Synthesis of thiols, sulfides, sulfoxides and sulfones

CHRISTOPHER M. RAYNER

School of Chemistry, University of Leeds, Leeds LS2 9JT, UK

Reviewing the literature published between October 1993 and February 1995
Continuing the coverage in *Contemporary Organic Synthesis*, 1994, **1**, 191

1 Introduction

This review continues from the previous one published in 1994,[1] and covers new methods for the synthesis of acyclic thiols, sulfides, sulfoxides and sulfones. Cyclic systems will be covered elsewhere. A similar format has been adopted to that of the previous review in that it is divided into three Sections: thiols and sulfides; sulfoxides; and sulfones. Each section begins with synthetic routes to simple systems, and then goes on to consider methods leading to more complex, polyfunctional molecules. Considerable emphasis has been placed on stereo- and enantio-selective reactions, reflecting the current interest in this area.

A number of new texts on organosulfur chemistry have appeared over the past year or so. There is a recent edition of Patai on the chemistry of sulfur-containing functional groups.[2] Along with the usual physical aspects of organosulfur compounds, it contains chapters on the carbon acidity, pyrolysis, and electrochemistry of organosulfur compounds, thiyl radicals, synthesis of isotopically labelled organosulfur compounds, soft metal ion promoted reactions, thiol-disulfide interchange, vinyl sulfides, high-coordinated sulfur compounds and biological activity of sulfoxides and sulfones. A more general text on sulfur reagents in organic synthesis has also been published.[3] Recently, the first of a new series of books on the synthetic aspects of organosulfur chemistry has also appeared, this volume containing chapters on β-ketosulfoxides, homolytic processes at sulfur, thiiranium ions, 1,3-dithioacetals and thioaldehydes.[4]

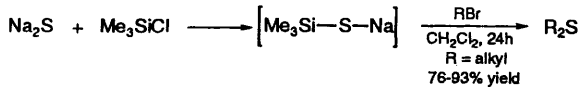
2 Synthesis of thiols and sulfides

There has been a review of thiols as synthons.[5] The chemistry of thiols is included in a lengthy review on organosulfur chemistry.[6] The manufacture, main uses, and potential developments of industrial sulfur compounds have also been reviewed.[7]

2.1 Simple alkylthiols and dialkylsulfides

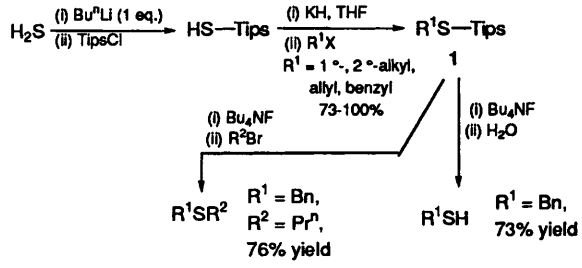
The reaction of alkyl halides with various nucleophilic sulfur species is one of the classic methods of thioether synthesis. A recent report utilizes a borohydride exchange resin with phenyldisulfide in MeOH to generate a nucleophilic phenylthiolate which reacts with primary alkyl bromides, iodides and epoxides to give the expected phenylthioethers.[8] Secondary alkyl halides are also successful but require the use of elevated temperatures. The main benefit of this procedure is that essentially pure product can be obtained simply by removing the resin by filtration. The use of freshly prepared Na_2S–Al_2O_3 for the synthesis of macrocyclic thioethers by reaction with dihalides has also been reported and obviates the need for the high dilution conditions often required for such macrocyclizations.[9] Other related reactions utilize Cs_2CO_3 in DMF[10,11] or KOH[12] to generate thiolate nucleophiles from thiols or thiolacetates respectively, which react with dihalides to form macrocyclic thioethers.

Recently, thiosilane reagents have been developed to extend this methodology. The use of TMSCl and anhydrous Na_2S can be used for the *in situ* generation of the equivalent of TMSSNa. This reacts with alkyl halides to give symmetrical dialkylsulfides in good overall yield (**Scheme 1**).[13]



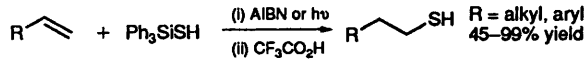
Scheme 1

In a related procedure, the use of the more robust triisopropylsilyl group in place of trimethylsilyl allows interception of the initial monoalkylation product **1**. This can be deprotected to give the thiolate which on aqueous work-up gives the thiol, or alternatively the intermediate thiolate can undergo further alkylation as a useful route to unsymmetrical sulfides (**Scheme 2**).[14–16]



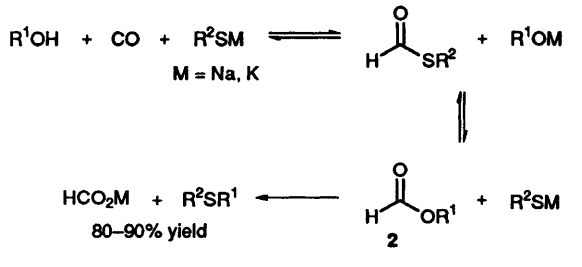
Scheme 2

Other silane-based H_2S equivalents have also provided routes to thiols, notably triphenylsilylthiol, which adds to alkenes under free radical initiation to give selectively, after deprotection, the primary thiol (**Scheme 3**).[17]



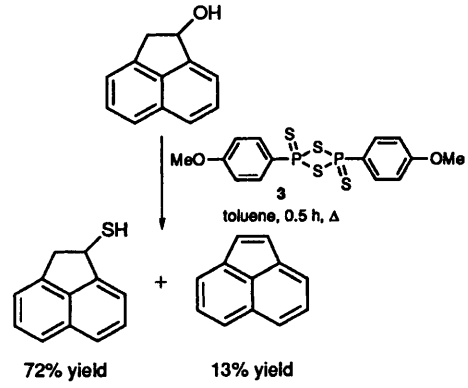
Scheme 3

A novel route to unsymmetrical thioethers utilizes the reaction of sodium or potassium thiolates with alcohols and carbon monoxide at elevated pressure and temperature (**Scheme 4**).[18] A series of equilibria allows generation of the formate **2** and thiolate, which undergo conventional nucleophilic coupling to give the thioether in good to excellent yield.



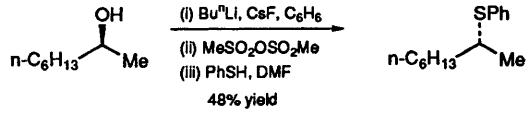
Scheme 4

Also, alcohols can be directly converted into thiols using Lawessons's reagent (**3**) (**Scheme 5**).[19] This is particularly successful for allylic and benzylic halides, with some dehydration often occurring as a side-reaction.



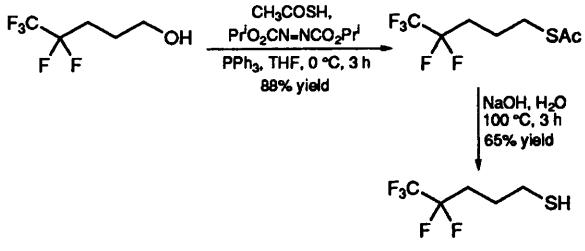
Scheme 5

Alcohols can also be converted into thioethers using a CsF catalysed displacement of mesylate by a thiophenylate, with inversion of stereochemical configuration (**Scheme 6**).[20,21] No elimination products are formed using this method.

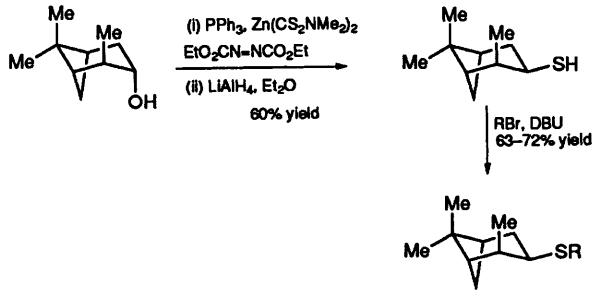


Scheme 6

The use of Mitsunobu chemistry with thiol-derived nucleophiles, followed by hydrolysis of intermediate thiolesters, also provides a convenient method of converting alcohols to thiols (**Scheme 7**).[22,23] A similar transformation has been achieved using $Zn(CS_2NMe_2)_2$ as the nucleophile in the Mitsunobu reaction (**Scheme 8**).[24]

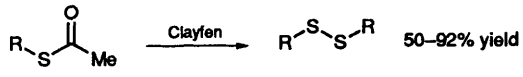


Scheme 7

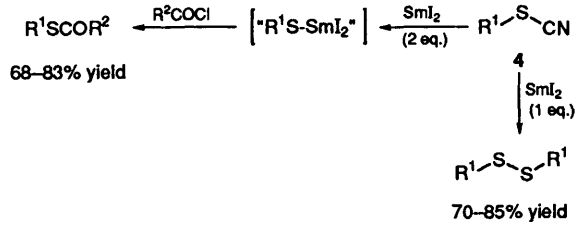


Scheme 8

Thiolacetate intermediates can also be directly converted into disulfides by treatment with clay supported $Fe(NO_3)_3$ (Clayfen) (**Scheme 9**).[25] The thiocyanates **4** can also be converted into disulfides by treatment with one equivalent of SmI_2.[26] Alternatively, if two equivalents are used, a nucleophilic samarium thiolate is generated which reacts with acid chlorides to produce thiolesters in good yield (**Scheme 10**).

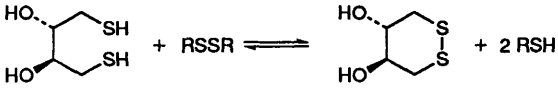


Scheme 9



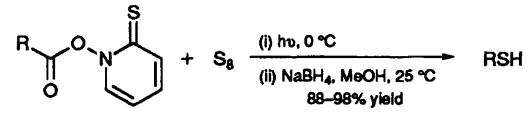
Scheme 10

The cleavage of disulfides to give thiols using reagents such as dithiothreitol has been extensively investigated (**Scheme 11**). This has led to a useful, coherent set of equilibrium constants for a variety of thiol–disulfide interchange reactions.[2,27]



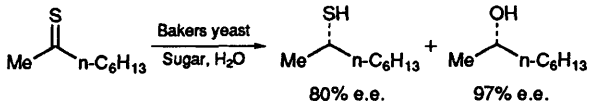
Scheme 11

Carboxylic acids have been converted into thiols via their *N*-hydroxy-2-thiopyrone esters, by photolytic decarboxylation in the presence of sulfur and reduction of the initial polysulfide products (**Scheme 12**).[28] This is successful for a wide variety of primary, secondary and tertiary alkyl carboxylic acids in high yield.



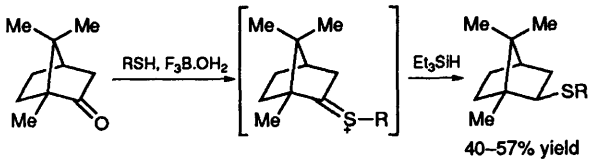
Scheme 12

Enzymatic reduction of thioketones provides a novel route to enantiomerically enriched thiols. Unfortunately, alcohol biproducts are also formed during reaction, resulting from thioketone hydrolysis by water in the reaction medium and subsequent enzymatic reduction, however, both products are obtained in high enantiomeric excess (**Scheme 13**).[29]



Scheme 13

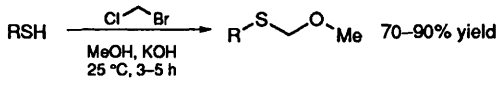
The Lewis acid catalysed addition of thiols to ketones with *in situ* reduction of the thionium ion intermediate using Et_3SiH has been applied to the synthesis of a number of chiral sulfides derived from camphor (**Scheme 14**).[30] A single diastereoisomeric sulfide is formed, resulting from attack of hydride at the less-hindered face of the thionium ion.



Scheme 14

Thioethers can also be prepared by reduction of sulfoxides and sulfones. The use of Mg with $HgCl_2$ catalyst,[31] $SOCl_2/SiO_2$,[32] Me_3SiSNa,[13] and $TeCl_4/NaI$[33] have all recently been reported to reduce efficiently sulfoxides to the corresponding sulfides. Similarly, $LiAlH_4/TiCl_4$ reduces sulfones to sulfides in reportedly better and more reproducible yields than SmI_2.[34]

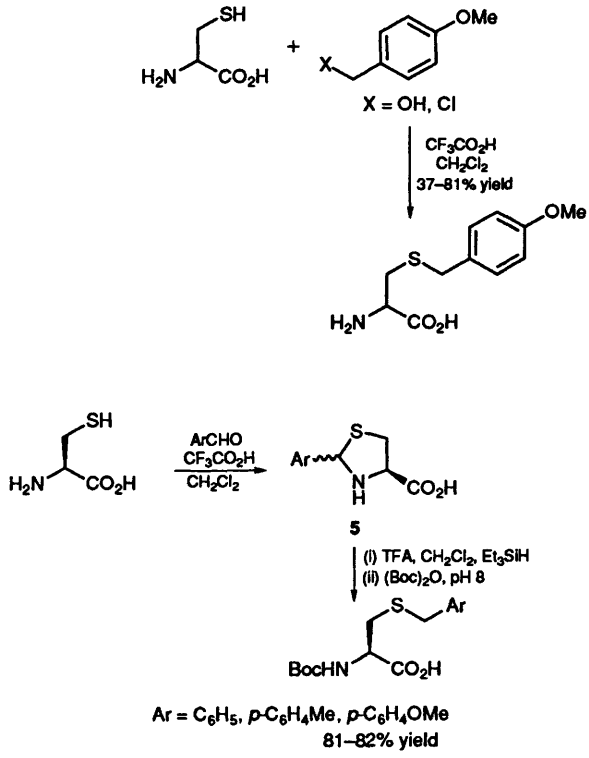
Finally, some new thiol protecting group chemistry has been reported. The use of bromochloromethane and KOH allows introduction of the MOM protecting group to a thiol, avoiding carcinogenic MOMCl (**Scheme 15**).[35] Selective protection of thiols in the presence of alcohols is possible using this system.



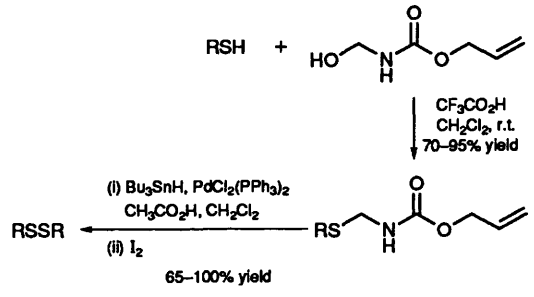
Scheme 15

The introduction of benzyl-type protecting groups (including solid support resins) onto thiols using benzylic alcohols and chlorides, and benzaldehydes, is also reported, and is particularly useful for amino acid based systems (**Scheme 16**).[36] In the case of aldehydes, the initial cyclic thioaminal products **5** are reduced with Et_3SiH under Lewis acidic conditions to give the required benzylthioethers.

The allyloxycarbonylaminomethyl (allocam) group has also been introduced as a new method for the protection of the thiol group on cysteine.[37] It is readily introduced in high yield, and can be deprotected under mild conditions (**Scheme 17**).

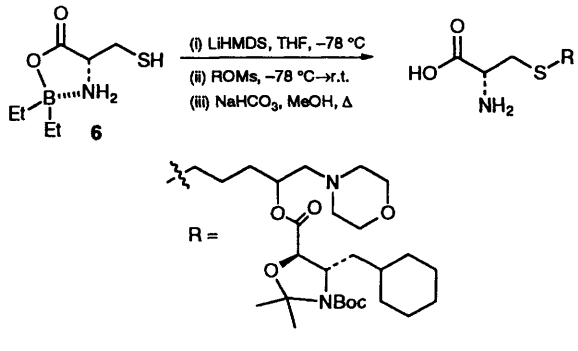


Scheme 16



Scheme 17

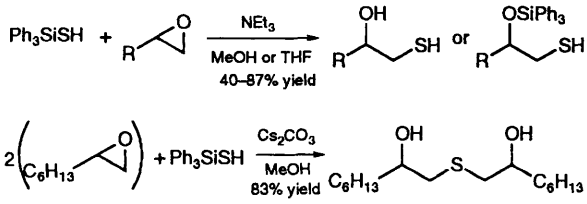
The nucleophilic boroxazolidinone cysteine equivalent **6**, soluble in organic media, has also been developed and has been shown to displace primary mesylates to form *S*-substituted cysteine derivatives which are precursors to potential renin inhibitors (**Scheme 18**).[38]



Scheme 18

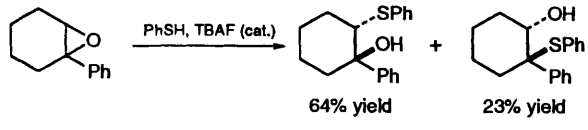
2.2 Substituted thiols and sulfides

The nucleophilic ring-opening of epoxides with thiol-derived nucleophiles is a well established route to β-hydroxysulfides and thiols. Triphenylsilane thiol has been introduced as a solid H_2S equivalent for this reaction (**Scheme 19**).[39] If an epoxide is treated with Ph_3SiSH in methanol then β-hydroxythiols can be isolated directly. Alternatively, if the reaction is carried out in THF then the intermediate *O*-triphenylsilylether, formed by silyl transfer within the initial epoxide ring-opened product, can be obtained. In the presence of excess epoxide, the intermediate thiols can be made to react further to give symmetrical β-dihydroxythioethers by using Cs_2CO_3 as base.

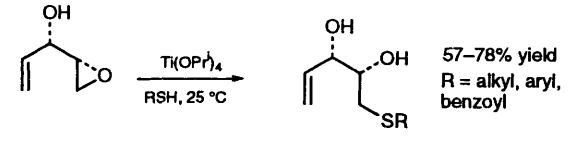


Scheme 19

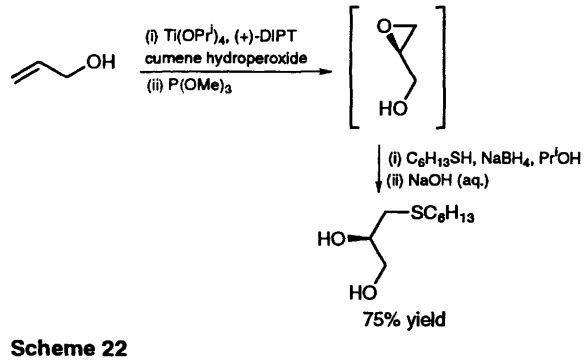
A number of other reagent systems have also been reported to catalyse the nucleophilic ring-opening of epoxides with thiols, including tetrabutylammonium fluoride (TBAF) (**Scheme 20**),[40] titanium tetraisopropoxide (**Scheme 21**)[41] and sodium borohydride, used *in situ* after Sharpless asymmetric epoxidation and is superior to the corresponding titanium-catalysed process (**Scheme 22**).[42]



Scheme 20

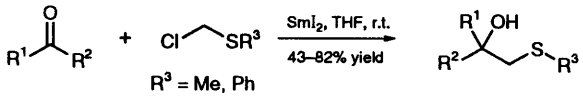


Scheme 21



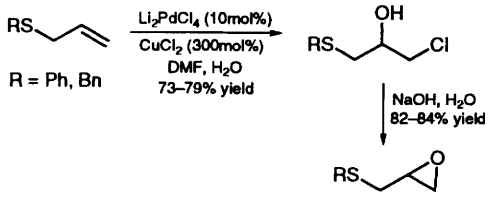
Scheme 22

A new synthesis of β-hydroxythioethers from carbonyl compounds using SmI_2 and an α-chlorosulfide has been reported (**Scheme 23**).[43] Yields are moderate to good, and the reaction is successful with aromatic and aliphatic aldehydes and ketones.

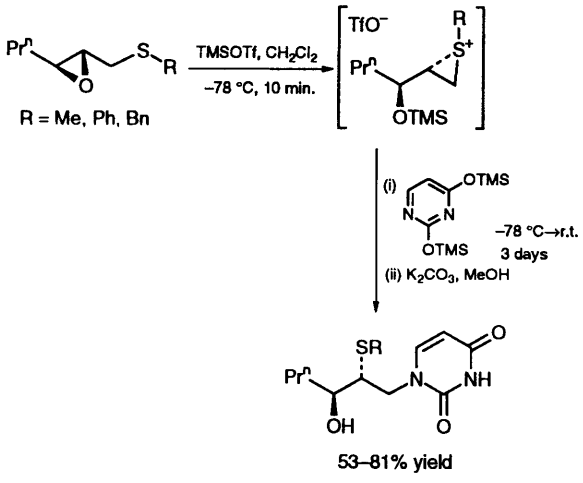


Scheme 23

The selective heteroatom directed chlorohydroxylation of an allylthioether allows access to chlorohydrins which, on treatment with base, give 2,3-epoxysulfides (**Scheme 24**).[44] Related systems, prepared in a homochiral form via Sharpless asymmetric epoxidation can be used as sources of reactive thiiranium ions which react regiospecifically with nucleophiles at C-(1), to generate 1-substituted 3-hydroxy-2-thioethers in moderate to excellent yield and with full control of absolute and relative stereochemistry (**Scheme 25**).[45]

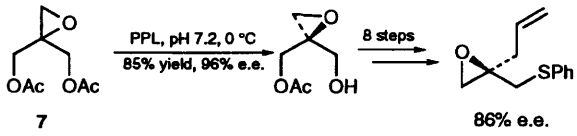


Scheme 24



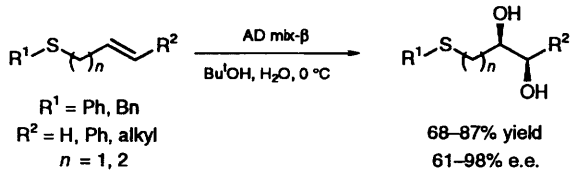
Scheme 25

An alternative approach to optically active 2,3-epoxy sulfides relies on the lipase hydrolysis of the prochiral diacetate **7** (**Scheme 26**).[46] The initial product is converted, in a further eight steps, into the phenyl glycidyl sulfide which has potential as a new chiral building block for the synthesis of tertiary alcohols.



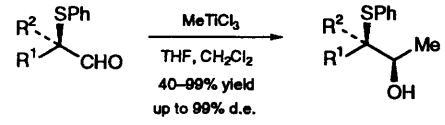
Scheme 26

The asymmetric dihydroxylation of unsaturated sulfides provides an attractive route to the synthesis of optically active dihydroxy sulfides, with good to excellent enantiomeric excesses being achievable (**Scheme 27**), and with only minor traces of S-oxidation observed in a few cases.[47]



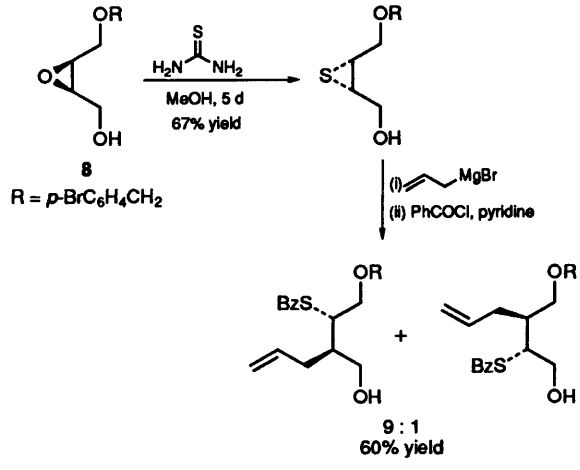
Scheme 27

High levels of stereocontrol have been obtained in the addition of organometallic reagents to α-phenylthioaldehydes (**Scheme 28**).[48] Addition of $MeTiCl_3$ gave the highest *syn*:*anti* ratios, whereas Grignard and organolithium reagents gave significantly lower stereoselectivity. The product β-hydroxy sulfides are obtained in good yield.



Scheme 28

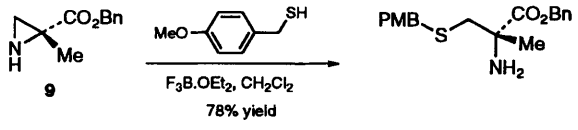
The nucleophilic opening of thiiranes has also been used for the synthesis of substituted thiol derivatives. The epoxide **8**, obtained via Sharpless epoxidation, is converted into the thiirane using



Scheme 29

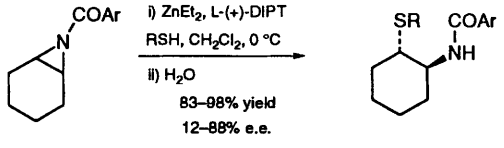
thiourea. Subsequent treatment with allylmagnesium bromide results in regioselective ring-opening of the thiirane (**Scheme 29**).[49] The initial unsaturated thiol products were too unstable to be isolated cleanly, and were therefore isolated as their benzoate thioesters, which also served to protect the thiol groups in a subsequent osmylation reaction.

The nucleophilic ring-opening of aziridines by thiols provides a route to β-amino sulfides, and has been used in the synthesis of unusual amino acids. Thus treatment of aziridine **9**, again obtained via Sharpless asymmetric epoxidation, with a thiol in the presence of BF_3/OEt_2 gives the protected α-methylcysteine in good yield (**Scheme 30**).[50]



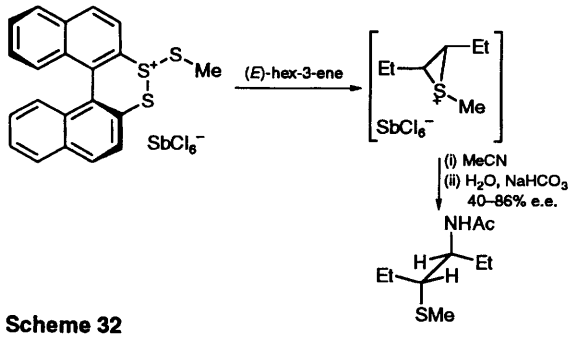
Scheme 30

An alternative approach for the synthesis of optically active β-amino sulfides is nucleophilic ring-opening of prochiral *N*-acyl aziridines by thiols in the presence of a chiral zinc-based Lewis acid (**Scheme 31**). The complex formed by reacting diethylzinc with L-(+)-diisopropyl tartrate (DIPT) catalyses such a reaction with up to 88% e.e.[51] Use of less than stoichiometric quantities of catalyst is also successful but gives significantly lower enantioselectivities.



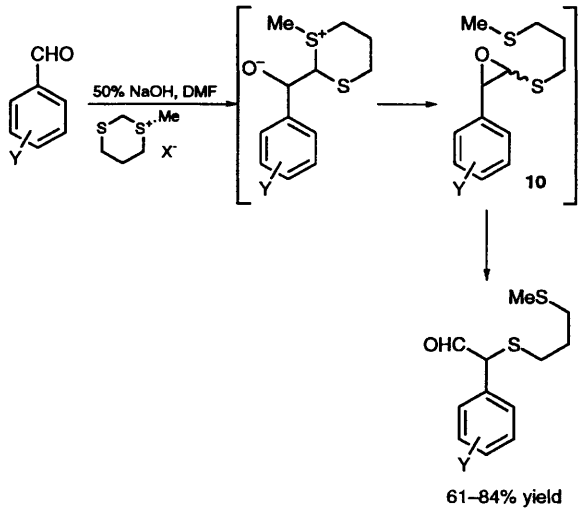
Scheme 31

Recently, the use of enantiopure thiosulfonium salts has led to a method for synthesis of optically active β-amidosulfides. Addition of a homochiral thiosulfonium salt to *trans*-hex-3-ene forms a thiiranium ion which reacts with acetonitrile to give the acetamide after aqueous hydrolysis, in a Ritter type reaction. Enantioselectivities are moderate to good, but side-reactions are observed under reaction conditions favouring high e.e.s (**Scheme 32**).[30,52]



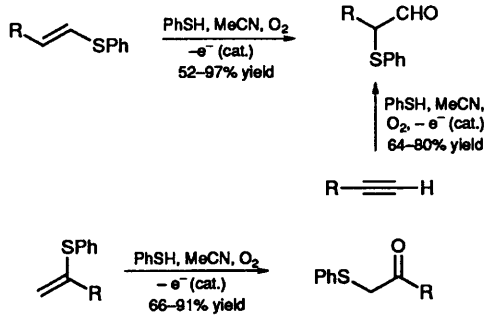
Scheme 32

New methods for the synthesis of α-sulfenyl carbonyl compounds have been reported. Sulfonium salts derived from formaldehyde dithioacetals react with aromatic aldehydes under basic conditions to give 2-aryl-2-thioalkyl acetaldehydes in good yield (**Scheme 33**).[53] The reaction proceeds by initial formation and subsequent rearrangement of the epoxide **10** under the reaction conditions. The products are reported to be in equilibrium with their enol tautomers.



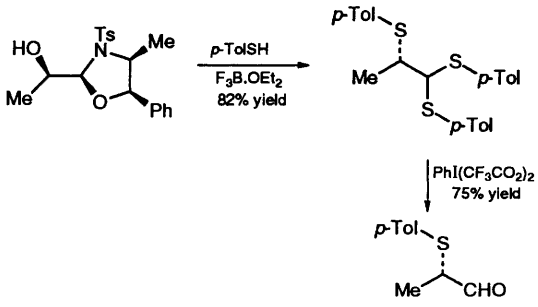
Scheme 33

The electrolysis of alkenylsulfides, in the presence of thiols and oxygen, provides an alternative route to α-(phenylthio)carbonyl compounds via an electroinitiated radical reaction, with net 1,2-transposition of the carbonyl group (**Scheme 34**).[54] A similar oxygenation of alkynes also provides a route to this class of compounds.



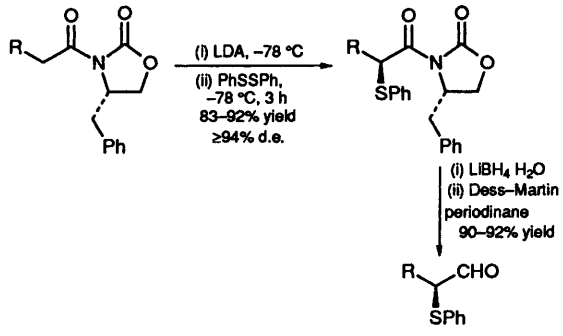
Scheme 34

Optically active α-sulfenyl aldehydes can be prepared from enantiopure α-sulfenyl dithioacetals (**Scheme 35**).[55] Hydrolysis of the dithioacetal functionality gives α-sulfenyl aldehydes which can be isolated in an optically active form in good yield but racemize on attempted purification by column chromatography on silica gel.



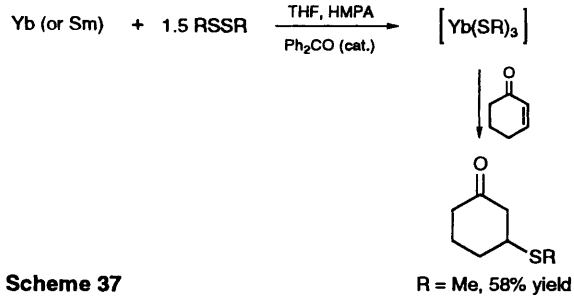
Scheme 35

An attractive alternative route to α-sulfenyl aldehydes utilizes an Evan's oxazolidinone chiral auxiliary to control stereochemistry during sulfenylation of an enolate anion (**Scheme 36**).[56] The product is then best converted into the aldehyde by reduction ($LiBH_4$) to the alcohol and oxidation with the Dess–Martin periodinane. Other procedures resulted in significant racemization.

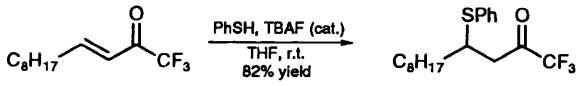


Scheme 36

The addition of thiols to α,β-unsaturated carbonyl compounds provides a route to β-sulfenyl carbonyl compounds. Recent developments in this area include the use of ytterbium or samarium metals which react with disulfides in the presence of catalytic benzophenone to generate lanthanoid thiolates, which in turn react with enones to give Michael adducts in good yield (**Scheme 37**).[57] TBAF has also been reported to catalyse the addition of thiols to β-alkyl-α,β-unsaturated trifluoromethyl ketones, giving exclusive 1,4-addition in good yield (**Scheme 38**).[58] Phase transfer catalysis has also been shown to promote similar reactions between polysulfide anions and α,β-unsaturated carbonyl compounds.[59]

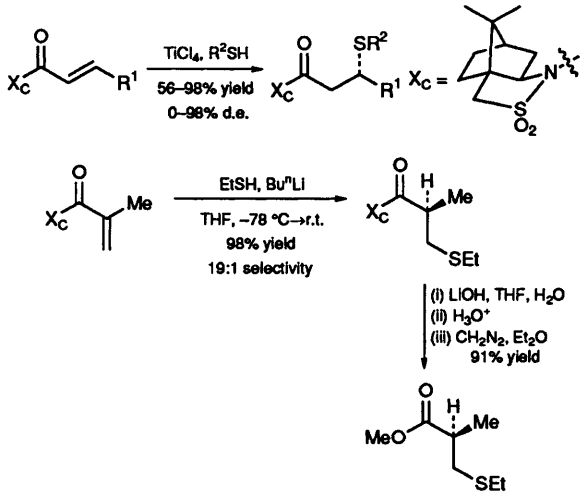


Scheme 37



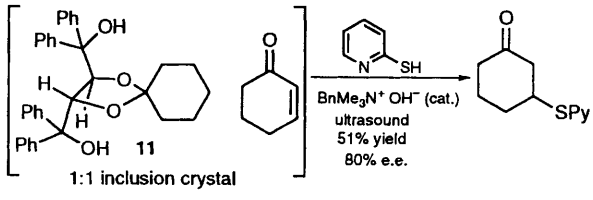
Scheme 38

Related processes have also been used to prepare optically active β-sulfenyl carbonyl compounds. These include the Lewis acid catalysed conjugate addition of thiols to camphorsultam derivatives,[60] and also the corresponding base-catalysed process (**Scheme 39**).[61]



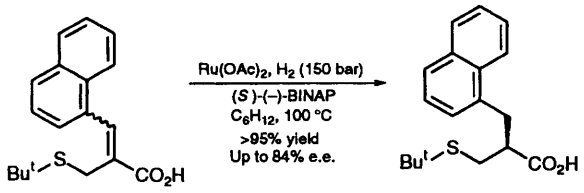
Scheme 39

An interesting alternative method of asymmetric induction involves the enantioselective Michael addition of thiols to α,β-unsaturated ketones as their inclusion crystals with optically active hosts such as **11** (**Scheme 40**).[62] The reaction occurs in the solid state and is catalysed by ultrasound. Very good e.e.s are obtained with pyridyl thiols, but no enantioselectivity is observed with simple thiophenols, even though the reaction occurs in quantitative yield, implying that the pyridine nitrogen plays a crucial role in the stereocontrol.



Scheme 40

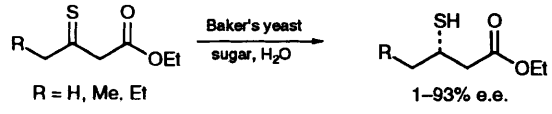
Other methods of synthesizing optically active β-sulfenyl carbonyl compounds include asymmetric hydrogenation of unsaturated carboxylic acids using a ruthenium catalyst modified with a chiral BINAP ligand (**Scheme 41**).[63] High enantioselectivities can be obtained, with the enantiofacial selectivity being



Scheme 41

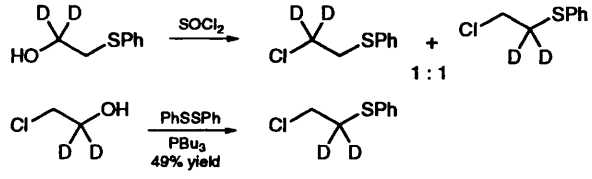
reversed if the reaction is carried out in trifluoroethanol rather than cyclohexane (up to 64% e.e.)

Baker's yeast reduction of β-thioketoesters gives the corresponding β-mercaptoester with low to very high enantiomeric excess (**Scheme 42**).[29] A serious limitation on this reaction is that significant amounts of β-hydroxyesters are also produced, resulting from reduction of a β-ketoester formed *in situ* by hydrolysis of the thioketone in aqueous media.



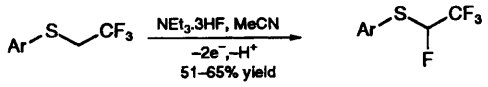
Scheme 42

The preparation of isotopically labelled β-chlorosulfides shows interesting scrambling properties depending on the synthetic route used (**Scheme 43**).[64] If a deuterium labelled β-hydroxy sulfide is treated with thionyl chloride then complete scrambling of the carbon atoms is observed, probably due to participation by the sulfur atom. If, however, a labelled chlorohydrin is used, and the alcohol converted into the thioether using a disulfide and tributyl phosphine, then no scrambling of the label is observed.

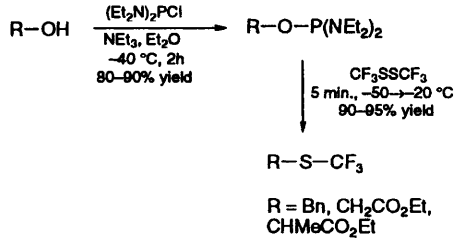


Scheme 43

New methods for the preparation of fluorinated sulfides have also been reported. The selective anodic monofluorination of fluoroalkyl and alkyl sulfides provides access to α-fluorosulfides in good yield (**Scheme 44**).[65] Alcohols are converted into trifluoromethyl sulfides by treatment with bis-(diethylamido)chlorophosphite followed by trifluoromethyl disulfide (**Scheme 45**).[66,67]

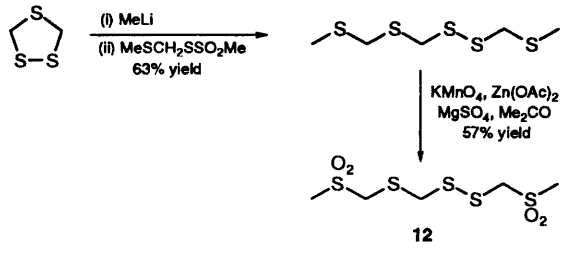


Scheme 44



Scheme 45

Finally, in a synthesis of dysoxysulfone **12**, a sulfenylsulfonate is reacted with a thiolate to form a complex polysulfide by disulfide bond formation (**Scheme 46**).[68] The final product, **12**, is an active component of a tea made from the leaves of *Dysoxylum richii*, which, according to a wise old native, when prepared by boiling the plant with water in a bully beef (or salmon) tin, is capable of relieving all pains in the head, arms, legs, or body!



Scheme 46

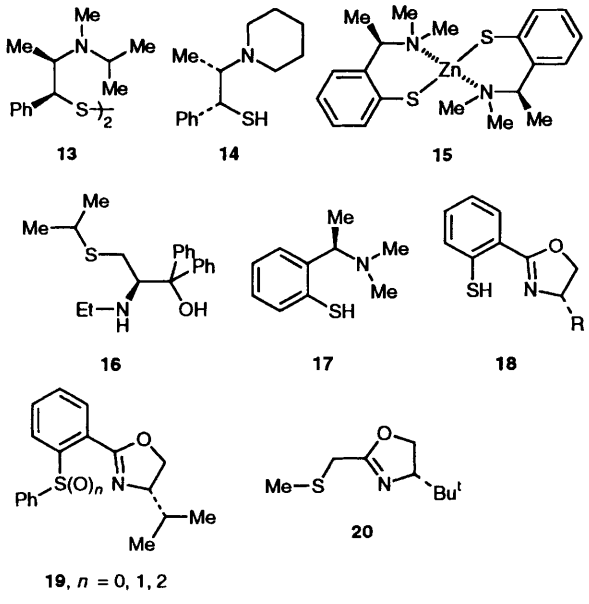
2.3 Thiols and sulfides as mediators of asymmetric transformations

There have been a number of reports of the use of functionalized homochiral thiols and thioethers for controlling asymmetric induction in new enantioselective processes. The asymmetric reactions of high symmetry chiral organosulfur reagents has been reviewed.[69] Whilst it is beyond the scope of this review to discuss these in any detail, the potential importance of this area warrants brief discussion of the use and efficiencies of these compounds. New synthetic routes to these compounds are included in the appropriate section.

The β-aminothiol derivatives **13**,[70] **14**,[71] and **15**,[72] and the thioether **16**[73] have been shown to promote asymmetric addition of organozinc reagents to aldehydes. All are capable of excellent asymmetric induction.

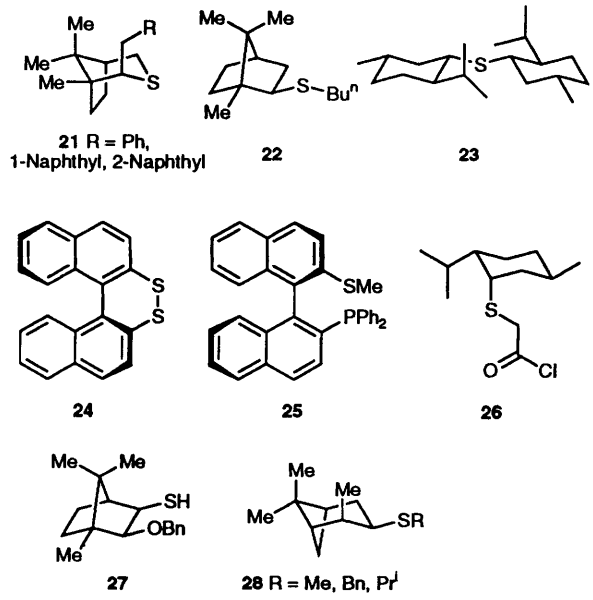
The thiols **17**[74] and **18**[75] are both efficient ligands for enantioselective Michael addition to α,β-unsaturated ketones. Moderate to good

enantioselectivities can be achieved with either ligand. Related systems, such as **19**, have been used in asymmetric palladium-catalysed allylic substitution reactions with up to 96% e.e.[76,77] Sulfides tethered to oxazolines, *e.g.* **20**, also give high selectivity in similar reactions.[77]



The homochiral sulfides (**21–23**)[30] and **24**[52] have been investigated as asymmetric sulfenylating agents when converted into the corresponding thiosulfonium salts. Highest enantioselectivities are reported with (**24, Scheme 32**). The related ligand **25** has been used in asymmetric hydroformylation reactions, and gives up to 20% e.e.[78]

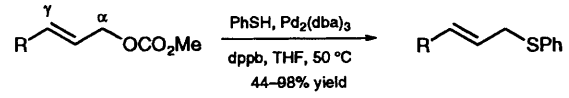
Neomenthylthioacetic acid chloride (**26**) has been introduced as a new chiral resolving agent, and has been used to resolve racemic binaphthol.[79] The application of the new, camphor-derived chiral auxiliary **27** for the synthesis of optically active



primary amines via the corresponding sulfinimines has been reported,[80] and sulfide **28**, prepared from (+)-isopinocampheol, has been used for asymmetric epoxidation of carbonyl compounds via the corresponding sulfur ylide with up to 43% e.e.[24]

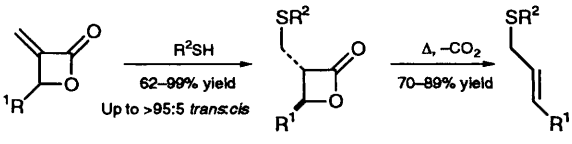
2.4 Allyl, homoallyl and benzyl thiols and sulfides

The Pd^0 catalysed allylation of thiols using allylic carbonates and aromatic thiols provides a route to allyl and cinnamyl aryl sulfides in moderate to excellent yield (**Scheme 47**).[81] The products of α-substitution predominate; however, γ-substitution is observed in some cases.



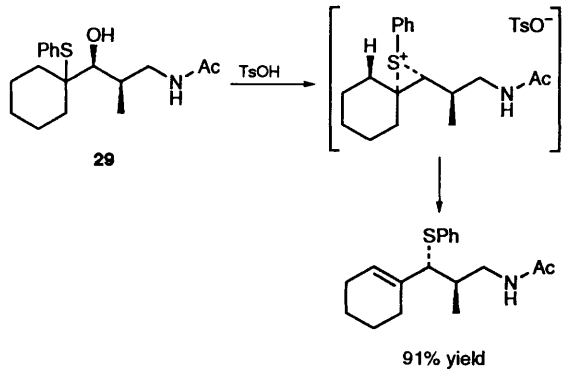
Scheme 47

An interesting route to allyl sulfides is by loss of CO_2 from a substituted β-lactone. The substrates are prepared by Michael addition of a thiol to an exocyclic α,β-unsaturated β-lactone. High *trans* selectivity can be obtained in the reaction (up to >95:5) and this stereochemistry is retained in the allyl sulfides after extrusion of CO_2 (**Scheme 48**).[82]



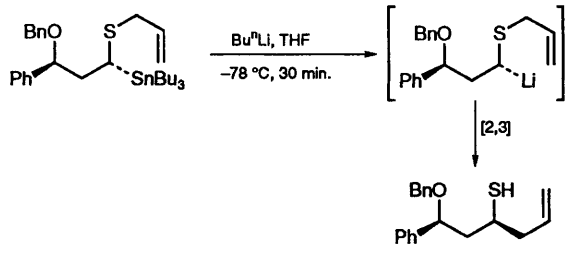
Scheme 48

The migration of a phenylthio group of a β-hydroxy sulfide can in some cases lead to formation of allylic sulfides by elimination of a proton in a thiiranium ion intermediate (**Scheme 49**).[83] In the case of the acetamide **29** the allyl sulfide is obtained in high yield; however, other reaction pathways can be dominant if subtle structural modifications are made.

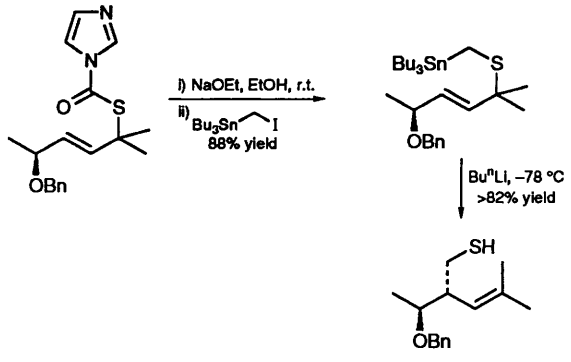


Scheme 49

Homoallyl thiols can be obtained in an optically active form by stereospecific [2,3]-thia-Wittig rearrangement of *S*-allyl α-lithiated sulfides (**Scheme 50**).[84] The α-lithio sulfides are generated *in situ* by tin–lithium exchange, and were found to be sufficiently configurationally stable to allow stereospecific rearrangement with inversion at the carbanionic centre. In less favourable cases (*S*-benzyl thioethers) much lower stereoselectivity was observed probably due to some loss of configuration at the carbanionic centre prior to rearrangement. In a related reaction, high 1,2-asymmetric induction was observed in a [2,3]-thia-Wittig rearrangement giving the homoallyl thiol product as a single isomer (**Scheme 51**).[85]

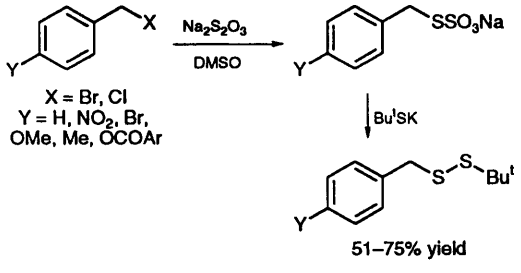


Scheme 50



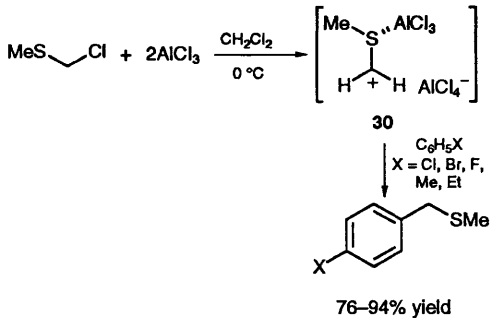
Scheme 51

Unsymmetrical benzylic disulfides have been synthesized via the corresponding Bunte salts derived from benzylic bromides and chlorides (**Scheme 52**).[86] The Bunte salts are synthesized in the usual manner using thiosulfate in DMSO, and subsequent treatment with thiolate generates the unsymmetrical disulfide.



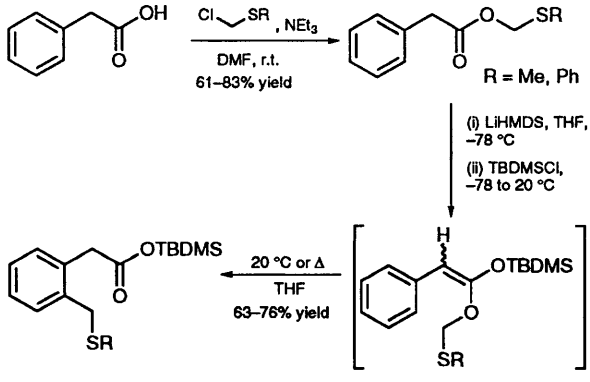
Scheme 52

A new method of preparing benzyl methyl thioethers involves the 'superelectrophilic' methylthiomethylation of aromatics rings with a chloromethyl methyl sulfide:$AlCl_3$ (1:2) reagent (**Scheme 53**).[87] Predominant *para*-disubstitution is observed in the products (up to 93:7). The highly electrophilic complex **30** is believed to be the active species in the reaction, requiring two equivalents of Lewis acid for formation.



Scheme 53

Finally, an unusual rearrangement leads to *ortho*-thiomethylation of arylacetic acid derivatives (**Scheme 54**).[88] The ester precursors are readily prepared from an arylacetic acid and an α-chlorosulfide in the presence of NEt_3. Subsequent formation of the ketene acetal by deprotonation and *O*-silylation followed by warming to 20 °C or above results in formation of the *ortho*-thiomethylated arylacetic acid derivatives in good yield. The precise mechanism of this process is unclear at present.

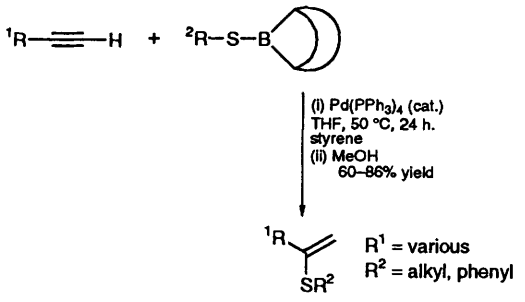


Scheme 54

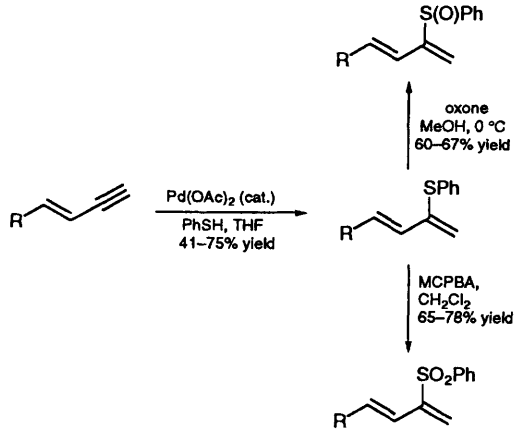
2.5 Vinyl, allenyl and alkynyl thiols and sulfides

The palladium(0)-catalysed thioboration of terminal alkynes with 9-(alkylthio)-BBN derivatives provides a route to vinyl sulfides (**Scheme 55**).[89] Protonolysis of the initial thioboration product using MeOH provides the terminal 2-(alkyl- or phenylthio)alkene with high regioselectivity. The reaction is successful for a wide variety of substrates. With more hindered thiols (*e.g.* Bu^t) a more reactive form of palladium, generated from $Pd(dba)_2$ and Ph_2[2,4,6-

$(MeO)_3C_6H_2]P$ is required for good yields. The palladium-catalysed regioselective addition of thiophenol to conjugated enynes also results in formation of the terminal 2-(thiophenyl)-1,3-dienes (**Scheme 56**).[90]

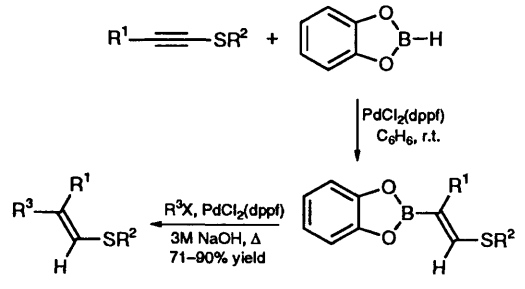


Scheme 55



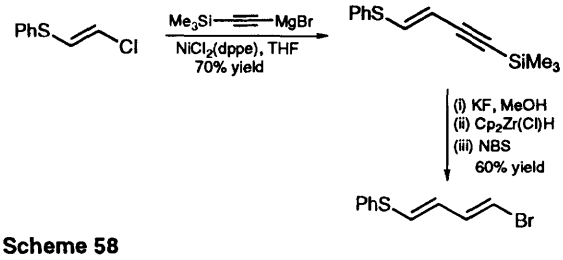
Scheme 56

A very powerful one-pot method for vinyl sulfide synthesis is via catalytic hydroboration/cross-coupling of thioalkynes. Treatment of a thioalkyne with catechol borane in the presence of a Pd^0 catalyst regioselectively gives the terminal 1-(alkyl- or phenylthio) alkene (**Scheme 57**).[91] The intermediate borane can be further utilized in a cross-coupling reaction to give a trisubstituted alkene with full control of double bond geometry.

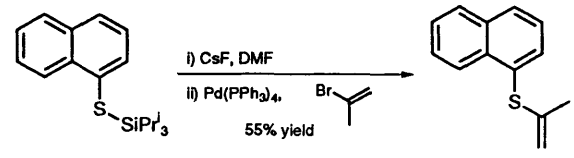


Scheme 57

Conjugated (*E*,*E*)-1-phenylthiobuta-1,3-dienes have been synthesized via a trimethylsilylalkyne using a Ni^{II}-based cross-coupling between Grignard reagents and (*E*)-1-chloro-2-phenylthioethene (**Scheme 58**).[92] The initial coupling product, after desilylation, undergoes regio- and stereo-specific hydrozirconation. Work-up using *N*-bromosuccinimide (NBS) gives the vinyl bromide, which can undergo further cross-coupling if required. Reaction of aromatic thiolates with vinyl bromides in the presence of a Pd^0 catalyst also allows access to vinyl aryl sulfides (**Scheme 59**).[14,15]

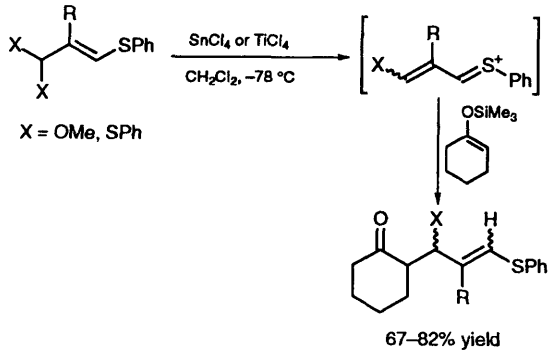


Scheme 58

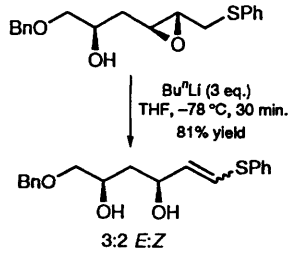


Scheme 59

The regioselective allylation of enol silyl ethers with γ-heterosubstituted vinyl thionium ions provides a route to 1-(phenylthio)-alk-1-en-5-ones. The reactive thionium ion intermediates are generated under Lewis acid conditions from the corresponding dimethoxy- or bis-(phenylthio)acetals (**Scheme 60**).[93] γ-Hydroxy-α,β-unsaturated sulfides have been prepared by base-induced elimination in a 2,3-epoxysulfide. Although high yields are obtained, *E*:*Z* ratios can be low (**Scheme 61**).[94]

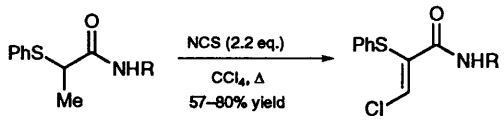


Scheme 60

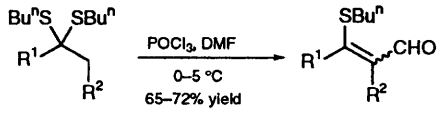


Scheme 61

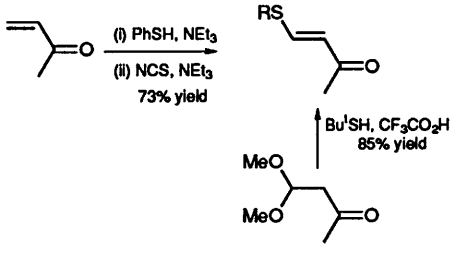
A number of routes to carbonyl-substituted vinyl thioethers have been reported. These include the oxidative chlorination of α-(phenylthio)amides to give (*Z*)-3-chloro-2-phenylthio acrylamides (**Scheme 62**),[95] the Vilsmaier reaction of dithioketals for the synthesis of β-(alkylthio)ethylenic aldehydes (**Scheme 63**),[96] and addition of thiols to the monoacetal of a β-ketoaldehyde, or an α,β-unsaturated ketone and oxidation, for the synthesis of β-(alkyl- or arylthio)-α,β-unsaturated ketones (**Scheme 64**).[97]



Scheme 62

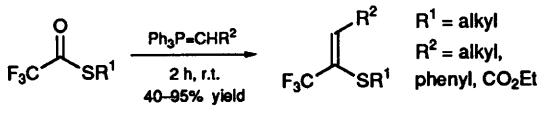


Scheme 63



Scheme 64

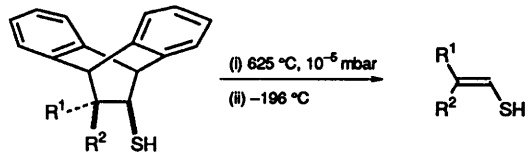
Trifluoromethyl vinyl sulfides can be prepared by a Wittig reaction on thioltrifluoroacetates. High (*Z*)-selectivity is observed, and both stabilized and non-stabilized ylides can be used (**Scheme 65**).[98]



Scheme 65

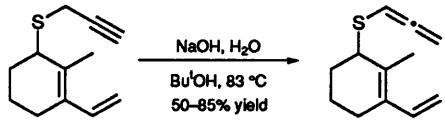
A novel synthesis of enethiols by the retro-Diels–Alder reaction of dihydroanthracene derivatives has been reported (**Scheme 66**).[99] The reaction is stereospecific in appropriate systems, consistent with the concerted nature of the reaction. The ethene derivative ($R^1 = R^2 = H$) is unstable and polymerizes at room temperature, however, more substituted systems are stable in solution.

A number of allenic sulfides have been prepared by base-catalysed isomerization of prop-2-ynylic

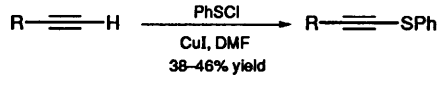


Scheme 66

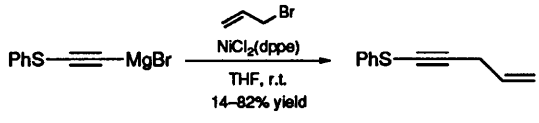
sulfides (**Scheme 67**).[100] Alkynyl sulfides have been synthesized either using phenylsulfenyl halides and terminal alkynes in the presence of CuI which avoids the use of the HMPA required for previously reported procedures (**Scheme 68**),[101] or by using Ni^{II} or Pd^{II} catalysed coupling of phenylthioethynyl magnesium bromide with allylic halides (**Scheme 69**).[102]



Scheme 67



Scheme 68

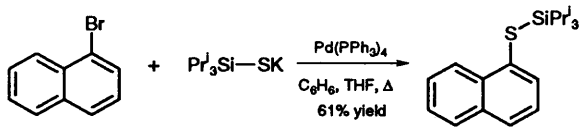


Scheme 69

2.6 Aryl thiols and sulfides

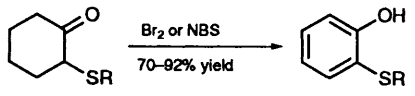
A new method for the synthesis of aryl thiols and sulfides utilizes the Pd^0-catalysed coupling of aromatic halides with the potassium salt of triisopropylsilylthiol (**Scheme 70**).[14,15] The initial products can be further transformed into the corresponding thiols or aryl alkyl thioethers (**Scheme 2**), or aryl vinyl thioethers (**Scheme 59**).

The brominative aromatization of 2-alkylthio- and 2-arylthio-cyclohexanones provides a novel route to



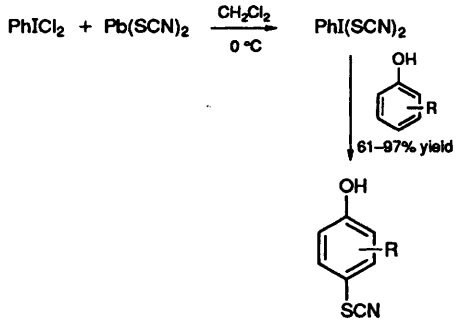
Scheme 70

ortho-(hydroxyaryl)thioethers (**Scheme 71**).[103] Mechanistic studies on S_NAr reactions of thiolate anions with *ortho*-halonitrobenzenes have also been reported, and have shown that the efficiencies of the reactions with the chloro-, bromo- and fluoronitrobenzenes are greater than those with the corresponding iodonitrobenzenes.[104,105]



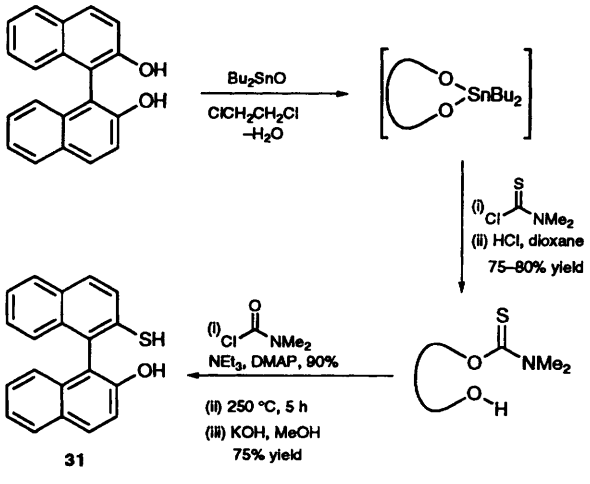
Scheme 71

The thiocyanation of phenols using phenyliodine dichloride and lead(II) thiocyanate proceeds with high *para*-selectivity (**Scheme 72**).[106] The active species in the reaction, generated *in situ*, is believed to be phenyliodine bis(thiocyanate).

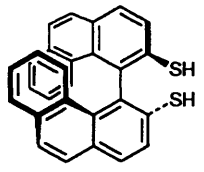


Scheme 72

There has been considerable recent interest in the synthesis of axially chiral binaphthyl thiol and sulfide derivatives, mainly because of their potential use for asymmetric synthesis (Section 2.3). The aromatic thiol precursors are almost invariably prepared by a Newman–Kwart rearrangement of an *O*-thiocarbamate, obtained by acylation of the corresponding phenol. An elegant example of this is the formation of the phenolthiophenol (±)-**31** which is an effective catalyst for Michael additions using organocuprate reagents. Selective monoacylation is achieved by use of the stannylene acetal intermediate (**Scheme 73**).[107] Protection of the remaining phenol as its carbamate, thermolysis, and hydrolysis gives (±)-**31** in three steps from binaphthol. The Newman–Kwart rearrangement has been used for the synthesis of a number of related systems, including **32**[108] and **25**.[78,109,110]



Scheme 73



32

New methods for the optical resolution of such binaphthyl systems have also been reported. These include formation and chromatographic separation of diastereomeric dithioacetals derived from glucose (**Scheme 74**),[111] an esterase resolution of a dipentanoate thioester (**Scheme 75**)[112] and by asymmetric oxidation (**Scheme 84**).[113]

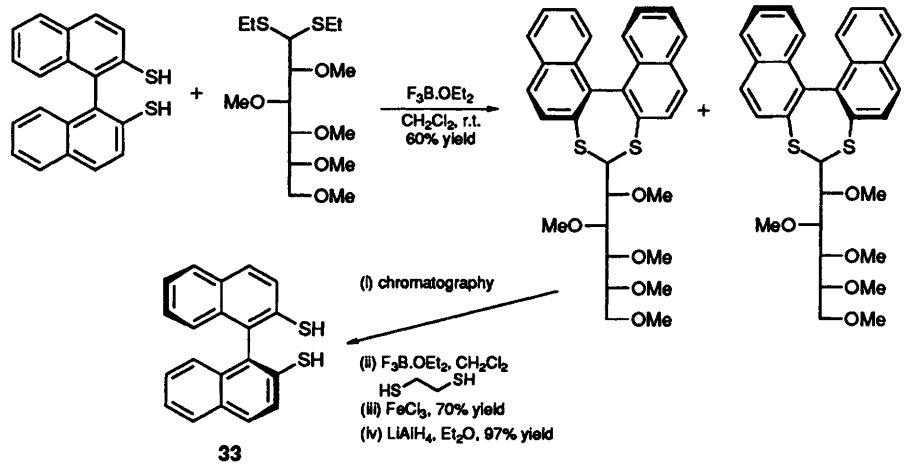
3 Synthesis of sulfoxides

3.1 Oxidation of sulfides

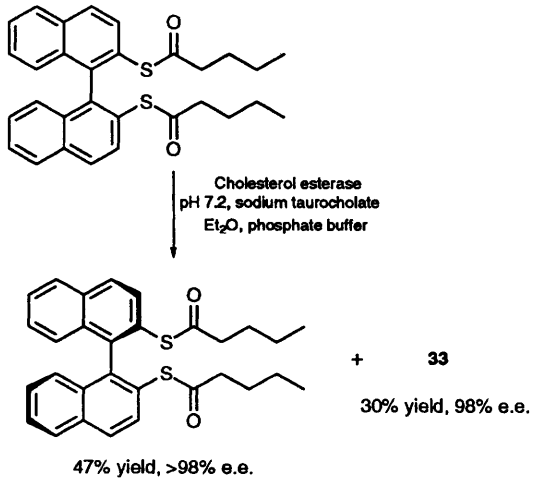
The preparation of sulfoxides by oxidation of the corresponding sulfides continues to be an important area of research. This section is divided into three parts. The first is concerned with new methods of oxidation where the problem of chirality at sulfur is not addressed. The second part is concerned with diastereoselective processes, whereas the final part concentrates on new methods for the enantioselective oxidation of sulfides to sulfoxides.

3.1.1 Non-stereoselective oxidation

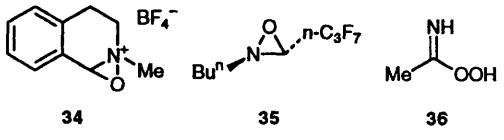
A number of new reagent systems have been developed for the simple oxidation of sulfides to sulfoxides. These include the following: the oxaziridinium salt **34**, derived from dihydroisoquinoline, which can also be used catalytically with similar efficiency using oxone as reoxidant for the iminium salt,[114] the perfluoro-*cis*-2,3-dialkyloxaziridine **35** at −40 °C (the volatile imine biproduct is easily removed),[115] salts between selenoxides and sulfonic acids,[116,117] dimethyldioxirane (DMDO), generated *in situ* using



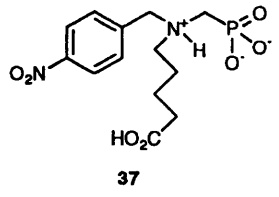
Scheme 74



Scheme 75



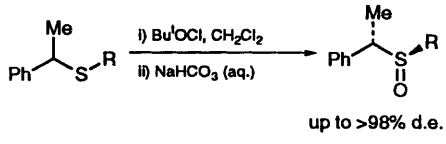
acetone and oxone in water (particularly good for large-scale),[118,119] TBHP with or without H_2SO_4 catalyst,[120] H_2O_2 and MeCN at 0 °C (via peroxyimidic acid intermediate **36**),[121] $TiCl_3/H_2O_2$ in $MeOH/H_2O$,[122] methylrhenium trioxide/H_2O_2,[123] MnO_2/TMSCl,[124] MnO_2/HCl,[125] nitric acid catalysed by $FeBr_3$,[126] Fe^{III}, Ni^{II} or Co^{II} β-ketoester complexes in the presence of a branched aldehyde and O_2,[127,128] $NaBrO_2/3H_2O$ in the presence of an H^+ exchanged zeolite,[129] iodosylbenzene and TsOH catalyst,[130] metallophthalocyanine and iodosylbenzene (accelerated by ultrasound)[131] and photooxidation using tetranitromethane[132] or O_2 and 1,4-dimethoxynaphthalene as sensitizer.[133] Finally, oxidation of *p*-nitrobenzylthioethers and *p*-nitrobenzenethioethers using $NaIO_4$ catalysed by an antibody raised against hapten **37** has been reported, and shows considerable promise for the future.[134]



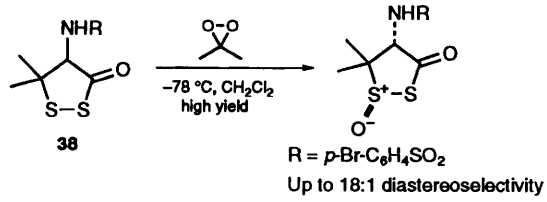
3.1.2 Stereoselective oxidation

There have been a limited number of studies on the diastereoselective oxidation of sulfides to sulfoxides, where the stereochemical configuration at sulfur is at least partly determined by pre-existing chiral centres in the substrate.

The oxidation of a range of α-methylbenzyl sulfides with Bu^tOCl, followed by aqueous base hydrolysis proceeds to give the sulfoxides with good to excellent diastereoselectivity for a range of systems, the best being α-methylbenzyl phenyl sulfides (**Scheme 76**).[135] One of the advantages of using DMDO as oxidant is that it can be used at low temperatures (−78 °C). This can allow a high degree of diastereo- and chemo-selectivity to be achieved, as demonstrated by the oxidation of the chiral disulfide (**38**, **Scheme 77**).[136]

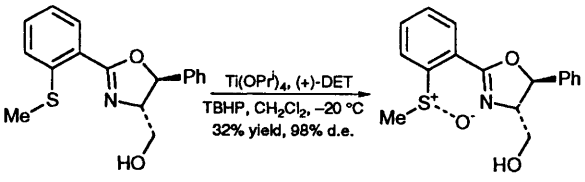


Scheme 76



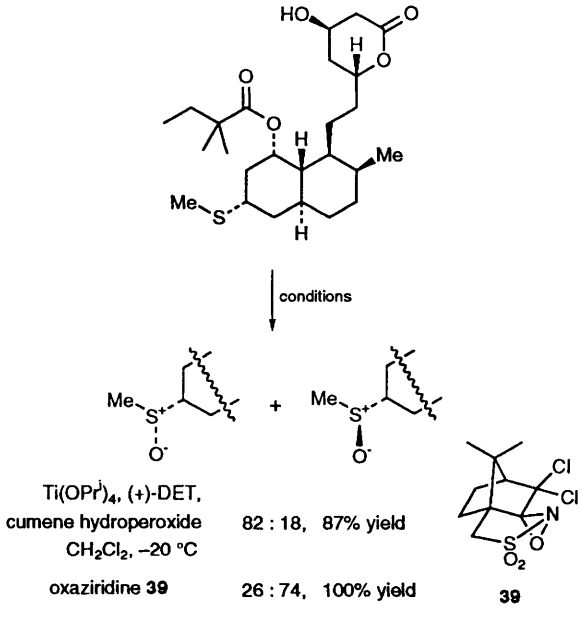
Scheme 77

Finally, some of the established asymmetric oxidation systems have been used to achieve what is in effect a diastereoselective oxidation. The use of modified Sharpless asymmetric epoxidation conditions gives a very high diastereoselectivity for the oxidation of hydroxythioethers, although yields can be modest (**Scheme 78**).[137]



Scheme 78

Similar reaction conditions also give high diastereoselectivity in the preparation of novel 6-sulfinyl tetrahydromevinic acids (**Scheme 79**).[138] The opposite diastereomer of similar diastereomeric excess can be prepared by oxidation using the dichlorooxaziridine **39**.



Scheme 79

3.1.3 Enantioselective oxidation

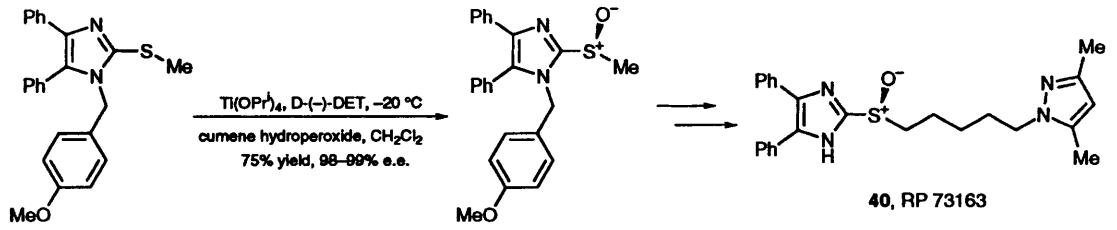
The enantioselective oxidation of sulfides to sulfoxides continues to be a popular and important area of organosulfur chemistry and has been the subject of a number of reviews.[139,140]

There are four main methods used for asymmetric sulfur oxidation. These are systems based on modified Sharpless asymmetric epoxidation conditions further developed by Kagan and Modena; chiral oxaziridines developed by Davis; the (salen)manganese(III) complexes of Jacobsen and Katsuki; and enzymatic oxidation procedures. Some of these are now well established and so the basic procedures for these will not be discussed in any detail, but relevant references are included in the previous review of this series.[1] However, important improvements on these methods and examples of applications will be included here. It is important to be aware of an intriguing recent report which describes how the optically activity of sulfoxides can be further enriched by preparative-scale flash chromatography on an achiral stationary phase.[141] For example, (*R*)-methyl *p*-tolyl sulfoxide of 86% e.e., on chromatography, has an e.e. of 99% e.e. in the first sulfoxide-containing fraction off the column, but this decreases to 63% in the last fraction.

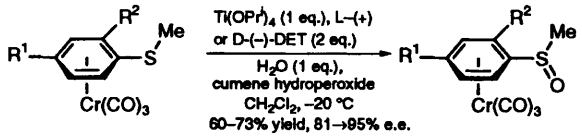
The titanium-based procedure of Kagan (*e.g.* **Scheme 81**) has recently been adapted to be carried out using a catalytic heterogeneous system, using solid supports such as Al_2O_3, SiO_2, ZrO_2 and montmorrilonite. High enantiomeric excesses could be achieved, and a system using montmorrilonite K10 gave optimum results.[142,143] The Kagan oxidation has also been used for the multi-kilogram scale asymmetric synthesis of the biologically active sulfoxide RP73163 (**40**, **Scheme 80**).[144] By judicious choice of substrate structure and reaction conditions very high enantiomeric excess and good chemical yields were achieved. Interestingly, the optimized reaction utilizes anhydrous conditions, rather than including the one equivalent of water which is often required for optimum enantioselectivity with a titanium:tartrate ratio of 1:2. More conventional Kagan conditions have been used for the enantioselective oxidation of organometallic complexes containing thioether groups, including chromium tricarbonyl complexes (**Scheme 81**),[97,145,146] and ferrocenyl sulfides (**Scheme 82**).[147]

The enantioselective oxidation conditions developed by Modena employ the use of four equivalents of tartrate relative to titanium, under anhydrous conditions. These have been used to synthesize C_2-symmetrical bis-methylsulfinyl-benzenes by double asymmetric oxidation (**Scheme 83**).[148] Very high chemical and optical yields can be obtained for the *ortho*, *meta* and *para*-disubstituted systems.

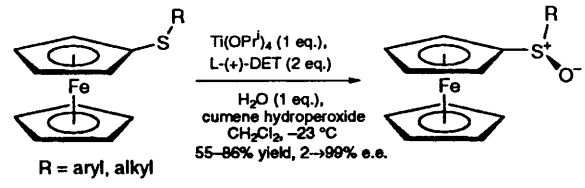
This oxidation protocol has also been used in a kinetic resolution of [1,1′-binaphthylene]-2,2′-bis-methylthioether (**Scheme 84**).[113] High enantioselectivity has been achieved with respect to



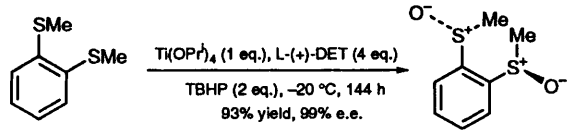
Scheme 80



Scheme 81



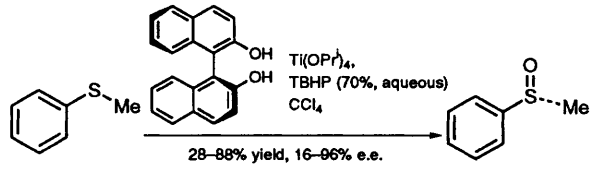
Scheme 82



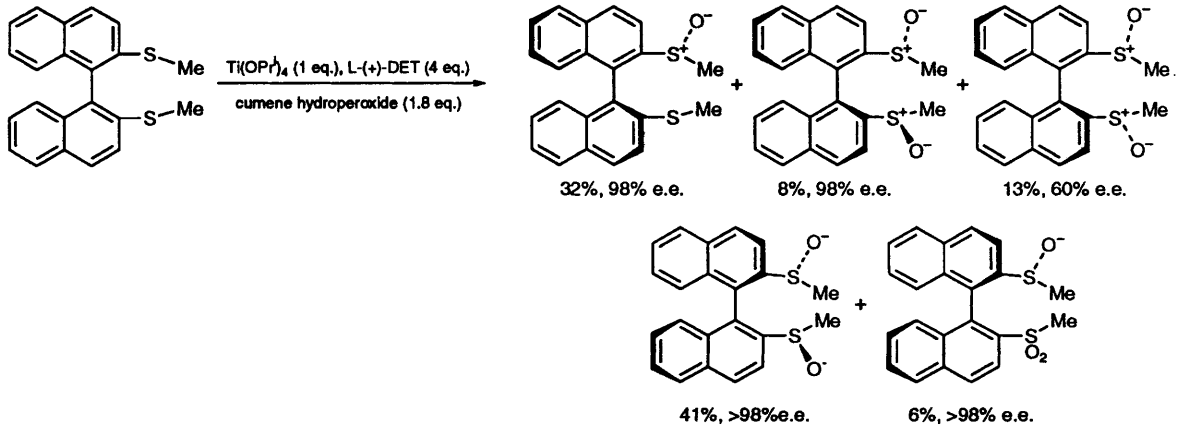
Scheme 83

both sulfoxide and binaphthyl chirality. A mixture of products is formed, however, this can be simplified greatly by Pummerer rearrangement of the sulfoxide functionalities. In total, there is a net 81% recovery of resolved products [40% (*S*)-binaphthyl and 41% (*R*)-binaphthyl] based on racemic starting material.

A related titanium-based oxidation procedure utilizes a chiral binaphthol ligand rather than tartrate esters. This system is capable of very high enantioselectivities, and has the added advantages that commercial 70% TBHP (aqueous) can be used as oxidant at room temperature, and with just 2.5 mol% catalyst (**Scheme 85**).[149] The presence of >1 equivalent of water was crucial for high enantioselectivity, and to maintain catalyst activity. The enantioselectivities can be amplified by kinetic resolution during further oxidation of the sulfoxide to the sulfone.[149,150]

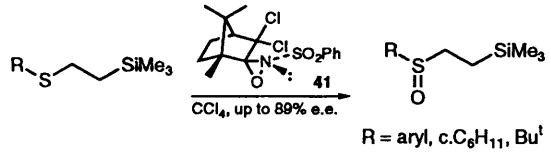


Scheme 85

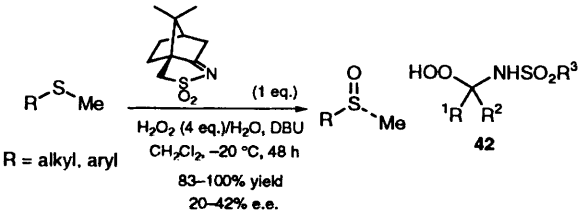


Scheme 84

The oxaziridines developed by Davis have been used for the asymmetric chemical oxidation of 2-(trimethylsilyl)ethyl sulfides. A variety of oxidation protocols were investigated, but the oxaziridine **41** was found to be the best reagent for these particular substrates (**Scheme 86**).[151] A recently developed modification of the use of oxaziridine-type methodology involves the use of the well established imine precursors, hydrogen peroxide and DBU (**Scheme 87**).[152] However, under these conditions, the reactive intermediate is likely to be the peroxyaminal **42** generated *in situ*, rather than an oxaziridine.

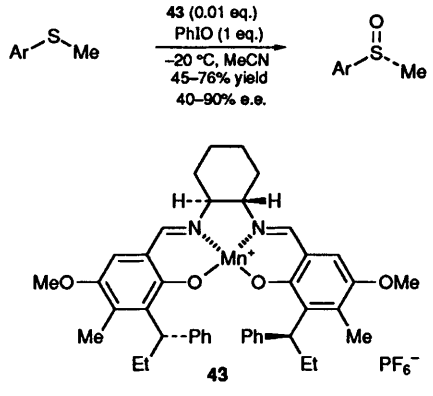


Scheme 86



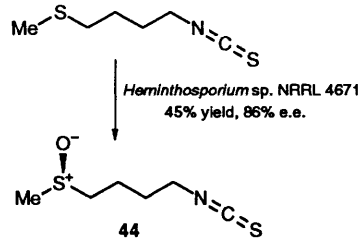
Scheme 87

There has been a recent report on the oxidation of aryl methyl sulfides using the (salen)manganese(III) complex **43** with iodosylbenzene reoxidant (**Scheme 88**).[153] Good yields and moderate to excellent enantioselectivities are obtained. A patent for these types of system has also recently been published.[154]



Scheme 88

There has been considerable progress on the biochemical asymmetric oxidation of sulfides to sulfoxides. A study on the mechanism of enzymatic and biomimetic oxidation of aromatic sulfides and sulfoxides has been reported.[155] The *Helminthosporium* species NRRL 4671 oxidizes *p*-alkyl benzyl sulfides and phenyl alkyl sulfides to the corresponding sulfoxides to give predominantly the (*S*)-sulfoxide enantiomer.[156,157] Good yields and high enantiomeric excesses can be achieved in some cases. The same species has been used for the preparation of (*R*)-sulforaphane **44**, a significant component in the anticarcinogenic action of broccoli (**Scheme 89**).[158]



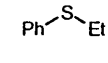
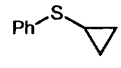
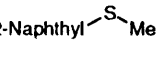
Scheme 89

Different strains of the bacterium *Pseudomonas putida* can give opposite enantioselectivity for asymmetric oxidation of aryl alkyl thioethers.[159] The UV4 strain gives predominantly the (*R*)-sulfoxide (>98% e.e.) whereas the NCIMB 8859 strain gives the (*S*)-isomer (76–91% e.e.). Chemical yields decrease dramatically as the alkyl group becomes larger. Camphor-grown *P. putida* NCIMB 10007 is also reported to catalyse the stereospecific oxidation of aryl alkyl sulfides to give the (*S*)-sulfoxides.[160] The structure of the sulfide substrate again significantly influences the yield and enantioselectivity of the reaction.

An exciting new development is the use of molecular engineering to improve the efficiency and selectivity of biochemical oxidations. Native horseradish peroxidase (HRP) oxidizes alkyl aryl sulfides with low to moderate enantioselectivities. If the phenylalanine-41 residue of HRP is mutated to a leucine residue then the enantioselectivity and rate of the oxidation improve dramatically (**Table 1**).[161]

Finally, microperoxidase-11, a very simple 11 residue peroxidase with an iron-protoporphyrin covalently linked via a thioether, catalyses the enantioselective oxidation of alkyl aryl sulfides by H_2O_2 to give predominantly the (*S*)-sulfoxides in 35–50% yield and 16–25% e.e.[162]

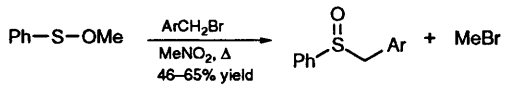
Table 1: Oxidation of thioethers using native HRP & F41L HRP

Substrate	Native HRP (%e.e.)	F41L HRP (%e.e.)
	35	94
	7	94
	69	99

3.2 Non-oxidative sulfoxide synthesis

3.2.1 General methods for sulfoxide synthesis

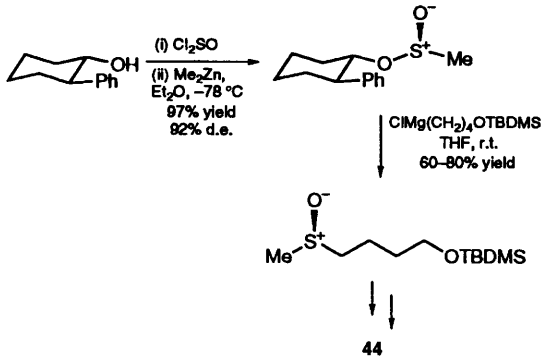
The thio-Arbuzov reaction has been reported to be an efficient method for the preparation of unsymmetrical aryl sulfoxides from arenesulfenate esters and a variety of benzyl bromides (**Scheme 90**).[163]



Scheme 90

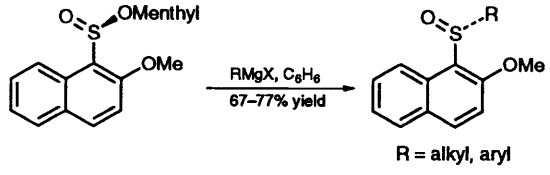
One of the most powerful methods of synthesizing optically active sulfoxides is by the use of a resolved sulfinate ester and an organometallic nucleophile, usually a Grignard or organolithium reagent. This was originally developed by Andersen, many years ago, who used menthyl sulfinate esters. Unfortunately, this procedure was unsuccessful for the synthesis of dialkyl sulfoxides because of problems accessing the required resolved alkyl sulfinate esters. Recently, alternative procedures to alleviate this problem have been developed, such as the use of sulfinate esters derived from diacetone-D-glucose (DAG).[164,165] These were discussed in the previous review,[1] but have now been further adapted for the synthesis of optically pure *tert*-butyl sulfoxides (**Scheme 91**).[166] The required sulfinate esters are readily prepared by treatment of DAG with *tert*-butyl sulfinyl chloride in the presence of either pyridine or triethylamine, which give diastereoisomeric sulfinate esters of good d.e., which can be further enhanced by recrystallization. Treatment of the individual diastereoisomers with Grignard reagents results in clean inversion of stereochemical configuration at sulfur (not retention as had previously been reported) and formation of the *tert*-butyl sulfoxides in high enantiomeric excess.

Other chiral sulfinate esters have also been reported. Treatment of resolved *trans*-2-phenylcyclohexanol with thionyl chloride followed by dimethyl zinc gives a methane sulfinate ester with high diastereoselectivity (**Scheme 92**).[167] This reacts with Grignard reagents with inversion of configuration at sulfur to give methyl alkyl sulfoxides of high enantiomeric purity. This approach has been used in a synthesis of (*R*)-sulforaphane **44** (*cf.* **Scheme 89**).

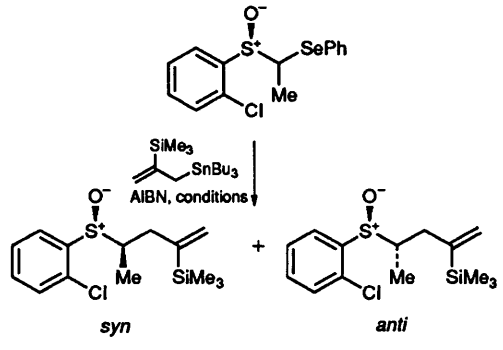


Scheme 92

In an extension of the original Andersen procedure, menthyl sulfinate esters have been developed for the synthesis of optically active aryl and alkyl 2-methoxynaphthalene-1-sulfoxides (**Scheme 93**).[168,169] The diastereoisomeric menthyl sulfinate reagents are separable by recrystallization, and react with Grignard reagents with inversion of stereochemical configuration at sulfur. Use of an excess of the Grignard reagent results in cleavage of the methyl ether to give the naphthol derivative directly.

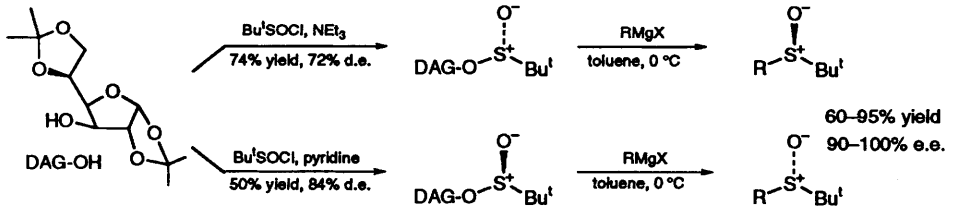


Scheme 93

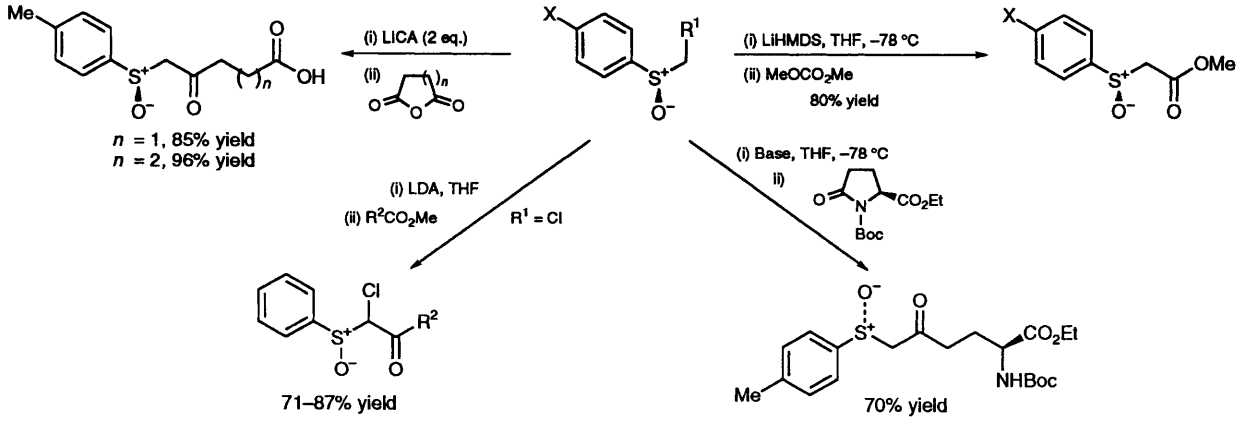


Conditions	*syn*:*anti*	Yield (%)
toluene, – 70 °C	95:5	20
benzene, 10 °C	90:10	60

Scheme 94



Scheme 91

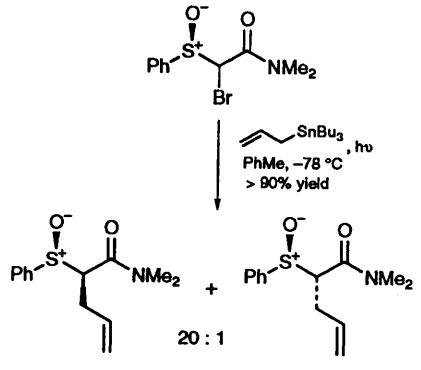


Scheme 95

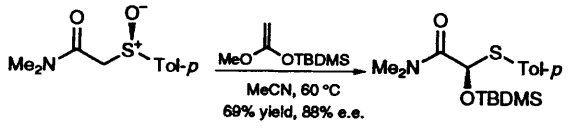
Recently, the use of α-sulfinyl radicals has been developed for the synthesis of sulfoxides, in some cases with considerable stereocontrol. Generation of an α-sulfinyl radical from the selenosulfinyl acetal using AIBN initiation, and allylation gives the product with high *syn*-selectivity, but low yield (**Scheme 94**).[170–174] Higher yields can be obtained if the reaction is carried out higher temperatures, however, diastereoselectivity is reduced somewhat.

3.2.2 Functionalized sulfoxides

Sulfoxides containing a β-carbonyl group are readily prepared by reaction of an α-lithiosulfoxide with a carboxylic acid derivative (**Scheme 95**), including carbonates,[175] anhydrides,[176] esters[177,178] and N-Boc amides.[179]



Scheme 96



Scheme 97

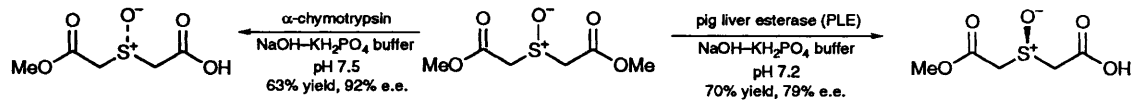
β-Amido-α-bromo sulfoxides undergo allylation via α-sulfinyl radicals with excellent stereoselectivity and in high yield (**Scheme 96**).[174] The corresponding esters are also successful in this reaction. β-Amido sulfoxides and related systems are also known to undergo efficient asymmetric Pummerer rearrangement, with good chirality transfer from sulfoxide to the *S,O*-acetal (**Scheme 97**).[180,181]

A novel approach to the synthesis of optically active sulfoxides with a β-carbonyl group utilizes the enzymatic hydrolysis of prochiral sulfinyl dicarboxylates with pig liver esterase (PLE), which gives predominantly the (*S*)-sulfoxide, or α-chymotrypsin, which gives the (*R*)-sulfoxide (**Scheme 98**).[182]

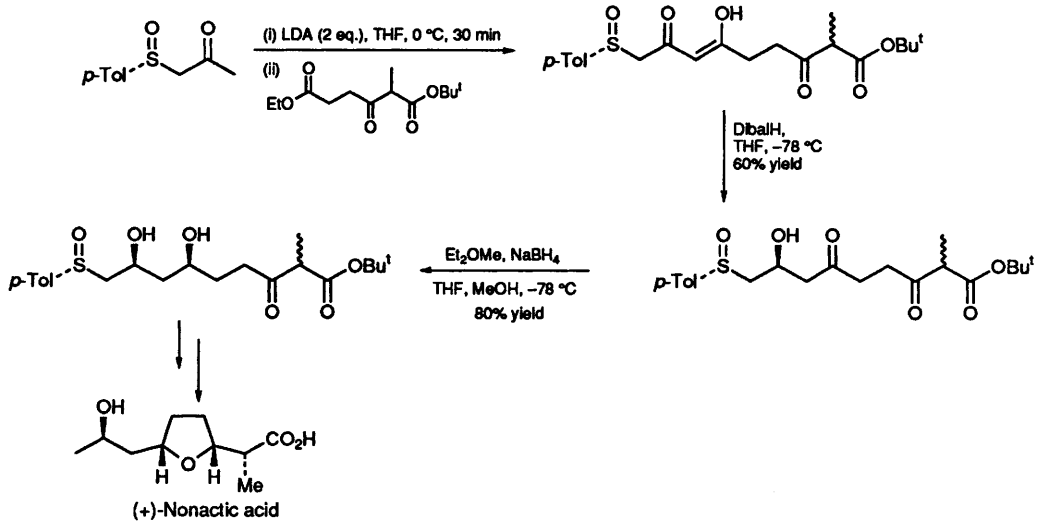
The reactions of β-keto sulfoxides with nucleophiles provide routes to β-hydroxy sulfoxides, often with considerable stereocontrol. These reactions are now well established, and have been recently reviewed.[183,184] Considerable work on stereochemical assignment in these systems has also been carried out.[185] The stereoselective reduction of β-keto sulfoxides has been applied to the synthesis of a number of natural products,[186,187] including (+)-nonactic acid (**Scheme 99**),[188] various sugars[178,189] and (−)-cladospolide A (**Scheme 100**).[190] It has also been used for the synthesis of optically active allylic alcohols via a recoverable sulfoxide chiral auxiliary (**Scheme 101**).[191] Reduction can also give very high stereoselectivities in more substituted systems (**Scheme 102**).[176,192]

Nucleophiles other than hydride can also be added stereoselectively to β-keto sulfoxides. These include cyanide (**Scheme 103**)[193] and trimethylaluminium (**Scheme 104**).[194] In the case of the latter, a significant increase in the yield and stereoselectivity of the process is observed if the reaction is carried out in the presence of $ZnCl_2$. High stereoselectivity is also observed in the addition of diazomethane to fluorinated β-keto sulfoxides, forming the epoxides in poor to excellent yields (**Scheme 105**).[195]

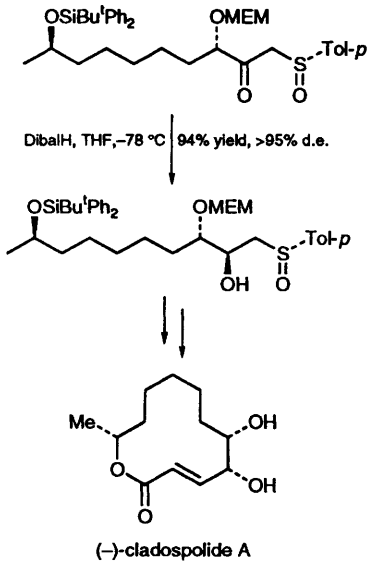
The addition of Grignard reagents to 2-formyl-3-sulfinyl furans can also occur with high diastereoselectivity, particularly if the reaction is



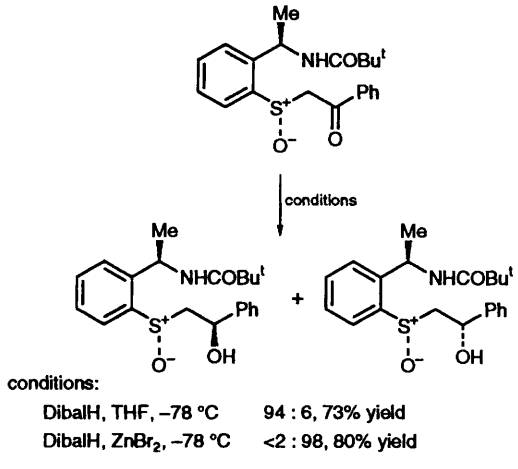
Scheme 98



Scheme 99



Scheme 100

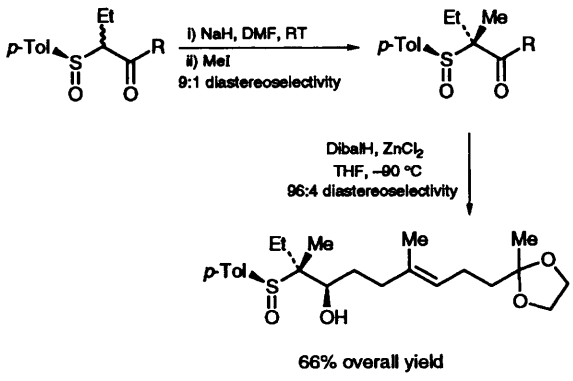


Scheme 101

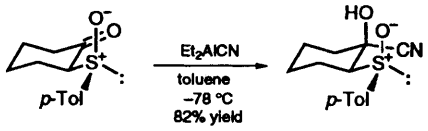
carried out in the presence of $ZnBr_2$ (**Scheme 106**).[196]

Another synthetic approach to β-hydroxy sulfoxides utilizes the reaction of metallated sulfoxides with aldehydes. Chiral 2-(trimethylsilyl) ethyl sulfoxides can be prepared in an optically active form (**Scheme 86**),[151] and can be deprotonated using LDA and react with aldehydes to give β-hydroxy sulfoxides. Chemical yields are high, and stereoselectivities relative to the alcohol chiral centre are poor; however, there is almost total stereocontrol for bond formation adjacent to the sulfoxide (**Scheme 107**).[197] Related alkylations have also been reported for α-fluorosulfoxides.[198,199]

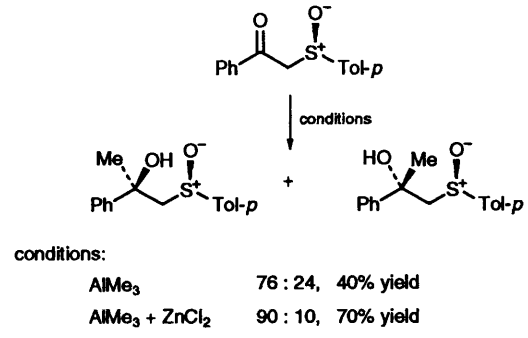
β-Amino sulfoxides can be prepared by Michael addition of amine nucleophiles to unsaturated sulfoxides. This has recently been demonstrated for amino acid derived systems, which give a moderate



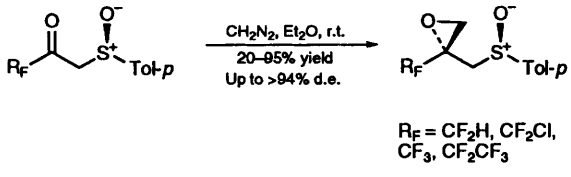
Scheme 102



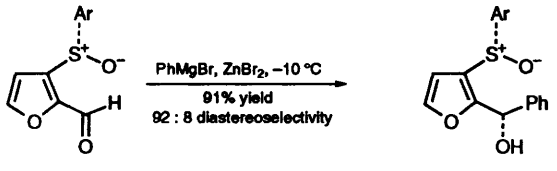
Scheme 103



Scheme 104



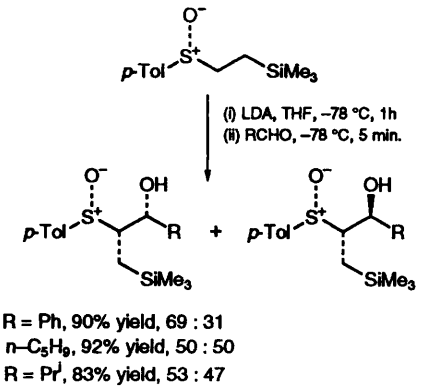
Scheme 105



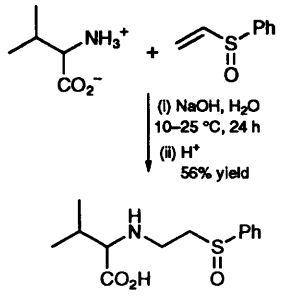
Scheme 106

yield of the conjugate addition product (**Scheme 108**).[200–202]

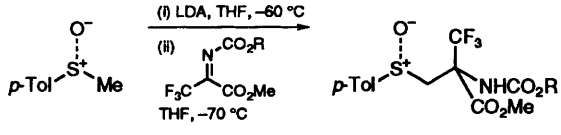
Related systems have also been prepared by the addition of α-lithio sulfoxides to imine electrophiles.



Scheme 107



Scheme 108



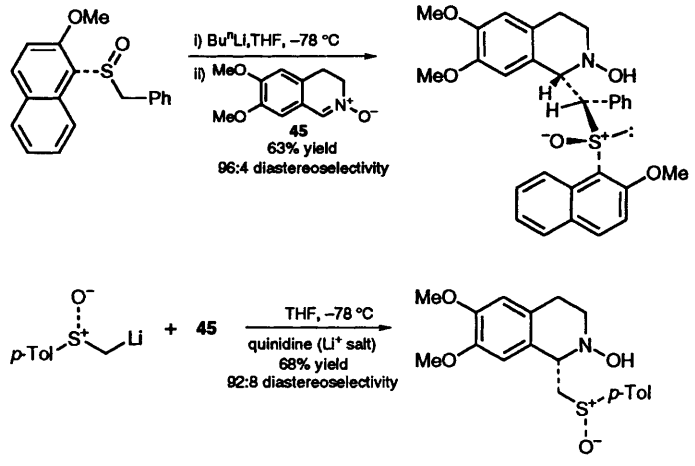
Scheme 109

For example, *N*-acyl imines give reasonable yields but only very low diastereoselectivities (**Scheme 109**).[203] The addition of sulfoxide anions to nitrones has also been reported (**Scheme 110**).[169,204] Good yields and excellent diastereoselectivities can be obtained, however, in the second example, if the reaction is carried out in the absence of the quinidine auxiliary, only low stereoselectivity is observed (64:36).

3.2.3 Unsaturated sulfoxides

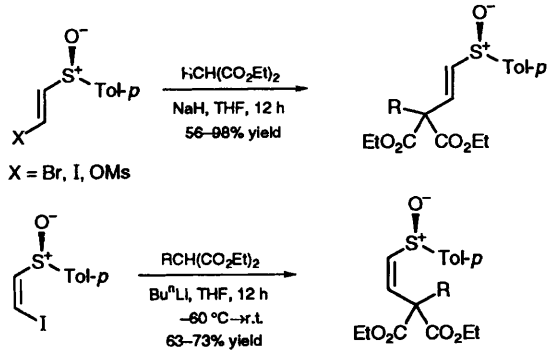
A transition state model for the π-facial selection for electrophilic addition to α,β-unsaturated sulfoxides has been proposed which is consistent with a number of experimental observations, and will be of use in predicting stereoselectivity for related reactions.[205]

The addition–elimination reaction of 2-halo- and 2-(mesyloxy)vinyl sulfoxides with malonate nucleophiles provides a route to 2-malonylvinyl sulfoxides (**Scheme 111**).[206] A wide variety of

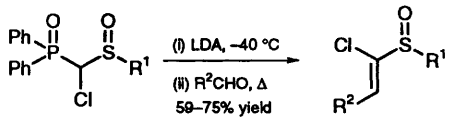


Scheme 110

malonate derivatives can be synthesized using this methodology, and importantly, the double bond geometry of the precursor is retained in the substitution product. A Horner–Wittig reaction has been exploited for the synthesis of 1-chlorovinyl sulfoxides (**Scheme 112**).[207] Excellent (*Z*)-selectivity is observed in most cases.



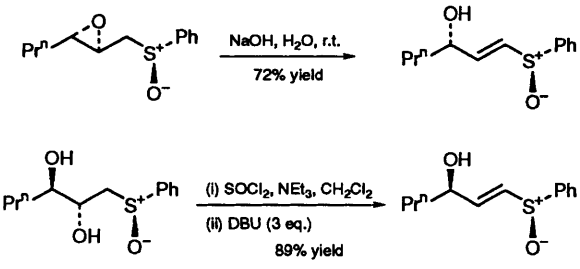
Scheme 111



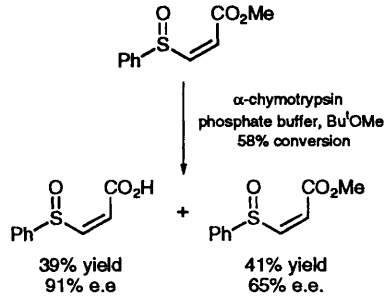
Scheme 112

Diastereomerically pure 2,3-epoxy sulfoxides undergo a facile elimination reaction to give homochiral γ-hydroxy-α,β-unsaturated sulfoxides when treated with base (**Scheme 113**).[208,209] The opposite diastereoisomeric series can be accessed from the related 2,3-dihydroxy sulfoxides, by elimination of the corresponding cyclic sulfites using DBU.

A novel approach to optically active α,β-unsaturated sulfoxides is by the enzymatic kinetic resolution by ester hydrolysis of (*Z*)-β-methoxycarbonyl-α,β-unsaturated sulfoxides using



Scheme 113

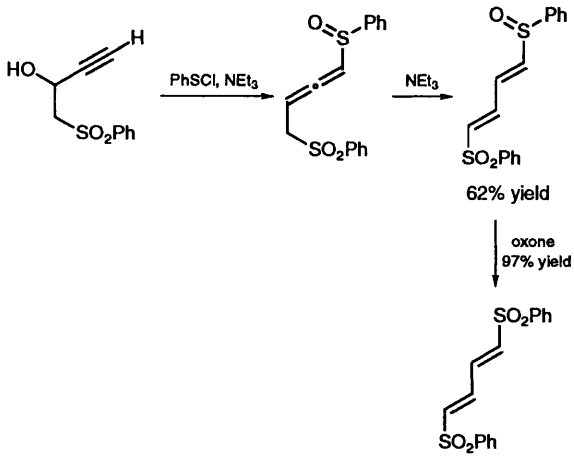


Scheme 114

α-chymotrypsin (**Scheme 114**).[210] High enantiomeric excesses of either the ester or acid can be achieved depending on the % conversion during the hydrolysis reaction.

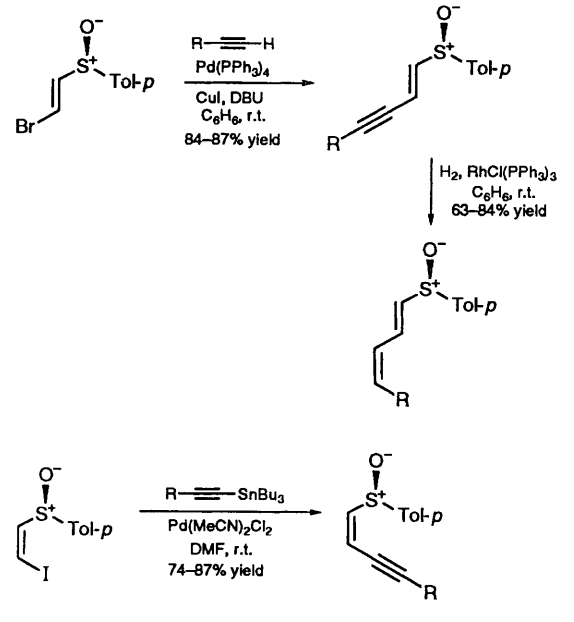
The [2,3]-sigmatropic rearrangement of β-phenylsulfonyl prop-2-ynylic sulfenates has been applied as a method for the preparation of 1-(phenylsulfinyl)-4-(phenylsulfonyl)-buta-1,3-dienes (**Scheme 115**).[211] Prop-2-ynylic alcohols are sulfenylated using phenyl sulfenyl chloride. Subsequent [2,3]-sigmatropic rearrangement occurs *in situ* to give an allenyl sulfoxide, which on treatment with base isomerizes to the dienyl sulfoxide.

Enantiomerically pure enynyl sulfoxides can be accessed by the palladium-catalysed coupling of β-halovinyl sulfoxides with an alkyne (**Scheme**



Scheme 115

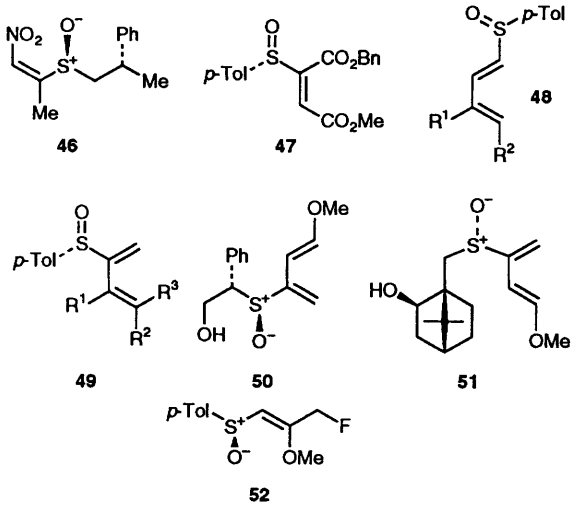
116).[212] A variety of functional groups can be tolerated in the reaction including alcohols and triethylsilyl ethers. Retention of double bond geometry is observed in the coupling reaction, however, for the synthesis of (*Z*)-enynyl systems, an acetylenic stannane is required for efficient reaction. The (*E*)-enyne products can be selectively hydrogenated to give (1*E*,3*Z*)-1-sulfinyl dienes; the corresponding (*Z*)-isomers are not reduced cleanly. (3*E*)-2-Sulfinyl dienes have been prepared by selective oxidation of the corresponding sulfides (**Scheme 56**).[90,97]



Scheme 116

Alkenyl and dienyl sulfoxides have been the subject of considerable investigation as dienes, dienophiles, and dipolarophiles in cycloaddition reactions. Whilst it is beyond the scope of this chapter to discuss such reactions in any detail, a brief discussion of the kinds of system which have been reported will be included. Syntheses of many of these compounds have been reported previously; any important new synthetic routes have been discussed above.

The use of camphor-derived α,β-unsaturated sulfoxides and other chiral sulfinylethenes as dienophiles in asymmetric Diels–Alder reactions, and their use in natural product synthesis, has been reviewed.[213,214] The α,β-unsaturated sulfoxides **46**[215] and **47**[216] have been reported to act as dienophiles in a Diels–Alder cycloaddition.[217–219] A number of dienyl sulfoxides have also been investigated as Diels–Alder dienes, including simple 1-sulfinyl-**48**[220] and 2-sulfinyl-dienes **49**,[221,222] and the more complex systems **50**[223] and **51**.[224] Chiral vinyl sulfoxides such as **52** have also been investigated as dipolarophiles.[225]



4 Synthesis of sulfones

An excellent text on the use of sulfones in organic synthesis has been published. It contains detailed sections on many aspects of sulfone synthesis and is highly recommended.[226]

4.1 Oxidation of sulfides and sulfoxides

New methods for the oxidation of simple sulfides and sulfoxides to sulfones have been reported, many of which can also be used for sulfoxide synthesis, but under harsher reaction conditions or with more equivalents give the sulfone. These include dimethyl dioxirane (DMDO) generated *in situ* using oxone and acetone,[118] trifluoromethyl methyl dioxirane,[227] oxaziridinium salts **34** derived from dihydroisoquinoline;[114] H_2O_2 and MeCN at room temperature (via peroxyimidic acid intermediate **36**);[121] the perfluoro-*cis*-2,3-dialkyloxaziridine **35** at −20 °C (the volatile imine biproduct is easily removed);[115] HOF/MeCN generated *in situ* from F_2, H_2O, and MeCN;[228] $NaIO_4$ with $RuCl_3/H_2O$ catalyst (particularly good for highly unreactive sulfides);[229] and *N*-methyl morpholine *N*-oxide with Pr^n_4N/RuO_4 (TPAP) catalyst.[230]

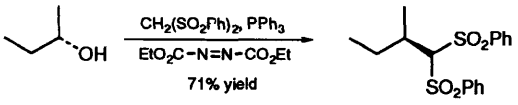
There has also recently been reported a nice example of chemoselective sulfur oxidation in the

synthesis of dysoxysulfone (**12**, **Scheme 46**). Using $KMnO_4$ and $Zn(OAc)_2$ the bis-sulfone **12** can be isolated in 57% yield by selective oxidation of the two external thioether groups.[68]

4.2 Non-oxidative sulfone synthesis

4.2.1 General methods for sulfone synthesis

New methods for the synthesis of sulfones using methods other than oxidation have been reported. It has been shown that bis-sulfones undergo a stereospecific alkylation when treated with secondary alcohols under Mitsunobu conditions (**Scheme 117**).[231] The reaction is successful with a wide variety of substrates and has been used in the enantioselective synthesis of the pheromone of the lesser tea tortrix.

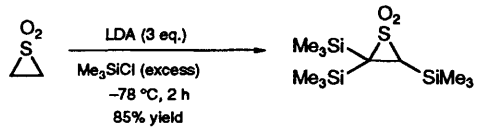


Scheme 117

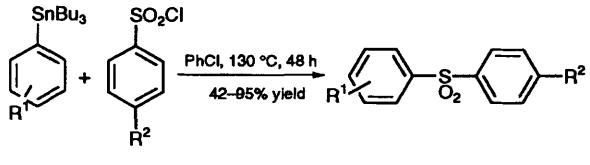
The first examples of episulfone substitution reactions via α-sulfonyl carbanion intermediates have been reported (**Scheme 118**).[232,233] So far the range of electrophiles which can be used in the reaction are severely limited, but high yields can be obtained in some cases.

A route to diaryl sulfones involving coupling between sulfonyl chlorides and arylstannanes has been reported (**Scheme 119**).[234] Moderate to good yields can be obtained with high regioselectivity in the coupling reaction.

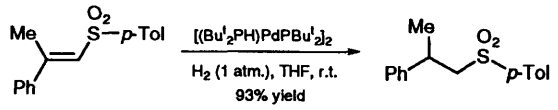
Finally, aryl alkyl sulfones have been synthesized by hydrogenation of the corresponding α,β-unsaturated sulfones (**Scheme 120**).[235] In this case the catalyst used, $[(Bu^t_2PH)PdPBu^t_2]_2$, needs to be pretreated with oxygen to generate the active catalyst.



Scheme 118



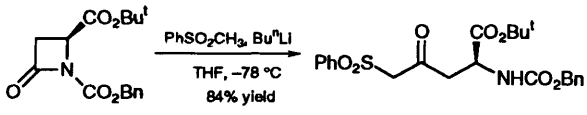
Scheme 119



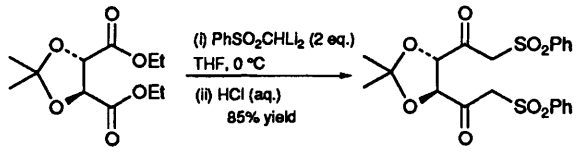
Scheme 120

4.2.2 Functionalized sulfones

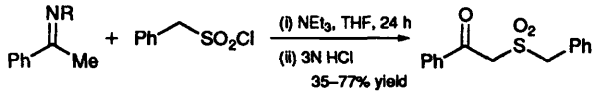
The reaction of α-sulfonyl anions with carboxylic acid derivatives provides a route to β-keto sulfones. Recent examples of this reaction are the use of β-lactams (**Scheme 121**)[236] and tartaric acid derivatives (**Scheme 122**)[237] as electrophiles. Alternatively, β-keto sulfones have been synthesized by reacting imines with sulfonyl chlorides (**Scheme 123**).[238] In this case the reactive electrophile is a sulfene generated *in situ* from the sulfonyl chloride and base, and the initial imine product is hydrolysed by aqueous acid to give the desired β-keto sulfone.



Scheme 121

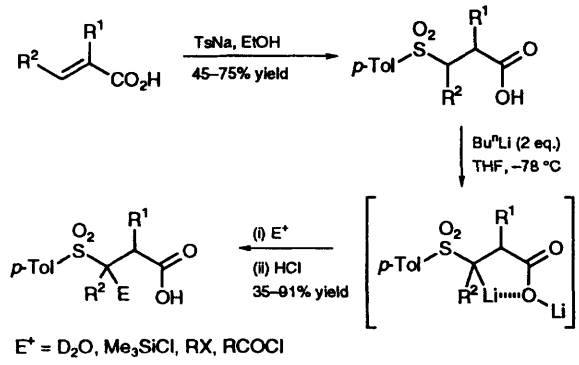


Scheme 122

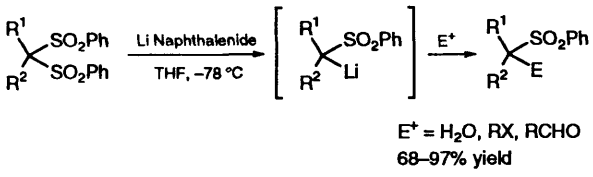


Scheme 123

The addition of sulfinate anions to α,β-unsaturated carboxylic acids generates the Michael adducts in moderate to good yield, which can act as β-acyl vinyl anion equivalents. These can then be further functionalized by double deprotonation and treatment with a range of electrophiles to give the substituted β-sulfonyl carboxylic acids (**Scheme 124**).[239] Alternatively, α-sulfonyl anions can be accessed by reductive lithiation of bis-phenyl sulfones using lithium naphthalenide (**Scheme 125**).[240–243]

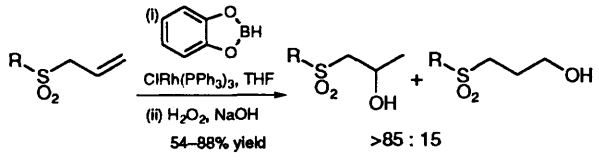


Scheme 124

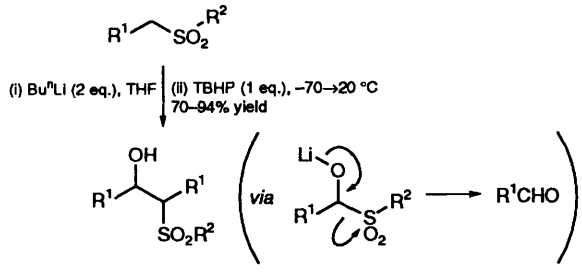


Scheme 125

A new route to β-hydroxy sulfones has been reported which uses the sulfone-directed rhodium-catalysed hydroboration–oxidation of allyl sulfones. The Markownikoff product is obtained preferentially with high regioselectivity (**Scheme 126**).[244] β-Hydroxy sulfones have also been prepared by oxidation of α-sulfonyl carbanions with lithium *tert*-butyl peroxide, the carbonyl compound being generated *in situ* by loss of sulfinate (**Scheme 127**).[245]

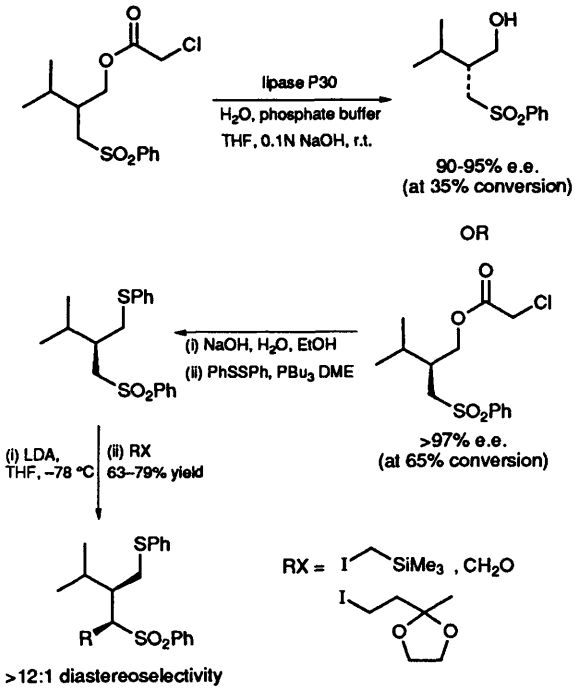


Scheme 126



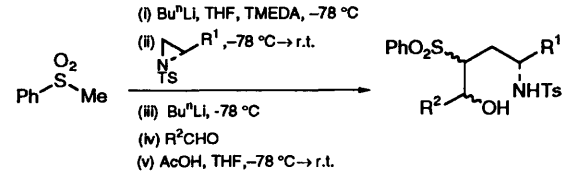
Scheme 127

β-Alkyl-γ-hydroxy sulfones can be obtained in an optically active form by enzymatic hydrolysis of the corresponding chloroacetate esters using lipase P30 (**Scheme 128**).[246] At 35% conversion the hydrolysed alcohol has an enantiomeric excess of 90–95%. If the reaction is allowed to progress to 65% conversion then, after conventional hydrolysis, the enantiomeric alcohol can be obtained of >97% e.e. The product alcohols can then be readily converted into the phenylthioethers, which undergo regioselective lithiation α-to the sulfone and subsequent alkylation, with high stereoselectivity.



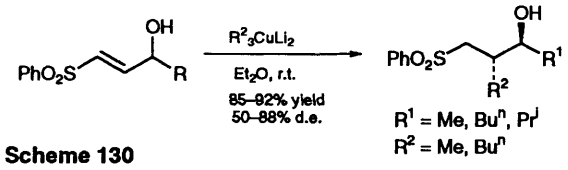
Scheme 128

α-Lithio sulfones have also been reacted with enantiomerically pure *N*-tosyl aziridines to form γ-amino sulfones, which can be further substituted by *in situ* lithiation and reaction with aldehydes to give the β-hydroxy sulfone in good overall yield (**Scheme 129**).[247]



Scheme 129

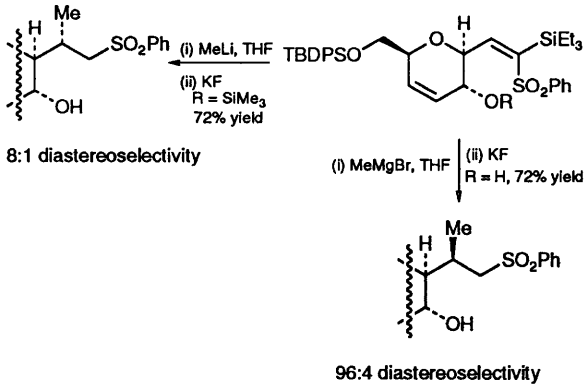
The conjugate addition of organocopper reagents to (*E*)-γ-hydroxy-α,β-unsaturated sulfones proceeds in excellent yield and with high *anti* selectivity (**Scheme 130**).[248] Interestingly, if the alcohol group



Scheme 130

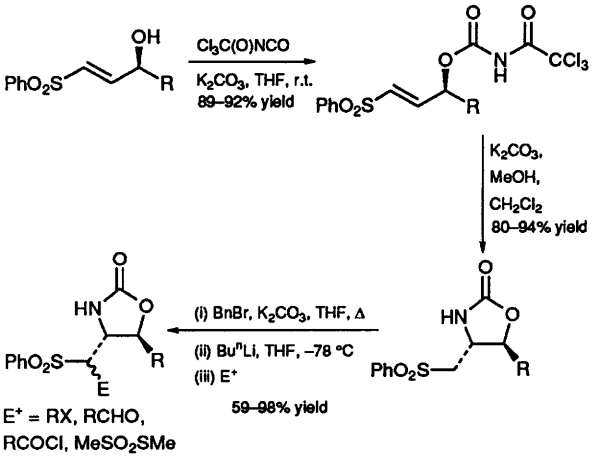
in the substrate is protected as the acetate ester, or the MOM or *tert*-butyldimethylsilyl ethers, then S_N2' allylic displacement is observed with cuprate reagents.

Other highly stereoselective conjugate addition reactions to α,β-unsaturated sulfones have also been reported. In the system shown in **Scheme 131**, if the free alcohol is used then attack of the Grignard reagent occurs from the top face, however, if the trimethylsilyl ether is used with methyl lithium as the nucleophile, then the opposite stereoselectivity is observed.[249]



Scheme 131

In an interesting approach to the synthesis of homochiral *syn*-2-amino alcohol derivatives, (*E*)-γ-hydroxy-α,β-unsaturated sulfones are treated with trichloroacetylisocyanate to give an imide which undergoes stereoselective intramolecular addition of the nitrogen to the unsaturated sulfone, and partial hydrolysis, to give a cyclic urethane (**Scheme 132**).[250] After benzylation, these systems can be further functionalized by lithiation and subsequent alkylation in good to excellent yield. The lithiation and subsequent alkylation of related β-amino sulfones has also been reported,[243,251] as has the intermolecular addition of hydroxylamine to α,β-unsaturated sulfones, leading to formation of β-hydroxylamino sulfones.[252,253]

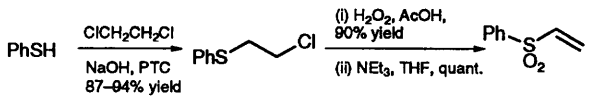


Scheme 132

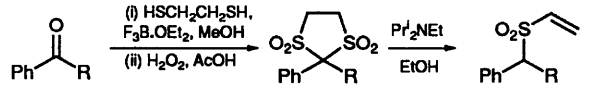
4.2.3 Unsaturated sulfones

α,β-Unsaturated sulfones can be prepared by the oxidation of the corresponding unsaturated sulfides (**Scheme 56**)[90,97] and sulfoxides (**Scheme 115**).[211] A convenient and economical synthesis of phenyl vinyl sulfone has been published, from simple precursors and in high overall yield (**Scheme 133**).[254] An interesting synthesis of vinyl sulfones from 1,3-dithiolane tetraoxides has also been reported, and provides a direct route to vinyl sulfones from carbonyl compounds by thiolane formation, oxidation, and elimination of SO_2 (**Scheme 134**).[255]

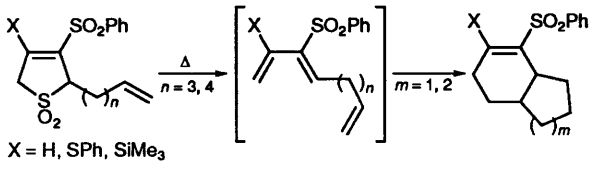
The well known extrusion of SO_2 from sulfolenes has also been exploited in the preparation of dienyl sulfones, which undergo *in situ* intramolecular cycloaddition in this case (**Scheme 135**).[256]



Scheme 133

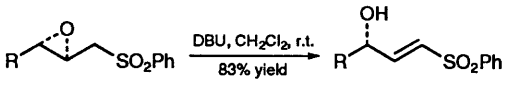


Scheme 134



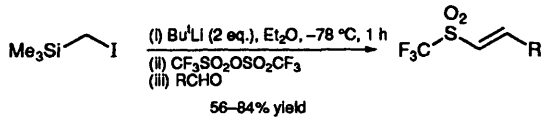
Scheme 135

(*E*)-γ-Hydroxy-α,β-unsaturated sulfones have been prepared in an optically active form, by the base-induced elimination of 2,3-epoxy sulfones (**Scheme 136**).[208,257] The optically active precursors were prepared via the Sharpless asymmetric epoxidation.



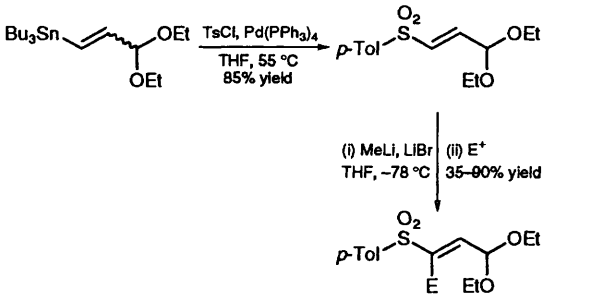
Scheme 136

Vinyl triflones (trifluoromethyl sulfones), which are known to be excellent substrates for Michael addition, have been prepared by a Peterson-type olefination. Treatment of trimethylsilyl methyl iodide with two equivalents of *tert*-butyl lithium followed by sequential condensation with the triflone anhydride and an aldehyde gives the alkene directly (**Scheme 137**).[258]



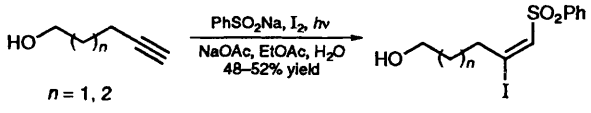
Scheme 137

Alkenyl stannanes can be coupled with sulfonyl chlorides with Pd^0 catalysis to selectively give (*E*)-α,β-unsaturated sulfones, irrespective of the initial alkene geometry (**Scheme 138**).[259] These systems can be further substituted by lithiation α-to the sulfone and alkylation with a range of electrophiles.

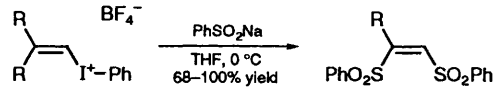


Scheme 138

(*E*)-β-iodo-α,β-unsaturated sulfones have been prepared by photolytic addition of iodine to alkynes in the presence of sodium benzenesulfinate (**Scheme 139**).[260] (*Z*)-1,2-bis(phenylsulfonyl) alkenes can also be prepared using sodium benzenesulfinate by substitution of the appropriate vinyl iodonium tetrafluoroborates (**Scheme 140**).[261,262]



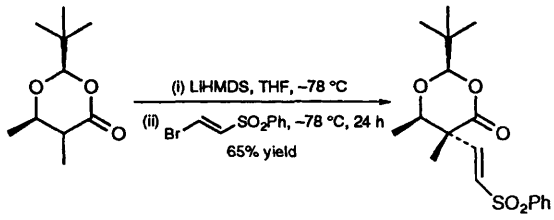
Scheme 139



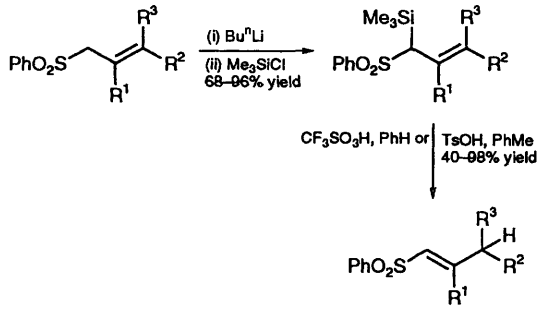
Scheme 140

Lithium enolates of dioxanones add to β-bromo-α,β-unsaturated sulfones to give the substitution product with retention of double bond geometry, and high stereoselectivity (**Scheme 141**).[263] The reaction works best with (*E*)-isomers although (*Z*)-isomers can also be used but are less reactive.

Allyl sulfones can also be used as precursors to vinyl sulfones, via a protiodesilylation route (**Scheme 142**).[264–266] The allyl sulfone precursors are lithiated and regiospecifically silylated α-to the sulfone. Treatment with strong acid results in protiodesilylation with clean allylic rearrangement to give the (*E*)-vinyl sulfone selectively.

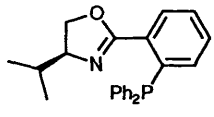


Scheme 141

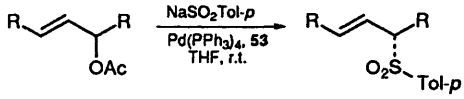


Scheme 142

A review on the chemistry of 3-heteroatom substituted allyl sulfones has been published.[257] Optically active allyl sulfones have been prepared by reaction of an allyl acetate with sodium *p*-toluene sulfinate in the presence of Pd^0 modified with the chiral ligand **53** (**Scheme 143**).[267] Enantiomeric excesses of up to 93% can be achieved with this methodology.



53

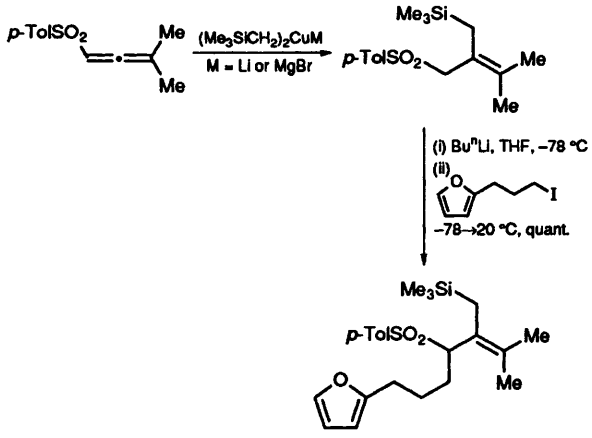


R = Me, 40–83% yield, up to 59% e.e.
R = Ph, 87–98% yield, up to 93% e.e.

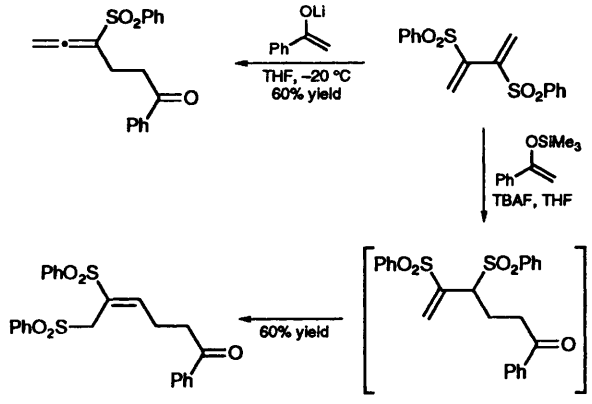
Scheme 143

Allyl sulfones have also been prepared by the addition of organocopper reagents to allenic sulfones. The products can also be further functionalized by lithiation and regiospecific alkylation, although direct alkylation of the initial cuprate adduct is not very efficient (**Scheme 144**).[268] Other alkylations of allyl sulfones have also been reported.[269]

Allenic sulfones can be accessed from 2,3-bis-(phenylsulfonyl)-buta-1,3-diene by Michael addition of an enolate and subsequent elimination of sulfinate (**Scheme 145**).[270,271] If silylenol ethers and TBAF are used rather than lithium enolates then no elimination is observed and instead the intermediates undergo a 1,3-sulfonyl shift to give the observed allyl sulfone product.[265,266,270,271]

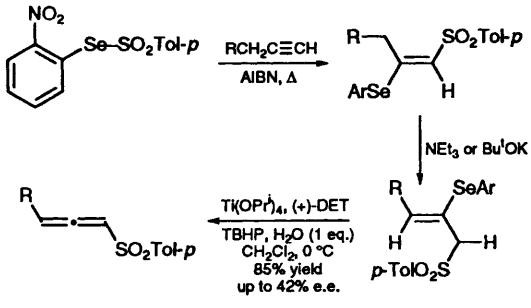


Scheme 144



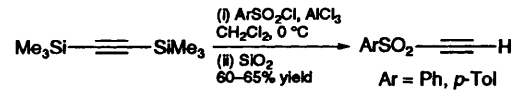
Scheme 145

Chiral allenic sulfones have been prepared by asymmetric selenoxide elimination in an allyl sulfone (**Scheme 146**).[272] The selenoxide substrates are best prepared by asymmetric oxidation of the corresponding vinyl selenide using the Kagan oxidation protocol (*cf.* **Scheme 81**). Enantiomeric excesses of up to 42% were achieved.

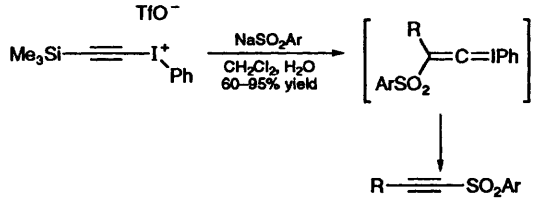


Scheme 146

Finally, two new routes to acetylenic sulfones have been published. The first involves the reaction of bis-trimethylsilylacetylene with a sulfonyl chloride under Lewis acidic conditions (**Scheme 147**).[273] Selective mono-sulfonation is possible, the remaining trimethylsilyl group being removed on column chromatography. The second new method of acetylenic sulfone synthesis utilizes the reaction of a wide range of acetylenic iodonium triflates with sodium salts of aromatic sulfinates (**Scheme 148**).[274] The reaction proceeds via initial addition of sulfinate to the triple bond to form an iodonium ylide which subsequently rearranges to give the acetylenic sulfone.



Scheme 147



Scheme 148

5 Conclusion

Organosulfur chemistry continues to play a crucial role in organic synthesis, particularly with the new stereoselective and asymmetric processes being developed. I hope this review has demonstrated the wide variety of methods available for the synthesis of organosulfur compounds, and will encourage their further development and exploitation in the future.

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