asymmetry* **1992**, *3*, 961–998; (c) Solladié, G. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, Chapter 3, pp 148–170; (d) Kresze, G. Methoden der Organischen Chemie (Houben-Weyl). Klamann, D., Ed.; Georg Thieme: Stuttgart, 1985; pp 669–886; (e) Solladié, G.; Carreno, M. C. *Organosulfur Chemistry. Synthetic Aspects*; Page, P. C. B., Ed.; Academic: New York, NY, 1995; Chapter 1, pp 1–47.
4. (a) Solladié, G. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, NY, 1983; Vol. 2, pp 157–199; (b) Cinquini, M.; Cozzi, F.; Montanari, F. *Organic Sulfur Chemistry, Theoretical and Experimental Advances*; Bernardi, F., Csizmadia, G., Mangini, A., Eds.; Elsevier: Amsterdam, 1985; (c) Hua, D. H. *Advances in Carbanion Chemistry*; Snieckus, V., Ed.; JAI: London, 1992; Vol. 1, pp 249–281; (d) Hua, D. H. *Adv. Heterocycl. Nat. Prod. Synth.* **1996**, *3*, 151–177.
5. (a) Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 641–668; (b) Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 835–871.
6. (a) Khiar, N.; Fernandez, I.; Alcudia, A.; Alcudia, F. *Advances in Sulfur Chemistry*; Rayner, C. M., Ed.; JAI: Stanford, CT, 2000; Vol. 2; Chapter 3, p 57; (b) Rayner, C. M. *Contemp. Org. Synth.* **1994**, *1*, 191–203; (c) Procter, D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 335–354.
7. Drabowicz, J.; Kielbasinski, P.; Mikolajczyk, M. *The Chemistry of Sulfones and Sulfoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; Wiley: New York, NY, 1988; pp 233–378.
8. Legros, J.; Dehli, J. R.; Bolm, C. *Adv. Synth. Catal.* **2005**, *347*, 19–31.
9. (a) Kagan, H. B.; Rebiere, F.; Samuel, O. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *58*, 89–110; (b) Allin, S. M. *Organosulfur Chemistry*; Academic: London, 1998; p 41.
10. Andersen, K. K. *Tetrahedron Lett.* **1962**, *3*, 93–95.
11. Andersen, K. K.; Gaffield, W.; Papanikolau, N. E.; Foley, J. W.; Perkins, R. I. *J. Am. Chem. Soc.* **1964**, *86*, 5637–5646.
12. Axelrod, M.; Bickart, P.; Jacobus, J.; Green, M. M.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *90*, 4835–4842.
13. (a) Wudl, F.; Lee, T. B. K. *J. Am. Chem. Soc.* **1973**, *95*, 6349–6358; (b) Rebiere, F.; Kagan, H. B. *Tetrahedron Lett.* **1989**, *30*, 3659–3662; (c) Fernandez, I.; Khiar, N.; Llera, J. M.; Alcudia, F. *J. Org. Chem.* **1992**, *57*, 6789–6796; (d) Fernandez, I.; Khiar, N.; Alcudia, F. *Tetrahedron Lett.* **1994**, *35*, 5719–5722.
14. Korte, A.; Legros, J.; Bolm, C. *Synlett* **2004**, 2397–2399.
15. Maguire, A. R.; Papot, S.; Ford, A.; Touhey, S.; O'Connor, R.; Clynes, M. *Synlett* **2001**, 41–44.
16. Matsugi, M.; Fukuda, N.; Muguruma, Y.; Yamaguchi, T.; Minamikawa, J.-i.; Otsuka, S. *Tetrahedron* **2001**, *57*, 2739–2744.
17. Wang, C.-C.; Huang, H.-C.; Reitz, D. B. *Org. Prep. Proced. Int.* **2002**, *34*, 271–319.
18. Fernandez, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651–3705.
19. (a) Mikolajczyk, M.; Drabowicz, J.; Kielbasinski, P. *Chiral Sulfur Reagents: Applications in Asymmetric and Stereoselective*; CRC: Boca Raton, FL, 1997; p 195; (b) Zhou, P.; Chen, B.-C.; Davis, F. A. *Advances in Sulfur Chemistry*; Rayner, C. M., Ed.; JAI: Stanford, CT, 2000; Vol. 2, p 249; (c) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13–18; (d) Ellman, J.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984–995; (e) Hua, D. H.; Chen, Y.; Millward, G. S. *Sulfur Rep.* **1999**, *2*, 211–239.
20. Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003–8030.
21. (a) Okamura, H.; Bolm, C. *Chem. Lett.* **2004**, *33*, 482–487; (b) Reggelin, M.; Zur, C. *Synthesis* **2000**, 1–64; (c) Reggelin, M.; Weinberger, H.; Spohr, V. *Adv. Synth. Catal.* **2004**, *346*, 1295–1306.
22. Motohashi, S.; Yasukawa, K.; Takido, M.; Akihisa, T.; Takagi, T.; Nishioka, R.; Tokutake, N. *Synth. Commun.* **2000**, *30*, 4467–4472.
23. Stefani, H.; Menezes, P. H.; Costa, I. M.; Silva, D. O.; Petragnani, N. *Synlett* **2002**, 1335–1336.
24. (a) Solladié, G.; Salom-Roig, X. J.; Hanquet, G. *Tetrahedron Lett.* **2000**, *41*, 551–554; (b) Solladié, G.; Salom-Roig, X. J.; Hanquet, G. *Tetrahedron Lett.* **2000**, *41*, 2737–2740.
25. Colobert, F.; Des Mazery, R.; Solladié, G.; Carreno, M. C. *Org. Lett.* **2002**, *4*, 1723–1725.

26. Bonini, C.; Chiummiento, L.; Pullez, M.; Solladié, G.; Colobert, F. *J. Org. Chem.* **2004**, *69*, 5015–5022.
27. Marino, J. P.; McClure, M. S.; Holub, D. P.; Comasseto, J. V.; Tucci, F. C. *J. Am. Chem. Soc.* **2002**, *124*, 1664–1668.
28. Carreno, M. C.; Des Mazery, R.; Urbano, A.; Colobert, F.; Solladié, G. *J. Org. Chem.* **2003**, *68*, 7779–7787.
29. Carreno, M. C.; Des Mazery, R.; Urbano, A.; Colobert, F.; Solladié, G. *Org. Lett.* **2004**, *6*, 297–299.
30. Brinkmann, Y.; Carreno, M. C.; Urbano, A.; Colobert, F.; Solladié, G. *Org. Lett.* **2004**, *6*, 4335–4338.
31. Nakamura, S.; Nakayama, J.-i.; Toru, T. *J. Org. Chem.* **2003**, *68*, 5766–5768.
32. Carreno, M. C.; Sanz-Cuesta, M. J.; Colobert, F.; Solladié, G. *Org. Lett.* **2004**, *6*, 3537–3540.
33. Solladié, G.; Gressot, L.; Colobert, F. *Eur. J. Org. Chem.* **2000**, 357–364.
34. Yuste, F.; Diaz, A.; Ortiz, B.; Sanchez-Obregon, R.; Walls, F.; Garcia Ruano, J. L. *Tetrahedron: Asymmetry* **2003**, *14*, 549–554.
35. Nakamura, S.; Kuroyanagi, M.; Watanabe, Y.; Toru, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3143–3148.
36. Nakamura, S.; Oda, M.; Yasuda, H.; Toru, T. *Tetrahedron* **2001**, *57*, 8469–8480.
37. Solladié, G.; Colobert, F.; Somny, F. *Tetrahedron Lett.* **1999**, *40*, 1227–1228.
38. Wang, C.-C.; Li, J. J.; Huang, H.-C.; Lee, L. F.; Reitz, D. B. *J. Org. Chem.* **2000**, *65*, 2711–2715.
39. Garcia Ruano, J. L.; Fernandez-Ibanez, M. A.; Maestro, M. C.; Rodriguez-Fernandez, M. M. *J. Org. Chem.* **2005**, *70*, 1796–1801.
40. Solladié, G. *Heteroat. Chem.* **2002**, *13*, 443–452.
41. Solladié, G.; Gressot-Kempf, L. *Tetrahedron: Asymmetry* **1996**, *7*, 2371–2379.
42. Solladié, G.; Almario, A. *Tetrahedron: Asymmetry* **1995**, *6*, 559–576.
43. Solladié, G.; Huser, N. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 153–156.
44. Solladié, G.; Bauder, C.; Rossi, L. *J. Org. Chem.* **1995**, *60*, 7774–7777.
45. Solladié, G.; Huster, N. *Tetrahedron: Asymmetry* **1995**, *6*, 2679–2682.
46. Solladié, G.; Arce, E.; Bauder, C. *J. Org. Chem.* **1998**, *63*, 2332–2337.
47. Izzo, I.; Crumbie, R.; Solladié, G.; Hanquet, G. *Tetrahedron: Asymmetry* **2005**, *16*, 1503–1511.
48. (a) Page, P. C. B.; *Organosulfur Chemistry, Synthetic and Stereochemical Aspects*; Academic: London, 1998; Vol. 2; (b) Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1339–1367; (c) Rayner, C. M. *Contemp. Org. Synth.* **1996**, *3*, 499–533; (d) Metzner, P.; Thuillier, A. *Sulfur Reagents in Organic Synthesis*; Academic: London, 1994; (e) Solladié, G. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, p 133.
49. Maignan, C.; Raphael, R. A. *Tetrahedron* **1983**, *39*, 3245–3249.
50. (a) Guessous, A.; Rouessac, F.; Maignan, C. *Bull. Soc. Chim. Fr.* **1986**, 837–843; (b) De Lucchi, O.; Lucchini, V.; Marchioro, C.; Valle, G.; Modena, G. *J. Org. Chem.* **1986**, *51*, 1457–1466.
51. Fuji, K.; Tanaka, K.; Abe, H.; Matsumoto, K.; Harayama, T.; Ikeda, A.; Taga, T.; Miwa, Y.; Node, M. *J. Org. Chem.* **1994**, *59*, 2211–2218.
52. Lopez, R.; Carretero, J. C. *Tetrahedron: Asymmetry* **1991**, *2*, 93–96.
53. (a) Arai, Y.; Kuwayama, S.; Takeuchi, Y.; Koizumi, T.; Masuda, T.; Masaki, Y. *Synth. Commun.* **1986**, *16*, 233–244; (b) De Lucchi, O.; Fabbri, D.; Lucchini, V. *Synlett* **1991**, 565–568; (c) Aggarwal, V. N.; Lightower, M.; Lindell, S. D. *Synlett* **1992**, 730–732; (d) Katagiri, N.; Ise, S.; Watanabe, N.; Kaneko, C. *Chem. Pharm. Bull.* **1990**, *38*, 3242–3248; (e) Carretero, J. C.; Garcia Ruano, J. L.; Martin-Cabrejas, L. M. *Tetrahedron: Asymmetry* **1997**, *8*, 409–416.
54. (a) Garcia Ruano, J. L.; Alemparte, C.; Martin Castro, A. M.; Adams, H.; Rodriguez Ramos, J. H. *J. Org. Chem.* **2000**, *65*, 7938–7943; (b) Garcia Ruano, J. L.; Gamboa, A. E.; Martin Castro, A. M.; Rodriguez, J. H.; Lopez-Solera, M. I. *J. Org. Chem.* **1998**, *63*, 3324–3332.
55. Arai, Y.; Koizumi, T. *Sulfur Rep.* **1993**, *15*, 41–65.
56. De Lucchi, O.; Pasquato, L. *Tetrahedron* **1988**, *44*, 6755–6794.
57. Arai, Y.; Koizumi, T. *Rev. Heteroat. Chem.* **1992**, *6*, 202–217.
58. Carreno, M. C.; Ribagorda, M.; Somoza, A.; Urbano, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 2755–2757.
59. (a) Lee, A. W. M.; Chan, W. H. *Top. Curr. Chem.* **1997**, *190*, 103–129; (b) Garcia Ruano, J. L.; Carretero, J. C.; Carreno, M. C.; Martin, L. C.; Urbano, A. *Pure Appl. Chem.* **1996**, *68*, 925–930; (c) Garcia Ruano, J. L.; Cid, B. *Top. Curr. Chem.* **1999**, *204*, 1–126.
60. (a) Carreno, M. C.; Garcia Ruano, J. L.; Toledo, M. A.; Urbano, A.; Remor, C. Z.; Stefani, V.; Fischer, J. *J. Org. Chem.* **1996**, *61*, 503–509; (b) Carreno, M. C.; Garcia Ruano, J. L.; Remor, C. Z.; Urbano, A. *Tetrahedron Lett.* **1997**, *38*, 9077–9090; (c) Carreno, M. C.; Garcia-Cerrada, S.; Urbano, A.; Di Vitta, C. *Tetrahedron: Asymmetry* **1998**, *9*, 2965–2969; (d) Carreno, M. C.; Urbano, A. *Synlett* **2005**, 1–25.
61. Carreno, M. C.; Urbano, A.; Di Vitta, C. *Chem. Commun.* **1999**, 817–818.
62. Carreno, M. C.; Garcia Ruano, J. L.; Urbano, A.; Remor, C. Z.; Arroyo, Y. *J. Org. Chem.* **2000**, *65*, 453–458.
63. Carreno, M. C.; Garcia Ruano, J. L.; Remor, C. Z.; Urbano, A. *Tetrahedron: Asymmetry* **2000**, *11*, 4279–4296.
64. Carreno, M. C.; Garcia-Cerrada, S.; Sanz-Cuesta, J. S.; Urbano, A. *J. Org. Chem.* **2003**, *68*, 4315–4321.
65. Garcia Ruano, J. L.; Alemparte, C. *J. Org. Chem.* **2004**, *69*, 1405–1408.
66. Carreno, M. C.; Garcia Ruano, J. L.; Toledo, M. A. *Chem.—Eur. J.* **2000**, *6*, 288–291.
67. (a) Carreno, M. C.; Garcia-Cerrada, S.; Sanz-Cuesta, M. J.; Urbano, A. *Chem. Commun.* **2001**, 1452–1453; (b) Carreno, M. C.; Garcia-Cerrada, S.; Urbano, A. *J. Am. Chem. Soc.* **2001**, *123*, 7929–7930; (c) Carreno, M. C.; Garcia-Cerrada, S.; Urbano, A. *Chem. Commun.* **2002**, 1412–1413; (d) Carreno, M. C.; Garcia-Cerrada, S.; Urbano, A. *Chem.—Eur. J.* **2003**, *9*, 4118–4131.
68. Carreno, M. C.; Garcia-Cerrada, S.; Urbano, A.; Di Vitta, C. *J. Org. Chem.* **2000**, *65*, 4355–4363.
69. Carreno, M. C.; Urbano, A.; Di Vitta, C. *Chem.—Eur. J.* **2000**, *6*, 906–913.
70. Garcia Ruano, J. L.; Gutiérrez, L. G.; Martin Castro, A. M.; Yuste, F. *Tetrahedron: Asymmetry* **2002**, *13*, 2003–2010.
71. Garcia Ruano, J. L.; Bercial, F.; Fraile, A.; Martin Castro, A. M.; Martin, M. R. *Tetrahedron: Asymmetry* **2000**, *11*, 4737–4752.
72. Ordonez, M.; Guerrero de la Rosa, V.; Alcudia, F.; Llera, J. M. *Tetrahedron* **2004**, *60*, 871–875.

73. Gonzalez-Temprano, I.; Sotomayor, N.; Lete, E. *Synlett* **2002**, 593–597.
74. Aucagne, V.; Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P.; Rollin, A.; Tatibouët, A. *J. Org. Chem.* **2002**, *67*, 6925–6930.
75. Delouvrié, B.; Fensterbank, L.; Nàjera, F.; Malacria, M. *Eur. J. Org. Chem.* **2002**, 3507–3525.
76. (a) Carreno, M. C.; Cid, M. B.; Garcia Ruano, J. L. *Tetrahedron: Asymmetry* **1996**, *7*, 2151–2158; (b) Gosselin, P.; Bonfand, E.; Maignan, C. *J. Org. Chem.* **1996**, *61*, 9049–9052; (c) Yang, T.; Chu, H.; Lee, D.; Jiang, Y.; Chou, T. *Tetrahedron Lett.* **1996**, *37*, 4537–4540.
77. Aranda, M. T.; Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Carreno, M. C.; Cid, M. B.; Garcia Ruano, J. L. *Tetrahedron: Asymmetry* **2000**, *11*, 1217–1225.
78. Chou, S.-S. P.; Liang, P.-W. *Tetrahedron Lett.* **2002**, *43*, 4865–4870.
79. Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Bruno, G.; Caruso, F.; Giannetto, P. *Tetrahedron: Asymmetry* **2001**, *12*, 2901–2908.
80. De la Pradilla, F. R.; Montero, C.; Tortosa, M.; Viso, A. *Chem.—Eur. J.* **2005**, *11*, 5136–5145.
81. De la Pradilla, R. F.; Baile, R.; Tortosa, M. *Chem. Commun.* **2003**, 2476–2477.
82. Arribas, C.; Carreno, M. C.; Garcia Ruano, J. L.; Rodriguez, J. F.; Santos, M.; Sanz-Tejedor, M. A. *Org. Lett.* **2000**, *2*, 3165–3168.
83. Aversa, M. C.; Barattucci, A.; Bilardo, M. C.; Bonaccorsi, P.; Giannetto, P. *Synthesis* **2003**, *14*, 2241–2248.
84. Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P.; Policicchio, M. *J. Org. Chem.* **2001**, *66*, 4845–4851.
85. Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–909.
86. (a) Garcia Ruano, J. L.; Fraile, A.; Martin, M. R. *Tetrahedron: Asymmetry* **1996**, *7*, 1943–1950; (b) Garcia Ruano, J. L.; Fraile, A.; Martin, M. R. *Tetrahedron* **1999**, *55*, 14491–14500.
87. Garcia Ruano, J. L.; Tito, A.; Peromingo, M. T. *J. Org. Chem.* **2002**, *67*, 981–985.
88. Garcia Ruano, J. L.; Tito, A.; Peromingo, M. T. *J. Org. Chem.* **2003**, *68*, 10013–10019.
89. Garcia Ruano, J. L.; Bercial, F.; Gonzalez, G.; Martin Castro, A. M.; Rosario Martin, M. *Tetrahedron: Asymmetry* **2002**, *13*, 1993–2002.
90. Garcia Ruano, J. L.; Fraile, A.; Gonzalez, G.; Rosario Martin, M.; Clemente, F. R.; Gordillo, R. *J. Org. Chem.* **2003**, *68*, 6522–6534.
91. (a) Garcia Ruano, J. L.; Alonso de Diego, S. A.; Blanco, D.; Martin Castro, A. M.; Rosario Martin, M.; Rodriguez Ramos, J. H. *Org. Lett.* **2001**, *3*, 3173–3176; (b) Garcia Ruano, J. L.; Alonso de Diego, S. A.; Martin, M. R.; Torrente, E.; Martin Castro, A. M. *Org. Lett.* **2004**, *6*, 4945–4948.
92. Garcia Ruano, J. L.; Andrés Gil, J. I.; Fraile, A.; Martin Castro, A. M.; Rosario Martin, M. *Tetrahedron Lett.* **2004**, *45*, 4653–4656.
93. Prakash, K. R. C.; Trzcinska, M.; Johnson, K. M.; Kozikowski, A. P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1443–1446.
94. Aggarwal, V. K.; Grainger, R. S.; Newton, G. K.; Spargo, P. L.; Hobson, A. D.; Adams, H. *Org. Biomol. Chem.* **2003**, *1*, 1884–1893.
95. (a) Aggarwal, V. K.; Roseblade, S.; Alexander, R. *Org. Biomol. Chem.* **2003**, *1*, 684–691; (b) Aggarwal, V. K.; Roseblade, S.; Barrell, J. K.; Alexander, R. *Org. Lett.* **2002**, *4*, 1227–1229.
96. Montana, A. M.; Grima, P. M. *Tetrahedron Lett.* **2002**, *43*, 2017–2021.
97. (a) Lopez, F.; Castedo, L.; Mascarenas, J. L. *Org. Lett.* **2000**, *2*, 1005–1007; (b) Lopez, F.; Castedo, L.; Mascarenas, J. L. *Org. Lett.* **2001**, *3*, 623–625; (c) Lopez, F.; Castedo, L.; Mascarenas, J. L. *Org. Lett.* **2002**, *4*, 3683–3685.
98. Lopez, F.; Castedo, L.; Mascarenas, J. L. *Chem.—Eur. J.* **2002**, *8*, 884–899.
99. Chai, Y.; Hong, S.-P.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905–2928.
100. (a) Nowaczyk, S.; Alayrac, C.; Reboul, V.; Metzner, P.; Averbuch-Pouchot, M.-T. *J. Org. Chem.* **2001**, *66*, 7841–7848; (b) Blot, V.; Brière, J.-F.; Davoust, M.; Minière, S.; Reboul, V.; Metzner, P. *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, *180*, 1171–1182.
101. De la Pradilla, R. F.; Montero, C.; Tortosa, M. *Org. Lett.* **2002**, *4*, 2373–2376.
102. Marino, J. P.; Rubio, M. B.; Cao, G.; de Dios, A. *J. Am. Chem. Soc.* **2002**, *124*, 13398–13399.
103. Solladié, G. *Synthesis* **1981**, 185–196.
104. Nakamura, S.; Takemoto, H.; Ueno, Y.; Toru, T.; Kakumoto, T.; Hagiwara, T. *J. Org. Chem.* **2000**, *65*, 469–474.
105. (a) Van Steenis, J. H.; van Es, J. J. G. S.; van der Gen, A. *Eur. J. Org. Chem.* **2000**, 2787–2793; (b) Van Steenis, J. H.; Boer, P. W. S.; van der Hoeven, H. A.; van der Gen, A. *Eur. J. Org. Chem.* **2001**, 911–918.
106. Satoh, T.; Hirano, M.; Kuroiwa, A. *Tetrahedron Lett.* **2005**, *46*, 2659–2662.
107. Delouvrié, B.; Nàjera, F.; Fensterbank, L.; Malacria, M. *J. Organomet. Chem.* **2002**, *643–644*, 130–135.
108. Aggarwal, V. K.; Schade, S.; Adams, H. *J. Org. Chem.* **1997**, *62*, 1139–1145.
109. Vargas-Diaz, M. E.; Lagunas-Rivera, S.; Joseph-Nathan, P.; Tamariz, J.; Zepeda, L. G. *Tetrahedron Lett.* **2005**, *46*, 3297–3300.
110. Ronan, B.; Marchalin, S.; Samuel, O.; Kagan, H. B. *Tetrahedron Lett.* **1988**, *29*, 6101–6104.
111. Garcia Ruano, J. L.; Alcudia, A.; del Prado, M.; Barros, D.; Maestro, M. C.; Fernandez, I. *J. Org. Chem.* **2000**, *65*, 2856–2862.
112. (a) Volonterio, A.; Bravo, P.; Pesenti, C.; Zanda, M. *Tetrahedron Lett.* **2001**, *42*, 3985–3988; (b) Naimi-Jamal, M. R.; Ipaktschi, J.; Saidi, M. R. *Eur. J. Org. Chem.* **2000**, 1735–1739; (c) Zucca, C.; Bravo, P.; Corradi, E.; Meille, S. V.; Volonterio, A.; Zanda, M. *Molecules* **2001**, *6*, 424–432; (d) Cabiddu, S.; Cadoni, E.; Ianni, A.; Gelli, G.; Melis, S.; Bernard, A. M.; Cabbidu, M. G.; De Montis, S.; Fattuoni, C. *Eur. J. Org. Chem.* **2002**, 3393–3401.
113. Pedersen, B.; Rein, T.; Sotofte, I.; Norrby, P.-O.; Tanner, D. *Collect. Czech. Chem. Commun.* **2003**, *68*, 885–898.
114. Pesenti, C.; Arnone, A.; Arosio, P.; Frigerio, M.; Meille, S. V.; Panzeri, W.; Viani, F.; Zanda, M. *Tetrahedron Lett.* **2004**, *45*, 5125–5129.
115. Pesenti, C.; Bravo, P.; Corradi, E.; Frigerio, M.; Meille, S. V.; Panzeri, W.; Viani, F.; Zanda, M. *J. Org. Chem.* **2001**, *66*, 5637–5640.
116. Sivakumar, A. V.; Babu, G. S.; Bhat, S. V. *Tetrahedron: Asymmetry* **2001**, *12*, 1095–1099.
117. Raghavan, S.; Rajender, A. *Tetrahedron* **2004**, *60*, 5059–5067.
118. Satoh, T.; Matsue, R.; Fujii, T.; Morikawa, S. *Tetrahedron* **2001**, *57*, 3891–3898.
119. Hanrahan, J. R.; Knight, D. W.; Salter, R. *Synlett* **2001**, 1587–1589.

120. Nakamura, S.; Kusuda, S.; Kawamura, K.; Toru, T. *J. Org. Chem.* **2002**, *67*, 640–647.
121. De la Pradilla, R. F.; Fernandez, J.; Manzano, P.; Mendez, P.; Priego, J.; Tortosa, M.; Viso, A.; Martinez-Ripoll, M.; Rodriguez, A. *J. Org. Chem.* **2002**, *67*, 8166–8177.
122. De la Pradilla, R. F.; Buergo, M. V.; Martinez, M. V.; Montero, C.; Tortosa, M.; Viso, A. *J. Org. Chem.* **2004**, *69*, 1978–1986.
123. Garcia Ruano, J. L.; Carreno, M. C.; Toledo, M. A.; Aguirre, J. M.; Aranda, M. T.; Fischer, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2736–2737.
124. (a) Garcia Ruano, J. L.; Aranda, M. T.; Aguirre, J. M. *Tetrahedron* **2004**, *60*, 5383–5392; (b) Garcia Ruano, J. L.; Aleman, J.; Aranda, M. T.; Fernandez-Ibanez, M. A.; Rodriguez-Fernandez, M. M.; Maestro, M. C. *Tetrahedron* **2004**, *60*, 10067–10075.
125. Garcia Ruano, J. L.; Aleman, J.; Soriano, J. F. *Org. Lett.* **2003**, *5*, 677–680.
126. Garcai Ruano, J. L.; Aleman, J. *Org. Lett.* **2003**, *5*, 4513–4516.
127. Garcia Ruano, J. L.; Martin Castro, A. M.; Tato, F.; Pastor, C. J. *J. Org. Chem.* **2005**, *70*, 7346–7352.
128. Maezaki, N.; Izumi, M.; Yuyama, S.; Sawamoto, H.; Iwata, C.; Tanaka, T. *Tetrahedron* **2000**, *56*, 7927–7945.
129. Nakamura, S.; Watanabe, Y.; Toru, T. *J. Org. Chem.* **2000**, *65*, 1758–1766.
130. Nakamura, S.; Uchiyama, Y.; Ishikawa, S.; Fukinbara, R.; Watanabe, Y.; Toru, T. *Tetrahedron Lett.* **2002**, *43*, 2381–2383.
131. Acherki, H.; Alvarez-Ibarra, C.; de Dios, A.; Gutiérrez, M.; Quiroga, M. L. *Tetrahedron: Asymmetry* **2001**, *12*, 3173–3183.
132. Nowaczyk, S.; Alayrac, C.; Metzner, P.; Averbuch-Pouchot, M.-T. *J. Org. Chem.* **2002**, *67*, 6852–6855.
133. Fernandez, I.; Araujo, C. S.; Romero, M. J.; Alcudia, F.; Khiar, N. *Tetrahedron* **2000**, *56*, 3749–3753.
134. (a) Maezaki, N.; Yutama, S.; Sawamoto, H.; Suzuki, T.; Izumi, M.; Tanaka, T. *Org. Lett.* **2001**, *3*, 29–31; (b) Maezaki, N.; Sawamoto, H.; Yuyama, S.; Yoshigami, R.; Suzuki, T.; Izumi, M.; Ohishi, H.; Tanaka, T. *J. Org. Chem.* **2004**, *69*, 6335–6340.
135. Lu, J.; Xie, X.; Chen, B.; She, X.; Pan, X. *Tetrahedron: Asymmetry* **2005**, *16*, 1435–1438.
136. (a) Forristal, I.; Rayner, C. M. *Advances in Sulfur Chemistry: Recent Advances in the Chemistry of α,β-Unsaturated Sulfoxides and Sulfones*; Rayner, C. M., Ed.; JAI: Stanford, CT, 2000; pp 155–213; (b) Forristal, I. *J. Sulfur Chem.* **2005**, *26*, 163–195.
137. Posner, G. H.; Mallamo, J. P.; Miura, K. *J. Am. Chem. Soc.* **1981**, *103*, 2886–2888.
138. Marino, J. P.; Anna, L. J.; de la Pradilla, R. F.; Martinez, M. V.; Montero, C.; Viso, A. *J. Org. Chem.* **2000**, *65*, 6462–6473.
139. Garcia Ruano, J. L.; Cifuentes Garcia, M.; Laso, N. M.; Martin Castro, A. M.; Rodriguez Ramos, J. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 2507–2509.
140. Garcia Ruano, J. L.; Cifuentes Garcia, M.; Martin Castro, A. M.; Rodriguez Ramos, J. H. *Org. Lett.* **2002**, *4*, 55–57.
141. Satoh, T.; Yoshida, M.; Ota, H. *Tetrahedron Lett.* **2001**, *42*, 9241–9244.
142. Satoh, T.; Yoshida, M.; Takahashi, Y.; Ota, H. *Tetrahedron: Asymmetry* **2003**, *14*, 281–288.
143. Wakasuki, D.; Satoh, T. *Tetrahedron* **2005**, *61*, 1245–1256.
144. Satoh, T.; Kawashima, T.; Takahashi, S.; Sakai, K. *Tetrahedron* **2003**, *59*, 9599–9607.
145. (a) Sugiyama, S.; Satoh, T. *Tetrahedron: Asymmetry* **2005**, *16*, 665–673; (b) Sugiyama, S.; Kido, M.; Satoh, T. *Tetrahedron Lett.* **2005**, *46*, 6771–6775.
146. Brebion, F.; Delouvrié, B.; Nàjera, F.; Fensterbank, L.; Malacria, M.; Vaissermann, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5342–5345.
147. Brebion, F.; Goddard, J. P.; Fensterbank, L.; Malacria, M. *Synthesis* **2005**, *14*, 2449–2452.
148. Maezaki, N.; Sawamoto, H.; Yoshigami, R.; Suzuki, T.; Tanaka, T. *Org. Lett.* **2003**, *5*, 1345–1347.
149. Maezaki, N.; Sawamoto, H.; Suzuki, T.; Yoshigami, R.; Tanaka, T. *J. Org. Chem.* **2004**, *69*, 8387–8391.
150. Sklute, G.; Amsallem, D.; Shabli, A.; Varghese, J. P.; Marek, I. *J. Am. Chem. Soc.* **2003**, *125*, 11776–11777.
151. Midura, W. H.; Krysiak, J. A. *Tetrahedron* **2004**, *60*, 12217–12229.
152. (a) Midura, W. H.; Mikolajczyk, M. *Tetrahedron Lett.* **2002**, *43*, 3061–3065; (b) Midura, W. H.; Krysiak, J. A.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1245–1249; (c) Midura, W. H.; Krysiak, J. A.; Cypryk, M.; Mikolajczyk, M.; Wieczorek, M. W.; Filipczak, A. D. *Eur. J. Org. Chem.* **2005**, 653–662; (d) Garcia Ruano, J. L.; Fajardo, C.; Martin, M. R.; Midura, W.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **2004**, *15*, 2475–2482.
153. De la Pradilla, R. F.; Viso, A.; Castro, S.; Fernandez, J.; Manzano, P.; Tortosa, M. *Tetrahedron* **2004**, *60*, 8171–8180.
154. Matsuyama, H.; Itoh, N.; Matsumoto, A.; Ohira, N.; Hara, K.; Yoshida, M.; Iyoda, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2924–2930.
155. Montoro, R.; Marquez, F.; Llebaria, A.; Delgado, A. *Eur. J. Org. Chem.* **2003**, 217–223.
156. Tsuchihashi, G.; Mitamura, S.; Ogura, K. *Tetrahedron Lett.* **1973**, 2469–2470.
157. De la Pradilla, R. F.; Tortosa, M. *Org. Lett.* **2004**, *6*, 2157–2160.
158. Ma, D.; Zou, B.; Zhu, W.; Xu, H. *Tetrahedron Lett.* **2002**, *43*, 8511–8513.
159. Forristal, I.; Lawson, K. R.; Rayner, C. M. *Sulfur Lett.* **2003**, *26*, 89–94.
160. De la Pradilla, R. F.; Buergo, M. V.; Manzano, P.; Montero, C.; Priego, J.; Viso, A.; Cano, F. H.; Martinez-Alcazar, M. P. *J. Org. Chem.* **2003**, *68*, 4797–4805.
161. Pummerer, R. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1401–1412.
162. (a) Marino, J. P.; Perez, A. D. *J. Am. Chem. Soc.* **1984**, *106*, 7643–7644; (b) Numata, T.; Itoh, O.; Yoshimura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 257–265; (c) Itoh, O.; Numata, T.; Yoshimura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 266–269.
163. (a) Oae, S.; Numata, T. The Pummerer Type of Reactions. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: New York, NY, 1980; Vol. 5, Chapter 2; (b) Lucchi, O. D.; Miotti, U.; Modena, G. *Org. React.* **1990**, *40*, 157–184.
164. (a) Padwa, A.; Gunn, D. E.; Osterhout, H. M. *Synthesis* **1997**, 1353–1377; (b) Padwa, A. *Pure Appl. Chem.* **2003**, *75*, 47–62.
165. Garcia Ruano, J. L.; Garcia Paredes, C. *Tetrahedron Lett.* **2000**, *41*, 261–265.
166. Garcia Ruano, J. L.; Aleman, J.; Padwa, A. *Org. Lett.* **2004**, *6*, 1757–1760.
167. Garcia Ruano, J. L.; Aleman, J.; Aranda, M. T.; Arévalo, M. J.; Padwa, A. *Org. Lett.* **2005**, *7*, 19–22.
168. Crucianelli, M.; Bravo, P.; Arnone, A.; Corradi, E.; Meille, S. V.; Zanda, M. *J. Org. Chem.* **2000**, *65*, 2965–2971.

169. Volonterio, A.; Bravo, P.; Pesenti, C.; Zanda, M. *Tetrahedron Lett.* **2001**, *42*, 3985–3988.
170. Nakamura, S.; Yasuda, H.; Toru, T. *Tetrahedron: Asymmetry* **2002**, *13*, 1509–1518.
171. Nakamura, S.; Yasuda, H.; Watanabe, Y.; Toru, T. *J. Org. Chem.* **2000**, *65*, 8640–8650.
172. Almorin, A.; Carreno, M. C.; Somoza, A.; Urbano, A. *Tetrahedron Lett.* **2003**, *44*, 5597–5600.
173. Garcia Ruano, J. L.; Barros, D.; Maestro, M. C.; Martin Castro, A. M.; Raithby, P. R. *Tetrahedron: Asymmetry* **2000**, *11*, 4385–4395.
174. Garcia Ruano, J. L.; Rodriguez-Fernandez, M. M.; Maestro, M. C. *Tetrahedron* **2004**, *60*, 5701–5710.
175. Carreno, M. C.; Garcia Luzon, C.; Ribagorda, M. *Chem.—Eur. J.* **2002**, *8*, 208–216.
176. Garcia Ruano, J. L.; Martin Castro, A. M.; Tato, F.; Cardenas, D. J. *Tetrahedron: Asymmetry* **2005**, *16*, 1963–1968.
177. Obringer, M.; Colobert, F.; Neugnot, B.; Solladié, G. *Org. Lett.* **2003**, *5*, 629–632.
178. (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1995; (b) Smadja, W. *Synlett* **1994**, 1–26; (c) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296–304.
179. (a) Roth, M.; Damm, W.; Giese, B. *Tetrahedron Lett.* **1996**, *37*, 351–354; (b) Urabe, H.; Yamashita, K.; Suzuki, K.; Kobayashi, K.; Sato, F. *J. Org. Chem.* **1995**, *60*, 3576–3577; (c) Kundig, E. P.; Xu, L.-H.; Romanens, P. *Tetrahedron Lett.* **1995**, *36*, 4047–4050.
180. (a) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562–2579; (b) Renaud, P. *Chimia* **1997**, *51*, 236–238.
181. Toru, T.; Watanabe, Y.; Mase, N.; Tsusaka, M.; Hayakawa, T.; Ueno, Y. *Pure Appl. Chem.* **1996**, *68*, 711–714.
182. Mase, N.; Watanabe, Y.; Ueno, Y.; Toru, T. *J. Org. Chem.* **1997**, *62*, 7794–7800.
183. Zahouily, M.; Journet, M.; Malacria, M. *Synlett* **1994**, 366–368.
184. Keum, G.; Bang Kang, S.; Kim, Y.; Lee, E. *Org. Lett.* **2004**, *6*, 1895–1897.
185. Brebion, F.; Vitale, M.; Fensterbank, L.; Malacria, M. *Tetrahedron: Asymmetry* **2003**, *14*, 2889–2896.
186. Satoh, T.; Hanaki, N.; Kuramochi, Y.; Inoue, Y.; Hosoya, K.; Sakai, K. *Tetrahedron* **2002**, *58*, 2533–2549.
187. (a) Annunziata, M.; Capozzi, M.; Cardellicchio, C.; Naso, F.; Tortorella, P. *J. Org. Chem.* **2000**, *65*, 2843–2846; (b) Annunziata, M.; Capozzi, M.; Cardellicchio, C.; Naso, F.; Spina, G.; Tortorella, P. *J. Org. Chem.* **2001**, *66*, 5933–5936.
188. Annunziata, M.; Capozzi, M.; Cardellicchio, C.; Naso, F.; Rosito, V. *J. Org. Chem.* **2002**, *67*, 7289–7294.
189. Clara-Sosa, A.; Perez, L.; Sànchez, M.; Melgar-Fernandez, R.; Juaristi, E.; Quintero, L.; Anaya de Parodi, C. *Tetrahedron* **2004**, *60*, 12147–12152.
190. Baker, R. W.; Rea, S. O.; Sargent, M. V.; Schenkelaars, M. C.; Tjahjandarie, T. S.; Totaro, A. *Tetrahedron* **2005**, *61*, 3733–3743.
191. (a) Satoh, T.; Matsue, R.; Fujii, T.; Morikawa, S. *Tetrahedron Lett.* **2000**, *41*, 6495–6499; (b) Satoh, T.; Ozawa, M.; Takano, K.; Chyouma, T.; Okawa, A. *Tetrahedron* **2000**, *56*, 4415–4425.
192. Hitchcock, P. B.; Rowlands, G. J.; Parmar, R. *Chem. Commun.* **2005**, 4219–4221.
193. Maezaki, N.; Li, Y.-X.; Ohkubo, K.; Goda, S.; Iwata, C.; Tanaka, T. *Tetrahedron* **2000**, *56*, 4405–4413.
194. Maezaki, N.; Sakamoto, A.; Nagahashi, N.; Soejima, M.; Li, Y.-X.; Imamura, T.; Kojima, N.; Ohishi, H.; Sakaguchi, K.-i.; Iwata, C.; Tanaka, T. *J. Org. Chem.* **2000**, *65*, 3284–3291.
195. Maezaki, N.; Kojima, N.; Sakamoto, A.; Iwata, C.; Tanaka, T. *Org. Lett.* **2001**, *3*, 429–432.
196. Hegedus, L. S. Transition Metals. In *The Synthesis of Complex Organic Molecules*; University Science Books: Mill Valley, CA, 1994.
197. Diaz Buezo, N.; Mancheno, O. G.; Carretero, J. C. *Org. Lett.* **2000**, *2*, 1451–1454.
198. Diaz Buezo, N.; de la Rosa, J. C.; Priego, J.; Alonso, I.; Carretero, J. C. *Chem.—Eur. J.* **2001**, *7*, 3890–3900.
199. De la Rosa, J. C.; Diaz, N.; Carretero, J. C. *Tetrahedron Lett.* **2000**, *41*, 4107–4111.
200. (a) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263–3283; (b) Bonaga, L. V. R.; Krafft, M. E. *Tetrahedron* **2004**, *60*, 9795–9833; (c) Rodriguez Rivero, M.; Adrio, J.; Carretero, J. C. *Synlett* **2005**, 26–41.
201. (a) Carretero, J. C.; Adrio, J. *Synthesis* **2001**, *12*, 1888–1896; (b) Rodriguez Rivero, M.; Adrio, J.; Carretero, J. C. *Eur. J. Org. Chem.* **2002**, 2881–2889.
202. Rodriguez Rivero, M.; de la Rosa, J. C.; Carretero, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 14992–14993.
203. Rodriguez Rivero, M.; Alonso, I.; Carretero, J. C. *Chem.—Eur. J.* **2004**, *10*, 5443–5459.
204. Hiroi, K.; Watanabe, T. *Heterocycles* **2001**, *54*, 73–76.
205. Marquez, F.; Llebaria, A.; Delgado, A. *Org. Lett.* **2000**, *2*, 547–549.
206. Marquez, F.; Llebaria, A.; Delgado, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1625–1634.
207. Marquez, F.; Montoro, R.; Llebaria, A.; Lago, E.; Molins, E.; Delgado, A. *J. Org. Chem.* **2002**, *67*, 308–311.
208. De la Rosa, V. G.; Ordonez, M.; Llera, J. M. *Tetrahedron: Asymmetry* **2001**, *12*, 1089–1094.
209. Hiroi, K.; Suzuki, Y.; Kato, F.; Kyo, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 37–40.
210. Broutin, P.-E.; Colobert, F. *Org. Lett.* **2003**, *5*, 3281–3284.
211. (a) Broutin, P.-E.; Colobert, F. *Eur. J. Org. Chem.* **2005**, 1113–1128; (b) Broutin, P.-E.; Colobert, F. *Org. Lett.* **2005**, *7*, 3737–3740.
212. Rodriguez, N.; Cuenca, A.; Ramirez de Arellano, C.; Medio-Simon, M.; Peine, D.; Asensio, G. *J. Org. Chem.* **2004**, *69*, 8070–8076.
213. Veya, P.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Organometallics* **1994**, *13*, 441–450.
214. (a) Maezaki, N.; Yagi, S.; Ohsawa, S.; Ohishi, H.; Tanaka, T. *Tetrahedron* **2003**, *59*, 9895–9906; (b) Maezaki, N.; Yagi, S.; Ohsawa, S.; Ohishi, H.; Tanaka, T. *Tetrahedron: Asymmetry* **2002**, *13*, 1961–1964.
215. Hiroi, K.; Yamada, A. *Tetrahedron: Asymmetry* **2000**, 1835–1841.
216. Maezaki, N.; Sawamoto, H.; Ishihara, H.; Tanaka, T. *Chem. Commun.* **2005**, 3992–3994.
217. Narita, M.; Urabe, H.; Sato, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 3671–3674.
218. Carreno, M. C.; Ribagorda, M.; Posner, G. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2753–2754.
219. Okamura, H.; Bolm, C. *Org. Lett.* **2004**, *6*, 1305–1307.

Biographical sketch

Hélène Pellissier was born in Gap, France. She carried out her PhD under the supervision of Dr. G. Gil in Marseille and then entered the Centre National de la Recherche Scientifique in 1988. After a postdoctoral period in Professor K.P.C. Vollhardt's group, she joined the group of Professor M. Santelli in Marseille in 1992, where she focused on the chemistry of BISTRO and its large application in organic synthesis. Thus, she developed several new very short total syntheses of steroids starting from 1,3-butadiene and benzocyclobutenes.