REVIEW

The synthesis of thiols, selenols, sulfides, selenides, sulfoxides, selenoxides, sulfones and selenones

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1 Introduction

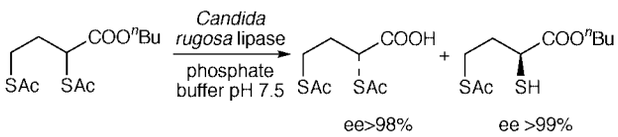
This review continues a series that began in 1994 and deals with new approaches to the synthesis of thiols and selenols, disulfides and diselenides, sulfides and selenides, sulfoxides and selenoxides, and sulfones and selenones. Each section begins by dealing with general routes or reactions that give simple, unfunctionalised compounds, before dealing with processes that give products with greater functionality. Within each section, reactions have been ordered, in the main, according to reaction type although on occasion reactions that give a particular class of products have been collected together. Cyclic systems are covered alongside analogous acyclic systems.

As with previous reviews in the series, emphasis has been placed on new reactions and strategies, stereo- and enantioselective reactions, and emerging areas of interest such as solid phase chemistry including solid-supported reagents.

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

2.1 Preparation of thiols, disulfides, selenols and diselenides

Thiols are commonly prepared by the reduction of disulfides. An efficient approach to thiols by reduction of dialkyl and diaryl disulfides with tributylphosphine in DMF and water has been reported.[1] The reduction of aromatic sulfonyl chlorides with zinc, dimethylsilane and dimethylacetamide also provides access to aryl thiols.[2] Thioacetates are common precursors to thiols and an improved route to thiols *via* the reaction of alkyl halides with potassium thioacetate followed by hydrolysis has been developed.[3] The *in situ* generation of thiols from thioacetates has been achieved using pyrrolidine in a variety of solvents.[4] Enzymatic hydrolysis of the thioacetate group has been used to prepare enantiomerically pure thiols. For example, *Candida rugosa* lipase has been found to enantioselectively and regiospecifically hydrolyse 2,4-bis(thioacetyl)butanoic acid butyl ester either at the ester group or at the α-thioacetate. Both products are isolated in excellent enantiomeric excess and have been utilised in a route to both enantiomers of α-lipoic acid (Scheme 1).[5]



Scheme 1

Efficient protection of thiols can often be problematic. The 2-thioquinoline group has been employed as a masked thiol. The group can be introduced by simple nucleophilic displacement and is removed by reduction with sodium cyanoborohydride in the presence of acetic acid (Scheme 2).[6] The 2-thioquinoline sulfide group is stable to various nucleophiles, acidic and basic conditions, and to mild oxidising agents. Two new allylic protecting groups for thiols have been developed. The allyloxycarbonylaminomethyl (Allocam) protecting group is introduced under acidic conditions and can be removed *via* palladium catalysed hydrostannolysis. Unfortunately, under the conditions of deprotection, the product is isolated as the symmetrical disulfide, and the thiol must subsequently be regenerated (Scheme 3).[7] The [*N*-(2,3,5,6-tetrafluoro-4-piperidinophenyl)-*N*-allyloxycarbonyl]aminomethyl (Fnam) group shows considerably more potential as both protection and deprotection steps are convenient, and the group is more stable to both acidic and basic conditions (Scheme 4).[8]

Benzylic thiols with electron-rich aromatic rings have been prepared by the reaction of the corresponding benzyl alcohols with thiourea under acid conditions followed by base hydrolysis of the intermediate isothiouronium salts.[9] The reaction of alkenylthiazolines with benzeneselenenyl bromide and aqueous base gives lactams possessing both phenylselanyl and thiol groups (Scheme 5).[10] A new family of potent yet selective inhibitors of matrix metalloproteinases containing a γ-sulfone thiol moiety have recently been developed.[11]

The preparation of C_2-symmetrical 2,2′-dimercapto-6,6′-dimethoxy-1,1′-biphenyl has been reported and the racemic

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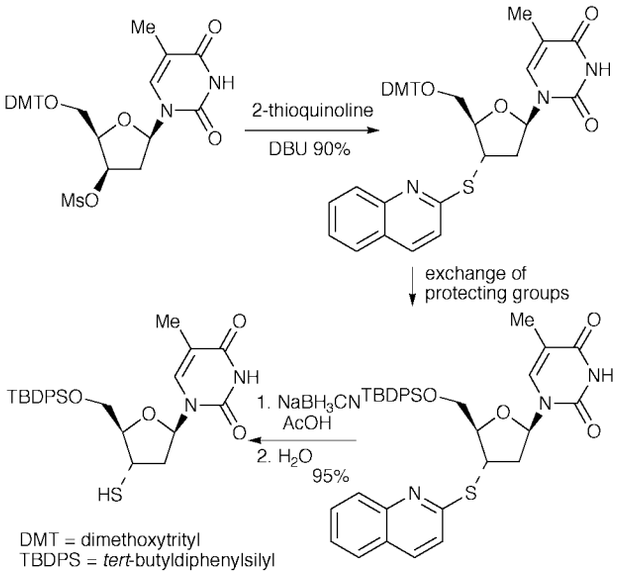
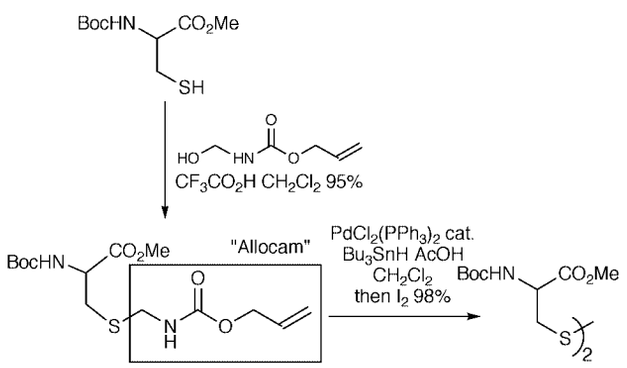
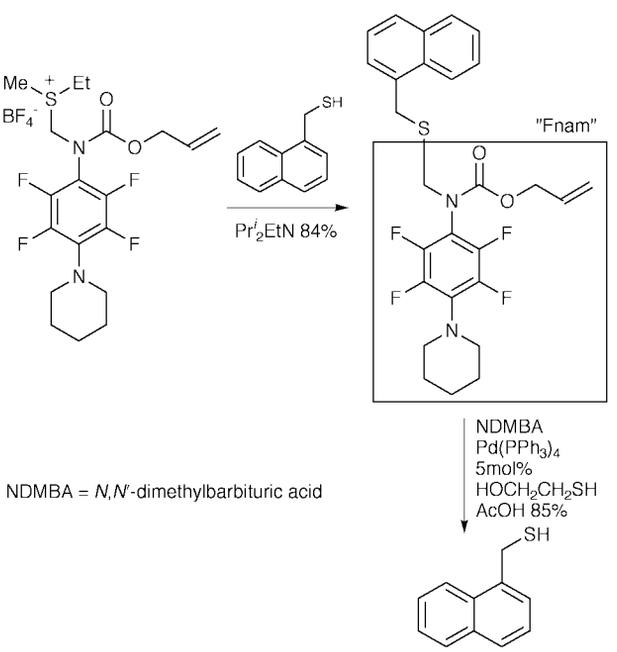


Scheme 2

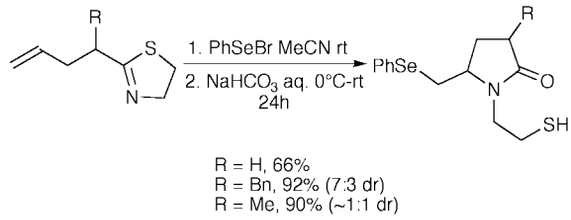


Scheme 3

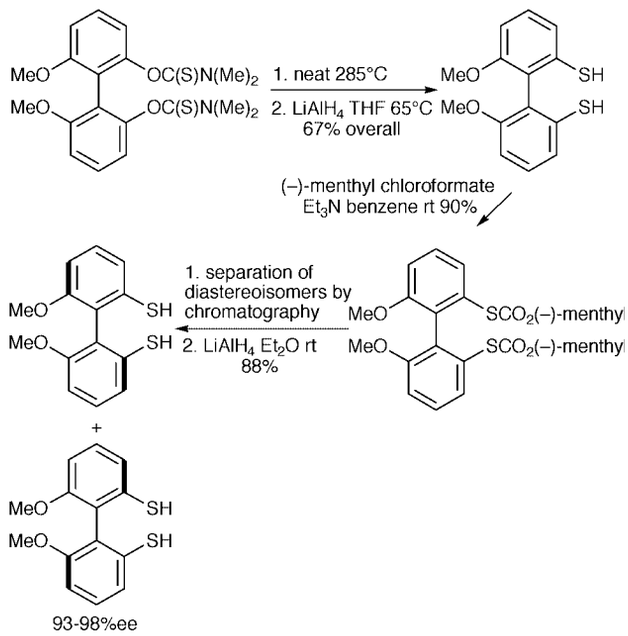


Scheme 4

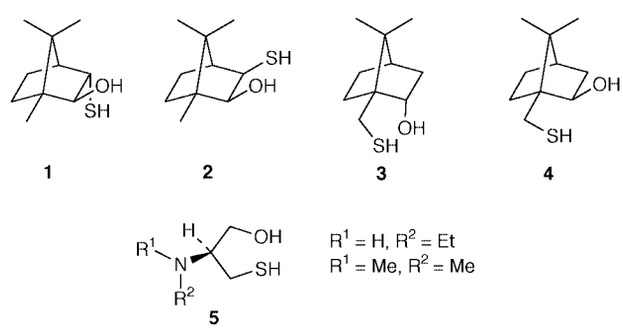
compound resolved by derivatisation with (−)-menthyl chloroformate (Scheme 6).[12] Finally, a variety of enantiomerically pure 1,2- and 1,3-hydroxythiols, **1**–**5**, derived from (*R*)-camphor, (*S*)-(+)-10-camphorsulfonyl chloride and cysteine, have been prepared and evaluated as catalysts in borane ketone



Scheme 5



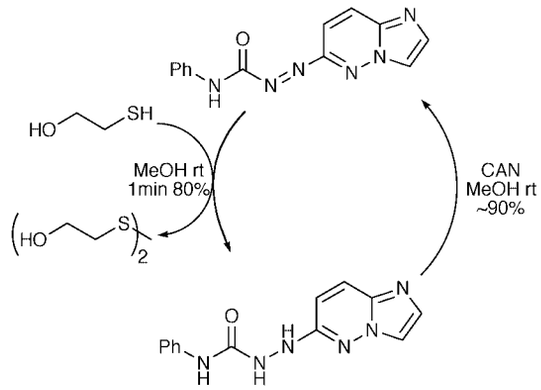
Scheme 6



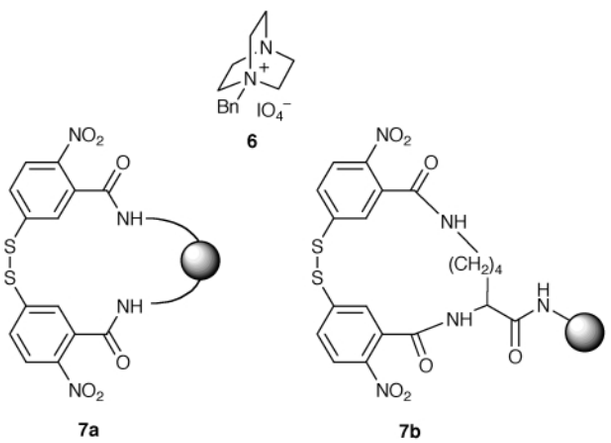
reductions. Under optimised conditions, moderate to good enantioselectivities have been observed.[13]

Symmetrical aryl and alkyl disulfides are readily prepared by the oxidation of the corresponding thiols. New reagent systems for this transformation include permanganate oxidation under heterogeneous conditions;[14] sodium iodate and moist alumina;[15] air oxidation with catalytic iron(III) chloride and sodium iodide;[16] benzyltriphenylphosphonium peroxodisulfate;[17] air oxidation catalysed by hydrotalcite clay;[18] neutral alumina and dimethyl sulfoxide;[19] a basic mineral support under solvent-free conditions;[20] 4-benzyl-1-aza-4-azoniabicyclo[2.2.2]octane periodate **6**;[21] and manganese dioxide or barium manganate under solvent-free conditions.[22] In addition, diazenecarboxamides have been employed in a mild oxidation of alkyl and aryl thiols to disulfides (Scheme 7).[23]

The reduction of arenesulfonyl chlorides, bromides, and sodium arenesulfinates, with samarium metal and Cp_2TiCl_2,[24] and the reduction of alkane- and arenesulfonyl chlorides with tungsten hexachloride with either sodium iodide or zinc powder, give symmetrical disulfides.[25]

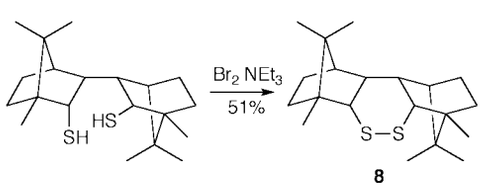


Scheme 7

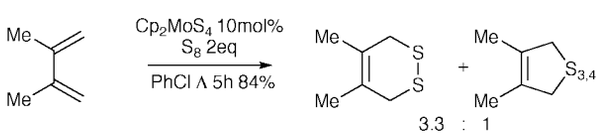


The synthesis of solid-supported Ellman reagents has been reported. Ellman's reagent, 5,5′-dithiobis(2-nitrobenzoic acid), was originally developed to measure the concentration of free thiols in peptides. Novel solid phase Ellman reagents **7a** and **7b** have been prepared and used for the mild formation of disulfide bridges in peptides. Importantly, the solid phase reagent can be readily recovered and reused.[26]

Mild oxidation of a camphor-derived dithiol gave strained, cyclic disulfide **8** in moderate yield (Scheme 8).[27] Cyclic disulfides have also been prepared by the sulfurisation of dienes with elemental sulfur in the presence of a catalytic amount of metallocene polysulfide (Scheme 9).[28]



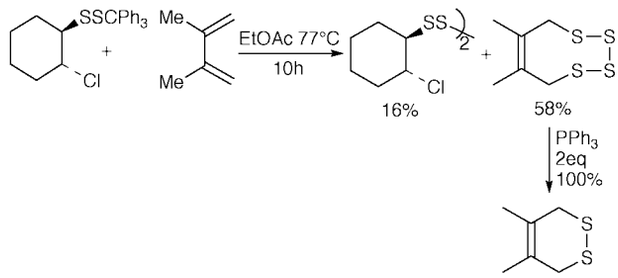
Scheme 8



Scheme 9

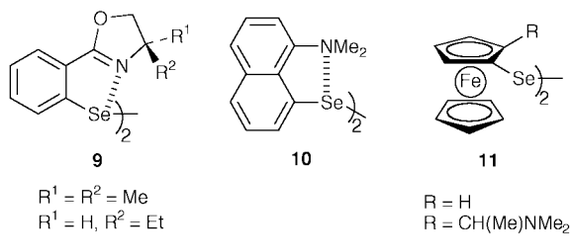
Finally, triphenylmethanesulfenyl chloride, and its dithio analogue, add to reactive olefins to give di- and trisulfides in excellent yield.[29] These compounds transfer diatomic sulfur to dienes to give tetrasulfide adducts as the major products. These adducts can then be quantitatively converted into the corresponding cyclic disulfides (Scheme 10).[29]

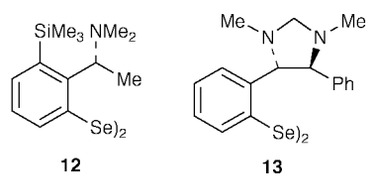
Diselenides and, in particular, enantiomerically pure



Scheme 10

diselenides are most often employed as precursors for electrophilic selenenylating agents. However, diselenides **9**–**11**, having intramolecular Se–N coordination, have been investigated as peroxidase-like antioxidants.[30] Enantiomerically pure diselenides **12** and **13** have been prepared and found to be efficient catalyst precursors for the enantioselective addition of diethylzinc to benzaldehyde.[31] Finally, enantiomerically pure diselenides containing chiral ester and sulfonate groups have been prepared and employed as oxygen transfer catalysts in the hydrogen peroxide oxidation of simple prochiral sulfides. Although yields were high, no enantioselectivity was observed.[32]



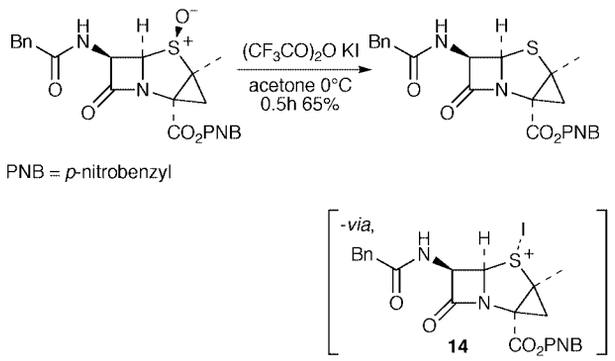


2.2 Synthesis of sulfides and selenides

2.2.1 Simple sulfides and selenides

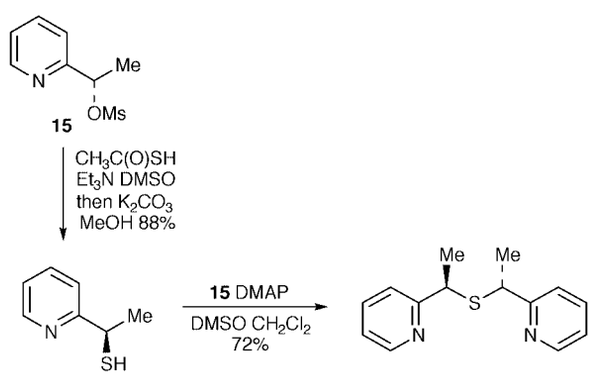
The deoxygenation of sulfoxides perhaps provides the simplest route to sulfides. Tungsten hexachloride and either sodium iodide or zinc powder efficiently deoxygenate diaryl, aryl alkyl, and dialkyl sulfoxides.[25] The mild deoxygenation of methionine sulfoxide residues in peptides has been achieved with ammonium iodide and trifluoroacetic acid.[33] In a sulfoxide-mediated approach to enantiomerically pure aziridines, sulfoxide deoxygenation has been acheived using $BF_3{\cdot}OEt_2$ and sodium iodide.[34] Rapid oxygen transfer from sulfoxides to a carbonyl ligand in a zirconium–ruthenium heterobimetallic cluster has been observed.[35] Finally, the deoxygenation of penam β-sulfoxides with potassium iodide and trifluoroacetic anhydride has been reported.[36] The reaction appears to proceed *via* formation of iodosulfonium intermediate **14**. Interestingly, the rate of reduction is greater for the cyclopropane-containing substrates relative to related sulfoxides having a *gem*-dimethyl group α to sulfur (Scheme 11).[36]

The displacement of leaving groups with sulfur nucleophiles is one of the most common methods for the preparation of sulfides. The selective synthesis of sulfides and disulfides *via* the reduction of elemental sulfur with samarium(II) iodide has recently been described.[37] A related approach has been applied to the synthesis of α-benzotriazol-1-yl sulfides.[38] (*S*)-1-(2-Pyridyl)ethyl methanesulfonate **15** reacts with sulfur nucleophiles with clean inversion of stereochemistry thus allowing the

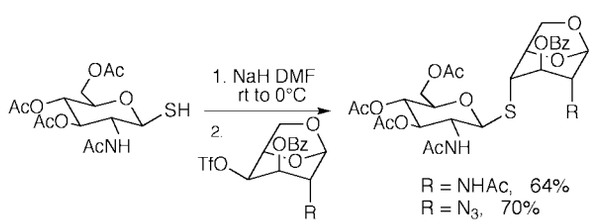


Scheme 11

synthesis of enantiomerically pure C_2-symmetric sulfide ligands (Scheme 12).[39] *S*-Linked thiodisaccharides have been prepared by the reaction of a glucosamide 1-thiolate with 1,6-anhydro-4-*O*-triflyl galactosaminide derivatives (Scheme 13).[40]



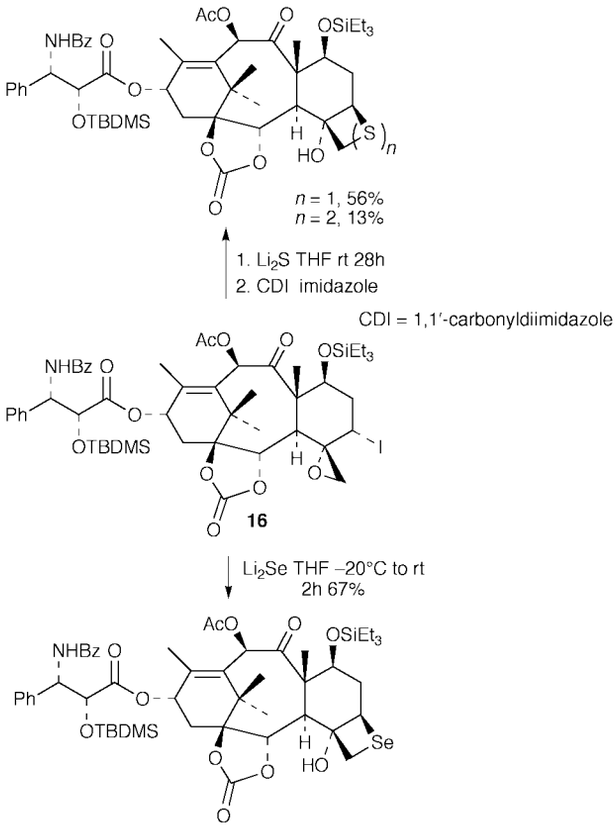
Scheme 12



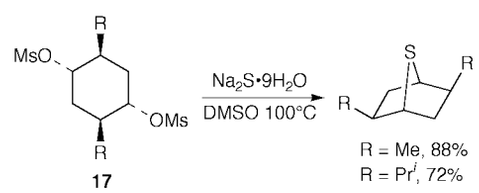
Scheme 13

Strategies of this type are also useful for the formation of cyclic sulfides and selenides. Analogues of paclitaxel have been prepared in which the oxygen atom in the oxetane D-ring has been replaced by sulfur and selenium.[41] The analogues were prepared from the key 4,20-epoxide intermediate **16**, by nucleophilic ring-opening of the epoxide with lithium sulfide or selenide (Scheme 14).[41] Similarly, enantiomerically pure 2,5-dialkyl-7-thiobicyclo[2.2.1]heptanes for use in asymmetric synthesis, have been prepared by nucleophilic addition of sodium sulfide to dimesylates **17** (Scheme 15).[42] A conformationally restricted sulfur-containing, locked nucleic acid (LNA) has been prepared *via* treatment of ditosylate **18** with potassium thioacetate (Scheme 16).[43] The overall retention at the 2′-position suggests that intramolecular displacement by the carbonyl in the base is occurring in a double-inversion process. Thiofuranoside **19** has been prepared and has been assessed as an antiviral agent (Scheme 17).[44]

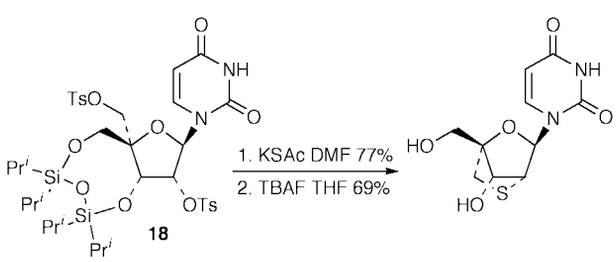
Unsymmetric dialkyl sulfides have recently been prepared using a modified Mitsunobu reaction. The method is effective for primary and secondary thiols but only primary alcohols give satisfactory yields.[45] A new route to pyrrolobenzothiazepine derivatives has been reported which employs inter- and intramolecular Mitsunobu reactions.[46] A related



Scheme 14



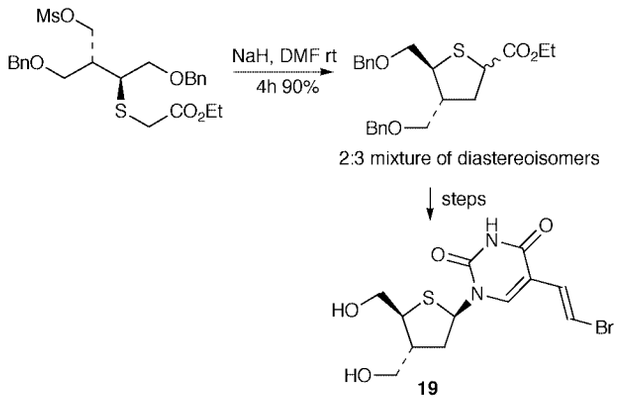
Scheme 15



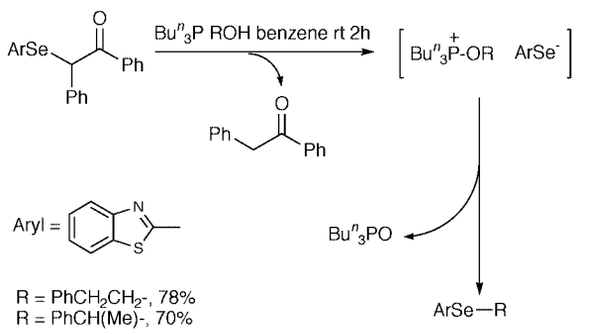
Scheme 16

Mitsunobu-type process has been used for the direct preparation of 2-alkylselenobenzothiazoles from alcohols by treatment with 2-(1,2-diphenyl-2-oxoethylseleno)benzothiazole and a tertiary phosphine (Scheme 18).[47] In an unusual reaction, trichloromethyl compounds are converted into phenylthiomethyl compounds with sodium phenyl thiolate and thiophenol.[48]

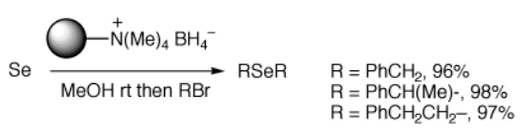
The *in situ* reduction of elemental selenium or diselenides provides access to nucleophilic selenium species which are used extensively for the preparation of selenides. A convenient and odour-free preparation of symmetrical dialkyl selenides using borohydride exchange resin (BER) has been reported (Scheme 19).[49] The reduction of diaryl diselenides with samarium metal and either titanium tetrachloride,[50] trimethylsilyl chloride with a trace amount of water,[51] or mercury(II) chloride,[52] give the corresponding arylselenolates which react with electrophiles to give unsymmetrical aryl alkyl selenides. Two studies detailing the development of polymer bound selenium reagents



Scheme 17



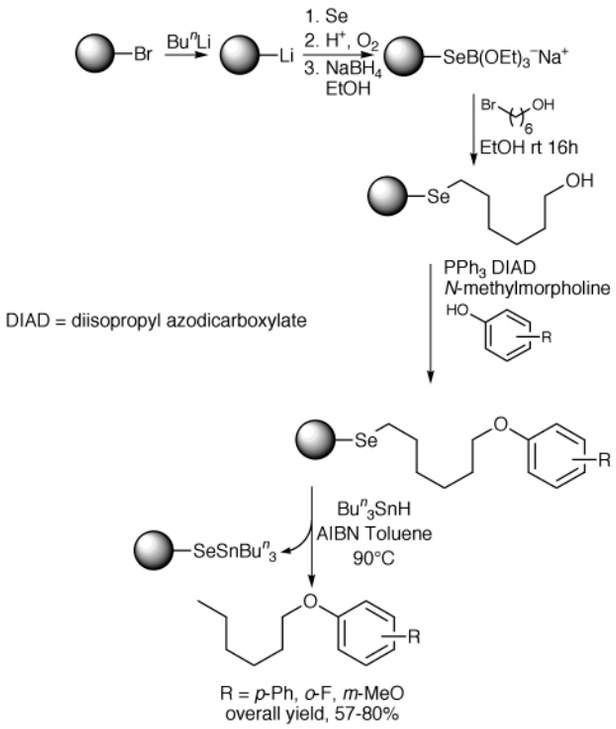
Scheme 18



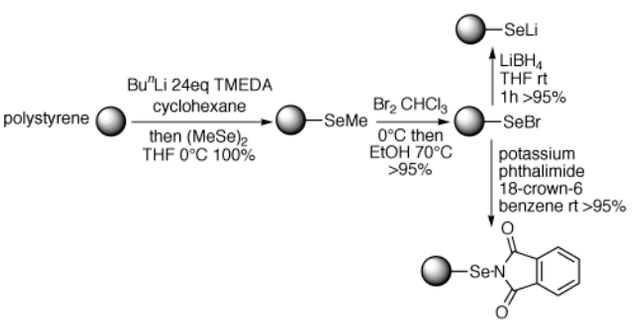
Scheme 19

have recently appeared. Both employ polymer-bound selenium reagents in the formation of linkers which can be cleaved reductively in a traceless fashion, or by oxidation and elimination. In the first case, a polymer-bound selenolate was alkylated to form the linkage in a synthesis of an aryl alkyl ether library (Scheme 20).[53] Although cleavage involves the use of toxic tributyltin hydride, the organotin by-products formed are immobilised on the resin and hence, separation from the products can be readily achieved.[53] In the second more extensive study, several organoselenium resins have been prepared by lithiation of polystyrene beads followed by quenching with dimethyl diselenide. Modification of the methyl selenide resin allows polymer-bound selenenyl bromide, selenium phthalimide, and lithium selenolate reagents to be prepared thus allowing organic substrates to be tethered through these linkers by both electrophilic and nucleophilic processes (Scheme 21).[54]

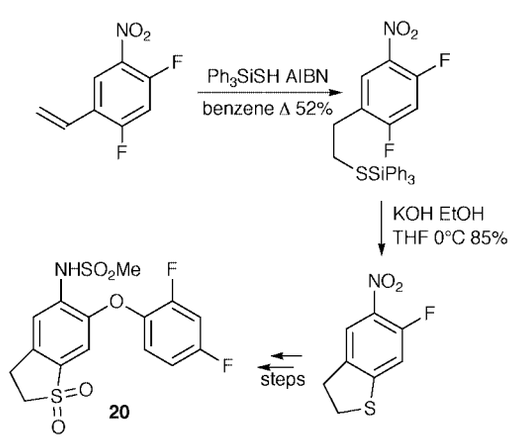
Nucleophilic aromatic substitution with sulfur nucleophiles provides convenient access to diaryl and alkyl aryl sulfides. Potassium fluoride alumina and 18-crown-6 have been used to mediate the addition of aryl thiols to aryl halides.[55] A sulfonyl analogue **20** of the selective cyclooxygenase-2 inhibitor flosulide, has been prepared using a sequence involving the radical addition of triphenylsilanethiol followed by deprotection and nucleophilic aromatic substitution (Scheme 22).[56] In a related reaction, sulfoxide activation has been used to facilitate nucleophilic aromatic substitution in aryl halides (Scheme 23).[57] Diaryl selenides have been prepared by nucleophilic aromatic substitution on η^6-chloroarene transition metal complexes with areneselenolates followed by decomplexation.[58] Diaryl selenides have also been prepared by the reaction of triarylbismuthine reagents with either elemental selenium, to give



Scheme 20



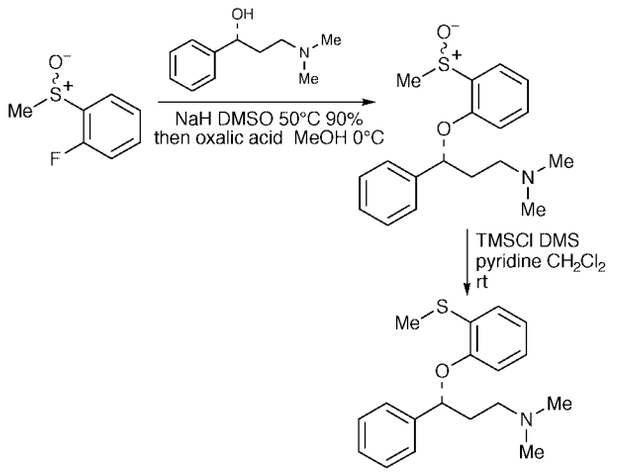
Scheme 21



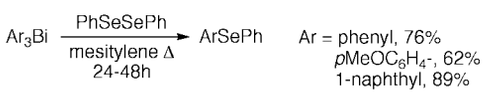
Scheme 22

symmetrical selenides, or diaryl diselenides, to give unsymmetrical selenides (Scheme 24).[59]

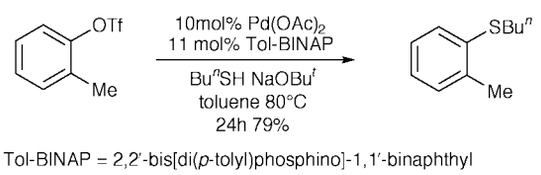
The synthesis of simple aryl alkyl sulfides has been achieved *via* palladium-catalysed cross coupling of sodium alkanethiolates with aryl triflates (Scheme 25).[60] The reaction was found to be effective for a wide range of substituted aryl triflates however, the coupling of arenethiolates under these conditions was unsuccessful.[60] The electrochemical oxidation of disulfides generates reactive sulfenium cations (RS^+) which



Scheme 23



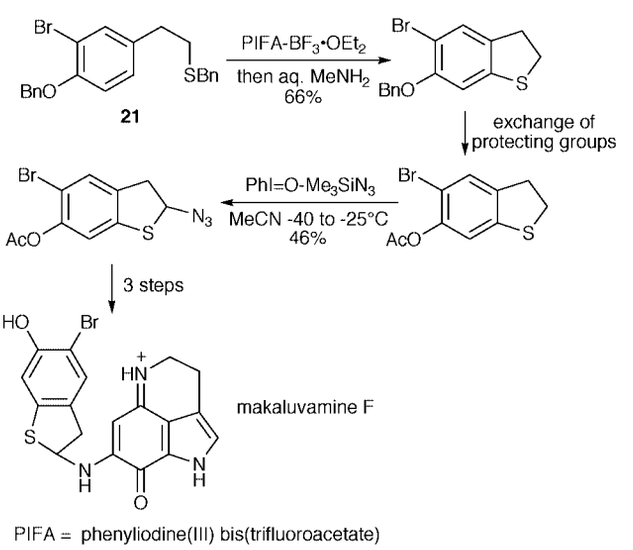
Scheme 24



Tol-BINAP = 2,2′-bis[di(*p*-tolyl)phosphino]-1,1′-binaphthyl

Scheme 25

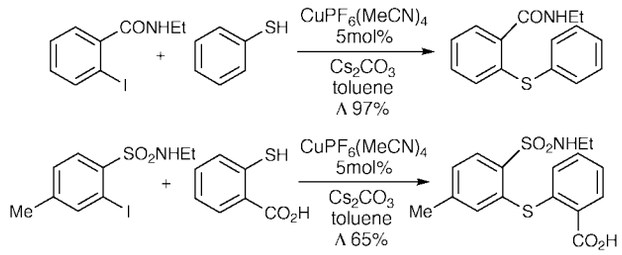
react with phenols, aryl ethers, and ketones to give aryl alkyl sulfides, and β-keto sulfides in moderate yield.[61] The first total synthesis of makaluvamine F, a cytotoxic, sulfur-containing, marine natural product, has been reported and features the cyclisation of benzyl sulfide **21** using phenyliodine(III) bis-(trifluoroacetate) in the presence of boron trifluoride–diethyl ether (Scheme 26).[62]



PIFA = phenyliodine(III) bis(trifluoroacetate)

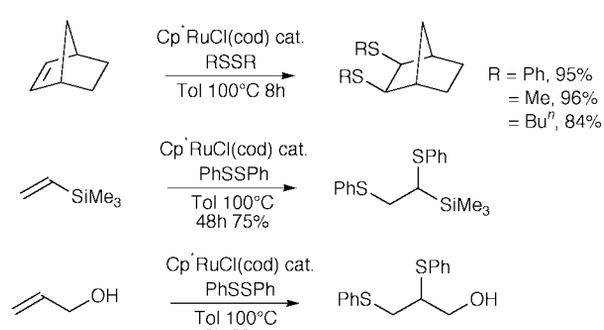
Scheme 26

A new Cu(I)-catalysed variant of the directed *ortho*-metallation–Ullmann coupling reaction has been reported which allows diaryl sulfides to be prepared by the coupling of *ortho*-halo benzamides or sulfonamides with aromatic thiols (Scheme 27).[63] A similar Ullmann coupling reaction has been employed in the synthesis of imidazopyridine sulfides.[64]



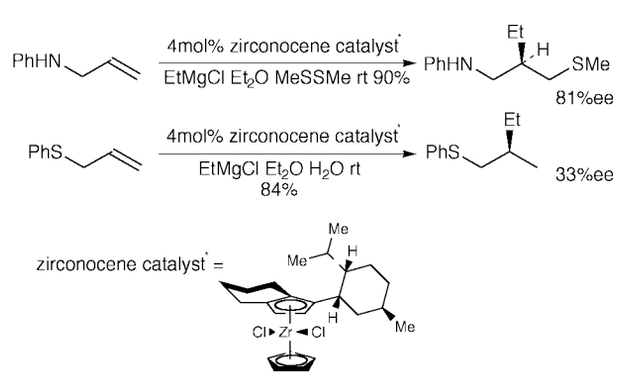
Scheme 27

There is considerable current interest in the development of transition metal systems capable of catalysing the addition of organosulfur and organoselenium species to unsaturated substrates. A recent review article deals with the transition metal catalysed addition of hydrogen–heteroatom, and heteroatom–heteroatom bonds to unsaturated carbon–carbon bonds.[65] In particular, the addition reactions of substrates having P–Se, S–H, S–S, Se–Se, S–Si, Se–Si and Se–Ge, bonds are discussed. The first synthetically useful catalytic system for the preparation of vicinal sulfides from organic disulfides and alkenes has been reported and employs a ruthenium(0) catalyst.[66] Both diaryl and dialkyl disulfides can be used in the reaction but only terminal alkenes and 2-norbornene react efficiently (Scheme 28).[66] Evidence suggests that the reaction proceeds *via* a thiolate-bridged diruthenium complex.



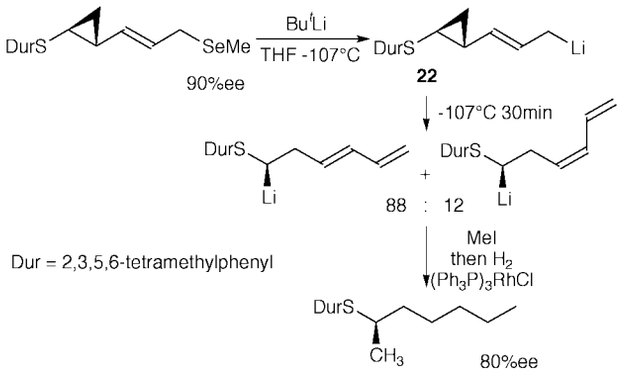
Scheme 28

A novel zirconocene catalyst has been developed for the asymmetric ethylmagnesiation of unactivated terminal alkenes.[67] Using allylic sulfides as the initial substrates, or by using dimethyl disulfide as the electrophile in reactions with other substrates, a variety of sulfides can be prepared in moderate to good enantiomeric excess (Scheme 29).[67]



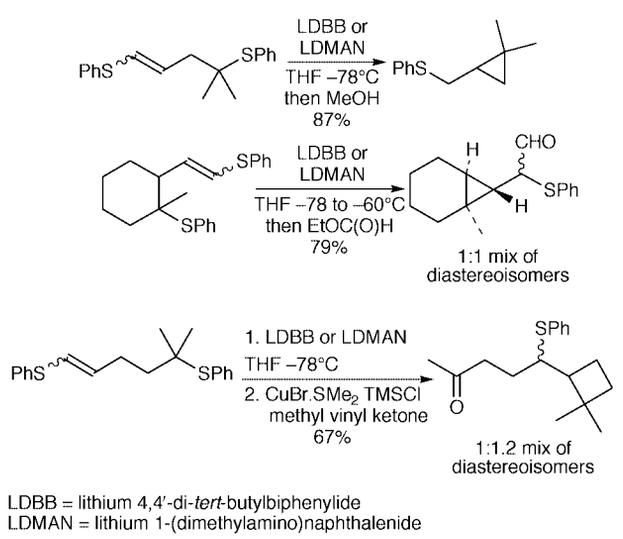
Scheme 29

The retro carbo-lithiation reaction of cyclopropylmethyl lithium **22** has been shown to proceed in a stereochemically defined manner (Scheme 30).[68] The process appears to occur with stereochemical retention in both the cyclopropyl-opening and methylation steps, and gives enantiomerically enriched sulfides in

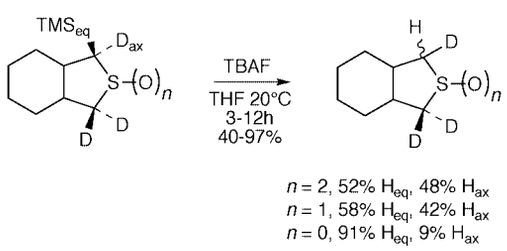


Scheme 30

good yield.[68] In an interesting recent study, the reductive lithiation of 1,4- and 1,5-bis(phenylsulfanyl)-1-alkenes with aromatic radical-anions selectively generates sp^3 carbanions which cyclise efficiently to give phenylsulfanyl stabilised cyclopropyl- and cyclobutylmethyl carbanions (Scheme 31).[69] Sequential processes in which the initially formed anions are quenched with external electrophiles have also been carried out.[69] The configuration stability of carbanions generated by the desilylation of cyclic α-silyl sulfides, sulfoxides and sulfones has been studied.[70] For sulfoxides and sulfones, the intermediate carbanions rapidly invert, leading to a mixture of products. However, sulfides have been shown to undergo protiodesilylation with a significant degree of retention (Scheme 32).[70] The reaction of bissilylated α-lithiomethylphenyl sulfides with 3,4-epoxybutyl tosylate proceeds *via* alkylation, a 1,4-Brook rearrangement to regenerate a sulfur stabilised carbanion, and a second alkylation to give sulfur-containing cyclopentenols (Scheme 33).[71]

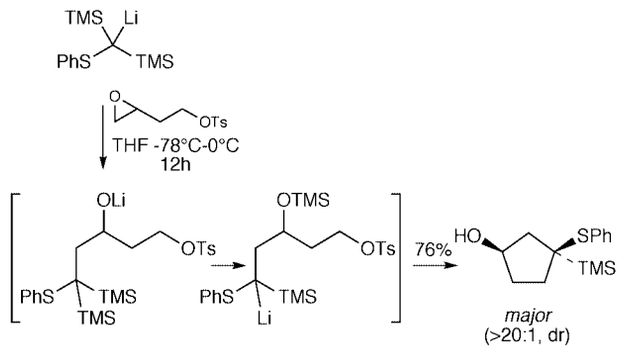


Scheme 31



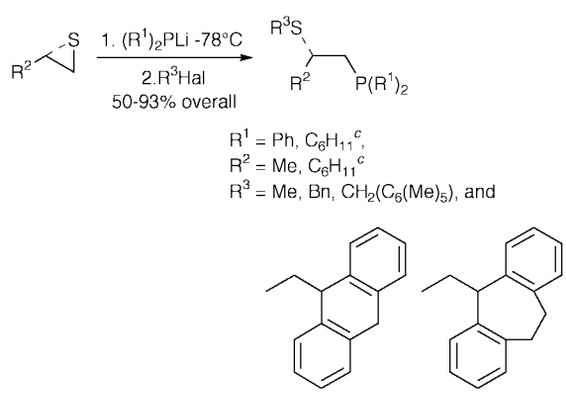
Scheme 32

Thiiranes are useful intermediates for the synthesis of sulfur-containing molecules. For example, the regioselective ring-opening of thiiranes with phosphorous nucleophiles has been



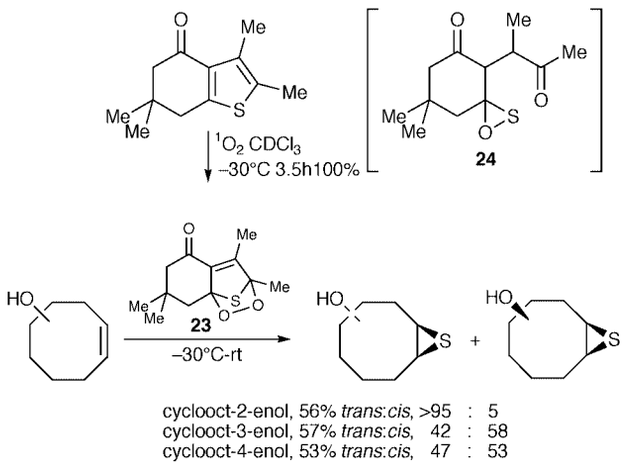
Scheme 33

used in the preparation of enantiomerically pure *P*,*S*-ligands (Scheme 34).[72] Direct episulfidation of alkenes represents the simplest and most versatile approach to thiiranes and several sulfur-transfer reagents have been developed for this purpose. Endoperoxide **23**, formed by the addition of singlet oxygen to the parent thiophene, transfers a sulfur atom to strained cycloalkenes, thus forming thiiranes (Scheme 35).[73] Kinetic studies have shown that **23** is not the active sulfur-transferring species, instead an oxathiirane intermediate such as **24** is thought to be responsible. The conversion of epoxides into the corresponding thiiranes has been achieved using ammonium thiocyanate and an iron(III) porphyrin catalyst.[74] Thiirane **25** has been prepared from a ribopyranoside derivative and shows promising proteinase-inhibiting activity.[75] The baker's yeast reduction of 1-(benzothiazol-2-ylsulfanyl)alkan-2-ones, and treatment of the enantiomerically enriched β-hydroxysulfides with base gives thiiranes in moderate yield with clean inversion of stereochemistry (Scheme 36).[76] Vinyl thiiranes have been prepared by reduction of α,β-unsaturated ketones having an α-thiophosphate group.[77] Finally, the first *gem*-difluorothiiranes have been prepared from sterically crowded aliphatic ketones by treatment with phenyl(trifluoromethyl)mercury and sodium iodide (Scheme 37).[78]

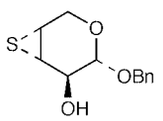


Scheme 34

Enantiomerically pure sulfides are becoming increasingly important as ligands in asymmetric synthesis. The base-induced addition of 2,6-lutidine to thiofenchone has been used in the synthesis of novel enantiomerically pure pyridine thiol and sulfide ligands (Scheme 38).[79] Novel chiral bis(phosphinite) ligands derived from (*R*,*R*)-*trans*-tetrahydrothiophene-2,5-dimethanol have recently been used with moderate success in asymmetric hydrogenation reactions.[80] The ligands are prepared from the bis-thioacetate derived from *meso*-2,5-dibromoadipate (Scheme 39).[80] Finally, enantiomerically pure sulfide derivatives of ferrocenyl-oxazolines have been employed as ligands in palladium-catalysed allylic substitution reactions. The sulfide ligands are conveniently prepared by directed metallation and quenching with appropriate sulfur electrophiles.[81]



Scheme 35



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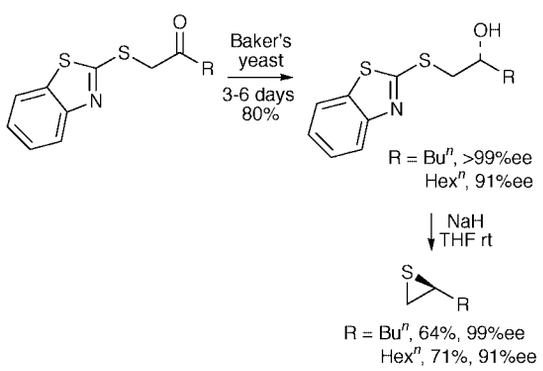
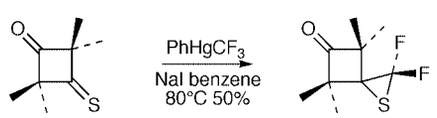
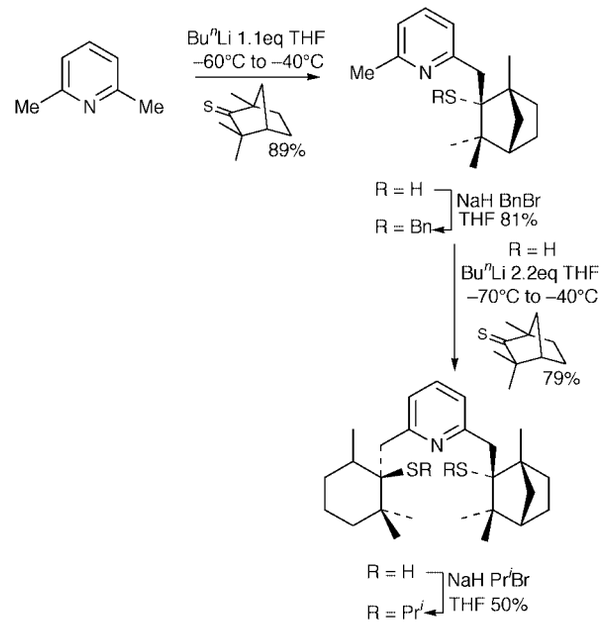


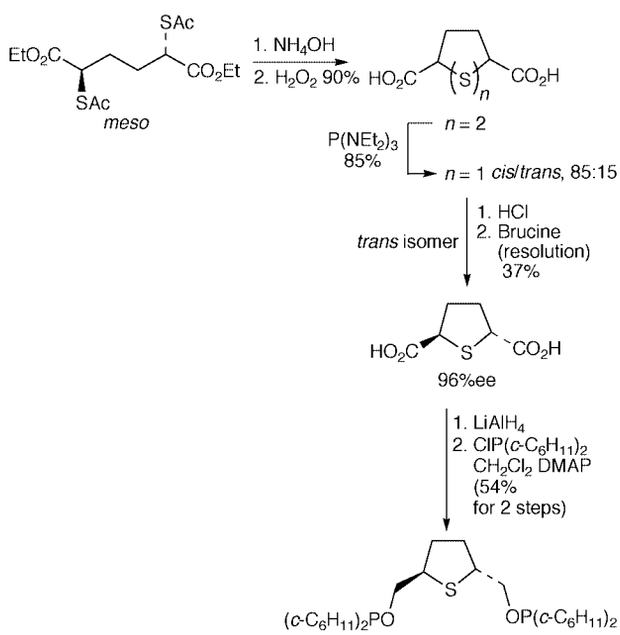
Scheme 36



Scheme 37



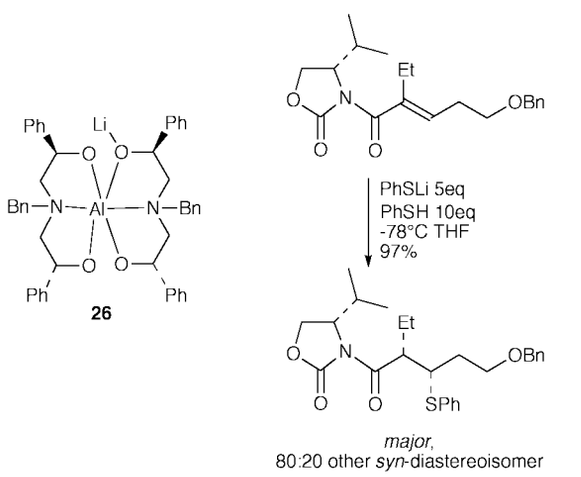
Scheme 38



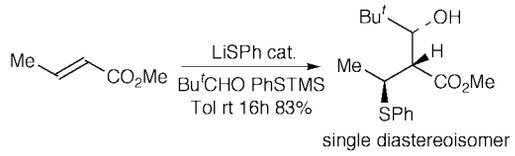
Scheme 39

2.2.2 Functionalised sulfides and selenides

The Michael addition of thiols or thiolates to electron-deficient alkenes is a well established method for the synthesis of functionalised sulfides. Several methods for the asymmetric addition of thiols have now been developed. Recently, a new heterobimetallic catalyst **26**, derived from lithium aluminium hydride and a C_2-symmetrical amino diol, has been found to catalyse the Michael addition of thiophenols to cyclic enones, α,β-unsaturated aldehydes, and nitro alkenes, although the degree of enantioselectivity achieved is not clear.[82] The Michael addition of lithium benzenethiolate to an α,β-unsaturated carboxylic acid derivative bearing an oxazolidinone auxiliary proceeds with good diastereoselectivity and in high yield (Scheme 40).[83] The auxiliary is believed to hold the substrate in the s-*trans* conformation in addition to controlling the face of the olefin to which the thiolate adds. Reactions of α,β-unsaturated esters with aldehydes catalysed by lithium benzenethiolate and in the presence of stoichiometric phenyl trimethylsilyl sulfide, gives products arising from tandem Michael–aldol reaction (Scheme 41).[84] In some examples, stereocontrol at all three newly formed stereocentres was achieved. In

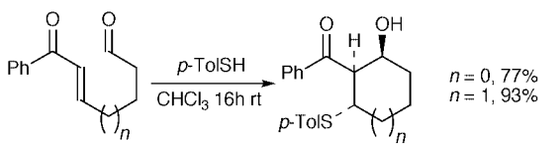


Scheme 40

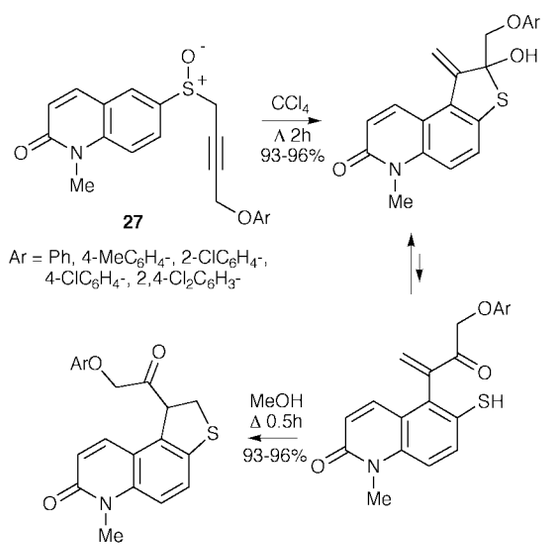


Scheme 41

a separate study, an intramolecular version of this sequential reaction has been reported (Scheme 42).[85] Yet another variant has been used to prepare benzothiopyran derivatives.[86] Finally, sulfoxides **27** undergo an interesting sequence of [2,3] and [3,3] sigmatropic rearrangements to give hemithioacetal intermediates, which upon treatment with methanol give cyclic sulfides *via* an intermolecular thiol Michael addition (Scheme 43).[87]



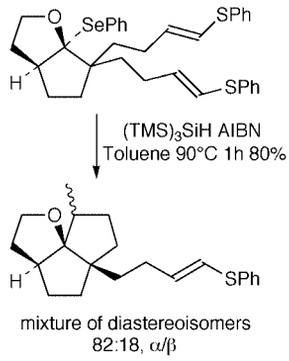
Scheme 42



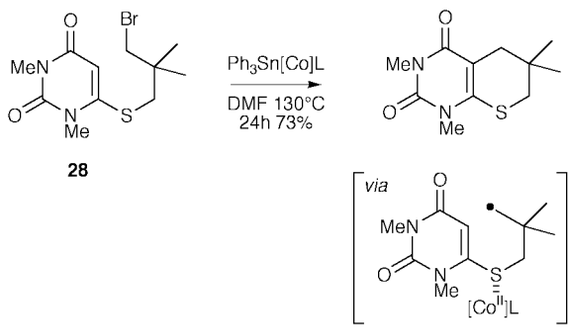
Scheme 43

The radical addition of thiols to methylenecyclopropane derivatives has been found to occur at room temperature, in the absence of an initiator, and in most cases, the cyclopropyl ring remains intact.[88] Several other radical approaches to the synthesis of functionalised sulfides have been reported. A 5-*exo*-*trig* radical cyclisation onto a vinyl sulfide followed by sequential elimination of the phenylsulfanyl radical has been employed in an approach to a functionalised diquinane skeleton (Scheme 44).[89] The effect of a cobalt(II) complex on radical additions to vinyl sulfides has been studied. The thermolysis of a cobalt triphenyltin complex generates a tin radical which reacts with alkyl bromide **28** to generate the corresponding radical. The cobaloxime(II) radical which is also formed coordinates to the *exo*-sulfur atom promoting radical addition to the vinyl sulfide (Scheme 45).[90]

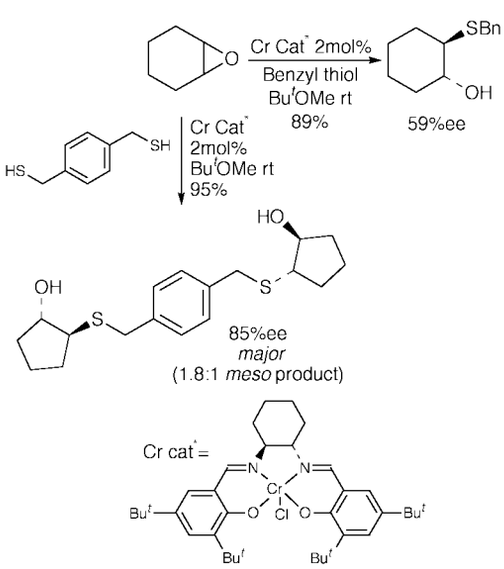
The ring-opening of epoxides with sulfur nucleophiles is an important strategy for the synthesis of sulfides. The synthesis of C_2-symmetrical and pseudosymmetrical sulfides for evaluation as HIV protease inhibitors *via* the ring-opening of aminoalkyl epoxides with triphenylsilylthiol has been reported.[91] The asymmetric ring-opening of *meso*-epoxides represents a powerful strategy for generating two stereocentres in a single operation. The reaction of *meso*-epoxides with dithiols in the presence of an enantiomerically pure (salen)Cr(III) complex gives a mixture of C_2-symmetrical and *meso*-products in good



Scheme 44



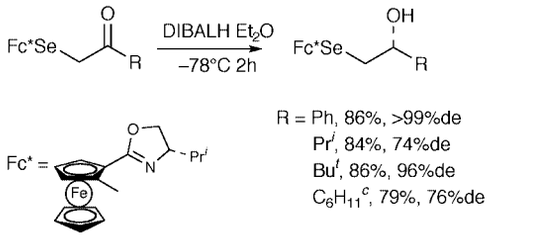
Scheme 45



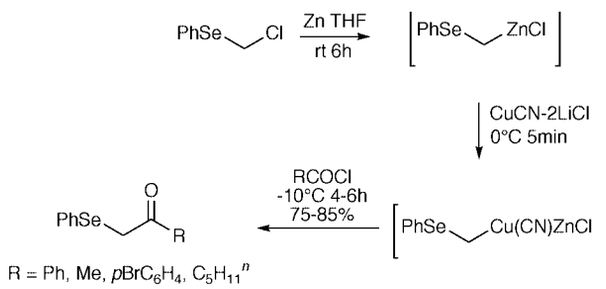
Scheme 46

yield (Scheme 46).[92] As expected, this reaction gave chiral products with higher enantiomeric excesses than those obtained from the reaction with simple monofunctional thiols. An enantiomerically pure (salen)Ti(IV) complex has also been employed in the desymmetrisation of *meso*-epoxides by ring-opening with thiol nucleophiles.[93]

Reduction of enantiomerically pure (ferrocenylselanyl)-methyl ketones gives β-hydroxy ferrocenyl selenides in good yield and with high diastereoselectivity (Scheme 47).[94] The synthesis of functionalised selenides using α-selanyl-substituted organometallic reagents has been reported. α-Arylselanyl-organozinc reagents have been prepared by zinc insertion into α-chloromethyl aryl selenides. Subsequent transmetallation to form the corresponding organocopper reagents and reaction with acid chlorides gives α-arylselanylmethyl ketones in good yield (Scheme 48).[95] These useful reagents have also been shown to react with aldehydes under Lewis acid conditions, and in a Michael sense with electron-deficient alkenes.[96] The preparation of the analogous α-arylselanyl organosamarium reagents has



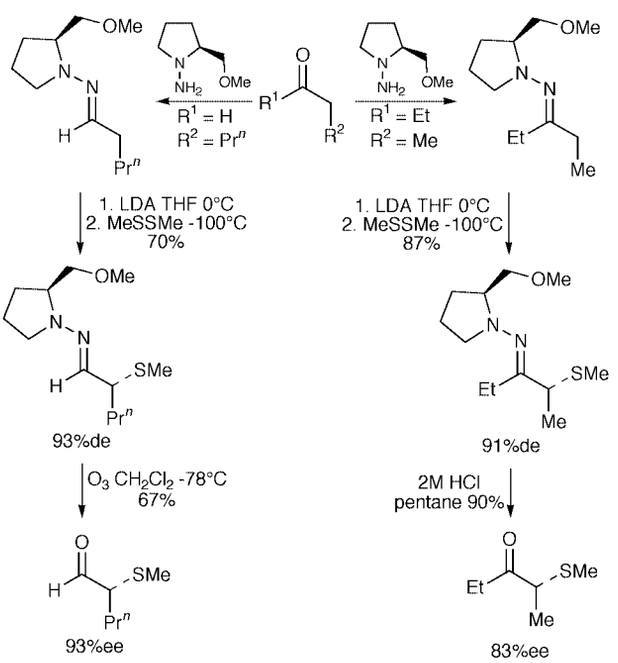
Scheme 47



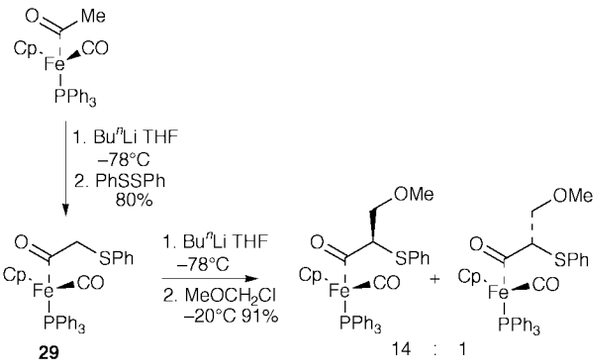
Scheme 48

also been reported and these have been shown to react efficiently with ketones.[97]

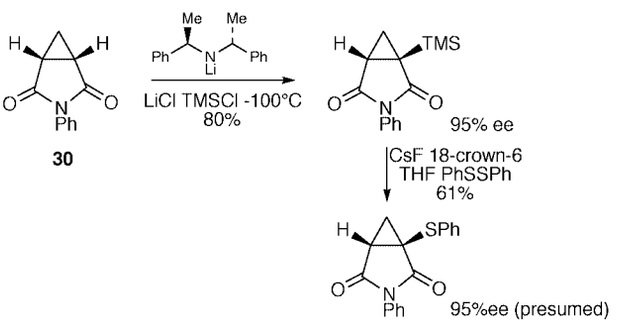
The reaction of stabilised anions with sulfur electrophiles is a common method for the introduction of sulfur into functionalised molecules. The asymmetric α-sulfenylation of lithiated SAMP and RAMP hydrazones derived from aldehydes and ketones, gives the corresponding α-sulfenylated hydrazones. Cleavage of the auxiliary then gives α-sulfenylated ketones and aldehydes in good yield and in high enantiomeric excess (Scheme 49).[98] The deprotonation and alkylation of racemic (phenylsulfanyl)acetyliron complex **29** has been studied. Alkylation with primary alkyl halides occurs with good diastereoselectivity (Scheme 50).[99] The chiral lithium amide base mediated desymmetrisation of multifunctional substrates represents a new strategy in synthesis. Asymmetric deprotonation of bicyclic imide **30** and trapping with trimethylsilyl chloride gave the desymmetrised product in good yield and high enantiomeric excess (Scheme 51).[100] Although the use of other electrophiles proved difficult, fluoride-mediated substitution allowed the phenylsulfanyl group to be efficiently introduced.



Scheme 49

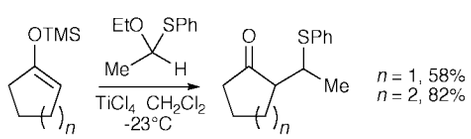


Scheme 50

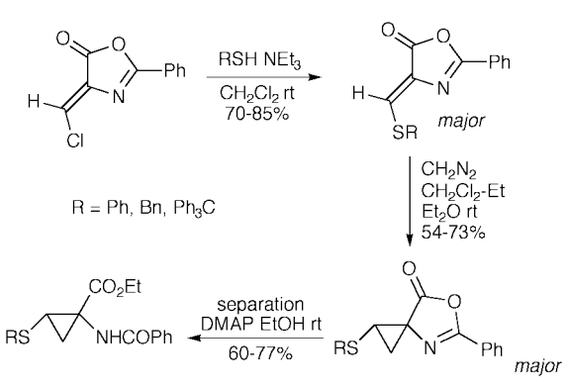


Scheme 51

Silyl enol ethers react with [*O*,*S*]-acetals in the presence of $TiCl_4$ to give 2-phenylsulfanyl ketone adducts in good yield (Scheme 52).[101] The selectivity arises due to preferential complexation of titanium to the oxygen atom of the thioacetal. The synthesis of masked, conformationally constrained, cysteine analogues has been achieved *via* the cyclopropanation of oxazolones having an exocyclic double bond (Scheme 53).[102]



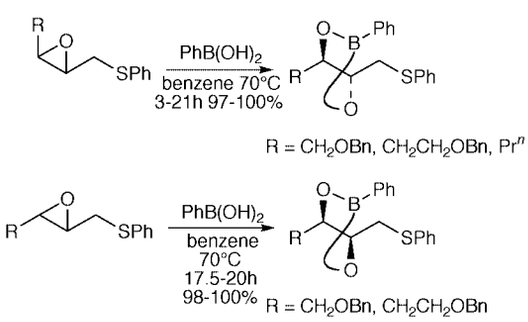
Scheme 52



Scheme 53

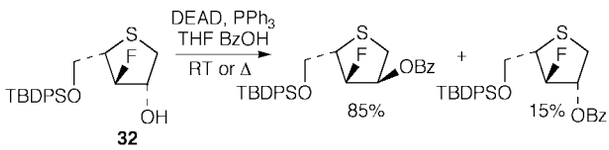
Thiiranium and, to a lesser extent, thiirenium ions are important intermediates in many approaches to functionalised sulfides. A recent kinetic and theoretical study has examined the reaction of thiiranium and thiirenium ions with disulfides.[103] The studies suggest the intermediacy of an episulfurane species, which by the principle of microscopic reversibility, must be the first intermediate in the electrophilic sulfenylation of unsaturated double bonds.[103] The ring-opening reaction of

epoxy sulfides with phenylboronic acid proceeds *via* thiiranium ion formation to give *syn* or *anti* boronate esters of 2,3-dihydroxy sulfides depending upon the stereochemistry of the starting epoxide (Scheme 54).[104] Treatment of D-glucal with arenesulfenyl chlorides gives adduct **31** as a mixture of diastereoisomers (Scheme 55). Under Lewis acid conditions these adducts undergo reaction with vinyl ethers to give *C*-glycosides with excellent β-selectivity.[105] The *anti*-selectivity in the products suggests the reaction proceeds *via* a thiiranium ion intermediate. Interestingly, the product ratio is independent of the starting mixture suggesting that the α and β-thiiranium ion intermediates may be in equilibrium.[105] The formation of a thiiranium ion has recently been used to explain the stereochemical retention observed in the glycosylation of a thionucleoside under Mitsunobu conditions.[106] Similarly, Mitsunobu reaction of 4-thiofuranose derivative **32** gives a small amount of product which is believed to result from participation of the ring sulfur atom (Scheme 56).[107] During synthetic studies towards potential antiviral agents, the attempted fluorination of thiofuranose derivative **33** triggered an interesting ring-contraction *via* thiiranium ion formation and opening with fluoride ion (Scheme 57).[108] Mixtures of hydroxy sulfides cyclise regioselectively under acidic conditions *via* a common thiiranium ion intermediate to give tetrahydrofuran products in good yield (Scheme 58).[109] The related cyclisation of hydroxy selenides was also studied. The isolation and characterisation of tetrahydrothiophenium ion **34** has recently been reported and its reactions with nucleophiles suggest it is an intermediate in the aryl sulfinyl chloride mediated multicomponent coupling of vinyl ethers and carbon nucleophiles to give polyfunctional sulfides (Scheme 59).[110]

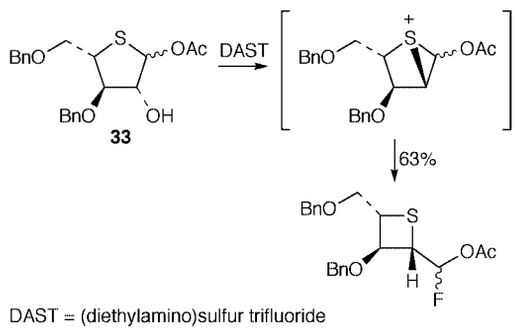


Scheme 54

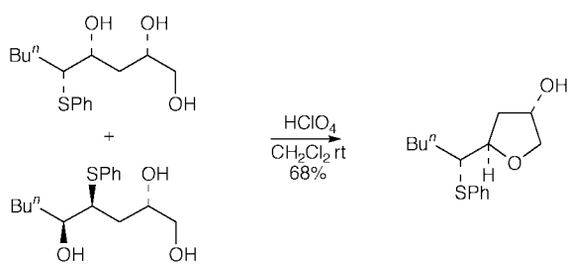
Seleniranium ions are important intermediates in the electrophilic selenenylation of olefins and an understanding of the properties and reactivity of these intermediates is central to the development of asymmetric selenenylation reactions. A recent review discussing the use of chiral selenium compounds in organic synthesis describes in detail the current state of



Scheme 56



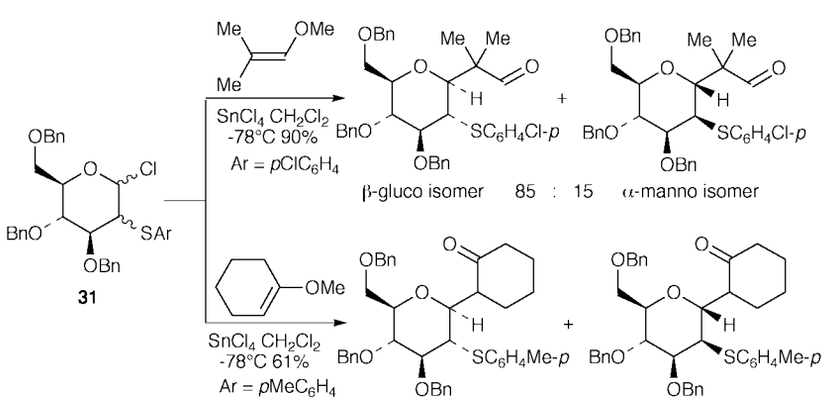
Scheme 57



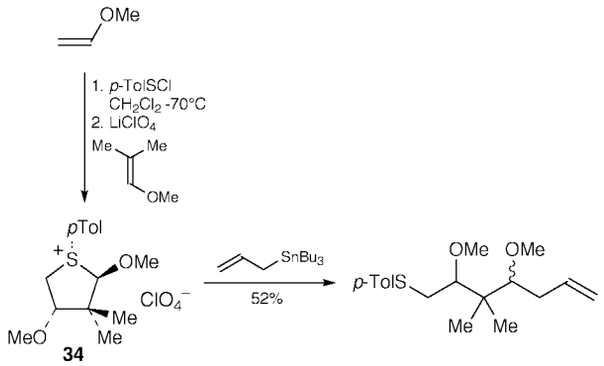
Scheme 58

asymmetric selenenylation methodology.[111] Camphorselenenyl sulfate **35** has been used in the asymmetric selenohydroxylation of olefins,[112] and in a stoichiometric, asymmetric oxyselenenylation–deselenenylation approach to allylic alcohols and ethers.[113] The asymmetric methoxyselenenylation of olefins with a variety of camphor-derived selenenyl triflates has been studied.[114] In this study, the parent selenenyl triflate **36** was found to be the most effective. The electrophilic selenenyl triflate and sulfate derived from new enantiomerically pure diselenide **37** give excellent diastereoselectivities and high yields in the stoichiometric methoxyselenenylation of styrene at temperatures up to room temperature.[115]

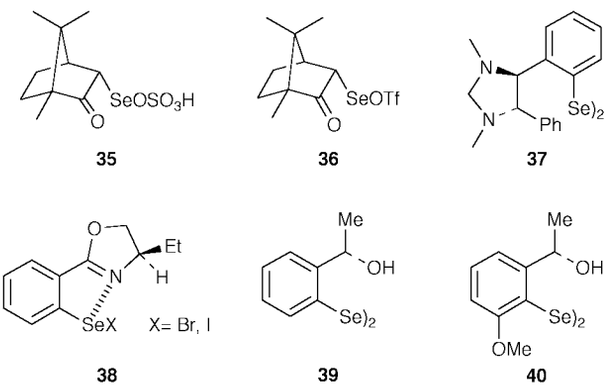
The successful use of organoselenenyl halides as chiral electrophilic reagents is often explained by invoking an interaction of a nearby heteroatom with the selenium atom. These interactions result in the chiral groups on the heteroatom being held close to the reaction centre in addition to increasing the



Scheme 55

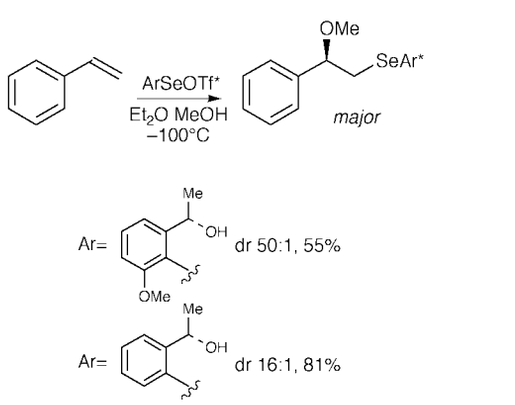


Scheme 59



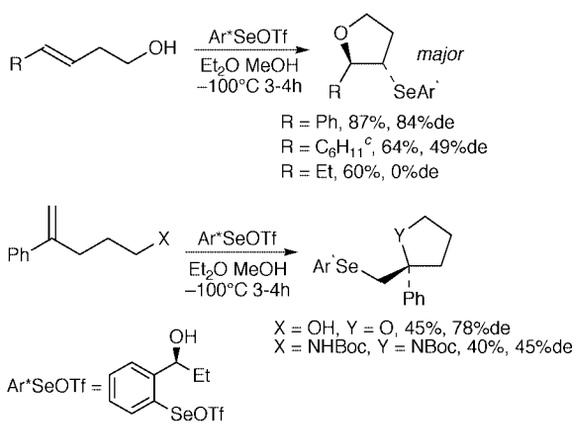
electrophilicity of the reagent. The isolation and X-ray characterisation of enantiomerically pure organoselenenyl halides **38** containing strong, non-bonded Se–N interactions lends support to this explanation.[116] In a separate study, ^{17}O and ^{77}Se NMR studies on 'ArSeX' systems suggest that selenium–oxygen non-bonded interaction is due to orbital interaction between the oxygen lone-pair and a low-lying anti-bonding sigma Se–X orbital.[117] A recent study has explored further the importance of interactions between oxygen and selenium in selenenylating agents derived from diselenides **39** and **40**.[118] In diselenide **40**, having a methoxy substituent in the second *ortho*-position, X-ray and NOE studies suggest the diselenide has a very different conformation in both the solid state and in solution. In diselenide **40** a strong interaction between the selenium atom and the methoxy group dictates the conformation and little interaction with the side-chain oxygen is observed.[118] Selenenyl triflates derived from **40** gave improved selectivities in a series of reactions when compared to the triflate derived from **39** (Scheme 60).[118]

Recent advances in asymmetric selenenylation have focused on the systematic study of cyclisation reactions mediated by enantiomerically pure selenenylating agents. In an early study,

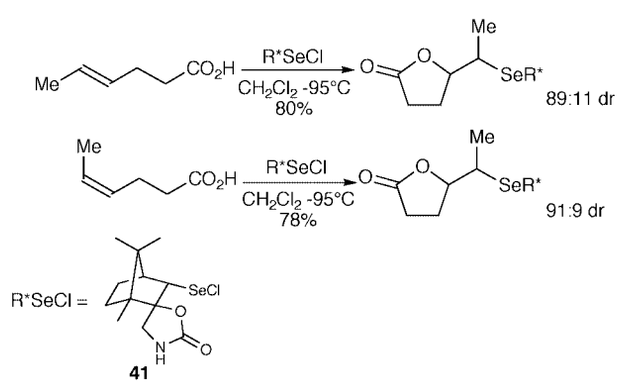


Scheme 60

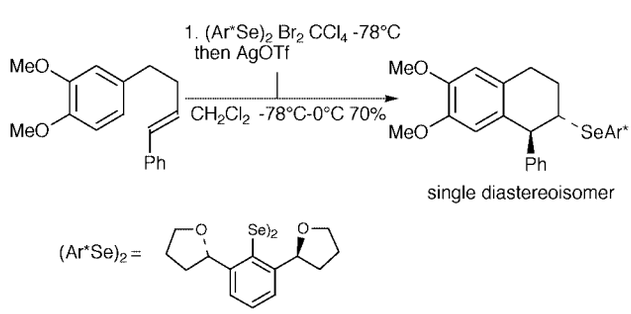
the influence of substituents and double stereochemistry on the asymmetric selenocyclisation to form simple heterocyclic systems was clearly illustrated (Scheme 61).[119] In some examples, the cyclisation involved the formation of quaternary stereocentres. A later study found spiro[oxazolidinone-camphor]-selenenyl chloride **41** to be particularly effective for asymmetric cyclisation reactions (Scheme 62).[120] Interestingly, in contrast to the study previously discussed, *cis*-alkenes gave similar selectivities to *trans*-alkenes. Enantiomerically pure selenium electrophiles derived from diferrocenyl diselenides have also been employed in asymmetric selenocyclisation reactions.[121] The counter anions of the selenenylating agent proved to have a dramatic effect on both the efficiency and diastereoselectivity of the various cyclisation processes examined.[121] Finally, the asymmetric cyclisation of electron rich aromatics bearing alkene tethers using the selenenyl triflate derived from diselenide **42** has been reported (Scheme 63).[122]



Scheme 61



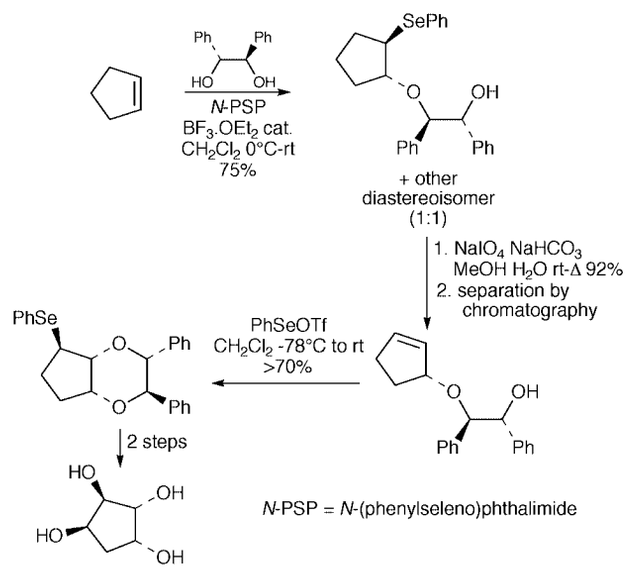
Scheme 62



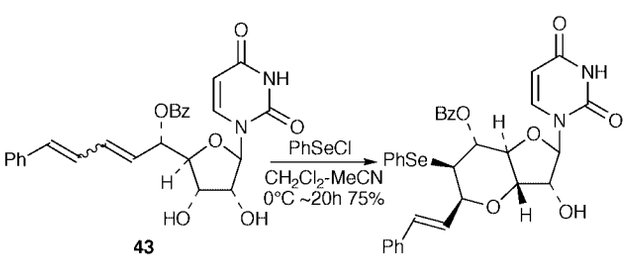
Scheme 63

The non-asymmetric selenenylation of olefins is a common method for the preparation of functionalised selenides. The synthesis of cyclopentitols has been achieved *via* an approach involving two successive oxyselenenylation steps, the second of which proceeds with excellent regio- and diastereo-

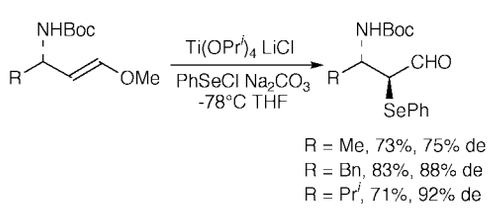
selectivity (Scheme 64).[123] An analogous approach to cyclitols *via* the oxyselenenylation of cyclohexene has also been reported.[124] The 5-*endo* selenoetherification reaction of diprotected pent-4-ene-1,2,3-triols has been used in an approach to furanoid glycals.[125] A 6-*endo* selenoetherification reaction is the key step in a new approach to octosyl nucleosides. Both double-bond isomers of diene **43** lead to the same product suggesting that the seleniranium ion intermediates can interconvert *via* a stabilised carbanion (Scheme 65).[126] The stereocontrolled synthesis of substituted tetrahydrofurans and tetrahydropyrans from hydroxyselenides *via* seleniranium ion formation has been reported.[109,127] The attempted oxidation of allyl phenyl selenide with *m*-chloroperbenzoic acid gave instead products appearing to arise from addition of the reagent to the double bond instead of reaction at selenium.[128] The reaction is believed to proceed *via* the formation and opening of a seleniranium ion intermediate. (*E*)-Methoxy alkenes derived from α-amino acids undergo selenenylation to give the corresponding α-phenylselanyl aldehydes in good yield and with good diastereoselectivity (Scheme 66).[129] Finally, direct amino-phenylselenenylation of α,β-unsaturated esters has been achieved using benzeneselenenyl chloride, activated by a Lewis acid, and in the presence of a primary amine (Scheme 67).[130] Treatment of the product α-phenylseleno β-amino esters with *tert*-butyllithium gives α-phenylseleno β-lactams apparently *via* the cyclisation of a dianionic intermediate.



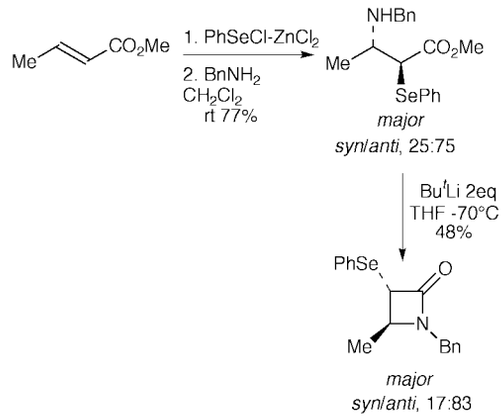
Scheme 64



Scheme 65

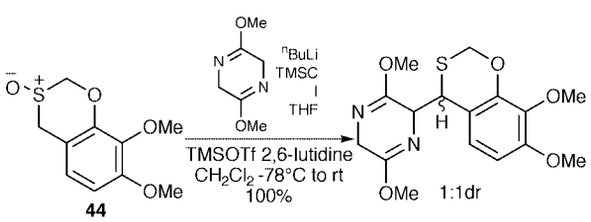


Scheme 66

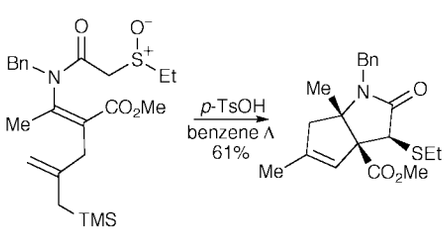


Scheme 67

New variants on the Pummerer reaction of sulfoxides have been reported and provide access to many types of cyclic sulfide. The sulfonium ion formed during the Pummerer reaction of cyclic hemithioacetal sulfoxide **44** can be intercepted with a variety of carbon nucleophiles. Use of an α-amino acid anion equivalent forms the basis of an approach to the antibiotic gliovirin (Scheme 68).[131] Under acidic conditions, α-sulfinylenamides undergo tandem cyclisation processes involving α-acylthionium ion formation, cyclisation to give *N*-acyliminium ions, and subsequent trapping with tethered nucleophiles (Scheme 69).[132] The sequential cascade processes occur stereoselectively and show considerable potential for the construction of alkaloid skeletons. An approach to large *N*,*S*-heterocyclic ring systems has been reported using the sulfoxide electrophilic sulfenylation (SES) of electron-rich aromatics.[133] These processes are related to the Pummerer reaction but involve electrophilic attack at sulfur before loss of an α-proton to form a sulfenium ion. The strategy has been used to form nine- and ten-membered heterocycles.[133] In one example, only the *syn*-sulfoxide diastereoisomer **45a** underwent efficient cyclisation while *anti*-sulfoxide **45b** gave a mixture of uncyclised products (Scheme 70).[133] In the first example of such a rearrangement, 3,3-dimethyl-3-silathiane *S*-oxide underwent a sila-Pummerer ring-expansion to give a seven-membered cyclic *O*,*S*-acetal (Scheme 71).[134]

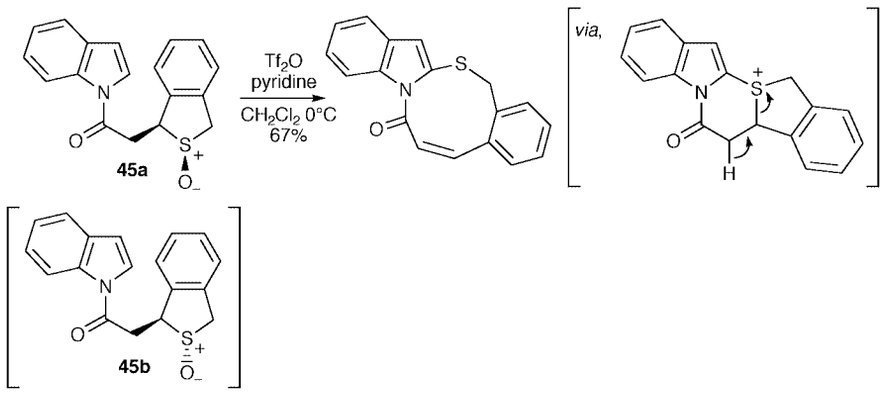


Scheme 68

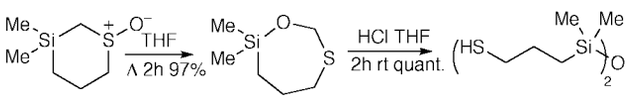


Scheme 69

The development of methods for the preparation of fluorinated organic molecules is currently a popular area of research. This is reflected by numerous studies on the synthesis of fluorinated sulfides. The fluoro-Pummerer rearrangement of sulfides can be achieved under mild conditions to give

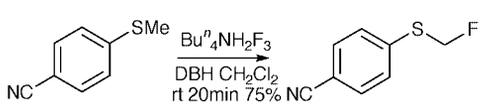


Scheme 70

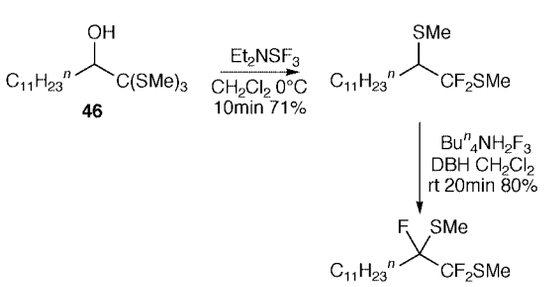


Scheme 71

α-fluorinated sulfides in moderate to good yield (Scheme 72).[135] Also in this study, hydroxyorthothioesters, such as **46**, have been converted by rearrangement and fluorination into di- and trifluorinated products (Scheme 73).[135] Further studies have shown that the oxidative desulfurisation–fluorination of orthothioesters gives bromodifluorination products while hydroxyorthothioesters give difluoro methylsulfanyl ketones in moderate to excellent yield (Scheme 74).[136] The electrochemical fluorination of 1,3-oxathiolan-5-one derivatives[137] and 4-(7-trifluoromethyl)quinolyl sulfides[138] using tetraethylammonium fluoride–HF reagents has been reported. Trifluoromethyl sulfides and selenides have been prepared by decarbonylation or desulfonylation of trifluorothioacetates and trifluoromethanethio- or selenosulfonates.[139] α-Alkylsulfanyl-α-fluoro esters are readily prepared by halogen exchange with triethylamine hydrogen fluoride complex. Formation of the corresponding ester enolates and condensation with carbonyl compounds gave adducts with little diastereoselectivity (Scheme 75).[140] The reduction of sulfur-containing trifluoromethyl ketones with an alcohol dehydrogenase enzyme (APG4) has been shown to proceed with high enantioselectivity for a limited number of substrates (Scheme 76).[141] Finally, the synthesis of enantiomerically pure, partially fluorinated γ-butyrolactones has been achieved by lactonisation of β-fluoroalkyl vinyl sulfoxides with dichloroketene (Scheme 77).[142]

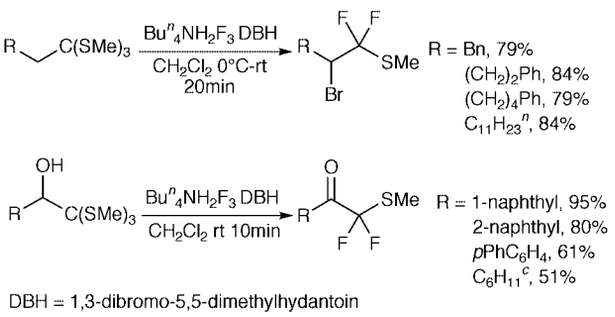


Scheme 72

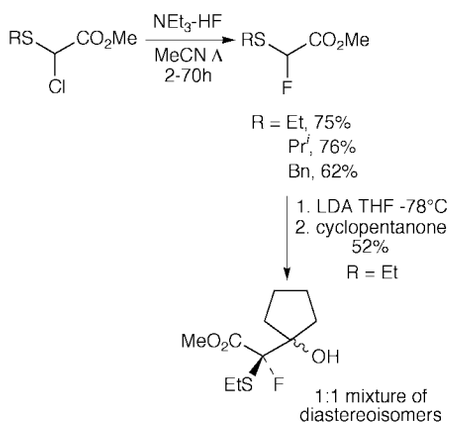


Scheme 73

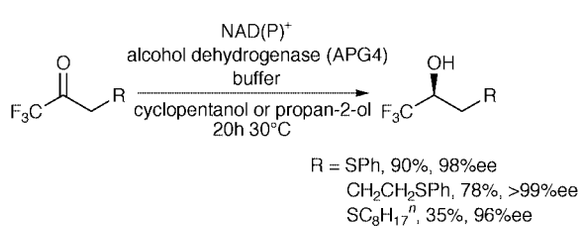
The [4 + 2] cycloadditions of thio and selenocarbonyl compounds with cyclic and acyclic dienes gives cyclic sulfide and selenide adducts.[143,144] α,β-Unsaturated selenoaldehydes



Scheme 74

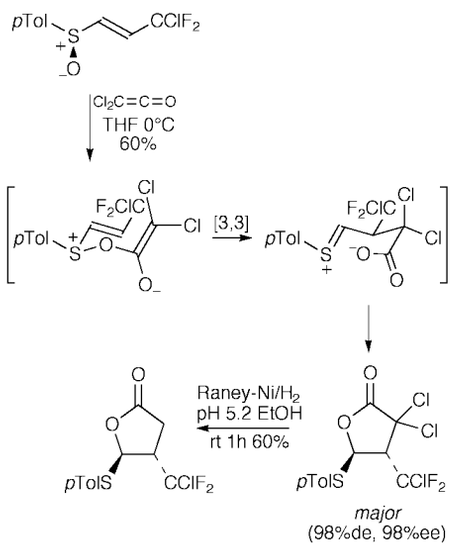


Scheme 75

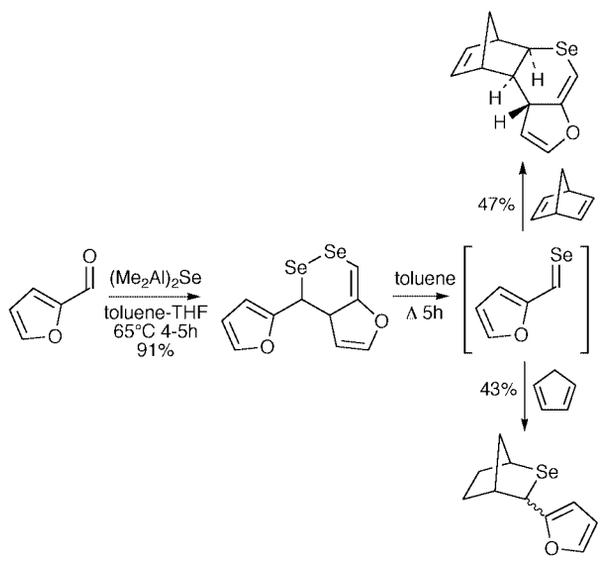


Scheme 76

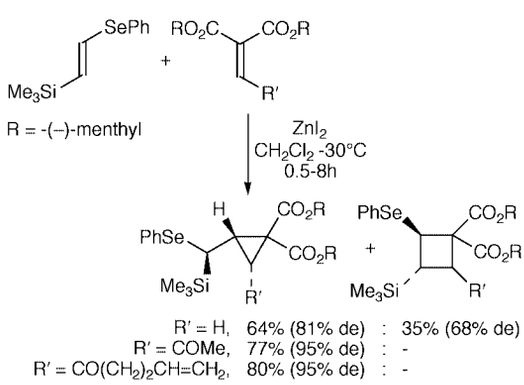
prepared by treatment of unsaturated aldehydes with bis-(dimethylaluminium)selenide, undergo regioselective [4 + 2] dimerisation to give cyclic dimers in good yield.[145] On heating these dimers break down and the resultant selenoaldehyde can be trapped. Interestingly, trapping with cyclopentadiene sees the selenoaldehyde acting as a dienophile whilst in the Diels–Alder reaction with norbornadiene, the selenoaldehyde acts as a diene (Scheme 78).[145] Finally, the [2 + 1] cycloaddition of ethenedicarboxylates bearing menthyl chiral auxiliaries with 1-seleno-2-silylethene in the presence of Lewis acids proceeds



Scheme 77



Scheme 78

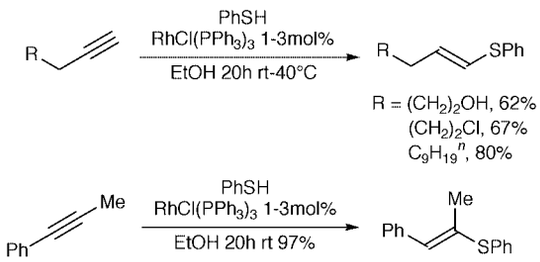


Scheme 79

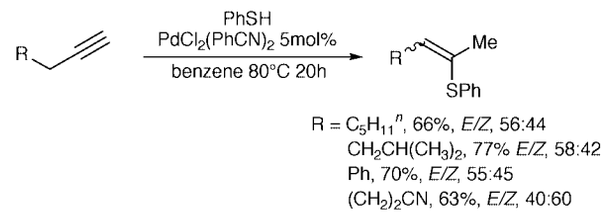
with good diastereoselectivity to give functionalised cyclopropanes (Scheme 79).[146]

2.2.3 Vinylic and acetylenic sulfides and selenides

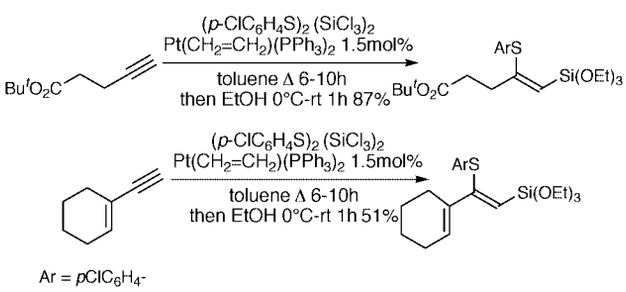
The preparation of vinyl sulfides by the transition metal-catalysed addition of thiols or disulfides to alkynes is a growing area of research. The highly regio- and stereoselective anti-Markovnikov addition of aryl thiols to alkynes using Wilkinson's catalyst has been reported.[147] The addition to terminal alkynes has been studied in detail and in each case (*E*)-vinyl sulfides are obtained in good yield. In one example, addition to an internal alkyne also proceeds with good regio- and stereoselectivity (Scheme 80).[147] In the same study, a useful regioselective addition–isomerisation route to internal vinyl sulfides was described which involves the palladium-catalysed addition of benzenethiol to terminal alkynes having propargylic hydrogens (Scheme 81).[147] The manganese(III)-mediated addition of thiols to alkynes has also been shown to give (*E*)-vinyl sulfides with moderate selectivity.[148] Using a simple mixture of disulfide, disilane and catalyst, the first platinum(0) catalysed regio- and stereoselective thiosilylation of alkynes has been achieved (Scheme 82).[149]



Scheme 80



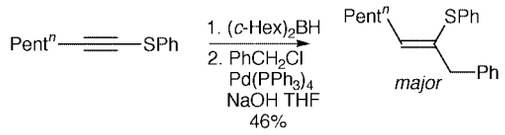
Scheme 81



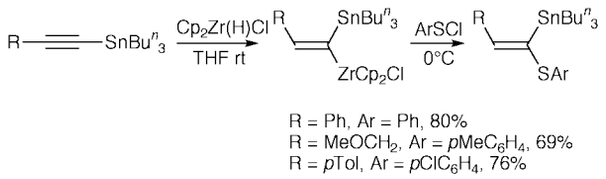
Scheme 82

The hydroboration or hydrozirconation of alkynes has been employed in several stereoselective approaches to vinyl sulfides. The regio- and stereoselective synthesis of vinyl sulfides and selenides from simple alkynes *via* sulfur or selenium substituted vinyl boranes has been reported.[150] In addition, hydroboration of 1-phenylsulfanylalkynes was found to occur with high regioselectivity and the resultant 1-(phenylsulfanyl)alk-1-enylborane underwent Suzuki coupling to give vinyl sulfide products in moderate yield (Scheme 83).[150] The hydrozirconation of terminal alkynes and quenching of the intermediate alkenyl zirconium species with disulfides gives (*E*)-vinyl sulfides in good yield.[151] Similarly, the hydrozirconation of alkynyl stannanes followed by quenching with arenesulfenyl chlorides gives (*Z*)-1-arylsulfanyl vinyl stannanes (Scheme 84).[152] In an analogous reaction, quenching with arene- and alkaneselenenyl bromides gives (*Z*)-1-selanylvinyl stannanes.[153]

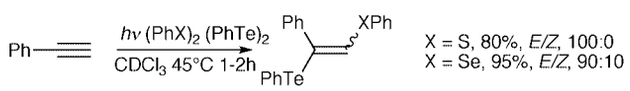
The thiotelluration and the selenotelluration of alkynes has been reported and gives vicinally thiotellurated and selenotellurated alkenes in good yield and with excellent regio and stereoselectivity (Scheme 85).[154] A one pot procedure for the preparation of ketene *S*,*Te*-acetals involves the Horner-type reaction of *in situ* prepared thio(telluro)phosphonate derivatives



Scheme 83

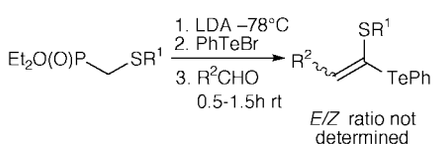


Scheme 84



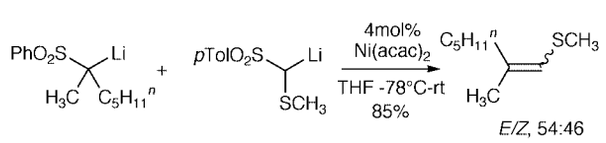
Scheme 85

with aldehydes (Scheme 86).[155] The resultant ketene *S*,*Te*-acetals undergo Li–Te exchange to give vinyllithiums which react with DMF to form (*Z*)-α-phenylsulfanyl-α,β-unsaturated aldehydes.[155] An efficient procedure for the regioselective coupling of different lithiated sulfones to give vinyl sulfides has been reported (Scheme 87).[156] Nickel or iron catalysis gives the product sulfides in good yield but with little stereocontrol.



R^1 = Ph, R^2 = Ph, 75%
Ph, R^2 = 2-furyl, 70%
Ph, R^2 = Pr^n, 60%
R^1 = Me, R^2 = 2-furyl, 67%
Me, R^2 = Ph, 71%

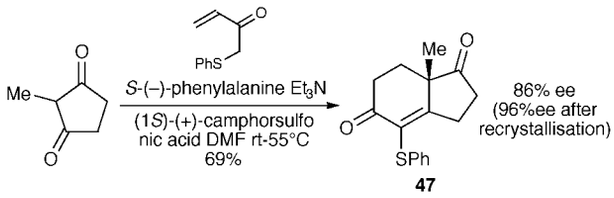
Scheme 86



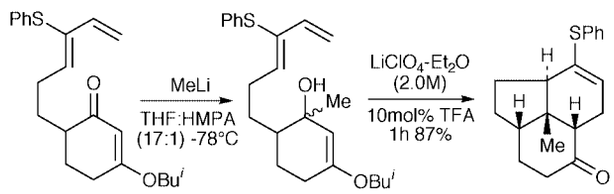
Scheme 87

Asymmetric annulation of 2-methylcyclopentane-1,3-dione with phenylsulfanylmethyl vinyl ketone, mediated by (*S*)-(−)-phenylalanine, gives bicyclic vinyl sulfide **47**, a key intermediate for the synthesis of vitamin D_3 analogues (Scheme 88).[157] Heteroatom stabilised allylic cations having a substituent at the γ-position can be generated *in situ* by treatment of tertiary allylic alcohols with $LiClO_4$ in diethyl ether. In the presence of a tethered 1-substituted-2-phenylsulfanylbuta-1,3-diene group, Diels–Alder reaction occurs to give vinyl sulfide cycloadducts (Scheme 89).[158] The first catalytic asymmetric hetero Diels–Alder reactions of thiabutadienes using a range of Lewis acids in the presence of bis(oxazoline) and bis(imine) ligands give dihydrothiopyrans in good yield and in high enantiomeric excess (Scheme 90).[159] Finally, cyclic vinyl sulfides have been prepared in moderate to good yield using a nickel complex catalysed electroreduction of unsaturated thioacetates and thiosulfonates (Scheme 91).[160]

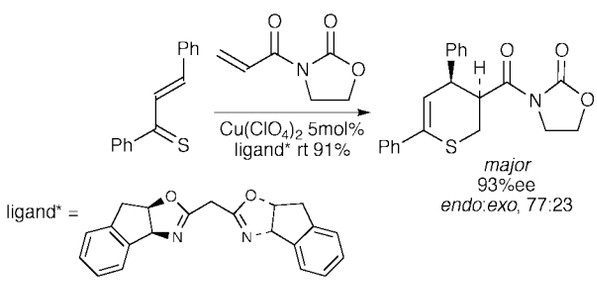
A recent review on the application of selenides and tellurides in organic synthesis details in particular the synthesis of vinyl



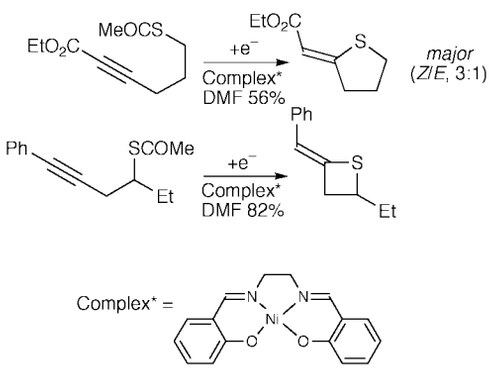
Scheme 88



Scheme 89

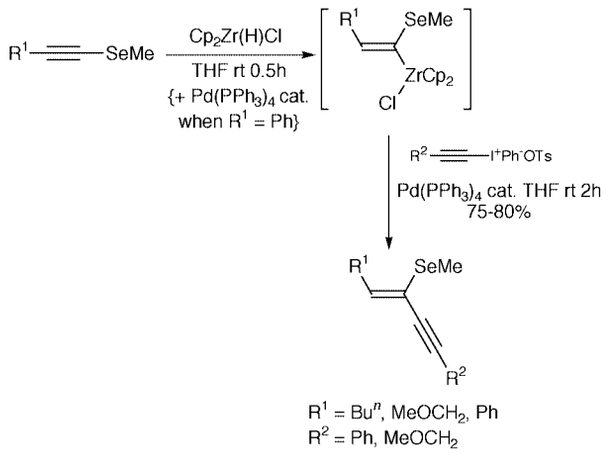


Scheme 90

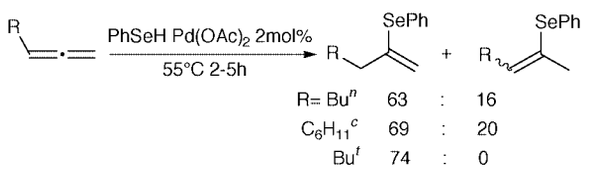


Scheme 91

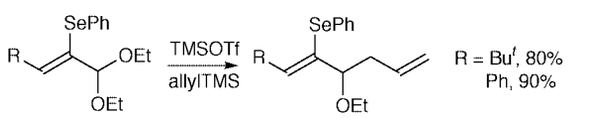
selenides from alkynyl selenides *via* hydrozirconation, hydrostannylation and hydroboration.[161] The palladium catalysed cross-coupling of (*E*)-1-selanylvinyl zirconium species, formed by the hydrozirconation of alkynyl selenides, with alkynyliodonium tosylates gives 1,3-enynyl selenides stereoselectively and in good yield (Scheme 92).[162] Alternatively, the intermediate (*E*)-1-selanylvinyl zirconium species have been quenched with aldehydes.[163] Similarly, (*E*)-1-silylvinyl selenides have been prepared by hydrozirconation of alkynyl silanes and subsequent reaction of the intermediate (*E*)-1-silylvinyl zirconiums with areneselenenyl bromides.[164] The palladium(II) catalysed addition of benzeneselenol to allenes gives vinyl selenides in good yields (Scheme 93).[165] The reaction is believed to proceed *via* ligand-exchange to give a palladium selenide complex and shows some selectivity for products arising from addition to the most electron-rich double bond. The method is complementary to the radical addition of benzeneselenol to allenes which proceeds to give mainly internal vinyl selenides. Exposure of 2-(chalcogeno)prop-2-enal and 2,4-bis(chalcogeno)penta-2,4-dienal acetals to Lewis acid conditions generates allylic and dienyl cations. Reaction with a variety of nucleophiles gives the expected vinyl selenide and sulfide adducts in good yield (Scheme 94).[166] 4,5-Dihydroselenophenes have been prepared



Scheme 92

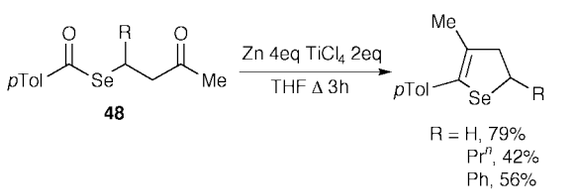


Scheme 93



Scheme 94

in modest yield by the cyclisation of substrates **48** using a low-valent titanium species generated from $TiCl_4$ and zinc (Scheme 95).[167]



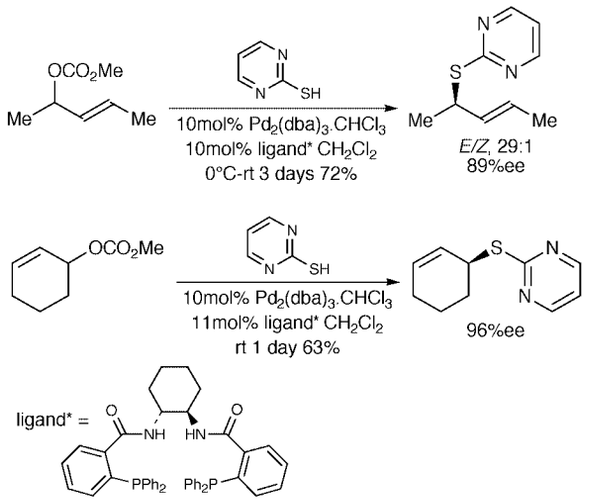
Scheme 95

Finally, alkynyl selenides have been prepared by the copper(I) mediated coupling of alkynyl silanes with areneselenenyl bromides in an approach to novel selenium-containing analogues of alkynyl retinoids.[168]

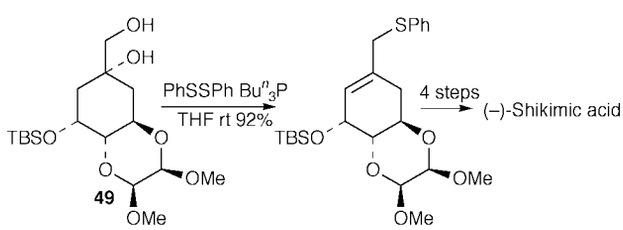
2.2.4 Allylic, homoallylic and benzylic sulfides and selenides

The asymmetric synthesis of aromatic and heteroaromatic allylic sulfides *via* the palladium-catalysed allylation of thiols has been reported (Scheme 96).[169] The direct conversion of 1,2-diol **49** into an allylic sulfide has been employed in a route to (−)-shikimic acid (Scheme 97).[170] The reaction is thought to proceed *via* exocyclic thiiranium ion formation and elimination. Preliminary studies on related diols suggest that this is a general reaction.

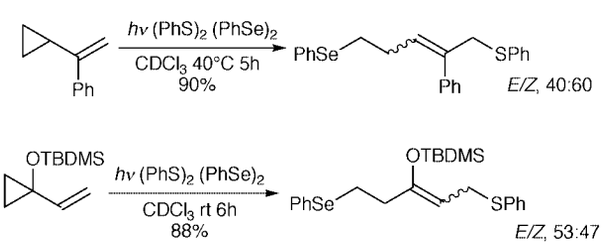
Highly selective thioselenation of vinylcyclopropanes has been achieved by photolysis in the presence of diphenyl disulfide and diphenyl diselenide.[154] γ-(Selenoethyl)allylic sulfides are formed in excellent yield and with good regioselectivity (Scheme 98). The analogous thiotelluration reaction gives product tellurides which are useful precursors to more complex allylic sulfides *via* Li–Te exchange and quenching with carbon electrophiles (Scheme 99).[154] 3-Amino-4-phenylsulfanylhexa-



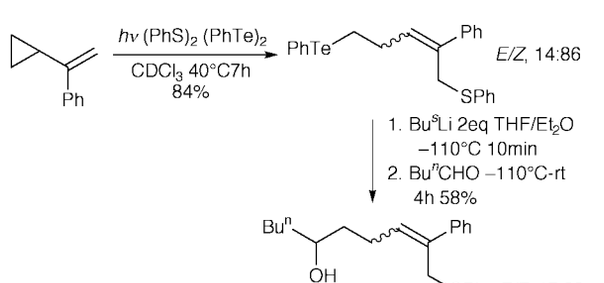
Scheme 96



Scheme 97



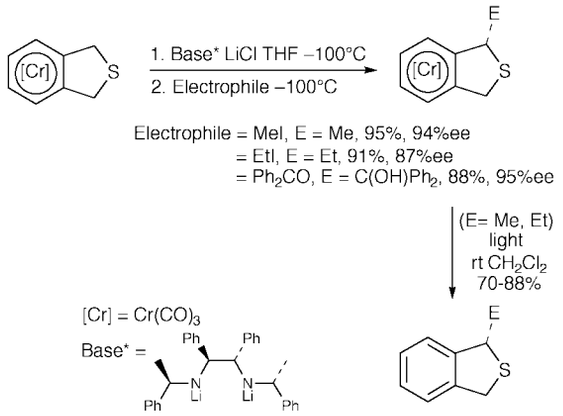
Scheme 98



Scheme 99

1,3-dienes undergo anionic [1,3] and [3,3] rearrangements giving either allylic or vinylic sulfide products.[171] A degree of selectivity for each particular process can be achieved by varying the solvent. The photochemical [1,3]-allylic shift of a phenylsulfanyl group has been employed in an approach to functionalised diquinanes.[89] The synthesis of *cis*-enediynes possessing a 2,5-dihydro-2-benzothiophene moiety has been achieved *via* regiospecific allylic cation generation and addition of an internal thiol nucleophile.[172]

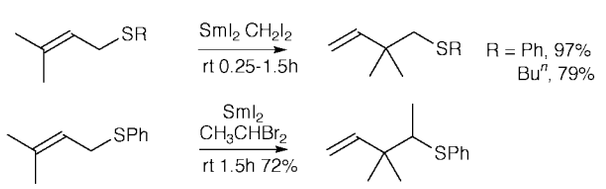
Enantiomerically enriched cyclic sulfides have been prepared by an improved enantioselective metallation at the benzylic position of tricarbonyl(η⁶-1,3-dihydrobenzothiophene) chromium(0) complexes using an enantiomerically pure lithium amide base (Scheme 100).[173] Subsequent quenching with a range of electrophiles followed by decomplexation



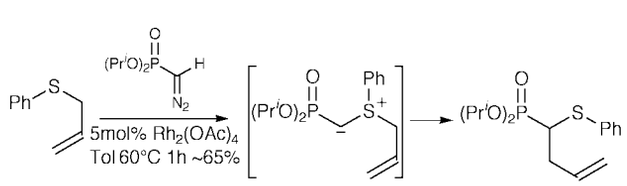
Scheme 100

gives the expected sulfide products in good yield and in high enantiomeric excess.

Treatment of allylic sulfides with samarium carbenoids generates sulfonium ylides which undergo [2,3]-sigmatropic rearrangement to give homoallylic sulfides (Scheme 101).[174,175] Unfortunately the reaction is limited, as substrates bearing γ-vinylic hydrogens give rise to products which undergo elimination, *via* sulfonium ylides, in the presence of excess reagent.[174] In a related process, diisopropyl diazomethylphosphonate reacts with allylic sulfides in the presence of copper(II) acetylacetonate or rhodium acetate dimer, to give the corresponding α-phosphorylated homoallylic sulfides *via* [2,3]-sigmatropic rearrangement of the intermediate sulfonium ylide (Scheme 102).[176] α-Silyl homoallylic sulfides have also been prepared from allylic sulfides *via* rhodium or copper catalysed ylide formation with trimethylsilyldiazomethane followed by [2,3]-sigmatropic rearrangement.[177] The reaction of aryl allyl sulfides with α-diazoacetic acid esters in the presence of a catalytic amount of a cobalt(III)-salen complex, gave substituted 2-arylsulfanylpent-4-enoic acid esters with good stereoselectivity (Scheme 103).[178] Finally, the catalytic asymmetric Diels–Alder reaction of α-thioacrylates with cyclopentadiene in the presence of a copper(II)-bisoxazoline complex gives homoallylic sulfide cycloadducts in high diastereoisomeric and enantiomeric excess although selectivities were found to be highly substrate dependent (Scheme 104).[179]

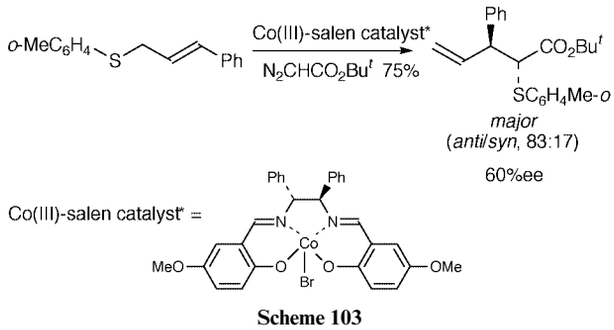


Scheme 101

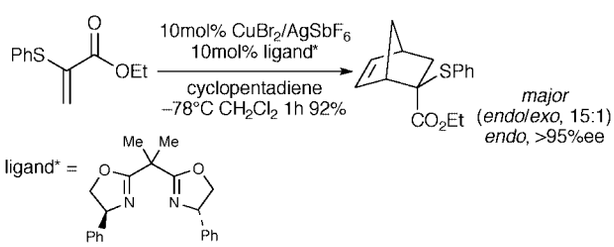


Scheme 102

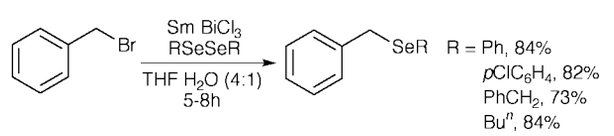
The synthesis of allylic selenides and sulfides using an interesting samarium–bismuth trichloride system in aqueous media has been reported.[180] This reaction has been applied to the synthesis of benzyl selenides and sulfides (Scheme 105).[181] The deprotonation and alkylation of 1-alkoxy-3-phenylselenoalk-1-enes occurs with complete regioselectivity and has been employed in the preparation of substituted allylic selenides.[182] The study of new reagents having a selenium–metal bond is an area of increasing interest. Diisobutylaluminium phenyl selenol-



Scheme 103

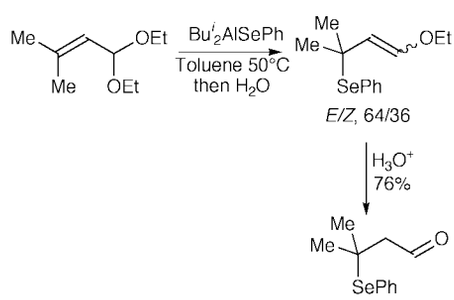


Scheme 104



Scheme 105

ate, readily prepared by the reduction of diphenyl diselenide with DIBAL-H, reacts with α,β-unsaturated acetals to give either 1-alkoxy-3-phenylselenoalk-1-enes or the corresponding aldehydes depending upon the work up conditions employed (Scheme 106).[183]



Scheme 106

Finally, phenyl or methyl trimethylsilyl selenide and aluminium bromide provide a convenient reagent system for the direct conversion of benzylic alcohols into phenyl or methyl selenides.[184]

3 Synthesis of sulfoxides and selenoxides

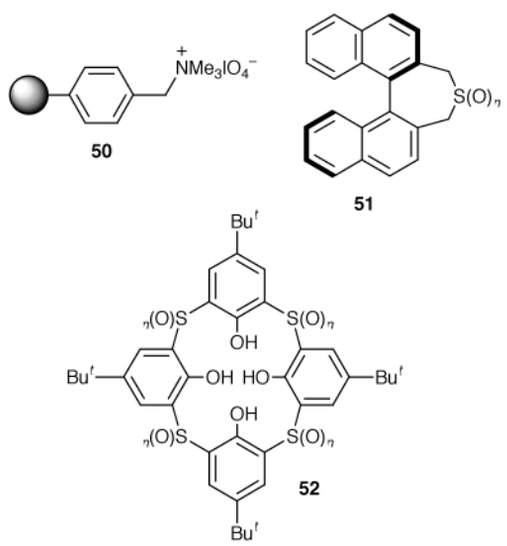
3.1 Oxidation of sulfides and selenides

3.1.1 Achiral oxidising systems

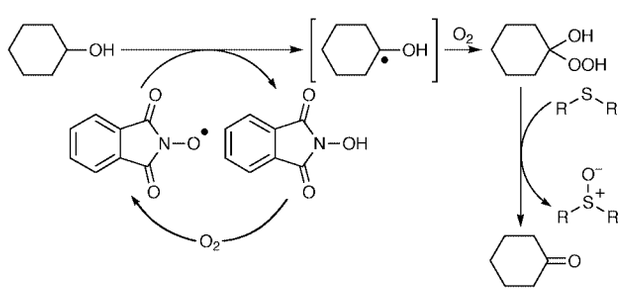
Several new reagent systems for the oxidation of dialkyl, aryl alkyl and dialkyl sulfides to sulfoxides have been reported. These include pyridinium dichromate in acetonitrile;[185] molecular oxygen and transition metal complexes in the presence of aldehydes;[186] iron(III) nitrate impregnated clay ('clayfen') and microwave thermolysis under solvent-free conditions.[187] In addition, dialkyl, aryl alkyl and diaryl sulfides have been oxidised selectively to the corresponding sulfoxides in excellent yield using hydrogen peroxide in hexafluoropropan-2-ol.[188] No overoxidation to the sulfone was observed even in the presence of

excess oxidant for prolonged periods. The hydrogen bonding abilities of the trifluoromethyl group in the solvent have been used to explain the enhanced rate and selectivity of the oxidation reaction. The oxidation of sulfides using *in situ* generated peroxynitrous acid has also been studied.[189] The photooxidations of cyclic aliphatic sulfides and diphenyl sulfide in zeolites doped with methylene blue gave mixtures of the expected sulfoxide and sulfone products.[190]

Dialkyl and aryl alkyl sulfides have been oxidised using several new systems including bromine on hydrated silica;[191] the polymer supported periodate reagent **50**;[192] ceric ammonium nitrate and hydrated silica gel;[193] and manganese dioxide catalysed by H_2SO_4 absorbed onto silica gel.[194] A silica-supported titanium catalyst, prepared by treatment of silica with $Ti(OPr^i)_4$ is an effective catalyst for the oxidation of aryl alkyl and dialkyl sulfides with *tert*-butyl hydroperoxide or hydrogen peroxide.[195]

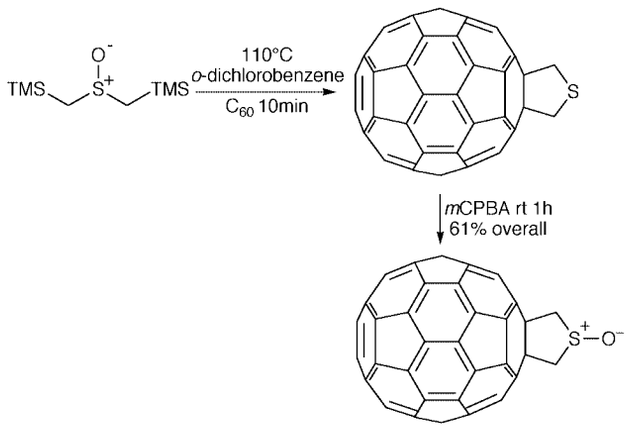


Aryl alkyl sulfides have been oxidised using molecular oxygen catalysed by *N*-hydroxyphthalimide in the presence of cyclohexanol.[196] The active oxidising reagent is believed to be the cyclohexyl α-hydroxy hydroperoxide formed by reaction of dioxygen with the 1-hydroxycyclohexyl radical (Scheme 107). The oxidising system was found to be ineffective for dialkyl sulfides. The results of a limited study on the oxidation of dialkyl sulfides with chlorine dioxide have been reported.[197] A mechanism has been proposed for the oxidation of aryl alkyl sulfides with nitric acid and the catalyst $[(FeBr_3)_2(DMSO)_3]$.[198]



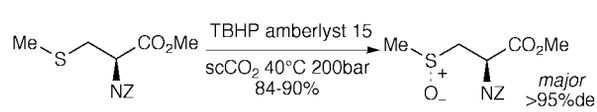
Scheme 107

The oxidation of racemic binaphthyl-based sulfide **51** ($n = 0$) with sodium perborate tetrahydrate in acetic acid gave the novel sulfoxide ($n = 1$) or sulfone ($n = 2$) depending upon the amount of oxidant employed,[199] while *p-tert*-butylthiacalix-[4]arene **52** ($n = 0$) under the same oxidation conditions gave the corresponding sulfoxide ($n = 1$).[200] Sila-Pummerer rearrangement of bis(trimethylsilylmethyl) sulfoxide generates a thiocarbonyl ylide which adds to C_{60} to give the cyclic sulfide adduct. Subsequent oxidation using standard conditions gives the expected sulfoxide (Scheme 108).[201] The oxidation of 2-substituted 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones with dimethyldioxirane gives *anti*-sulfoxides in good yield.[202]

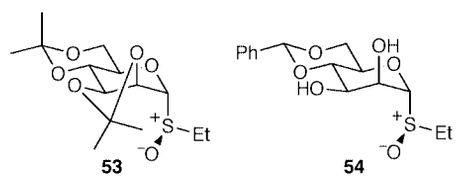


Scheme 108

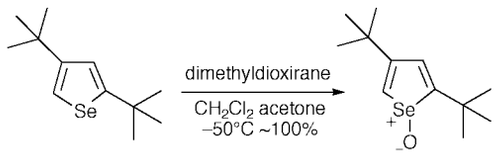
In a recent paper, the diastereoselectivity of a sulfoxidation reaction was found to increase dramatically when carried out in super critical carbon dioxide ($scCO_2$).[203] The oxidation of benzyloxycarbonyl protected methionine methyl ester with *tert*-butyl hydroperoxide in the presence of catalytic ion exchange resin, in dichloromethane or toluene, gives the desired sulfoxide with no appreciable diastereoselectivity. However, when the oxidation was carried out in $scCO_2$, selectivity was observed and was found to depend markedly on the pressure at which the oxidation was performed. Diastereoselectivities of >95% could be obtained under optimised conditions (Scheme 109). The oxidation of a wide range of α-mannopyranosyl thioglycosides under various conditions proceeds with high stereoselectivity to give essentially a single sulfoxide diastereoisomer.[204] For sulfoxides **53** and **54**, the stereochemistry at sulfur was determined by X-ray analysis. The stereoselectivity was found to be independent of the oxidant and the selectivity instead appears to arise from a conformational preference of the thioglycoside as dictated by the *exo*-anomeric effect.[204]



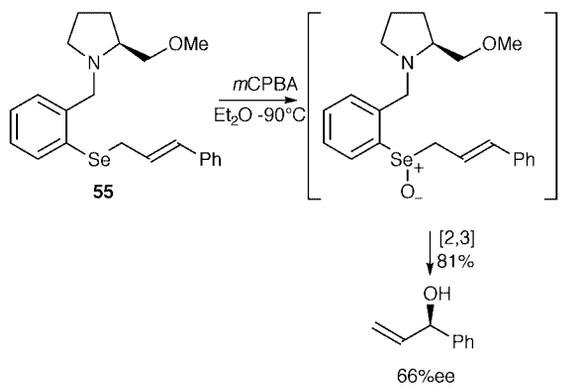
Scheme 109



The first synthesis and characterisation of monocyclic selenophene 1-oxides has been achieved by oxidation of sterically hindered selenophenes with dimethyldioxirane at low temperature (Scheme 110).[205] The selenophene 1-oxide was found to be very reactive, oxidising methyl phenyl sulfide and triphenylphosphine to methyl phenyl sulfoxide and triphenylphosphine oxide respectively. Oxidation of allylic selenide **55** bearing a tertiary amine stereocontrol element gives, after spontaneous [2,3]-sigmatropic rearrangement, enantiomerically enriched allylic alcohols in good yield (Scheme 111).[206] The enantiomerically pure amine is believed to direct selenide oxidation and suppress racemisation of the intermediate selenoxide by the



Scheme 110



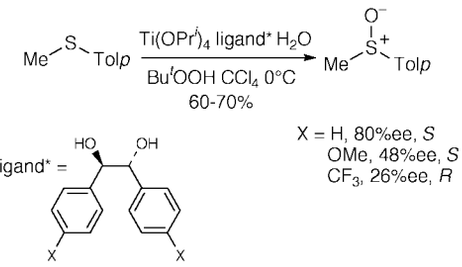
Scheme 111

formation of a Se–N interaction. The diastereoisomeric purity of the intermediate selenoxide was not discussed.[206]

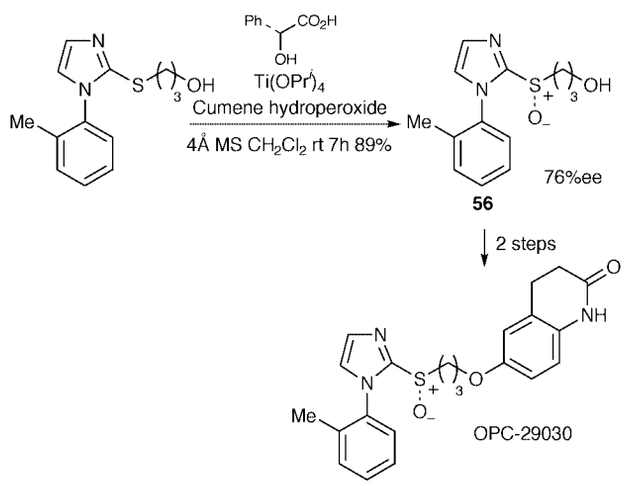
3.1.2 Stereoselective oxidising systems

Titanium-based systems still dominate the now large array of procedures available for the asymmetric oxidation of sulfides, and the use of new ligands and experimental modifications in oxidations with $Ti(OPr^i)_4$, is an area of intense interest. A new method uses a chiral titanium complex formed *in situ* from $Ti(OPr^i)_4$, (*R*,*R*)-diphenylethane-1,2-diol, and water, with *tert*-butyl hydroperoxide as the stoichiometric oxidant.[207] The reagent system is particularly useful for the oxidation of aryl benzyl sulfides which are normally bad substrates for titanium-based oxidations with diethyl tartrate ligands. In a related study using similar ligands, the observed stereoselectivity was found to be highly dependent on the substituent at the *p*-position of the ligand aryl groups.[208] In one example, an interesting reversal of selectivity was observed on introduction of a *p*-trifluoromethyl group into the ligand (Scheme 112). Sulfoxide **56** is a key intermediate in the synthesis of OPC-29030, a platelet adhesion inhibitor currently undergoing clinical trials. Asymmetric sulfoxidation of the parent sulfide using a variety of established methods gave **56** in low enantiomeric excess. A modified $Ti(OPr^i)_4$-based procedure employing mandelic acid as the enantiomerically pure ligand gave the desired sulfoxide in good enantiomeric excess and in high yield at room temperature (Scheme 113).[209] The use of binaphthol ligands in oxidations of this type is well established. Such an oxidation has been used in the synthesis of pyrimidinylpropanamide antibiotics sparsomycin, sparoxomycins A1 and A2, and related analogues,[210] and also in the oxidation of aryl and alkylsulfanyl methylphosphonates.[211] Binaphthol-based ligand **57** has been prepared from equilenine and employed in the $Ti(OPr^i)_4$-mediated asymmetric oxidation of aryl alkyl sulfides.[212] In contrast to previous systems employing binaphthol ligands, over-oxidation to the sulfone does not occur and hence, the high enantiomeric excesses observed are not due to kinetic resolution.[212] The asymmetric oxidation of β-ketosulfides using $Ti(OPr^i)_4$–(+)-diethyl tartrate but employing furyl hydroperoxides as stoichiometric oxidants gives enantiomerically enriched β-ketosulfoxides *via* a combination of asymmetric oxidation and kinetic resolution in the over-oxidation to the sulfone.[213]

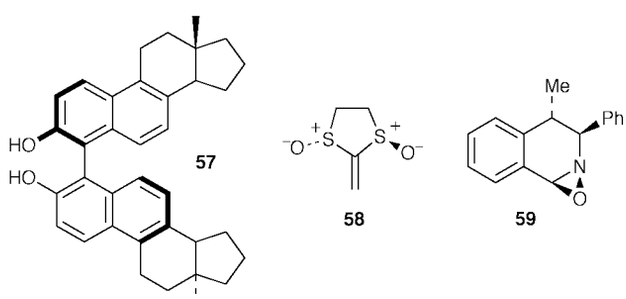
Using more classical modified-Sharpless conditions, the enantioselective oxidation of (methylthio)methylphosphonates gives product sulfoxides in good yield and in high enantiomeric



Scheme 112

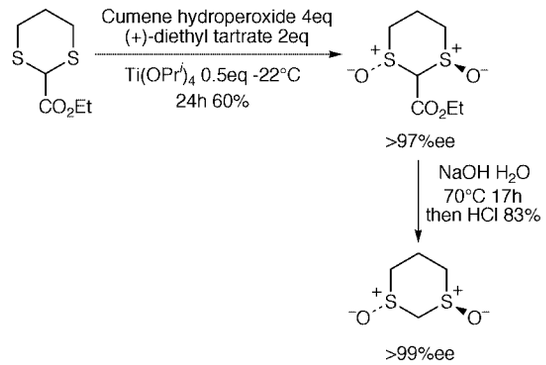


Scheme 113

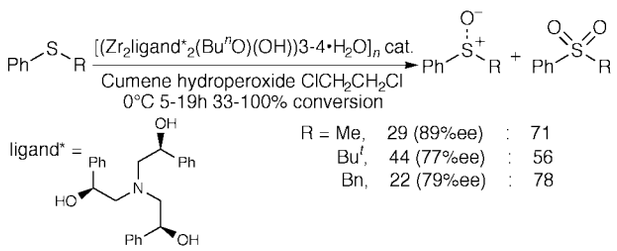


excess.[214] An improved synthesis of *trans*-1,3-dithiane 1,3-dioxide involves the asymmetric oxidation of 2-carboxyethyl-1,3-dithiane under modified Modena conditions (Scheme 114).[215] (1*R*,3*R*)-2-Methylene-1,3-dithiolane 1,3-dioxide **58** is a highly reactive chiral ketene equivalent which shows moderate to high diastereoselectivities in cycloadditions with a range of dienes. Full details for the preparation of **58** *via* the asymmetric oxidation of 2-benzyloxymethyl-1,3-dithiolane have appeared.[216] Finally, asymmetric sulfoxidation of a racemic 1,3-oxathiolane using $Ti(OPr^i)_4$ and (+)-diethyl tartrate has been used in a new approach to 1,3-oxathiolane-based nucleoside analogues.[217]

The first asymmetric sulfoxidation procedure using a zirconium(IV) catalyst has been reported.[218] The catalyst, although not fully characterised, is prepared from $Zr(OBu^n)_4$, a C_3-symmetric trialkanolamine ligand, and water. Oxidation of aryl alkyl sulfides with cumene hydroperoxide as the stoichiometric oxidant, gives the corresponding sulfoxides in high enantiomeric excess although yields are low due to over-oxidation to the sulfone (Scheme 115). The high selectivities arise from initial asymmetric oxidation followed by kinetic resolution in the over-oxidation step.[218] The vanadium catalysed enantioselective sulfoxidation of dithioacetals and dithioketals has been studied.[219] The oxidation of dialkyl and aryl alkyl sulfides using rhenium(V) oxides and urea–hydrogen peroxide complex as the stoichiometric oxidant gives sulfoxides in excellent

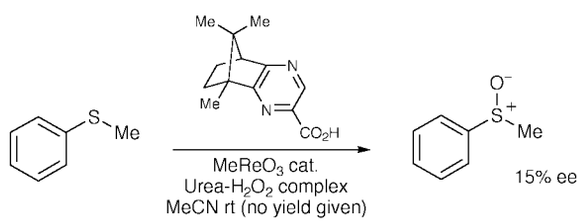


Scheme 114



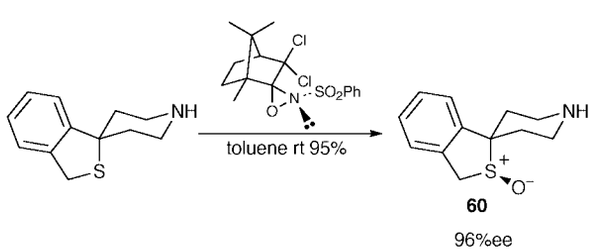
Scheme 115

yield.[220] The related methyltrioxorhenium catalysed oxidation of methyl phenyl sulfide in the presence of an enantiomerically pure pyrazine carboxylic acid gives the sulfoxide product in low but potentially significant enantiomeric excess (Scheme 116).[220]



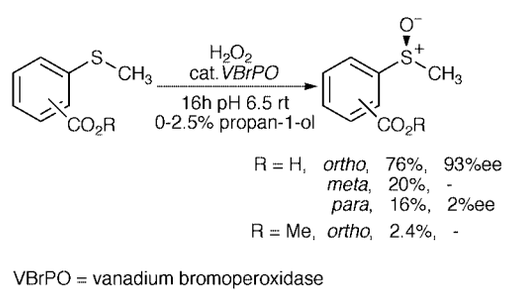
Scheme 116

Enantiomerically pure *N*-alkyl oxaziridine **59**, and the corresponding methyl oxaziridinium salt, oxidise aryl methyl sulfides to the corresponding sulfoxides with modest enantioselectivity in an acid-promoted oxygen transfer reaction.[221] Enantiomerically pure spirocyclic sulfoxide **60** is a key intermediate in the preparation of tachykinin receptor antagonists and can be prepared by the asymmetric oxidation of the parent sulfide using Davis' oxaziridine. Using this procedure, and in stark contrast to the use of transition metal-based procedures, **60** is obtained in high enantiomeric excess (Scheme 117).[222] A hypervalent iodine(v)-based asymmetric oxidation of aryl alkyl sulfides in a reversed micellar system has been reported.[223] Sulfoxides are obtained in high yields and moderate enantiomeric excess. The kinetics of the process have also been examined.[223]

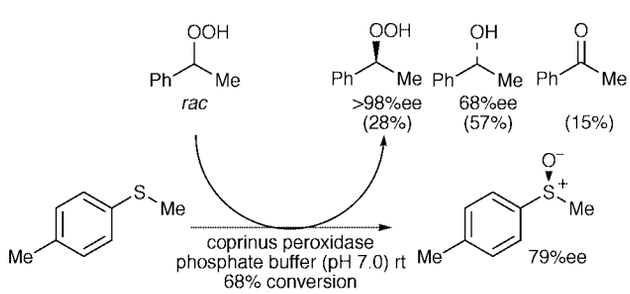


Scheme 117

The use of enzymes for the asymmetric oxidation of sulfides continues to prove a popular area of research although most systems to date suffer from a lack of generality. Recent advancements include the modification of a hydrolase enzyme from *Aspergillus ficuum* by the addition of vanadate ions thus producing a semi-synthetic peroxidase for the asymmetric oxidation of sulfides with *tert*-butyl hydroperoxide.[224] This modified enzyme was found to oxidise thioanisole to the corresponding sulfoxide with moderate enantioselectivity. However, the unmodified hydrolase was also found to catalyse the enantioselective oxidation by what appears to be a metal-free process.[224] In addition, active site mutants of sperm whale myoglobin have been found to oxidise aryl alkyl sulfides to the corresponding sulfoxides in moderate to excellent enantiomeric excess.[225] The oxidation of various aryl alkyl and dialkyl sulfides with hydrogen peroxide catalysed by vanadium bromoperoxidase has been studied. While, in general, the enzyme shows a very restricted substrate tolerance, sulfides having a *cis*-positioned carboxy group proved to be excellent substrates for the enzyme (Scheme 118).[226] In a separate study on vanadium haloperoxidases, enzymes isolated from different organisms have been found to oxidise aryl methyl sulfides with moderate to good enantioselectivity but often with the opposite sense of asymmetric induction.[227] Finally, the asymmetric oxidation of sterically-biased aryl alkyl sulfides with *Coprinus peroxidase* and *rac*-(1-phenyl)ethyl hydroperoxide gives sulfoxides of high enantiomeric excess with simultaneous resolution of the hydroperoxide oxidant.[228] This leads to the additional isolation of enantiomerically enriched hydroperoxide and alcohol from the reaction mixture (Scheme 119).[228]



Scheme 118



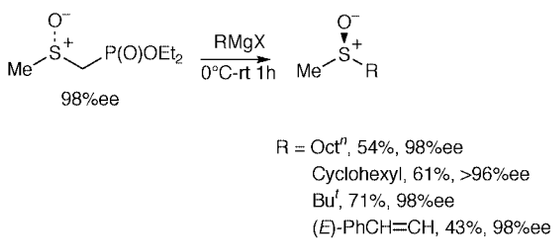
Scheme 119

3.2 Non-oxidative routes to sulfoxides and selenoxides

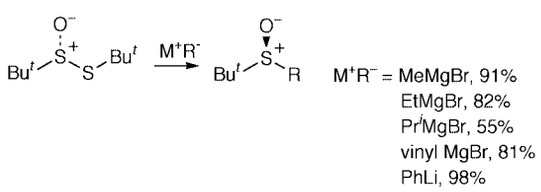
3.2.1 Unfunctionalised sulfoxides and selenoxides

Several non-oxidative routes to enantiomerically pure sulfoxides have recently been described. Carbanionic leaving groups at sulfur have been employed in an Andersen-type procedure. The reaction of enantiomerically enriched sulfoxides derived from (methylsulfanyl)methylphosphonates with alkyl Grignard reagents gives enantiomerically enriched dialkyl sulfoxides resulting from clean inversion of stereochemistry at sulfur.[214] In an extension of this work, sulfoxides derived from aryl and alkylsulfanyl methylphosphonates react with a wide range of Grignard reagents to give dialkyl, aryl alkyl and diaryl

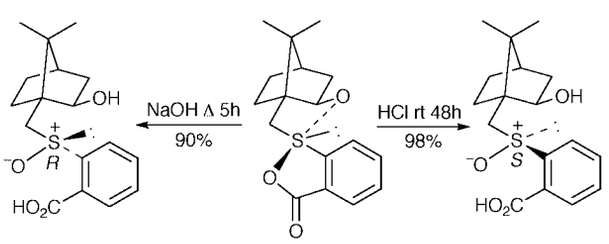
sulfoxides in excellent enantiomeric excess (Scheme 120).[211] Conversion is often low, however, due to metallation α to the sulfinyl group. This problem can be circumvented to some extent by quenching the anion with methyl iodide before adding more Grignard reagent.[211] Enantiomerically enriched *tert*-butyl 2-methylpropane thiosulfinate prepared by the previously reported asymmetric oxidation of *tert*-butyl disulfide, reacts cleanly with Grignard and organolithium reagents to give *tert*-butyl sulfoxides with clean inversion (Scheme 121).[229] The synthesis of enantiomerically pure *ortho*-chloro and *ortho*-bromophenyl sulfoxides using the Andersen approach has been reported.[230] Finally, diastereoisomerically pure alkoxy(acyloxy)-spirosulfuranes have been found to undergo hydrolysis giving either sulfoxide diastereoisomer depending upon the conditions employed (Scheme 122).[231] Labelling studies have shown that the sulfoxide oxygen is derived from water under both acidic and basic conditions.



Scheme 120



Scheme 121

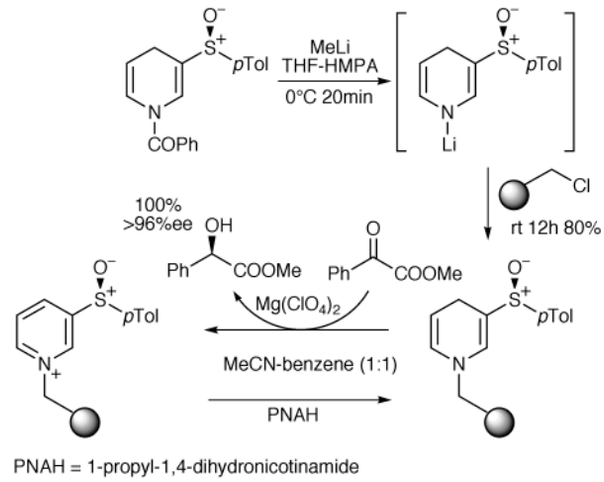


Scheme 122

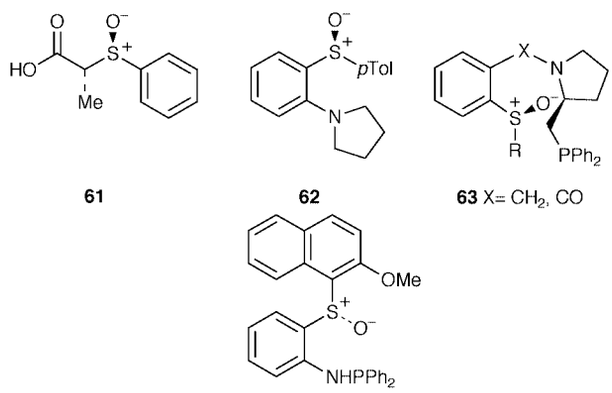
In a fundamental study on simple episulfoxides, isomeric species derived from 2-methylpent-2-ene episulfide have been found to be unstable above −50 °C. Characterisation has been achieved however, using low-temperature FAB mass and NMR spectroscopy.[232]

A polymer supported model for NADPH (nicotinamide adenine dinucleotide phosphate) bearing a chiral sulfoxide group has been prepared and utilised in a highly selective biomimetic reduction of methyl benzoylformate (Scheme 123).[233] The supported reagent can be conveniently regenerated and when recycled, gives identical enantioselectivities in the reduction with only a slight decrease in chemical yield.[233]

Sulfoxide ligands are playing an increasingly important role in metal-mediated organic reactions. The bidentate, enantiomerically pure sulfoxide ligand **61**, has been used to prepare several chiral-at-metal complexes.[234] In a series of reports, enantiomerically pure sulfoxide ligands containing amino **62**,[235] phosphino **63**,[236–238] and phosphinoamido **64**,[239] donor groups have been prepared and employed in palladium-catalysed allylic alkylations.



Scheme 123



61 **62** **63** X= CH_2, CO

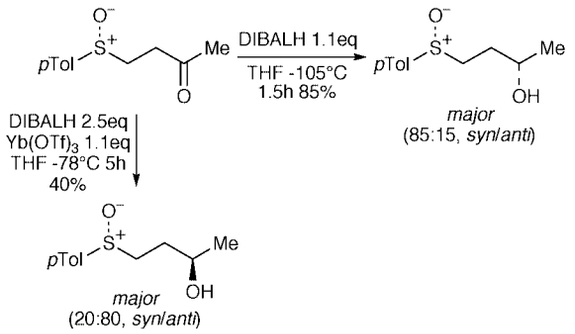
64

3.2.2 Functionalised sulfoxides and selenoxides

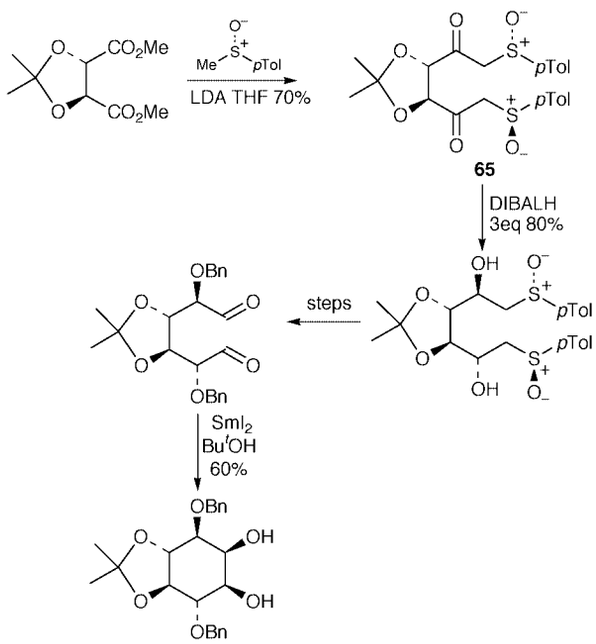
The sulfoxide moiety is used extensively as a stereocontrol element in organic synthesis. Remote asymmetric induction using enantiomerically pure sulfoxides is the subject of a recent, selective review.[240]

In several studies, the sulfoxide moiety has been used to control the stereochemical course of carbonyl reduction elsewhere in the molecule. The sulfoxide-directed DIBAL-H reduction of enantiomerically pure sulfoxides having a methyl ketone in the γ-position proceeds to give *syn*-products in high diastereoisomeric excess (Scheme 124).[241] Addition of a lanthanide(III) Lewis acid results in a reversal of diastereoselectivity to give predominantly the *anti*-products. A similar reduction of β-silyloxy-γ-keto sulfoxides has also been reported.[242,243] An enantioselective approach to a C_2-symmetric hexol precursor to the alkaloid (−)-lythranidine involves the stereoselective reduction of β,δ-keto sulfoxides.[244] The synthesis of the pheromone (*R*)-sulcatol and several partially fluorinated analogues, has been achieved *via* a route involving a directed reduction of a β-keto sulfoxide.[245] A *myo*-inositol derivative has been prepared from dimethyl-2,3-*O*-isopropylidene tartrate *via* key β-diketo sulfoxide **65** (Scheme 125).[246] Sulfoxide-directed reduction of **65** gave the C_2 symmetrical dihydroxy sulfoxide and subsequent steps including a key samarium(II) iodide pinacol coupling, gave the desired product.[246] Finally, the stereoselective reduction of β-keto sulfoxide intermediates is a key step in the asymmetric synthesis of α-acetylenic epoxides.[247]

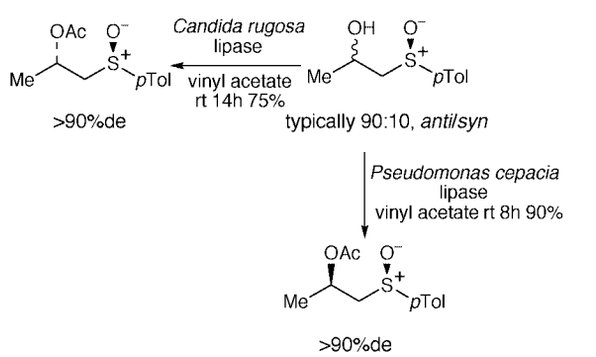
As β-hydroxy sulfoxides obtained by diastereoselective reduction of β-keto sulfoxides can often be difficult to separate by crystallisation or chromatography, a technique involving the lipase-catalysed acylation of the diastereoisomeric mixture allows both alcohols to be obtained in high enantiomeric excess simply by varying the lipase (Scheme 126).[248] Diastereo-



Scheme 124



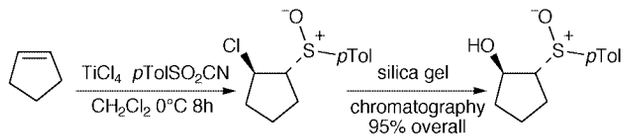
Scheme 125



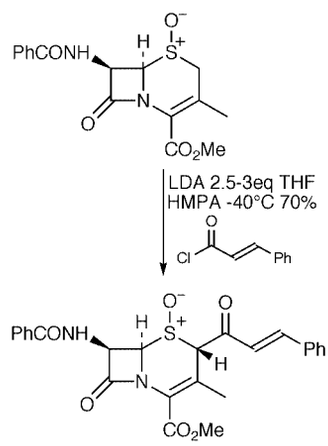
Scheme 126

isomerically pure β-hydroxy sulfoxides have been shown to undergo Mitsunobu azidation to give β-sulfinyl azides.[249] In an alternative approach to β-hydroxy sulfoxides, the titanium(IV) chloride mediated addition of tosyl cyanide to alkenes gives *anti*-β-chloro sulfoxides which readily hydrolyse on silica gel to give the corresponding *anti*-β-hydroxy sulfoxides (Scheme 127).[250] The overall retention in the hydrolysis step suggests the participation of the sulfoxide group.

The alkylation of α-lithio sulfoxides is a common method for the preparation of functionalised sulfoxides. The deprotonation and acylation of cephalosporin sulfoxides under carefully optimised conditions gives α-substituted cephalosporin sulfoxides in good yield (Scheme 128).[251] An approach to the synthesis of novel 1′-substituted thionucleosides *via* alkylation of the corresponding sulfoxides has been reported.[252] The addition

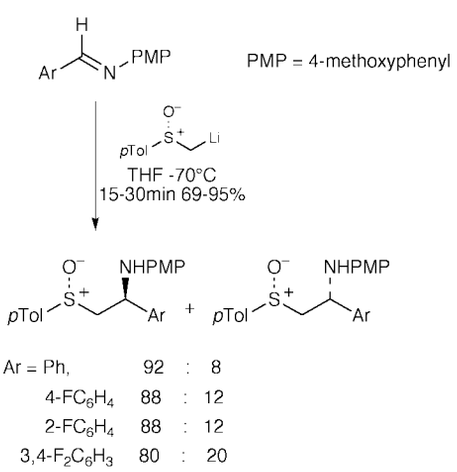


Scheme 127

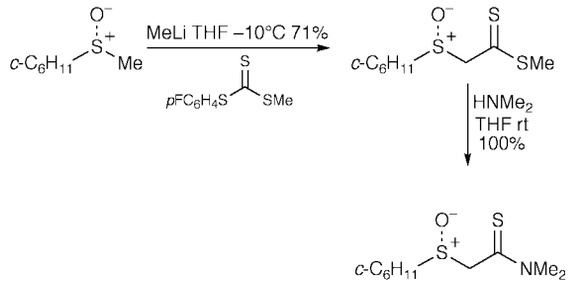


Scheme 128

of α-lithio sulfoxides to protected aldimines bearing fluorinated alkyl or aryl substituents, has been the subject of several studies. The addition of α-lithio methyl *p*-tolyl sulfoxide to protected aryl aldimines gives high diastereoselectivities when carried out under kinetic control.[253] When the reaction was allowed to warm to room temperature, equilibration led to a 1 : 1 mixture of diastereoisomers (Scheme 129). Interestingly, as the fluorine content of the aryl group increases, the observed diastereoselectivity decreased.[253] Analogous additions to protected aldimines bearing fluorinated alkyl substituents have also been reported[254] and the methodology employed in the synthesis of dipeptide isosteres.[255] Enantiomerically pure β-imino sulfoxides have been prepared by reaction of imidoyl chlorides with lithiated enantiomerically pure methyl *p*-tolyl sulfoxide and by aza-Wittig reaction on β-keto sulfoxides.[256] Alternative methods for the preparation of β-imino sulfoxides include the condensation of β-keto sulfoxides with amines, or the α-sulfinylation of ketimines.[257] Racemic 2-alkylsulfinyl dithioacetates have been prepared by condensation of α-lithiosulfoxides with 4-fluorophenyl methyl trithiocarbonate. The corresponding thiacetamides can then be readily obtained by reaction of the thioacetates with dimethylamine.[258] Enantiomerically pure cyclohexyl methyl sulfoxide was used in the preparation of enantiomerically pure 2-cyclohexylsulfinyl dithioacetate and the corresponding thioacetamide (Scheme 130).[258]

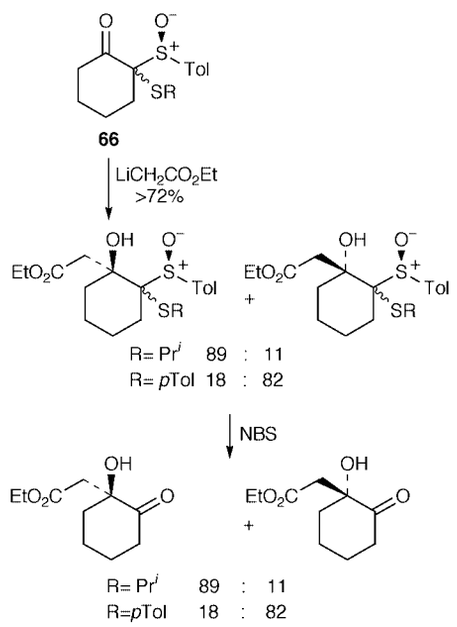


Scheme 129

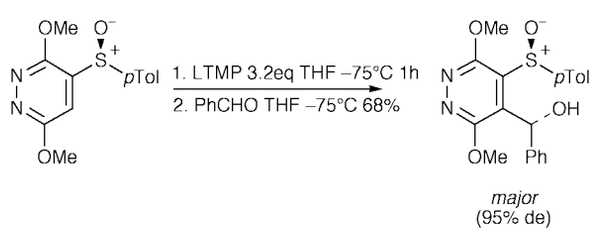


Scheme 130

The sulfinyl group has been used to control the stereochemistry of several other types of alkylation reaction. Enantiomerically enriched α-substituted α-hydroxy cyclohexanones have been prepared from diastereoisomerically enriched sulfinyl cyclohexanone **66** by aldol reaction and subsequent hydrolysis to give the enantiomerically enriched products (Scheme 131).[259] Selection of the group on sulfur allows access to either enantiomer of the product.[259] Enantiomerically pure sulfoxide groups in diazine and pyridine substrates have been used to direct *ortho*-lithiation and the stereochemistry of subsequent additions to aldehydes (Scheme 132).[260] Finally, the stereochemical course of epoxidations on β-keto sulfoxides by methylene transfer has been studied.[261,262]

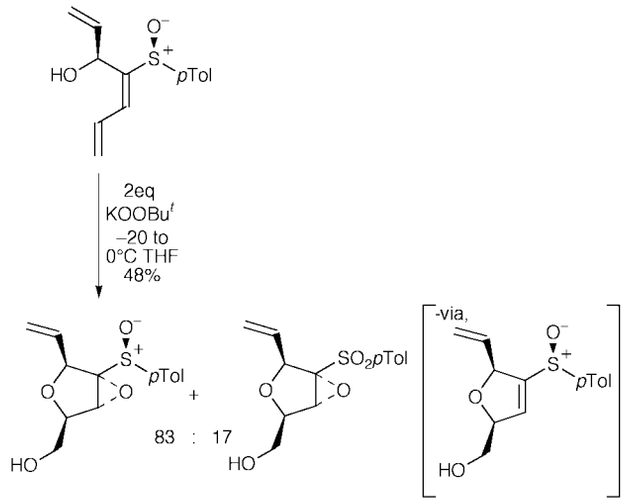


Scheme 131



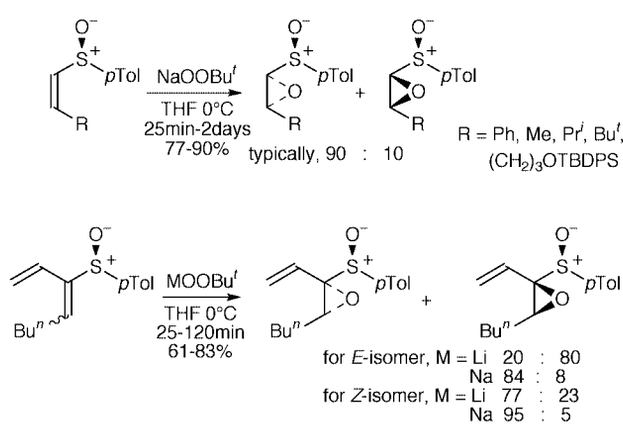
Scheme 132

Sulfoxide-directed oxidation has been explored in several recent studies. A highly stereoselective sequential sulfoxide-directed approach to substituted tetrahydrofurans from sulfinyl dienes has recently been reported.[263] Initial stereoselective nucleophilic epoxidation at the terminal double bond of the diene is followed by 5-*exo*-*trig* cyclisation and a second epoxidation step to give the observed products (Scheme 133).[263] The

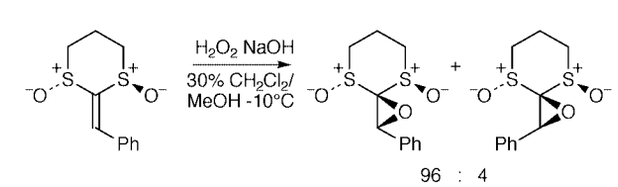


Scheme 133

nucleophilic epoxidation of enantiomerically pure vinyl and dienyl sulfoxides has been studied. The reaction is effective for (*Z*)-vinyl sulfoxides and (1*E*)- or (1*Z*)-2-sulfinyl dienes (Scheme 134).[264] Interestingly, in the epoxidation of (1*E*)-2-sulfinyl dienes, the diastereoselectivity of the epoxidation can be controlled by simply changing the metal cation.[264] Enantiomerically pure spirocyclic bis-sulfinyl epoxides have been prepared by epoxidation of the corresponding olefin (Scheme 135).[265] Unfortunately, epoxidation of substrates having substituted aryl or aliphatic substituents showed lower diastereofacial selectivity. Chemoselective dihydroxylation of double bonds in substituted 1,3-dithiane 1-oxides has been achieved using osmium trichloride and potassium ferricyanide, however, only modest diastereocontrol was observed in the oxidation step.[266]

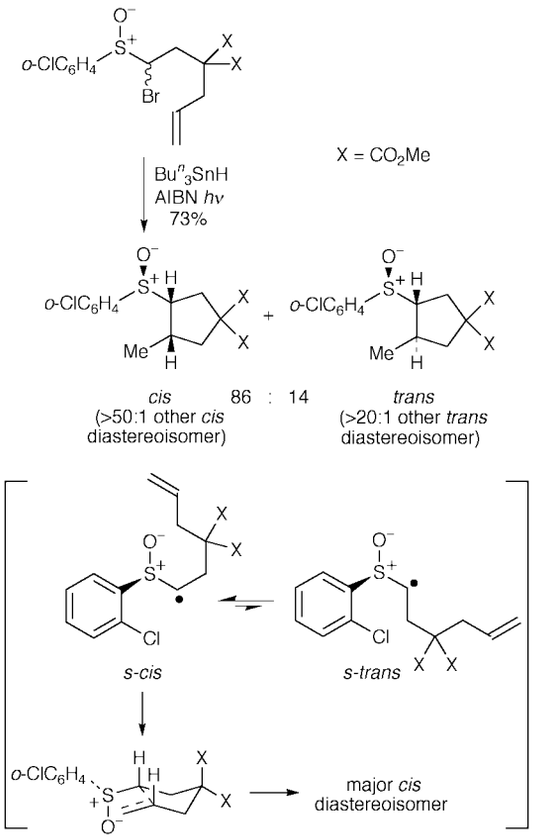


Scheme 134



Scheme 135

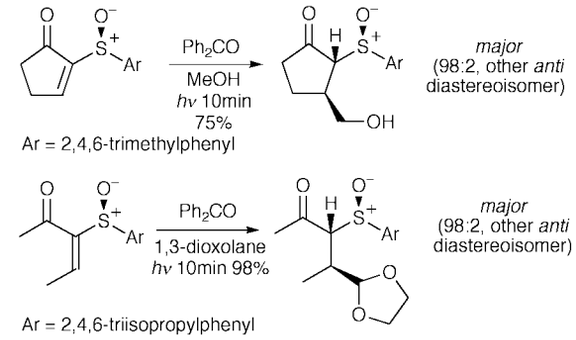
Sulfoxides are becoming increasingly important as stereocontrol elements in radical chemistry. High levels of 1,2-asymmetric induction have been observed for the first time in the cyclisation of non-stabilised sulfinylated alkyl radicals (Scheme 136).[267] The *ortho*-chlorophenyl group plays a crucial role in favouring the s-*cis* conformation of the radical intermediate. A chair-like transition state for the cyclisation, with attack *anti* to the *ortho*-chlorophenyl group can then be used to



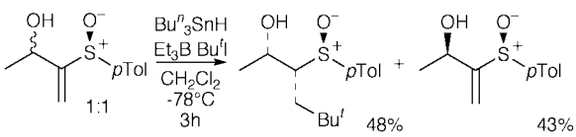
Scheme 136

explain the selectivities observed.[267] Vinyl sulfoxides are good radical acceptors and the addition of radicals to enantiomerically pure vinyl sulfoxides is currently a popular area of study. High 1,3-asymmetric induction has been observed in the photo-induced addition of alcohol and 1,3-dioxolane radicals to enantiomerically pure 2-(arylsulfinyl)cyclopent-2-enones having bulky aryl groups on sulfur (Scheme 137).[268] Unlike previous radical additions of this type, high asymmetric induction was also observed in the addition to an acyclic system. In a related study, the addition of alkyl radicals to chiral α-(1-hydroxyethyl)vinyl sulfoxides has been studied. Interestingly, whereas the (2*S*,S_S)-substrate undergoes efficient, highly *syn*-selective addition, the (2*R*,S_S)-substrate is unreactive (Scheme 138).[269] This observation has been employed to separate a diastereoisomeric mixture of the vinyl sulfoxides. The dramatic difference in reactivity and the diastereoselectivity of the radical hydrogenation step, have been explained in terms of intramolecular hydrogen bonding effects.[269] Finally, an elegant strategy involving radical cyclisation onto an enantiomerically pure vinyl sulfoxide, followed by sequential β-sulfinyl radical elimination has been used for the preparation of enantiomerically enriched alkylidene cyclopentyl derivatives (Scheme 139).[270] The enantioselectivity of the process can be reversed simply by the addition of methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide). High selectivities, however, are dependent upon the presence of terminal disubstitution in the vinyl sulfoxide substrate.[270]

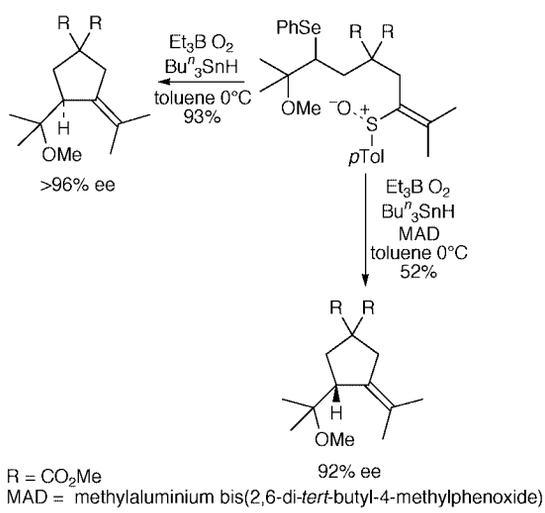
The use of enantiomerically pure sulfoxides in Diels–Alder reactions remains an active area of research. Kinetic resolution in the Diels–Alder reaction of an enantiomerically pure sulfinyl naphthoquinone dienophile with racemic vinyl cyclohexenes gives adducts in moderate yield and good enantiomeric excess (Scheme 140).[271] A similar strategy has been used for the kinetic resolution of acyclic dienes having a chiral allylic centre.[272] Related enantiomerically pure S_S-(2-*p*-tolylsulfinyl)-1,4-benzoquinone **67** has been employed in an asymmetric approach to helicenebisquinones,[273] and a systematic study of the Diels–



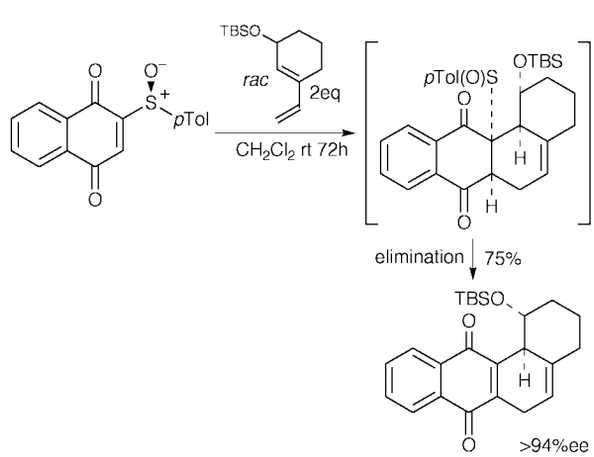
Scheme 137



Scheme 138

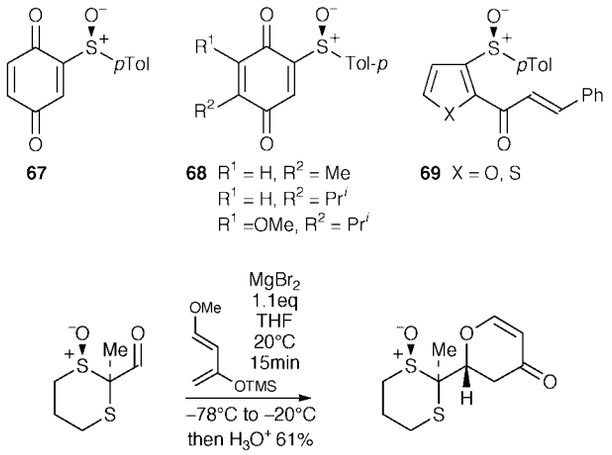


Scheme 139



Scheme 140

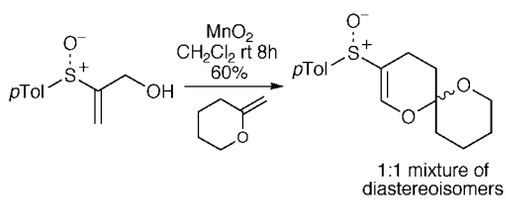
Alder chemistry of more substituted derivatives **68** has also been carried out.[274] 2-Furyl and 2-thienyl α,β-enones **69**, bearing a chiral sulfinyl group on the heterocyclic ring, have been shown to be efficient dienophiles in Diels–Alder reactions with cyclopentadiene in the presence of Lewis acid catalysts.[275] *syn*-2-Formyl-2-methyl-1,3-dithiane 1-oxide undergoes a diastereoselective hetero Diels–Alder reaction with Danishefsky's diene (Scheme 141).[276] The resultant adduct has been used in an



67 68 R^1 = H, R^2 = Me; R^1 = H, R^2 = Pr^i; R^1 = OMe, R^2 = Pr^i 69 X = O, S

Scheme 141

approach to 2-bromo-4-deoxypyranoside derivatives. Oxidation of S_S-2-(*p*-tolylsulfinyl)prop-2-en-1-ol and *in situ* hetero Diels–Alder reaction gave a mixture of vinyl sulfoxide spirocycles which were used in the preparation of pheromone components of the olive fruit-fly (Scheme 142).[277] A related hetero Diels–Alder approach has been used in an approach to the *mus musculus* pheromone.[278]

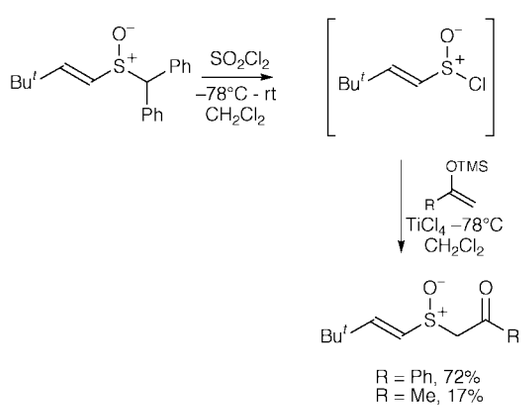


Scheme 142

3.2.3 Unsaturated sulfoxides and selenoxides

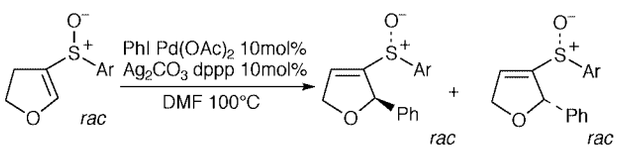
p-Tolylvinyl sulfoxide has been resolved by an interesting procedure using (−)-menthol.[279] Michael addition of (−)-menthol to the vinyl sulfoxide, separation of the diastereoisomers by crystallisation, and elimination under basic conditions releases the enantiopure vinyl sulfoxides.[279]

The first preparation of alk-1-enesulfinyl chlorides *via* the oxidative fragmentation of diphenylmethyl and *p*-methoxybenzyl sulfoxides has been achieved.[280] The sulfinyl chlorides can be isolated or used *in situ*. Under Lewis acid conditions they react with trimethylsilyl enol ethers to give β-keto vinyl sulfoxides in yields which vary largely depending on the substrates involved (Scheme 143).[280]



Scheme 143

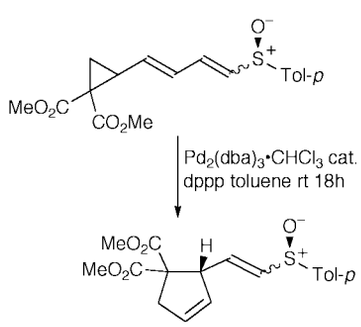
The sulfoxide group has been used as a stereocontrol element in several palladium-catalysed reactions. The novel use of a sulfinyl group in the asymmetric Heck reactions of dihydrofurans has been reported.[281] The aryl substituent on the sulfoxide was found to be important and when a substituent with a coordinating dimethylamino group was used, a dramatic switch in selectivity was observed (Scheme 144). The use of enantiomerically pure sulfoxide substrates was also investigated and gave the expected non-racemic product vinyl sulfoxides.[281] The palladium-catalysed 1,3-rearrangement of enantiomerically pure (4-arylsulfinylbuta-1,3-dienyl)cyclopropanes gives cyclopentenes in high diastereoisomeric excess (Scheme 145).[282] Results suggest that the chiral sulfoxide interacts directly with the palladium centre during formation of the intermediate π-allyl complex. The palladium-catalysed cyclisation of *N*-Boc and *N*-trifluoroacetyl substituted 4-acetoxy-5-(*p*-tolylsulfinyl)-hex-5-enylamines has been utilised in the synthesis of pyrrolidines (Scheme 146).[283] Interestingly, the diastereoselectivity was found to be highly dependent on the nitrogen substituent.



Ar = 2,4-$Me_2C_6H_3$-, 80%, 78 : 22
Ar = *o*-$(Me_2N)C_6H_4$-, 80%, 6 : 94

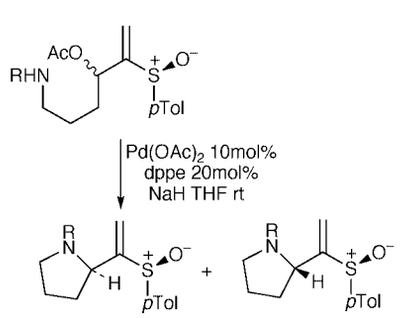
dppp = 1,3-bis(diphenylphosphino)propane

Scheme 144



starting material, *E*/product, *E*, 72%, 68% de
starting material, *Z*/product, *Z*, 8%, 79% de

Scheme 145

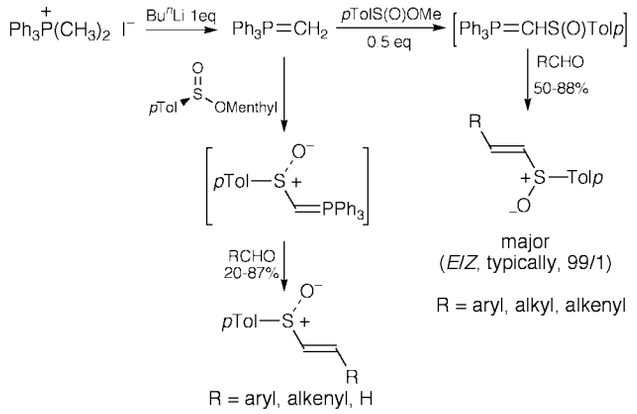


R = Boc, 88% yield, 90 : 10
R = $COCF_3$, 61% yield, 40 : 60

dppe = 1,2-bis(diphenylphosphino)ethane

Scheme 146

Cobalt hexacarbonyl complexes derived from enantiomerically pure alkynyl sulfoxides have been used in Pauson–Khand reactions and give cyclic vinyl sulfoxides with moderate stereoselectivity.[284] α-Sulfinyl phosphonium ylides have been obtained *via* reaction of phosphonium ylides with sulfinate esters. Subsequent reaction with a range of aldehydes gave (*E*)-vinyl sulfoxides or (*E*)-dienyl sulfoxides in good yield

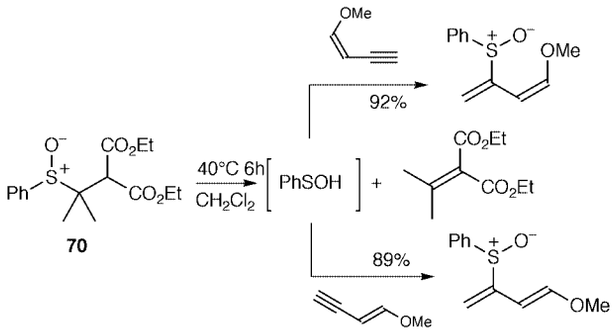


Scheme 147

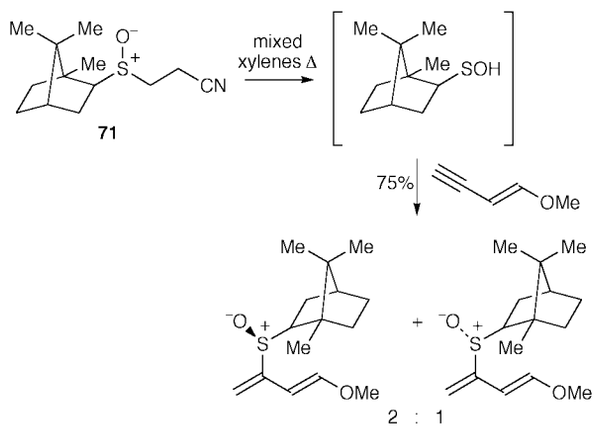
and with excellent selectivity (Scheme 147).[285] Enantiomerically pure (*E*)-vinyl sulfoxides were obtained when diastereoisomerically and enantiomerically pure sulfinate esters were used.[285]

C-Disaccharides have become important as potential glycosidase and disaccharidase inhibitors. In the synthesis of a novel *C*-disaccharide, the reaction of 1-*C*-lithiated 2-phenylsulfinyl-D-glucal with DMF gave the corresponding 1-formyl derivative (Scheme 148).[286] Treatment with a second equivalent of the 1-*C*-lithiated species gave the key bis-sulfoxide intermediate in modest yield.[286]

Trapping benzenesulfenic acid formed on decomposition of sulfoxide **70** with (*E*)- and (*Z*)-1-methoxybut-2-en-3-yne gave (*E*)-1-methoxy-3-(phenylsulfinyl)buta-1,3-diene and (*Z*)-1-methoxy-3-(phenylsulfinyl)buta-1,3-diene, respectively (Scheme 149).[287] The lithium perchlorate catalysed Diels–Alder reactions of these sulfinyl dienes were also studied.[287] Thermolysis of cyanosulfoxide **71** gives a camphor-derived sulfenic acid which undergoes efficient addition to (*E*)-1-methoxybut-1-en-3-yne to give 3-sulfinyl-1-methoxybuta-1,3-dienes in good yield (Scheme 150).[288] The diastereoisomeric dienes can be conveniently separated and have been employed in Diels–Alder reactions.



Scheme 149



Scheme 150

4 Synthesis of sulfones and selenones

As in previous years, the chemistry of selenones has received little attention and this section will deal solely with the preparation of sulfones.

Recent reviews in the area of sulfone chemistry detail developments in episulfone chemistry and in particular, the Ramberg–Backlund reaction,[289] and in the application of sulfonyl 1,3-dienes in organic synthesis.[290]

4.1 Oxidation of sulfides and sulfoxides

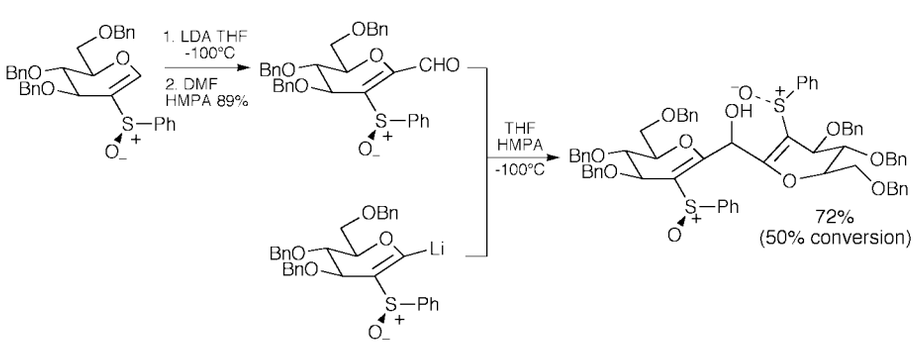
A limited number of reports dealing specifically with the oxidation of sulfides to sulfones have appeared. Diaryl, dialkyl, and aryl alkyl sulfides have been oxidised efficiently to the corresponding sulfones using urea–hydrogen peroxide and trifluoroacetic anhydride.[291] An efficient oxidation of sulfides to sulfones using periodic acid and a Mn^{IV}–Mn^{IV} binuclear complex as catalyst has been reported.[292] The reaction is chemoselective in the presence of other functional groups and only amines were found to hinder the reaction (Scheme 151).[292] Importantly, the catalyst can be readily recovered after reaction and reused with no appreciable loss in activity. The oxidation of thiophenes having an electron-withdrawing substituent is known to be difficult. Oxidation with dimethyldioxirane, however, gives sulfone products whereas oxidation with hydrogen peroxide or MCPBA give cycloadduct dimers of the corresponding thiophene 1-oxide.[293]

The oxidation of aryl methyl sulfoxides to the corresponding sulfones by oxo(salen)manganese(v) complexes has been the subject of a kinetic and mechanistic study.[294]

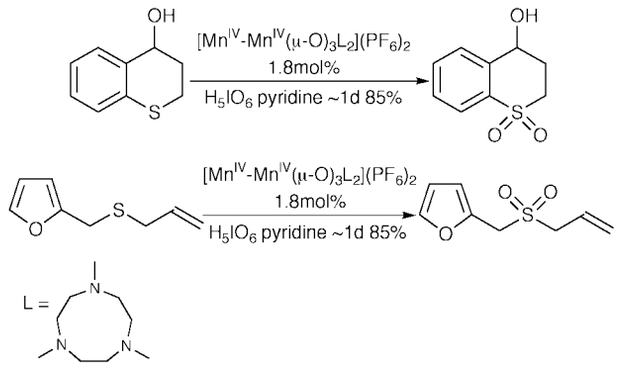
4.2 Non-oxidative routes to sulfones

4.2.1 Simple sulfones

The hydrogenation of vinyl sulfones represents a convenient method for the preparation of simple sulfones. A new chemoselective system for carrying out this transformation uses palladium on carbon and ammonium formate and gives the

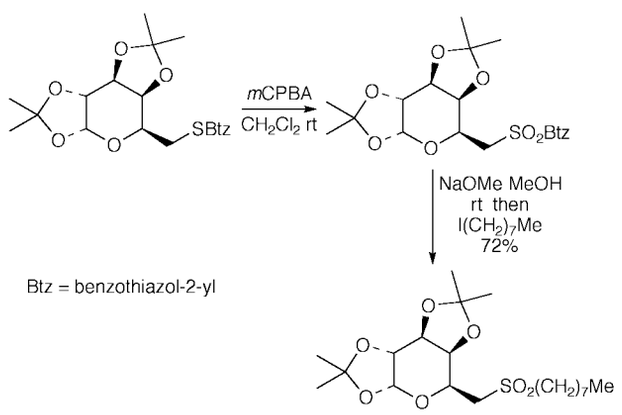


Scheme 148

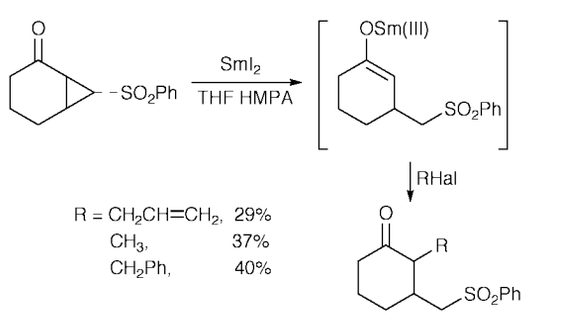


Scheme 151

corresponding saturated sulfones in high yield.[295] A variety of sugar-derived sulfones have been prepared from heteroaryl sulfones using a trans-sulfonylation reaction. Base-catalysed cleavage of the heteroaryl sulfones followed by *in situ* alkylation gives the desired sulfones in good yield (Scheme 152).[296] The reductive ring-opening of phenylsulfonyl cyclopropylketones with samarium(II) iodide, generates samarium(III) enolates which can be alkylated *in situ* to give substituted γ-phenylsulfonyl ketones in moderate yield (Scheme 153).[297]



Scheme 152

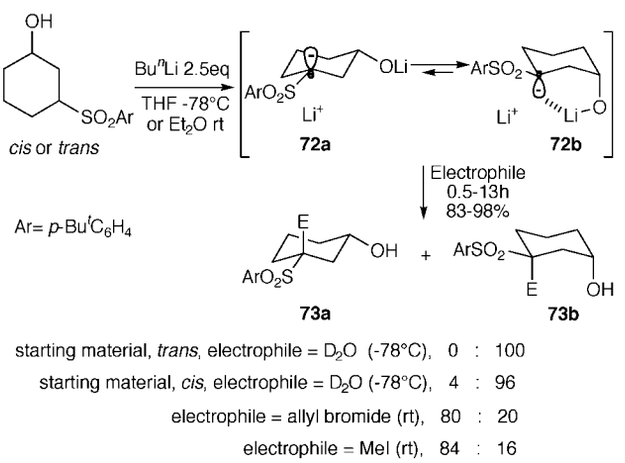


Scheme 153

Diaryl sulfones have been prepared by the Friedel–Crafts sulfonylation of simple aromatics with aryl sulfonyl chlorides catalysed by Fe(III) exchanged montmorillonite clay.[298]

4.2.2 Functionalised sulfones

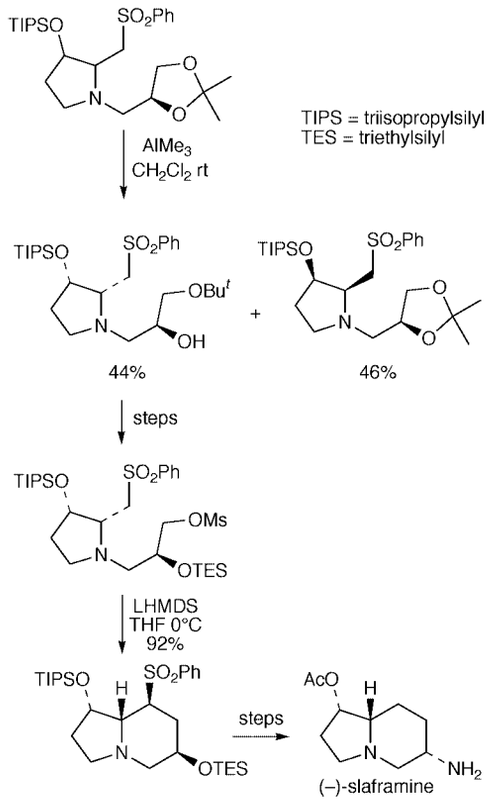
α-Arylsulfonyl carbanions are important intermediates for the synthesis of functionalised sulfones and an understanding of their reactivity is crucial. In a recent study, the dianion derived from either *cis* or *trans* 3-hydroxy-1-(arylsulfonyl)cyclohexane was quenched by D_2O to give **73b** as the major product, thus suggesting that isomerisation occurs during reaction of the *cis* hydroxy sulfone to give the more stable, chelated dianion **72b**. Interestingly, quenching with carbon electrophiles, albeit under modified conditions, gives predominantly **73a** suggesting that reaction of **72b** with these electrophiles occurs with inversion of configuration at the carbanionic centre (Scheme 154).[299] The monoanions derived from the corresponding protected hydroxy compounds were shown to give very different product ratios. A recent synthesis of (−)- and (+)-slaframine uses the stereoselective intramolecular alkylation of a sulfonyl carbanion to construct the indolizidine skeleton (Scheme 155).[300] Earlier in the synthesis, an interesting kinetic resolution was observed in the deprotection of a diastereoisomeric mixture of *syn*-sulfone acetals.[300] A new one-pot preparation of benzothiopyran derivatives involves the dilithiation of phenyl isopropyl sulfone followed by reaction with 1,2-diketones (Scheme 156).[301] Studies on the acylation and aldol reactions of α-sulfonyl cyclopropyl carbanions have shown that regardless of the relative stereochemistry in the starting sulfone, *anti*-products are invariably obtained.[302] A formal synthesis of hemibrevetoxin B has been reported which uses a linear approach involving key coupling steps using sulfonyl-stabilised oxiranyl anions (Scheme 157).[303] Finally, an asymmetric approach to sulfonyloxiranes using a phase-transfer catalysed Darzens reaction allows aromatic aldehydes to be converted into the corresponding sulfonyloxiranes with moderate to good enantioselectivity (Scheme 158).[304]



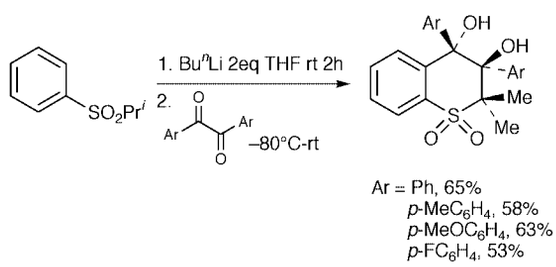
Scheme 154

The deprotonation of allylic sulfones gives more stabilised α-sulfonylcarbanions. The alkylation of these carbanions can sometimes be regiochemically ambiguous. 3-(Phenylsulfonyl)-methyl-substituted cyclopentanones undergo facile mono- and dialkylation reactions. The intramolecular alkylation of allylic sulfone **74** gave a spirocyclic vinyl sulfone rather than the seven-membered ring product (Scheme 159).[305] The Michael addition of allylic phenyl sulfone anions to enantiomerically pure enoate acceptors gives adducts with high diastereoselectivity (Scheme 160).[306] The sense of the diastereoselection was found to depend markedly on the presence of HMPA, the temperature, and the ester derivative employed as the Michael acceptor. The synthesis of piperidine derivatives has been carried out by the addition of an allylic sulfone dianion to enantiomerically pure sulfinimines.[307] Remote asymmetric induction has been achieved in the Michael addition of allylic α-phenylsulfonyl carbanions bearing chiral auxiliaries to acyclic α,β-unsaturated esters (Scheme 161).[308]

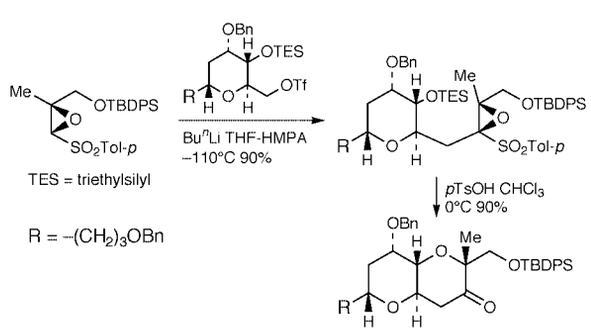
Vinyl sulfones are good Michael acceptors and such reactions are commonly employed for the synthesis of functionalised sulfones. The enantioselective synthesis of β-amino sulfones *via* the aza-Michael addition of enantiomerically pure ammonia equivalents has recently been reported.[309] Although yields are only moderate, diastereoselectivities are often high, and access to product sulfones in either stereochemical series is possible



Scheme 155

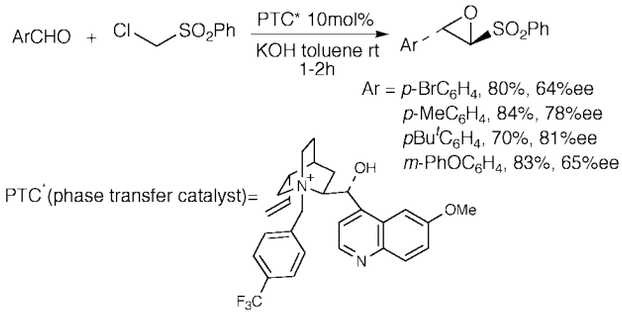


Scheme 156

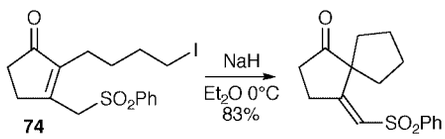


Scheme 157

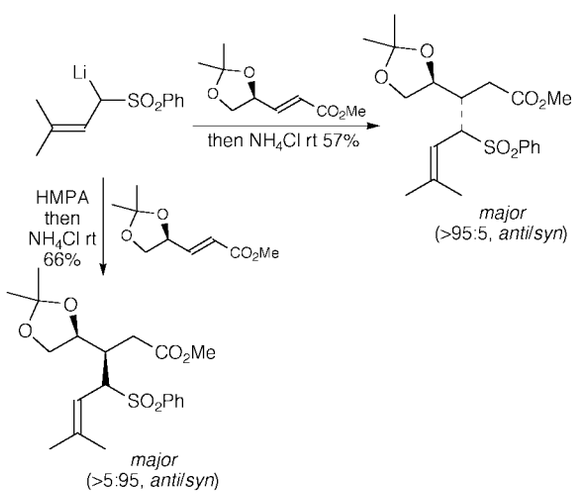
by using complementary 1-amino-pyrrolidine reagents (Scheme 162).[309] In an extension of this work, protection of the amine in β-amino sulfones, and deprotonation–alkylation gives *anti*-α-alkyl-β-amino sulfones with good selectivity.[310] Deprotonation of 1,4-oxathiane *S*,*S*-dioxide results in ring-opening elimination. The resultant vinyl sulfone intermediate can be trapped by Michael addition thus providing a route to a variety of difunctionalised sulfones (Scheme 163).[311] α,β-Unsaturated acid chlorides having an arylsulfonyl group in the α-position selectively undergo 1,4-addition on exposure to ammonia, and primary or secondary amines.[312] Subsequent cyclisation gives *trans*-azetidin-2-ones in moderate to good yield (Scheme 164). The nucleophilic epoxidation of vinyl sulfone **75** derived from



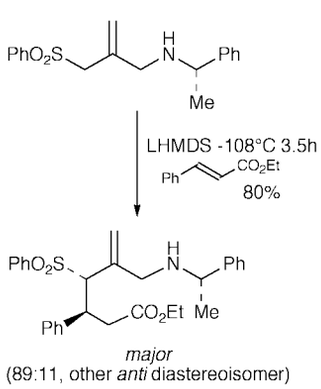
Scheme 158



Scheme 159



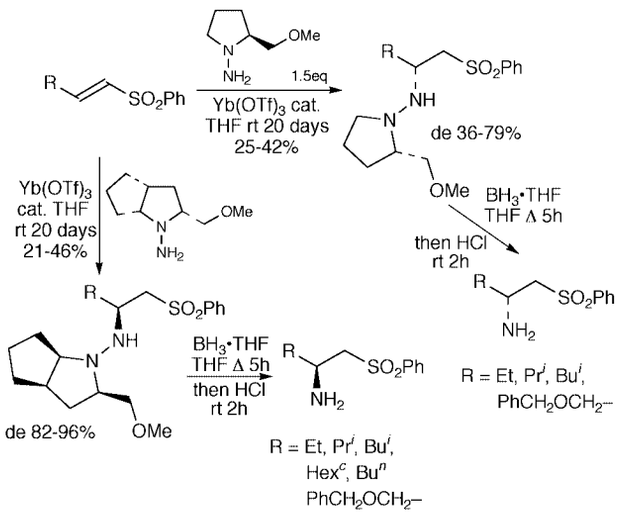
Scheme 160



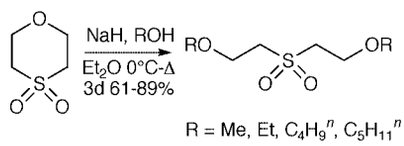
Scheme 161

isopropylidene glyceraldehyde using potassium alkyl peroxides proceeds with high diastereoselectivity (Scheme 165).[313] On treatment with *tert*-butyl hydroperoxide and $VO(acac)_2$, acyclic α-hydroxy vinyl sulfoxides undergo oxidation to the sulfone followed by a regio- and diastereoselective epoxidation to give sulfonyloxiranes in good yield (Scheme 166).[314]

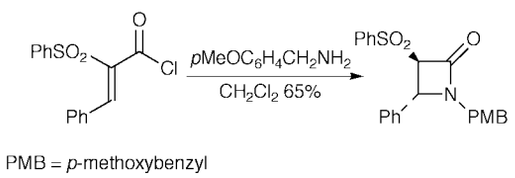
Vinyl sulfones are good radical acceptors. The addition of acyl radicals, generated from aliphatic and aromatic aldehydes by photolysis, to 3-hydroxy-1-(methylthio)-1-(*p*-tolylsulfonyl)-1-alkenes and their acetates, gives addition products with high *syn*-selectivity (Scheme 167).[315] In an earlier study, indanone derivatives were prepared using a similar approach.[316]



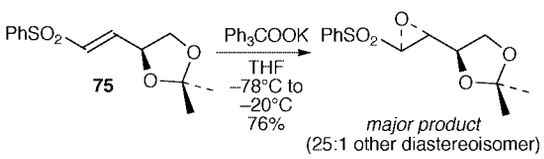
Scheme 162



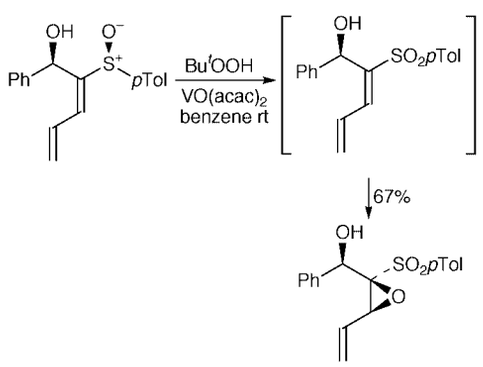
Scheme 163



Scheme 164

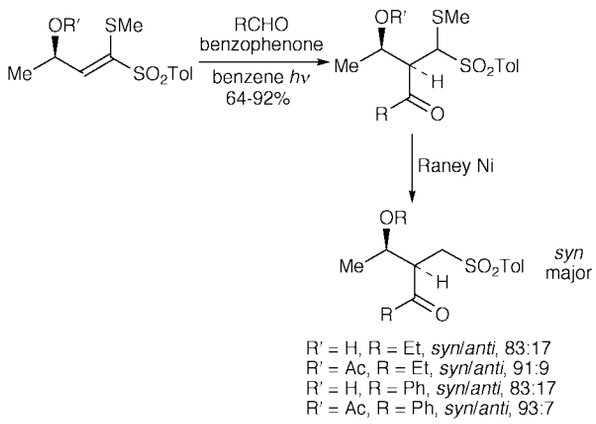


Scheme 165

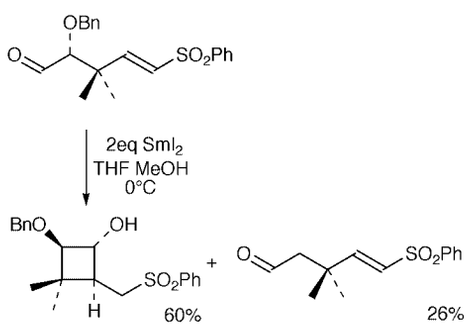


Scheme 166

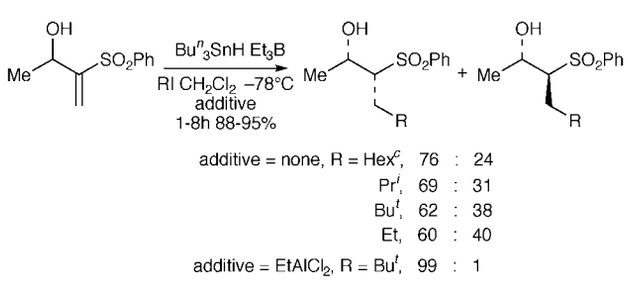
Aldehydes having a vinyl sulfone radical acceptor group in the γ-position undergo an unusual 4-*exo-trig* ketyl–olefin cyclisation on treatment with samarium(II) iodide.[317] The cyclisation proceeds with complete diastereoselectivity to give *anti*-cyclobutanols in moderate yield (Scheme 168). The addition of alkyl radicals to α-(1-hydroxyethyl)vinyl sulfone proceeds with modest preference for the *syn*-products (Scheme 169).[318] Selectivity in the reduction of the intermediate radical appears to arise from a conformational preference due to selective intra-



Scheme 167



Scheme 168

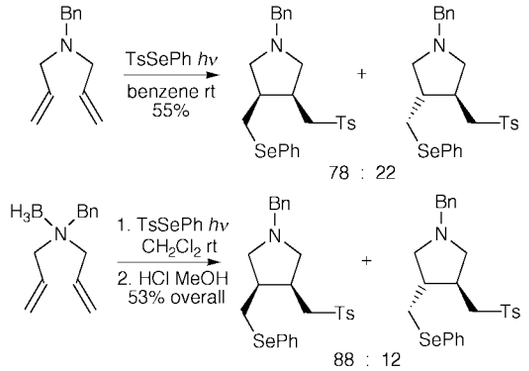


Scheme 169

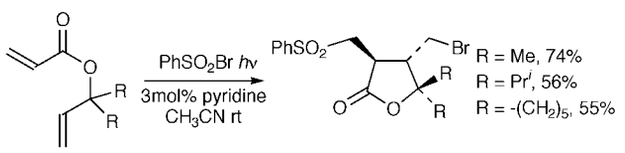
molecular hydrogen-bonding between the hydroxy group and one of the diastereotopic sulfone oxygens. Sulfones have also been prepared by other radical approaches. In the 5-*exo-trig* ring-closure of 3-azahex-5-enyl radicals, quaternisation at nitrogen facilitated cyclisation and led to a modest increase in diastereoselectivity (Scheme 170).[319] Functionalised γ-lactones have been prepared by the photochemical addition of benzenesulfonyl bromide to diene and enyne systems (Scheme 171).[320] *gem*-Dialkyl substitution in the substrate was found to be necessary for efficient cyclisation. The outcome of the cyclisation was found to depend on the structure of the substrate.[320]

In water and in the presence of indium metal, aryl sulfonyl chlorides react with α-bromo carbonyl compounds to give the corresponding β-keto sulfones in moderate yield.[321] Interestingly, the addition of aprotic solvents was found to slow the reaction. The (*R*) or (*S*)-MeO-BIPHEP–ruthenium catalysed asymmetric hydrogenation of β-keto sulfones gives the corresponding β-hydroxy sulfones in high enantiomeric excess (Scheme 172).[322,323] The enantioselective hydrogenation of sulfone acid **76** has been employed in the synthesis of an enantiomerically enriched sulfone building block for the preparation of renin inhibitors (Scheme 173).[324]

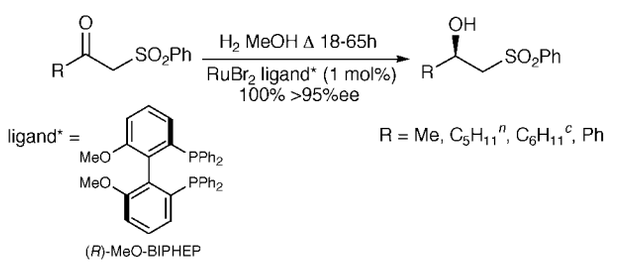
Vinyl sulfones are excellent dienophiles and have been employed recently in both inter- and intramolecular Diels–Alder reactions to give functionalised sulfone cycloadducts. The Diels–Alder cycloaddition reactions of (*E*)-1,2-bis(phenyl-



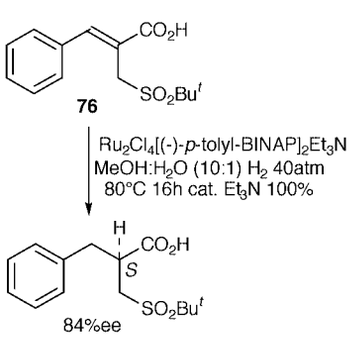
Scheme 170



Scheme 171



Scheme 172

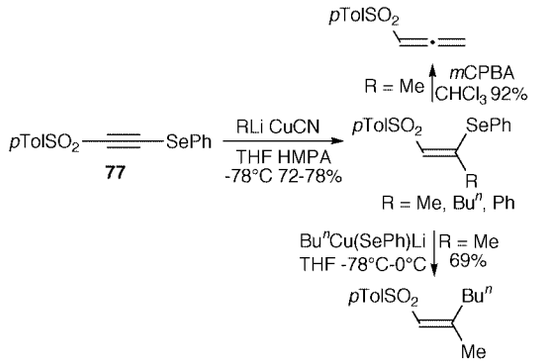


Scheme 173

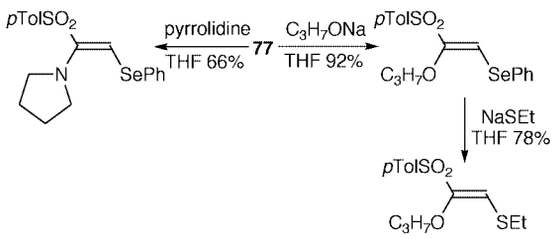
sulfonyl)ethene with 2- and 3-substituted furans has been studied and the selectivity explained using molecular modelling.[325] Finally, the intramolecular Diels–Alder reaction of sulfonyl trienes to form isoindole products has been reported.[326]

4.2.3 Vinylic and acetylenic sulfones

The addition of organocopper reagents to 1-phenylseleno-2-(*p*-tolylsulfonyl)ethyne **77** gives (*Z*)-β-(phenylseleno)vinyl sulfones in good yield.[327] Further treatment of these adducts with reagents of the form RCu(SePh)Li, results in displacement of the phenylseleno group with retention of configuration. Thus, by varying the order of reagent addition, a variety of β,β-disubstituted vinyl sulfones can be prepared stereoselectively (Scheme 174).[327] Alternatively, oxidation of (*Z*)-β-(phenylseleno)vinyl sulfones gives allenic sulfones *via* selenoxide elimination. Surprisingly, the addition of various heteroatom nucleophiles to **77** occurs in an anti-Michael sense and the products are obtained as single geometrical isomers (Scheme 175).[327] A convenient route to β-arylsulfonyl-α,β-unsaturated

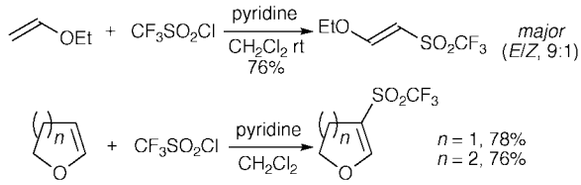


Scheme 174



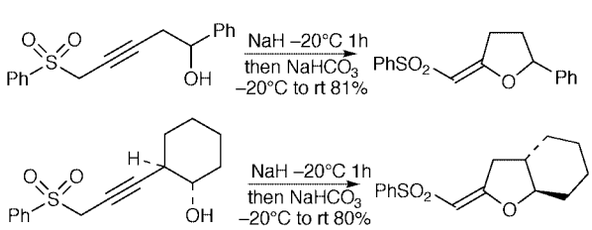
Scheme 175

ketones and vinyl bis-sulfones involving Friedel–Crafts addition of aryl acid chlorides and aryl sulfonyl chlorides to vinyl chloride has been reported.[328] (*E*)-β-Iodovinyl phenyl sulfone has been prepared in good yield from 1,2,2-trichloroethane *via* a sequence of reactions including a stereospecific addition–elimination step which converts (*E*)-β-chlorovinyl phenyl sulfone into the corresponding iodide.[329] The addition of trifluoromethanesulfonyl chloride to acyclic and cyclic vinyl ethers gives the corresponding β-alkoxy vinyl trifluoromethyl sulfones in good yield (Scheme 176).[330] A chiral pool approach to enantiomerically pure γ-hydroxy and γ-amino vinyl sulfones has been reported.[331]



Scheme 176

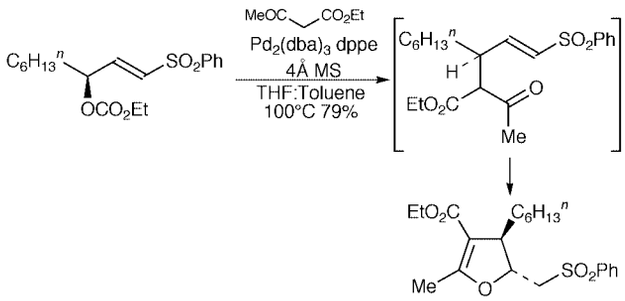
The cyclisation of an internal alkoxide onto allenic sulfones, formed by the base-promoted isomerisation of propargylic sulfones, has been used in the preparation of (*E*)-[(phenylsulfonyl)-methylene]tetrahydrofurans (Scheme 177).[332] In a separate study, the deprotonation and alkylation of vinyl sulfones of this type has been found to proceed regio- and stereoselectively.[333]



Scheme 177

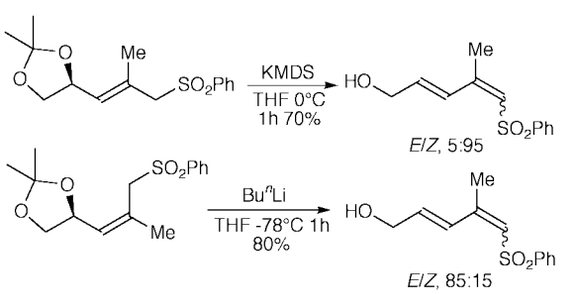
The palladium-catalysed nucleophilic allylic substitution of carbonates derived from γ-hydroxy vinyl sulfones with β-keto esters, 1,3-diketones and α-sulfonyl ketones gives tetrasubstituted dihydrofurans *via* an interesting sequential process.[334]

Regioselective allylic substitution initially gives the expected vinyl sulfone derivatives, however, stereoselective cyclisation then occurs to give predominantly *trans*-substituted dihydrofuran products (Scheme 178).[334]

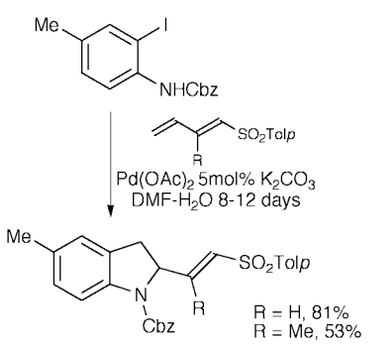


Scheme 178

The stereoselective synthesis of 1-hydroxymethyl-4-phenylsulfonylbutadienes has been achieved *via* the elimination of functionalised allylic sulfones derived from D-mannitol (Scheme 179).[335] This methodology has been applied to an elegant synthesis of isosorbide analogues.[336] The palladium-catalysed coupling of protected iodoanilines with 1-sulfonyl-1,3-dienes gives indolines having a vinyl sulfone moiety in the 2-position (Scheme 180).[337]



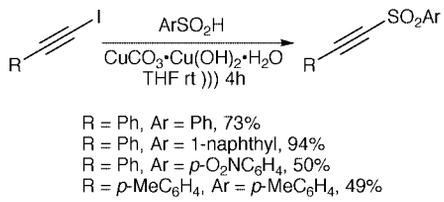
Scheme 179



Scheme 180

When acetylenic sulfones are employed as dienophiles in Diels–Alder reactions, cyclic vinyl sulfone cycloadducts are obtained. Readily accessible 2-bromoethynyl aryl sulfones have been found to be versatile dienophiles in [4 + 2] cycloadditions.[338] 1,3-Bis(phenylsulfonyl)allene has been prepared and employed as a new dienophile in [2 + 4] and [2 + 2] cycloaddition reactions.[339]

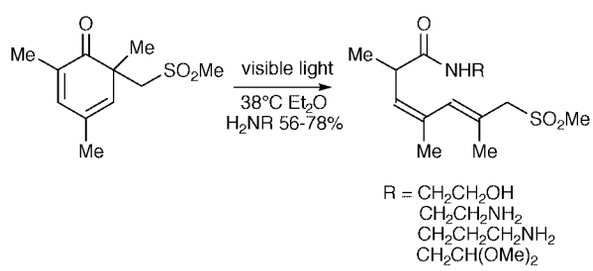
Finally, the copper-mediated sulfonylation of 1-haloalkynes with arylsulfinic acids under sonication gives the corresponding alkynyl aryl sulfones in moderate to good yield (Scheme 181).[340]



Scheme 181

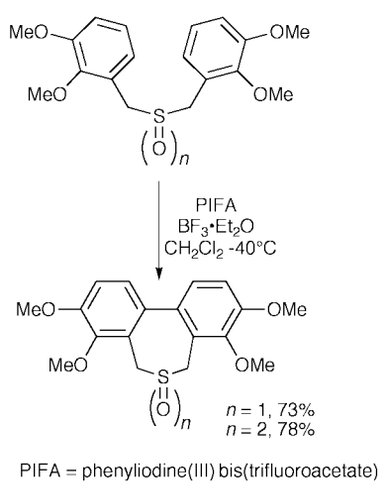
4.2.4 Allylic and benzylic sulfones

The synthesis of allylic sulfones from allylic halides and aryl and alkyl sulfonyl chlorides using bismuth or cadmium has been reported.[341] The reaction also works to a lesser extent for the conversion of alkyl halides into alkyl sulfones. Ester-containing allylic sulfones have been prepared stereoselectively from γ-hydroxy vinyl sulfones by ketene acetal formation and *in situ* Claisen rearrangement.[342] The hydrohalogenation of 1,2-allenic sulfones has been used to prepare 2-haloallyl sulfones.[343] Cyclohexa-2,4-dienone sulfone derivatives undergo facile ring cleavage upon exposure to visible light to give ketene intermediates which can be trapped by amines to give amide products in good yield (Scheme 182).[344]



Scheme 182

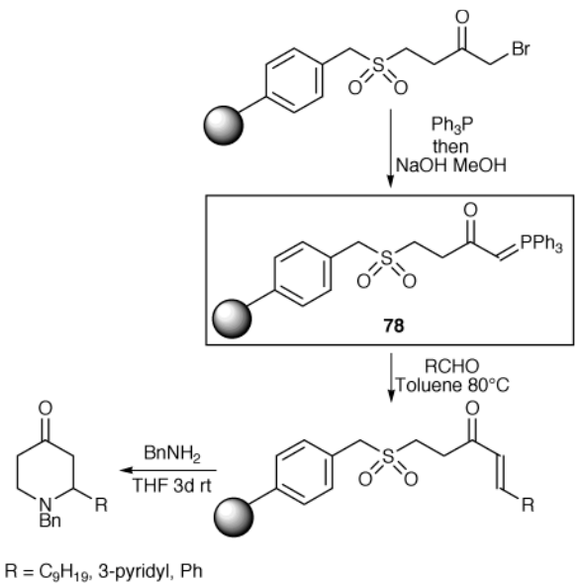
A novel biaryl coupling reaction of dibenzyl sulfones using a hypervalent iodine reagent has been reported.[345] Using a sulfone or sulfoxide tether the two aromatic rings are coupled to give interesting sulfur-containing dibenzoheterocyclic compounds (Scheme 183). Polymer-bound 4-benzylsulfonyl-1-(triphenylphosphoranylidene)butan-2-one **78** has been employed in an elegant solid phase synthesis of piperidin-4-one derivatives.[346] Wittig reaction followed by sequential Michael addition of benzylamine to the enone, sulfone elimination, and intramolecular Michael addition to the newly formed double bond, releases the piperidone products (Scheme 184).[346]



Scheme 183

5 Conclusion

Organosulfur and selenium chemistry play a crucial role in organic synthesis and, as such, are used widely throughout the many areas where synthetic chemistry finds application. The increasing importance of sulfur and selenium-containing



Scheme 184

enantiomerically pure ligands in asymmetric synthesis, and the continuing use of chiral sulfur and selenium groups as stereocontrol elements in many reactions, ensures that the synthesis of organosulfur and selenium compounds will continue to grow in importance. The development of new and improved asymmetric methods for the synthesis of these compounds, and the application of more established organosulfur and selenium chemistry to new problems in emerging areas, such as solid phase synthesis, represent some of the current challenges.

6 References

1 J. T. Ayers and S. R. Anderson, *Synth. Commun.*, 1999, **29**, 351.
2 H. Uchiro and S. Kobayashi, *Tetrahedron Lett.*, 1999, **40**, 3179.
3 T.-C. Zheng, M. Burkart and D. E. Richardson, *Tetrahedron Lett.*, 1999, **40**, 603.
4 K. E. Yelm, *Tetrahedron Lett.*, 1999, **40**, 1101.
5 N. W. Fadnavis, R. L. Babu, S. K. Vadivel, A. A. Deshpande and U. T. Bhalerao, *Tetrahedron: Asymmetry*, 1998, **9**, 4109.
6 J. Zhang and M. D. Matteucci, *Tetrahedron Lett.*, 1999, **40**, 1467.
7 A. M. Kimbonguila, A. Merzouk, F. Guibe and A. Loffet, *Tetrahedron*, 1999, **55**, 6931.
8 P. Gomez-Martinez, A. M. Kimbonguila and F. Guibe, *Tetrahedron*, 1999, **55**, 6945.
9 S. Vetter, *Synth. Commun.*, 1998, **28**, 3219.
10 K. Terao, M. Kunishima and S. Tani, *Synlett*, 1999, 733.
11 J. N. Freskos, B. V. Mischke, G. A. DeCrescenzo, R. Heintz, D. P. Getman, S. C. Howard, N. N. Kishore, J. J. McDonald, G. E. Munie, S. Rangwala, C. A. Swearingen, C. Voliva and D. J. Welsch, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 943.
12 G. Delogu, D. Fabbri and M. A. Dettori, *Tetrahedron: Asymmetry*, 1998, **9**, 2819.
13 J.-C. Fiaud, F. Maze and H. B. Kagan, *Tetrahedron: Asymmetry*, 1998, **9**, 3647.
14 N. A. Noureldin, M. Caldwell, J. Hendry and D. G. Lee, *Synthesis*, 1998, 1587.
15 M. Hirano, S. Yakabe, K.-I. Ando and T. Morimoto, *J. Chem. Res.* (*S*), 1998, 816.
16 N. Iranpoor and B. Zeynizadeh, *Synthesis*, 1999, 49.
17 I. Mohammadpoor-Baltork, A. R. Hajipour and H. Mohammadi, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 1649.
18 M. Hirano, H. Monobe, S. Yakabe and T. Morimoto, *J. Chem. Res.* (*S*), 1999, 374.
19 M. Hirano, S. Yakabe, H. Monobe and T. Morimoto, *J. Chem. Res.* (*S*), 1998, 472.
20 L. Sainte-Marie, E. Guibé-Jampel and M. Therisod, *Tetrahedron Lett.*, 1998, **39**, 9661.
21 A. R. Hajipour and N. Mahboubghah, *Indian J. Chem., Sect. B*, 1998, **37**, 1041.
22 H. Firouzabadi, M. Abbassi and B. Karimi, *Synth. Commun.*, 1999, **29**, 2527.
23 J. Kosmrlj, M. Kocevar and S. Polanc, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3917.
24 Y. Huang, H. Guo, Y. Zhang and Y. Wang, *J. Chem. Res.* (*S*), 1999, 214.
25 H. Firouzabadi and B. Karimi, *Synthesis*, 1999, 500.
26 I. Annis, L. Chen and G. Barany, *J. Am. Chem. Soc.*, 1998, **120**, 7226.
27 S. Otten, R. Frohlich and G. Haufe, *Heterocycles*, 1999, **51**, 505.
28 A. Z. Rys and D. N. Harpp, *Tetrahedron Lett.*, 1998, **39**, 9139.
29 I. A. Abu-Yousef and D. N. Harpp, *J. Org. Chem.*, 1998, **63**, 8654.
30 G. Mugesh, A. Panda, H. B. Singh, N. S. Punekar and R. J. Butcher, *Chem. Commun.*, 1998, 2227.
31 C. Santi and T. Wirth, *Tetrahedron: Asymmetry*, 1999, **10**, 1019.
32 J. Palus, J. Mlochowski and L. Juchniewicz, *Pol. J. Chem.*, 1998, **72**, 1931.
33 M. Vilaseca, E. Nicolas, F. Capdevila and E. Giralt, *Tetrahedron*, 1998, **54**, 15273.
34 J. L. G. Ruano, A. Lorente and J. H. R. Ramos, *Tetrahedron Lett.*, 1998, **39**, 9765.
35 S. Fabre, B. Findeis, D. J. M. Trosch, L. H. Gade, I. J. Scowen and M. McPartlin, *Chem. Commun.*, 1999, 577.
36 R. M. Adlington, J. E. Baldwin and G. L. Challis, *Tetrahedron Lett.*, 1998, **39**, 8537.
37 A. Ogawa, N. Takami, M. Sekiguchi, N. Sonoda and T. Hirao, *Heteroatom. Chem.*, 1998, **9**, 581.
38 G. Lu, Z. Zhan and Y. Zhang, *Synth. Commun.*, 1998, **28**, 3657.
39 J. Uenishi, T. Takagi, T. Ueno, T. Hiraoka, O. Yonemitsu and H. Tsukube, *Synlett*, 1999, 41.
40 F.-I. Auzanneau, K. Bennis, E. Fanton, D. Prome, J. Defaye and J. Gelas, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3629.
41 A. A. L. Gunatilaka, F. D. Ramdayal, M. H. Sarragiotto, D. G. I. Kingston, D. L. Sackett and E. Hamel, *J. Org. Chem.*, 1999, **64**, 2694.
42 D. Xiao, Z. Zhang, Q. Jiang and X. Zhang, *Tetrahedron Lett.*, 1998, **39**, 5331.
43 S. K. Singh, R. Kumar and J. Wengel, *J. Org. Chem.*, 1998, **63**, 6078.
44 E. Ichikawa, S. Yamamura and K. Kato, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1113.
45 J. R. Falck, J.-Y. Lai, S.-D. Cho and J. Yu, *Tetrahedron Lett.*, 1999, **40**, 2903.
46 A. Garofalo, G. Campiani, I. Fiorini and V. Nacci, *Tetrahedron*, 1999, **55**, 1479.
47 K. Shibata, H. Yamaga and O. Mitsunobu, *Heterocycles*, 1999, **50**, 947.
48 M. Romero-Ortega, A. Fuentes, C. Gonzalez, D. Morales and R. Cruz, *Synthesis*, 1999, 225.
49 K. Yanada, T. Fujita and R. Yanada, *Synlett*, 1998, 971.
50 L.-H. Zhou and Y.-M. Zhang, *Synth. Commun.*, 1999, **29**, 533.
51 L. Wang and Y. Zhang, *J. Chem. Res.* (*S*), 1998, 598.
52 L. Wang and Y. Zhang, *Heteroatom. Chem.*, 1999, **10**, 203.
53 T. Ruhland, K. Andersen and H. Pedersen, *J. Org. Chem.*, 1998, **63**, 9204.
54 K. C. Nicolaou, J. Pastor, S. Barluenga and N. Winssinger, *Chem. Commun.*, 1998, 1947.
55 J. S. Sawyer, E. A. Schmittling, J. A. Palkowitz and W. J. Smith III, *J. Org. Chem.*, 1998, **63**, 6338.
56 W. C. Black and B. Guay, *Synthesis*, 1998, 1101.
57 A. M. Ratz and L. O. Weigel, *Tetrahedron Lett.*, 1999, **40**, 2239.
58 A. A. Vasil'ev, L. Engman, J. P. Storm and C.-M. Andersson, *Organometallics*, 1999, **18**, 1318.
59 T. Arnauld, D. H. R. Barton and J.-F. Normant, *J. Org. Chem.*, 1999, **64**, 3722.
60 N. Zheng, J. C. McWilliams, F. J. Fleitz, J. D. Armstrong III and R. P. Volante, *J. Org. Chem.*, 1998, **63**, 9606.
61 Q. T. Do, D. Elothmani and G. Le Guillanton, *Tetrahedron Lett.*, 1998, **39**, 4657.
62 Y. Kita, M. Egi and H. Tohma, *Chem. Commun.*, 1999, 143.
63 A. V. Kalinin, J. F. Bower, P. Riebel and V. Snieckus, *J. Org. Chem.*, 1999, **64**, 2986.
64 C. Hamdouchi, J. de Blas and J. Ezquerra, *Tetrahedron*, 1999, **55**, 541.
65 L.-B. Han and M. Tanaka, *Chem. Commun.*, 1999, 395.
66 T. Kondo, S. Uenoyama, K. Fujita and T. Mitsudo, *J. Am. Chem. Soc.*, 1999, **121**, 482.
67 L. Bell, D. C. Brookings, G. J. Dawson, R. J. Whitby, R. V. H. Jones and M. C. H. Standen, *Tetrahedron*, 1998, **54**, 14617.
68 R. W. Hoffmann and R. Koberstein, *Chem. Commun.*, 1999, 33.
69 F. Chen, B. Mudryk and T. Cohen, *Tetrahedron*, 1999, **55**, 3291.
70 V. Cere, F. Peri and S. Pollicino, *Heterocycles*, 1999, **51**, 1025.
71 N. Brauer, T. Michel and E. Schaumann, *Tetrahedron*, 1998, **54**, 11481.
72 E. Hauptman, P. J. Fagan and W. Marshall, *Organometallics*, 1999, **18**, 2061.

73 W. Adam, B. Frohling, K. Peters and S. Weinkotz, *J. Am. Chem. Soc.*, 1998, **120**, 8914.
74 S. Tangestaninejad and V. Mirkhani, *J. Chem. Res.* (*S*), 1999, 370.
75 R. A. Al-Qawasmeh, R. J. Abdel-Jalil, T. H. Al-Tel, R. Thurmer and W. Voelter, *Tetrahedron Lett.*, 1998, **39**, 8257.
76 L. Di Nunno, C. Franchini, A. Nacci, A. Scilimati and M. A. Sinicropi, *Tetrahedron: Asymmetry*, 1999, **10**, 1913.
77 I. Maciagiewicz, P. Dybowski and A. Skowronska, *Tetrahedron Lett.*, 1999, **40**, 3791.
78 G. Mloston, J. Romanski and H. Heimgartner, *Heterocycles*, 1999, **50**, 403.
79 B. Koning, A. Meetsma and R. M. Kellogg, *J. Org. Chem.*, 1998, **63**, 5533.
80 E. Hauptman, R. Shapiro and W. Marshall, *Organometallics*, 1998, **17**, 4976.
81 S.-L. You, Y.-G. Zhou, X.-L. Hou and L.-X. Dai, *Chem. Commun.*, 1998, 2765.
82 G. Manickam and G. Sundararajan, *Tetrahedron*, 1999, **55**, 2721.
83 O. Miyata, Y. Fujiwara, I. Ninomiya and T. Naito, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2167.
84 M. Ono, K. Nishimura, Y. Nagaoka and K. Tomioka, *Tetrahedron Lett.*, 1999, **40**, 1509.
85 F. Dinon, E. Richards, P. J. Murphy, D. E. Hibbs, M. B. Hursthouse and K. M. A. Malik, *Tetrahedron Lett.*, 1999, **40**, 3279.
86 K. Kobayashi, R. Nakahashi, A. Shimizu, T. Kitamura, O. Morikawa and H. Konishi, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1547.
87 K. C. Majumdar and P. Biswas, *Tetrahedron*, 1998, **54**, 11603.
88 S. I. Kozhushkov, M. Brandl and A. de Meijere, *Eur. J. Org. Chem.*, 1998, 1535.
89 S. Usui and L. A. Paquette, *Tetrahedron Lett.*, 1999, **40**, 3495.
90 M. Tada, T. Uetake and Y. Hanaoka, *Chem. Commun.*, 1999, 75.
91 N. Aguilar, A. Moyano, M. A. Pericas and A. Riera, *Tetrahedron Lett.*, 1999, **40**, 3913.
92 M. H. Wu and E. N. Jacobsen, *J. Org. Chem.*, 1998, **63**, 5252.
93 J. Wu, X.-L. Hou, L.-X. Dai, L.-J. Xia and M.-H. Tang, *Tetrahedron: Asymmetry*, 1998, **9**, 3431.
94 M. Shirahata, H. Yamazaki and S. Fukuzawa, *Chem. Lett.*, 1999, 245.
95 X. Huang and D.-H. Duan, *J. Chem. Res.* (*S*), 1998, 396.
96 D.-H. Duan and X. Huang, *J. Chem. Res.* (*S*), 1999, 26.
97 X. Huang and D.-H. Duan, *Synlett*, 1998, 1191.
98 D. Enders, T. Schafer and W. Mies, *Tetrahedron*, 1998, **54**, 10239.
99 K. Wisniewski, A. Zamojski and R. D. Rogers, *Tetrahedron*, 1998, **54**, 14201.
100 D. J. Adams, N. S. Simpkins and T. J. N. Smith, *Chem. Commun.*, 1998, 1605.
101 A. L. Braga, L. Dornelles, C. C. Silveira and L. A. Wessjohann, *Synthesis*, 1999, 562.
102 F. Clerici, M. L. Gelmi and D. Pocar, *J. Org. Chem.*, 1999, **64**, 726.
103 M. Fachini, V. Lucchini, G. Modena, M. Pasi and L. Pasquato, *J. Am. Chem. Soc.*, 1999, **121**, 3944.
104 H. Hayakawa, N. Okada and M. Miyashita, *Tetrahedron Lett.*, 1999, **40**, 3191.
105 I. P. Smoliakova, M. Han, J. Gong, R. Caple and W. A. Smit, *Tetrahedron*, 1999, **55**, 4559.
106 K. Yamada, S. Sakata and Y. Yoshimura, *J. Org. Chem.*, 1998, **63**, 6891.
107 L. S. Jeong, S. J. Yoo, H. R. Moon, Y. H. Kim and M. W. Chun, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3325.
108 L. S. Jeong, H. R. Moon, S. J. Yoo, S. N. Lee, M. W. Chun and Y.-H. Lim, *Tetrahedron Lett.*, 1998, **39**, 5201.
109 M. Gruttadauria, P. Lo Meo and R. Noto, *Tetrahedron*, 1999, **55**, 4769.
110 M. I. Lazareva, Y. K. Kryschenko, R. Caple, D. Wakefield, A. Hayford, W. A. Smit and A. S. Shashkov, *Tetrahedron Lett.*, 1998, **39**, 8787.
111 T. Wirth, *Tetrahedron*, 1999, **55**, 1.
112 M. Tiecco, L. Testaferri, C. Santi, F. Marini, L. Bagnoli, A. Temperini and C. Tomassini, *Eur. J. Org. Chem.*, 1998, 2275.
113 M. Tiecco, L. Testaferri, F. Marini, C. Santi, L. Bagnoli and A. Temperini, *Tetrahedron: Asymmetry*, 1999, **10**, 747.
114 T. G. Back and S. Nan, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3123.
115 C. Santi, G. Fragale and T. Wirth, *Tetrahedron: Asymmetry*, 1998, **9**, 3625.
116 G. Mugesh, H. B. Singh and R. J. Butcher, *Tetrahedron: Asymmetry*, 1999, **10**, 237.
117 H. Komatsu, M. Iwaoka and S. Tomoda, *Chem. Commun.*, 1999, 205.
118 G. Fragale, M. Neuberger and T. Wirth, *Chem. Commun.*, 1998, 1867.
119 G. Fragale and T. Wirth, *Eur. J. Org. Chem.*, 1998, 1361.
120 T. G. Back, B. P. Dyck and S. Nan, *Tetrahedron*, 1999, **55**, 3191.
121 H. Takada, Y. Nishibayashi and S. Uemura, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1511.
122 R. Deziel, E. Malenfant and C. Thibault, *Tetrahedron Lett.*, 1998, **39**, 5493.
123 K. S. Kim, J. I. Park and P. Ding, *Tetrahedron Lett.*, 1998, **39**, 6471.
124 K. S. Kim, J. I. Park, H. K. Moon and H. Yi, *Chem. Commun.*, 1998, 1945.
125 F. Bravo, M. Kassou and S. Castillon, *Tetrahedron Lett.*, 1999, **40**, 1187.
126 K. Haraguchi, M. Hosoe, H. Tanaka, S. Tsuruoka, K. Kanmuri and T. Miyasaka, *Tetrahedron Lett.*, 1998, **39**, 5517.
127 L. Arista, M. Gruttadauria and R. Noto, *Heterocycles*, 1998, **48**, 1325.
128 T. Hirose, N. Morita, M. Asakura, K. Kitahara, S. Toyota and M. Oki, *Tetrahedron Lett.*, 1998, **39**, 8877.
129 M. Demarcus, S. N. Filigheddu, A. Mann and M. Taddei, *Tetrahedron Lett.*, 1999, **40**, 4417.
130 G. C. Torchiarolo, F. D'Onofrio, R. Margarita, L. Parlanti, G. Piancatelli and M. Bella, *Tetrahedron*, 1998, **54**, 15657.
131 P. Magnus and I. S. Mitchell, *Tetrahedron Lett.*, 1998, **39**, 9131.
132 A. Padwa, T. M. Heidelbaugh, J. T. Kuethe and M. S. McClure, *J. Org. Chem.*, 1998, **63**, 6778.
133 D. K. Bates and M. Xia, *J. Org. Chem.*, 1998, **63**, 9190.
134 S. V. Kirpichenko, E. N. Suslova, A. I. Albanov and B. A. Shainyan, *Tetrahedron Lett.*, 1999, **40**, 185.
135 S. Furuta, M. Kuroboshi and T. Hiyama, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 2687.
136 S. Furuta, M. Kuroboshi and T. Hiyama, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 1939.
137 S. Higashiya, S. Narizuka, A. Konno, T. Maeda, K. Momota and T. Fuchigami, *J. Org. Chem.*, 1999, **64**, 133.
138 K. M. Dawood and T. Fuchigami, *J. Org. Chem.*, 1999, **64**, 138.
139 T. Billard, N. Roques and B. R. Langlois, *J. Org. Chem.*, 1999, **64**, 3813.
140 C. Jouen, S. Lemaitre, T. Lequeux and J. C. Pommelet, *Tetrahedron*, 1998, **54**, 10801.
141 K. Nakamura, T. Matsuda, M. Shimizu and T. Fujisawa, *Tetrahedron*, 1998, **54**, 8393.
142 P. Bravo, A. Arnone, P. Bandiera, L. Bruche, Y. Ohashi, T. Ono, A. Sekine and M. Zanda, *Eur. J. Org. Chem.*, 1999, 111.
143 J. Breu, P. Hocht, U. Rohr, J. Schatz and J. Sauer, *Eur. J. Org. Chem.*, 1998, 2861.
144 U. Rohr, J. Schatz and J. Sauer, *Eur. J. Org. Chem.*, 1998, 2875.
145 G. M. Li, S. Niu, M. Segi, R. A. Zingaro, H. Yamamoto, K. Watanabe, T. Nakajima and M. B. Hall, *J. Org. Chem.*, 1999, **64**, 1565.
146 S. Yamazaki, H. Kataoka and S. Yamabe, *J. Org. Chem.*, 1999, **64**, 2367.
147 A. Ogawa, T. Ikeda, K. Kimura and T. Hirao, *J. Am. Chem. Soc.*, 1999, **121**, 5108.
148 V.-H. Nguyen, H. Nishino, S. Kajikawa and K. Kurosawa, *Tetrahedron*, 1998, **54**, 11445.
149 L.-B. Han and M. Tanaka, *J. Am. Chem. Soc.*, 1998, **120**, 8249.
150 J. Gerard, E. Bietlot and L. Hevesi, *Tetrahedron Lett.*, 1998, **39**, 8735.
151 X. Huang, X.-H. Xu and W.-X. Zheng, *Synth. Commun.*, 1999, **29**, 2399.
152 X. Huang and P. Zhong, *J. Chem. Res.* (*S*), 1999, 290.
153 Y. Ma and X. Huang, *Synth. Commun.*, 1999, **29**, 429.
154 A. Ogawa, I. Ogawa, R. Obayashi, K. Umezu, M. Doi and T. Hirao, *J. Org. Chem.*, 1999, **64**, 86.
155 C. C. Silveira, G. Perin, A. L. Braga, M. J. Dabdoub and R. G. Jacob, *Tetrahedron*, 1999, **55**, 7421.
156 I. Daub, A.-K. Habermann, A. Hobert and M. Julia, *Eur. J. Org. Chem.*, 1999, 163.
157 A. Przezdziecka, W. Stepanenko and J. Wicha, *Tetrahedron: Asymmetry*, 1999, **10**, 1589.
158 P. A. Grieco and M. D. Kaufman, *Tetrahedron Lett.*, 1999, **40**, 1265.
159 T. Saito, K. Takekawa and T. Takahashi, *Chem. Commun.*, 1999, 1001.
160 S. Ozaki, E. Matsui, T. Saiki, H. Yoshinaga and H. Ohmori, *Tetrahedron Lett.*, 1998, **39**, 8121.
161 X. Huang and Y. Ma, *Chin. J. Chem.*, 1998, **16**, 483.

162 A.-M. Sun and X. Huang, *J. Chem. Res.* (*S*), 1998, 616.
163 X. Huang and A.-M. Sun, *J. Chem. Res.* (*S*), 1999, 292.
164 X.-H. Xu, W.-X. Zheng and X. Huang, *Synth. Commun.*, 1998, **28**, 4165.
165 A. Ogawa, A. Kudo and T. Hirao, *Tetrahedron Lett.*, 1998, **39**, 5213.
166 M. Yoshimatsu, S. Gotoh, K. Ikeda and M. Komori, *J. Org. Chem.*, 1998, **63**, 6619.
167 M. Koketsu, Y. Miyajima and H. Ishihara, *Chem. Lett.*, 1998, 645.
168 P. Diaz, F. Gendre and J.-M. Bernardon, *Tetrahedron Lett.*, 1998, **39**, 9003.
169 M. Frank and H.-J. Gais, *Tetrahedron: Asymmetry*, 1998, 3353.
170 T. Shinada, Y. Yoshida and Y. Ohfune, *Tetrahedron Lett.*, 1998, **39**, 6027.
171 H. K. Dobson, R. LeBlanc, H. Perrier, C. Stephenson, T. R. Welch and D. Macdonald, *Tetrahedron Lett.*, 1999, **40**, 3119.
172 W.-M. Dai and Y. H. Lee, *Tetrahedron Lett.*, 1998, **39**, 8149.
173 A. Ariffin, A. J. Blake, R. A. Ewin and N. S. Simpkins, *Tetrahedron: Asymmetry*, 1998, **9**, 2563.
174 M. Kunishima, D. Nakata, C. Goto, K. Hioki and S. Tani, *Synlett*, 1998, 1366.
175 M. Kunishima and S. Tani, *J. Synth. Org. Chem. Jpn.*, 1999, **57**, 127.
176 M. Gulea, P. Marchand, S. Masson, M. Sacquet and N. Collignon, *Synthesis*, 1998, 1635.
177 D. S. Carter and D. L. Van Vranken, *Tetrahedron Lett.*, 1999, **40**, 1617.
178 T. Fukuda, R. Irie and T. Katsuki, *Tetrahedron*, 1999, **55**, 649.
179 V. K. Aggarwal, E. S. Anderson, D. E. Jones, K. B. Obierey and R. Giles, *Chem. Commun.*, 1998, 1985.
180 Z. Zhan, G. Lu and Y. Zhang, *J. Chem. Res.* (*S*), 1999, 280.
181 G. Lu and Y. Zhang, *Synth. Commun.*, 1998, **28**, 4479.
182 Y. Nishiyama, Y. Kishimoto, K. Itoh and N. Sonoda, *Synlett*, 1999, 611.
183 Y. Nishiyama, T. Asano, Y. Kishimoto, K. Itoh and Y. Ishii, *Tetrahedron Lett.*, 1998, **39**, 8685.
184 H. Abe, A. Yamasaki and T. Harayama, *Chem. Pharm. Bull.*, 1998, **46**, 1311.
185 S. Meenakshisundaram and M. Amutha, *J. Chem. Res.* (*S*), 1999, 2.
186 G. Song, F. Wang, H. Zhang, X. Lu and C. Wang, *Synth. Commun.*, 1998, **28**, 2783.
187 R. S. Varma and R. Dahiya, *Synth. Commun.*, 1998, **28**, 4087.
188 K. S. Ravikumar, Y. M. Zhang, J.-P. Begue and D. Bonnet-Delpon, *Eur. J. Org. Chem.*, 1998, 2937.
189 S. Vayssie and H. Elias, *Angew. Chem., Int. Ed.*, 1998, **37**, 2088.
190 W. Zhou and E. L. Clennan, *J. Am. Chem. Soc.*, 1999, **121**, 2915.
191 M. H. Ali and G. J. Bohnert, *Synthesis*, 1998, 1238.
192 N. B. Karalkar, M. M. Salunkhe, K. P. Talekar and N. N. Maldar, *Indian. J. Chem., Sect. B*, 1998, **37**, 1184.
193 M. H. Ali, D. R. Leach and C. E. Schmitz, *Synth. Commun.*, 1998, **28**, 2969.
194 H. Firouzabadi and M. Abbasi, *Synth. Commun.*, 1999, **29**, 1485.
195 J. M. Fraile, J. I. Garcia, B. Lazaro and J. A. Mayoral, *Chem. Commun.*, 1998, 1807.
196 T. Iwahama, S. Sakaguchi and Y. Ishii, *Tetrahedron Lett.*, 1998, **39**, 9059.
197 A. V. Kuchin, S. A. Rubtsova, L. P. Karmanova, S. N. Subbotina and I. V. Loginova, *Russ. Chem. Bull.*, 1998, **47**, 2051.
198 A. R. Suarez, A. M. Baruzzi and L. I. Rossi, *J. Org. Chem.*, 1998, **63**, 5689.
199 A. D. M. Curtis, R. McCague, C. A. Ramsden and M. R. Raza, *Chem. Commun.*, 1999, 189.
200 N. Iki, H. H. Kumagai, N. Morohashi, K. Ejima, M. Hasegawa, S. Miyanari and S. Miyano, *Tetrahedron Lett.*, 1998, **39**, 7559.
201 H. Ishida and M. Ohno, *Tetrahedron Lett.*, 1999, **40**, 1543.
202 T. Patonay, W. Adam, J. Jeko, K. E. Kover, A. Levai, M. Nemeth and K. Peters, *Heterocycles*, 1999, **51**, 85.
203 R. S. Oakes, A. A. Clifford, K. D. Bartle, M. Thornton Pett and C. M. Rayner, *Chem. Commun.*, 1999, 247.
204 D. Crich, J. Mataka, S. Sun, K.-C. Lam, A. L. Rheingold and D. J. Wink, *Chem. Commun.*, 1998, 2763.
205 T. Umezawa, Y. Sugihara, A. Ishii and J. Nakayama, *J. Am. Chem. Soc.*, 1998, **120**, 12351.
206 K.-i. Fujita, M. Kanakubo, H. Ushijima, A. Oishi, Y. Ikeda and Y. Taguchi, *Synlett*, 1998, 987.
207 M. I. Donnoli, S. Superchi and C. Rosini, *J. Org. Chem.*, 1998, **63**, 9392.
208 S. Superchi, M. I. Donnoli and C. Rosini, *Tetrahedron Lett.*, 1998, **39**, 8541.
209 M. Matsugi, N. Fukuda, J. Minamikawa and S. Otsuka, *Tetrahedron Lett.*, 1998, **39**, 5591.
210 N. Nakajima, T. Enomoto, N. Matsuura and M. Ubukata, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 3331.
211 M. A. M. Capozzi, C. Cardellicchio, G. Fracchiolla, F. Naso and P. Tortorella, *J. Am. Chem. Soc.*, 1999, **121**, 4708.
212 C. Bolm and O. A. G. Dabard, *Synlett*, 1999, 360.
213 A. Lattanzi, F. Bonadies, A. Schiavo and A. Scettri, *Tetrahedron: Asymmetry*, 1998, **9**, 2619.
214 C. Cardellicchio, G. Fracchiolla, F. Naso and P. Tortorella, *Tetrahedron*, 1999, **55**, 525.
215 V. K. Aggarwal, B. N. Esquivel-Zamora, G. R. Evans and E. Jones, *J. Org. Chem.*, 1998, **63**, 7306.
216 V. K. Aggarwal, Z. Gultekin, R. S. Grainger, H. Adams and P. L. Spargo, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2771.
217 R. Caputo, A. Guaragna, G. Palumbo and S. Pedatella, *Eur. J. Org. Chem.*, 1999, 1455.
218 M. Bonchio, G. Licini, F. Di Furia, S. Mantovani, G. Modena and W. A. Nugent, *J. Org. Chem.*, 1999, **64**, 1326.
219 C. Bolm and F. Bienewald, *Synlett*, 1998, 1327.
220 H. Q. N. Gunaratne, M. A. McKervey, S. Feutren, J. Finlay and J. Boyd, *Tetrahedron Lett.*, 1998, **39**, 5655.
221 L. Bohe, M. Lusinchi and X. Lusinchi, *Tetrahedron*, 1999, **55**, 155.
222 T. Nishi, K. Nakajima, Y. Iio, K. Ishibashi and T. Fukazawa, *Tetrahedron: Asymmetry*, 1998, **9**, 2567.
223 H. Tohma, S. Takizawa, H. Watanabe, Y. Fukuoka, T. Maegawa and Y. Kita, *J. Org. Chem.*, 1999, **64**, 3519.
224 F. van de Velde, L. Konemann, F. van Rantwijk and R. A. Sheldon, *Chem. Commun.*, 1998, 1891.
225 S. Ozaki, H.-J. Yang, T. Matsui, Y. Goto and Y. Watanabe, *Tetrahedron: Asymmetry*, 1999, **10**, 183.
226 M. A. Andersson and S. G. Allenmark, *Tetrahedron*, 1998, **54**, 15293.
227 H. B. ten Brink, A. Tuynman, H. L. Dekker, W. Hemrika, Y. Izumi, T. Oshiro, H. E. Schoemaker and R. Wever, *Inorg. Chem.*, 1998, **37**, 6780.
228 W. Adam, C. Mock-Knoblauch and C. R. Saha-Moller, *J. Org. Chem.*, 1999, **64**, 4834.
229 D. A. Cogan, G. Liu, K. Kim, B. J. Backes and J. A. Ellman, *J. Am. Chem. Soc.*, 1998, **120**, 8011.
230 C. Imboden and P. Renaud, *Tetrahedron: Asymmetry*, 1999, **10**, 1051.
231 J. Zhang, S. Saito and T. Koizumi, *J. Org. Chem.*, 1998, **63**, 9375.
232 A. Greer, K. A. Conklin, K. Faull, K. N. Houk and C. S. Foote, *J. Org. Chem.*, 1999, **64**, 1432.
233 S. Obika, T. Nishiyama, S. Tatematsu, M. Nishimoto, K. Miyashita and T. Imanishi, *Heterocycles*, 1998, **49**, 261.
234 M. Otto, J. Parr and A. M. Z. Slawin, *Organometallics*, 1998, **17**, 4527.
235 K. Hiroi, Y. Susuki, I. Abe, Y. Hasegawa and K. Suzuki, *Tetrahedron: Asymmetry*, 1998, **9**, 3797.
236 K. Hiroi, Y. Suzuki and I. Abe, *Tetrahedron: Asymmetry*, 1999, **10**, 1173.
237 K. Hiroi, Y. Suzuki and I. Abe, *Chem. Lett.*, 1999, 149.
238 K. Hiroi, Y. Suzuki and R. Kawagishi, *Tetrahedron Lett.*, 1999, **40**, 715.
239 K. Hiroi and Y. Suzuki, *Tetrahedron Lett.*, 1998, **39**, 6499.
240 Y. Arai, *J. Synth. Org. Chem. Jpn.*, 1998, **56**, 789.
241 G. Solladie, F. Colobert and F. Somny, *Tetrahedron Lett.*, 1999, **40**, 1227.
242 G. Solladie, G. Hanquet and C. Rolland, *Tetrahedron Lett.*, 1999, **40**, 177.
243 G. Solladie, G. Hanquet, I. Izzo and R. Crumbie, *Tetrahedron Lett.*, 1999, **40**, 3071.
244 G. Solladie, F. Colobert and D. Denni, *Tetrahedron: Asymmetry*, 1998, **9**, 3081.
245 A. Arnone, P. Bravo, W. Panzeri, F. Viani and M. Zanda, *Eur. J. Org. Chem.*, 1999, 117.
246 F. Colobert, A. Tito, N. Khiar, D. Denni, M. A. Medina, M. Martin-Lomas, J.-L. Garcia Ruano and G. Solladie, *J. Org. Chem.*, 1998, **63**, 8918.
247 R. Sanchez-Obregon, B. Ortiz, F. Walls, F. Yuste and J. L. Garcia Ruano, *Tetrahedron: Asymmetry*, 1999, **10**, 947.
248 M. Medio-Simon, J. Gil, P. Aleman, T. Varea and G. Asensio, *Tetrahedron: Asymmetry*, 1999, **10**, 561.
249 P. Bravo, G. Cavicchio, M. Crucianelli, A. Poggiali, A. Volonterio and M. Zanda, *J. Chem. Res.* (*S*), 1998, 666.
250 P. E. Morgan, R. McCague and A. Whiting, *Tetrahedron Lett.*, 1999, **40**, 4857.
251 L. Tamas, T. E. Gunda and F. Sztaricskai, *J. Chem. Soc., Perkin Trans. 1*, 1999, 721.
252 A. C. MacCulloch, P. L. Coe and R. T. Walker, *J. Chem. Soc., Perkin Trans. 1*, 1999, 335.

253 P. Bravo, S. Capelli, M. Crucianelli, M. Guidetti, A. L. Markovsky, S. V. Meille, V. A. Soloshonok, A. E. Sorochinsky, F. Viani and M. Zanda, *Tetrahedron*, 1999, **55**, 3025.
254 P. Bravo, M. Guidetti, F. Viani, M. Zanda, A. L. Markovsky, A. E. Sorochinsky, I. V. Soloshonok and V. A. Soloshonok, *Tetrahedron*, 1998, **54**, 12789.
255 P. Bravo, E. Corradi, C. Pesenti, B. Vergani, F. Viani, A. Volonterio and M. Zanda, *Tetrahedron: Asymmetry*, 1998, **9**, 3731.
256 S. Fustero, A. Navarro, B. Pina and A. Asensio, *J. Org. Chem.*, 1998, **63**, 6210.
257 J. L. Garcia Ruano, A. Lorente and J. H. Rodriguez Ramos, *Tetrahedron: Asymmetry*, 1998, **9**, 2437.
258 C. Alayrac, S. Nowaczyk, M. Lemarie and P. Metzner, *Synthesis*, 1999, 669.
259 J. L. Garcia Ruano, D. Barros, M. Carmen Maestro, A. Alcudia and I. Fernandez, *Tetrahedron: Asymmetry*, 1998, **9**, 3445.
260 P. Pollet, A. Turck, N. Ple and G. Queguiner, *J. Org. Chem.*, 1999, **64**, 4512.
261 A. Arnone, P. Bravo, M. Frigerio, F. Viani and V. A. Soloshonok, *Tetrahedron*, 1998, **54**, 11841.
262 A. Arnone, P. Bravo, M. Frigerio, F. Viani and V. A. Soloshonok, *Tetrahedron*, 1998, **54**, 11825.
263 R. Fernandez de la Pradilla, C. Montero, J. Priego and L. A. Martinez-Cruz, *J. Org. Chem.*, 1998, **63**, 9612.
264 R. Fernandez de la Pradilla, S. Castro, P. Manzano, M. Martin-Ortega, J. Priego, A. Viso, A. Rodriguez and I. Fonseca, *J. Org. Chem.*, 1998, **63**, 4954.
265 V. K. Aggarwal, J. K. Barrell, J. M. Worrall and R. Alexander, *J. Org. Chem.*, 1998, **63**, 7128.
266 P. C. B. Page, M. J. McKenzie and D. R. Buckle, *Tetrahedron*, 1998, **54**, 14581.
267 C. Imboden, T. Bourquard, O. Corminboeuf, P. Renaud, K. Schenk and M. Zahouily, *Tetrahedron Lett.*, 1999, **40**, 495.
268 N. Mase, Y. Watanabe and T. Toru, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 2957.
269 N. Mase, S. Wake, Y. Watanabe and T. Toru, *Tetrahedron Lett.*, 1998, **39**, 5553.
270 E. Lacote, B. Delouvrie, L. Fensterbank and M. Malacria, *Angew. Chem., Int. Ed.*, 1998, **37**, 2116.
271 M. C. Carreno, A. Urbano and C. Di Vitta, *J. Org. Chem.*, 1998, **63**, 8320.
272 M. C. Carreno, S. Garcia-Cerrada, A. Urbano and C. Di Vitta, *Tetrahedron: Asymmetry*, 1998, **9**, 2965.
273 M. C. Carreno, R. Hernandez-Sanchez, J. Mahugo and A. Urbano, *J. Org. Chem.*, 1999, **64**, 1387.
274 M. C. Carreno, J. L. Garcia Ruano, C. Lafuente and M. A. Toledo, *Tetrahedron: Asymmetry*, 1999, **10**, 1119.
275 Y. Arai, T. Masuda and Y. Masaki, *Chem. Pharm. Bull.*, 1998, **46**, 1078.
276 P. C. B. Page, M. J. McKenzie and D. R. Buckle, *Tetrahedron*, 1998, **54**, 14573.
277 P. Hayes and C. Maignan, *Synthesis*, 1999, 783.
278 P. Hayes and C. Maignan, *Tetrahedron: Asymmetry*, 1999, **10**, 1041.
279 C. Alexandre, C. Guillot, P. Hayes and C. Maignan, *Tetrahedron Lett.*, 1998, **39**, 5769.
280 A. L. Schwan, R. R. Strickler, Y. Lear, M. L. Kalin, T. E. Rietveld, T.-J. Xiang and D. Brillon, *J. Org. Chem.*, 1998, **63**, 7825.
281 N. D. Buezo, I. Alonso and J. C. Carretero, *J. Am. Chem. Soc.*, 1998, **120**, 7129.
282 K. Hiroi, Y. Yoshida and Y. Kaneko, *Tetrahedron Lett.*, 1999, **40**, 3431.
283 M. Henrich, A. Delgado, E. Molins, A. Roig and A. Llebaria, *Tetrahedron Lett.*, 1999, **40**, 4259.
284 E. Montenegro, A. Moyano, M. A. Pericas, A. Riera, A. Alvarez-Larena and J.-F. Piniella, *Tetrahedron: Asymmetry*, 1999, **10**, 457.
285 M. Mikolajczyk, W. Perlikowska, J. Omelanczuk, H.-J. Cristau and A. Perraud-Darcy, *J. Org. Chem.*, 1998, **63**, 9716.
286 B. Patro and R. R. Schmidt, *Synthesis*, 1998, 1731.
287 H. Adams, J. C. Anderson, R. Bell, D. N. Jones, M. R. Peel and N. C. O. Tomkinson, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3967.
288 M. C. Aversa, A. Barattucci, P. Bonaccorsi, P. Giannetto and F. Nicolo, *J. Org. Chem.*, 1999, **64**, 2114.
289 R. J. K. Taylor, *Chem. Commun.*, 1999, 217.
290 J.-E. Backvall, R. Chinchilla, C. Najera and M. Yus, *Chem. Rev.*, 1998, **98**, 2291.
291 R. Balicki, *Synth. Commun.*, 1999, **29**, 2235.
292 D. H. R. Barton, W. Li and J. A. Smith, *Tetrahedron Lett.*, 1998, **39**, 7055.
293 M. T. Ho, A. Treiber and P. M. Dansette, *Tetrahedron Lett.*, 1998, **39**, 5049.
294 A. Chellamani, P. Kulanthaipandi and S. Rajagopal, *J. Org. Chem.*, 1999, **64**, 2232.
295 B. C. Ranu, S. K. Guchhait and K. Ghosh, *J. Org. Chem.*, 1998, **63**, 5250.
296 C. Lorin and P. Rollin, *Synthesis*, 1998, 1506.
297 V. Reutrakul, R. Saeeng, M. Pohmakotr and P. Kongsaeree, *Tetrahedron Lett.*, 1999, **40**, 1019.
298 B. M. Choudary, N. S. Chowdari, M. L. Kantam and R. Kannan, *Tetrahedron Lett.*, 1999, **40**, 2859.
299 M. Tanaka, M. Nakatani and M. Asaoka, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3519.
300 J. C. Carretero and R. G. Arrayas, *Synlett*, 1999, 49.
301 M. G. Cabiddu, S. Cabiddu, E. Cadoni, P. Demurtas, C. Fattuoni, C. Floris and S. Melis, *Synthesis*, 1998, 1098.
302 R. Tanikaga, S. Yamada, T. Nishikawa and A. Matsui, *Tetrahedron*, 1998, **54**, 8933.
303 Y. Mori, K. Yaegashi and H. Furukawa, *J. Org. Chem.*, 1998, **63**, 6200.
304 S. Arai, T. Ishida and T. Shioiri, *Tetrahedron Lett.*, 1998, **39**, 8299.
305 A. Padwa, C. L. Muller, A. Rodriguez and S. H. Watterson, *Tetrahedron*, 1998, **54**, 9651.
306 A. R. G. Ferreira, A. G. Dias, A. C. Pinto, P. R. R. Costa, E. Miguez and A. J. R. da Silva, *Tetrahedron Lett.*, 1998, **39**, 5305.
307 T. Balasubramanian and A. Hassner, *Tetrahedron: Asymmetry*, 1998, **9**, 2201.
308 E. Ghera, V. Kleiman and A. Hassner, *J. Org. Chem.*, 1999, **64**, 8.
309 D. Enders, S. F. Muller and G. Raabe, *Angew. Chem., Int. Ed.*, 1999, **38**, 195.
310 D. Enders, S. F. Muller and G. Raabe, *Synlett*, 1999, 741.
311 N. Hammad and A. G. Sutherland, *J. Chem. Res.* (*S*), 1999, 376.
312 F. Zhou, J. Rosen, J. M. Zebrowski-Young, P. M. Freihammer, M. R. Detty and R. J. Lachicotte, *J. Org. Chem.*, 1998, **63**, 5403.
313 A. D. Briggs, R. F. W. Jackson and P. A. Brown, *J. Chem. Soc., Perkin Trans. 1*, 1998, 4097.
314 R. Fernandez de la Pradilla, P. Mendez, J. Priego and A. Viso, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1247.
315 K. Ogura, T. Arai, A. Kayano and M. Akazome, *Tetrahedron Lett.*, 1999, **40**, 2537.
316 K. Ogura, T. Arai, A. Kayano and M. Akazone, *Tetrahedron Lett.*, 1998, **39**, 9051.
317 D. Johnston, C. M. McCusker and D. J. Procter, *Tetrahedron Lett.*, 1999, **40**, 4913.
318 N. Mase, Y. Watanabe and T. Toru, *Tetrahedron Lett.*, 1999, **40**, 2797.
319 M.-P. Bertrand, S. Gastaldi and R. Nouguier, *Tetrahedron*, 1998, **54**, 12829.
320 C. Wang and G. A. Russell, *J. Org. Chem.*, 1999, **64**, 2066.
321 L. Wang and Y. Zhang, *J. Chem. Res.* (*S*), 1998, 588.
322 P. Bertus, P. Phansavath, V. Ratovelomanana-Vidal, J.-P. Genet, A. R. Touati, T. Homri and B. Ben Hassine, *Tetrahedron Lett.*, 1999, **40**, 3175.
323 P. Bertus, P. Phansavath, V. Ratovelomanana-Vidal, J.-P. Genet, A. R. Touati, T. Homri and B. Ben Hassine, *Tetrahedron: Asymmetry*, 1999, **10**, 1369.
324 Y. Yuasa, Y. Yuasa and H. Tsuruta, *Can. J. Chem.*, 1998, **76**, 1304.
325 O. Arjona, F. Iradier, R. M. Manas, J. Plumet, X. Grabuleda and C. Jaime, *Tetrahedron*, 1998, **54**, 909.
326 H. Takeuchi, T. Fujimoto, K. Hoshino, J. Motoyoshiya, A. Kakeki and I. Yamamoto, *J. Org. Chem.*, 1998, **63**, 7172.
327 T. G. Back, R. J. Bethell, M. Parvez and D. Wehrli, *J. Org. Chem.*, 1998, **63**, 7908.
328 D. B. Reddy, N. C. Babu, V. Padmavathi and R. P. Sumathi, *Synthesis*, 1999, 491.
329 T. Zoller, D. Uguen, A. De Cian and J. Fischer, *Tetrahedron Lett.*, 1998, **39**, 8089.
330 S. Zhu, C. Qin, G. Xu and Q. Chu, *Tetrahedron Lett.*, 1998, **39**, 5265.
331 S. Sengupta, D. Sen Sarma and S. Mondal, *Tetrahedron: Asymmetry*, 1998, **9**, 2311.
332 W.-M. Dai and M. Y. H. Lee, *Tetrahedron*, 1998, **54**, 12497.
333 G. L. Edwards and D. J. Sinclair, *Tetrahedron Lett.*, 1999, **40**, 3933.
334 J. L. Garrido, I. Alonso and J. C. Carretero, *J. Org. Chem.*, 1998, **63**, 9406.
335 J. G. Urones, I. S. Marcos, N. M. Garrido, G. P. Basabe, A. J. Bastida, S. G. San Feliciano, D. Diez and J. M. Goodman, *Synlett*, 1998, 1361.
336 J. G. Urones, I. S. Marcos, N. M. Garrido, G. P. Basabe, S. G. San Feliciano, R. Coca and D. Diez, *Synlett*, 1998, 1364.

337 T. G. Back and R. J. Bethell, *Tetrahedron Lett.*, 1998, **39**, 5463.
338 C. Zhang, C. J. Ballay II and M. L. Trudell, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 675.
339 J. R. Bull, N. S. Desmond-Smith, S. J. Heggie, R. Hunter and F.-C. Tien, *Synlett*, 1998, 900.
340 H. Abe and H. Suzuki, *Bull. Chem. Soc. Jpn.*, 1999, **72**, 787.
341 M. Baruah, A. Boruah, D. Prajapati and J. S. Sandhu, *Synlett*, 1998, 1083.
342 R. Giovannini, E. Marcantoni and M. Petrini, *Tetrahedron Lett.*, 1998, **39**, 5827.
343 S. Ma and Q. Wei, *J. Org. Chem.*, 1999, **64**, 1026.
344 Y. M. Kim, T. W. Kwon, S. K. Chung and D. H. R. Barton, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1175.
345 T. Takada, M. Arisawa, M. Gyoten, R. Hamada, H. Tohma and Y. Kita, *J. Org. Chem.*, 1998, **63**, 7698.
346 A. Barco, S. Benetti, C. De Risi, P. Marchetti, G. P. Pollini and V. Zanirato, *Tetrahedron Lett.*, 1998, **39**, 7591.

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