Synthesis of thiols, selenols, sulfides, selenides, sulfoxides, selenoxides, sulfones and selenones

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Reviewing the literature published between March 1995 and May 1996
Continuing the coverage in *Contemporary Organic Synthesis*, 1995, **2**, 409

1 Introduction
2 Synthesis of thiols and disulfides, selenols and diselenides, sulfides and selenides
2.1 Simple alkanethiols and dialkyl disulfides, alkaneselenols and dialkyl diselenides, dialkyl sulfides and selenides
2.2 Unsaturated thiols, disulfides, selenols, diselenides, sulfides and selenides
2.3 Substituted thiols and disulfides, selenols and diselenides, sulfides and selenides
2.4 Thiols, disulfides, selenols, diselenides, sulfides and selenides as mediators of asymmetric transformations
3 Synthesis of sulfoxides
3.1 Oxidation of sulfides and selenides
3.1.1 Non-stereoselective oxidation
3.1.2 Stereoselective oxidation
3.1.3 Enantioselective oxidation
3.2 Non-oxidative sulfoxide and selenoxide synthesis
3.2.1 General methods for sulfoxide and selenoxide synthesis
3.2.2 Functionalised sulfoxides and selenoxides
3.2.3 Unsaturated sulfoxides and selenoxides
4 Synthesis of Sulfones and Selenones
4.1 Oxidation of sulfides and sulfoxides
4.2 Non-oxidative sulfone synthesis
4.2.1 General methods for sulfone synthesis
4.2.2 Functionalised sulfones
4.2.3 Unsaturated sulfones
5 Conclusion
6 References

1 Introduction

This review continues from the previous ones published in 1994[1] and 1995.[2] It covers new methods for the synthesis of acyclic thiols, sulfides, sulfoxides and sulfones. In addition, the coverage has now been extended to include the analogous selenium derivatives. 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, selenols, sulfides and selenides; sulfoxides and selenoxides; and sulfones and selenones. 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 new introductory text on organosulfur chemistry has been published which is suitable for undergraduates, postgraduates and anyone involved in research needing to refresh their knowledge of this area.[3] Reviews on S-cationoid reagents in organic synthesis[4] and recent advances in synthetic reactions using organoselenium reagents have been published.[5] The latter includes sections on the addition of electrophilic selenium species to double bonds, including asymmetric processes, and catalytic oxyselenation and intramolecular oxyselenation reactions.

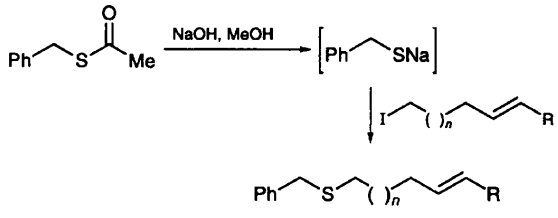
2 Synthesis of thiols and disulfides, selenols and diselenides, sulfides and selenides

Methods of preparation, reactions and physicochemical properties of sulfides have recently been reviewed.[6] The chemistry of disulfides has also been reviewed,[7] as have applications of organosulfur compounds[8] and elemental selenium[9] in organic synthesis. The origins of acidity trends for sulfides and oxidised derivatives[10,11] and radical stabilities[11] have also been investigated.

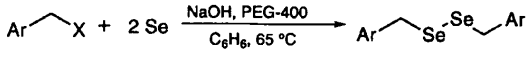
2.1 Simple alkanethiols, dialkyl disulfides, alkaneselenols, dialkyl diselenides, dialkylsulfides and selenides

The reactions of alkyl halides and related electrophiles with nucleophilic sulfur or selenium species are amongst the most established methods of sulfide and selenide synthesis. Recent advances have been reported which include the use of borohydride exchange resin (BER) which promotes reaction between thiols and alkyl halides or epoxides to form unsymmetrical sulfides.[12,13] The use of hydrosulfide exchange resin, prepared from the chloride form of Amberlite IRA-400 and sodium hydrosulfide, can be used for the direct synthesis of thiols from alkyl halides (*cf.* **Scheme 51**).[14] Addition of triethylamine

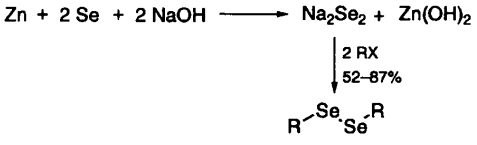
hydrochloride minimises formation of the more usual symmetrical sulfide products. Benzyl sulfides can be prepared by reaction of thiols with benzyl chloride in the presence of montmorillonite–3-aminopropyl(triethoxy)silane.[15] Alternatively, benzyl thioacetate in the presence of NaOH and methanol generates phenylmethanethiolate which reacts with alkyl halides to give benzyl thioethers (**Scheme 1**).[16,17] Symmetrical dibenzyl diselenides can be synthesised from elemental selenium, NaOH and benzyl halides under phase transfer conditions using polyethylene glycol (PEG) (**Scheme 2**).[18] Diselenides can also be formed directly using elemental selenium and zinc in the presence of sodium hydroxide, reacting with either alkyl halides, nitrohaloaromatics and acyl halides (**Scheme 3**).[19] Bis(benzyltriethylammonium) tetrathiomolybdate[20,21] reacts with alkyl halides and toluene-*p*-sulfonates to form disulfides directly and has found particular application in macrocyclic disulfide synthesis (**Scheme 4**), whereas sodium sulfide adsorbed on



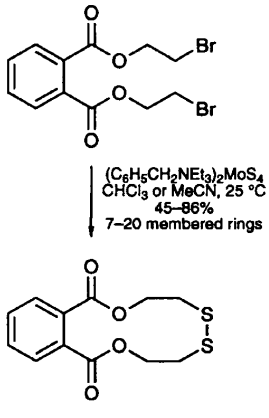
Scheme 1



Scheme 2

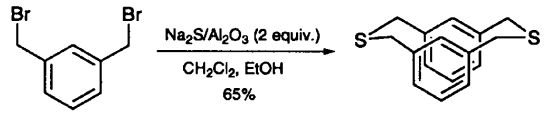


Scheme 3

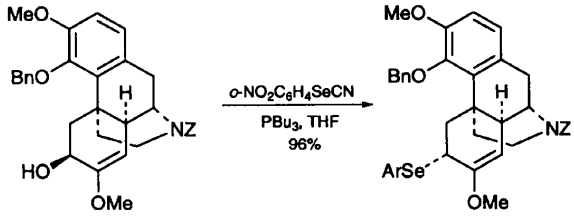


Scheme 4

alumina has been used for the synthesis of macrocyclic sulfides (**Scheme 5**).[22,23] The reaction of alcohols with *o*-$NO_2C_6H_4SeCN$ under Mitsunobu conditions[24] results in formation of the selenide with clean inversion of stereochemistry (**Scheme 6**).[25] It has also been reported that zeolites catalyse the formation of thiols and sulfides by reaction between alcohols and hydrogen sulfide.[26]



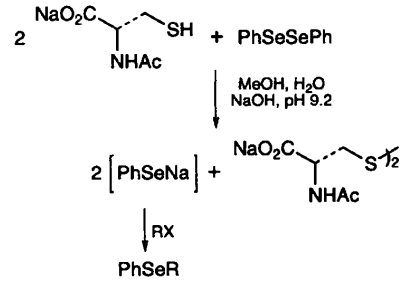
Scheme 5



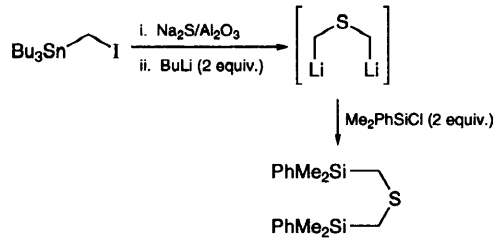
Scheme 6

A new method of selenolate generation relies on a thiolate–diselenide exchange reaction using the sodium salt of *N*-acetylcysteine (**Scheme 7**). The produced benzeneselenolate reacts with various electrophiles, including alkyl halides, epoxides and epoxy ketones in high yields.[27] The major byproduct is the disodium salt of cystine, which is easily removed due to its high water solubility. Tin–lithium exchange can be used to prepare bis(lithiomethyl) sulfide, an unusually stable 1,3-dilithiated synthetic building block which reacts with electrophiles such as dimethylphenylsilyl chloride to give symmetrical sulfide products (**Scheme 8**).[23] A novel route to unsymmetrical dithia compounds relies on cleavage of a disulfide by a nucleophilic reagent such as an organolithium, followed by trapping of the intermediate thiolate with an alkyl halide (**Scheme 9**).[28]

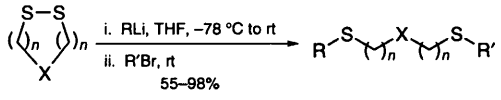
The photochemically initiated radical addition of disulfides and diselenides to alkenes provides a



Scheme 7

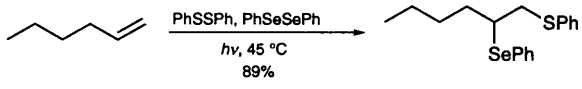


Scheme 8

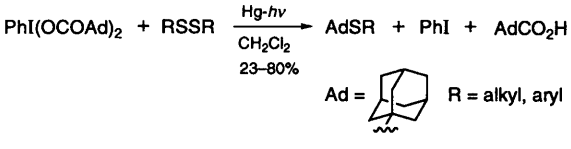


Scheme 9

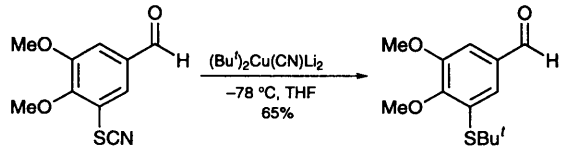
route to 1-thio-2-seleno substituted systems. Interestingly, the reaction is much more efficient if mixed PhSSPh–PhSeSePh reagents are used rather than individual disulfides or diselenides; however high regioselectivity is possible with a wide variety of substrates (**Scheme 10**).[29] The photochemical degradation of [bis(1-adamant-3-yl-carbonyloxy)-iodo]benzene in the presence of disulfides provides a route to adamantyl sulfides (**Scheme 11**).[30] Other hindered sulfides can be prepared by ligand transfer of aryl thiocyanates with higher order cyanocuprate reagents (**Scheme 12**).[31] The reaction can be carried out in the presence of reactive groups such as aldehydes, halides and NHBoc, but nitro groups are reduced under the reaction conditions. With simple Grignard reagents, thiols are the major products.



Scheme 10

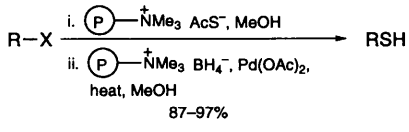


Scheme 11

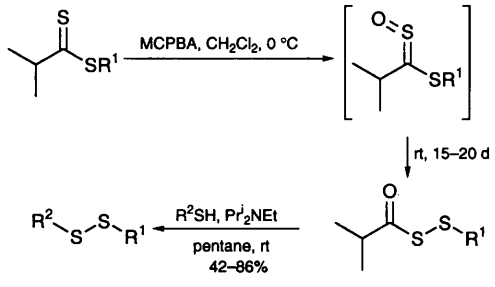


Scheme 12

Organic thiocyanates undergo reductive dimerisation to give disulfides using bis(benzyltriethylammonium) tetrathiomolybdate. A wide range of structures and functional groups can be tolerated in this reaction (*cf.* **Scheme 4**).[20,21,32] Similarly, selenocyanates can be converted to diselenides using hydride reducing agents ([diisobutylaluminium hydride (DIBAL-H), $LiEt_3BH$] even in the presence of sensitive functionality such as ketones and alkyl bromides.[33] Use of excess reagent however does result in reduction of carbonyl groups. Other recently reported methods of symmetrical disulfide synthesis include the reductive cleavage of Bunte salts ($RSSO_3Na$) derived from primary alkyl halides using samarium(II) iodide;[34] methanolysis of thioacetates and disproportionation catalysed by nickel boride, generated *in situ* from nickel(II) acetate and borohydride exchange resin (BER);[35] and the copper catalysed disproportionation of thiols using copper(II) sulfate and BER.[36] Thioacetates can be converted into thiols using palladium catalysed methanolysis with BER.[37] This has also led to the development of a one pot synthesis of thiols from alkyl halides, using thioacetate exchange resin to prepare the initial thioacetate intermediate, then followed by BER, MeOH and $Pd(OAc)_2$ for the hydrolysis (**Scheme 13**). Unsymmetrical disulfides can be prepared by the reaction of dithioperoxyesters (formed by oxidation of dithiocarboxylic esters and rearrangement of the intermediate *S*-oxide) with thiols (**Scheme 14**).[38]



Scheme 13

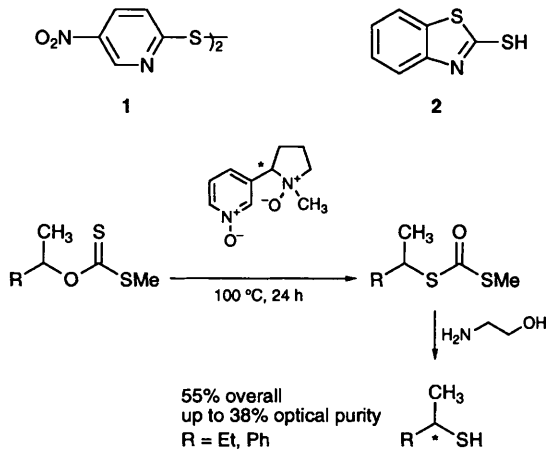


Scheme 14

Various reagents have been developed to oxidise thiols to disulfides. These include methyltrichlorosilane with diphenyl sulfoxide, which regioselectively couples two cysteine residues of human endothelin-1 in quantitative yield;[39] 2,2′-dithiobis(5-nitropyridine) **1** and the corresponding sulfenyl chloride, which have also found application in peptide chemistry;[40] and 2-mercaptobenzothiazole **2** which has been shown to be useful in the synthesis of a

wide variety of symmetrical and unsymmetrical disulfides.[41]

An interesting enantioselective thiol synthesis by thione–thiol rearrangement catalysed by optically active pyridine *N*-oxides has been reported (**Scheme 15**).[42] Low enantioselectivities have so far been achieved; however the use of diastereomeric mixtures of *N*-oxides and elevated temperatures may in part be responsible for this.



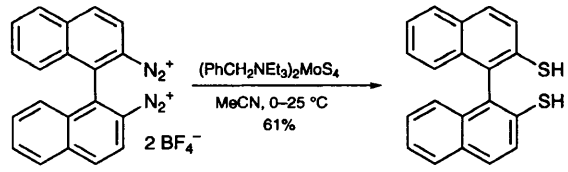
Scheme 15

One final method of synthesis of simple sulfides is by the reduction of sulfoxides. The metal ion mediated deoxygenation of sulfoxides has been reviewed.[43] Ammonium iodide has been reported for the reduction of methionine sulfoxides in peptides containing cysteine and cystine residues,[44] and dimethyl sulfoxide reductase from *Rhodobacter sphaeroides* f.s. denitrificans will reduce predominantly the *S*-enantiomer of racemic methyl phenyl sulfoxide to give thioanisole, although the unreduced optically active sulfoxide is of greater synthetic interest.[45]

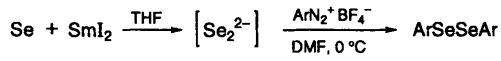
2.2 Unsaturated thiols, disulfides, selenols, diselenides, sulfides and selenides

The reaction of arene diazonium salts with sulfur based nucleophiles provides a route to the corresponding aryl thioethers. Bis(benzyltriethylammonium) tetrathiomolybdate can be used, usually to give the disulfide, but thiols can be obtained in some cases (**Scheme 16**).[20,21] To introduce selenium, reduction of amorphous selenium with SmI_2 gives the diselenide dianion which reacts with aryl diazonium compounds to give the corresponding diselenides (**Scheme 17**).[46] The diselenide dianion generated using zinc, NaOH and elemental selenium reacts with halonitroaromatics also to form aryl diselenides (*cf.* **Scheme 3**).[19]

The direct nucleophilic sulfenylation and thiocyanation of phenolic ethers using hypervalent iodine(III) provides an attractive route to aryl

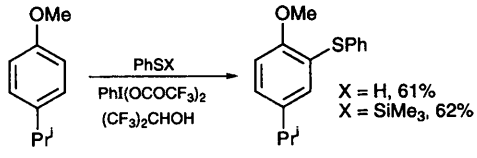


Scheme 16

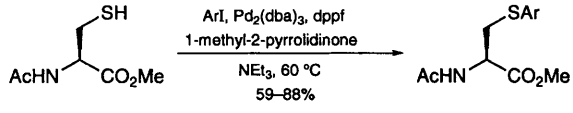


Scheme 17

sulfides. The reaction is believed to proceed by addition of the nucleophilic sulfur species (either a thiol, or its *S*-trimethylsilyl thioether) to the cation radical of the phenolic ether (**Scheme 18**).[47] Alternatively, palladium-catalysed coupling of a variety of aromatic iodides with thiols (cysteine derivatives) provides access to mercapturic acid (*N*-acetylcysteine) derivatives in good yield (**Scheme 19**).[48] The choice of catalyst is crucial for the success of this reaction with tris(dibenzylideneacetone)-dipalladium [$Pd_2(dba)_3$] modified with 1,1′-bis(diphenylphosphino)ferrocene (dppf) giving by far the best yields, but only if the catalyst is stirred at room temperature with the aromatic iodide for 15 min prior to addition of the thiol.

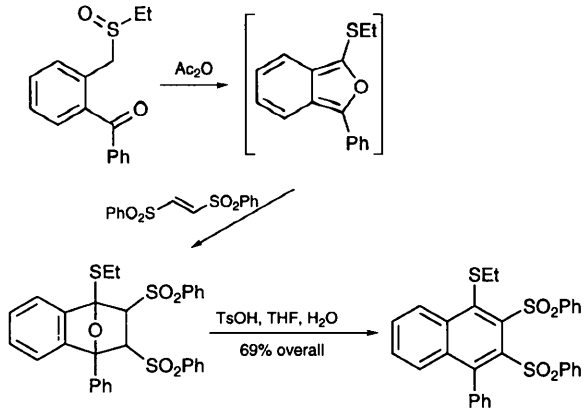


Scheme 18

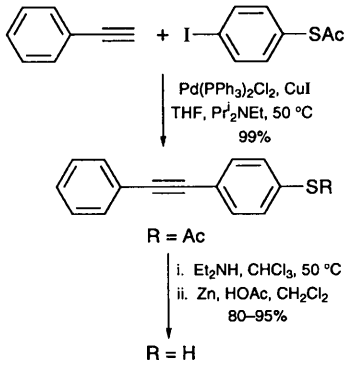


Scheme 19

A tandem Pummerer rearrangement–Diels–Alder reaction sequence can be used for the preparation of α-thio-substituted naphthalene derivatives (**Scheme 20**).[49] A variety of dienophiles can be used, allowing considerable variation in substitution on the new ring. A very versatile method of constructing conjugated arenethiols is by palladium-mediated Heck coupling of thiophenols. Choice of *S*-protecting group is important for the efficiency of this process, and of a variety investigated (Me, Bn,



Scheme 20



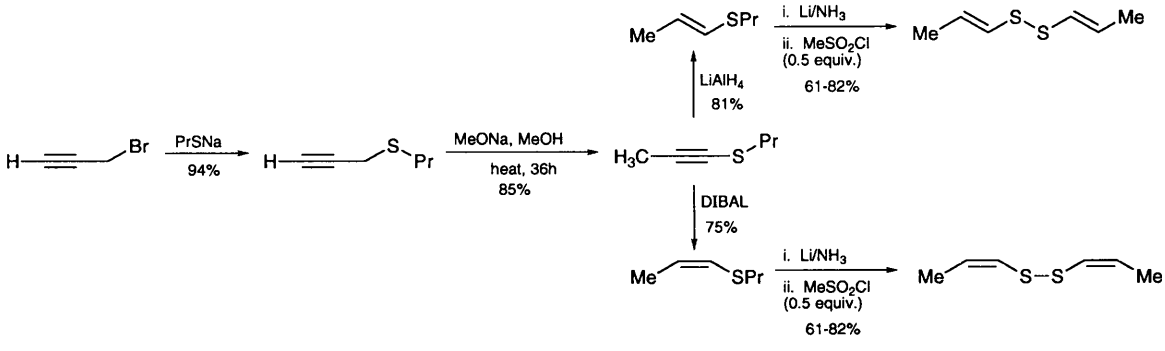
Scheme 21

CPh_3 and Ac) the acetyl derivative was found to be best for the coupling reaction and also for deprotection to the thiol (**Scheme 21**).[50] (−)-Menthyl chloroformate has recently been introduced as a new reagent for the resolution of 1,1′-binaphthalene-2,2′-dithiol by derivatisation and fractional recrystallisation of the menthyl thiocarbonate esters.[51] Subsequent hydrolysis gives a high yield of the required dithiol of excellent enantiomeric purity.

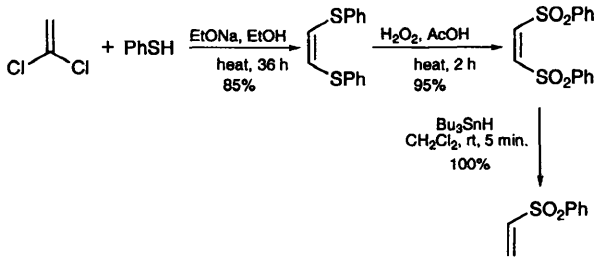
Some useful methods of stereoselective vinyl sulfide synthesis are demonstrated by approaches to alkenyl prop-1-enyl disulfides.[52] Prop-2-ynyl propyl sulfide, when treated with base, isomerises to the acetylenic sulfide which can then be stereoselectively converted into either the *E*-vinyl sulfide using $LiAlH_4$, or the *Z*-vinyl sulfide using DIBAL. Reductive removal of the propyl group ($Li–NH_3$) gives the ethenethiolates with retention of double bond geometry. The ethenethiolates can be dimerised to the disulfides using $MeSO_2Cl$ (**Scheme 22**). Unsymmetrical *E*,*Z* isomers can also be accessed by isolating the sulfenylsulfonate intermediates and reacting them with the appropriate ethenethiolate.

Reaction between 1,1-dichloroethene and thiophenol results in formation of *Z*-1,2-bis(phenylsulfenyl)ethene in high yield (**Scheme 23**).[53] Alternatively, thiols react with 1,1,2-trichloroethene *via* dichloroethyne to give acetylenic sulfides which can be further functionalised in one pot by lithiation and reaction with electrophiles, to give a variety of substituted acetylenic sulfides. Subsequent reduction with either $LiAlH_4$ or $LiAlH(OBu^t)_3$–CuBr gives the *E*- or *Z*-vinylic sulfides respectively (**Scheme 24**).[54] Acetylenic sulfides can undergo hydrozirconation followed by transmetallation to give vinyl cuprate reagents which undergo Michael additions to enones (**Scheme 25**).[55] This has been exploited in the synthesis of prostaglandin analogues such as (±)-15-thia-15-deoxy PGE_1 methyl ester. Hydrozirconation can also be used for vinyl selenide synthesis. Treatment of terminal alkynes with Schwartz's reagent (Cp_2ZrHCl) selectively generates the *E*-vinylzirconocene intermediate, which reacts stereospecifically with diselenides to form vinyl selenides in good overall yield (**Scheme 26**).[56] Palladium catalysed coupling of 1-bromo-1-phenylthioethene to an organoborane generated *in situ* by hydroboration of a terminal alkene with 9-borabicyclo[3.3.1]nonane (9-BBN) provides a route to a wide variety of vinyl sulfides, and has been used as a key step in the synthesis of laurencin (**Scheme 27**).[57]

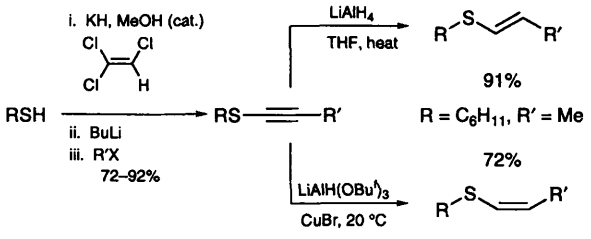
β-Sulfonylacrylates and δ-sulfonyldienamides react with thiolate nucleophiles to give β-thioacrylates and δ-thiodienamides respectively, by stereospecific addition–elimination (**Schemes 28 and 29**).[58,59] This reaction is successful for a wide variety of substrates, including relatively hindered thiols. The reagent 1-(phenylseleno)-2-(*p*-tolyl-



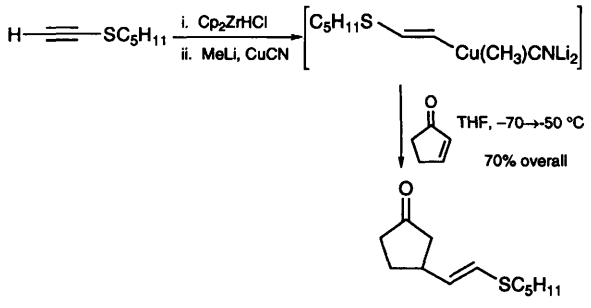
Scheme 22



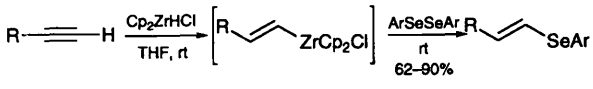
Scheme 23



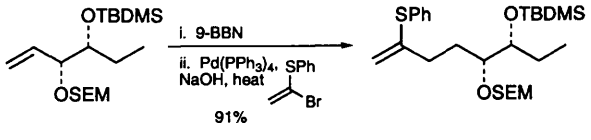
Scheme 24



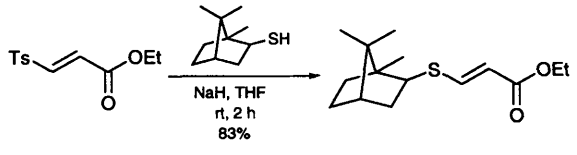
Scheme 25



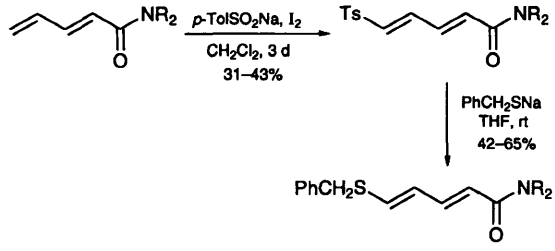
Scheme 26



Scheme 27



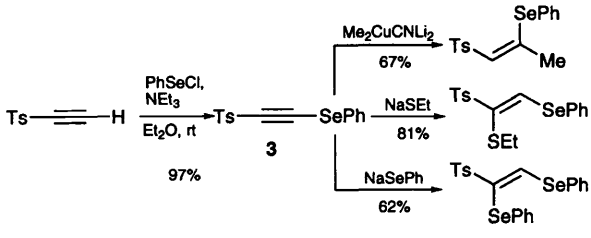
Scheme 28



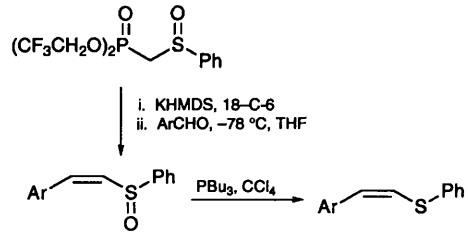
Scheme 29

sulfonyl)ethyne **3** is a novel acetylenic sulfone that can undergo both normal and anti-Michael nucleophilic addition, and as such can be used to prepare a wide variety of substituted selenides and sulfides (**Scheme 30**).[60] Organocuprate reagents tend to add with Michael-type regioselectivity, whereas thiolate and selenolate nucleophiles tend to give mainly products of anti-Michael addition to the double bond relative to the sulfone. The precise reason for the change in regiochemistry for the nucleophilic addition is unclear at present. It has also been shown that **3** can act as a dienophile.[61]

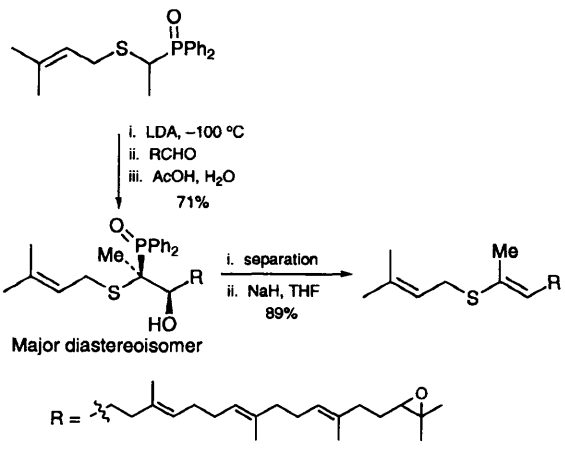
Wittig–Horner methodology has been applied to the synthesis of vinyl sulfides. This can involve either phosphono sulfoxide-derived (**Scheme 31**),[62] or phosphono sulfide-derived (**Scheme 32**)[63] reagents. In the case of the former, use of the bis(2,2,2-trifluoroethyl)phosphono sulfoxide derivative leads to high *Z*-selectivity, the initially formed vinyl sulfoxide being subsequently reduced to the corresponding sulfide under mild conditions with tributylphosphine. Diethylphosphono sulfoxides have also been used for the synthesis of unsaturated selenides, however little control of double bond geometry is possible and the products are 1 : 1 mixtures of *E* and *Z* isomers (**Scheme 33**).[64]



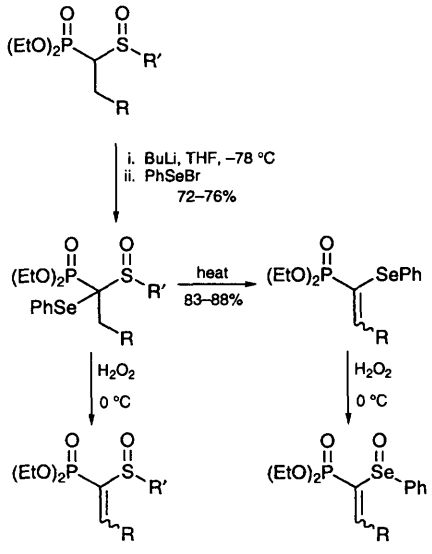
Scheme 30



Scheme 31

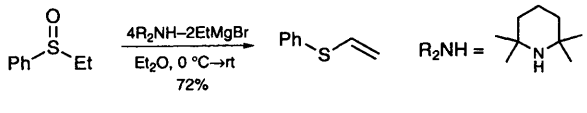


Scheme 32

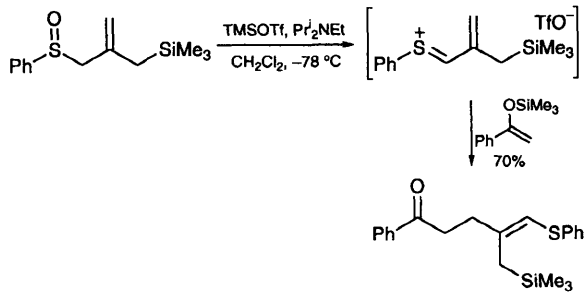


Scheme 33

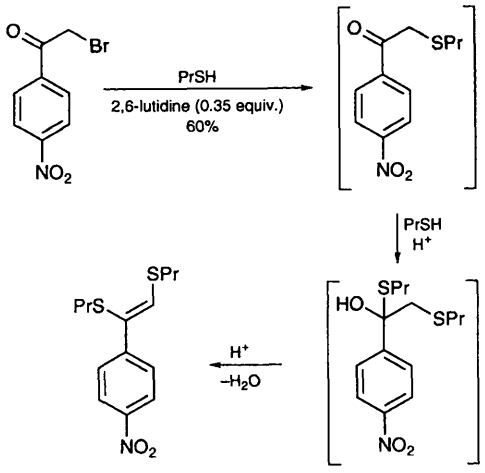
The reaction of sulfoxides with magnesium amides provides a novel route to vinyl sulfides. A number of byproducts can also be formed during the reaction, including dithioacetals (**Scheme 34**).[65] The allylation of silyl enol ethers and a variety of similar compounds, with Pummerer generated vinyl thionium ions provides a versatile method for the synthesis of polyfunctional vinyl sulfides (**Scheme 35**).[66] Vinylic bis-thioethers can be synthesised from aromatic α-bromo ketones using the appropriate thiol in the presence of 2,6-lutidine (2,6-dimethyl-pyridine).[67] The presence of HBr is essential for efficient reaction; if excess 2,6-lutidine is used then products resulting from simple thiolate displacement of the bromide are produced (**Scheme 36**).



Scheme 34

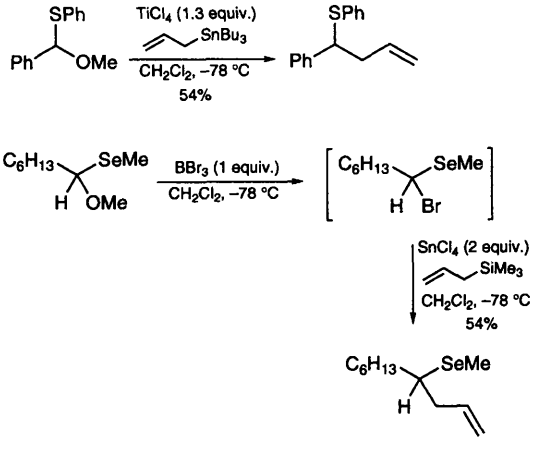


Scheme 35



Scheme 36

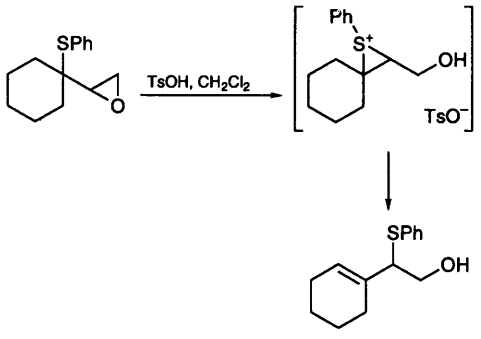
Allyl sulfides and selenides are available by Lewis acid-induced cleavage of the corresponding *S,O*- and *Se,O*-acetals respectively, in the presence of an allyl-stannane or -silane (**Scheme 37**).[68] In the case of *S,O*-acetals, selective C–O bond cleavage is observed with $TiCl_4$ as the Lewis acid, however no analogous reaction is observed with a similar selenium based system. Instead, selective cleavage of the C–O bond of the *Se,O*-acetal is achieved using BBr_3 to give an intermediate α-bromo selenide, which then reacts under Lewis acid conditions



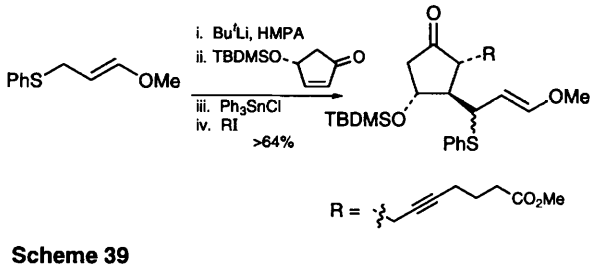
Scheme 37

($SnCl_4$) with allyltrimethylsilane to give the desired allyl selenide. Allyl sulfides can also be prepared in some cases by acid catalysed rearrangement of a 2,3-epoxy sulfide and elimination (**Scheme 38**).[69] Alternatively, α-lithio-γ-methoxyallyl phenyl sulfide will regioselectively add in a Michael fashion to enones resulting in allyl sulfide formation (**Scheme 39**).[70] The intermediate enolate can be further reacted with electrophiles to form highly substituted ketones with good stereochemical control. The use of the triphenyltin enolate however would appear to be essential for an efficient alkylation step.

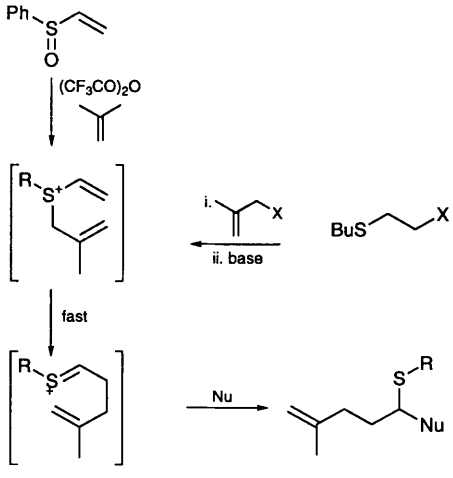
Finally, sigmatropic rearrangements have been used in unsaturated sulfide synthesis. The 3-thio-Claisen rearrangement of an allyl vinyl sulfonium ion leads to formation of a sulfenium ion which can be trapped by appropriate nucleophiles (**Scheme 40**).[71] Alternatively, the use of a chiral rhenium



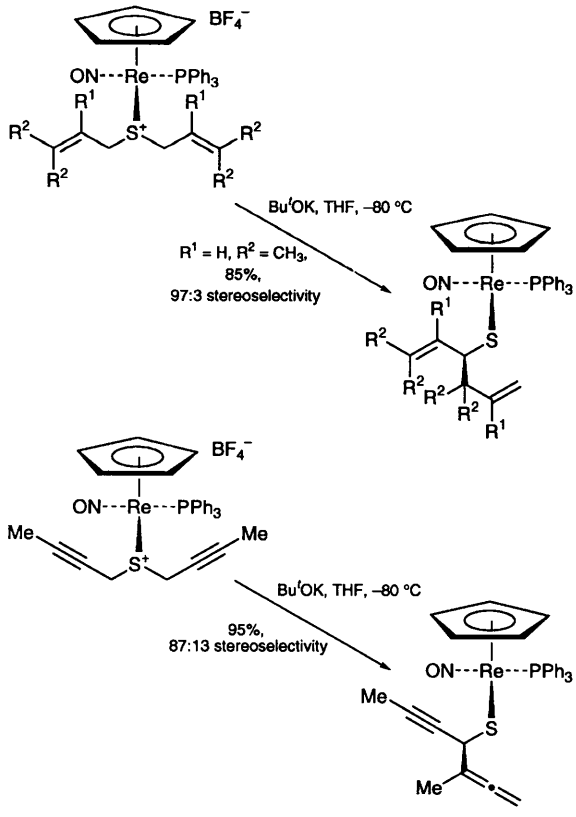
Scheme 38



Scheme 39



Scheme 40

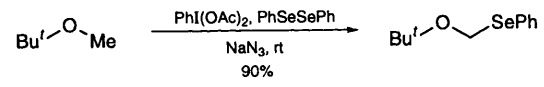


Scheme 41

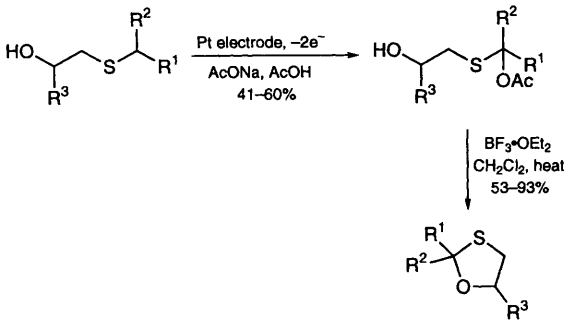
auxiliary allows access to a variety of unsaturated thiols *via* the 2,3-sigmatropic rearrangement of ylides derived from complexes with diallyl, diprop-2-ynyl and dibenzyl sulfide (**Scheme 41**).[72] The authors report that the rhenium auxiliary is easily resolved and can be recycled.

2.3 Substituted thiols and disulfides, selenols and diselenides, sulfides and selenides

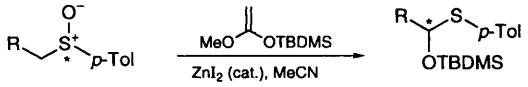
Mixed *O,S*- and *O,Se*-acetals can be prepared by oxidation of dialkyl ethers using iodobenzene diacetate in the presence of a disulfide or diselenide (**Scheme 42**).[73] Alternatively, electrochemical oxidation of a thioether in acetic acid provides access to α-acetoxy sulfides which, with suitable substituents, can undergo Lewis acid-induced cyclisation to an oxathiolane (**Scheme 43**).[74] Another very versatile route to *S,O*-acetals is by Pummerer rearrangement. This has been particularly useful with the development of the asymmetric Pummerer reaction, where chirality in the original sulfoxide is relayed to the product *S,O*-acetal chiral centre (**Scheme 44**). This reaction has recently been reviewed.[75] Other routes to α-acetoxy sulfides include treatment of a dithioacetal with mercuric acetate (**Scheme 45**),[76,77] other Pummerer rearrangements (**Scheme 46**),[78–80] and acetylation of a hemithioacetal (**Scheme 46**).[78,79] It has recently been shown that α-acetoxy sulfides can be efficiently resolved by treatment with *Pseudomonas fluorescens* lipase (PFL) (**Scheme 47**).[78,80] A further develop-



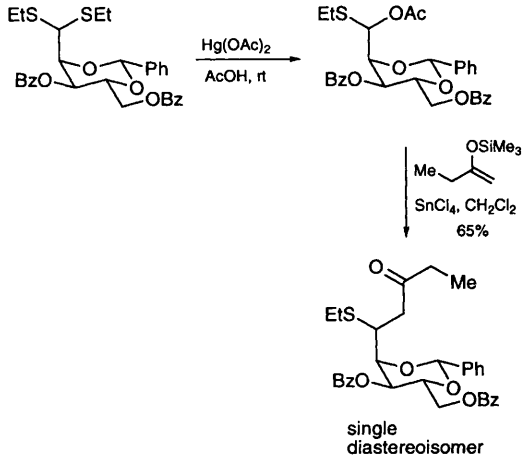
Scheme 42



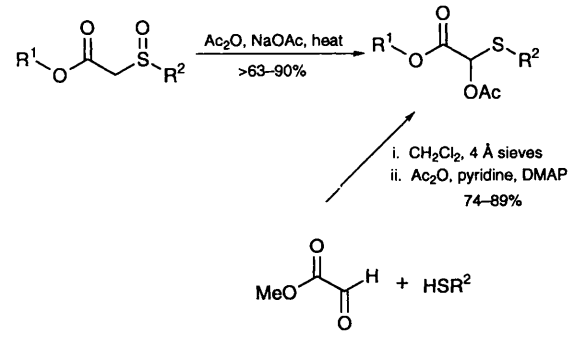
Scheme 43



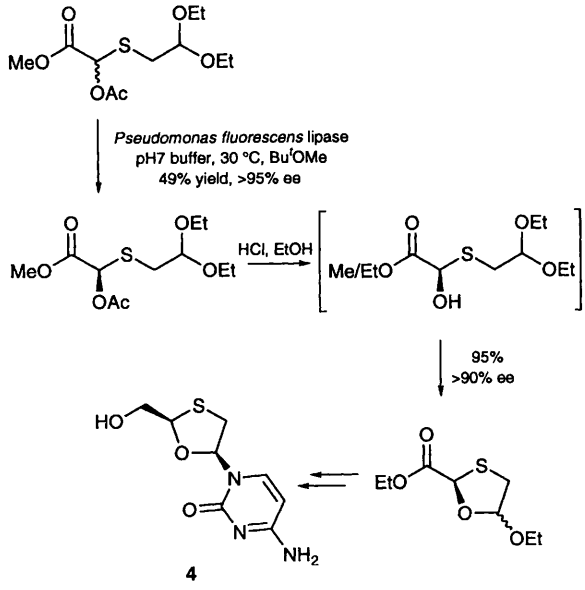
Scheme 44



Scheme 45



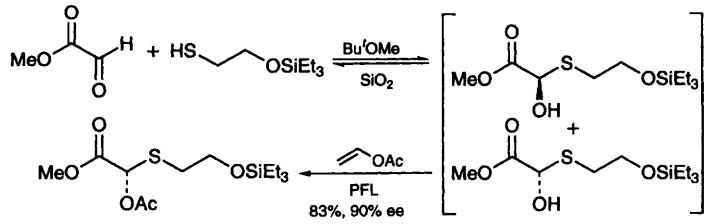
Scheme 46



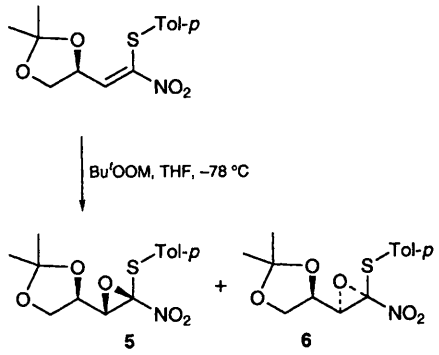
Scheme 47

ment of this involves the dynamic kinetic resolution (DKR) of an epimerising hemithioacetal by enzymatic acylation allowing up to 100% yield of resolved α-acetoxy sulfide (**Scheme 48**),[79] rather than the 50% limit on yield for most enzymatic resolutions. Hemithioacetals can be made to epimerise using SiO_2 which plays a crucial role in the DKR process. In contrast, optically active hemithioacetals are sufficiently configurationally stable under acid conditions to allow cyclisation onto an adjacent acetal functionality to form oxathiolanes and oxathianes of high enantiomeric excess (Scheme 47).[80] This has been exploited in a synthesis of the antiviral agent Lamivudine (3TC) **4**.[81] Finally, (arylthio)nitrooxiranes can be accessed by nucleophilic epoxidation of the corresponding nitroalkene (**Scheme 49**).[82] In some cases, significant stereoselectivity can be achieved, and this can be reversed by changing the metal counter-ion.

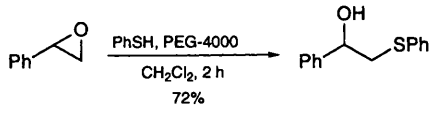
One of the classic methods for the synthesis of β-hydroxy sulfides and selenides is the nucleophilic ring opening of epoxides with thiolate and selenolate nucleophiles respectively. Recent developments include the use of thiol–diselenide exchange for the generation of benzeneselenolate using *N*-acetylcysteine and diphenyl diselenide (*cf.* **Scheme 7**);[27] silica gel[83] and polyethylene glycol (PEG)[84] catalysis for the addition of thiophenol to epoxides (**Scheme 50**); and the use of hydrosulfide exchange resin, prepared from the chloride form of Amberlite IRA-400 and sodium hydrosulfide, for the direct synthesis of β-hydroxy thiols from epoxides (**Scheme 51**).[14] Addition of triethylamine hydrochloride minimises formation of the more usual symmetrical sulfide products. The addition of chiral selenolates to prochiral epoxides proceeds with moderate to excellent stereoselectivity (**Scheme 52**).[85–87] The selenolate can be generated from the corresponding diselenide using either $LiAlH_4$ or $NaBH_4$.



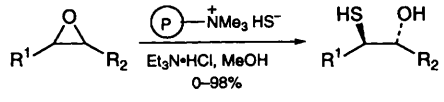
Scheme 48



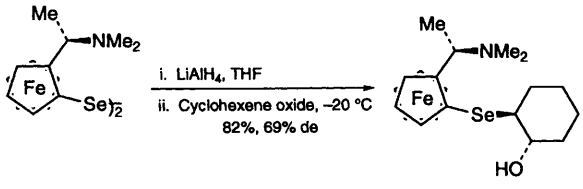
Scheme 49



Scheme 50

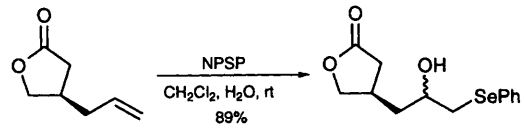


Scheme 51

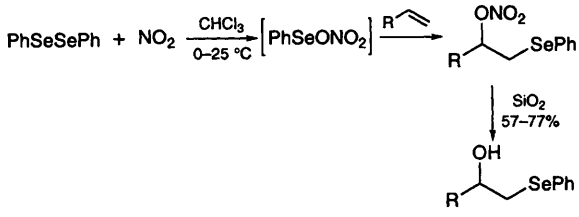


Scheme 52

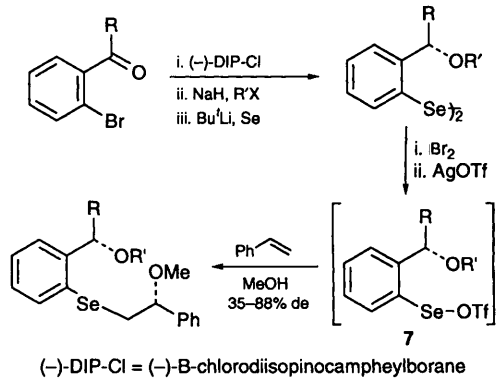
An alternative approach to β-hydroxy sulfides and selenides is by oxysulfenylation and oxyselenylation of alkenes. This is illustrated by a recent example where *N*-(phenylseleno)phthalimide (NPSP) adds to alkenes in the presence of water to give a β-hydroxy selenide as a mixture of diastereoisomers (**Scheme 53**).[88] Interestingly, if phenyl selenyl chloride is used instead of NPSP then simple addition is observed with no incorporation of water. Phenylselenyl nitrate can be generated *in situ* from diphenyl diselenide and NO_2. It is a novel oxyselenylating agent, and adds to alkenes to give β-phenylseleno nitrates which are readily hydrolysed to the corresponding alcohols by silica gel (**Scheme 54**).[89] The reagent (2,4,6-triisopropylphenyl)selenyl bromide has recently been introduced, and reportedly gives up to a 10- to 100-fold increase in stereoselectivity for selenylation reactions relative to PhSeCl and NPSP.[90] Asymmetric selenylating agents have also recently appeared, and can be used for β-alkoxy selenide synthesis. Selenylation of styrene with chiral selenyl trifluoromethanesulfonate **7** in the presence of methanol gives moderate to good levels of diastereoselectivity (**Scheme 55**).[91] The selenyl-



Scheme 53



Scheme 54



(–)-DIP-Cl = (–)-B-chlorodiisopinocampheylborane

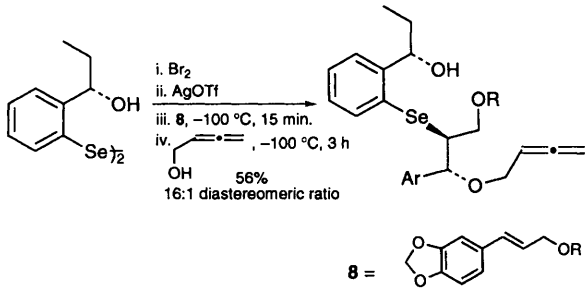
Scheme 55

ating agent is generated *in situ* from the corresponding diselenide. In an approach to the synthesis of (+)-samin, a diastereomeric ratio of up to 16:1 was achieved for addition to alkene **8** using a related system (**Scheme 56**).[92] Selenyl bromides having chiral C_2-symmetric pyrrolidine rings have also been investigated as asymmetric selenylating agents and give poor to moderate stereoselectivity in a selenomethoxylation reaction (**Scheme 57**).[93] A practical synthesis of the asymmetric selenylating agent **9** has been reported which is a significant improvement on the originally reported procedure (**Scheme 58**).[94]

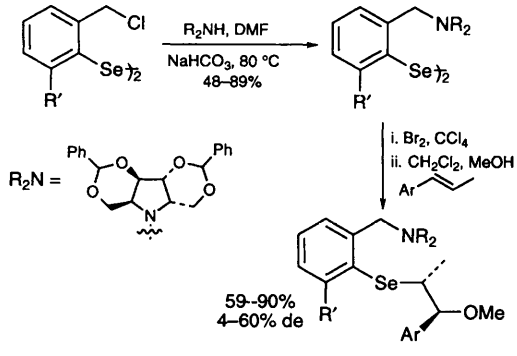
An interesting deprotection reaction of β-hydroxy aryl selenides has been reported (**Scheme 59**). Photolysis of a phenylselenoalkane results in cleavage of the Se–aryl bond rather than the alkyl–Se bond which often occurs using conventional reductive cleavage protocols (Birch reduction). Olefinic byproducts are also formed in this reaction.[95]

Reduction of a β-keto sulfide using baker's yeast provides access to optically active β-hydroxy sulfides in good yield and with high enantioselectivity (**Scheme 60**).[96] Dihydroxylation of an allyl sulfide provides a route to β,γ-dihydroxy sulfides using a modified Sharpless-style racemic dihydroxylation procedure (**Scheme 61**).[97] Nucleophilic displacement of a glycerol-derived toluene-*p*-sulfonate by phenylmethanethiolate provides access to related systems. Interestingly, alcohol protection and subsequent treatment of the benzyl thioether with tributyltin hydride produces a nucleophilic tributylstannyl sulfide which reacts with sugar derived electrophiles with good control of anomer selectivity (**Scheme 62**).[98]

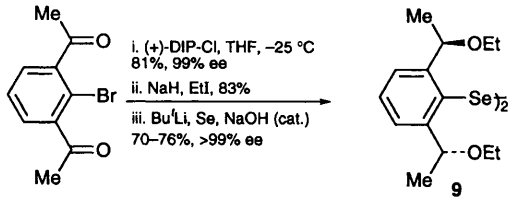
2,3-Epoxy sulfides, available in an optically active form *via* the Sharpless asymmetric epoxidation, represent new readily available synthons for use in asymmetric synthesis. On treatment with Lewis acids, they rearrange to the corresponding thiiranium ions which can be trapped with various nitrogen-based nucleophiles.[99] Recent developments include the use of imines as synthetic equivalents of simple primary amines for overall clean monoalkylation with the thiiranium ion intermediates.[100] The initially produced iminium ions are isolable, but are



Scheme 56

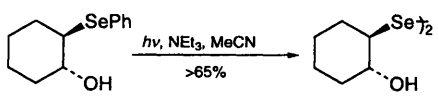


Scheme 57

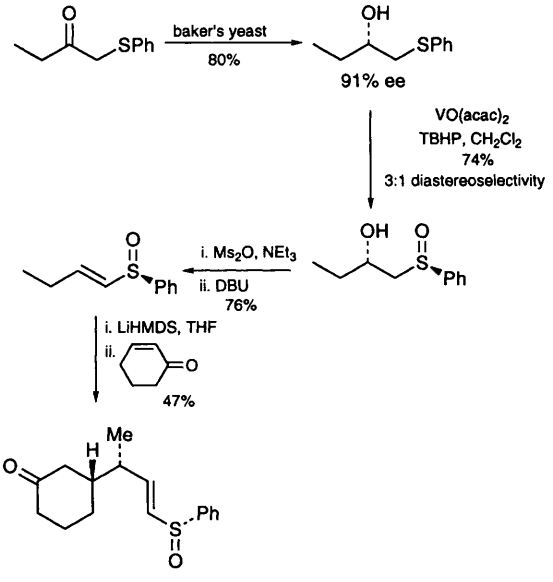


(+)-DIP-Cl = (+)-B-chlorodiisopinocampheylborane

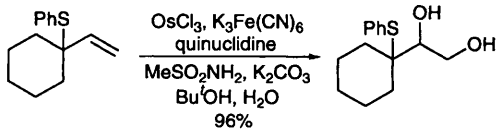
Scheme 58



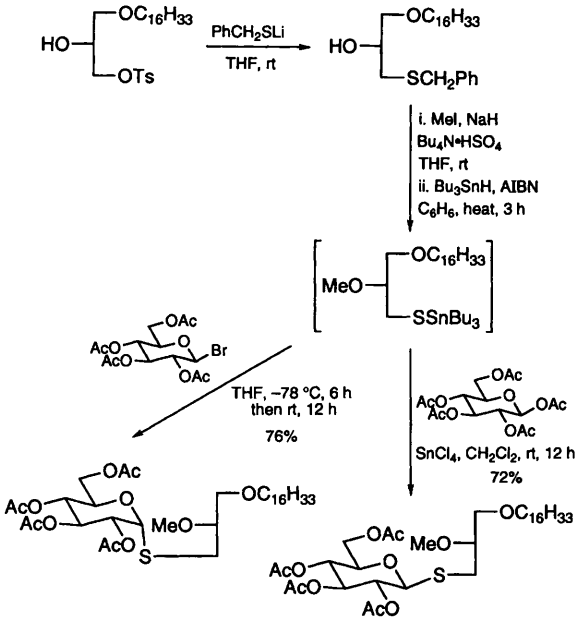
Scheme 59



Scheme 60



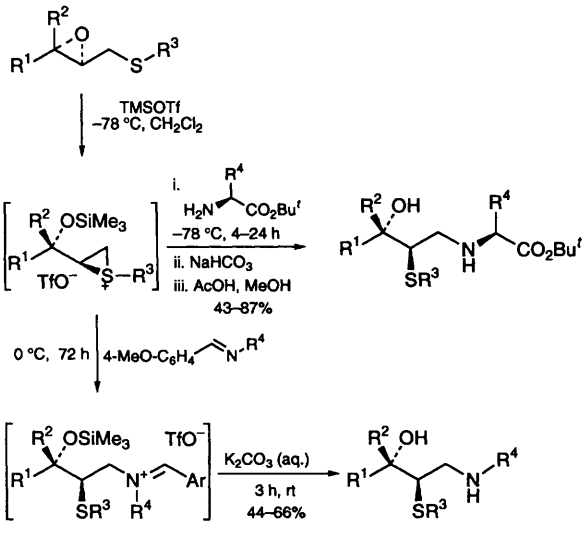
Scheme 61



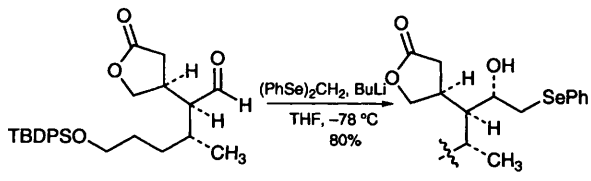
Scheme 62

usually hydrolysed immediately to form the required secondary amines (**Scheme 63**). By comparison, with amino ester nucleophiles, polyalkylation is not a problem, and the free amines can be used with moderate to good efficiency (**Scheme 63**).[101] In the absence of nucleophiles, related thiiranium ion intermediates undergo elimination to give allylic β-hydroxy sulfide derivatives (**Scheme 38**).[69]

The nucleophilic addition of α-metallo selenides to aldehydes also provides a route to β-hydroxy selenides (**Scheme 64**).[102] In this case, the organolithium species is generated from the selenoacetal and adds to the aldehyde to give a single stereoisomer of the product. The enantioselective aldol reaction between benzaldehyde and β-thio-substituted silyl enol ethers, catalysed by a chiral Sn^{II}



Scheme 63

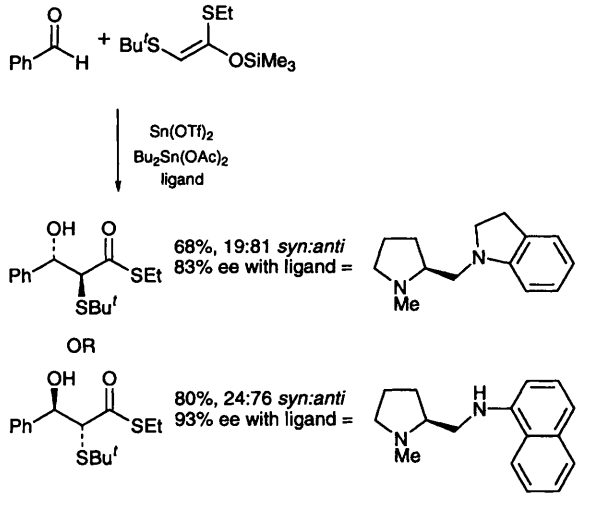


Scheme 64

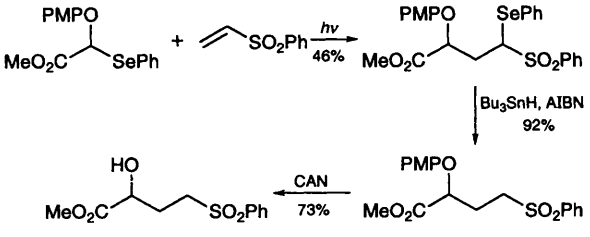
complex, also allows access to β-hydroxy sulfide derivatives with good control of both relative and absolute stereochemistry. Interestingly, products with opposite absolute configuration can be obtained by relatively minor modification of the chiral ligand (**Scheme 65**).[103]

Mixed *O,Se*-acetals have been used for radical mediated phenylseleno group transfer reactions, adding to a wide variety of electron-rich and electron-deficient alkenes under photochemical initiation (**Scheme 66**).[104,105] Related systems involving sulfur stabilised radicals also add to electron-deficient alkenes with phenyl selenide transfer (**Scheme 67**).[106]

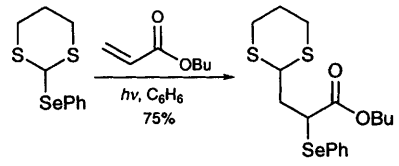
A new route to substituted phenylmethanethiols involves the reductive ring opening of thiophthalan (dihydro-2-benzothiophene), and quenching of the resulting dianion with electrophiles such as water, aldehydes and ketones (**Scheme 68**).[107] Related



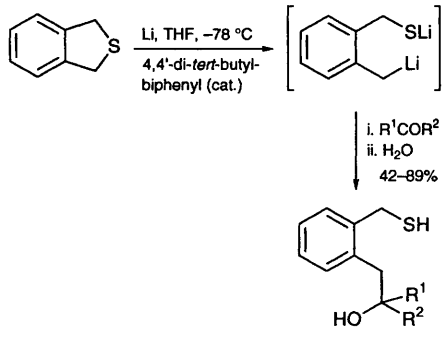
Scheme 65



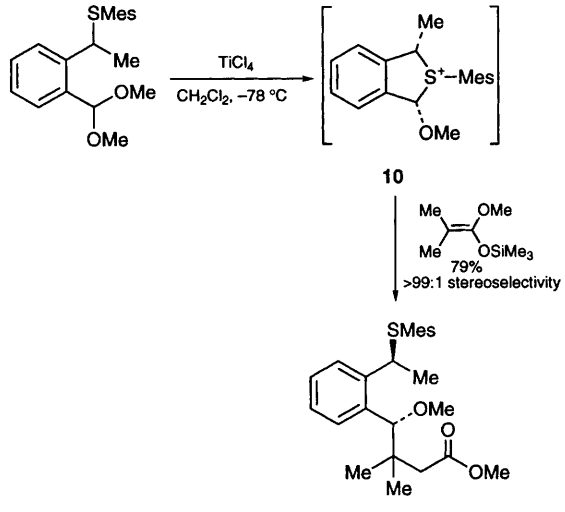
Scheme 66



Scheme 67



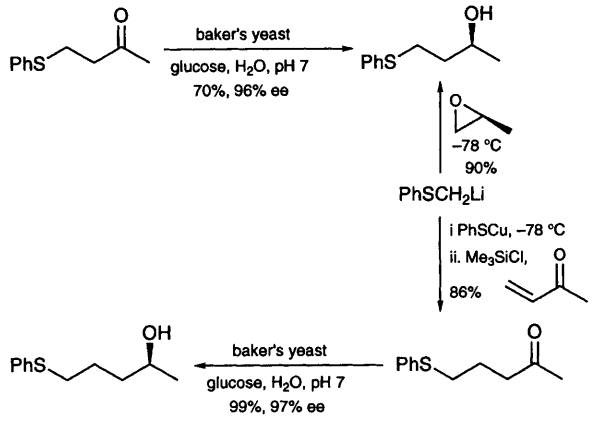
Scheme 68



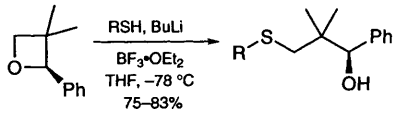
Scheme 69

systems can also be prepared by an alternative route (**Scheme 69**) which also allows for remote stereocontrol by neighbouring group participation of the sulfenyl group.[108] In this case the reaction proceeds *via* the cyclic sulfonium salt **10** which accounts for the stereochemical outcome of the reaction.

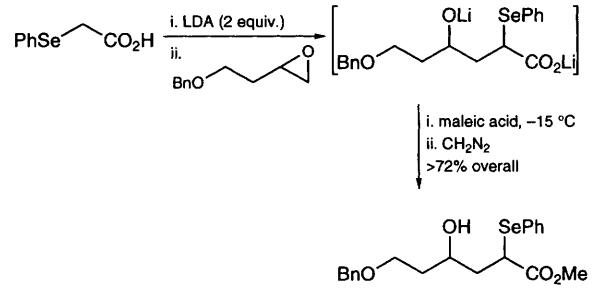
Optically active γ- and δ-hydroxy sulfides can be produced in high enantiomeric excess by baker's yeast reduction of the corresponding ketone (**Scheme 70**).[109] Alternatively, γ-hydroxy sulfides can be prepared by ring opening of (*S*)-(−)-propylene oxide with phenylthiomethyllithium (**Scheme 70**),[109] or the Lewis acid catalysed ring opening of oxetanes by lithium thiolates (**Scheme 71**).[110] Finally, the dilithium salt of phenylselenoacetic acid reacts with epoxides to form γ-hydroxy selenide derivatives (**Scheme 72**).[111] The use of maleic acid in the work up procedure prevents lactonisation observed with stronger acids.



Scheme 70

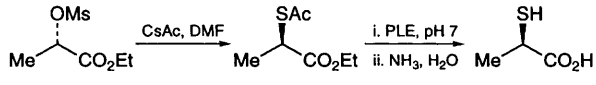


Scheme 71

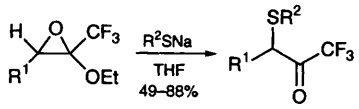


Scheme 72

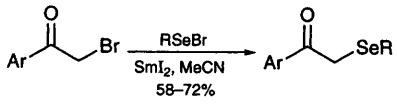
The synthesis of (*R*)- or (*S*)-2-sulfanylpropanoic acid from ethyl lactate relies on clean inversion of configuration of the derived methanesulfonate using caesium acetate in DMF. Conventional acid or base hydrolysis of the ethyl ester usually results in some degree of racemisation, however hydrolysis using pig liver esterase (PLE) at neutral pH alleviates this problem (**Scheme 73**).[112] Subsequent thioester hydrolysis is readily achieved using aqueous ammonia. The ring opening of trifluoromethyl-substituted epoxy ethers by thiolates leads to α-thiotrifluoromethyl ketones in good to moderate yield (**Scheme 74**).[113] Alternatively, samarium iodide induces coupling between selenyl bromides and α-bromo ketones to give α-selenyl ketones (**Scheme 75**).[114] Both SmI_2 and SmI_3 can be used to induce this reaction.



Scheme 73

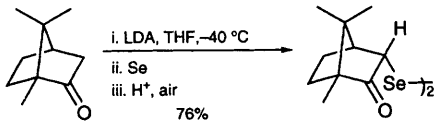


Scheme 74



Scheme 75

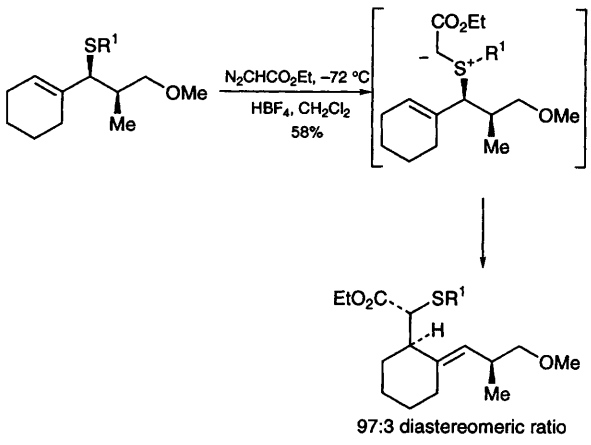
Reaction of the lithium enolate of camphor with elemental selenium results in formation of camphoryl diselenide in good yield (**Scheme 76**); however related reactions usually give more complex results.[115] Alternative new selenium transfer reagents such as $PhSO_2SeCl$ and $PhSO_2SeSeSO_2Ph$ have been developed which help alleviate some of these problems.[116] The reaction between α-thio[103] or α-selenoenolates[111] with electrophiles (**Schemes 65** and **72**) and radical mediated phenyl selenide transfer (**Schemes 66** and **67**)[104,106] also provide routes to related compounds, and have been discussed previously.



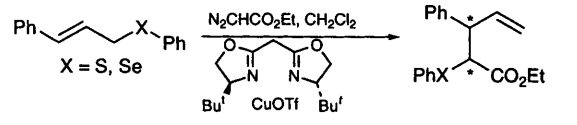
Scheme 76

Sigmatropic rearrangements have also be used to access carbonyl compounds with α-thio substituents. The [2,3]-sigmatropic rearrangement of sulfonium ylides leads to the formation of *E*-homoallylic sulfides with a high degree of stereocontrol (**Scheme 77**).[117] Alternatively, enantioselective carbenoid addition to allylic sulfides and selenides and subsequent [2,3]-sigmatropic rearrangement also allows access to similar compounds but with lower stereoselectivity (**Scheme 78**).[118] A number of different chiral catalysts were investigated, but all gave the products as a mixture of diastereomers.

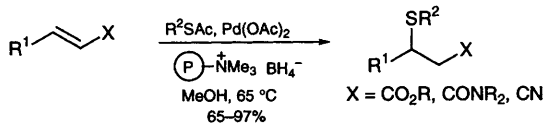
The addition of thiolate nucleophiles to α,β-unsaturated carbonyl compounds is the most common method of synthesising β-thiocarbonyl compounds. Reaction of a thioacetate with borohydride exchange resin and Pd^{II} catalysis generates a thiolate which efficiently adds to α,β-unsaturated esters, amides and nitriles (**Scheme 79**).[119] Addition of potassium thiolates and selenolates to α,β-unsaturated nitriles have also been reported,[120] as have similar additions to more complex substrates (**Scheme 80**).[121] Additions to α,β-unsaturated ketones have been discussed previously (**Schemes 39** and **70**).[70,109] Diastereoselective addition of sulfur



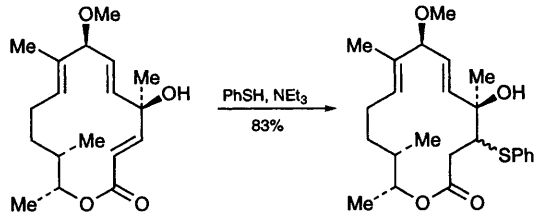
Scheme 77



Scheme 78

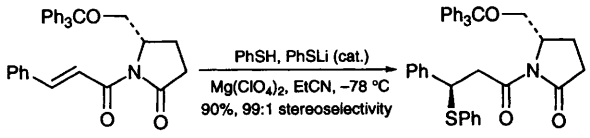


Scheme 79

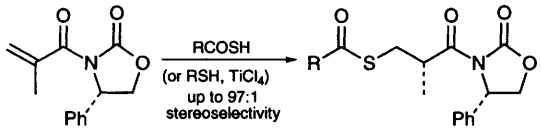


Scheme 80

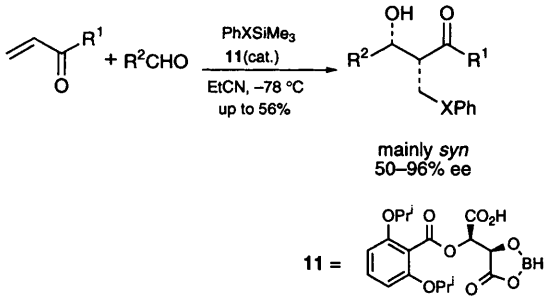
nucleophiles to chiral Michael acceptors have also been reported. The use of γ-(trityloxymethyl)-γ-butyrolactams (**Scheme 81**)[122] and oxazolidinones (**Scheme 82**)[123] as chiral auxiliaries both give high levels of stereoselection. In the more complex example of the asymmetric Bayliss–Hillman reaction, the enolate formed after initial thiolate or selenolate addition to an α,β-unsaturated ketone can react with aldehydes to give mainly the *syn*-diastereomeric aldol-like product of moderate to excellent enantiomeric excess (**Scheme 83**).[124] Finally, the Lewis acid mediated reaction between



Scheme 81



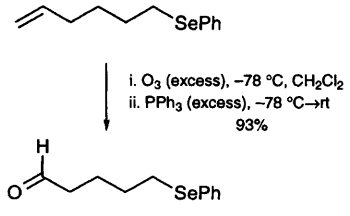
Scheme 82



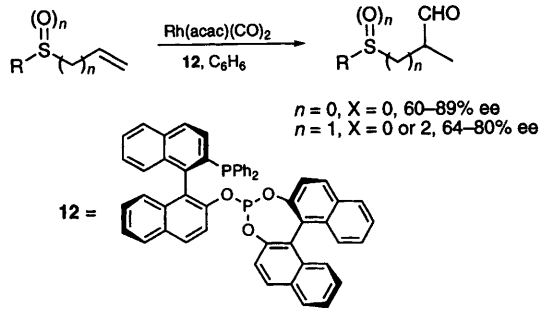
Scheme 83

sulfides and silyl enol ethers provides an alternative route to β-thio carbonyl compounds (**Scheme 45**).[76,77]

Routes to other carbonyl containing sulfides and selenides have also been reported. An interesting reaction is the ozonolysis of unsaturated selenides. The carbon–carbon double bond is cleaved in the usual manner, and the selenide is also oxidised to the selenoxide. Under reductive work-up conditions (PPh_3), the ozonide is cleaved as usual, however excess reducing agent also results in reduction of the selenoxide back to the selenide. The latter reaction is much faster than any competing selenoxide elimination. Thus the overall transformation is selective cleavage of the carbon–carbon double bond in the presence of the selenide (**Scheme 84**).[125] Asymmetric rhodium(I)-catalysed hydroformylation of sulfur-containing alkenes can be used to make a variety of sulfur-substituted sulfides (**Scheme 85**).[126] High enantiomeric excesses can be achieved using the (*R*,*S*)-BINAPHOS ligand **12**.

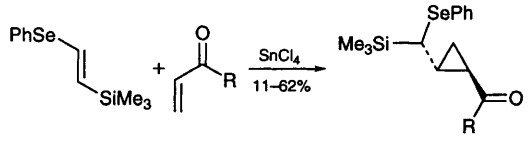


Scheme 84

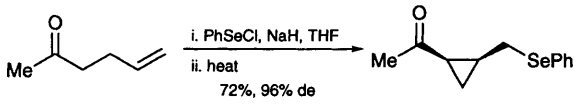


Scheme 85

The synthesis of selenium substituted cyclopropanes has been described using two different methods. The first involves the [2+1] cycloaddition of 1-seleno-2-silylethenes to unsaturated carbonyl compounds. Poor to moderate yields of the products can be isolated (**Scheme 86**).[127] Alternatively, the phenylselenyl chloride-mediated cyclofunctionalisation of γ,δ-unsaturated carbonyl compounds also allows access to similar systems in good to moderate yield, and with high stereoselectivity (**Scheme 87**).[128] If *N*-phenylselenophthalimide (NPSP) is used rather than PhSeCl, then simple α-selenylation of the carbonyl group is observed.

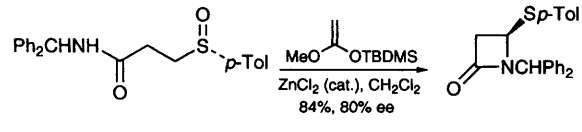


Scheme 86

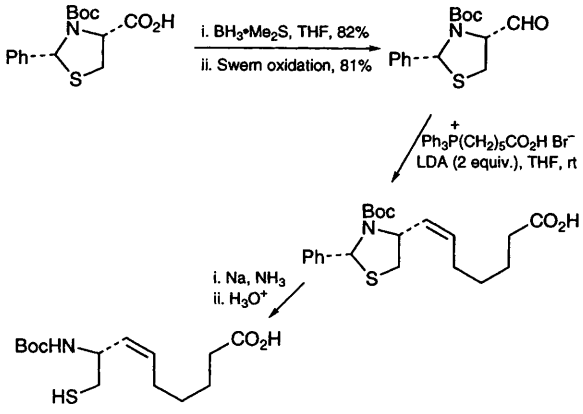


Scheme 87

The Pummerer rearrangment of β-amido sulfoxides leads to the formation of enantiomerically enriched β-lactams containing *S*,*N*-acetal functionality (**Scheme 88**).[75,129] The use of a benzylidene *N*,*S*-acetal to protect cysteine through subsequent synthetic manipulations has also been reported (**Scheme 89**).[130] This methodology was used in an enantioselective synthesis of (+)-biotin. Other new protection reagents for cysteine have also been introduced.[131]

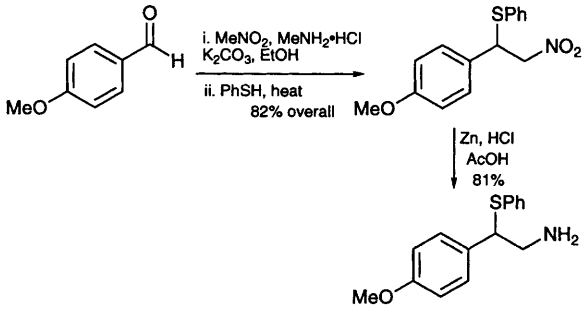


Scheme 88

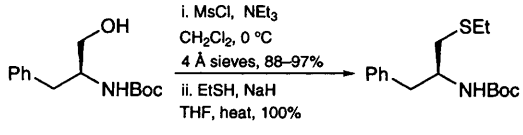


Scheme 89

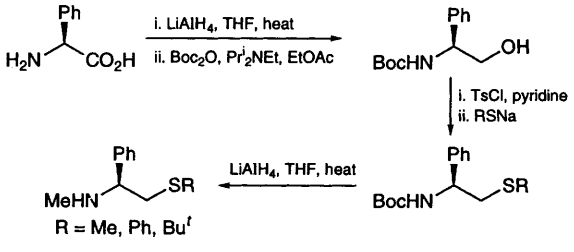
Conjugate addition of thiols to α,β-unsaturated nitro compounds followed by reduction of the nitro group allows access to β-amino sulfides in good overall yield (**Scheme 90**).[132] Related compounds can be obtained in an optically active form from the corresponding amino alcohols by methanesulfonate (**Scheme 91**)[133] or toluene-*p*-sulfonate (**Scheme 92**)[134] formation and thiolate displacement, or using PBu_3 and a diaryl disulfide on the free alcohol (**Scheme 93**).[135] Alternatively, palladium-catalysed arylation of cysteine derivatives can be used to synthesise similar compounds as previously discussed (**Scheme 19**).[48] The preparation of protected lanthionine (the monosulfide analogue of cystine) derivatives, has been achieved by selective ring opening of serine β-lactones by cysteine thiolates (**Scheme 94**).[136] Use of Cs_2CO_3 as base is crucial for this reaction as it cleanly gives O–alkyl fission of the β-lactone ring, whereas other bases investigated led to O–acyl fission. The preparation of more complex peptides where disulfide bonds have been replaced by thioether linkages have also been reported including an HIV-1 protease analogue which retains its enzymatic activity after modification,[137] and the cyclic 10 residue peptide C_1-oxytocin.[138] Other new methods for the preparation of large cyclic disulfide peptides have also been reported.[139]



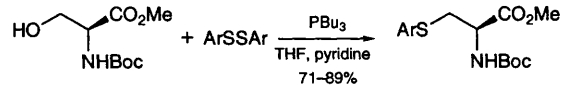
Scheme 90



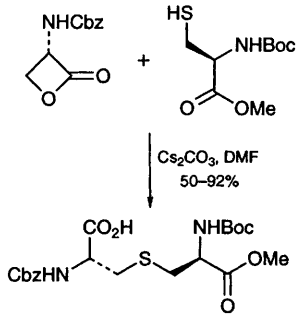
Scheme 91



Scheme 92

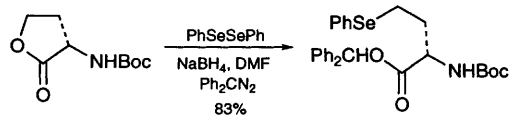


Scheme 93



Scheme 94

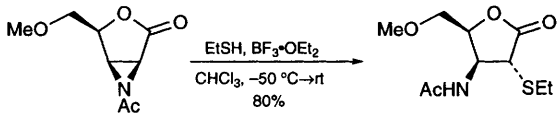
The nucleophilic ring cleavage of L-homoserine lactone derivatives by selenolate can be used to prepare selenium containing amino acids. Use of the diselenide and $NaBH_4$ to generate the nucleophilic selenolate anion is crucial to the success of the reaction as alternative sources of selenolate led to significant racemisation (**Scheme 95**).[140] The coupling of amino esters with thiiranium ions derived from homochiral 2,3-epoxy sulfides under Lewis acid conditions has been reported, and provides a route to novel stereochemically defined sulfur containing amino acid derivatives (**Scheme 63**).[99,101]



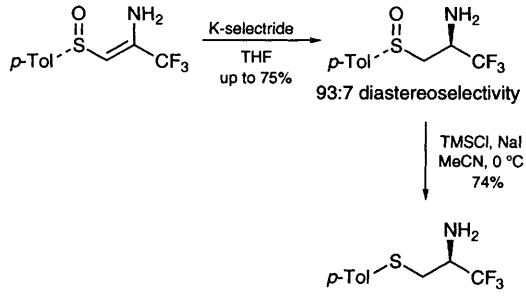
Scheme 95

Nucleophilic ring opening of *N*-acylaziridines by thiolates can also lead to formation of β-amino sulfides. In the example given (**Scheme 96**) the product is formed as a single regioisomer, although lower selectivities are observed in other cases.[141] The facial selectivity for the reduction of α-(fluoroalkyl)-β-sulfinylenamines using K- or L-Selectride, is controlled by the sulfoxide, and proceeds with high diastereoselectivity. The product can then be converted into a β-amino sulfide by reduction of the sulfoxide under standard conditions (**Scheme 97**).[142]

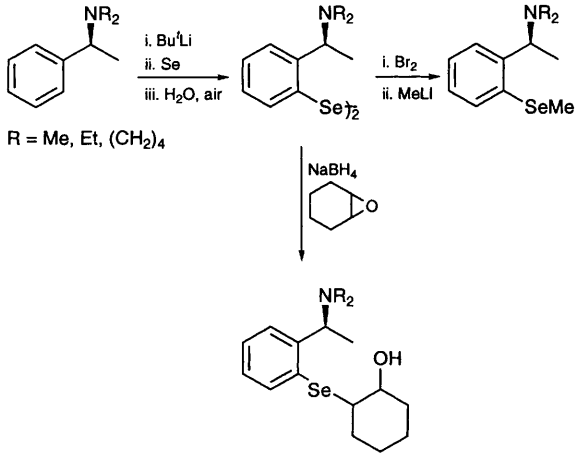
The synthesis of new chiral diselenides derived from α-methylbenzylamine has been reported. *ortho*-Lithiation, directed by the tertiary amino group, and reaction with selenium, results in diselenide formation, which can be further functionalised to give a variety of new chiral selenides (**Scheme 98**).[87] A related approach has also been adopted for the synthesis of chiral ferrocene-derived diselenides (**Scheme 99**).[85,86,143,144]



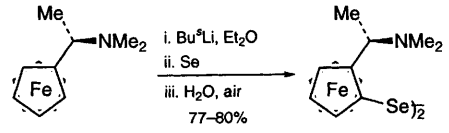
Scheme 96



Scheme 97



Scheme 98

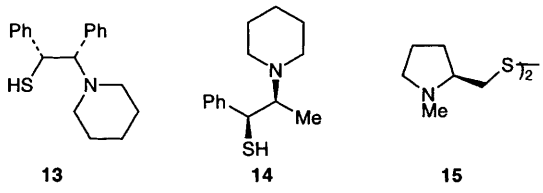


Scheme 99

2.4 Thiols, disulfides, selenols, diselenides, sulfides and selenides as mediators of asymmetric transformations

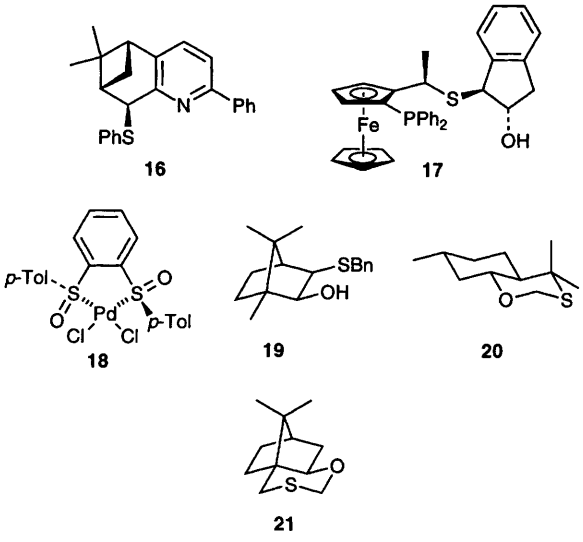
There have been a number of reports of the use of organo-sulfur and -selenium compounds for controlling asymmetric induction in new enantioselective processes. Whilst it is beyond the scope of this review to discuss these processes in any detail, the potential importance of this area warrants a brief discussion of the structural classes of the organo-sulfur and -selenium compounds used, and the types of reaction that have been reported. When their preparation involves new synthetic methodology, this has been included in the relevant section of the review.

The enantioselective addition of organozinc reagents to aldehydes can be catalysed by a number of sulfur- and selenium-containing moieties. Recent developments include thiols and the related disulfides **13**,[145] **14**,[146,147] and **15**,[148] and various amino selenides (**Scheme 98**)[87] and ferrocenyl selenides (**Scheme 52**)[85,86] which have been discussed previously. Asymmetric seleno-etherification and -esterification reactions have received considerable recent attention. This includes the use of C_2-symmetrical pyrrolidine-derived selenides (**Scheme 57**),[93,149] various α-methylbenzyl alcohol derived selenides (**Schemes 55**, **56** and **58**),[91,92,94,150] and ferrocenyl selenides (**Scheme 99**).[143,144,151] Such ferrocenyl selenides have also found application in asymmetric selenoxide elimination chemistry[143,144] and/or stereoselective [2,3]-sigmatropic rearrangements.[152,153]



Some new sulfur containing chiral ligands have found application in palladium-catalysed allylic substitution reaction of allylic acetates, including **16**,[154] **17**[155] and the C_2-symmetric bis-sulfoxide–Pd^{II} complex **18**.[156] The asymmetric synthesis of epoxides from carbonyl compounds and sulfur ylides has also been further reported. The chiral sulfides **19**,[157] **20**[158] and **21**,[159] give low to excellent enantiomeric excess in the product epoxides, with **21** inducing asymmetry in a catalytic asymmetric epoxidation.[160]

Other applications include the use of γ-hydroxy selenoxides[161,162] and β-hydroxy sulfoxides[163] for the



enantioselective protonation of prochiral enolates, and the use of a novel C_3-symmetric sulfur-based chiral stationary phase for the resolution of amino acid derivatives.[164]

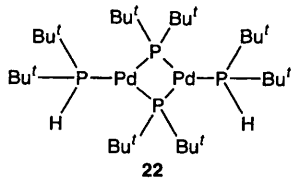
3 Synthesis of sulfoxides and selenoxides

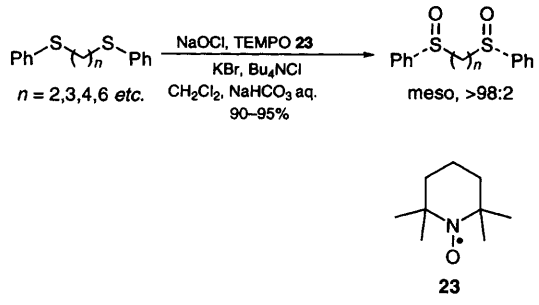
3.1 Oxidation of sulfides and selenides

The preparation of sulfoxides and selenoxides by oxidation of the corresponding sulfides and selenides respectively, 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 chirality is not addressed. The second part is concerned with diastereoselective processes, whereas the final part concentrates on new methods for enantioselective oxidation.

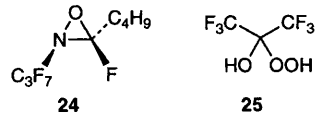
3.1.1 Non-stereoselective oxidation

New methods for the oxidation of simple sulfides to sulfoxides have been reported. These include methyltrioxorhenium(VII) with H_2O_2[165] (significant amounts of sulfone by-products formed in some cases); the novel palladium catalyst **22** with O_2 (1 atm);[166] various Mn^{III}, Fe^{III}, Co^{II} and Ni^{II} complexes with air, O_2 or PhIO as reoxidants;[167] *tert*-butyl hydroperoxide (TBHP) with silica gel;[168] 2,2,6,6-tetramethylpiperidin-1-yloxy free radical (TEMPO) **23** and NaOCl (**Scheme 100**);[169] HgO and I_2;[170] fluorooxaziridines such as **24**;[171] salts between selenoxides and sulfonic acids;[172] and electrolysis in the presence of *meso*-tetraphenylporphyrinato-manganese(III) chloride and O_2, which is a model system for electrocatalytic cytochrome P-450 oxidation.[173]

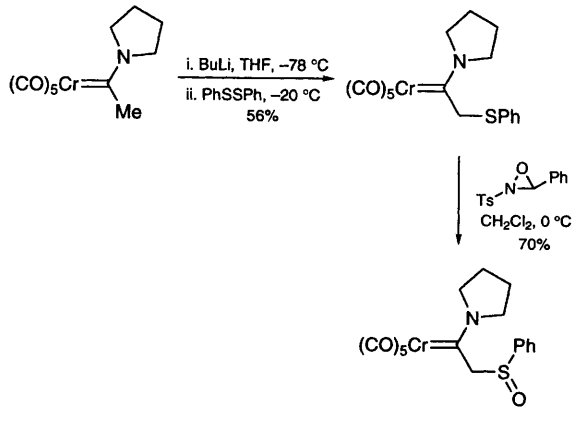




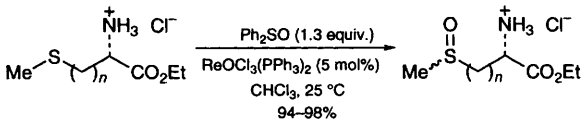
Scheme 100



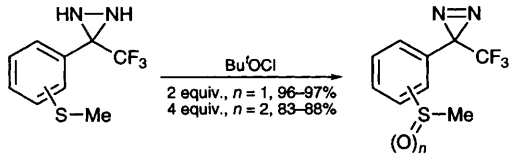
A review on α-hydroxy hydroperoxides (*e.g.* **25**) as oxygen transfer reagents in organic synthesis includes a section on sulfur oxidation.[174] Mechanistic studies on sulfur oxidation using transition metal peroxide complexes,[175] peracids,[176] $^1O_2$,[177] (methyltrifluoromethyl)dioxirane,[178] O_2 with NO_2,[179] and MoO_5•HMPT[180] have also been reported. A comparative study on the oxidation of thianthrene derivatives with chromyl chloride (CrO_2Cl_2), benzyltriethylammonium permanganate and ruthenium tetraoxide, has been published,[181] as has a study on the oxidation of *S,S*-acetals using varying equivalents of dimethyldioxirane (DMDO).[182] Little sulfone product is observed until >2 equiv. of DMDO are used. Thioether-containing chromium carbene complexes undergo chemoselective oxidation to the sulfoxide using oxaziridines (**Scheme 101**).[183] An interesting new method for the oxidation of cysteine derivatives uses diphenyl sulfoxide as stoichiometric oxidant in the presence of a rhenium catalyst (**Scheme 102**).[184] Excellent yields are obtained, with no overoxidation to the corresponding sulfone. Finally, a simple and efficient preparation of 3-aryl-3-trifluoromethyl-3*H*-diazirinyl sulfoxides relies on Bu^{t}OCl oxidation of an aryl sulfide with concomitant oxidation of the diaziridine to the diazirine (**Scheme 103**).[185]



Scheme 101



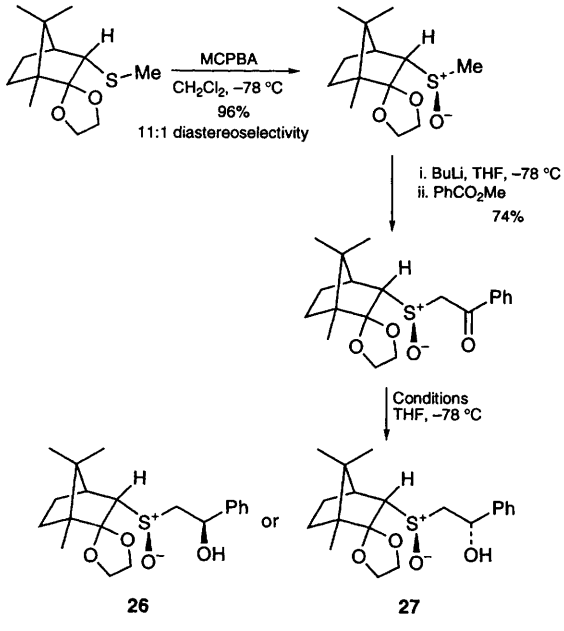
Scheme 102



Scheme 103

3.1.2 Stereoselective oxidation

There have been a limited number of studies on the diastereoselective oxidation of sulfides to sulfoxides. Oxidation of a β-hydroxy sulfide using $VO(acac)_2$ with TBHP as stoichiometric oxidant provides moderate stereoselectivity for sulfoxide formation (**Scheme 60**)[96] whereas camphor-derived sulfides, oxidised using MCPBA, give high diastereoselectivity when the reaction is carried out at -78 °C (**Scheme 104**).[186] The oxidation of bis-phenylthioalkanes with TEMPO and NaOCl (**Scheme 100**) proceeds to give the *meso*-disulfoxide with 90–98% distereoselectivity[169] although the actual cause of this stereoselectivity is unclear at present.

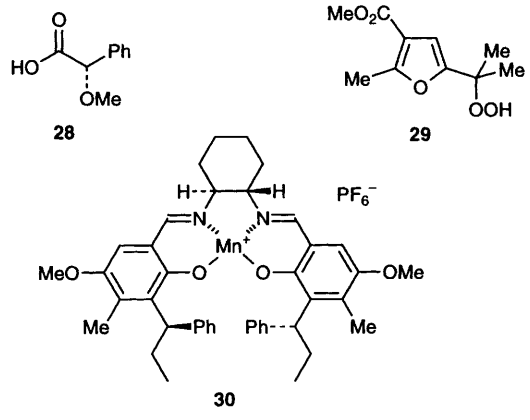


Conditions	26 : 27	Yield(%)
DIBAL, $ZnCl_2$	100:0	98
DIBAL	3:97	94

Scheme 104

3.1.3 Enantioselective oxidation

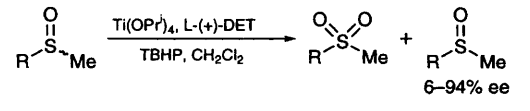
The enantioselective oxidation of sulfides to sulfoxides continues to be a popular and important area of organosulfur chemistry, and has been included in a recent review.[187] The reagent (*S*)-α-methoxyphenylacetic acid **28** has been introduced as a new chiral NMR shift reagent for the determination of the enantiomeric excess of sulfoxides.[188]



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; other metal catalysed oxidations such as the (salen)manganese(III) complexes of Jacobsen and Katsuki; oxaziridines developed by Davis; and enzymatic procedures. These are now well established and have been discussed in previous reviews of this series.[1,2] However significant improvements and applications will be included here.

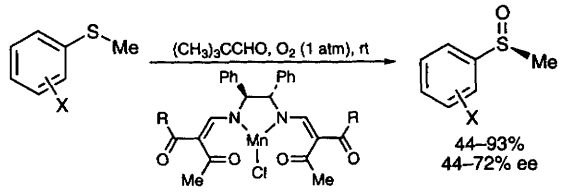
Optimised conditions for the enantioselective oxidation of alkyl aryl sulfides developed by Kagan have been reported.[189] The catalyst system is prepared from $Ti(OPr^i)_4$, diethyl tartrate and water in the ratio 1:2:1, with cumene hydroperoxide (CHP) as the stoichiometric oxidant at -20 °C in CH_2Cl_2. More recently, the furyl hydroperoxide **29** has been introduced as an alternative to more usual hydroperoxides (CHP, TBHP) for use in the titanium catalysed oxidation procedures and can give excellent enantioselectivity for sulfur oxidation (74–91% ee).[190] The kinetic resolution of racemic sulfoxides using a modified Sharpless procedure has been reported, one enantiomer being oxidised to the sulfone, the slower reacting enantiomer remaining with poor to excellent enantiomeric excess (**Scheme 105**).[191]

Full details on the catalytic oxidation of sulfides using the (salen)manganese(III) complex **30** and



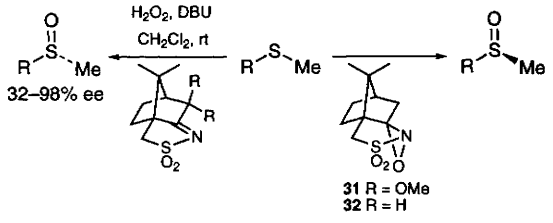
Scheme 105

iodosobenzene have been reported. Low to excellent enantiomeric excesses can be obtained for the oxidation of aryl alkyl thioethers.[192] Related β-oxo aldiminato manganese(III) complexes have also recently been reported, which are capable of asymmetric sulfur oxidation with O_2 (1 atm) as stoichiometric oxidant in the presence of pivalaldehyde (**Scheme 106**).[193,194]



Scheme 106

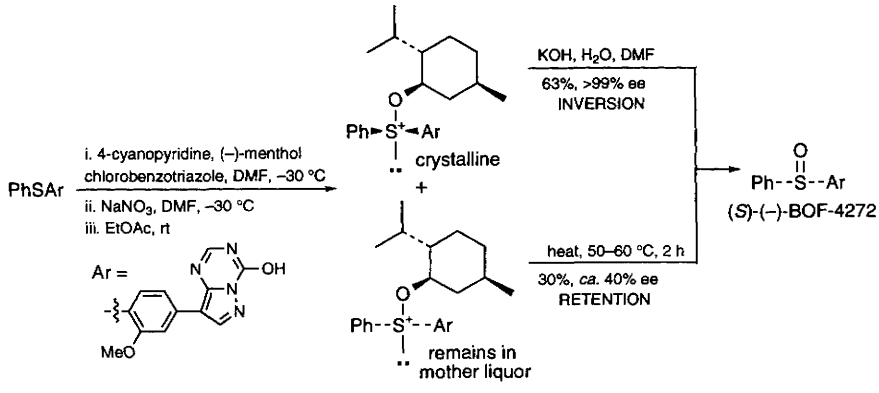
Recent developments on the use of oxaziridines and related compounds have led to catalytic asymmetric processes where the effective oxidising agent is generated *in situ* from an *N*-sulfonylimine and hydrogen peroxide. Interestingly, when the (3,3-dimethoxycamphorylsulfonyl)oxaziridine **31** or the corresponding imine precursor is used in the oxidation reaction, the same enantiopreference is observed. However, for the simple (camphorylsulfonyl)oxaziridine **32**, opposite enantioselection is observed depending on whether the oxaziridine is used stoichiometrically, or the imine is used catalytically with hydrogen peroxide reoxidant (**Scheme 107**).[195] This suggests that in the case of **32**, different active oxidants are operating in each case, either the parent oxaziridine, or an α-hydroperoxyamine generated *in situ* from hydrogen peroxide and the imine.[196] Mechanistic studies on oxaziridine oxidations of sulfides have also been published.[197]



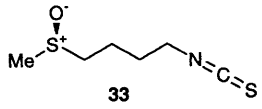
Scheme 107

A somewhat different approach to asymmetric chemical oxidation of sulfides has been applied to the synthesis of the xanthine dehydrogenase inhibitor (*S*)-(−)-BOF-4272 (**Scheme 108**). The process relies on the reaction of the required sulfide precursor with menthol and chlorobenzotriazole to give two diastereomeric sulfoxonium salts, one of which crystallises with high diastereomeric purity as the nitrate salt, the other remaining in solution. Subsequent conversion of the individual salts into the sulfoxide, either by hydrolysis (inversion of configuration) or thermolysis (retention of configuration) leads to the same desired sulfoxide whose enantiomeric purity can be further enriched by recrystallisation if necessary.[198]

There has been significant progress on the biochemical asymmetric oxidation of sulfides. The whole cell oxidation of aryl alkyl sulfides using *Acinetobacter* sp. NCIMB 9871 is only slightly less enantioselective than if the purified cyclohexanone monooxygenase (CMO) from the same species is used.[199] *Pseudomonas* sp. NCIMB 9872 oxidises similar substrates but with mostly opposite enantioselectivity. CMO can also be used to oxidise benzyl alkyl sulfides with up to 96% ee,[200,201] and dithioacetals to form the mono *S*-oxide (>98% ee) along with a small amount of sulfone (8%).[202] The fungus *Helminthosporium* sp. 4671 has been used to oxidise a wide variety of *para*-disubstituted benzyl methyl sulfides, including trifluoromethyl, halo, hydroxy, methoxy, acetoxy, nitro, cyano, amino, acetamido, acyl and carboxylic acid substituents with 52–98% ee.[203] The same species, along with *Mortierella isabellina* ATCC 42613, has also been used to oxidise isothiocyanato sulfides and related compounds in approaches to the synthesis of (−)-sulforaphane **33**. Note this paper also corrects previous erroneous stereochemical assignments.[204] The use of baker's yeast *Saccharomyces cerevisiae* NCYC73 for the oxidation of methyl aryl sulfides has been reported. The reaction involves the use of whole cells and



Scheme 108



33

gives the product sulfoxide in good yield and with high stereoselectivity.[205-207] Toluene and naphthalene deoxygenases have been shown to oxidise alkyl aryl sulfides to give mainly the (*S*)-sulfoxide with high enantioselectivity.[208] Chloroperoxidases have also been investigated,[209,210] and can give mainly the (*R*)-sulfoxide (>98% ee) for the oxidation of aryl alkyl sulfides,[208] and have also be used to prepare more complex aromatic cyclic sulfoxides of up to 99% ee.[210]

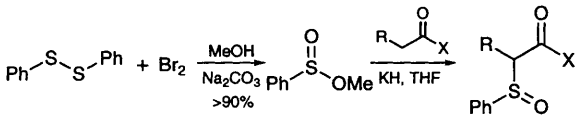
Finally, in a rather different approach, the enantioselective reduction of racemic methyl phenyl sulfoxide by dimethyl sulfoxide reductase from *Rhodobacter sphaeroides* f.s. denitrificans leads to predominantly the (*R*)-sulfoxide by preferential reduction of the (*S*)-enantiomer to thioanisole.[45]

3.2 Non-oxidative sulfoxide and selenoxide synthesis

3.2.1 General methods for sulfoxide and selenoxide synthesis

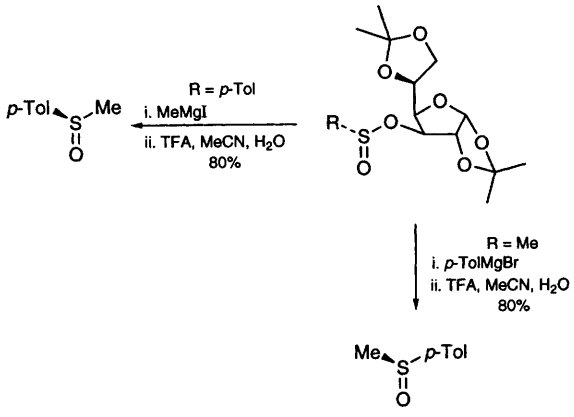
A review on recent advances in asymmetric synthesis using organochalcogen compounds includes sections on the synthesis and utility of chiral sulfoxides and selenoxides.[187] A review on the synthesis of sulfoxide-based ferrocenes using chiral sulfites, sulfinates and by asymmetric oxidation, has also been published.[211] Studies on the stereochemistry of α-sulfinyl carbanions have also been reviewed.[212]

An improved synthesis of methyl benzenesulfinate has been reported (**Scheme 109**).[213] The product reacts with various kinds of carbonyl compounds under basic conditions to produce β-carbonyl sulfoxides in good yield.

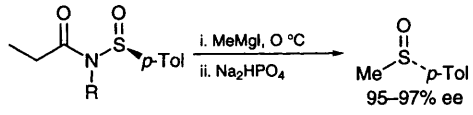


Scheme 109

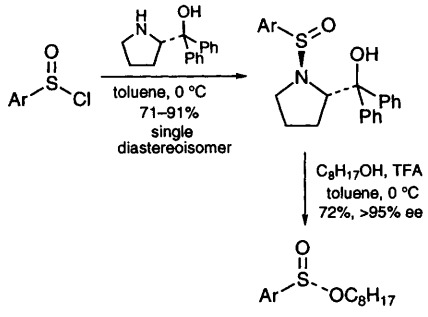
The reaction of resolved sulfinate esters (or their equivalents) with nucleophiles continues to be an important approach for the synthesis of optically active sulfoxides. Methods for large scale syntheses of both enantiomers of methyl *p*-tolyl sulfoxide from diacetone-D-glucose are significant improvements on procedures reported previously (**Scheme 110**).[1,2] The required diastereomerically pure methanesulfinate or toluene-*p*-sulfinate ester precursors are readily prepared from diacetone-D-glucose and the appropriate sulfinyl chloride.[214] Menthyl sulfinate esters continue to be useful precursors for the synthesis of optically active sulfoxides.[215-218] Resolved sulfinamides can also be used in a conceptually similar approach (**Scheme 111**),[219] and can also be used to synthesise new chiral sulfinate esters which in turn can provide access to optically active sulfoxides (**Scheme 112**).[220] Camphor derived cyclic sulfinates react with organometallic reagents to give 10-isobornyl sulfoxides (**Scheme 113**).[221]



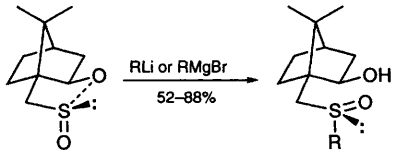
Scheme 110



Scheme 111



Scheme 112

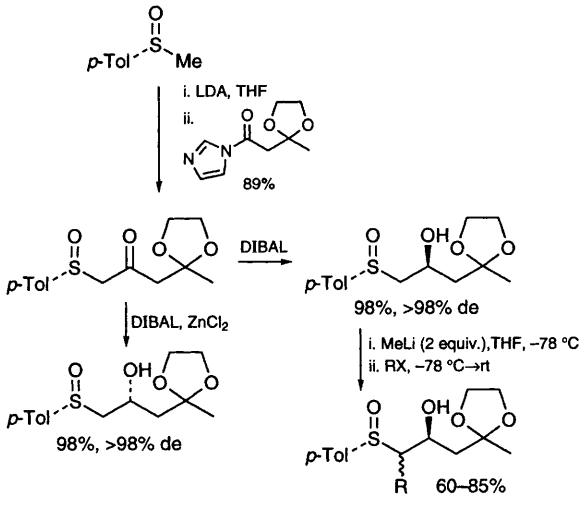


Scheme 113

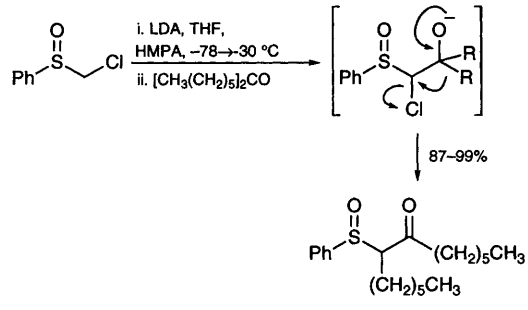
Finally, the use of sulfonic acid salts for the characterisation of selenoxides, including X-ray crystallography, have been reported, and overcome a number of problems associated with the instability of selenoxides.[172] Recent FT-IR studies of related complexes between sulfoxides and sulfonic acids have also been reported.[222]

3.2.2 Functionalised sulfoxides

The condensation between an α-metallo sulfoxide and a carboxylic acid derivative is one of the main methods for the preparation of β-keto sulfoxides. Recently *N*-acylimidazoles have been shown to be superior to a variety of carboxylic acid derivatives for this kind of reaction (**Scheme 114** *cf.* **Scheme 104**).[223] Other more complex carboxylic acid derivatives such as α-chloro-α-fluoroethyl acetate can also be used.[224] An alternative approach relies on the rearrangement of a chloro alkoxide produced from the reaction between a ketone and the anion of an α-chlorosulfoxide (**Scheme 115**).[225,226] Note that there is effectively a one carbon homologation of the ketone and, in the case of aryl alkyl ketones, the carbon is inserted between the carbonyl group and the aromatic ring.

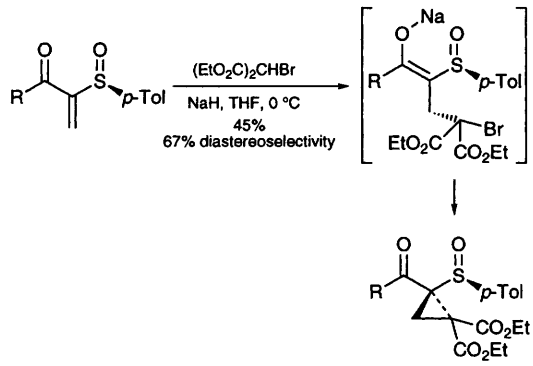


Scheme 114



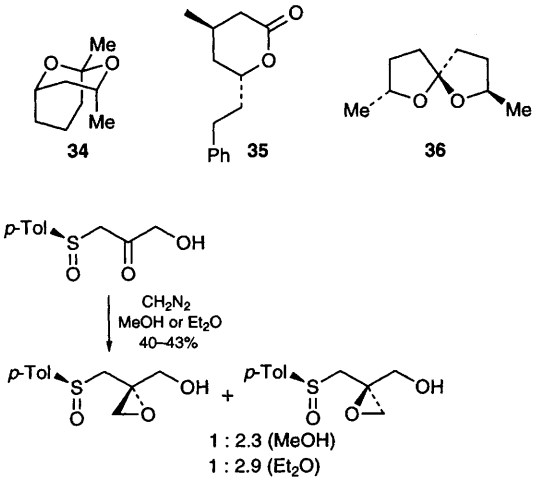
Scheme 115

The synthesis of optically active acyl(sulfinyl)-cyclopropane derivatives by addition of bromomalonate to α-acyl vinylic sulfoxides proceeds with moderate stereoselectivity and yield. The stereochemical outcome can be rationalised by steric interaction between the *p*-tolyl group of the sulfoxide and the electrophilic tetrasubstituted carbon atom (**Scheme 116**).[227,228]



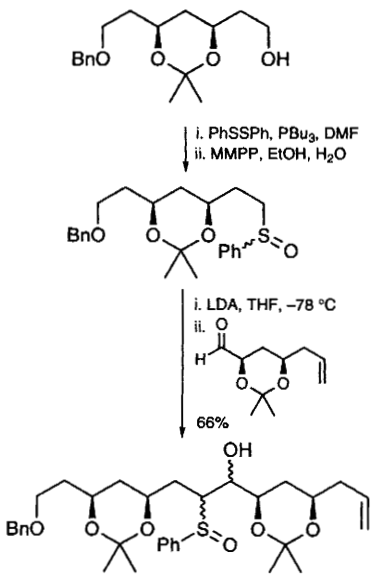
Scheme 116

The reduction of β-keto sulfoxides using DIBAL or DIBAL–$ZnCl_2$ is a well established method for the synthesis of diastereomerically pure β-hydroxy sulfoxides, the two reagent systems giving complementary stereoselectivity. This methodology has been used for the synthesis of a variety of types of compound including α-unsubstituted aldol adducts (**Scheme 114**);[223] (−)-(1*R*,3*R*,5*S*)-*endo*-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane **34**, an insect pheromone;[229] the lactonic acid moiety **35** of (+)-compactin and (+)-mevinolin;[230] the spiroketal (2*R*,5*S*,7*R*)-2,7-dimethyl-1,6-dioxaspiro[4.4]nonane **36**;[231] allylic alcohols;[232] 1,2-diols;[233] and α-substituted β-hydroxy sulfoxides.[234] Similar methodology has also been adapted for use with β-keto sulfoxides derived from camphor (**Scheme 104**) achieving equally high stereocontrol.[186] The addition of diazomethane to β-keto sulfoxides has also been investigated, and proceeds with modest diastereoselectivity to give 2,3-epoxy sulfoxides (**Scheme 117**).[235]



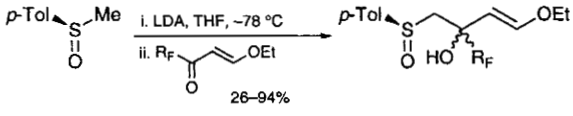
Scheme 117

The other main method for the preparation of β-hydroxy sulfoxides is by addition of an α-lithio sulfoxide to a carbonyl compound. This kind of reaction has been used as one of the main coupling reactions in an approach to the synthesis of amphotericin B (**Scheme 118**) although problems of stereo-

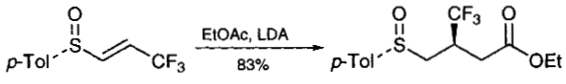


Scheme 118

control during C–C bond formation are not addressed.[236] The addition of α-lithio sulfoxides to fluoroalkyl vinylogous esters occurs with excellent regioselectivity (exclusive 1,2-addition), but poor diastereoselectivity (**Scheme 119**).[237] Use of non-fluorinated carbonyl compounds gives more complex results. An alternative route to β-fluoroalkyl sulfoxides is by conjugate addition of an ester enolate to β-trifluoromethyl-α,β-unsaturated sulfoxides (**Scheme 120**).[238] High regio- and stereo-selectivity are observed in this case.

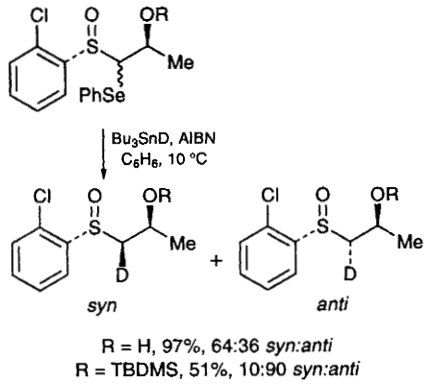


Scheme 119



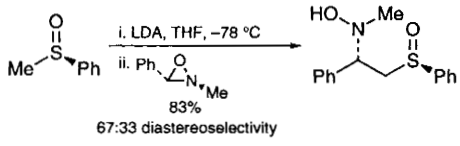
Scheme 120

Further functionalisation of β-hydroxy sulfoxides by dianion formation and alkylation is also possible although poor stereocontrol is generally observed (**Scheme 114**).[223] Better stereoselectivity can be obtained for the allylation or deuteriation of β-hydroxy-α-sulfinyl radicals generated using azoisobutyronitrile (AIBN) on the corresponding selenide (**Scheme 121**).[239] The choice of protecting group plays a crucial role in the stereoselectivity of the reaction. With the free alcohol, the *syn* product predominates, whereas for the TBDMS-protected alcohol, high *anti* selectivity is observed.

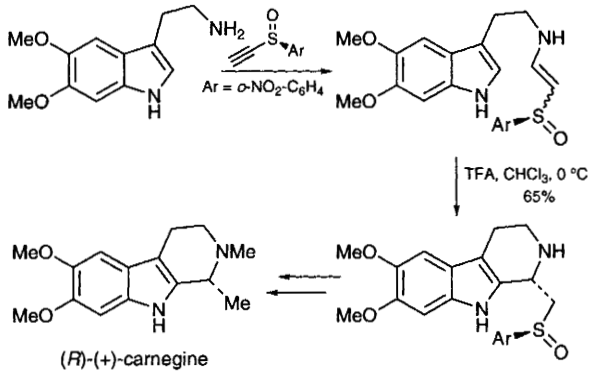


Scheme 121

Relatively few new routes to β-amino sulfoxides have been reported. The addition of α-lithio methyl phenyl sulfoxide to oxaziridines provides a route to β-hydroxyamino sulfoxides in good yield and with moderate diastereocontrol (**Scheme 122**).[240] The reduction of α-(fluoroalkyl)-β-sulfinylenamines with K- or L-Selectride® proceeds with high diastereoselectivity (**Scheme 97**).[142] In the enantioselective synthesis of the tetrahydroisoquinoline (*R*)-(+)-carnegine, the acid catalysed cyclisation of a β-amino-α,β-unsaturated sulfoxide onto an indole proceeds to give a single diastereomeric product in good overall yield (**Scheme 123**).[241]



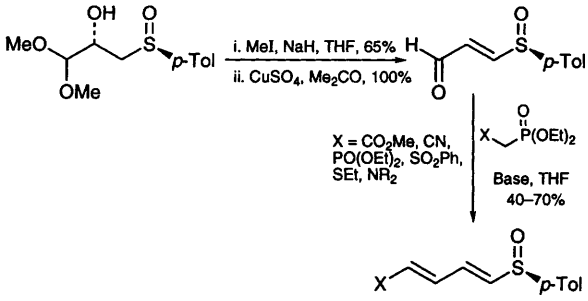
Scheme 122



Scheme 123

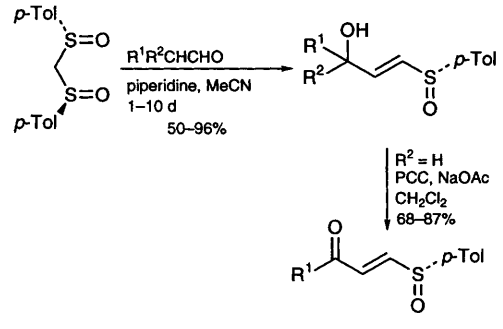
3.2.3 Unsaturated sulfoxides and selenoxides

The elimination of water from a β-hydroxy sulfoxide is one of the main methods for the synthesis of α,β-unsaturated sulfoxides[96,215,234] and can also allow access to dienyl sulfoxides (**Scheme 124**).[234,242] If a homochiral β-hydroxy sulfide is used as starting

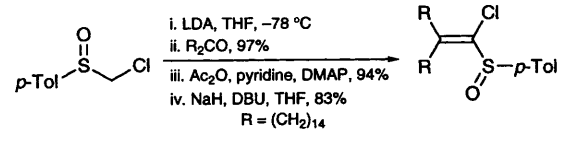


Scheme 124

material, the alcohol moiety can be used to control the absolute stereochemistry at sulfur in a diastereoselective thioether oxidation to give an intermediate β-hydroxy sulfoxide. Subsequent dehydration then gives an optically active α,β-unsaturated sulfoxide (**Scheme 60**).[96] Alternatively, the β-hydroxy sulfoxide precursors are commonly obtained by reduction of the corresponding β-keto sulfoxides (*e.g.* **Schemes 104** and **114**).[186,223] Full details of eliminative routes to γ-hydroxy-α,β-unsaturated sulfoxides from 2,3-epoxy sulfoxides and 2,3-dihydroxy sulfoxides have been published.[243] Such compounds can also be accessed by baker's yeast reduction of a γ-keto-α,β-unsaturated sulfoxide although yields are low (19%) and stereoselectivities only moderate (64% de, >55% ee);[244] or alternatively condensation of an aldehyde with a dithioacetal bis-*S*-oxide. In the latter synthesis, dehydration occurs followed by a double bond migration to allow a subsequent Evans–Mislow rearrangement, which in the presence of a thiophile gives the γ-hydroxy-α,β-unsaturated sulfoxide as a mixture of diastereoisomers (**Scheme 125**).[245] The condensation of an α-chloro sulfoxide anion with a carbonyl compound followed by dehydration leads to formation of 1-chlorovinyl sulfoxides (**Scheme 126**).[246] The



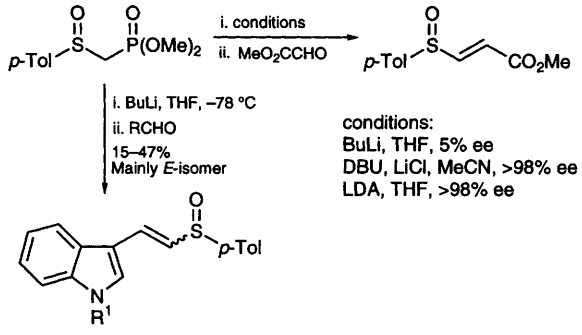
Scheme 125



Scheme 126

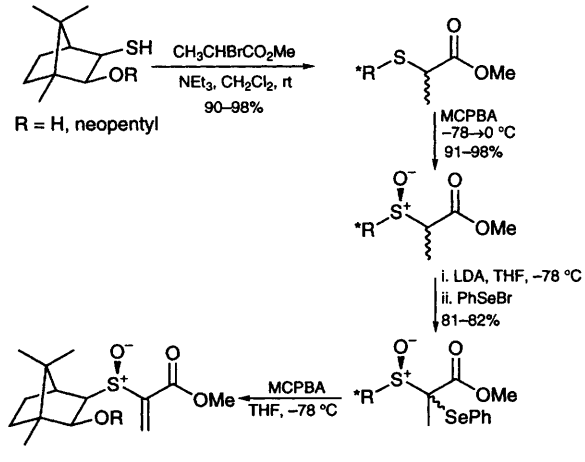
chemoselective oxidation of vinyl sulfides using perfluorooxaziridines also provides a route to α,β-unsaturated sulfoxides.[171]

The Horner–Wadsworth–Emmons reaction and related procedures, have been widely used for α,β-unsaturated sulfoxide synthesis by condensation of a sulfinyl phosphonate with an aldehyde (**Scheme 127**).[247,248] This can allow access to both *E*- and *Z*-alkenes (**Scheme 31**).[62] In some cases, sulfoxide racemisation can occur[242,247] however changing the base and/or substrate can in many cases alleviate such problems.



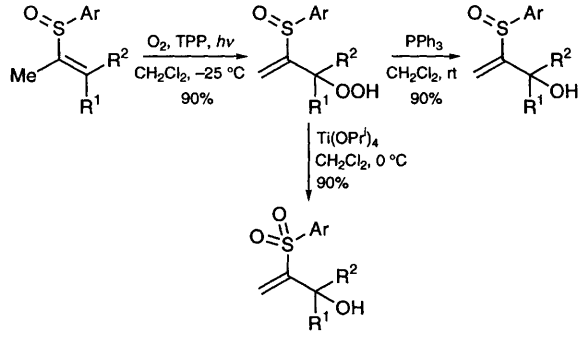
Scheme 127

Sulfinyl phosphonates can be used to prepare α,β-unsaturated sulfoxides and selenoxides by an alternative route (**Scheme 33**).[64] Treatment with base followed by reaction with PhSeBr introduces a phenylseleno substituent to give the key synthetic intermediate. Subsequent oxidation of the selenide and selenoxide elimination leads to formation of an unsaturated sulfinyl phosphonate, or alternatively, sulfoxide elimination by thermolysis gives the corresponding unsaturated selenide which can be oxidised to analogous phosphoryl selenoxide. Similar procedures involving mixed *S*,*Se*-acetals have also been used to prepare camphor-derived α,β-unsaturated sulfoxides (**Scheme 128**).[249]

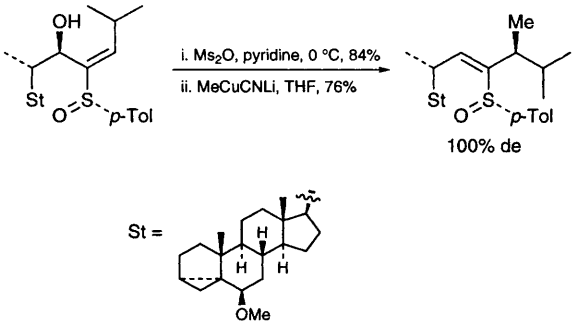


Scheme 128

The synthesis of α-methylene-β-hydroxy sulfoxides has been reported by regioselective photooxidation (Schenck reaction) of racemic vinyl sulfoxides (**Scheme 129**).[250] The intermediate hydroperoxide can be isolated, or is readily reduced using triphenylphosphine. The use of chiral sulfoxides as stereocontrolling elements in S_N2' reactions has also been reported. This methodology has been applied to a formal synthesis of brassinolide (**Scheme 130**).[251]



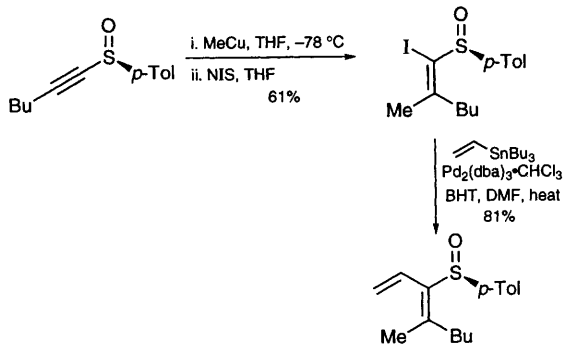
Scheme 129



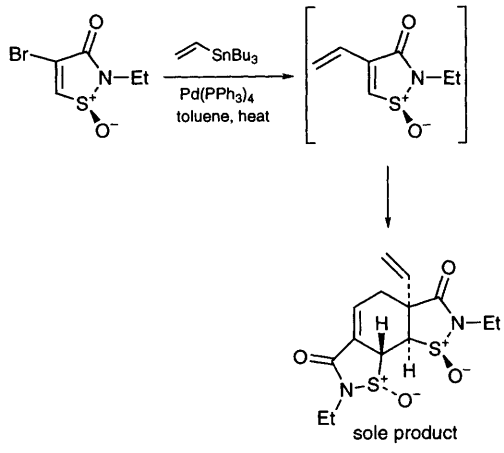
Scheme 130

The palladium-mediated cross-coupling of vinyl stannanes with halovinyl sulfoxides has been exploited in the synthesis of a wide variety of 2-sulfinyl-substituted butadienes (**Scheme 131**).[252] Similar methodology has also been used to access related systems (**Scheme 132**), however these undergo Diels–Alder dimerisation under the reaction conditions to give cycloadducts with remarkably high diastereoselection.[253]

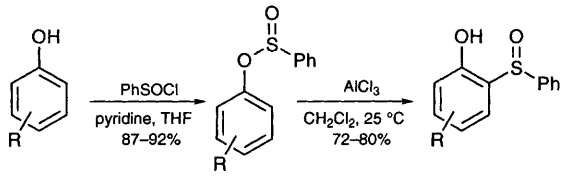
The preparation of (phenylsulfinyl)phenols from arenesulfinates using a 'thia-Fries' rearrangment has been reported (**Scheme 133**).[254] An interesting enzyme-mediated kinetic resolution of the related methyl arenesulfinates by hydrolysis of pendant acetoxy groups provides access to these types of compounds in an optically active form (**Scheme 134**).[255] A number of enzymes were investigated for this transformation, with cholesterol esterase (CE) giving the best results. Alternative routes to optically active diaryl sulfoxides have been reported which rely on the use of menthyl toluene-*p*-sulfinate



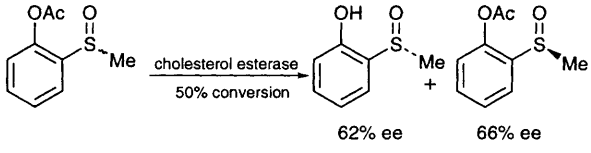
Scheme 131



Scheme 132



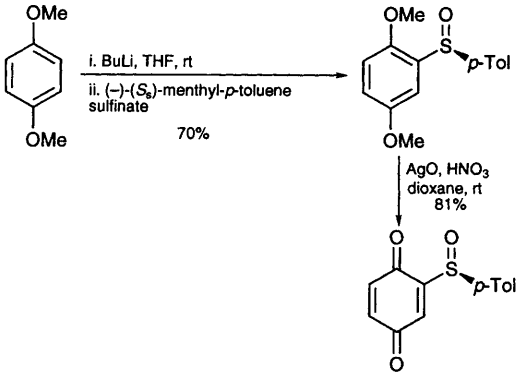
Scheme 133



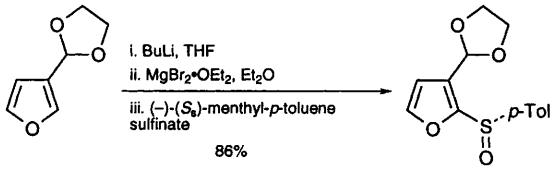
Scheme 134

to control the absolute stereochemistry of the sulfoxide. This allows access to quinol and quinone derivatives (**Scheme 135**),[216] and 2- or 3-sulfinylfurans (**Scheme 136**).[217]

The use of unsaturated sulfoxides as dienophiles, dienes and dipolarophiles in cycloadditions has continued to be an important area of research, and the use of the (2-*exo*-hydroxy-10-bornyl)sulfinyl



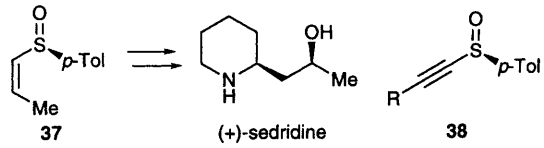
Scheme 135



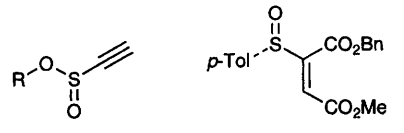
Scheme 136

group and derivatives in Diels–Alder reactions and applications in natural product synthesis has been reviewed.[256] Whilst it is beyond the scope of this review to give a detailed account of this area of chemistry, a brief discussion of the kinds of systems which have been investigated will be included. Syntheses of many of these compounds have been reported previously; any important new synthetic routes have been discussed above.

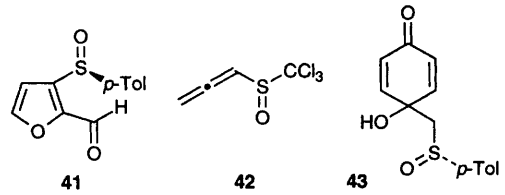
The 1,3-dipolar cycloaddition of *Z*-α,β-unsaturated sulfoxide **37** and a nitrone has been used in a synthesis of (+)-sedridine.[257] The acetylenic sulfoxide **38** has also been used in a 1,3-dipolar cycloaddition with a nitrone.[258] Acetylenic sulfinates **39** have also been investigated as dienophiles.[259] The asymmetric Diels–Alder reactions of more complex α-sulfinyl acrylates including **40**,[215] and related



37 (+)-sedridine **38**



39 **40**



41 **42** **43**

camphor derived systems (**Scheme 128**)[249] have also been reported. The 3-(*p*-tolylsulfinyl)furan-2-carbaldehyde **41** has been used as a hetero-Diels–Alder dienophile,[217,260] whereas the allenic trichloromethyl sulfoxide **42** undergoes conventional [4+2] cycloaddition with cyclopentadiene to give predominantly *endo* cycloadducts.[261] Various quinone derived sulfoxides have also been used as dienophiles (*e.g.* **43**[262] and **Scheme 135**).[216,263]

Further studies on the use of 1- and 2-sulfinyl-1,3-dienes in cycloadditions have been reported (**Schemes 124, 131** and **132**).[242,252,253,264] More recently, the use of 3-vinylsulfinylindoles as 4π components in Diels–Alder reactions has been reported (**Scheme 127**).[248]

4 Synthesis of sulfones and selenones

Although this section is supposed to include methods for the synthesis of selenones as well as sulfones, very little literature has been published on them, and they have found only limited synthetic utility and so will not be discussed in any detail here.

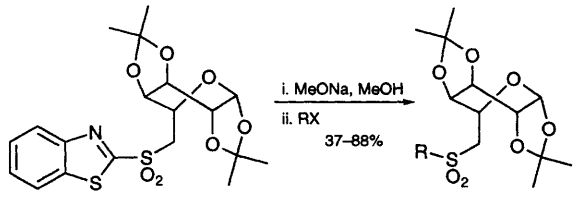
4.1 Oxidation of sulfides and sulfoxides

The use of *tert*-butyl hydroperoxide (TBHP) in the presence of SiO_2 or Al_2O_3 after prolonged reaction times will efficiently oxidise alkyl and aryl sulfides to the corresponding sulfones.[168] Dimethyldioxirane (DMDO) has also been used for sulfone formation in cephalosporins,[265] ketene *S,S*-acetals,[182] and thioether-containing chromium carbene complexes (*cf.* **Scheme 101**).[266] Related mechanistic studies have also appeared.[176,178] The oxidation of vinyl sulfides using MCPBA or perfluoroxaziridines provides a route to vinyl sulfones.[171] A review of α-hydroxy hydroperoxides (*e.g.* **25**) as oxygen transfer reagents in organic synthesis includes a section on sulfone formation.[174] Electron deficient sulfides can be oxidised to sulfones using HOF·MeCN.[267]

4.2 Non-oxidative sulfone synthesis

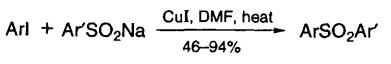
4.2.1 General methods for sulfone synthesis

A novel approach to sugar-derived sulfones utilises the benzothiazol-2-yl (Btz) group, which on treatment with sodium methoxide liberates a sulfinate anion, which can then react with electrophiles to give the desired products (**Scheme 137**).[268] The Btz

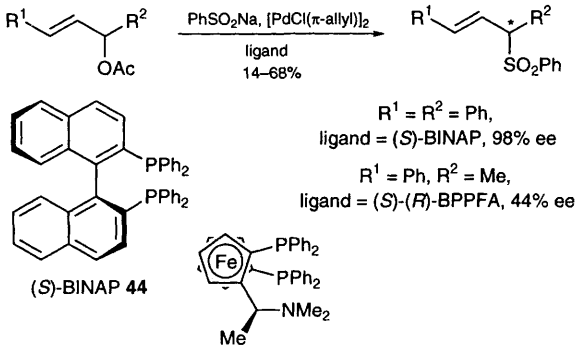


Scheme 137

group is originally introduced onto the sugar moiety by Mitsunobu reaction of the sugar alcohol and benzothiazole-2-thiol followed by oxidation. The copper-assisted displacement reaction of non-activated iodoarenes with arenesulfinates provides a convenient synthetic route to unsymmetrical diaryl sulfones (**Scheme 138**).[269] Low yields are obtained with the corresponding bromoarenes although the use of copper(II) bis(4-methylbenzenesulfinate) catalyst led to considerably improved yields in some cases. The asymmetric palladium-catalysed sulfonylation of α,γ-disubstituted allylic acetates has been investigated with a wide variety of chiral phosphine ligands. It was found that although moderate levels of asymmetric induction were observed with most of the ligands investigated, (*S*)-(−)-2,2′-bis(diphenylphosphino)-1,1-binaphthyl [(S)-BINAP **44**] gave highest selectivity for α,γ-diphenyl allylic acetates, whereas (*S*)-*N*,*N*-dimethyl-1-[(*R*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine [(S)-(R)-BPPFA **45**] was superior for α-methyl-γ-phenyl allylic acetates (**Scheme 139**).[270]



Scheme 138

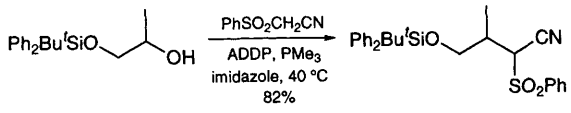


Scheme 139

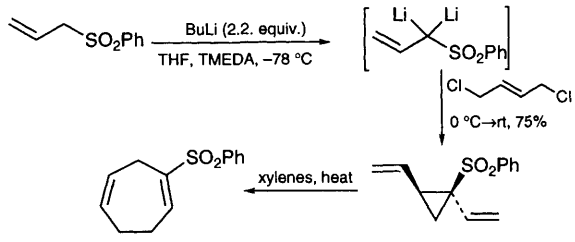
4.2.2 Functionalised sulfones

The Mitsunobu reaction of alcohols with phenylsulfonylacetonitrile, using trimethylphosphine and 1,1′-(azodicarbonyl)dipiperidine (ADDP) provides a versatile method for preparing functionalised sulfones (**Scheme 140**).[271] With unreactive alcohol substrates, the reaction can be carried out at 40 °C in the presence of imidazole to improve yields. The reaction of α,α-dilithiated allyl phenyl sulfone with *E*-1,4-dichlorobut-2-ene gives divinyl-substituted cyclopropyl sulfones with a high degree of stereocontrol (**Scheme 141**).[272] On thermolysis, the products undergo Cope rearrangment to form cycloheptadienyl sulfones.

Poly(ethylene glycol) (PEG) is reported to catalyse the regioselective nucleophilic ring opening

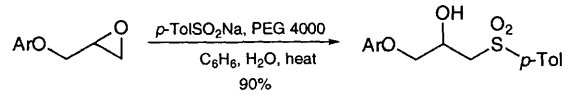


Scheme 140

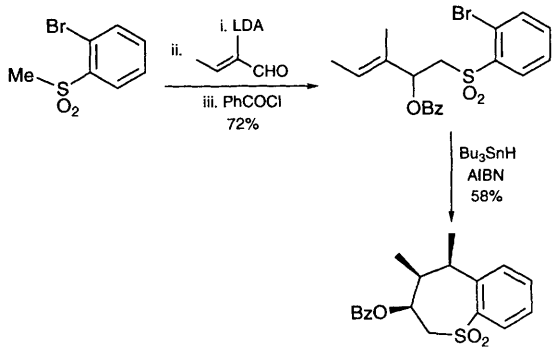


Scheme 141

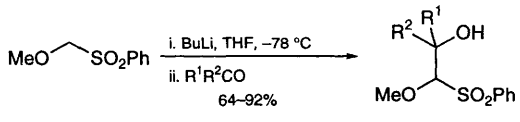
of oxiranes by sodium sulfinate resulting in the synthesis of β-hydroxy sulfones in good yield (**Scheme 142**).[84] An alternative well-established method for the preparation of β-hydroxy sulfones is by condensation of an α-sulfonyl anion with a carbonyl compound. For example, *o*-bromophenyl methyl sulfone can be lithiated and undergoes clean 1,2-addition to α,β-unsaturated aldehydes (**Scheme 143**).[273] The alkoxide intermediate is benzoylated and the product can then undergo radical cyclisation to give a benzo-fused seven-membered ring sulfone. The anion derived from [(methoxymethyl)sulfonyl]-benzene has also been reported to add to ketones (**Scheme 144**).[274] The use of a Schwesinger phospha-



Scheme 142



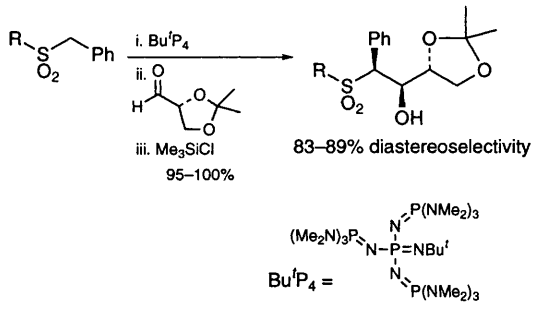
Scheme 143



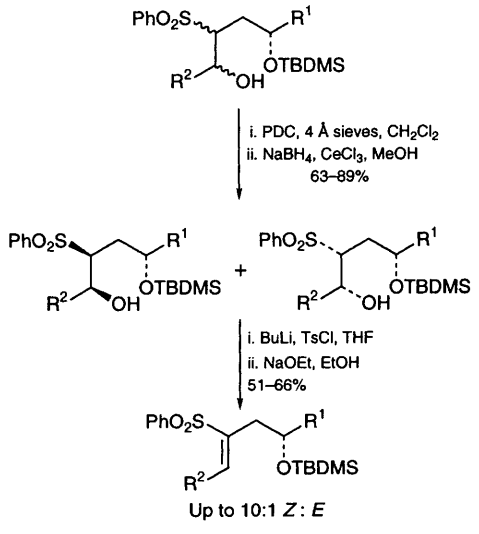
Scheme 143

zene base (Bu^tP_4) with Me_3SiCl quench gives significantly higher diastereoselectivity than other bases for the addition of α-sulfonyl anions to isopropylideneglyceraldehyde (**Scheme 145**).[275] This is rationalised by Bu^tP_4 being a strong cation free base, which results in the formation of a 'naked' α-sulfonyl carbanion that adds to carbonyl groups with enhanced stereoselectivity. An alternative diastereoselective approach to β-hydroxy sulfones relies on the *threo*-selective reduction of β-keto sulfones using $NaBH_4$–$CeCl_3$ (**Scheme 146**).[276] The precursor is prepared by oxidation of a diastereomeric mixture of β-hydroxy sulfones resulting from non-stereoselective addition of an α-sulfonyl anion to an aldehyde. Other related non-stereoselective processes have been reported,[277] including the reaction of the dianion of a β-amino sulfone, which adds to aldehydes to give a 1:1 mixture of diastereomeric β-hydroxy sulfones (**Scheme 147**).[278]

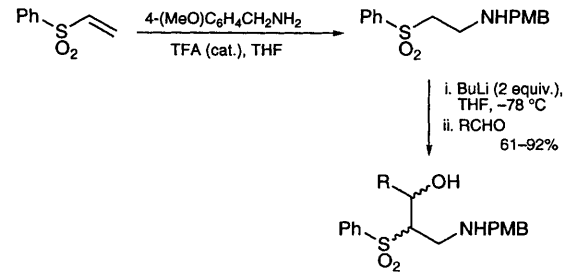
Immobilised *Candida antarctica* lipase (Novozyme 435) will catalyse the stereoselective esterification (vinyl acetate) of a β-hydroxy sulfone, or the hydrolysis of the corresponding racemic acetate with up to 99% enantiomeric excess in the products (**Scheme 148**).[279] It has also been reported that enzymatic reduction of γ-methyl-β-keto sulfones using *Candida*



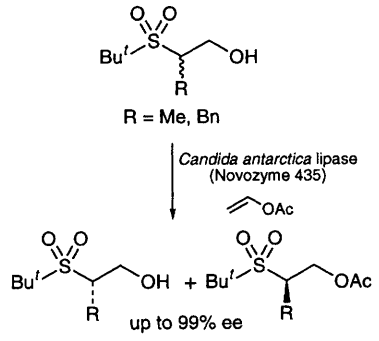
Scheme 145



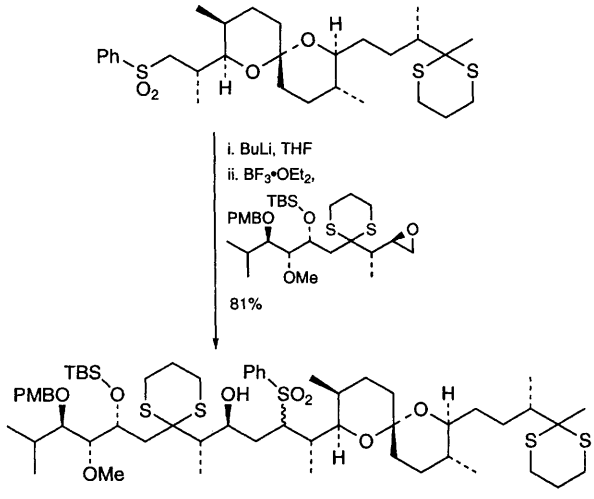
Scheme 146



Scheme 147



Scheme 148

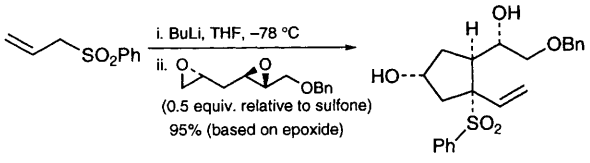


Scheme 149

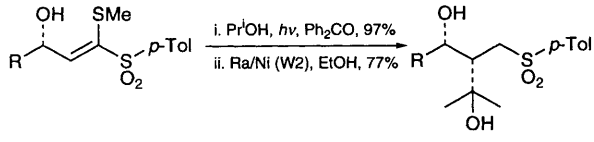
zeylanoides or a variety of other enzymes can give excellent enantioselectivity. However conversions are generally low and limit the synthetic utility.[280]

The synthesis of γ-hydroxy sulfones is usually carried out by reaction of an α-sulfonyl anion with an epoxide. This has been exploited in the synthesis of complex natural products, including key steps in the synthesis of (+)-bullatacin,[281] and (+)-tautomycin (**Scheme 149**); note that in the latter case the reaction is catalysed by the addition of $BF_3{\cdot}OEt_2$.[282] Another impressive example is the reaction between an allyl sulfonyl anion and a diepoxide which gives a single product in excellent overall yield (**Scheme 150**).[283] A rather different approach to γ-hydroxy

sulfones is the stereoselective radical addition to 3-hydroxy-1-(methylthio)-1-(*p*-tolylsulfonyl)alk-1-enes. Excellent yields and high stereoselectivity (>95:5) are observed (**Scheme 151**).[284]

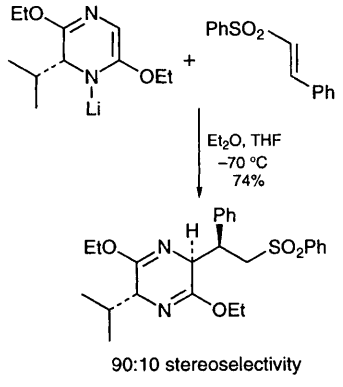


Scheme 150



Scheme 151

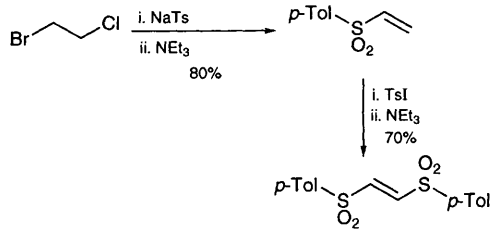
There has been relatively little published on the synthesis of amino sulfones. The conjugate addition of an amine to a vinyl sulfone provides a route to β-amino sulfones (**Scheme 147**).[278] These can then be further functionalised by dianion formation and alkylation α-to the sulfone group. In an approach to the synthesis of β-branched α-amino acids, the addition of a chiral bis-lactim ether glycine synthon to an α,β-unsaturated sulfone proceeds with high stereoselectivity (**Scheme 152**).[285]



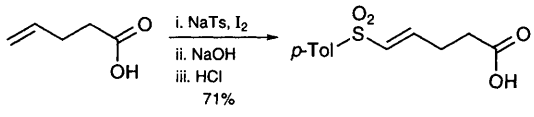
Scheme 152

4.2.3 Unsaturated sulfones

A review of new synthetic methods exploiting α,β-unsaturated sulfones during the synthesis of a natural product has been published.[286] An inexpensive procedure for the preparation of *Z*-1,2-bis-(phenylsulfonyl)ethene and phenylsulfonylethene from 1,1-dichloroethene and thiophenol has been reported (Scheme 23).[53] The initial 1,2-bis-thioether product is oxidised to the bis-sulfone which can be selectively monodesulfonylated using Bu_3SnH. Other routes to α,β-unsaturated sulfones by oxidation of the corresponding sulfide using MCPBA or oxaziridines have been reported.[171,287] Phenylsulfonylethene can also be prepared from thiophenol and 2-chloroethanol and oxidation;[288] and *p*-tolylsulfonylethene, from sodium toluene-*p*-sulfinate and 1-bromo-2-chloroethane. The *p*-tolylsulfonylethene can subsequently be converted to *E*-1,2-bis(*p*-tolylsulfonyl)ethene by addition of toluene-*p*-sulfonyl iodide and dehydroiodination (**Scheme 153**).[289] Similar reactions have also been reported for other electron deficient alkenes (**Scheme 29**),[59] and simple terminal alkenes (**Scheme 154**).[290]

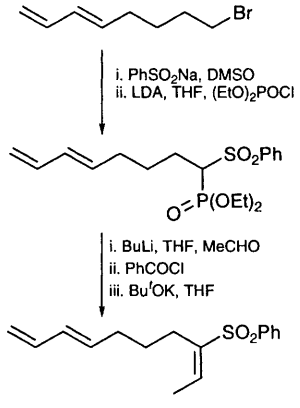


Scheme 153



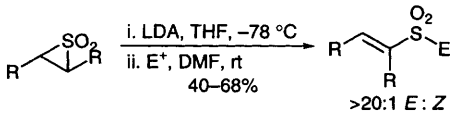
Scheme 154

The use of α-sulfonyl phosphonates for the synthesis of a wide variety of α,β-unsaturated sulfones has been reported (**Scheme 155**).[291] Introduction of the phosphonate group improves stereoselectivity in the double bond formation. A variety of selenium- and sulfur-substituted α,β-unsaturated sulfones have been synthesised from 1-(phenylseleno)-2-(*p*-tolylsulfonyl)ethyne **3**, a novel acetylenic sulfone that undergoes both normal and anti-Michael nucleophilic additions (Scheme 30).[60] Generally good to excellent control of double bond geometry is possible.



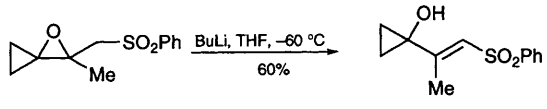
Scheme 155

Recently, the isolation of stable episulfones has led to increased interest in their synthetic potential. The base-mediated ring opening of episulfones leads to the formation of alkenylsulfinates which can undergo *in situ* alkylation leading to sulfone formation (**Scheme 156**).[292] High *E*-selectivity is observed, and the final alkylation reaction is most successful with reactive alkyl halides.



Scheme 156

The β-elimination reactions of β-hydroxy sulfone derivatives provides one of the most versatile methods for α,β-unsaturated sulfone synthesis. For example, 2,3-epoxy sulfones, when treated with base result in formation of γ-hydroxy-α,β-unsaturated sulfones (**Scheme 157**).[293] Further details on earlier examples of this reaction have also been reported.[243] A particularly elegant method of controlling the double bond geometry during elimination to form an α,β-unsaturated sulfone is by controlling the relative stereochemistry of phenylsulfonyl group and the alcohol leaving group. Reduction of a β-keto sulfone using $NaBH_4$–$CeCl_3$ provides selectively the *threo* β-hydroxy sulfone. Subsequent E_2-type elimination leads to predominantly the *Z*-α,β-unsaturated sulfones (up to 10:1) which can be separated from *E*-isomer by chromatography (**Scheme 146**).[276,291]

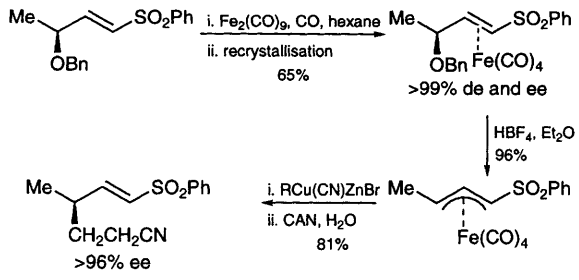


Scheme 157

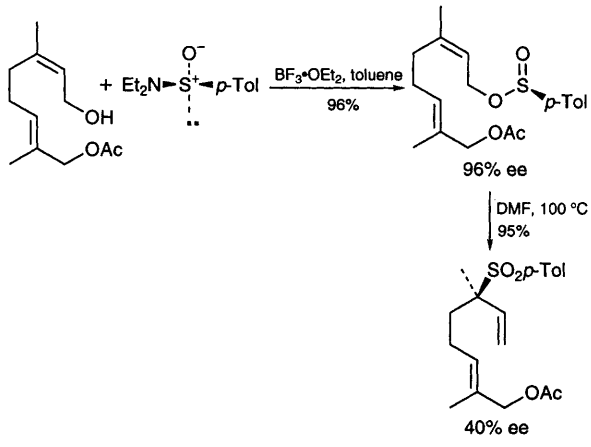
Iron-mediated allylic substitution reactions of γ-alkoxy-α,β-unsaturated sulfones have been shown to occur with complete chirality transfer, and lead to the synthesis of functionalised γ-substituted α,β-unsaturated sulfones of high enantiomeric purity (**Scheme 158**).[294] Thermal sulfinate–sulfone rearrangement of allylic sulfinates leads to the formation of allyl sulfones (**Scheme 159**).[295,296] If optically active sulfinates are used then the product allyl sulfones retain some of the optical purity after rearrangement.

The allyl sulfone anion is a versatile synthetic building block for the preparation of a variety of functionalised allyl sulfones. In many cases, the α-sulfonyl anion is stabilised by coordination of an adjacent heteroatom (Cl, O, N) to the metal counterion (usually lithium). This can then go on to react with electrophiles in good yield (**Scheme 160**).[297–299]

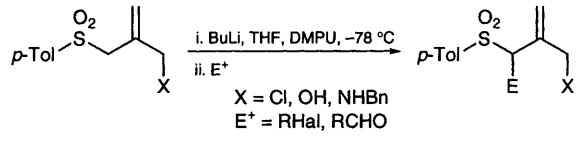
One of the most important reactions of α,β-unsaturated sulfones is their Diels–Alder reaction. Whilst it is beyond the scope of this review to discuss this



Scheme 158

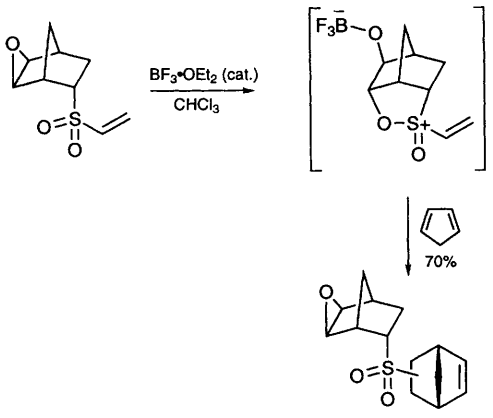


Scheme 159



Scheme 160

in detail, a brief discussion of some of the substrates that have been investigated will follow. The intramolecular cycloaddition of a variety of trienyl sulfones have been investigated (**Scheme 155**).[276,291] The cycloaddition reactions of 1-(phenylseleno)-2-(*p*-tolylsulfonyl)ethyne[61] and 1-(trimethylsilyl)-2-(phenylsulfonyl)ethyne[300] have been studied, the latter acting as a new acetylene equivalent in the Diels–Alder reaction. Divinyl sulfone has been shown to be a useful reagent for 1,3-azaprotio cyclotransfer–1,3-dipolar cycloadditions of oximes.[301] 1-(Trifluoromethyl)-2-(phenylsulfonyl)ethene has also been investigated as a 1,3-dipolarophile.[302] Allenic trichloromethyl sulfones undergo conventional [4 + 2] cycloadditions with dienes such as cyclopentadiene, and give much greater *endo*-selectivity than the corresponding allenic phenyl sulfones.[261] *E*-Bis(phenylsulfonyl)ethene has been shown to be an efficient dieneophile for reaction with isobenzofurans (**Scheme 20**).[49] Finally, one of the most interesting examples of α,β-unsaturated sulfone cycloaddition is by long range activation of the sulfonyl dienophile *via* its oxosulfoxonium salt.



Scheme 161

This is formed by a reversible Lewis acid-catalysed reaction between the sulfone moiety and a suitably positioned epoxide (**Scheme 161**).[303]

5 Conclusion

Organo-sulfur and -selenium chemistry continues to play a crucial role in organic synthesis, particularly with the new stereoselective and asymmetric processes being developed. I hope this review will encourage the further development and exploitation of these methods in the future.

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