Thiols, sulfides, sulfoxides, and sulfones

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Reviewing the literature published between July 1992 and September 1993

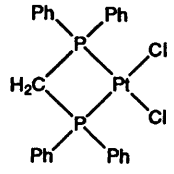
1 Introduction

This review covers new methods for the synthesis of acyclic thiols, sulfides, sulfoxides, and sulfones. Cyclic systems will be covered elsewhere. The review is divided into three sections: thiols and sulfides, sulfoxides, and sulfones. Each section begins with synthetic routes to simple systems, and then goes on to consider more complex, polyfunctional molecules. Considerable emphasis has been placed on stereo- and enantio-selective methods, reflecting the current interest in this area.

2 Synthesis of thiols and sulfides

2.1 Simple alkylthiols and dialkylsulfides

One of the simplest, well established procedures for the preparation of sulfides is the alkylation of thiols with alkyl halides, or their equivalent. Improved procedures for this reaction have been reported. The bis(diphenylphosphino)methane platinum (II) complex **1** catalyses the reaction between thiols and alkyl



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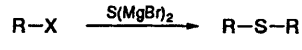
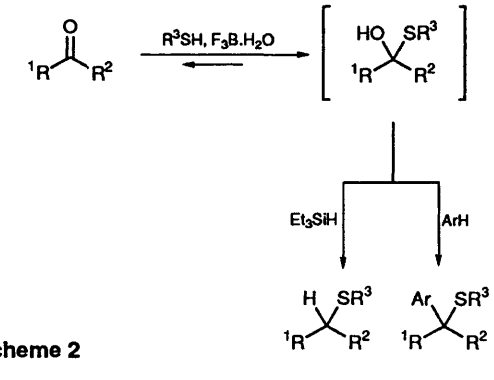
halides for the preparation of unsymmetrical sulfides and thioacetals.[1] It has also been reported that ultrasound can accelerate reactions between thiols and alkyl and aralkyl halides in the presence of K_2CO_3 in DMF.[2] Treatment of hydrogen sulfide with ethyl magnesium bromide generates $S(MgBr)_2$, which is an effective reagent for the synthesis of a wide variety of symmetrical sulfides when treated with appropriate electrophiles (**Scheme 1**).[3]



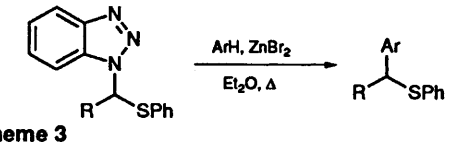
Scheme 1

The reduction of sulfoxides using sodium iodide and a sulfonic acid catalyst also provides access to sulfides, the procedure being particularly efficient for the reduction of benzylic sulfoxides which can often be problematic.[4] A particularly useful one-pot preparation of sulfides from carbonyl compounds uses boron trifluoride monohydrate to catalyse the addition of a thiol to the carbonyl group to form a hemithioacetal, which is reduced *in situ* using triethylsilane to give unsymmetrical sulfides in good overall yields (**Scheme 2**). The reaction is successful even with hindered thiols (*e.g.* Bu^{t}SH).[5] A related procedure has also been reported where replacement of Et_3SiH with an aromatic nucleophile leads to products resulting from electrophilic aromatic substitution.[6]



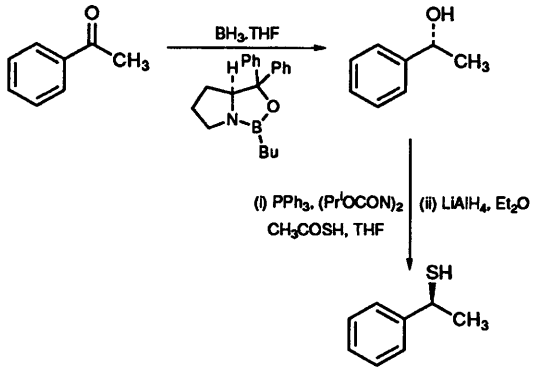
Scheme 2

Similar thioalkylation of electron-rich aromatic compounds has also been achieved using α-(benzotriazol-1-yl)benzyl phenyl sulfide under Lewis acidic conditions (**Scheme 3**).[7]



Scheme 3

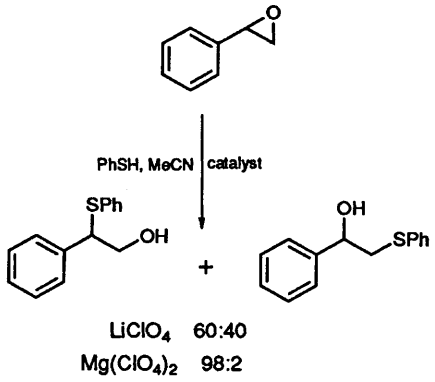
An adaptation of Corey's oxazaborolidine-based asymmetric reducing agent has led to the development of a route to homochiral benzylic thiols.[8] Enantioselective reduction of a prochiral ketone gives the alcohol (> 96% e.e.), which is converted to the thiol with clean inversion of configuration *via* an intermediate thioester and reduction (**Scheme 4**).



Scheme 4

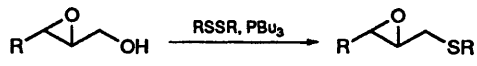
2.2 Substituted thiols and sulfides

The nucleophilic ring-opening of epoxides is a well known method for the preparation of β-hydroxysulfides. A recent study on the role of metal salts in promoting this reaction has shown that magnesium and lithium perchlorate are effective, with the former showing particularly useful regioselectivity (**Scheme 5**).[9] The use of proton exchanged X-type



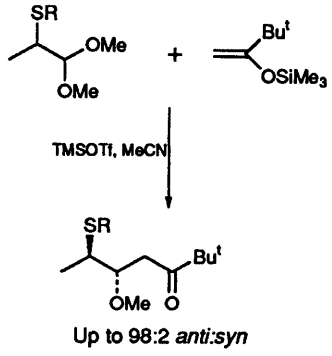
Scheme 5

zeolite as a catalyst for this reaction has also been demonstrated, and is a superior catalyst to sulfuric acid.[10] The direct conversion of a number of different β-alkoxyalcohols to the corresponding β-alkoxysulfides, using a disulfide and a phosphine, has been reported (**Scheme 6**).[11,12] The Lewis acid



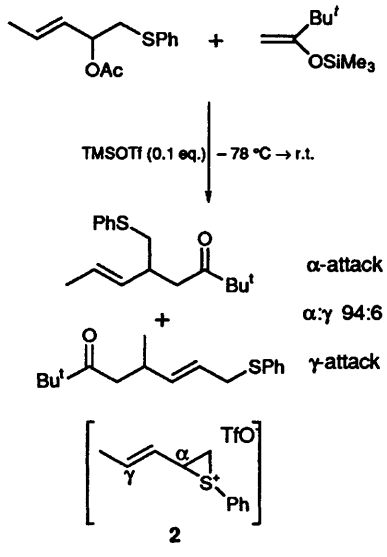
Scheme 6

catalysed reaction of α-sulfenyl acetals with silylated carbon nucleophiles provides a route to β-alkoxysulfides with high diastereoselectivity (**Scheme 7**). The reaction is believed to proceed *via* S_N2 displacement on the acetal-Lewis acid complex rather than an S_N1 process, or an intermediate thiiranium ion.[13]



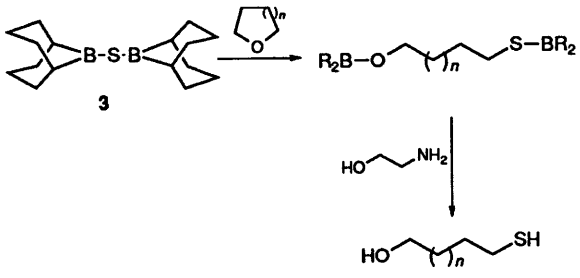
Scheme 7

In a related process, the highly regioselective reaction of allylic acetates with silylated carbon nucleophiles directed by a sulfenyl group gives moderate to good yields of addition products, with predominant α-attack (**Scheme 8**), rationalized by

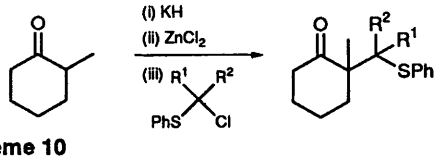


Scheme 8

consideration of an intermediate vinylthiiranium ion **2**.[14] The sulfoboration of cyclic ethers using bis(1,5-cyclooctanediylboryl)sulfide **3** (R = 9-BRN) gives a preparative route to mercaptoalkanols (**Scheme 9**). Cleavage initially forms a boryl complex, which on decomplexation gives the desired thiol.[15] The α-thioalkylation of zinc enolates of α,α-disubstituted ketones has been reported using α-chlorosulfides under Lewis acidic conditions, giving good to moderate yields of β-(arylthio)ketones (**Scheme 10**).[16]



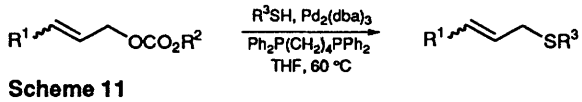
Scheme 9



Scheme 10

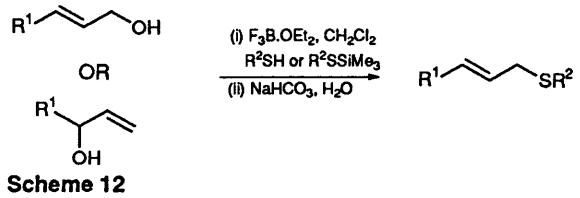
2.3 Allyl and benzyl thiols and sulfides

The synthesis of allylaryl sulfides by palladium (0)-mediated alkylation of arylthiols with allylic carbonates gives primarily the product of substitution at the less-hindered carbon atom of the allylic carbonate (**Scheme 11**). Double bond geometry is lost



Scheme 11

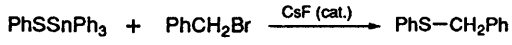
in the case of *Z*-allylic carbonates, but otherwise the reaction proceeds well.[17] The direct synthesis of allyl, benzyl, and cinnamyl sulfides and thiols from the corresponding alcohols under Lewis acidic catalysis has been reported. Again, the major product in all cases is that resulting from introduction of the sulfide group at the less-hindered carbon of the allylic system (**Scheme 12**). A mixture of double bond isomers is formed in cases where allylic rearrangement is observed.



Scheme 12

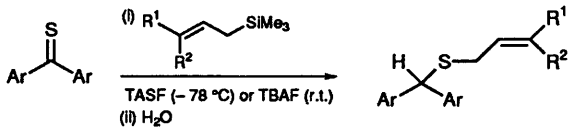
Unactivated primary alcohols remain unaffected by this reaction. Inversion of stereochemistry is observed at secondary centres, and the reaction works equally well with thiols or their trimethylsilyl ethers as the nucleophile. Use of bis(trimethylsilyl)sulfide provides direct access to allylic thiols (**Scheme 12**).[18]

The reaction of arylthiostannanes with benzyl bromide provide a route to unsymmetrical sulfides, although at present examples are limited (**Scheme 13**).[19]



Scheme 13

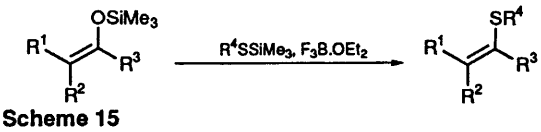
An alternative approach for the synthesis of allyl sulfides is the addition of allyl silane derivatives to bis(aryl)thioketones (**Scheme 14**). Dialkylthioketones are rather unreactive in this reaction.[20] The use of TBAF at room temperature or TASF at −78°C as catalyst is required, and the reaction is successful for a range of silane systems.



Scheme 14

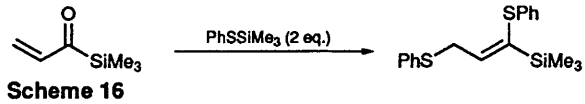
2.4 Vinyl and aryl sulfides

The reaction of trimethylsilyl thioethers with trimethylsilyl enol ethers under Lewis acidic catalysis provides a useful approach for the synthesis of vinyl sulfides from ketones and aldehydes (**Scheme 15**).

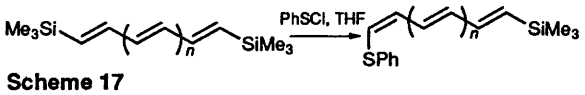


Scheme 15

Reaction of α,β-unsaturated carbonyl compounds with phenylthiotrimethylsilane (two equivalents) also allows efficient access to 1,3-bis(phenylthio)propenes (**Scheme 16**).[21] Polyunsaturated sulfides can be prepared from the appropriate vinyl silanes by treatment with a sulfenyl halide. The double bond geometry of the vinyl sulfide product is opposite to that of the original vinyl silane (**Scheme 17**).[22]

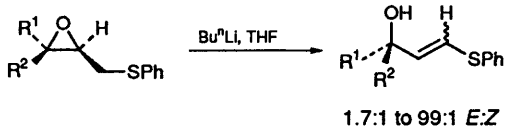


Scheme 16

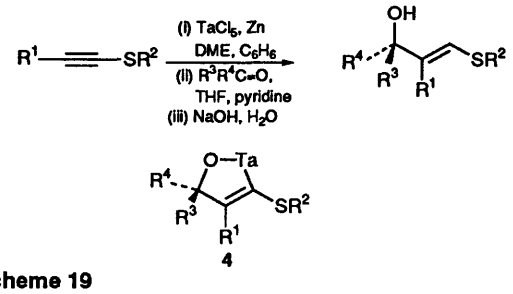


Scheme 17

Treatment of a β-alkoxy sulfide with strong base induces β-elimination to produce vinyl sulfides. Moderate to excellent control of geometry of the new double bond is possible, and is substrate dependent. This method also provides access to γ-hydroxy vinyl sulfides by elimination of β,γ-dialkoxy sulfides or β,γ-epoxy sulfides (**Scheme 18**).[12,23] An alternative approach to γ-hydroxy vinyl sulfides is by reaction of alkynyl sulfides with carbonyl compounds mediated by low-valent tantalum, generated *in situ* using $TaCl_5$ and zinc (**Scheme 19**).[24] This selectively gives the *E*-double bond isomer (usually >99:1) *via* the intermediate tantalum complex **4**.

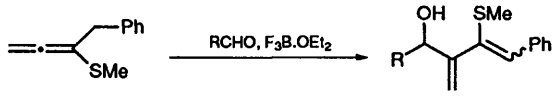


Scheme 18



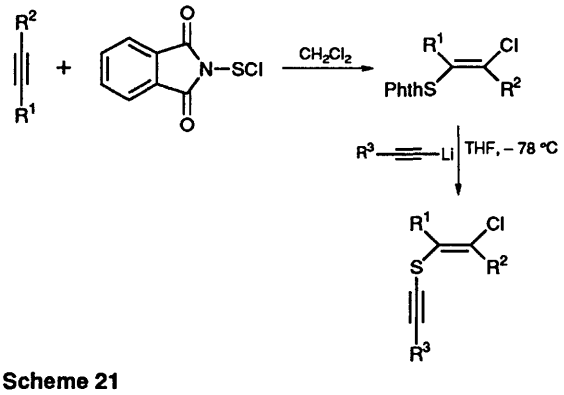
Scheme 19

The reaction of 1,2-propadienylsulfides with aldehydes and acetals under Lewis acidic conditions provides a route to substituted dienyl sulfides (**Scheme 20**). The allenic sulfide precursors are significantly more reactive than the corresponding allenic *O*-ethers.[25]

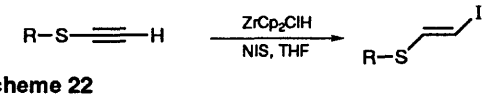


Scheme 20

Phthalimidosulfenyl chloride reacts with alkynes with formation of the *E*-vinylchlorosulfenimide. Substitution of the phthalimido residue by acetylide then provides access to alkynylvinyl sulfides in good overall yield (**Scheme 21**).[26] *E*-2-Iodoethynyl sulfides have been prepared by zirconium-catalysed addition of *N*-iodosuccinimide to a terminal alkyne, with full control of double bond geometry (**Scheme 22**).[27]

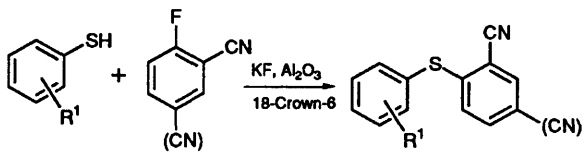


Scheme 21

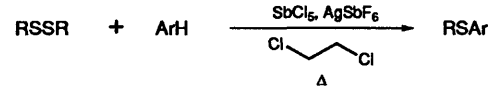


Scheme 22

The displacement of fluoride from activated fluoroaromatics using an aromatic thiol and KF–alumina with 18-crown-6 provides a route to unsymmetrical diaryl thioethers in excellent yield (**Scheme 23**).[28] Similar products have also been prepared by an electrophilic aromatic substitution reaction of a sulfenium ion equivalent, generated from a disulfide using the acidic catalyst $SbCl_5/AgSbF_6$. The *para*-disubstituted isomers, where appropriate, are the main products of this reaction (**Scheme 24**).[29]

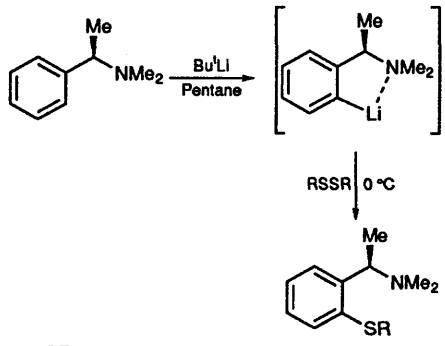


Scheme 23



Scheme 24

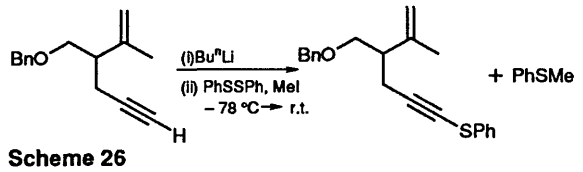
The *ortho*-sulfenylation of *N*,*N*-dimethyl-1-phenylethylamine by lithiation and quench with a disulfide provides a route to alkylaryl sulfides in good overall yield (**Scheme 25**).[30]



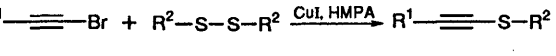
Scheme 25

2.5 Alkynyl sulfides

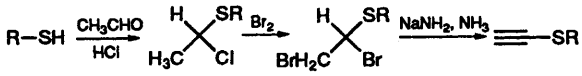
The reaction of acetylide anions with sulfenylsulfonium salts, generated *in situ* from a disulfide and methyl iodide, provides an efficient route to alkynyl sulfides. The reaction is successful with a range of functionalized acetylide nucleophiles (**Scheme 26**).[31] The copper (I) iodide catalysed reaction of disulfides (and diselenides) with alkynyl bromides in HMPA provides direct access to both aryl- and alkyl-alkynyl sulfides (**Scheme 27**).[32] The preparation of alkyl ethynyl sulfides has been reported.[27] Condensation of acetaldehyde with a thiol and HCl generates an α-chlorosulfide. This reacts with bromine to form a *vicinal*-dibromide, which is eliminated under strongly basic conditions to give an alkyl ethynyl sulfide (**Scheme 28**). The synthesis of alkynyl vinyl sulfides by nucleophilic displacement of phthalimide from a phthalimidosulfenate has been described previously (**Scheme 21**).[26]



Scheme 26



Scheme 27



Scheme 28

3 Synthesis of sulfoxides

3.1 Oxidation of sulfides

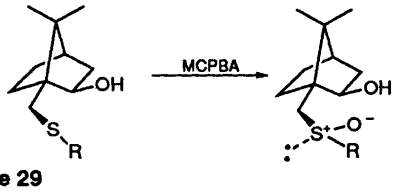
The oxidation of sulfides continues to be one of the most important routes for the preparation of sulfoxides. Whilst there are already many known oxidants that will carry out this process, more appear every year, along with applications of previously reported reagents. Important recent advances have been made in the enantioselective oxidation of prochiral sulfides to the corresponding sulfoxides, and a separate section will be dedicated to this area.

3.1.1 Non-stereoselective oxidation

A considerable number of new, non-stereoselective oxidizing agents have been reported for the oxidation of sulfides to sulfoxides. These include $[Ru(bpy)_2(O)PR_3][ClO_4]$,[33] $VOCl_3$/TBHP on montmorillonite,[34] $Zn(BiO_3)_2$/AcOH,[35] H_2O_2–Urea/phthalic anhydride (utilizes a stable, inexpensive, and easy to handle source of H_2O_2),[36] oxone on wet alumina (no overoxidation, alcohols and alkenes unaffected),[37] $Na_2B_2O_8$ (particularly good for β-disulfoxides),[38] and *o*-iodosylbenzoic acid/H_2SO_4.[39] The dramatic effect of alcohols, particularly methanol, on selectivity in the photo-oxidations of sulfides has also been reported.[40] *N*-Phenylsulfonyloxaziridines are superior reagents to MCPBA and oxone for the oxidation of alkynylsulfides to alkynylsulfoxides.[26,31]

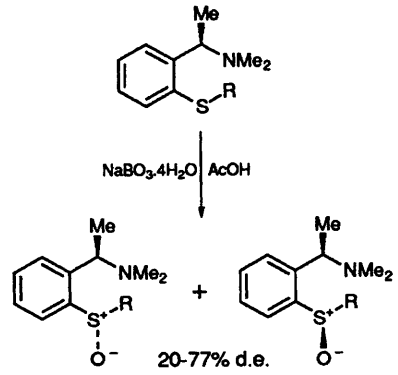
3.1.2 Stereoselective oxidation

There have been a number of reports of diastereoselective oxidation of sulfides to sulfoxides. These often involve an adjacent functional group to which the oxidant can bind, thus delivering its oxygen 'intramolecularly'. Good examples of this are the 2-*exo*-hydroxybornyl systems, with a sulfide in position 10, derived from camphor-10-sulfonic acid, where oxidation provides exclusively one diastereomeric product for a variety of sulfur substituents (including vinyl groups) in good yield (**Scheme 29**).[41] Protection of the alcohol as its MOM ether reduces diastereoselectivity to 30% d.e.



Scheme 29

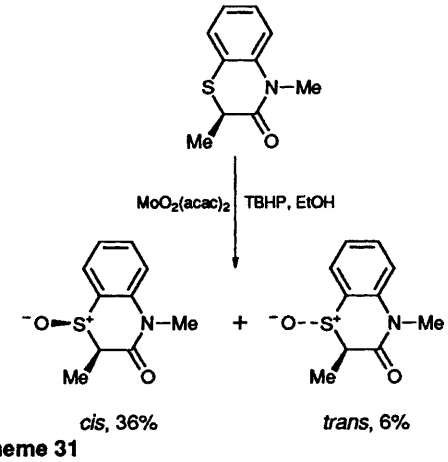
Sulfides prepared from α-methylbenzylamine by *ortho*-lithiation and disulfide quench can be stereoselectively oxidized with $NaBO_3 \cdot 4H_2O$ with up to 77% d.e. (**Scheme 30**).[30] Organic peracids were ineffective as diastereoselective oxidants.



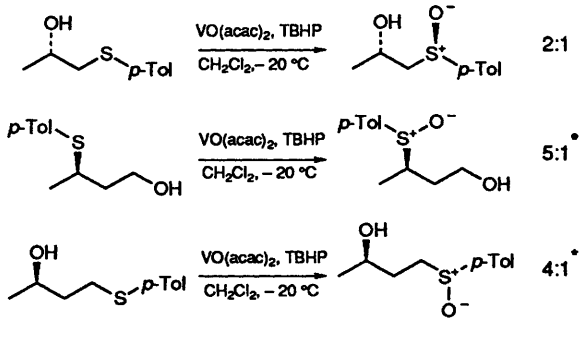
Scheme 30

The use of $MoO_2(acac)_2$ and TBHP as a diastereoselective oxidant has been reported, however, selectivity and yield are modest (**Scheme 31**). Use of MMPP provides selective access to the *trans*-isomer as the *cis*-isomer rearranges under these reaction conditions.

For the oxidation of a series of β- and γ-hydroxy sulfides, $VO(acac)_2$/TBHP gives moderate to good diastereoselectivity (**Scheme 32**).[42]



Scheme 31



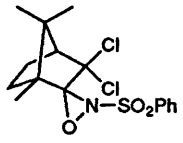
•Stereochemistry at sulfur not determined

Scheme 32

3.1.3 Enantioselective oxidation

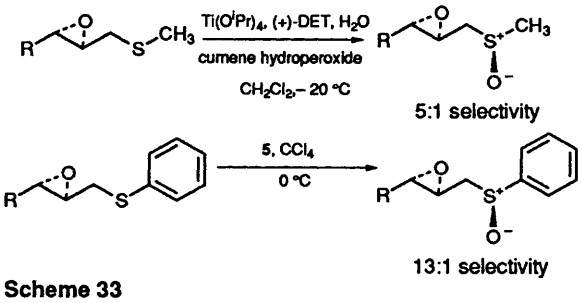
Potentially the most useful method for the preparation of enantiomerically pure sulfoxides is asymmetric oxidation. This area rightly continues to attract considerable attention. A number of reviews in this

area have appeared, including oxidation using chloroperoxidase and horseradish peroxidase enzymes,[43] strapped prophyrin catalysts,[44] and *N*-(phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine **5** (Davis oxaziridine).[45]



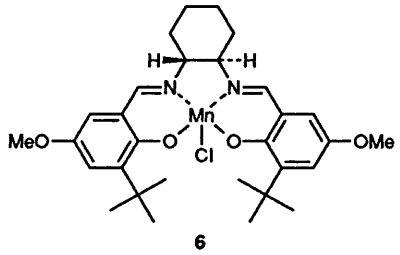
5

Further details on the Davis oxaziridine have been reported.[46] It has also been included in comparative studies with the Kagan oxidation [$Ti(OPr^i)_4$, DET, cumene hydroperoxide, H_2O] and fungal cultures for the preparation of vinyl sulfoxides,[47] and with the Kagan oxidation for the synthesis of substituted arylalkyl and methylalkyl sulfoxides.[11] In general the selectivity observed using the different oxidation procedures is very substrate dependent, however, the alternative procedures frequently provide complementary selectivity. For example, the Kagan oxidation gives good selectivity for methylalkyl sulfides but poor selectivity for phenylalkyl sulfides, whereas the Davis oxaziridine gives good selectivity for phenylalkyl sulfides but poor selectivity for methylalkyl sulfides (**Scheme 33**).[11]



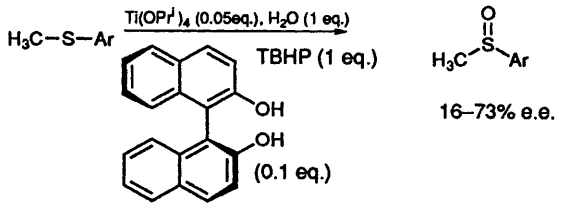
Scheme 33

New methods for asymmetric oxidation have been reported. A Japanese patent describes the use of iron-porphyrin catalysts with up to 46% e.e.[48] A series of manganese(salen) catalysts (2–3 mol.%) and H_2O_2 oxidize a range of arylalkyl sulfides in 34–68% e.e. and 80–95% yield, the best catalyst being **6**, derived from enantiomerically pure



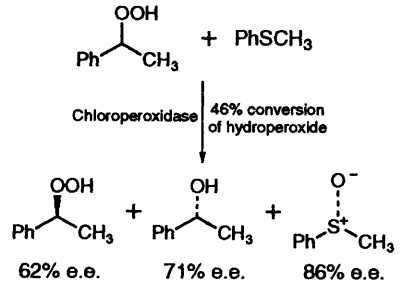
6

trans-1,2-diaminocyclohexane.[49] Modest to good selectivity has also been observed for the preparation of arylmethyl sulfoxides using $Ti(OPr^i)_4$ modified with *R*-(+)-binaphthol, with TBHP as oxidant. As with other related systems (Kagan oxidation) the addition of water (one equivalent relative to substrate) is of crucial importance for good selectivity (**Scheme 34**).[50]



Scheme 34

Enzymatic systems have also been reported. Chloroperoxidase from *Caldariomyces fumago* has been used in conjunction with chiral peroxides, which undergo kinetic resolution during asymmetric *S*-oxidation. A series of substituted arylmethyl sulfoxides can be prepared with 97–100% e.e. (**Scheme 35**).[51] The dramatic effect of substrate structure on enantioselectivity using cyclohexanone monooxygenase from *Acinetobacter* has been reported for a series of alkylaryl- and dialkyl-sulfides (3–99% e.e.).[52] It was shown that the substrate structure influenced not only the enantiomeric purity of the product, but also its absolute configuration.

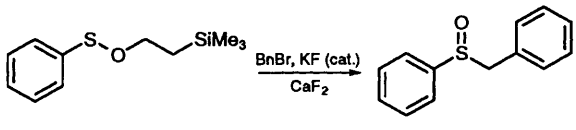


Scheme 35

3.2 Non-oxidative sulfoxide synthesis

3.2.1 General methods for sulfoxide synthesis

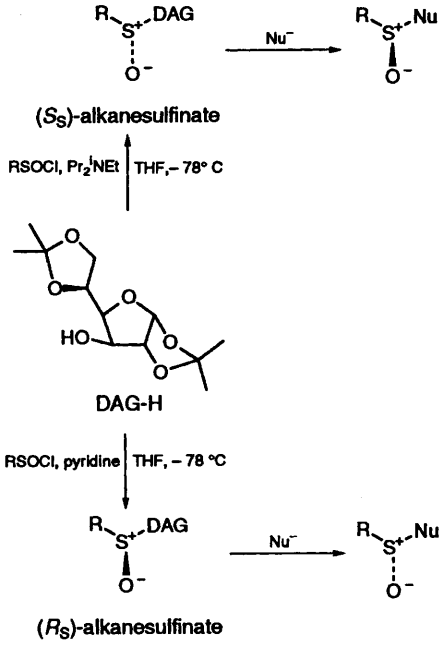
An interesting new route for the synthesis of alkylaryl sulfoxides has been reported, using 2-trimethylsilylethyl benzenesulfenate and an alkyl halide with fluoride catalysis. Alkylation of sulfur, with loss of trimethylsilyl fluoride and ethene, gives the sulfoxide (**Scheme 36**).[53]



Scheme 36

Most other reports in this area involve the preparation of homochiral sulfoxides. An extensive review of asymmetric carbon–carbon bond formation using sulfoxide stabilized carbanions has been published. This also includes a section on methods for the enantioselective synthesis of sulfoxides.[54] The nucleophilic displacement at sulfur in a chiral sulfinate, or its equivalent, continues to be an efficient route for

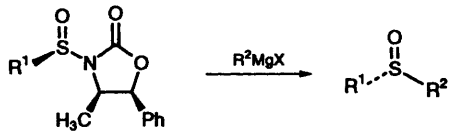
sulfoxide synthesis. Alkane- and arene-sulfinates of diacetone-D-glucose (DAG) provide a general route to both sulfoxide enantiomers. Sulfinylation of DAG with a sulfinyl chloride provides access to either sulfinate diastereomer depending on the nature of the base catalyst. Use of ethyl diisopropylamine selectively gives the (S_S)-alkanesulfinate, whereas pyridine gives the (R_S)-alkanesulfinate (**Scheme 37**).[55] Treatment with organometallic reagents then proceeds with clean inversion of stereochemistry, and provides access to a wide variety of sulfoxides, particularly methylalkyl, methylaryl, or *p*-tolylalkyl, of high enantiomeric purity. DAG gives superior selectivities for sulfinate formation compared to menthol or cholesterol.



Scheme 37

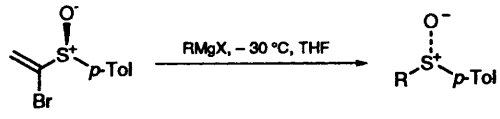
A report describing the preparation of isomeric butylethyl sulfoxides using sulfinate methodology and Grignard reagents, strongly suggests that, in reactions where one partner (either the nucleophile or sulfinate) is particularly sterically hindered, overall retention of configuration at sulfur is observed, in contrast to inversion which is normally expected.[56] In such cases therefore, caution should be exercised when assigning sulfur stereochemistry.

In an extension of previous work, Evans has reported the use of homochiral *N*-sulfinyloxazolidinones for sulfoxide synthesis.[57] They may be prepared either by sulfinylation of the parent oxazolidinone, or by oxidation of the appropriate sulfenimides. These reagents react readily with a wide variety of nucleophiles, including Grignard reagents, enolates, alkoxides, and amides to give sulfoxides, sulfinate esters, and sulfinamides in high yields and enantioselectivities (**Scheme 38**). These oxazolidinone-based reagents are > 100 times more reactive than menthyl sulfinate esters toward Grignard reagents.



Scheme 38

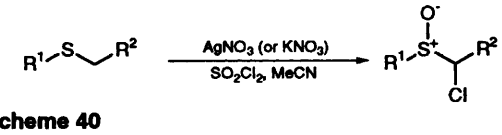
A related process involves the reaction of bromovinyl aryl sulfoxides and Grignard reagents for the preparation of homochiral sulfoxides. In this case, introduction of the nucleophile is accompanied by loss of ethyne and bromide (**Scheme 39**).[58] The bromovinyl sulfoxide precursors are readily prepared by addition of bromine to a vinyl sulfoxide, followed by base-catalysed elimination.



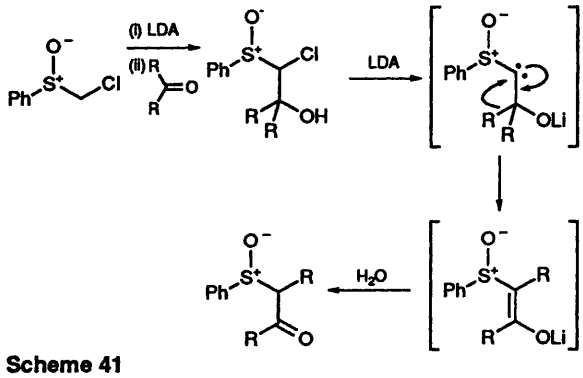
Scheme 39

3.2.2 Functionalized sulfoxides

The preparation and uses of α-chlorosulfoxides have recently been reviewed.[59,60] A recent paper has also described a one-pot synthesis of these reagents from the appropriate sulfides using sulfuryl chloride nitrate, generated *in situ* from sulfuryl chloride and silver (or potassium) nitrate (**Scheme 40**).[61] α-Chlorosulfoxides, when treated with base and a carbonyl compound, provide a route to β-ketosulfoxides. The reaction is believed to proceed *via* an α-sulfinyl carbenoid and 1,2-nucleophilic shift (**Scheme 41**).[62]

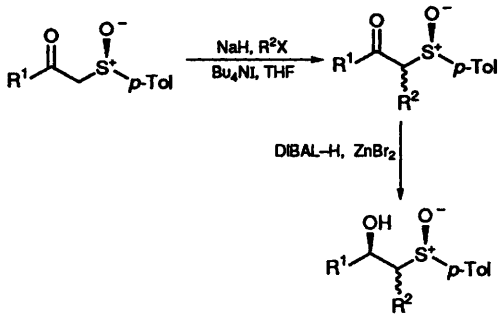


Scheme 40

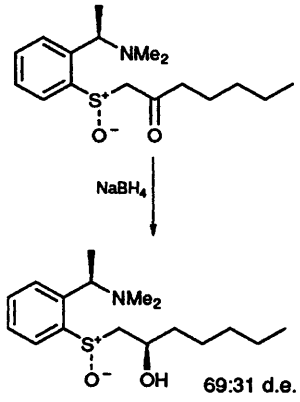


Scheme 41

The stereoselective reduction of β-ketosulfoxides provides a route to β-hydroxysulfoxides. Interestingly, the selectivity is relatively independent of stereochemistry of substituents in the α-position (1,2-asymmetric induction), and is governed almost exclusively by the sulfoxide stereochemistry (1,3-asymmetric induction) (**Scheme 42**).[63] A related reduction using $NaBH_4$ gives the opposite diastereomer with only modest selectivity, but was the



Scheme 42

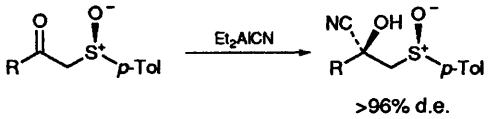


Scheme 43

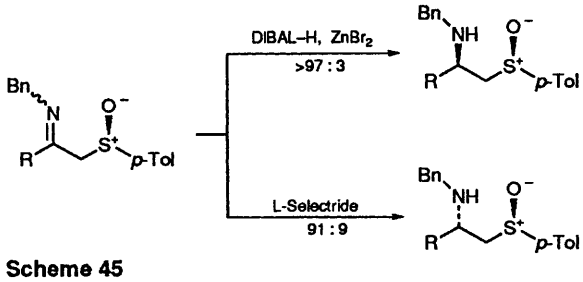
best of a number of other reducing agents tried (**Scheme 43**).[64]

The addition of diethylaluminium cyanide to β-ketosulfoxides shows very high levels of stereocontrol. Again 1,3-asymmetric induction is the dominant factor in controlling stereochemistry (**Scheme 44**).[65]

Condensation of a β-ketosulfoxide with benzylamine gives a β-iminosulfoxide, which can be reduced with DIBAL/$ZnBr_2$ with almost full stereocontrol to give the β-aminosulfoxide.[66] Reduction using L-Selectride gives almost complete reversal of selectivity (**Scheme 45**).

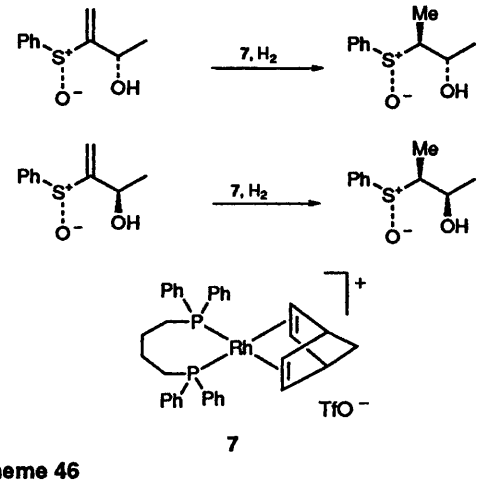


Scheme 44



Scheme 45

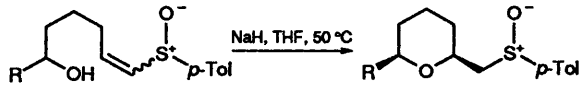
Hydrogenation of α-(hydroxyalkyl) vinyl sulfoxides with the rhodium complex **7** provides excellent stereocontrol at the new chiral centre, directed exclusively by the sulfoxide rather than hydroxyl group. This is illustrated by reduction of two diastereomeric substrates, differing in stereochemistry at the hydroxyl group but not the sulfoxide. Hydrogenation gives identical stereochemistry at the α-position for both compounds (**Scheme 46**).[67]



7

Scheme 46

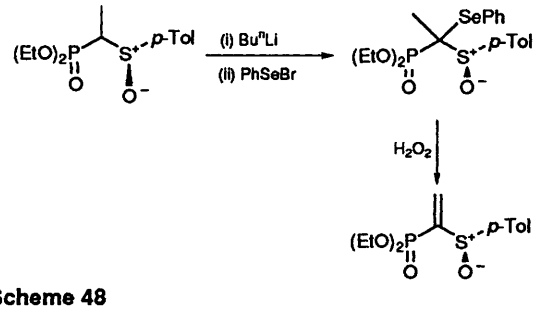
Intramolecular nucleophilic addition of alkoxides to vinylsulfoxides provides a route to β-alkoxysulfoxides. The *cis*-product is formed with up to 18:1 selectivity (**Scheme 47**).[68]



Scheme 47

3.2.3 Unsaturated sulfoxides

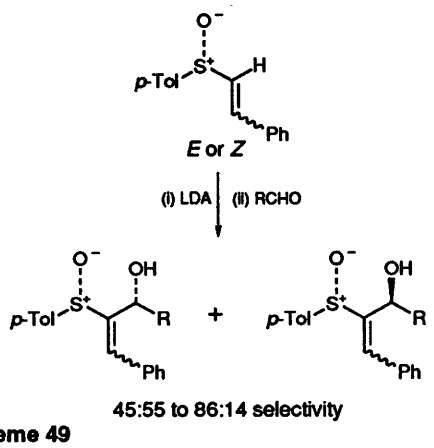
The synthesis of unsaturated sulfoxides using selenoxide elimination methodology has been used for the preparation of (+)-(*S*)-α-diethoxyphosphorylvinyl *p*-tolyl sulfoxide, a new chiral Michael acceptor and dienophile. Introduction of the selenide moiety is carried out by lithiation α-to the sulfoxide and quenching with phenylselenyl bromide. Oxidation to the selenoxide is then carried out using H_2O_2, with elimination to the vinylsulfoxide following rapidly (**Scheme 48**).[69]



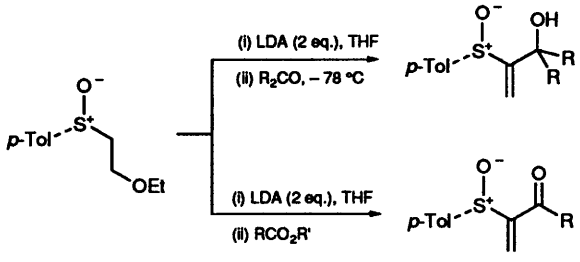
Scheme 48

The α-lithiation of vinylsulfoxides forms anions which are configurationally unstable, but react with electrophiles to give predominantly the *E*-isomer. Use

of an aldehyde as electrophile gives poor to good selectivity (**Scheme 49**).[70] An alternative to this process involves lithiation of a β-alkoxy sulfoxide followed by quenching with a carbonyl electrophile and β-elimination, resulting in a one-pot synthesis of 1-acyl- and 1-hydroxyalkyl-vinylsulfoxides (**Scheme 50**).[71] The starting material is readily prepared by addition of sodium ethoxide to *p*-tolyl vinyl sulfoxide.

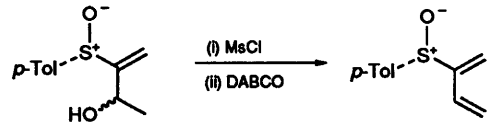


Scheme 49



Scheme 50

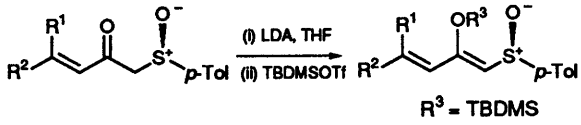
The products of such a reaction using acetaldehyde as the electrophile, can be dehydrated to give 'remarkably stable' 2-sulfinyl butadienes (**Scheme 51**).[72]



Scheme 51

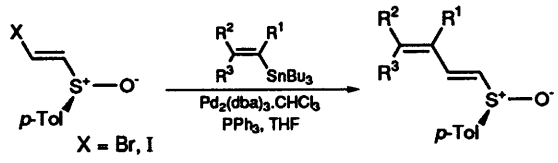
Similarly, the products of ester condensation can be converted into their trimethylsilyl enol ethers to form 2-sulfinyl-3-trimethylsilyloxy butadienes (**Scheme 52**). 1-Sulfinyl-2-t-butyldimethylsilyloxy butadienes have also been prepared using related methodology (**Scheme 53**).[73]

Scheme 52



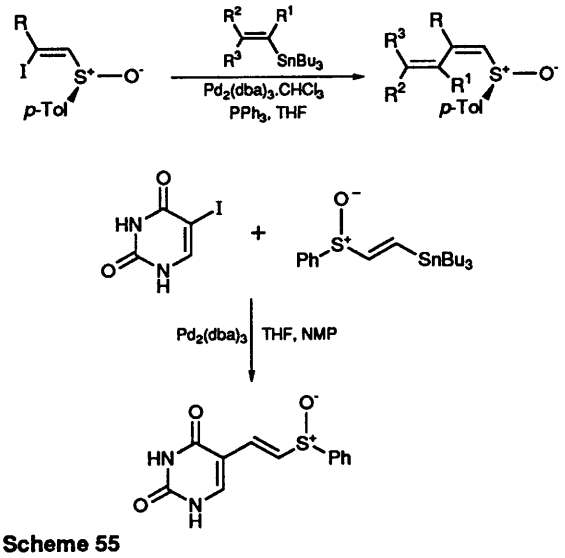
Scheme 53

The palladium-catalysed cross-coupling reaction of vinyl stannanes with β-halovinyl sulfoxides provides a route for the stereocontrolled synthesis of 1-sulfinyl butadienes (**Scheme 54**).[74] The stereochemistry of the halogen is retained in the product. A stereoselective route to *Z*-2-haloalkenyl sulfoxides by addition of zinc halides or sodium iodide to alkynyl sulfoxides enhances the synthetic utility of the cross-coupling procedure.[75]



Scheme 54

1-Sulfinyl-2-tributylstannyl alkenes have coupled with vinyl iodides, derived from nucleic acid bases, in a new approach to thymidylate synthetase inhibitors (**Scheme 55**). Again, full control over double bond geometry is possible.[76]



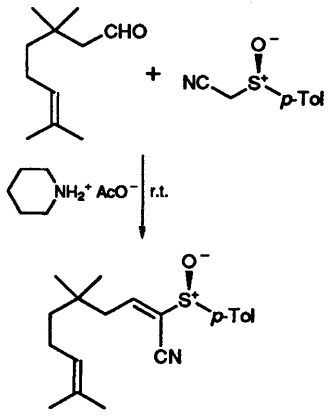
Scheme 55

Condensation of sulfoxide-stabilized carbanions with aldehydes has been used for the synthesis of unsaturated sulfoxides containing additional electron-withdrawing groups. These are of use as chiral dienophiles, enophiles, and Michael acceptors (**Schemes 56** and **57**).[77,78]

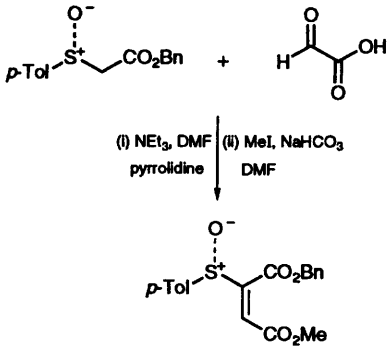
4 Synthesis of sulfones

4.1 Oxidation of sulfides

New procedures for the oxidation of sulfides to sulfones have been reported. A simple and efficient



Scheme 56



Scheme 57

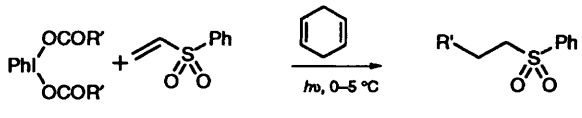
method utilizes a ruthenium tetraoxide catalyst with periodic acid reoxidant in a $CCl_4/CH_3CN/H_2O$ solvent system.[79] A comparison of peroxymolybdenum complexes for this oxidation has shown that $MoO_5 \cdot H_2O \cdot HMPA$ is particularly useful, showing good chemoselectivity, allowing the preparation of hydrolytically and acid-sensitive sulfones.[80] Sodium perborate in acetic acid is reported to be a good oxidizing agent for the preparation of electron-deficient sulfones by oxidation of the appropriate sulfide.[81]

4.2 Non-oxidative sulfone synthesis

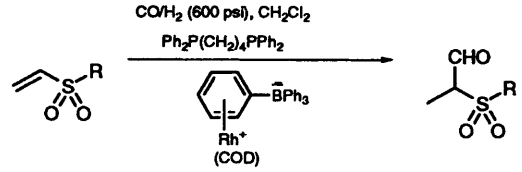
4.2.1 General methods for sulfone synthesis

The reductive addition of alkyl radicals to vinyl sulfones has been demonstrated. Photolysis of iodonium carboxylates generates the radical which, in the presence of a hydrogen atom donor, adds to phenyl vinyl sulfone in moderate to excellent yield (**Scheme 58**).[82] The hydroformylation of vinyl sulfones, catalysed by a zwitterionic rhodium complex gives excellent yields of α-formyl sulfones (**Scheme 59**).[83]

Treatment of phenyl alkyl sulfones with two equivalents of base results in lithiation α-to the sulfone

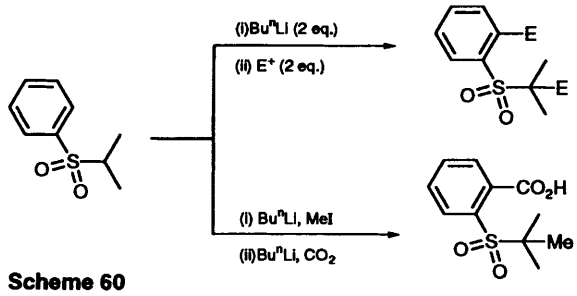


Scheme 58



Scheme 59

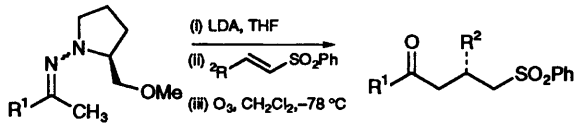
and in the *ortho*-position of the aromatic ring. The resulting dianion can be quenched with electrophiles (alkyl halides, esters, CO_2, and Me_3SiCl) in both positions. Two sequential, one-pot lithiations allows introduction of different electrophiles (**Scheme 60**).[84]



Scheme 60

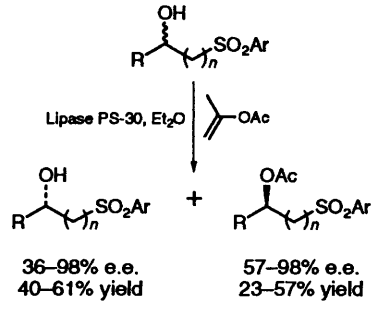
4.2.2 Functionalized sulfones

The asymmetric Michael addition of SAMP/RAMP hydrazones to vinyl sulfoxides leads to the enantioselective synthesis of 2-substituted 4-ketosulfones (**Scheme 61**).[85] High enantioselectivities are obtained in moderate to good overall yields.



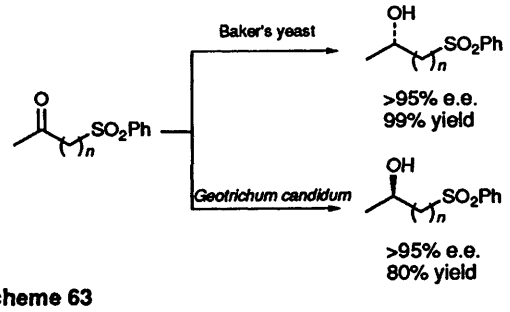
Scheme 61

The lipase PS-30 catalysed acylation of chiral γ- and δ-hydroxy sulfones allows resolution with enantioselectivity in the range 36–98% e.e. Lower selectivity is observed for δ-hydroxy sulfones, and systems containing relatively bulky substituents (R = ethyl, Ar = naphthyl) (**Scheme 62**).[86,87]



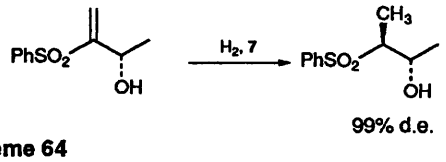
Scheme 62

Microbiological reduction of β- and γ-ketosulfones, using Baker's yeast or a number of other organisms, provides access to β- and γ-hydroxysulfones respectively, with high enantioselectivity and yield. The control of absolute stereochemistry is possible by choice of micro-organism (**Scheme 63**).[88]



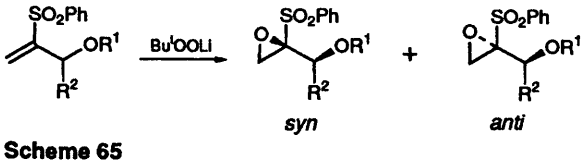
Scheme 63

The stereocontrolled reduction of (α-hydroxyalkyl)vinyl sulfones using the rhodium complex 7 has been reported. The very high levels of selectivity observed are accounted for by coordination of the reducing species to the adjacent hydroxyl group (**Scheme 64**).[67]



Scheme 64

Good levels of stereocontrol have been obtained in the nucleophilic epoxidation of α-(1-hydroxyalkyl)-α,β-unsaturated sulfones using the lithium salt of t-butyl hydroperoxide. On the free alcohol, the *syn*-isomer is favoured, whereas on the triisopropylsilyl ether the *anti*-isomer is predominant (**Scheme 65**).[89]

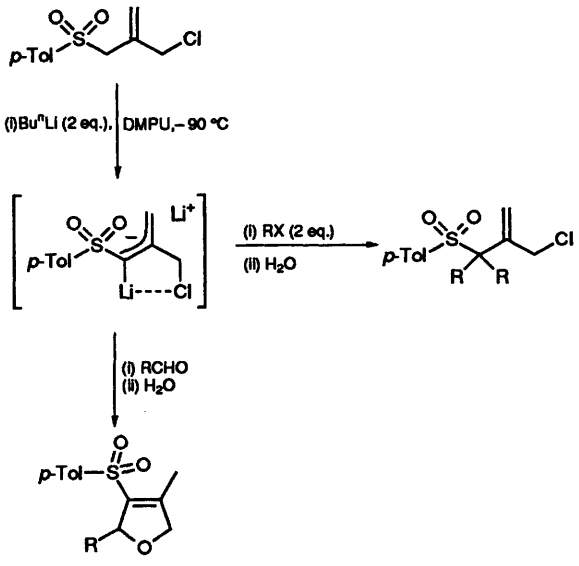


Scheme 65

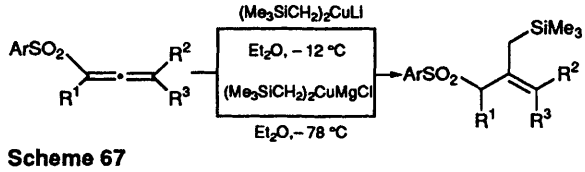
4.2.3 Unsaturated sulfones

Dilithiation of 2-(chloromethyl)-3-*p*-toluenesulfonylpropene allows introduction of electrophiles α-to the sulfone group in moderate yields. Use of carbonyl electrophiles provides direct access to 3-sulfonyl-2,5-dihydrofurans by intramolecular displacement of chloride (**Scheme 66**).[90]
A considerable number of other allyl sulfones have been prepared by simple displacement of chloride from the same starting material.[91]

3-Arylsulfonyl-2-[(trimethylsilyl)methyl]alkenes can be readily prepared by reaction of (trimethylsilyl)methyl cuprates with the appropriate 1-(arylsulfonyl)alka-1,2-dienes (**Scheme 67**).[92]
The addition of sodium *p*-toluenesulfonate and iodine to terminal alkynes provides a route to

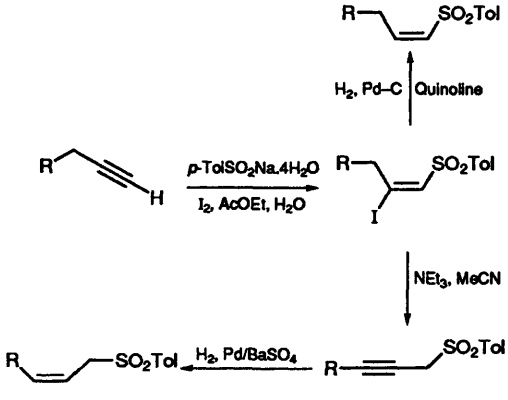


Scheme 66



Scheme 67

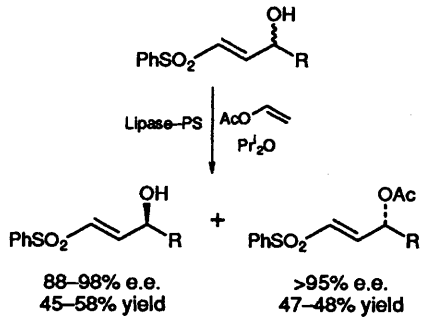
E-2-iodo-1-tosyl-1-alkenes with full control of double bond geometry. These useful intermediates can be converted into *Z*-vinyl sulfones by reductive de-iodination, and into propargyl- and *Z*-allyl sulfones by elimination and subsequent stereocontrolled hydrogenation, respectively (**Scheme 68**).[93]



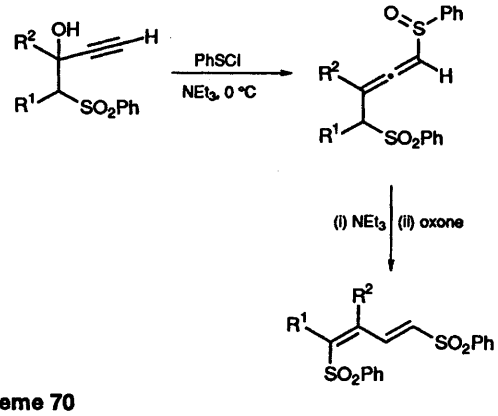
Scheme 68

The resolution of γ-hydroxy-α,β-unsaturated phenyl sulfones using lipase from *Pseudomonas cepacia* proceeds with high enantioselectivity and yield with a variety of substrates (**Scheme 69**).[87]

The 2,3-sigmatropic rearrangement of β-sulfonyl alkynyl carbinols allows access to 1,4-bis(phenylsulfonyl)-1,3-butadienes after subsequent, further oxidation (**Scheme 70**).[94]
A stereoselective route to *E*-(phenylsulfonyl)enynes using vinyl sulfone chemistry has been reported. Treatment of a sulfone anion with an acetylenic

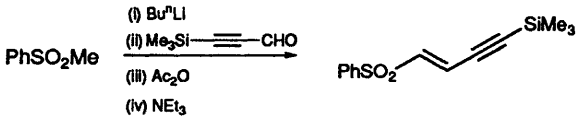


Scheme 69



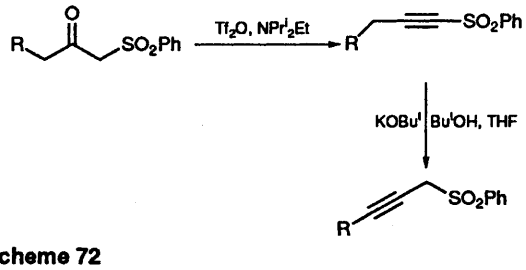
Scheme 70

aldehyde, followed by dehydration, selectively gives the trimethylsilyl (or t-butyldimethylsilyl) protected alkyne (**Scheme 71**).[95]



Scheme 71

Alkynyl sulfones may be prepared by dehydration of β-ketosulfones. The triple bond may then be moved out of conjugation with the sulfone by equilibration using catalytic potassium t-butoxide in t-butanol/THF (**Scheme 72**).[96]



Scheme 72

5 References

1 P.C.B. Page, S.S. Klair, M.P. Brown, C.S. Smith, S.J. Maginn, and S. Mulley, *Tetrahedron*, 1992, **48**, 5933.
2 J.M. Khurana and P.K. Sahoo, *Synth. Commun.*, 1992, **22**, 1691.
3 A.N. Nedugov and N.N. Pavlova, *Zh. Org. Chim*, 1992, **28**, 1401.
4 J. Drabowicz, B. Dudzinski, and M. Mikolajczyk, *Synlett*, 1992, 252.
5 G.A. Olah, Q. Wang, N.J. Trivedi, and G.K.S. Prakash, *Synthesis*, 1992, 465.
6 G.A. Olah, Q. Wang, X. Li, and G.K.S. Prakash, *Synlett*, 1993, 32.
7 A.R. Katritzky, L. Xie, A.S. Afridi, W.-Q. Fan, and W. Kuzmierkiewicz, *Synthesis*, 1993, 47.
8 E.J. Corey and K.A. Cimprich, *Tetrahedron Lett.*, 1992, **33**, 4099.
9 M. Chini, P. Crotti, E. Giovani, F. Macchia, and M. Pineschi, *Synlett*, 1992, 303.
10 H. Takeuchi, K. Kitajima, Y. Yamamoto, and K. Mizuno, *J. Chem. Soc., Perkin Trans. II*, 1993, 199.
11 C.M. Rayner, A.D. Westwell, and M.S. Sin, *Tetrahedron Lett.*, 1992, **33**, 7237.
12 S. Takano, Y. Sugihara, and K. Ogasawara, *Synlett*, 1992, 668.
13 K. Kudo, Y. Hashimoto, M. Sukegawa, M. Hasegawa, and K. Saigo, *J. Org. Chem.*, 1993, **58**, 579.
14 K. Kudo, Y. Hashimoto, H. Houchigai, M. Hasagawa, and K. Saigo, *Bull. Chem. Soc. Jpn*, 1993, **66**, 848.
15 R. Koster and R. Kucznierz, *Liebigs Ann. Chim.*, 1992, 835.
16 U. Groth, T. Huhn, and N. Richter, *Liebigs Ann. Chim.*, 1993, 49.
17 C. Goux, P. Lhoste, and D. Sinou, *Tetrahedron Lett.*, 1992, **33**, 8099.
18 S.-C. Tsay, L.C. Lin, P.A. Furth, C.C. Shum, D.B. King, S.F. Yu, B.-L. Chen, and J.R. Hwu, *Synthesis*, 1993, 329.
19 C.-J. Li and D.N. Harpp, *Tetrahedron Lett.*, 1992, **33**, 7293.
20 A. Capperucci, M.C. Ferrara, A. Degl'Innocenti, B.F. Bonini, G. Mazzanti, P. Zani, and A. Ricci, *Synlett*, 1992, 880.
21 A. Degl'Innocenti, P. Ulivi, A. Capperucci, A. Mordini, G. Reginato, and A. Ricci, *Synlett*, 1992, 499.
22 V. Fiandanese and L. Mazzone, *Tetrahedron Lett.*, 1992, **33**, 7067.
23 S. Takano, Y. Sugihara, and K. Ogasawara, *Tetrahedron Lett.*, 1993, **34**, 845.
24 Y. Kataoka, J. Miyai, M. Tezuka, M. Takai, and K. Utimoto, *J. Org. Chem.*, 1992, **57**, 6796.
25 K. Narasaka, T. Shibata, and Y. Hiyashi, *Bull. Chem. Soc. Jpn*, 1992, **65**, 2825.
26 E. Busi, G. Capozzi, S. Menichetti, and C. Nativi, *Synthesis*, 1992, 643.
27 H.L. Holland, L. Contreras, and E.S. Raterni, *Synth. Commun.*, 1992, **22**, 1473.
28 E.A. Schmittling and J.S. Sawyer, *J. Org. Chem.*, 1993, **58**, 3229.
29 T. Mukaiyama and K. Suzuki, *Chem. Lett.*, 1993, 1.
30 M. Shimazaki, M. Takahashi, H. Komatsu, A. Ohta, and Y. Komada, *Synthesis*, 1992, 555.
31 S.T. Kobanyane and D.G. MaGee, *Can. J. Chem.*, 1992, **70**, 2758.
32 A.L. Braga, A. Reckziegel, P.H. Menezes, and H.A. Stefani, *Tetrahedron Lett.*, 1993, **34**, 393.
33 J.H. Acquaye, J.G. Muller, and K.F. Takeuchi, *Inorg. Chem.*, 1993, **32**, 160.
34 B.M. Chondary and S.S. Rani, *J. Mol. Catal.*, 1992, **75**, L7.
35 H. Firouzabadi and I. Mohammadpour-Baltork, *Bull. Chem. Soc. Jpn*, 1992, **65**, 1131.
36 R. Balicki, L. Kaczmarek and P. Nantka-Namirski, *Liebigs Ann. Chim.*, 1992, 883.
37 R.P. Greenhalgh, *Synlett*, 1992, 235.
38 J. Bartulin, C. Franco, A. Ramirez, and H. Zunza, *Bol. Soc. Chil. Quim.*, 1992, **37**, 203; *Chem. Abstr.*, 1992, **118**, 212524d.

39 H.E. Folson and J. Castrillon, *Synth. Commun.*, 1992, **22**, 1799.
40 E.L. Clennan and K. Yang, *Tetrahedron Lett.*, 1993, **34**, 1697.
41 Y. Arai and T. Koizumi, *Rev. Heteratom Chem.*, 1992, **6**, 202.
42 R. Breitschuh and D. Seebach, *Synthesis*, 1992, **11**, 1170.
43 S. Colonna, N. Gaggero, and P. Pasta, *NATO ASI Ser., Ser. C*, 1992, **381** (Microbiol. reag. in Org. Synth.), 323.
44 S. Inoue, T. Aida, and K. Konishi, *J. Mol. Catal.*, 1992, **74**, 121.
45 F.A. Davis, R.T. Reddy, W. Han, and R.E. Reddy, *Pure Appl. Chem.*, 1993, **65**, 633.
46 F.A. Davis, M.C. Weissmiller, C.K. Murphy, R.T. Reddy, and B.-C. Chen, *J. Org. Chem.*, 1992, **57**, 7274.
47 C. Rossi, A. Fauve, M. Madesclaire, D. Roche, F.A. Davis, and R.T. Reddy, *Tetrahedron Asymm.*, 1992, **3**, 629.
48 K. Maruyama, Y. Watanabe, and F. Tani, *Jpn. Kokai Tokkyo Koho JP*, 04,169,567; *Chem. Abstr.*, 1993, **118**, P124200q.
49 M. Palucki, P. Hanson, and E.N. Jacobsen, *Tetrahedron Lett.*, 1992, **33**, 7111.
50 N. Komatsu, Y. Nishibayashi, T. Sugita, and S. Uemura, *Tetrahedron Lett.*, 1992, **33**, 5391.
51 H. Fu, H. Kondo, Y. Ichikawa, G.C. Look, and C.H. Wong, *J. Org. Chem.*, 1992, **57**, 7265.
52 G. Carrea, B. Redigolo, S. Riva, S. Colonna, N. Gaggero, E. Battistel, and D. Bianchi, *Tetrahedron Asymm.*, 1992, **3**, 1063.
53 T. Oida, M. Nakamura, Y. Takashima, and Y. Hayashi, *Bull. Inst. Chem. Res., Kyoto Univ.*, 1992, **70**, 295; *Chem. Abstr.* 1993, **118**, 168 769m.
54 A.J. Walker, *Tetrahedron Asymm.*, 1992, **3**, 961.
55 I. Fernandez, N. Khiar, J.M. Llera, and F. Alcudia, *J. Org. Chem.*, 1992, **57**, 6789.
56 J. Drabowicz, B. Dudzinski, and M. Mikolajczyk, *J. Chem. Soc., Chem. Commun.*, 1992, 1500.
57 D.A. Evans, M.M. Faul, L. Colombo, J.J. Bisaha, J. Clardy, and D. Cherry, *J. Am. Chem. Soc.*, 1992, **114**, 5977.
58 C. Cardellicchio, V. Fiandanese, F. Naso, and A. Scilimati, *Tetrahedron Lett.*, 1992, **33**, 5121.
59 T. Satoh and K. Yamakawa, *Synlett*, 1992, 455.
60 T. Satoh, N. Itoh, K. Onda, Y. Kitoh, and K. Yamakawa, *Bull. Chem. Soc. Jpn*, 1992, **65**, 2800.
61 Y.H. Kim, H.H. Shin, and Y.J. Park, *Synthesis*, 1993, 209.
62 T. Satoh, Y. Hayashi, Y. Mizu, and K. Yamakawa, *Tetrahedron Lett.*, 1992, **33**, 7181.
63 D. Barros, M.C. Carreno, J.L. Garcia Ruano, and M.C. Maestro, *Tetrahedron Lett.*, 1992, **33**, 2733.
64 M. Shimazaki, N. Ichihara, M. Goto, and A. Ohta, *Chem. Pharm. Bull.*, 1992, **40**, 3072.
65 J.L. Garcia Ruano, A.A. MartinCastro, and J.H. Rodriguez, *J. Org. Chem.*, 1992, **57**, 7235.
66 J.L. Garcia Ruano, A. Lorente, and J.H. Rodriguez, *Tetrahedron Lett.*, 1992, **33**, 5637.
67 D. Ando, C. Bevan, J.M. Brown, and D.W. Price, *J. Chem. Soc., Chem. Commun.*, 1992, 592.
68 T. Mandai, M. Ueda, K. Kashiwagi, M. Kawada, and J. Tsuji, *Tetrahedron Lett.*, 1993, **34**, 111.
69 M. Mikolajczyk and W.H. Midura, *Tetrahedron Asymm.*, 1992, **3**, 1515.
70 J. Fawcett, S. House, P.R. Jenkins, N.J. Lawrence, and D.R. Russell, *J. Chem. Soc., Perkin Trans. I*, 1993, 67.
71 C. Alexandre, O. Belkadi, and C. Maignan, *Synthesis*, 1992, 547.
72 E. Bonfand, P. Gosselin, and C. Maignan, *Tetrahedron Lett.*, 1992, **33**, 2347.
73 G. Solladie, N. Maugein, I. Morreno, A. Almario, M. Carmen, and J.L. Garcia Ruano, *Tetrahedron Lett.*, 1992, **33**, 4561.
74 R.S. Paley, A. de Dios, and R. Fernandez de la Pradilla, *Tetrahedron Lett.*, 1993, **34**, 2429.
75 R. Fernandez de la Pradilla, M. Morente, and R.S. Paley, *Tetrahedron Lett.*, 1992, **33**, 6101.
76 V. Farina and R.A. Firestone, *Tetrahedron*, 1993, **49**, 803.
77 K. Hiroi and M. Umemura, *Tetrahedron*, 1993, **49**, 1831.
78 I. Alonso, J.C. Carretero, and J.L. Garcia Ruano, *J. Org. Chem.*, 1993, **58**, 3231.
79 C.M. Rodriguez, J.M. Ode, J.M. Palazon, and V.S. Martin, *Tetrahedron*, 1992, **48**, 3571.
80 G. Keilen, T. Benneche, K. Gaare, and K. Undheim, *Acta Chem. Scand.*, 1992, **46**, 867.
81 G.O. Page, *Synth. Commun.*, 1993, **23**, 765; see also J.E. Brumwell, N.S. Simpkins, and N.K. Terrett, *Tetrahedron Lett.*, 1993, **34**, 1219.
82 H. Togo, M. Aoki, and M. Yokoyama, *Chem. Lett.*, 1993, 2169.
83 K. Totland and H. Alper, *J. Org. Chem.*, 1993, **58**, 3326.
84 M.G. Cabiddu, S. Cabiddu, C. Fattuoni, C. Floris, G. Gelli, and S. Melis, *P, S, Si, and rel. elem.*, 1992, **70**, 139.
85 D. Enders, K. Papadopoulos, and E. Herdtweck, *Tetrahedron*, 1993, **49**, 1821.
86 H.K. Jacobs, B.H. Mueller, and A.S. Gopalan, *Tetrahedron*, 1992, **48**, 8891.
87 J.C. Carretero and E. Dominguez, *J. Org. Chem.*, 1992, **57**, 3867.
88 S. Robin, F. Huet, A. Fauve, and H. Veschambre, *Tetrahedron Asymm.*, 1993, **4**, 239.
89 R.F.W. Jackson, S.P. Standen, W. Clegg, and A. McCamley, *Tetrahedron Lett.*, 1992, **33**, 6197.
90 K. Najera and J.M. Sansano, *Tetrahedron Lett.*, 1992, **33**, 6543.
91 K. Najera and J.M. Sansano, *Tetrahedron*, 1992, **48**, 5179.
92 M. Harmata and B.F. Herron, *Synthesis*, 1993, 202.
93 N. Iwata, T. Morioka, T. Kobayashi, T. Asada, H. Kinoshita, and K. Inomata, *Bull. Chem. Soc. Jpn*, 1992, **65**, 1379.
94 Z. Ni, X. Wang, A. Rodriguez, and A. Padwa, *Tetrahedron Lett.*, 1992, **33**, 7303.
95 A.B. Holmes and G.R. Pooley, *Tetrahedron*, 1992, **48**, 7775.
96 M.C. Clasby and D. Craig, *Synlett*, 1992, 825.