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THE CHEMISTRY OF VINYL SULPHONES

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CONTENTS

1 INTRODUCTION

Vinyl sulphones (α,β-unsaturated sulphones) have now become generally accepted as useful intermediates in organic synthesis. Thus vinyl sulphones serve efficiently as both Michael acceptors and as 2π partners in cycloaddition reactions. In Michael reactions, a vinyl sulphone can enable complementary chemistry (e.g. umpolung) to that available using conventional Michael acceptors such as α,β-unsaturated carbonyl compounds (phenyl vinyl sulphone itself acts as a two-carbon acceptor not directly available using carbonyl Michael acceptors).

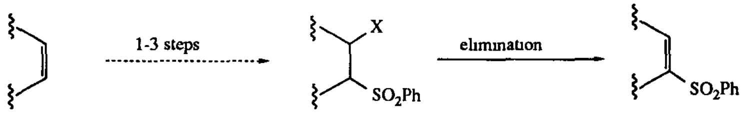
In cycloaddition reactions, vinyl sulphones again serve a useful function as convenient equivalents for ethylene, acetylene, ketene, etc. Other notable features of sulphones, including their ease of handling (many are nicely crystalline) and ready removal (desulphonylation), have added to the attractions of vinyl sulphones as intermediates. Thanks to the pioneering work of Julia, and others, many types of vinyl sulphones are readily available, often stereoselectively. The opportunitites for synthesis using these intermediates are considerable and are amply demonstrated by the synthetic efforts of Fuchs' group.

Vinyl sulphone chemistry has not been reviewed in detail before although some aspects have been covered previously in reviews,[1] and in a recent book.[2] The aim of this survey is to give a broad but concise coverage of vinyl sulphone chemistry, concentrating on more recent aspects, which will provide the reader with an entry to more extensive literature.

2 PREPARATION OF VINYL SULPHONES

2.1 Ionic and radical additions to alkenes, alkynes and allenes

A very broadly applicable strategy for the preparation of vinyl sulphones involves the construction of a β-heterosubstituted sulphone i.e. (**1**) which can then undergo elimination, Scheme 1.

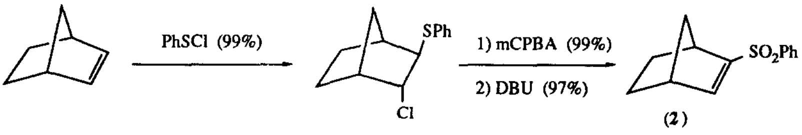


(**1**) e g X = OAc, SePh, halogen

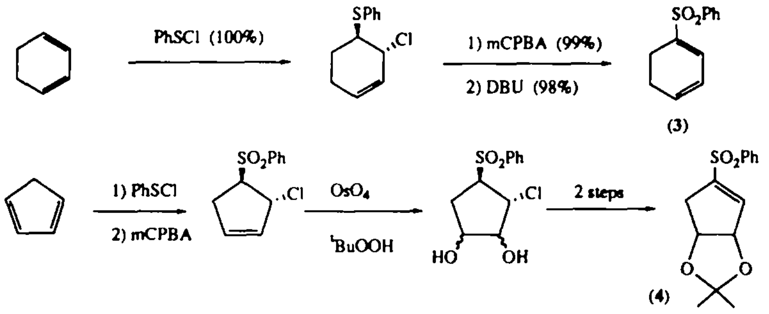
Scheme 1

Whereas intermediates such as (**1**) can be prepared in a convergent fashion by combination of a sulphone carbanion with a carbonyl compound (*vide infra*), this section is concerned with the use of unsaturated starting materials, particularly simple alkenes, for the preparation of (**1**) without changing the carbon skeleton.

An indirect but versatile approach involving chlorosulphenylation–dehydrochlorination has been used by Fuchs to prepare a variety of cyclic vinyl sulphones, e.g. (**2**)–(**4**), Scheme 2.[3]



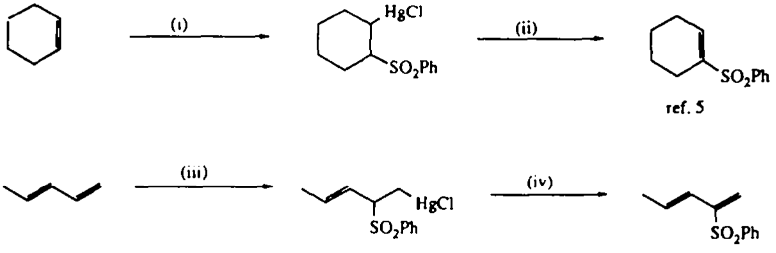
(**2**)



Scheme 2

Combined with an alternative epoxidation-thiolate opening-oxidation sequence this chemistry allowed the preparation of a number of key homochiral intermediates for natural product synthesis.[4]

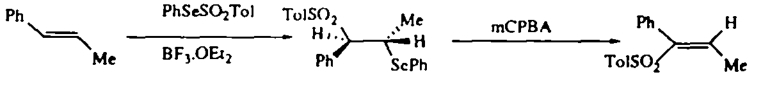
Several alternative methods are available for the direct synthesis of intermediates (**1**) which involve ionic or radical addition of $PhSO_2X$ (X = Cl, Br, I, SePh, etc.) to an alkene. The reaction of alkenes or 1,3-dienes with $HgCl_2$ in the presence of $NaSO_2Ph$ results in the formation of arenesulphonyl mercury intermediates, which can then be eliminated under basic conditions, Scheme 3.[5,6]



Reagents
(i) $HgCl_2$, $PhSO_2Na$, H_2O; (ii) 50% $NaOH_{aq}$/dioxane;
(iii) $HgCl_2$, $PhSO_2Na$, H_2O/DMSO, (iv) NaOH-Na_2CO_3, H_2O, DMSO.

Scheme 3

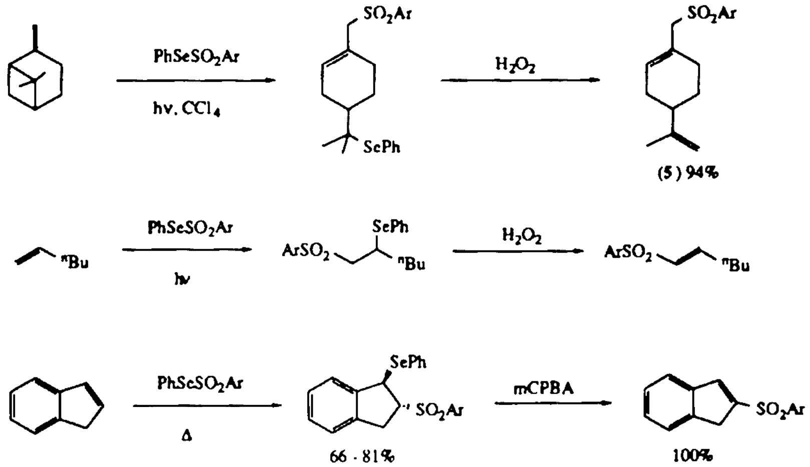
Alkene selenosulphonation can be carried out under ionic or free radical conditions with complementary regiochemical results. Thus, reaction of $PhSeSO_2Ar$ with alkenes in the presence of catalytic quantities of $BF_3{\cdot}OEt_2$ follows a similar course to the sulphonyl-mercuration described above, namely Markovnikov addition.[7] A subsequent oxidation *syn*-elimination step then provides vinyl sulphones in excellent yields, Scheme 4.



Scheme 4

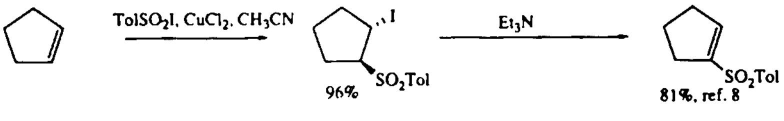
Since under these conditions both the initial addition step and the *syn*-elimination are stereoselective the sequence constitutes a stereoselective vinyl sulphone synthesis. The reaction has also been extended to dienes, providing an alternative procedure to that illustrated in Scheme 3 for the preparation of 2-

phenylsulphonyl-1,3-dienes.[8] Under thermal or photolytic conditions the selenosulphonation shows all the characteristics of a free radical chain reaction, giving anti-Markownikov addition and ring opening in certain cases e.g. (5), Scheme 5.[7,9]



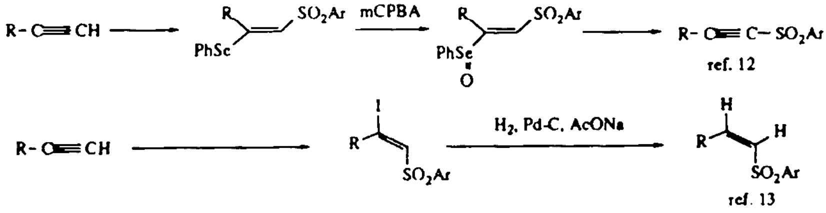
Scheme 5

Analogous chemistry can be carried out using sulphonyl iodides in place of selenides. Thus, Liu *et al.* carried out the radical addition of preformed $PhSO_2I$ or TsI to alkenes in the presence of catalytic quantities of $CuCl_2$.[10] Similar results can be obtained using the convenient $TsNa/I_2$ mixture in MeOH, which presumably forms the somewhat unstable TsI *in situ*, Scheme 6.[11]



Scheme 6

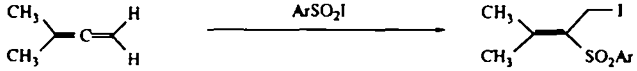
This approach avoids the use of selenium, which is both costly and toxic, and allows the second elimination step to be carried out under very mild, non-oxidative conditions. The instability of the intermediate iodosulphones is, however, one potential drawback in some cases. Both the seleno- and iodosulphonation procedures can also be conducted with acetylenes. In these cases the intermediate product is a β-seleno- or β-iodovinyl sulphone,[13,14] both of which can then be modified to give other products, Scheme 7.



Scheme 7

In both cases the addition process is anti-Markovnikov and gives the *trans*-disubstituted product. The high stereoselectivity is somewhat surprising in view of the known rapid isomerisation of the presumed intermediate vinyl radical, and is apparently a consequence of an even more rapid chain transfer reaction.[15] The use of β-functionalised vinyl sulphones, such as those in Scheme 7, in alkylative processes leading to substituted products is described later.

Further work by Truce's group has extended the scope of the iodosulphonation reaction to the use of allene substrates, e.g. Scheme 8.[16]

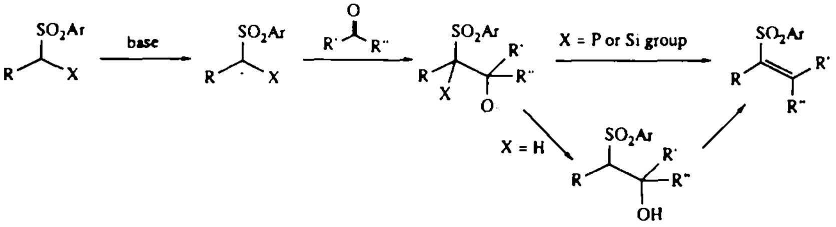


Scheme 8

The major products obtained result from addition of the $ArSO_2$ radical to the central position, followed by chain-transfer iodine abstraction at the terminal position.

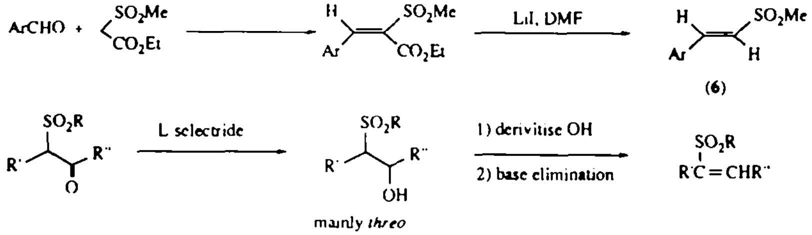
2.2 Aldol, Wittig, Peterson and related reactions using sulphone-stabilised carbanions

Many variants for the synthesis of vinyl sulphones rely on the addition of a sulphone carbanion to a carbonyl compound, followed by a subsequent elimination step, Scheme 9.

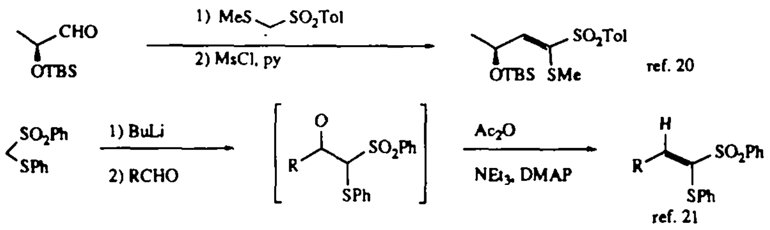


Scheme 9

In the simplest case where X = H dehydration of the intermediate hydroxysulphone (or some derivative thereof) is necessary, usually in a separate step,[17] whereas the use of phosphorus (e.g. X = $P(O)(OR)_2$) or silicon (X = $SiMe_3$) groups allows direct *in-situ* elimination to give the vinyl sulphone product. A variety of examples illustrating the first approach are shown in Scheme 10.



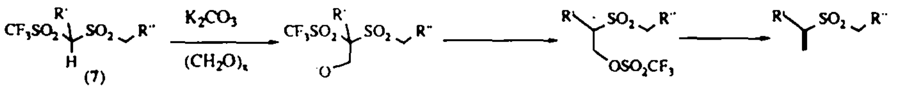
(6)



Scheme 10

Thus certain methyl styryl sulphones, i.e. (6), are very simply prepared by a classical Knoevenagel method involving condensation of an aromatic aldehyde with an ester of methylsulphonylacetic acid, followed by dealkylation–decarboxylation using LiI in DMF.[18] The *threo*-selective reduction of β-ketosulphones to β-hydroxysulphones using L-selectride, reported by Julia, provides a basis for a stereoselective synthesis of vinyl sulphones.[19] Elimination via the corresponding tosylates is stereospecific (*anti*) whereas both diastereoisomers of the derived acetates give predominantly the (*E*)-vinyl sulphone product. Coupled to stereoselective desulphonylation procedures, also developed by Julia, this chemistry allowed the development of a new stereodefined alkene synthesis, (*vide infra*). As illustrated, the same aldol–β-elimination protocol is also applicable to the synthesis of alkylthio- and arylthiovinyl sulphone derivatives.[20,21]

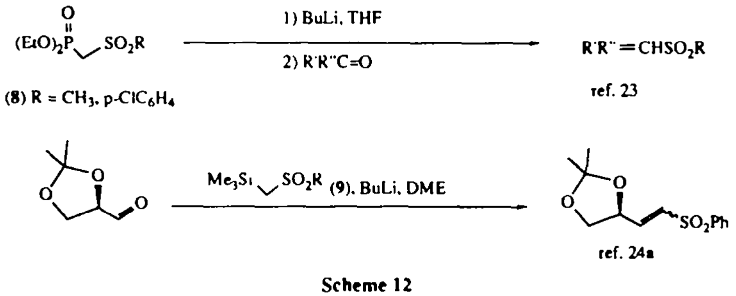
An interesting related process utilises the mesityltriflone reagent (7) which undergoes reaction with paraformaldehyde with rearrangement to give α-methylene sulphone products, Scheme 11.[22]



Scheme 11

Yields for this process with a few examples of R^1 and R^2 were generally quantitative although no reactions could be obtained with other aldehydes.

The sulphonylphosphonates (8)[23] and the silyl sulphone (9)[24] have proven useful in Horner-Emmons and Peterson reactions respectively, each process giving substituted vinyl sulphones, Scheme 12.

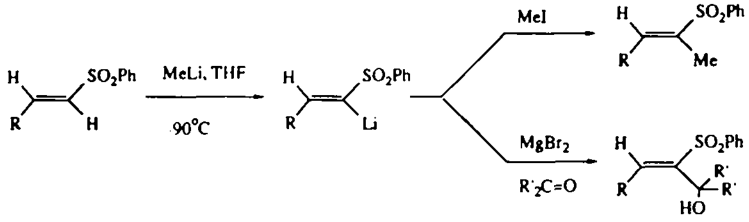


Scheme 12

The phosphonate method has the advantage that the products obtained using aldehydes are exclusively *trans*, whereas in the Peterson process mixtures of stereoisomers are usually (but not invariably) formed.

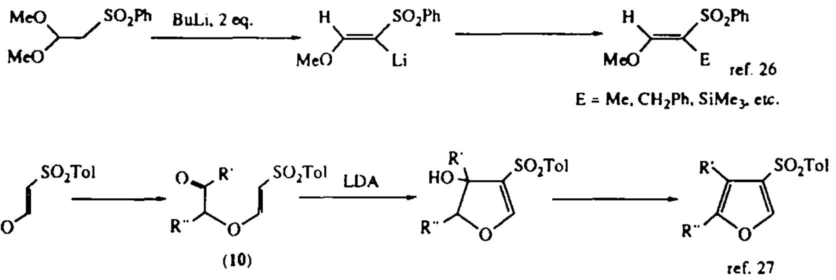
2.3 Preparation of substituted and heterosubstituted vinyl sulphones by manipulation of simple preformed vinyl sulphone starting materials (including vinyl sulphone synthons)

The discovery that simple vinyl sulphones can be deprotonated to give the corresponding vinylic anions opened up new and attractive possibilities for the direct synthesis of more highly substituted vinyl sulphones, Scheme 13.[25] The α-vinylic hydrogen is abstracted highly selectively under such kinetically controlled conditions, despite the possibility of forming the much more stable allylic α-sulphonyl carbanion via γ-deprotonation.



Scheme 13

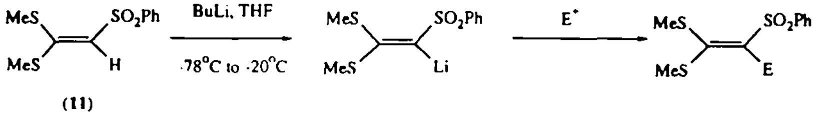
Vinyl anions have been formed similarly from vinyl sulphones having β-oxygenation, e.g. Scheme 14.[26,27]



Scheme 14

The intramolecular reaction using (**10**) underscores the high kinetic acidity of the vinyl sulphone, the alternative ketone enolisation not competing.[27] Whereas the (*E*)-2-alkoxy-1-phenylsulphonylvinyl lithium species reacts with clean retention of double bond geometry, the corresponding (*Z*)-anions isomerise to the (*E*)-form rapidly even at very low temperature.[28]

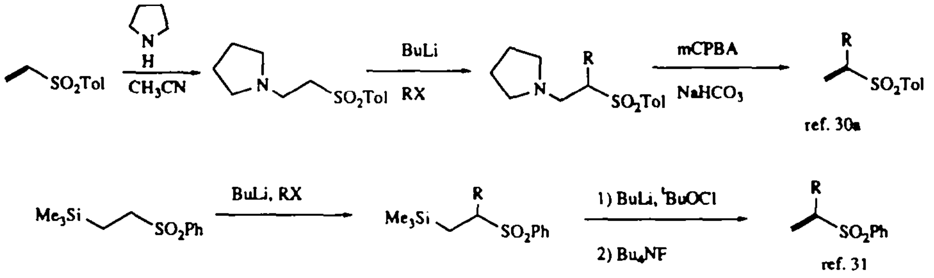
Deprotonation of the *S,S*-acetal (**11**) occurs in an analogous fashion to give an anion which reacts (albeit sluggishly in some cases) with a variety of electrophilic partners, Scheme 15.[29]



(**11**)

Scheme 15

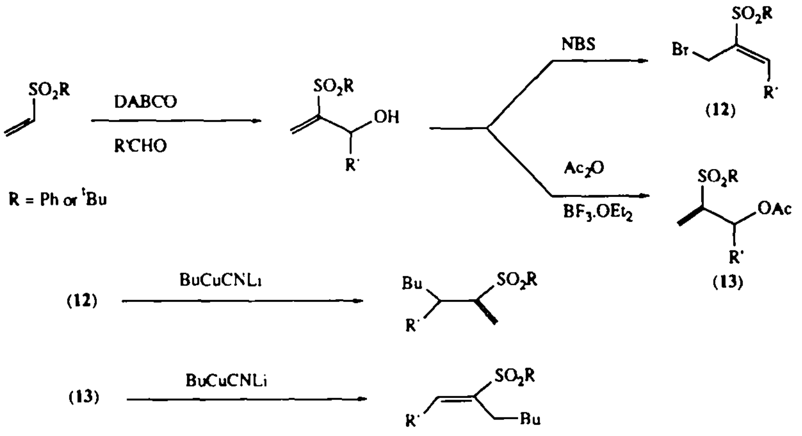
It is not possible to form such a vinylic anion from the parent unsubstituted vinyl sulphone, due to rapid polymerisation presumably initiated by Michael addition. This problem can be overcome by using suitably substituted sulphones as masked vinyl sulphones, e.g. Scheme 16.[30,31] The preparation of β-pyrrolidinosulphones also proved possible using allyl sulphones as starting materials, presumably due to double bond isomerisation under the reaction conditions.[30a]



Scheme 16

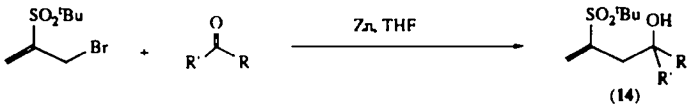
In the second sequence the Bu$_4$NF induced elimination of Me$_3$SiCl (from an intermediate α-chlorosulphone) is observed, underlining the relatively poor leaving group ability of the sulphone (the SO$_2$Ph group is lost in the analogous reaction of the non-chlorinated β-silylsulphone).[31]

In a series of papers, Knochel's group has shown that vinyl sulphones such as (**12**) and (**13**) react in a variety of ways to give substituted vinyl sulphone products, Scheme 17.[32]



Scheme 17

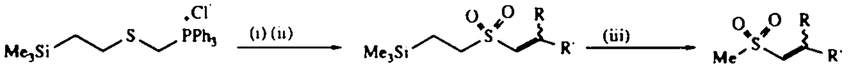
Thus reaction of (**12**) and (**13**) with carbon nucleophiles such as organocuprates takes place with complementary regiochemistry. The bromides (**12**) also proved amenable to zinc-promoted coupling with aldehydes to give hydroxysulphone products such as (**14**), Scheme 18.[33]



Scheme 18

Other bromomethyl- and hydroxymethyl-substitituted vinyl sulphones can be prepared starting with allylphenyl sulphone.[34]

An interesting extension of the chemistry of β-silylsulphones (see also Scheme 16) enables the formation of vinyl sulphinic acid salts which can be alkylated with MeI, Scheme 19.[35]



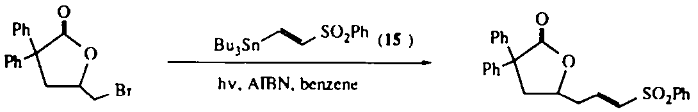
Reagents

(i) base (KO^{t}Bu or LDA), RR'C=O; (ii) mCPBA; (iii) Bu_4NF, CH_3I.

Scheme 19

The method affords roughly 1:1 mixtures of stereoisomers in most cases, although facile separation could be achieved by virtue of the more rapid oxidation of the (*E*)-vinyl sulphide to the vinyl sulphone (under the conditions used the (*Z*)-sulphide oxidises only as far as the sulphoxide). Unfortunately in the final step fluoride proves basic enough to promote isomerisation of some of the vinyl sulphone products to the corresponding allylic sulphones.

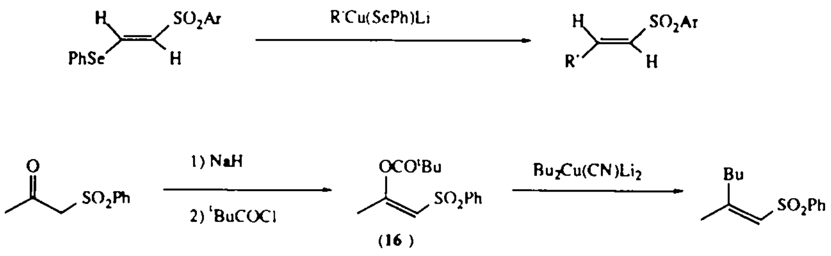
The β-stannylvinylsulphone (15) undergoes quite efficient intermolecular radical addition–fragmentation reactions to give substituted vinyl sulphone products, Scheme 20.[36]



Scheme 20

The corresponding vinyl phosphine oxides were also prepared via a similar route.

The β-phenylselenovinyl sulphones prepared by addition of $ArSO_2SePh$ to acetylenes (e.g. Scheme 7) are useful precursors to other alkylated vinyl sulphones.[37] Thus, reaction with the unconventional cuprate reagents R^{1}Cu(SePh)Li gave products arising from substitution of the SePh group, e.g. Scheme 21.



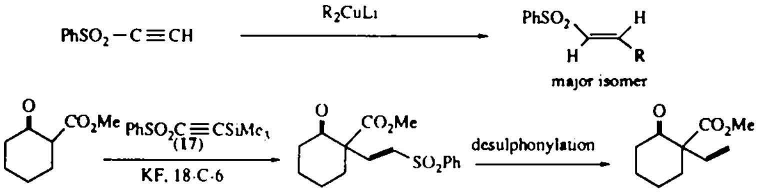
Scheme 21

Although the substitution reaction is efficient and stereoselective the necessity of using the selenocuprate, which requires prior preparation of CuSePh from PhSeH, is a significant drawback. Difficulties presumably also arise in many cases in controlling the regioselective construction of the phenylselenovinyl sulphone starting materials.

A similar but complementary approach involves the preparation of the enol pivalate derivatives (**16**) which undergo clean substitution on reaction with standard higher order cyanocuprates.[38] Here the construction of the β-substituted vinyl sulphone is clearly always regiospecific, although the stereochemical outcome usually favours the more stable (*E*)-vinyl sulphone product. Somewhat surprisingly, neither of these methods suffers from overreaction of the vinyl sulphone products, even with excess cuprate reagent.

2.4 From reactions of acetylenic sulphones

Both mono- and double-addition reactions are possible in reactions of organocuprates with acetylenic sulphones.[39] The stereochemical course of the mono-addition reaction to give the vinyl sulphone products involves mainly *syn*-addition, Scheme 22.

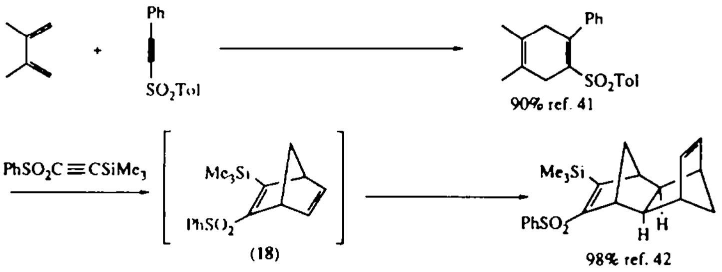


Scheme 22

If desired, the double addition reaction, i.e. reaction with a further cuprate reagent, could be carried out without isolating the initial adduct by quenching the first reaction with benzenethiol and then adding to another preformed cuprate mixture. Other such Michael additions using organocuprates are discussed later.

More stable anions such as those derived from malonates and β-ketoesters add smoothly to the sulphonyl acetylene (**17**) to give vinyl sulphone intermediates.[40] Desulphonylation was effected directly using aluminium amalgam, or in some cases indirectly via cyanohydrin intermediates, thus allowing overall vinylation of the carbonyl starting materials. Treatment of (**17**) with $^{i}Bu_2AlH$ results in clean formation of (*E*)-2-trimethylsilylvinyl sulphone.[24c] Either isomer of this product could be further substituted via deprotonation of the vinylic hydrogen α to the sulphone, as highlighted above in Scheme 13.

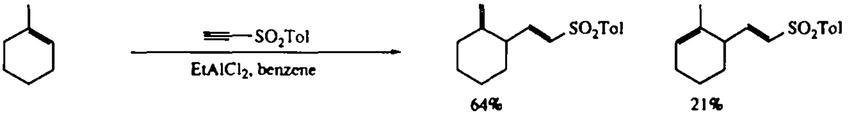
A number of substituted acetylenic sulphones including (**17**) can be employed in Diels-Alder cycloadditions to give cyclic β-silyl vinyl sulphone products, e.g. Scheme 23.[41,42]



Scheme 23

Somewhat surprisingly, intermediate (**18**) reacts with a further equivalent of cyclopentadiene with high regioselectivity at the unsubstituted alkene.[42] Cycloaddition chemisty of unsaturated sulphones is dealt with in detail in Section 4.

With suitable alkenyl substrates ethynyl-*p*-tolyl sulphone undergoes smooth $EtAlCl_2$-catalysed ene-reaction, Scheme 24.[43]



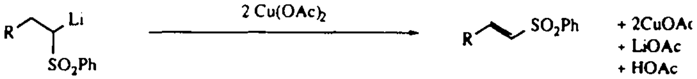
Scheme 24

The reaction is very sensitive to both the reaction conditions (the use of an aromatic solvent is important) and the substitution pattern of the starting alkene.

2.5 Miscellaneous vinyl sulphone preparations

A standard approach to the synthesis of sulphones involves oxidation of the corresponding sulphides. Vinyl sulphones can be prepared in this way, for example using the popular and economical Oxone® reagent.[44]

Treatment of lithiated sulphones with two equivalents of $Cu(OAc)_2$ results in the formation of the corresponding vinyl sulphones, Scheme 25.[45]

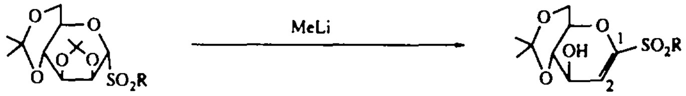


Scheme 25

This result contrasts with the dimerisation reaction obtained using $Cu(OTf)_2$ in place of $Cu(OAc)_2$.

Vinyl sulphones are formed in good yields from the corresponding alkenyl mercurials by treatment with the sodium salts of sulphinic acids under photochemical conditions.[46]

Optically active vinyl sulphones (**19**) were prepared by elimination from the corresponding mannose derivatives (**20**), Scheme 26.[47]

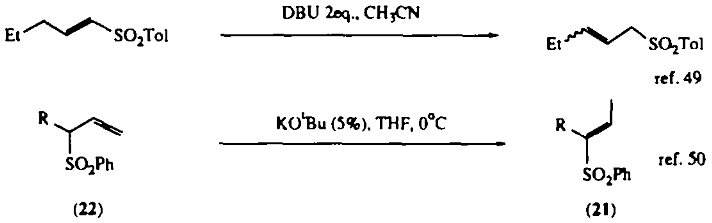


(**20**) R = Ph, ${}^tBu$ (**19**)

Scheme 26

Compound (**19**) resisted attempts to conduct Michael additions, but instead could be metallated at C-2 to form a vinyl anion which was reacted with MeI.

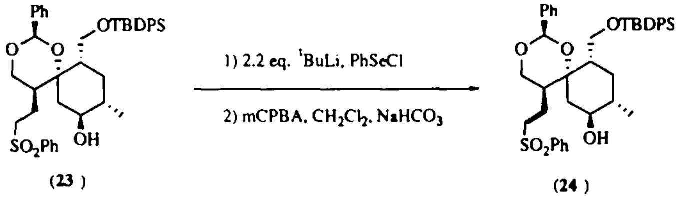
It has been reported that β,γ-unsaturated (allyl) sulphones are more thermodynamically stable than the corresponding α,β-unsaturated (vinyl) isomers.[48] However, depending on the substitution pattern of the sulphone in question, it is possible to isomerise in either direction (i.e. allyl→vinyl or vinyl→allyl) given the appropriate choice of reaction conditions, Scheme 27.[49,50]



Scheme 27

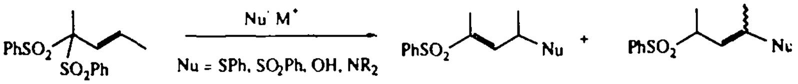
Thus the use of two equivalents of DBU in acetonitrile facilitates the isomerisation of a variety of vinyl sulphones to the corresponding allyl isomers.[49] A more limited selection of vinyl sulphones of general formula (**21**) could be obtained by treatment of allyl sulphones (**22**) with catalytic quantities of potassium *tert*-butoxide in THF at 0°C.[50] It seems likely that equilibration of the isomers occurs in most cases, the favoured product having the more highly alkyl-substituted alkene (although steric effects can also be important[48d]).

The selenation–selenoxide *syn*-elimination protocol, so popular for dehydrogenation of carbonyl compounds, has been rarely used for converting sulphones to vinyl sulphones.[11b] One notable recent example is the transformation of the highly functionalised sulphone (**23**) to the corresponding unsaturated compound (**24**) carried out by Ley's group in a recent synthesis of (+)-milbemycin β_1 Scheme 28.[52]



Scheme 28

Finally, Julia has shown that the substitution of a sulphonyl group in alkylidene disulphones can be carried out using a variety of heteronucleophiles to give γ-functionalised (*E*)-vinyl sulphones, Scheme 29.[52]



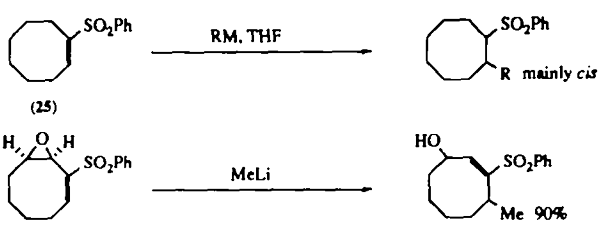
Scheme 29

3 REACTIONS OF VINYL SULPHONES INVOLVING MICHAEL ADDITIONS

3.1 Using non-stabilised organometallics

Without doubt the most significant contributions to the use of vinyl sulphones as Michael acceptors in synthesis have been made by Fuchs and co-workers. This chemistry has recently been reviewed[4] and so just a few examples from this significant body of work will be highlighted here for illustration.

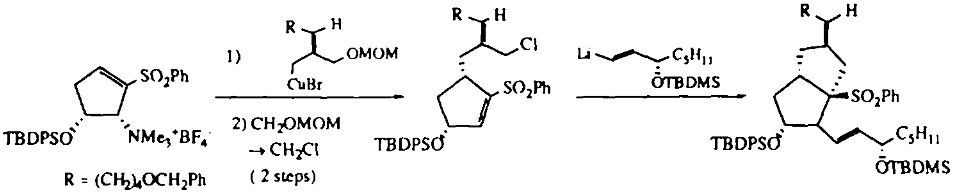
A number of interestingly functionalised cyclooctane products were built up using the addition of organometallics to cyclooctenyl phenyl sulphones, Scheme 30.[53]



Scheme 30

In reactions of the simple vinyl sulphone (25) no advantage is gained in using an organocuprate rather than a simple alkyllithium, indeed in reactions of some of the other vinyl sulphones in this study, cuprates gave inferior results. Perhaps surprisingly, competing deprotonation of these cyclic vinyl sulphones by the alkyllithiums, rather than conjugate addition, rarely causes problems.

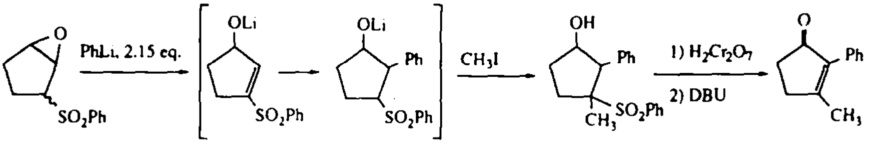
The total synthesis of (+)-carbacyclin reported by Hutchinson and Fuchs illustrates how useful the vinyl sulphone group can be in allowing regio- and stereoselective introduction of carbon substituents onto a preformed ring, Scheme 31.[54]



Scheme 31

Here a vinyl sulphone is utilised in two key reactions which allow construction of the required highly substituted bicyclic intermediate.

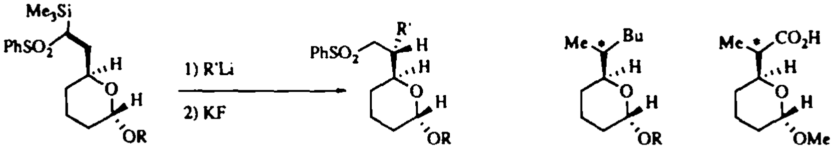
In another elegant contribution from the same group the vinyl sulphone acceptor is generated from a β,γ-epoxy sulphone and alkylated in the same pot, e.g. Scheme 32.[55]



Scheme 32

The initial deprotonation of the epoxysulphone opens the epoxide to give a vinyl sulphone which then undergoes conjugate addition-electrophilic trapping in very good overall yield. Subsequent oxidation of the resultant secondary alcohol followed by elimination of benzenesulphinic acid furnishes cycloalkenones in which the α- and β-alkyl substituents have been introduced as nucleophilic and electrophilic groups respectively (i.e. inverse polarity to that normally obtained). Such conjugate addition-electrophilic quenching sequences using vinyl sulphones are clearly powerful complementary reactions to those using α,β-unsaturated carbonyl compounds.

Isobe has used the conjugate addition of organolithiums to acyclic (with respect to the vinyl sulphone) vinyl sulphones having an additional α-silyl substituent, to synthesise fragments for maytansine synthesis.[56] The addition reaction using such substrates having a γ-chiral centre is highly stereocontrolled, e.g. Scheme 33.



R' = Me, Bu, 2-furyl, etc.

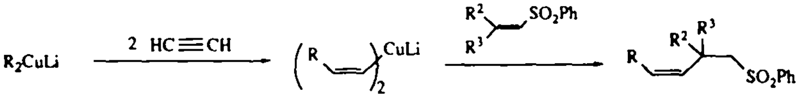
(26) R = H, Me

(27)

Scheme 33

By cleverly using the sulphone to introduce a complementary group to the group R' this method allowed the stereoselective preparation of two diastereomers of compounds (26) and (27) having either absolute configuration at the "off-template" chiral centre, C*.

In the early report by Posner concerning the reactions of organocuprate reagents with vinyl sulphones a number of problems were experienced.[57] Methyl vinyl sulphones suffered competing deprotonation at the methyl group, whilst some β,β-disubstituted sulphones gave very poor yields, even under forcing conditions. Other scattered reports indicate that in general the conjugate addition reaction to alkenyl aryl sulphones can be carried out quite efficiently, e.g. using vinyl cuprates, Scheme 34.[58]

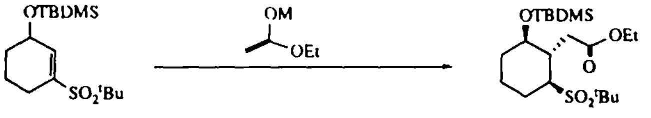


Scheme 34

In some cases direct, uncatalysed addition of Grignard reagents to vinyl sulphones takes place, but the reaction is not general and is usually complicated by competing deprotonation–self condensation of the sulphone starting materials.[59]

3.2 Addition of enolates and similar stabilised anions (including miscellaneous carbon nucleophiles and cyclopropanation reactions)

In a series of reactions of vinyl sulphone (28) with nitrile anions and ester- and ketone-derived enolates the potassium derivatives were found to be considerably more effective than the lithio species, e.g. Scheme 35.[60]



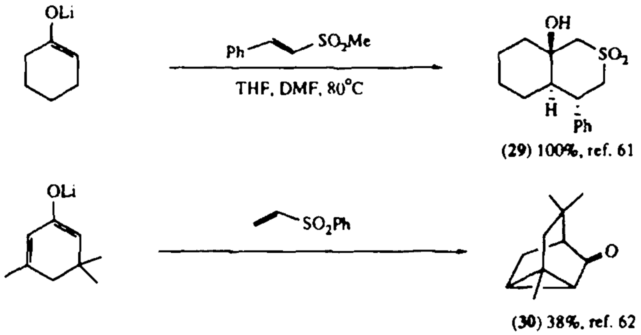
(28)

major diastereomer
M = Li 0% yield, M = K 88% yield

Scheme 35

The actual nature of the reactive species is somewhat ambiguous since the potassium species were not generated free of lithium salts (i.e. ^{n}BuLi/KO^{t}Bu or LDA/KO^{t}Bu mixtures were used), although the effect of the change in counterion is quite dramatic.

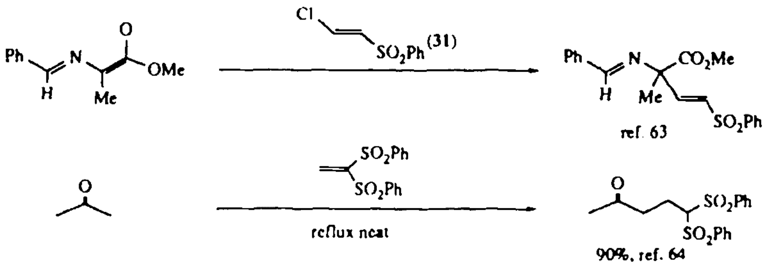
A very attractive feature of the Michael addition of enolates to vinyl sulphones is the possibility of devising tandem reaction sequences which allow cyclisation or annulation in one pot. Two examples which nicely illustrate this point are shown in Scheme 36.[61,62]



Scheme 36

The reaction of methyl styryl sulphone with lithium enolates derived from a selection of ketones gives cyclic β-hydroxy sulphones such as (**29**), usually in good yield. Subsequent attempts to effect Ramberg-Backlund reactions using these products were unsuccessful; however, other desulphonylations were described. Product (**30**) is the result of a double Michael reaction followed by intramolecular substitution of the sulphone group. The reaction allows a very rapid construction of this tricyclic skeleton although yields are moderate at best.

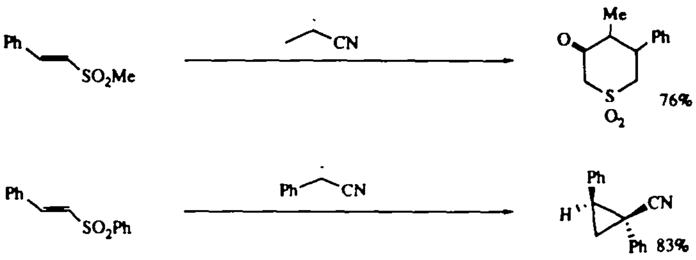
Other reactions of carbonyl substrates with vinyl sulphones include the addition–elimination sequence using an alanine-derived enolate with chlorovinyl sulphone (**31**),[63] and a neutral condensation of ketones with 1,1-bis(benzenesulphonyl)ethylene, Scheme 37.[64]



Scheme 37

In the latter sequence the reaction could be carried out using the ketone as solvent, or by combining the starting materials in equimolar amounts and using acetonitrile as solvent.

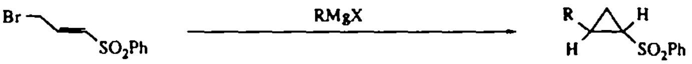
The reaction of metallated nitriles with vinyl sulphones can be carried out so as to give simple addition products, as in reference 60; however under appropriate conditions the reaction can give cyclised products (analogous to the preparation of (**29**)), or cyclopropanes, e.g. Scheme 38.[65]



Scheme 38

Thus with methyl styryl sulphone the initial Michael addition is followed by proton transfer to give a new sulphone carbanion which undergoes intramolecular attack on the nitrile group. Cyclopropanation is favoured by using an aryl vinyl sulphone and a nitrile with additional anion stabilising features such as a phenyl or phenylthio group. Cyclopropanation can also be effected using simple sulphur ylides,[66] and sulphur ylides having additional carbonyl stabilisation.[67]

A complementary approach to cyclopropanation involves the incorporation of a leaving group on the vinyl sulphone Michael acceptor. A report by Eisch and Galle describes the use of bromide (32) in this context. Reaction with unsaturated Grignard reagents proceeds smoothly to give sulphonyl cyclopropanes, Scheme 39.[34]



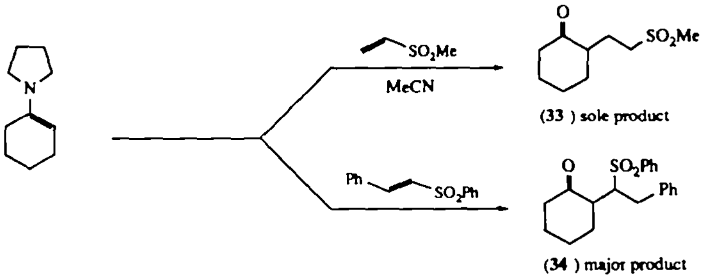
(32)

R = $CH_2{=}CHCH_2$-, $CH{\equiv}CCH_2$-, C_6H_5- etc

Scheme 39

Reaction with alkyl Grignards gave instead the products of coupling with the allylic bromide function, although alternative less direct routes could be used to obtain cyclopropanes in such cases.

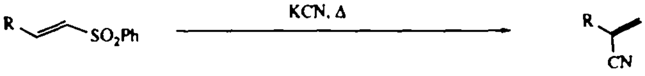
The reaction of enamines with vinyl sulphones has been known for some time.[68] A focus of recent interest has been the unexpected regiochemistry of attack of cyclohexanone-derived enamines with some β-phenyl substituted vinyl sulphones.[69] Thus whilst most vinyl sulphones give the expected Michael products, e.g. (33), the phenyl substituted derivatives can give products arising from attack at the α-position of the vinyl sulphone, e.g. (34), Scheme 40.



Scheme 40

Another report describes similar results, the regiochemistry of attack depending on the substituents on the enamine, and on the starting sulphone geometry.[70] Other cycloaddition reactions of vinyl sulphones with enamines and ynamines are dealt with in Section 4.

Finally the addition of cyanide to vinyl sulphones followed by *in-situ* elimination of arenesulphinate results in overall conversion to an α,β-unsaturated nitrile, Scheme 41.[71]

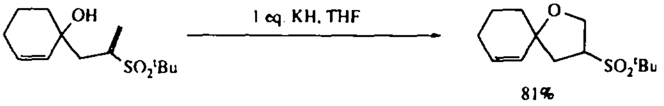


Scheme 41

Note that in this transposition of one Michael acceptor for another the electron demand at the two olefinic centres is reversed.

3.3 Addition of heteroatom groups (including epoxidation)

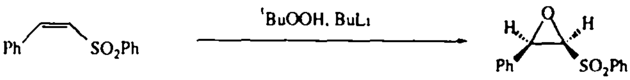
The addition of alkoxide groups to vinyl and allenyl sulphones is a well-known process.[72] An interesting development in this area is the finding by Knochel and coworkers that disfavoured 5-*endo*-trig cyclisations of suitably substituted vinyl sulphones can be carried out to give sulphonyl tetrahydrofurans, Scheme 42.[73]



Scheme 42

Analogous cyclisations to give a pyrrolidine and a cyclopentene product were also demonstrated.

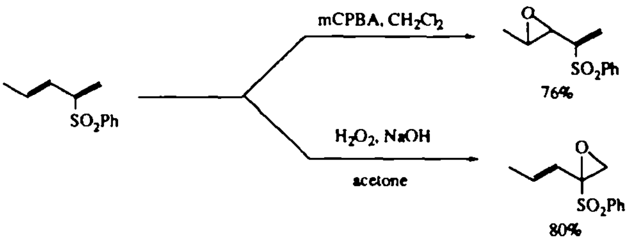
The conjugate additions of hydroperoxides to Michael acceptors is a standard method for the preparation of epoxides from electron-deficient alkenes. This approach has been used to epoxidise vinyl sulphones. The reaction with H_2O_2/HO^- is non-stereospecific,[74] whilst the use of an epoxidising nucleophile bearing a better leaving group such as ClO^- allows completely stereospecific reaction.[75] A new method for such epoxidations involves the use of lithium *tert*-butyl peroxide generated under anhydrous conditions, Scheme 43.[76]



Scheme 43

The method appears to be generally high-yielding and stereocontrolled although only two examples using vinyl sulphones were cited.

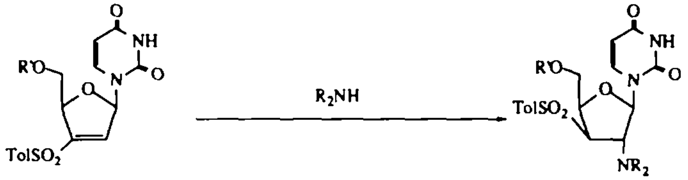
The contrasting reactivity of vinyl sulphones and unactivated alkenes was nicely highlighted in the regioselective epoxidations of dienyl sulphones reported recently by Backvall and Juntunen, Scheme 44.[77]



Scheme 44

Here the more conventional NaOH/H_2O_2 method was used for vinyl sulphone epoxidation, whilst mCPBA was used to epoxidise the more electron-rich alkene. By careful control of the reaction conditions a variety of hydroperoxy products can be isolated from this type of reaction, if desired.[78]

The reactions of vinyl sulphones with amines have been studied in detail by Stirling's group, revealing important trends in the reactivity of variously substituted sulphones.[79] An application of this reaction to the synthesis of some unusual nucleosides has recently appeared, e.g. Scheme 45.[80]



Scheme 45

The reaction almost always gave products having the *trans*-stereochemistry shown; some carbon nucleophiles were also used.

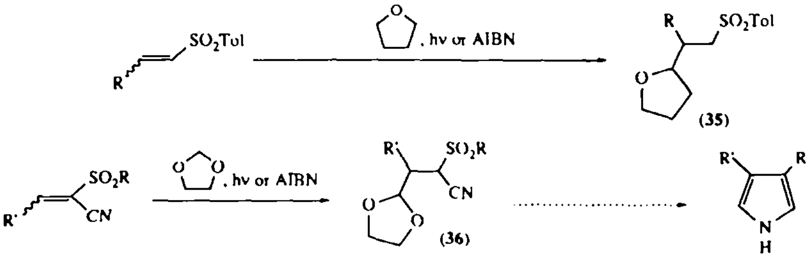
The addition reactions of thiols to vinyl sulphones have also been studied although there do not appear to have been any significant synthetic applications.[81]

Addition of trialkyltin groups to vinyl sulphones generates β-stannylsulphones which undergo facile elimination. This and related chemistry is described in Section 5.3.

Finally, conjugate reduction of vinyl sulphones is possible, for example using $LiEt_3BH$.[82]

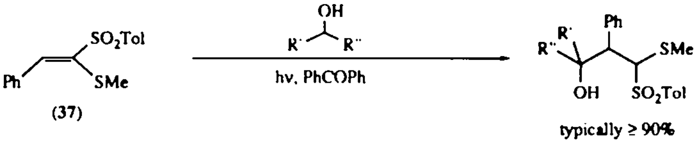
3.4 Radical additions

Vinyl sulphones undergo a variety of useful addition reactions involving carbon-centred radicals. Radicals generated from THF or 1,3-dioxolane add to both simple vinyl sulphones and to cyano-substituted vinyl sulphones to give products such as (35) and (36), Scheme 46.[83]



Scheme 46

Compound (**36**) could be alkylated (to introduce R‴), the nitrile reduced, and the product amine converted to a pyrrole *via* mesylation, cyclisation–elimination, and finally sulphonamide hydrolysis.
Similar chemistry can be conducted with sulphones such as (**37**) by irradiating in the presence of an ether or alcohol, and using benzophenone as photosensitiser, Scheme 47.[84]



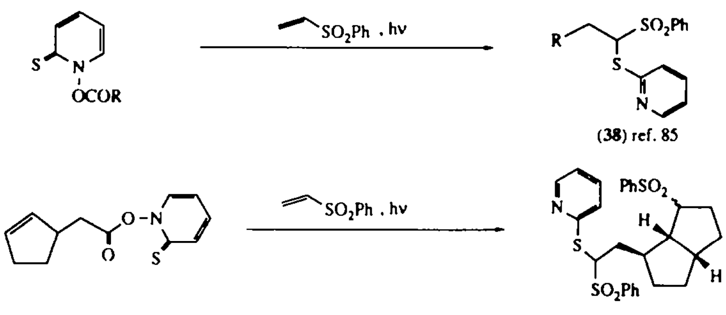
(**37**)

typically ≥ 90%

Scheme 47

This very under-utilised approach to hydroxyalkylation appears ripe for exploitation in synthesis.

A number of notable contributions to this area have come from Barton's group, two highlights of which are shown in Scheme 48.[85,86]



(**38**) ref. 85

(**39**) ref. 86

Scheme 48

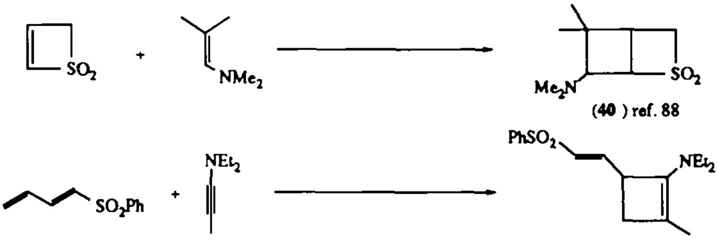
Thus, thiohydroxamate esters act as a source of radicals which add to electrophilic acceptors such as phenyl vinyl sulphone to give product radicals which are functionalised by a chain propagation step involving attack on another molecule of starting ester. The thiopyridyl group in (**38**) can subsequently be oxidatively eliminated providing a synthesis of substituted vinyl sulphones.[85] Two molecules of vinyl sulphone are incorporated in the generation of (**39**) which is formed stereoselectively with respect to three of the four chiral centres on the bicyclic nucleus.[86]

4 VINYL SULPHONES IN CYCLOADDITION REACTIONS

The [2+2] and [4+2] cycloaddition chemistry of vinyl sulphones has been described in some detail in a recent review by De Lucchi and Pasquato.[87]

4.1 [2+2] Cycloadditions

The cycloaddition reactions of enamines and ynamines with the strained cyclic vinyl sulphone thiete-1,1-dioxide to give bicyclic systems such as (**40**) were originally reported by Paquette.[88] Analogous chemistry using simple vinyl and dienyl sulphones has more recently been described by Eisch *et al.*, Scheme 49.[89]



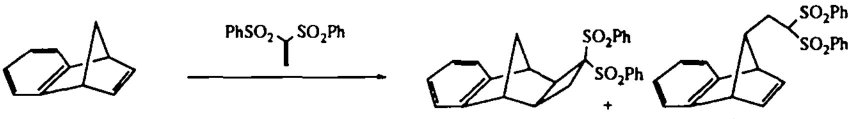
(40) ref. 88

ref. 89

Scheme 49

The reactions are regiospecific, and give good yields of four-membered ring products. The enamine products could be hydrolysed with dilute acid, thereby providing a good route to substituted cyclobutanones.

The products of a formal [2+2] cycloaddition were also obtained in the reaction of 1,1-bis(benzenesulphonyl)ethylene with norbornadiene and its benzofused analogue (41). The isolation of other products such as (42) in the latter reaction is good evidence of a zwitterionic intermediate in such processes, Scheme 50.

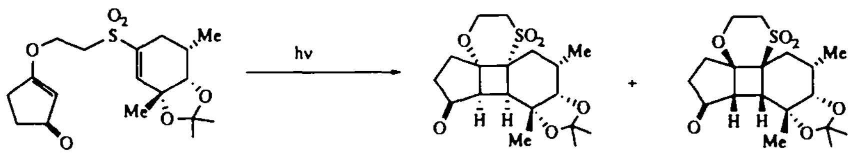


(41)

(42)

Scheme 50

Fuchs has studied the intramolecular [2+2] cycloadditions of some highly functionalised complex vinyl sulphones as a route to cytochalasin C intermediates.[91] Thus photolysis of (43) in acetonitrile at room temperature gave two products resulting from attack on both faces of the vinyl sulphone, Scheme 51.



(43)

major

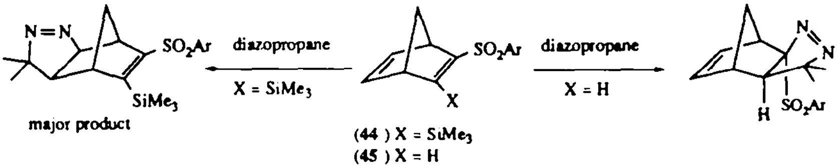
minor

Scheme 51

Unfortunately subsequent chemistry aimed at opening the cyclobutane ring proved unsuccessful.

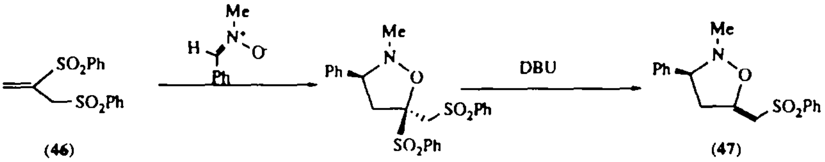
4.2 [3+2] Cycloadditions

In one of a series of significant contributions to the cycloaddition chemistry of vinyl sulphones Padwa's group have examined the reaction of 2-diazopropane with the bicycloheptadiene (44).[92] This reaction followed a similar unexpected course to that observed with cyclopentadiene (Scheme 23), reaction occurring on the electronically less activated alkene. By contrast, the corresponding desilylated diene (45) gave the product of addition to the vinyl sulphone, Scheme 52.



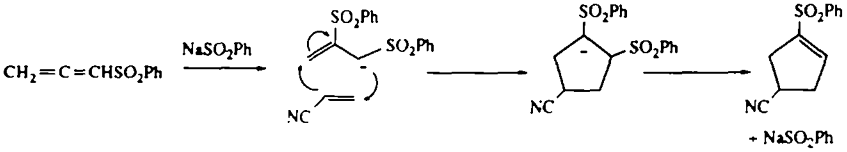
Scheme 52

Reactions of diazo compounds with allenylphenyl sulphone have also been examined by Padwa,[93] as have a variety of dipolar cycloadditions between unsaturated sulphones and nitrones.[94] An interesting development of the sulphonyl allene chemistry was the finding that the use of vinyl sulphone (46) allows access to nitrone cycloadducts, e.g. (47), formally derived from addition to the unactiviated double bond of a sulphonyl allene, Scheme 53.[95]



Scheme 53

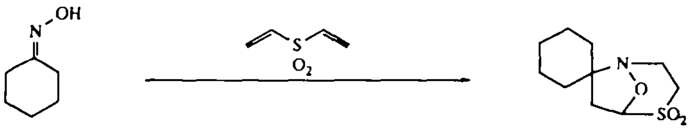
The anion derived from (46) can be generated by conjugate addition of sodium benzenesulphinate to phenylsulphonyl allene.[96] This allows for a number of interesting cyclisation-elimination reactions with Michael acceptors to give [3+2] type products, e.g. Scheme 54.

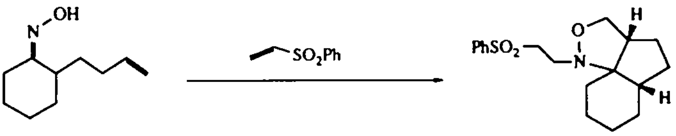


Scheme 54

The benzenesulphinate is regenerated in this sequence, and is required only in trace amounts. Analogous sequences were possible by using the addition of other anions to the starting allene to trigger cyclisation.

Grigg and coworkers have described the use of nitrones, generated from oximes by Michael addition, for cycloaddition reactions.[97] Vinyl sulphones can be used as reaction partners, either to generate the nitrone, or to participate in the cycloaddition, or in both steps, e.g. Scheme 55.

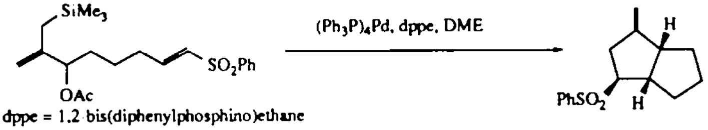




Scheme 55

Both the initial Michael reaction and the cycloaddition reaction can be carried out intra- or intermolecularly, allowing a broad range of interesting functionalised polycyclic products to be prepared.

Trost has included vinyl sulphones amongst the partners that react with trimethylenemethane-palladium complexes to give [3+2] adducts.[98] Scheme 56 highlights a particularly pleasing example in which two rings are constructed in a single step and with a high degree of stereocontrol.



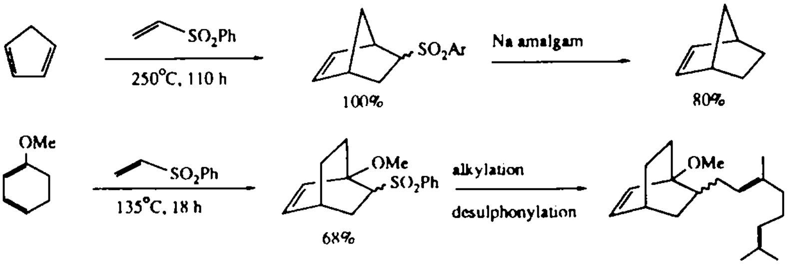
dppe = 1,2 bis(diphenylphosphino)ethane

Scheme 56

4.3 [4+2] Cycloadditions

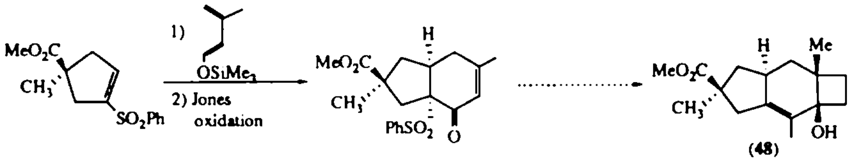
This area is dealt with in some detail by the review of De Lucchi and Pasquato,[87] and so only a few of the multitude of Diels-Alder cycloadditions using vinyl sulphones will be covered here.

Paquette's group has made significant contributions to the area, including the first systematic examination of the use of phenyl vinyl sulphone as an ethylene or terminal alkene equivalent in [4+2] cycloadditions.[99] Thus, cycloaddition takes place smoothly with a variety of dienes, to give sulphone products which can be either directly desulphonylated, or first alkylated and then desulphonylated, Scheme 57.



Scheme 57

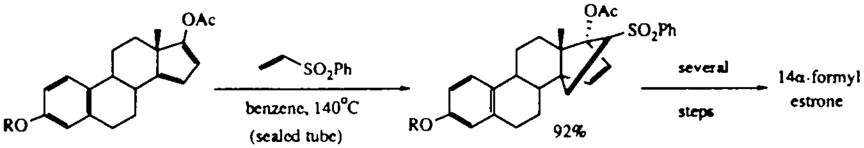
Later developments include the use of Danishefsky dienes to give products which could be manipulated to furnish variously substituted cyclohexenones,[100] and application to the synthesis of natural products such as sterpuric acid (**48**), Scheme 58.[101]



(48)

Scheme 58

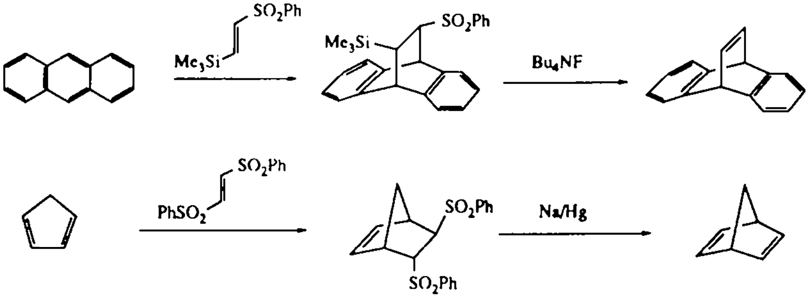
The Diels-Alder reaction of a steroidal acetoxy diene with phenyl vinyl sulphone provides a route into 14α-formylestrone, and other derived products, Scheme 59.[102]



Scheme 59

The reaction of phenylvinyl sulphone itself appears to take place readily with "normal" and activated dienes at temperatures ranging from benzene reflux to about 130°C. The use of less reactive dienes or more substituted sulphones usually requires more forcing conditions, although results can still be very good.

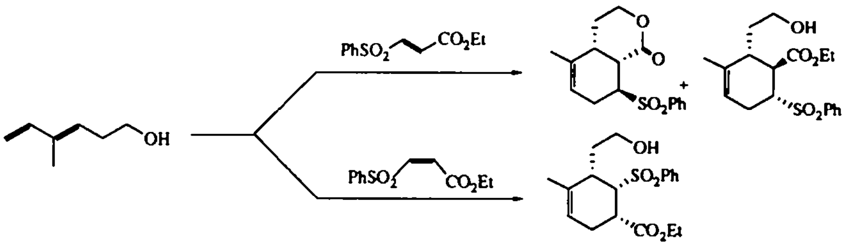
Details of the reactivity of various silyl-substituted vinyl sulphones and bis-sulphonyl ethylenes can be found in papers from the groups of Paquette[103] and De Lucchi.[104] The adducts formed using these compounds as dienophiles can undergo subsequent elimination reactions, thus the starting vinyl sulphones function as masked acetylene equivalents, e.g. Scheme 60.



Scheme 60

The cycloadditions of β-nitrophenylsulphonyl ethylene are apparently even more facile than those of the bis-sulphonyl derivative, and again subsequent elimination can be carried out, this time using Bu_3SnH.[105]

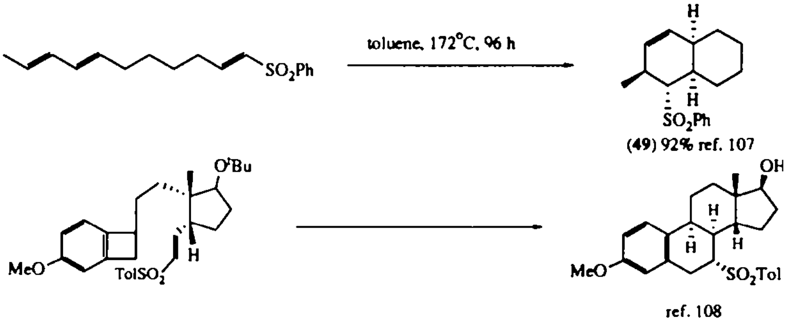
Other types of substituted vinyl sulphones which have been used in these reactions include those with additional carbonyl activating groups. A particularly nice example is the reaction of either (*E*)- or (*Z*)-β-phenylsulphonylacrylates with dienes, which occur with contrasting regiocontrol, Scheme 61.[106]



Scheme 61

In both the examples tried the (E)-isomer gave the product arising due to the CO_2Et group controlling the regiochemistry, whereas in the (Z)-isomer the sulphone appears to exert the dominating directing effect.

Intramolecular Diels-Alder (IMDA) reactions involving vinyl sulphones are rather rare. Simple examples were carried out recently by Craig *et al.*, giving sulphonyl-substituted indane and decalin products, such as (**49**).[107] Kametani has described the application of an IMDA reaction, using a vinyl sulphone, to the synthesis of estrane products, Scheme 62.[108]

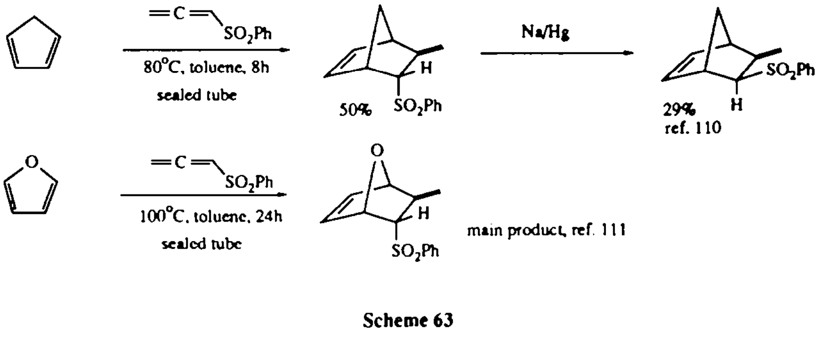


Scheme 62

These types of stereocontrolled cycloadditions appear promising candidates for future synthetic applications.

High diastereoselectivity has been observed in the reaction of a vinyl sulphone having an additional chiral sulphoxide substituent derived from 1-(S)-(+)-camphor-10-sulphonyl chloride.[109]

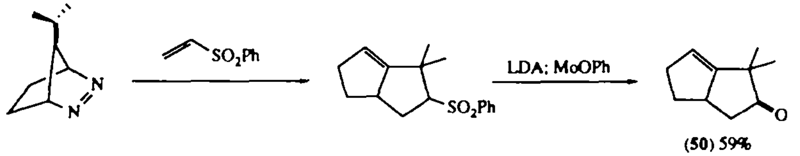
Cycloadditions using phenylsulphonyl allene are also facile and occur regioselectively on the sulphonyl-substituted alkene, e.g. Scheme 63.[110,111]



Scheme 63

In these examples the *endo/exo* ratio appears to be substrate dependant with the *endo*-adduct predominating. Alkylation and desulphonylation reactions of the adducts were studied,[110] and in the case of the furan adduct opening of the oxabicyclic system to give a sulphonyl-substituted phenol was effected using BuLi.[111]

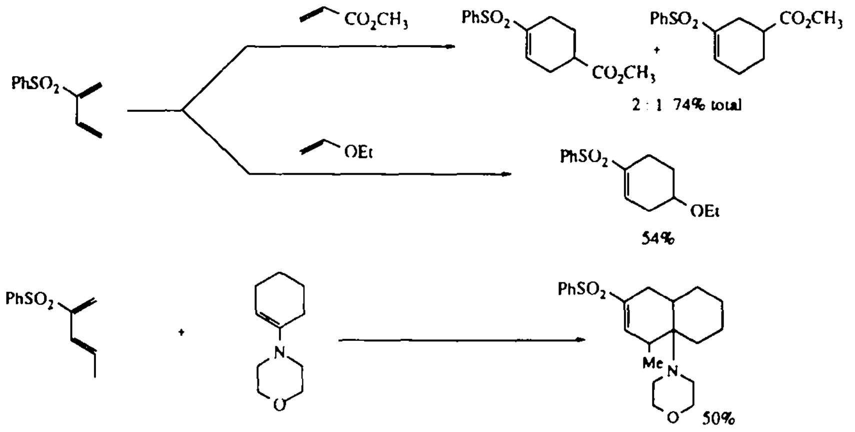
Little has used phenyl vinyl sulphone to trap a 1,3-diyl generated from a diazo precursor.[112] The yield for the combined cycloaddition reaction, followed by an oxidative desulphonylation to give ketone (**50**) was a respectable 59%, Scheme 64.



Scheme 64

This reaction sequence illustrates how phenyl vinyl sulphone can act as a ketene equivalent in cycloaddition reactions.

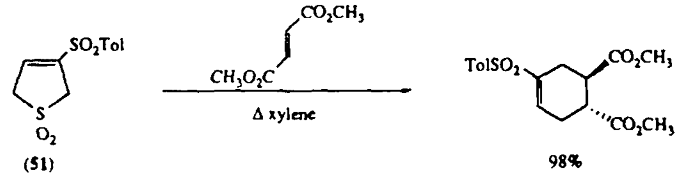
Interestingly, dienyl sulphones can also act as the 4π-components in [4+2] cycloaddition reactions, with either electron-rich or electron-poor 2π partners, e.g. Scheme 65.[113]



Scheme 65

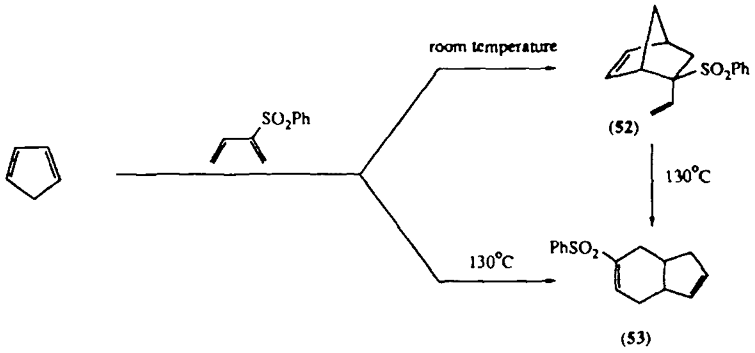
This [4+2] chemistry contrasts with the [2+2] reaction highlighted in Scheme 49. Whilst the regiochemical outcome of the reactions using electron-rich alkenes was predictably very good, the control with electron-deficient alkene partners was somewhat less consistent.

The *in-situ* generation of a sulphonyl diene, i.e. by heating 3-(*p*-toluenesulphonyl)-3-sulpholene (**51**), in the presence of suitable dienophiles also gives very good yields of cycloadducts, Scheme 66.[114]



Scheme 66

In these reactions the use of a sulpholene can help minimise side reactions due to dimerisation of the sulphonyl diene. The reaction of 3-phenylsulphonylbutadiene with cyclopentadiene at room temperature gives product (**52**) whereas reaction at 130°C gives (**53**), Scheme 67.[115]



Scheme 67

It was found that (**52**), the product of cycloaddition to the vinyl sulphone as 2π-component, rearranged to (**53**), the product of an apparent cycloaddition to the sulphonyl diene as 4π-component, on heating to 130°C. Cross-over experiments ruled out the retro-Diels-Alder reaction of (**52**) as an explanation and so a Cope rearrangement appears most likely.

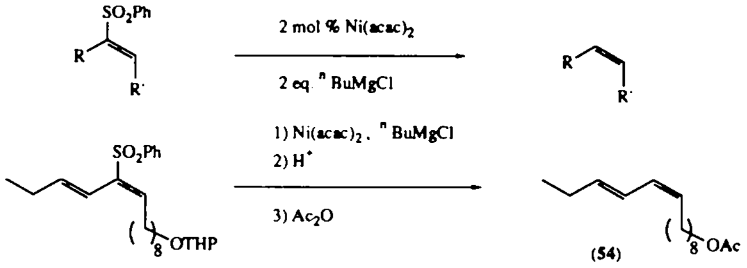
5 DESULPHONYLATION OF VINYL SULPHONES

This section covers desulphonylation reactions of vinyl sulphones excluding aspects of the Ramberg-Backlund reaction, which can be applied to certain unsaturated sulphones.[116]

5.1 Reductive desulphonylation ($RSO_2R' \rightarrow R\text{-}H$)

In general the reductive removal of the sulphonyl group from vinyl sulphones using dissolving metals or metal amalgams is not stereospecific. In some cases however the more stable desulphonylated product can be obtained highly selectively; for example, in the reduction of certain styryl sulphones using either aluminium amalgam or $LiAlH_4$–$CuCl_2$ the (*E*)-product was obtained exclusively.[117]

Julia has been a pioneer in the discovery of stereospecific methods for hydrogenolysis (and other reactions) of vinyl sulphones. Two important methodologies have emerged from this work. The first involves reaction of the vinyl sulphone with $^{n}BuMgCl$ in the presence of a transition metal catalyst such as $Ni(acac)_2$, Scheme 68.[118]

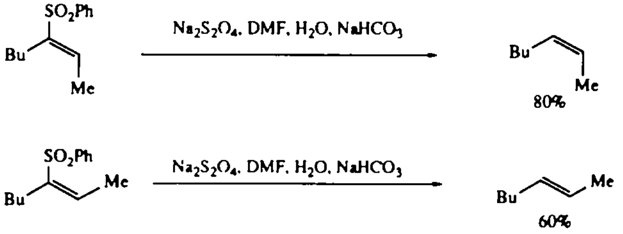


(54)

Scheme 68

The method was used to synthesise diene (54), a pheromone of *Spodoptera littoralis*, containing at least 93% of the desired (9*Z*,11*E*)-isomer. Palladium catalysis can also be used for this reaction, giving slightly superior results providing that the appropriate choice of metal ligands (and other additives) is made.

The other general method for vinyl sulphone hydrogenolysis introduced by Julia involves treatment of the vinyl sulphone with sodium dithionite and $NaHCO_3$ in aqueous DMF, e.g. Scheme 69.[120]

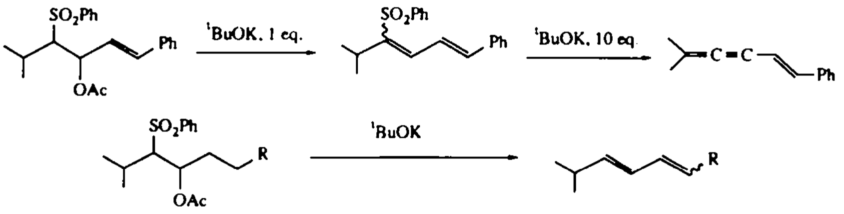


Scheme 69

The mechanism of the reaction involves the conjugate addition of HSO_2^- (*syn*) followed by loss of SO_2 and expulsion of sulphinate in an *anti*-elimination.[121] In the case of β,β-disubstituted vinyl sulphones the two methods described above are far less efficient,[122] although indirect methods can be used for non-stereoselective desulphonylation in such cases, (*vide infra*).

5.2 Elimination reactions

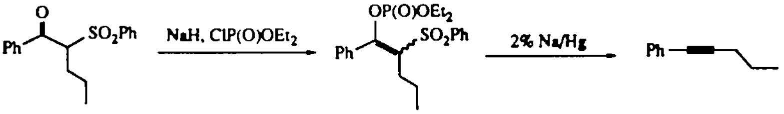
The abovementioned strategies used by Julia to prepare vinyl sulphones involving β-elimination from a β-substituted sulphone (e.g. Scheme 10) can be taken a step further to include subsequent elimination of sulphinate. Such reactions can give either acetylene, allene, or polyene products depending on the substrate structure, Scheme 70.[123]



Scheme 70

Vinyl sulphone intermediates could be isolated as the initial products, further elimination to give hydrocarbon products requiring more harsh base treatment. Formation of 1,3-dienes most likely occurs via isomerisation of the vinyl sulphone to an allylic sulphone, followed by 1,4-elimination of sulphinic acid.

Acetylenes can be cleanly prepared starting from β-keto-sulphones, via the easily derived enol phosphates (which can also be regarded as vinyl sulphone derivatives). Scheme 71.[124]

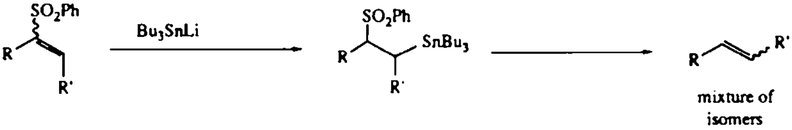


Scheme 71

Reductive elimination to give the desired acetylene occurs using Na/NH_3 or Na-Hg/THF, and the use of other enol derivatives and reducing agents is also discussed.

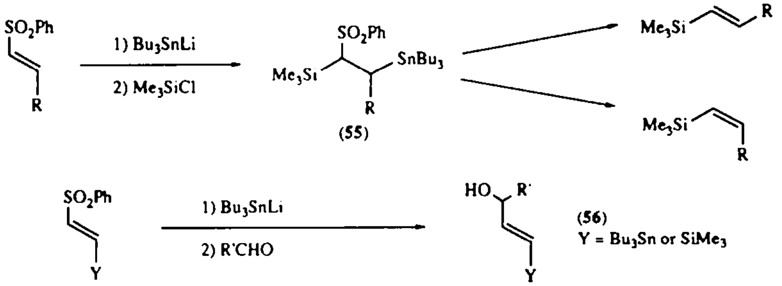
5.3 Tin-based methods

The addition of Bu_3SnLi to vinyl sulphones gives intermediate β-stannyl sulphones which undergo facile elimination to give alkene products, Scheme 72.[125]



Scheme 72

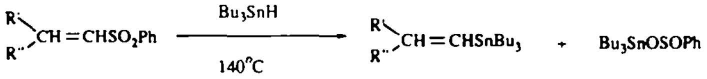
The elimination step was carried out either by stirring with silica, or by heating in xylene. Extensions of this basic idea reported by the same research group allow for the incorporation of additional functionality into the unsaturated products, e.g. Scheme 73.[126,127]



Scheme 73

The adduct (55) was found to be stereoselectively converted to either the (*E*)- or (*Z*)- vinyl silane product by choice of suitable elimination conditions.[126] The product stereochemistry was found to depend only on the elimination conditions and not on the stereochemistry of the starting material. The preparation of (56) in one step from a suitable β-stannyl or β-silyl sulphone represents an example of overall alkylative desulphonylation, see Section 5.4.[127]

A homolytic substitution reaction of vinyl sulphones occurs on treatment with Bu_3SnH at 140°C, Scheme 74.[128]

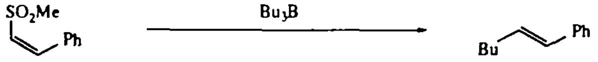


Scheme 74

The reaction may involve either an addition–elimination sequence, or alternatively an electron transfer process.

5.4 Alkylative desulphonylation ($RSO_2R' \rightarrow R\text{-}R''$)

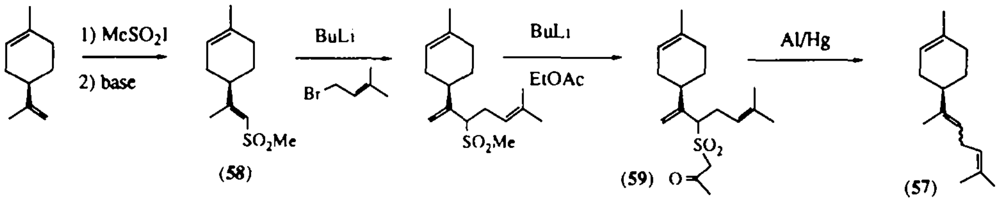
The reaction of methyl styryl sulphone with $^nBu_3B$ or $^iPr_3B$ yields the corresponding alkyl-substituted styrene in each case, Scheme 75.[129]



Scheme 75

In this reaction the (*E*)-product was formed regardless of starting material geometry. In THF or toluene some minor products arising from combination with solvent-derived radicals were also obtained.

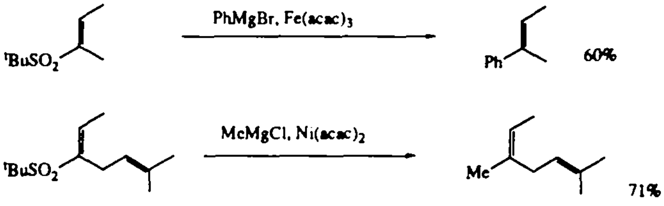
An indirect sequence for alkylative desulphonylation of methyl vinyl sulphones has been developed by Baldwin's group, allowing the synthesis of (*E*)- and (*Z*)-α-bisabolenes (**57**), Scheme 76.[130]



Scheme 76

The conversion of vinyl sulphone (**58**) to the mixture of stereoisomeric products (**57**) represents overall alkylative desulphonylation. The key step involves treatment of β-ketosulphone (**59**) with aluminium amalgam to give an intermediate allylic sulphinic acid which then rearranges to give the observed products. Although the process is highly regioselective and occurs without racemisation, the formation of mixtures of stereoisomers is a serious drawback.

The most significant advances in direct stereoselective alkylative desulphonylation of vinyl sulphones have undoubtably been made by Julia and coworkers. Thus, reaction of stereochemically pure vinyl sulphones (available using Julia's earlier chemistry) with Grignard reagents under nickel or iron catalysis gives substituted products, Scheme 77.[131]



Scheme 77

Other products can be formed in competition, for example from Michael addition or by hydrogenolysis (as in Scheme 68). The substitution appears most effective using α,β-disubstituted *tert*-butyl sulphones with Grignards not susceptible to β-hydride elimination. Most significantly a high degree of retention of stereochemistry can be attained, especially using Grignards having chloride counterions.[132]

6. CONCLUSION

In a relatively brief period of time the repertoire of vinyl sulphone chemistry has developed to the point where an armoury of methods is available for their preparation and manipulation. The ease with which vinyl sulphones allow regio- and stereoslective introduction of carbon and heteroatom groups, formation of rings, and assembly of carbon-carbon double bonds makes them attractive prospects for future widespread use in synthesis.

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