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The chemistry of acetylenic and allenic sulfones

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1. Introduction

The chemistry of sulfones has been extensively studied and widely exploited in organic synthesis for the past several decades, prompting several general reviews[1–9] of the subject. Vinylic (**1**), acetylenic (**2**) and allenic sulfones (**3**) have a particularly rich chemistry that is of special value to the synthetic chemist. Vinyl[1,10] and conjugated dienyl[11] sulfones have been reviewed elsewhere and are not covered here. However, acetylenic and allenic sulfones, which to date have received less attention in the review literature than their vinyl counterparts, are of growing importance as synthetically useful reagents that at times exhibit surprising behaviour. Consequently, the present review attempts to survey their preparations, reactions and applications.

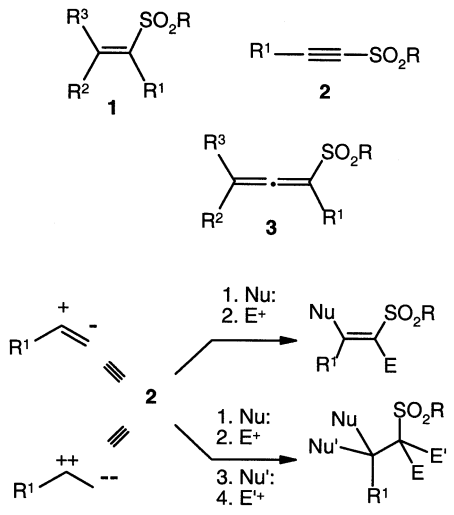
The sulfone group is strongly electron-withdrawing and has the ability to stabilize an α-carbanion. Thus, unsaturated sulfones undergo a variety of conjugate addition reactions and the corresponding α-carbanions can be alkylated or made to react with various other electrophiles. Alternatively, deprotonation with strong bases and alkylation of saturated, vinyl and allenic sulfones is also possible. Acetylenic sulfones are more reactive than analogous vinyl sulfones toward conjugate additions[12,13]and are potentially capable of undergoing single or double additions of nucleophiles at the β-position and, subsequently, single or double reactions with electrophiles at the α-position. In principle, they therefore behave as the synthetic equivalents of hypothetical dipole or multipole species (Scheme 1) upon cleavage of the sulfone residue.

A sulfone substituent also activates an adjacent π-system toward a variety of cycloaddition reactions. Unsaturated sulfones therefore act as excellent dienophiles in Diels–Alder reactions and exhibit enhanced reactivity and regioselectivity in many other types of cycloadditions.[14] There is a superficial similarity between the conjugate additions and cycloadditions of α,β-unsaturated sulfones and those of α,β-unsaturated carbonyl compounds. However, in contrast to the carbonyl group, which is generally desired and retained in the product, the sulfone moiety can be easily removed by various desulfonylation methods.[15] Thus, reductive, oxidative and alkylative desulfonylations at the end of a reaction sequence afford products where the sulfone group has been replaced by hydrogen, oxygen functions or alkyl groups, respectively. Alternatively, the sulfone functionality can be removed by elimination, since sulfinate anions (RSO_2^-) act as reasonably effective leaving groups. Overall, the sulfone moiety can therefore be exploited as a disposable activating group for an adjacent unsaturated carbon–carbon bond in a variety of synthetic protocols.

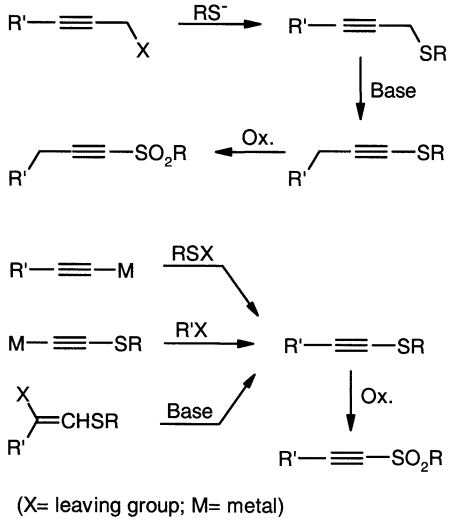
2. Preparation of acetylenic sulfones

2.1. From oxidation of acetylenic sulfides

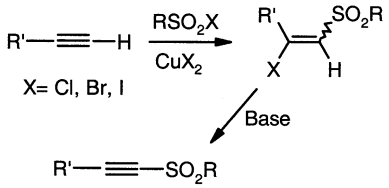
The earliest procedures for preparing acetylenic sulfones



Scheme 1.



Scheme 2.

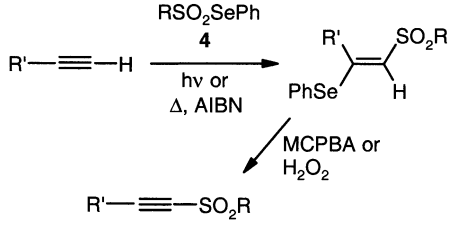


Scheme 3.

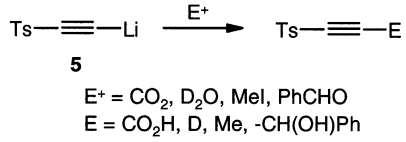
involved oxidation of the corresponding sulfides (Scheme 2). *m*-Chloroperbenzoic acid (MCPBA)[16] and hydrogen peroxide[12,16b,17–20] were among the first reagents used for this purpose, and they remain in common use today. Other oxidants include perbenzoic acid,[21,22] peracetic acid,[23] Oxone®,[24] dimethyldioxirane,[25] *t*-butyl hydroperoxide/MoO_3[26] and PhIO in the presence of $RuCl_2(PPh_3)_3$ catalyst.[27] In many cases, acetylenic sulfoxides were similarly obtained by employing a single equivalent of the oxidant. The sulfide precursors can in turn be prepared from propargylic halides and thiolates, followed by base-catalyzed isomerization of the resulting propargylic sulfides.[12,13,16b,16c,19a,28] Alternatively, sulfenylations of acetylides with disulfides,[18b,18c,24] sulfenyl chlorides,[18a] sulfur dichloride (to afford bisacetylenic sulfides),[29] thiophthalimides,[30] thiosulfonates[29b,31a,31c] or thiocyanates[31c,31d] provide the necessary sulfides. Terminal acetylenic sulfides can be alkylated via their acetylides,[22b,26,32] and various acetylenic sulfide precursors have been obtained by the dehydrohalogenation of the corresponding halovinyl derivatives.[18a,19b,23,33] Vinyl alkynyl[30,34] and bisalkynyl sulfones[29] have also been obtained by oxidation of their sulfides.

2.2. From acetylenes and sulfonyl halides

The free-radical additions of sulfonyl chlorides,[35,36] bromides[37,38] and iodides[39] to terminal acetylenes were reported to produce β-halovinyl sulfones, which underwent dehydrohalogenation with bases such as triethylamine,[37,38] basic alumina[36b] or potassium fluoride in acetonitrile[40] to afford acetylenic sulfones (Scheme 3). The presence of copper(II) chloride or bromide facilitates the additions of the respective sulfonyl halides and the additions of sulfonyl iodides can be photoinitiated.[39b] The *E,Z* ratio of the addition step depends on conditions such as the solvent and the presence of a copper salt. Elimination from the *anti* addition products, where the vinylic hydrogen atom and the sulfonyl group are *cis*, is generally more difficult than from the *syn* product.[30b,40] An alternative to the use of the relatively unstable sulfonyl iodide is to treat the acetylene with sodium benzene- or *p*-toluenesulfinate and iodine.[41–43] The resulting β-iodovinyl sulfones were dehydroiodinated with potassium



Scheme 4.



Scheme 5.

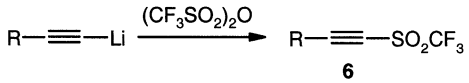
t-butoxide in THF at −78°C, but the use of triethylamine at or above room temperature resulted in the formation of isomeric propargylic sulfones.[41]

2.3. From selenosulfonation of acetylenes

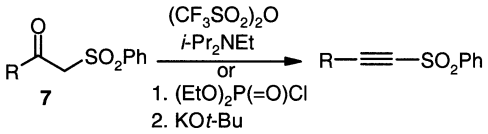
Selenosulfonates **4** also add to acetylenes by free-radical mechanisms. The reactions can be initiated photochemically (sunlamp, Rayonet® reactor or sunlight) or by heating with AIBN. The resulting adducts from terminal acetylenes are formed with high regio- and stereoselectivity, affording products of *anti* addition. Since the phenylseleno group and the vinylic hydrogen atom are *cis*-oriented, oxidation and selenoxide *syn*-elimination proceed under mild conditions, often affording nearly quantitative yields of acetylenic sulfones (Scheme 4).[44–53] The selenosulfonates **4** are odourless, crystalline solids that can be stored indefinitely in the refrigerator. They are readily available by the oxidation of either sulfinic acids[54] or sulfonylhydrazides[55,56] with benzeneseleninic acid. The latter procedure is particularly efficient when carried out in methanol,[55b,55c] instead of in dichloromethane,[55a,56] since the pure selenosulfonate crystallizes in high yield directly from the reaction mixture.

2.4. From acetylides

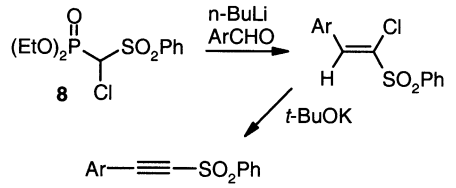
Lithium *p*-toluenesulfonylacetylide (**5**), can be generated from the parent acetylene (see section 2.7) at ca. −100°C with *n*-butyllithium and quenched with reactive electrophiles such as carbon dioxide,[57] methyl iodide,[58] D_2O[58] or benzaldehyde[58] (Scheme 5). However, the instability of **5**, even at low temperatures, limits the scope of this method. The preparation of the first acetylenic triflone (**6**, R=Ph) was reported by Glass and Smith[59] by the reaction of lithium phenylacetylide with triflic anhydride. A variety of acetylenic triflones,[60–64] as well as other perfluoroalkylsulfonyl acetylenes,[61a,64b,65] have since been prepared by similar procedures (Scheme 6). In contrast, the reaction of an acetylenic Grignard reagent with triflic anhydride led to the corresponding acetylenic halide as the major product instead of the triflone.[66]



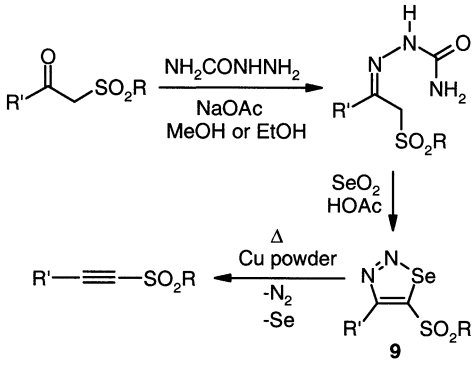
Scheme 6.



Scheme 7.



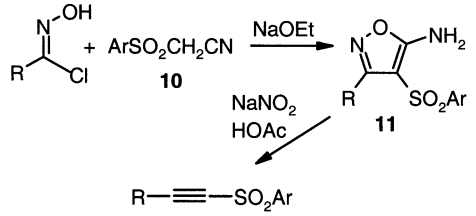
Scheme 8.



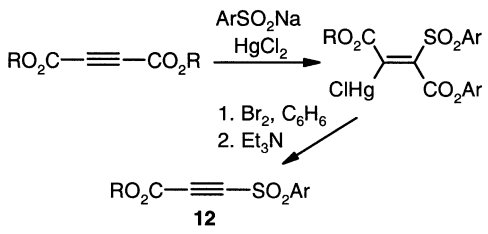
Scheme 9.

2.5. From β-keto sulfones, β-sulfonyl phosphonates and arylsulfonylacetonitriles

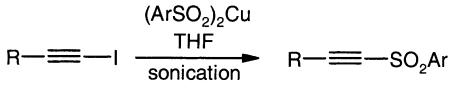
The overall dehydration of β-keto sulfones **7** to the corresponding acetylenic sulfones has been reported with triflic anhydride and diisopropylethylamine,[67] as well as with diethyl chlorophosphate, followed by potassium *t*-butoxide[68,69] (Scheme 7). The modified Wittig–Horner reaction of the sulfonyl phosphonate **8** shown in Scheme 8 is especially effective for the preparation of aryl derivatives.[70] A different approach is based on the conversion of a starting β-keto sulfone to its semicarbazone, followed by oxidation with selenium dioxide. The resulting selenadiazole **9** can then be pyrolyzed to produce the desired acetylene (Scheme 9).[71] Similarly, fragmentation of 5-aminoisoxazoles **11**, obtained from sulfonylacetonitriles **10**, afforded acetylenic sulfones upon diazotization (Scheme 10).[72]



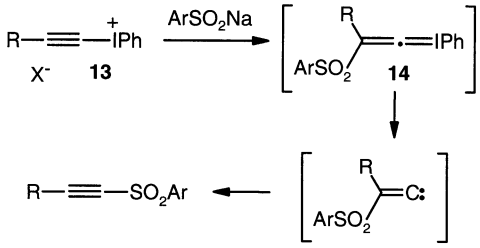
Scheme 10.



Scheme 11.



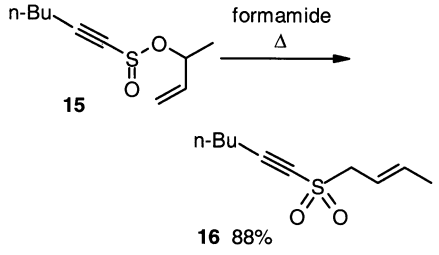
Scheme 12.



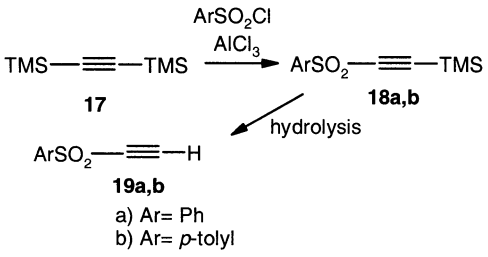
Scheme 13.

2.6. From acetylene derivatives and sulfinates

Acetylene dicarboxylates react with $HgCl_2$ and sodium arenesulfinates to afford β-sulfonylvinyl mercury species, that undergo oxidative demercuriation and decarboxylation to the corresponding acetylenes **12**[73] (Scheme 11). Acetylenic iodides[74] produce acetylenic sulfones when sonicated with cupric sulfinates in THF (Scheme 12), while alkynyliodonium salts **13** afford acetylenic sulfones when treated with sodium sulfinates via the addition products **14**, followed by a process reminiscent of the Fritsch–Buttenberg–Wiechell rearrangement (Scheme 13).[75–77] Intramolecular insertion reactions[75b,77b] of the resulting vinyl carbene intermediates have also been reported, as well as substitution reactions of **14** with halide ion to form the corresponding β-halovinyl sulfones.[75a] In a different type of process, the allyl alkynesulfinate **15** was reported to undergo [2,3]sigmatropic rearrangement to the corresponding acetylenic sulfone **16** upon heating (Scheme 14).[78a] A similar process was observed with allyl allenesulfinates, affording the corresponding allenic sulfones.[78b,78c]



Scheme 14.



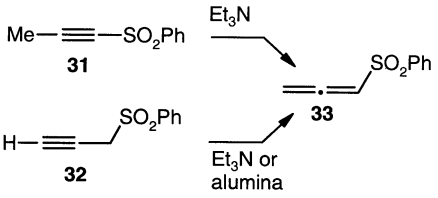
Scheme 15.

Table 1. Preparation of β-functionalized acetylenic sulfones

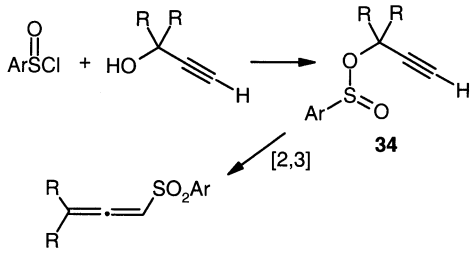
Acetylenic Sulfone	References
$ArSO_2$—≡—CO_2R **12**	31, 73
Ts—≡—CO_2H **20**	57b
Ts—≡—△ **21**	49
$ArSO_2$—≡—TMS **18**	46b, 79-82, 88
$ArSO_2$—≡—SnR_3 **22**	89, 90
Ts—≡—SePh **23**	91
Ts—≡—$P(NR_2)_2$ **24**	92
Ts—≡—$P(O)(OEt)_2$ **25**	93
$ArSO_2$—≡—Br **26**	94
Ts—≡—$^+$IPh $^-$OTf **27**	95
$PhSO_2$—≡—CF_3 **28**	96
t-$BuSO_2$—≡—SO_2t-Bu **29**	21, 97
$ArSO_2$—≡—SO_2Ar **30**	25

2.7. Preparation of terminal acetylenic sulfones

The widely used arylsulfonylacetylenes **19** are accessible from the $AlCl_3$-catalyzed reaction of arylsulfonyl chlorides with acetylene **17**, followed by hydrolysis of the remaining silyl residue in **18** (Scheme 15).[79] The *p*-tolyl derivative **19b** has been prepared on a 0.2 mol scale by this method[80] and more recent variations include the use of silica-gel[81] or NaF[82,83]in the hydrolysis of **18**. The selenosulfonation and selenoxide elimination (see Section 2.3) of trimethylsilylacetylene, followed by hydrolysis of the silyl group, provides an alternative approach.[46b] The oxidation of readily available terminal arylthioacetylenes[18a,84] with peracids also affords these products.[22a,85,86] Finally, the acetylenic sulfone **19b** was obtained in low yield from the direct sulfonylation of lithium or magnesium acetylides with *p*-toluenesulfonyl fluoride.[87]



Scheme 16.



Scheme 17.

2.8. Special cases

A number of acetylenic sulfones containing heteroatoms or substituents other than hydrogen or simple alkyl or aryl residues in the β-position have been reported. They are listed in Table 1 along with references for their preparation.

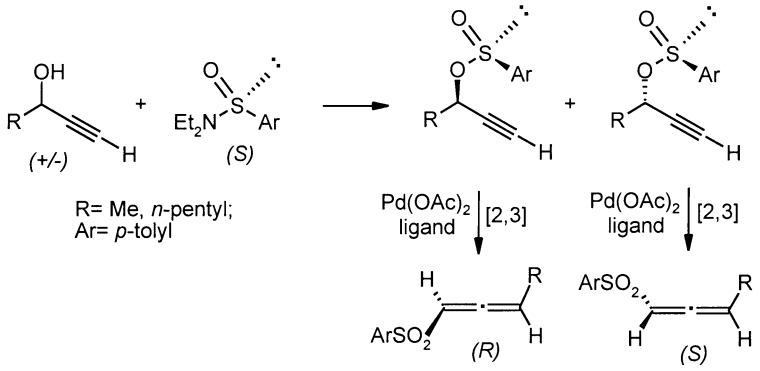
3. Preparation of allenic sulfones

3.1. From isomerization of acetylenic or propargylic sulfones

The first allenic sulfone **33** was reported by Stirling,[28] who observed that both 1- and 3-(phenylsulfonyl)propyne (**31** and **32**, respectively) undergo base-catalyzed isomerization in the presence of triethylamine to afford **33** (Scheme 16). The process is especially facile in the case of the propargylic sulfone **32**, where chromatography over alumina produced the allene **33** in high yield. Since propargylic sulfones are readily available from propargylic halides by substitution with thiolates, followed by oxidation, the approach serves as a means for generating **33** and related allenic sulfones. Thermochemical studies confirmed that the unsubstituted allenic sulfone **33** is more stable than its propargylic or acetylenic isomers by 8.2 and 9.9 kcal/mole, respectively.[98] However, in the γ-methyl-[99] or γ-phenyl-substituted series,[100] the propargylic sulfone predominates after similar treatment of the corresponding allene with base or alumina. Regardless of the exact position of the prototropic equilibrium, it is often possible to generate and then trap the allenic sulfone in situ by conjugate addition or cycloaddition, as described in later sections.

3.2. From [2,3]sigmatropic rearrangement of propargylic sulfinates

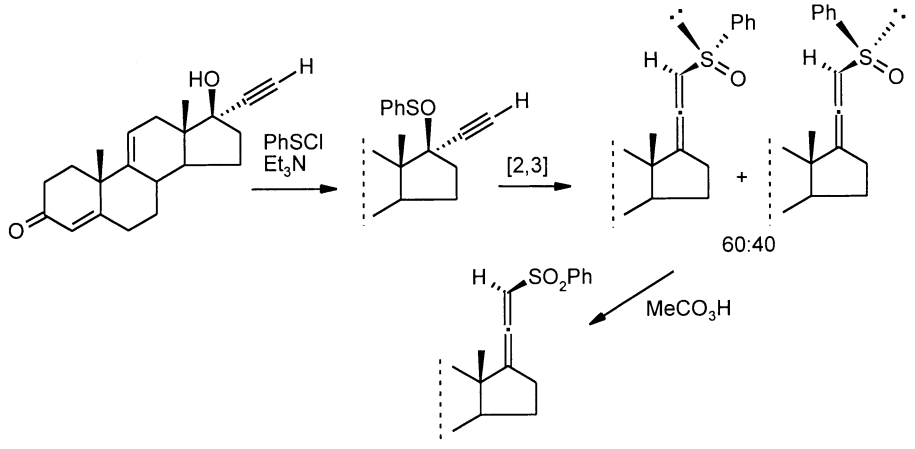
In 1967, Stirling,[101] and independently, Braverman and Mechoulam,[102] reported that propargylic esters of arenesulfinic acids (**34**) undergo [2,3]sigmatropic rearrangements when heated to afford the corresponding allenic sulfones (Scheme 17). Kinetic,[100,103] deuterium labelling[99] and stereochemical[99] studies indicated a cyclic, intramolecular mechanism, as opposed to a dissociative process via an intermediate carbocation and sulfinate anion. In most cases, the required sulfinate esters **34** were prepared by treating propargylic alcohols with sulfinyl chlorides,[99,100] as in Scheme 17. However, sulfinamides[104,105] can be employed instead of sulfinyl chlorides and, when optically pure, serve to resolve racemic propargylic alcohols. The stereospecific rearrangement of the resulting sulfinate ester



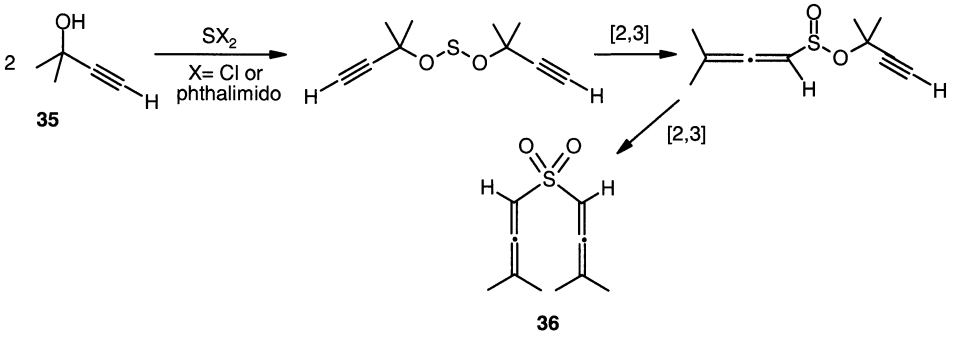
Scheme 18.

diastereomers is facilitated by palladium catalysis, with the two esters producing allenic sulfones of opposite configuration[105] (Scheme 18). The rearrangements of sulfinate esters derived from appropriately γ-substituted propargylic alcohols have also been employed in the preparation of allenic sulfones containing α-ester,[106] amide,[107] or halide[107] substituents.

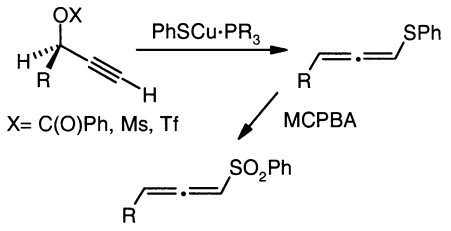
A similar rearrangement of sulfenate esters, obtained from propargylic alcohols and sulfenyl chlorides,[99,108] affords allenic sulfoxides. These can then be oxidized to the corresponding allenic sulfones,[99] thereby comprising an alternative synthesis of the latter compounds. Trichloromethanesulfenyl chloride thus leads to allenic sulfones with enhanced reactivity,[109] while chloromethyl analogues provide opportunities for further transformation via the Ramberg–Backlund reaction (see section 5.1).[110] Optically active allenic sulfoxides have been prepared from menthyl sulfinates and Grignard reagents derived from propargylic bromides by the Andersen method.[111] These compounds were then converted to the corresponding optically active allenic sulfones by oxidation.[112] The allenic sulfoxides epimerize via interconversion with the corresponding sulfenate esters, but this process does not affect the stereochemistry of the allene moiety. Enantioenriched allenic sulfones have also been obtained from optically active chiral propargylic alcohols via the rearrangement of their arenesulfinate esters,[112b] or by treating them with a sulfenyl chloride, followed by rearrangement and oxidation, as in Scheme 19.[113] In the latter case, which was used in the



Scheme 19.



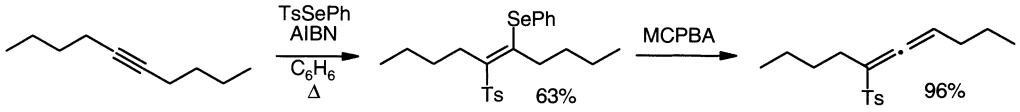
Scheme 20.



Scheme 21.

3.4. From selenosulfonation of acetylenes

The selenosulfonation of acetylenes,[44,45] which provides a convenient route to acetylenic sulfones (see section 2.3), can also be used for the preparation of allenic sulfones. First, selenosulfonation of an internal acetylene, such as 5-decyne, followed by selenoxide elimination, affords the corresponding allenic sulfone[120] (e.g. Scheme 22) in high yield. Second, the 1,2-adducts **37**, obtained from terminal



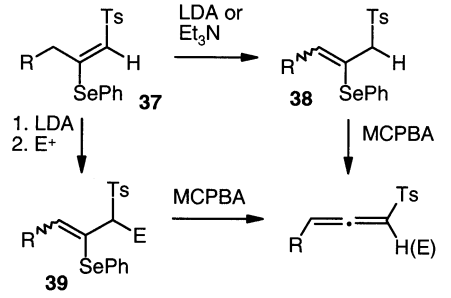
Scheme 22.

synthesis of corticosteroids, the two diastereomeric sulfoxides afforded the same allenic sulfone, indicating that the allene configuration was the same in both sulfoxide isomers.

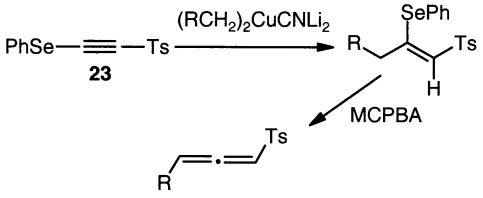
When two equivalents of propargylic alcohol **35**,[114,115] or other propargylic alcohols,[107,114] were treated with sulfur dichloride[107,114] or *N*,*N*'-thiobis(phthalimide),[115] a double rearrangement occurred to afford bis(allenic) sulfones such as **36** (Scheme 20).

3.3. From oxidation of allenic sulfides

The oxidation of several allenic sulfides with MCPBA was used to prepare the corresponding sulfones.[116–119] The allenic sulfides were obtained by the isomerization of their corresponding acetylenic sulfides,[116,119] or from the reactions of propargylic benzoates,[118] mesylates[117] or triflates[117] with $PhSCu{\cdot}PR_3$ (Scheme 21). A stereochemical study[117] of the latter process indicated that the triflates of chiral substrates undergo inversion of configuration, whereas the corresponding mesylates afford racemic products.

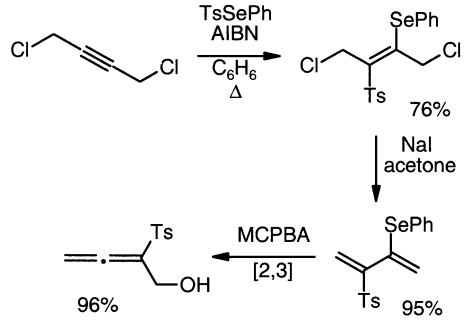


Scheme 23.

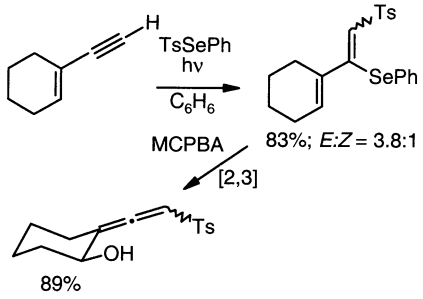


Scheme 24.

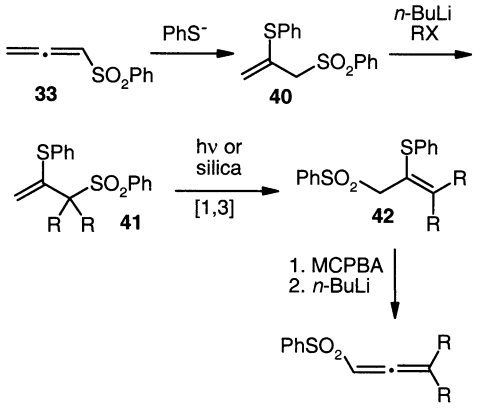
acetylenes, undergo base-catalyzed isomerization to their thermodynamically more stable allylic isomers **38**. Selenoxide elimination of the latter then proceeds toward the more acidic protons α to the sulfone group, as shown in Scheme 23,[50,121] to produce the corresponding allene. Chiral allenic sulfones have been prepared with modest enantioselectivity by employing chiral reagents (Sharpless oxidation, Davis oxaziridines) in the oxidation of **38** in Scheme 23.[122,123] Furthermore, the sulfone-stabilized allylic anion intermediates in the isomerization can be intercepted by suitable electrophiles prior to selenoxide elimination. Thus, the opportunity exists to incorporate deuterium, or alkyl, allyl or silyl substituents into the α-position of the allene via **39** (Scheme 23).[50,121] Third, the addition of higher order cuprates to acetylene **23** affords the corresponding *Z*-adducts stereoselectively[91] (Scheme 24; also see section 4.4 for related additions). These compounds are the geometric isomers of the selenosulfonation products in



Scheme 25.



Scheme 26.

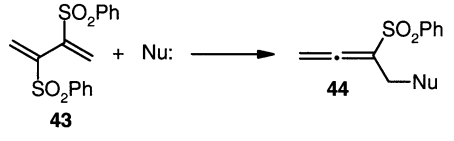


Scheme 27.

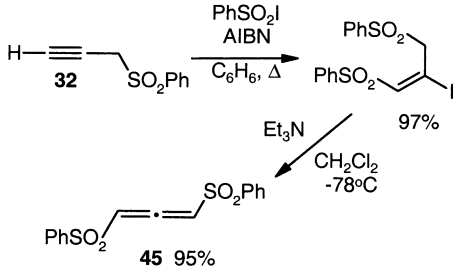
Scheme 4 and, in this case, the *trans* disposition of the phenylseleno group and the vinylic hydrogen atom precludes selenoxide *syn*-elimination to give the acetylene, resulting instead in the corresponding allenic sulfone. Consequently, the selenosulfonation procedure shown in Scheme 4 is complementary to those in Schemes 23 and 24, with respect to the type of sulfone product obtained. Fourth, selenosulfonation can be employed in conjunction with [2,3]sigmatropic rearrangements of the corresponding selenoxides, to afford hydroxyl-substituted allenic sulfones as in the examples in Schemes 25[124] and 26.[124b]

3.5. From other types of unsaturated sulfones

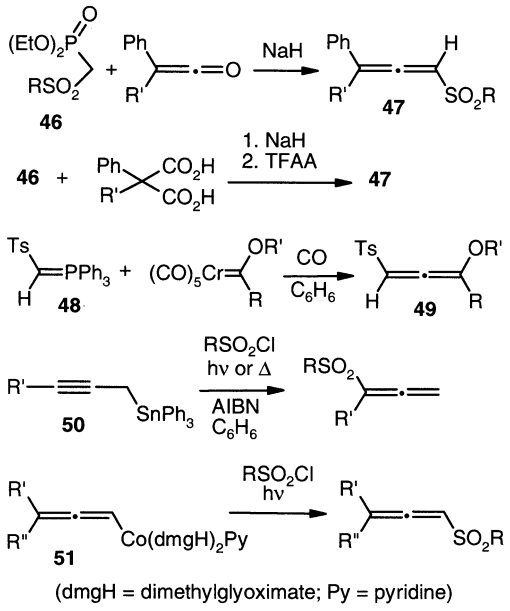
Apart from the prototropic isomerizations described in section 3.1, several other processes serve to produce allenic sulfones from other types of unsaturated sulfones. Padwa and coworkers reported that the addition of benzenethiolate to allene **33** (see section 4.3 for other conjugate additions of thiols to allenic sulfones) provided the vinyl sulfide **40** (Scheme 27). Deprotonation α to the sulfone group, followed by mono- or dialkylation, produced **41**, which underwent a facile [1,3] shift of the sulfonyl group. The corresponding γ-substituted allenic sulfones[125] were



Scheme 28.



Scheme 29.



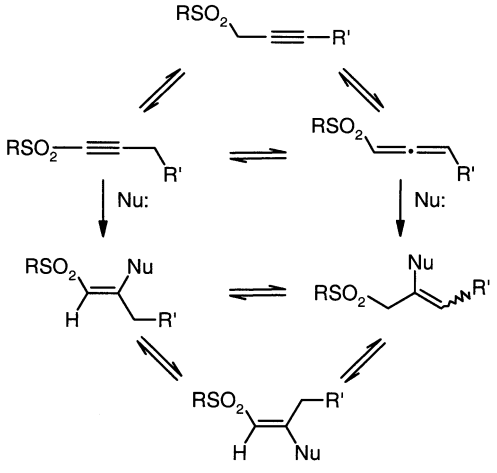
Scheme 30.

obtained after oxidation and elimination of **42**, while other transformations of **42** led to various dienyl sulfones and other products.[125,126] The dienyl sulfone **43**[127] reacted with nucleophiles by allylic substitution to afford allenic sulfones **44** (Scheme 28). The nucleophiles included enolates of ketones,[128] β-diketones[128b] β-keto esters[128b] and β-diesters,[128,129] anions derived from dinitriles[128b] and sulfones,[128a,128b,129a,129c,129e] as well as pyrrolyl,[130] indolyl[130,131] and other Grignard reagents.[130] Numerous further transformations of the products were also reported, some of which are described in later sections.

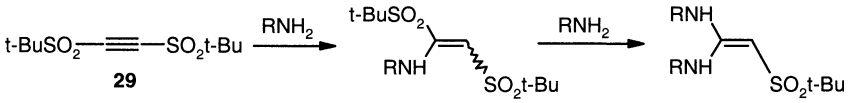
The bis(sulfonyl)allene **45** was obtained by free radical addition of benzenesulfonyl iodide to the propargylic sulfone **32**, followed by dehydroiodination (Scheme 29).[132]

3.6. Other methods

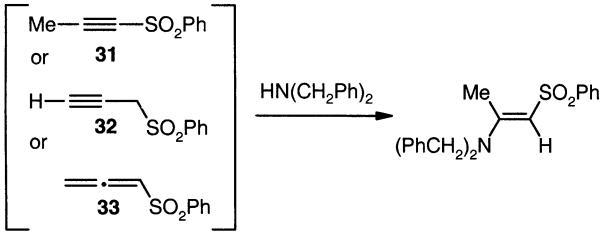
Several less frequently utilized procedures are summarized in Scheme 30. The reaction of ketenes with sulfonyl



Scheme 31.



Scheme 32.



Scheme 33.

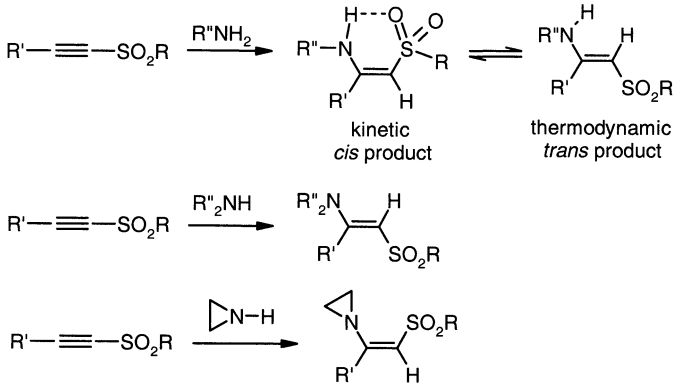
phosphonates **46** was employed in the preparation of allenic sulfones **47**.[133] β-Dicarboxylic acids reacted similarly with **46** in the presence of trifluoroacetic anhydride, and both processes were enhanced by sonication.[133c] Photolysis of chromium alkoxycarbene complexes in the presence of **48** and carbon monoxide produced the highly reactive alkoxyallenic sulfones **49**, which were typically used directly in further transformations.[134] Propargyl stannanes **50** reacted with sulfonyl chlorides in a free radical process that afforded the corresponding allenic sulfones in modest yields.[135] Allenic Co(III) complexes **51** were subjected to photochemical sulfonylations, producing mixtures of allenic and propargylic sulfones, whose ratio depends on the nature of the substituents and the type of light source.[136]

4. Conjugate additions

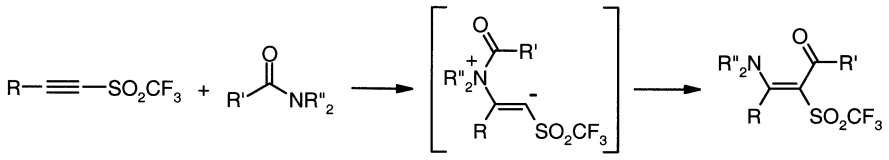
Conjugate additions of nucleophiles to acetylenic and allenic sulfones are possible because of the activating effect of the electron-withdrawing sulfone group upon the adjacent π-system, and its ability to stabilize the resulting anion. However, such processes are often complex because of the base-catalyzed prototropic equilibrations of acetylenic, allenic and propargylic sulfone isomers, noted in section 3.1, prior to attack of the nucleophile. Thus, even propargylic sulfones, which contain unactivated triple bonds, react with nucleophiles by first forming their more reactive allenic isomers in situ. Furthermore, conjugate addition products to acetylenic sulfones are typically formed by *anti* addition to afford *cis* products (i.e. *cis* with respect to the nucleophile and sulfone group) under kinetic conditions, but often isomerize to their more stable *trans* isomers. These general transformations are summarized in Scheme 31, while reactions with specific types of nucleophiles are described in sections 4.1 to 4.6.

4.1. Nitrogen nucleophiles

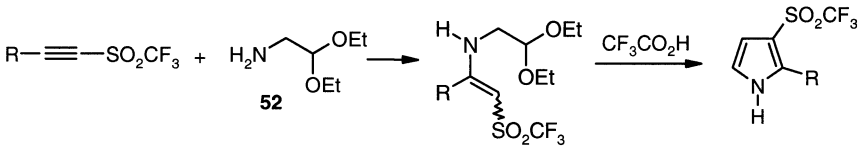
The addition of primary and secondary amines, including anilines, to the doubly activated acetylenic sulfone **29** was noted in 1954 by Strating and Backer.[137] A second addition of the amine, with elimination of sulfinate anion (i.e. overall substitution), was also observed (Scheme 32). Extensive studies of amine additions to unsaturated sulfones were reported by Stirling[12,138] and Truce[16] and their coworkers, as well as by other groups.[13,19b,139] Because of the base-catalyzed prototropic equilibrations of acetylenic, propargylic and allenic sulfones, these species are, in principle, rendered synthetically equivalent and the reactions of an amine with each type of sulfone can produce the same enamine product[12,16a,16b,19b,138b,138d,139] (e.g. Scheme 33).[138b] Investigations of the stereochemistry of addition to acetylenic sulfones[16,138b,138d] have revealed that primary amines typically afford *cis* adducts by *anti* addition under kinetic conditions, followed by partial isomerization to afford *cis*/*trans* mixtures (Scheme 34). The ratio of geometric isomers in the final product depends on the solvent, temperature and the nature of substituents in the starting materials. It has been suggested that intramolecular hydrogen bonding of the NH proton with a sulfone oxygen atom stabilizes the *cis* adduct.[16a,138b,138d] On the other hand, secondary amines, where such hydrogen bonding is precluded, produce chiefly the *trans* adducts because of dipole and steric repulsions between the amine and sulfone substituents (Scheme 34).[16a,138d] The additions of aziridine are anomalous, in that it sometimes forms the kinetic *cis*-adduct preferentially or exclusively as a result of inhibited isomerization (Scheme 34).[16]



Scheme 34.

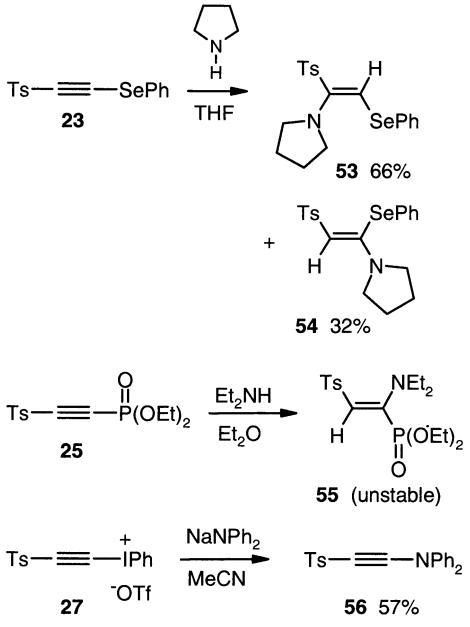


Scheme 35.

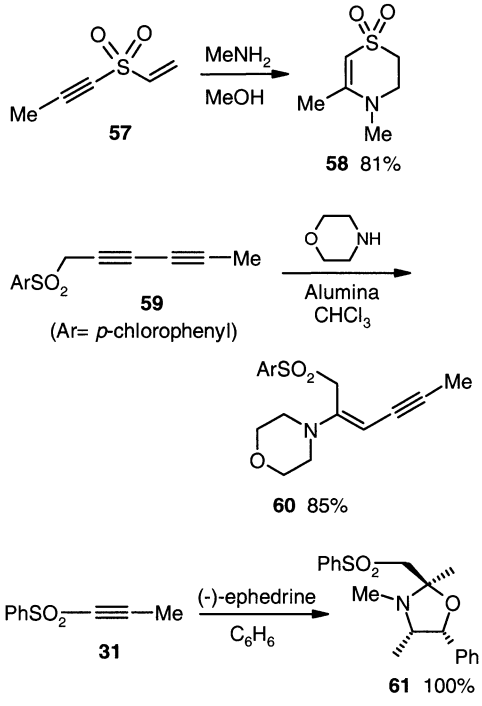


Scheme 36.

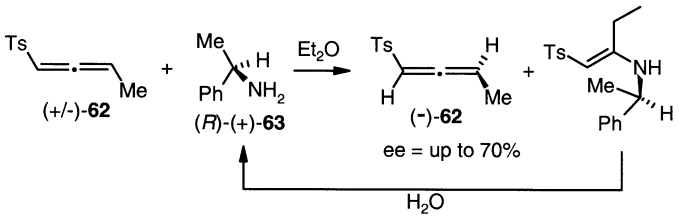
Conjugate additions of amines to acetylenic sulfones have been reported with many variations in the structures of both reactants. Even hindered amines such as 2,2,6,6-tetramethylpiperidine add to terminal acetylenic sulfones, but not to β-substituted ones.[140] Mono-*N*-substituted hydroxylamines usually attack acetylenic sulfones via the nitrogen atom to produce nitrones,[141,142] but attack through oxygen is sometimes observed when a bulky nitrogen substituent is present and an internal acetylene is used.[141] The reactions of *N*-alkyl- or *N*-phenylhydroxylamines with allenic sulfones produce nitrones that can then be employed in intramolecular 1,3-dipolar cycloadditions.[129d,143] These processes are discussed further in section 5.2 and the reactions of *N*,*N*-disubstituted hydroxylamines, which react through oxygen, are described in section 4.2. The highly electrophilic acetylenic triflones form enamine adducts with simple amines,[61b,144] as well as with phthalimide,[144] whereas amides produce dipolar intermediates that undergo transacylation[145] (Scheme 35). The amino acetal **52** afforded pyrroles by further intramolecular condensation of the initial enamine products (Scheme 36).[63] The selenoacetylene **23** displayed anomalous regiochemistry in its reaction with pyrrolidine, affording the '*anti*-Michael' (with respect to the sulfone group) adduct **53** as the principal product.[91] Thus, surprisingly, it appears that the effect of the phenylseleno group outweighs that of the sulfone moiety in regulating the position of attack. On the other hand, the alkynylphosphonate **25** reacted with diethylamine in the 'normal' fashion, β to the sulfone moiety,[93] while the alkynyliodonium salt **27** underwent overall substitution with diphenylamide to furnish the push-pull ynamine **56**.[146] These reactions are shown in Scheme 37. Double conjugate additions of amines to bifunctional acetylenic sulfones such as **57** have been reported[34] and allenic sulfones generated from diynes **59** were trapped with morpholine to give adducts **60**.[147] Enamines derived similarly from bis(propargylic) sulfones and morpholine, or other secondary amines, cyclized to afford thiopyran dioxides.[148] Chiral cyclic aminals **61** were obtained by double Michael additions of (−)-ephedrine to acetylenic sulfone **31**, or to the corresponding allenic or propargylic derivatives.[149]



Scheme 37.



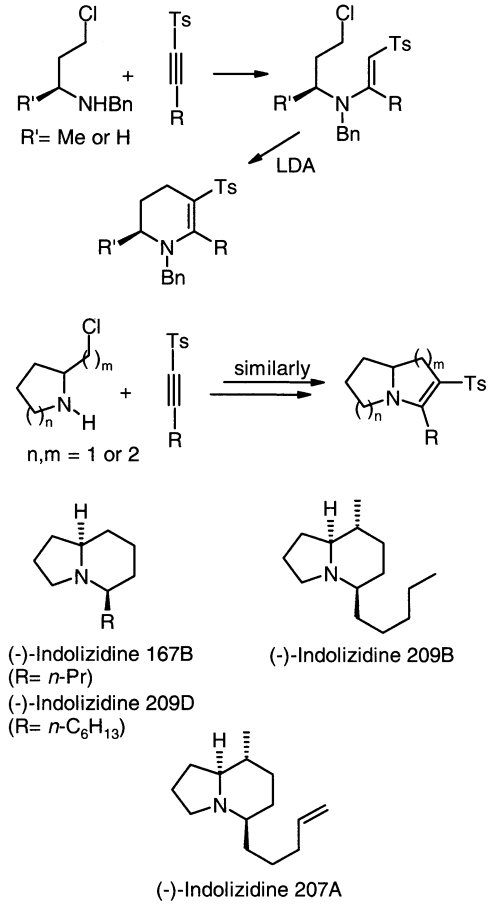
Scheme 38.



Scheme 39.

Examples are shown in Scheme 38. An interesting method for the kinetic resolution of racemic allenic sulfones is based on the preferential addition of the chiral amine **63** to one allene enantiomer of **62**. The procedure can be employed catalytically in aqueous media, since the byproduct enamine then hydrolyzes to regenerate the chiral amine (Scheme 39).[150]

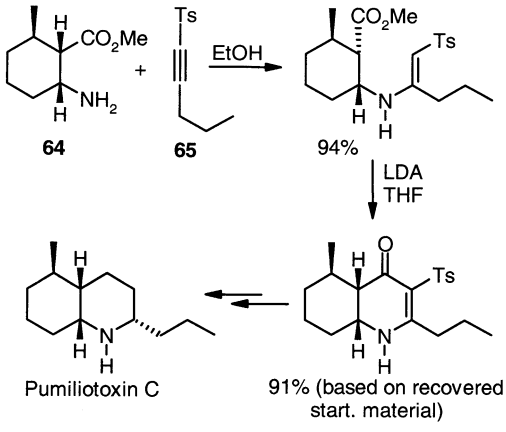
Conjugate additions of amines to acetylenic and allenic sulfones have also been used in conjunction with further transformations to afford more complex target compounds. Thus, a variety of piperidines, pyrrolizidines, indolizidines and quinolizidines were prepared by the conjugate additions of appropriate β- or γ-chloroamines to acetylenic sulfones, followed by intramolecular alkylation (Scheme 40).[53] The type of ring system produced is thus controlled by the ring size and chain length of the chloroalkyl substituent of the chloroamine. The products obtained included the dendrobatid alkaloids (−)-indolizidines 167B, 209D, 209B and 207A, after stereoselective reduction and desulfonylation. Since the chloroamines can be derived from (L)-amino acids, the products were obtained enantioselectively. Similarly, conjugate addition of amino ester **64** to acetylene **65**, followed by intramolecular acylation, comprised a key step in a recent enantioselective synthesis of pumiliotoxin C (Scheme 41).[52] In all of these processes, the acetylenic sulfone therefore functions as the synthetic equivalent of the corresponding alkene dipole, as shown in Scheme 1. Cyclizations based on similar conjugate additions to acetylene **19b** were used in conjunction with intramolecular Heck reactions[151] (Scheme 42) or enamine additions to thioaldehyde substituents[152] (Scheme 43), thus leading to nitrogen heterocycles **67** and **68**, respectively. The addition of thebaine (**69**) and related alkaloids to allenic sulfone **33** was followed by C–N cleavage and recombination at C-8, as in the example in Scheme 44, or at C-9.[153]



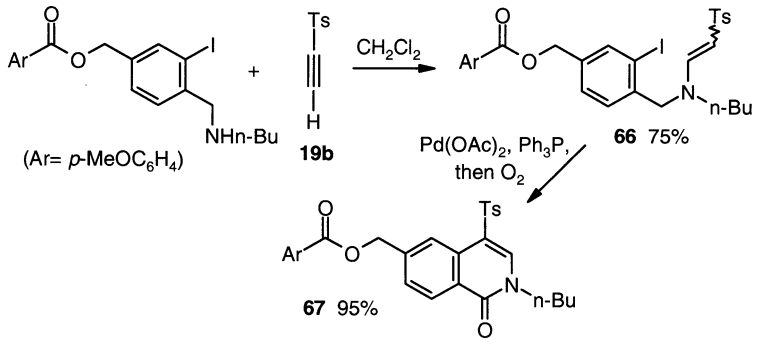
Scheme 40.

4.2. Alcohols, phenols and carboxylic acids

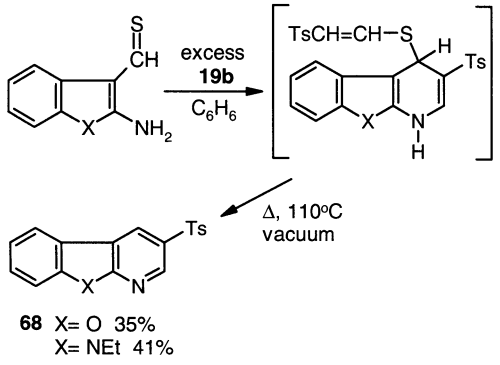
As in the case of amines, alkoxides can react with isomeric acetylenic, allenic or propargylic sulfones to afford identical conjugate addition products because of facile base-catalyzed equilibrations of the starting sulfones. Thus, Stirling[138b] reported that all three isomers in Scheme 45 (where Ar=Ph) reacted with sodium methoxide to afford **70**, the direct addition product to the corresponding allene under kinetic conditions, followed by isomerization to the *trans* product **71**. In contrast, the terminal acetylene **19b** produced the *cis*-isomer **74** by direct *anti* addition.[154] More forcing conditions resulted in double additions to acetylenic sulfones, affording the corresponding ketals **72**.[13,20,138b] Double additions of chiral alcohols, diols and thiols have been used to prepare the corresponding acetals and



Scheme 41.

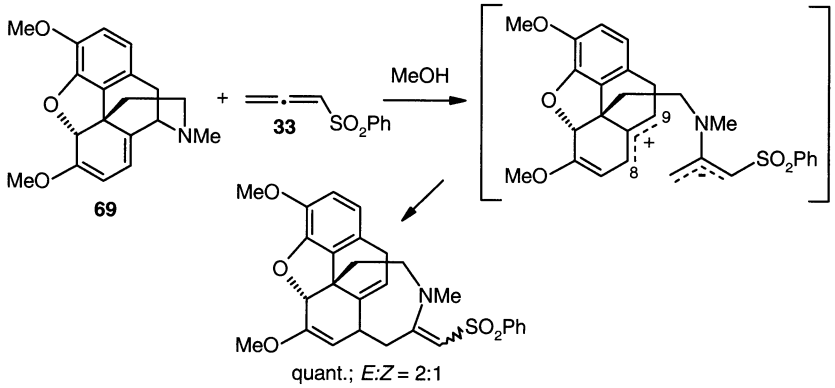


Scheme 42.

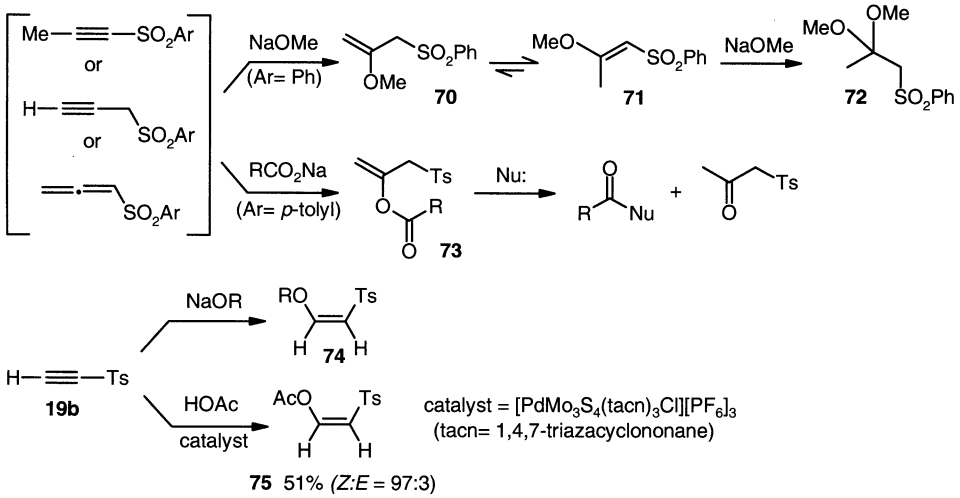


Scheme 43.

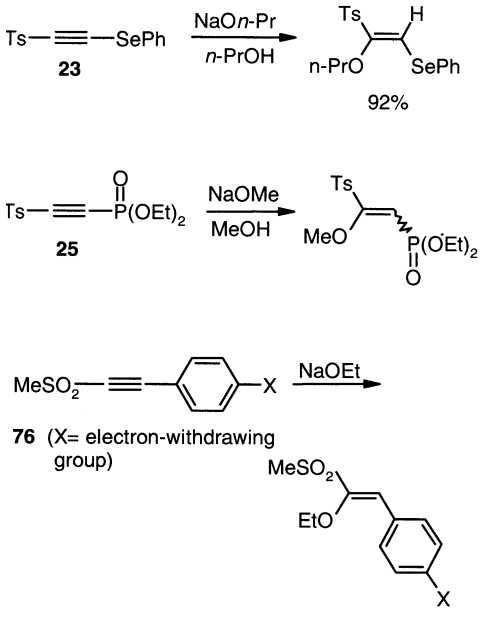
thioacetals.[155] Carboxylates add similarly, forming enol esters **73**, that function as activated acylating agents toward nucleophiles such as amines.[156] The addition of acetic acid to the terminal acetylene **19b** was reported to give the adduct **75**, obtained predominantly as the *cis*-isomer, in the presence of a $PdMo_3S_4$ cubane cluster catalyst.[157] These processes are summarized in Scheme 45. The more highly activated acetylenic bissulfones **29** and **30** react with alcohols even in the absence of base catalysts to afford mixtures of geometric isomers.[21,25] Phenols, however, require prior conversion into their phenoxides.[21] Acetylenic triflones **6** react similarly with methanol,[144] ethanol[61b] or carboxylates.[144] Surprisingly, the β-phenylseleno,[91]



Scheme 44.



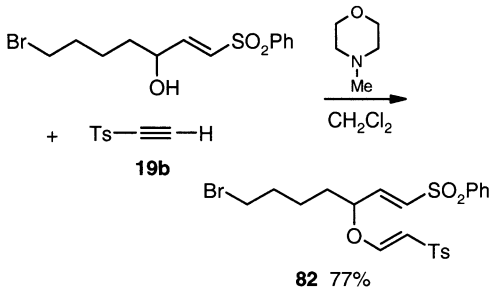
Scheme 45.



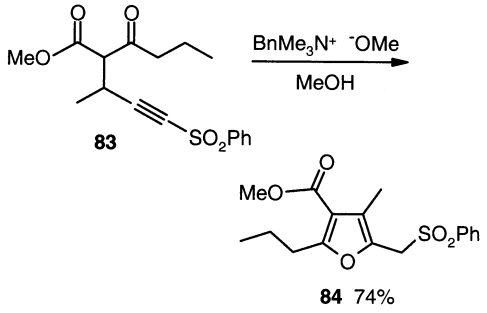
Scheme 46.

β-phosphinyl[93] and β-aryl[158] acetylenic sulfones **23**, **25** and **76**, respectively, all reacted with alkoxides predominantly or exclusively in the *anti*-Michael sense, with respect to the sulfone group (Scheme 46; cf. Scheme 37 for related reactions with amines). In the case of **76**, further reactions with the alkoxide, including substitution of the sulfone moiety, were also observed.[158]

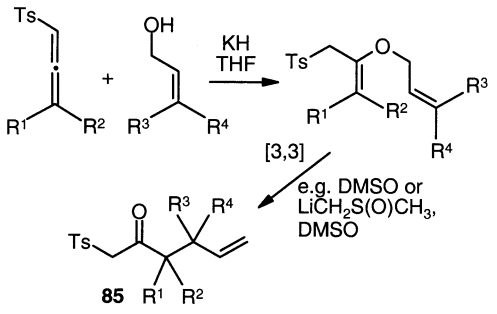
More complex transformations initiated by the conjugate additions of alkoxides or phenoxides to acetylenic sulfones or their isomers have also been reported. Thus, the adduct of phenoxide anion and allenic sulfone **33** can be mono- or dialkylated and subjected to a 1,3-sulfone shift, as in the case of the thiolate adduct **40** in Scheme 27.[125a,159] The conjugate additions of the chiral epoxy alcohol **77** to acetylenic sulfones **78** provided an enantioselective route to the corresponding dihydrofurans **81** via **79** in Scheme 47.[160] The concomitant formation of substantial amounts of the corresponding *anti*-Michael regioisomers **80** is again noteworthy. A similar approach to other furan and related pyran analogues from the hydroxyethyl homologue of **77** was also reported.[159] Adduct **82** was prepared via Scheme 48 and was used in radical cyclization studies,[161] while the intramolecular conjugate addition of the enolate of **83** (Scheme 49) afforded **84**, a key intermediate for the synthesis of calicogorgins.[162] Denmark and coworkers[163] prepared allyl vinyl ethers via the conjugate addition of allylic alcohols to allenic sulfones and reported extensive studies of their anionic and thermal Claisen rearrangements



Scheme 48.

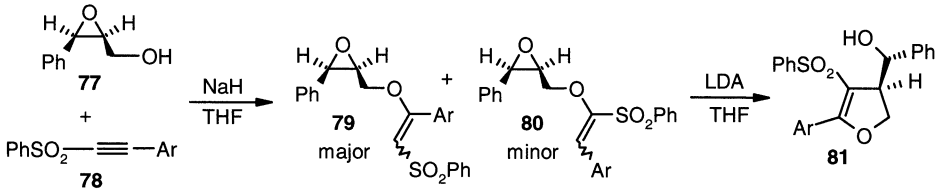


Scheme 49.

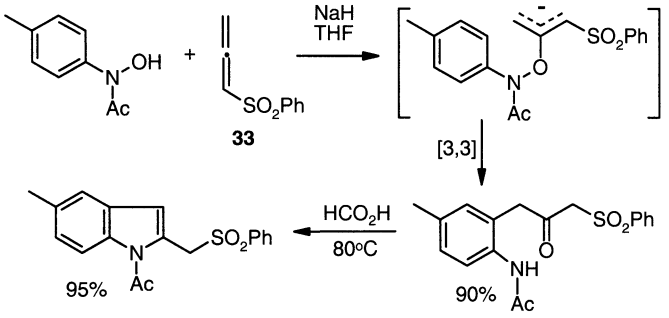


Scheme 50.

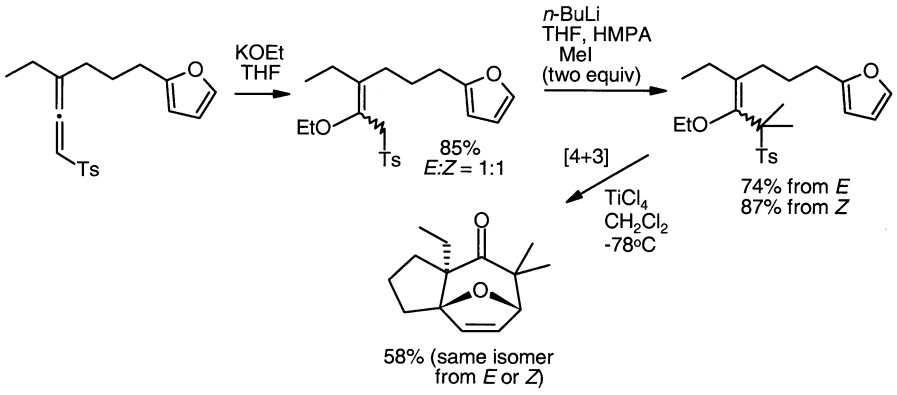
(Scheme 50). These processes are of special value in the stereoselective generation of products **85** with vicinal quaternary centers. In contrast to the nitrone-forming reactions of monosubstituted hydroxylamines (see sections 4.1 and 5.2), *N*,*N*-disubstituted hydroxylamines attack allenic sulfones via their hydroxyl groups. The resulting adducts undergo hetero-Claisen rearrangements, leading to indole[164] and hydrindanone[165] products (e.g. Scheme 51). The conjugate additions of alkoxides to a series of furan-substituted allenic sulfones were used to set up Lewis acid-catalyzed intramolecular [4+3] cycloadditions between the resulting enol ether and furan moieties (e.g. Scheme 52).[166]



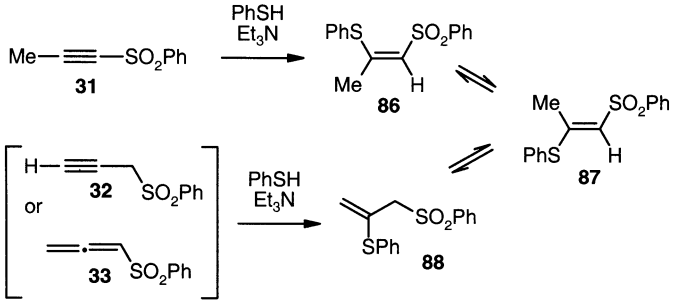
Scheme 47.



Scheme 51.



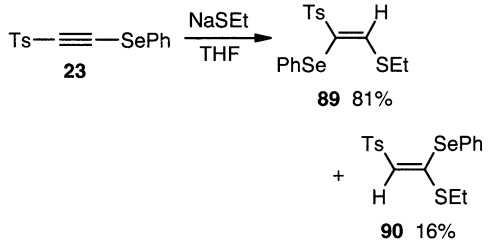
Scheme 52.



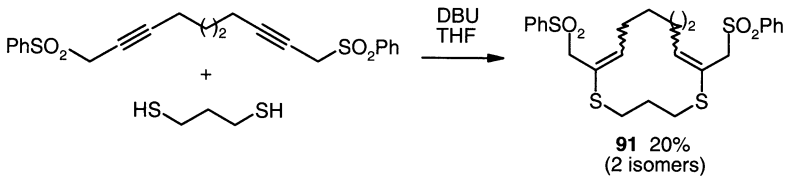
Scheme 53.

4.3. Thiols, sulfinates and related nucleophiles

As in the case of nitrogen and oxygen nucleophiles, the scenario with sulfur nucleophiles is again complicated by equilibration of the starting materials and products. Several reports demonstrated that additions of thiols to acetylenic sulfones in the presence of catalytic amounts of amines afford *cis* products **86** by *anti* addition under kinetic conditions, followed by isomerization to give predominantly or exclusively the corresponding *trans* adducts **87** (Scheme 53).[13,22a,28,167] Because of the lower basicity and higher nucleophilicity of thiolates compared to amines or alkoxides, products **86** and **88** can be isolated from the initial addition reaction, while isomerization to **87** takes place when a stronger base such as sodium methoxide is present.[28] Further oxidation of the products to the corresponding β-sulfonylvinyl sulfones can be achieved with hydrogen peroxide in acetic acid[28,168] or with perphthalic acid.[169] As expected, acetylenic bis(sulfones) such as **29** and **30** are especially powerful Michael acceptors of thiols.[21,25] *anti*-Michael regiochemistry has been reported in the additions of thiolates to acetylenic sulfones containing β-aryl groups,[158,169] even unactivated ones such as phenyl. Again, the β-phenylseleno acetylene **23** behaved anomalously, affording chiefly the rearranged product **89** (Scheme 54).[91] Rearranged products were also observed when **23** was treated with selenolate anions.[91,95c] Sulfinate anions also react with acetylenic sulfones by *anti* addition and second additions to afford tris(sulfones) are possible.[28]



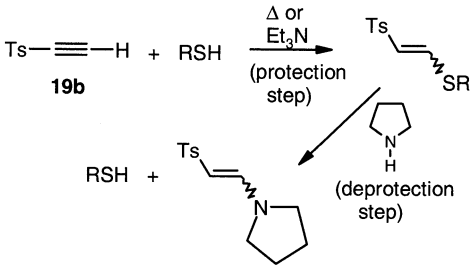
Scheme 54.



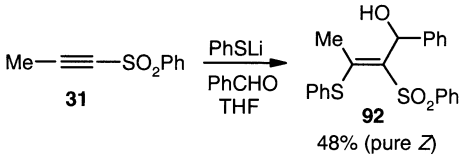
Scheme 55.

The stereo- and regiochemistry of thiolate and sulfinate additions to a series of more complex propargylic sulfones, including bis(sulfones) and conjugated diyne systems, was investigated by Thyagarajan et al.[147,170] As in the case of the amine addition in Scheme 38, these processes presumably proceed via the corresponding allenic sulfone isomers. Double additions of thioureas to afford 1,3-thiazolidine products were among the reactions observed.[170f,170g] Similar adducts of thiols and propargylic sulfones, including the double addition product **91** in Scheme 55,[171] were reported to possess DNA cross-linking activity (see also section 8).

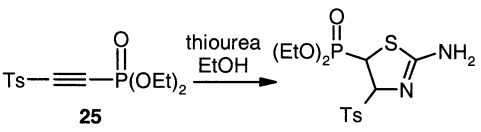
Further transformations of synthetic utility include the regeneration of the original thiol from its adduct with acetylenic sulfone **19b** by addition-elimination of pyrrolidine (Scheme 56). The acetylenic sulfone thus functions as a thiol protecting group.[172] The sulfone-stabilized allyl anion that was generated from deprotonation of the thiol addition product **40** in Scheme 27[125] has also been used as a nucleophile in Michael additions to enones,[173] as well as in other alkylations.[125b,173] Furthermore, the vinyl carbanion intermediate arising from the conjugate addition of benzenethiolate to acetylenic sulfone **31** was trapped in situ with benzaldehyde to afford carbinol **92** (Scheme 57).[174] The corresponding heterocyclic products were obtained when the phosphinyl acetylene **25** was treated with thioureas



Scheme 56.



Scheme 57.



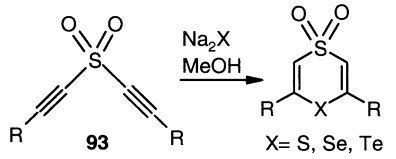
Scheme 58.

(Scheme 58),[93] or when sodium chalcogenides were added to bis(acetylenic) sulfones **93** (Scheme 59)[29] or to the vinyl acetylenic sulfone **57** in Scheme 38.[34] The conjugate addition in Scheme 60 was used to produce sulfide **94**, required for radical cyclization studies; however, ester substituents proved superior to sulfones in this endeavour.[175] Chiral 1,3-oxathianes **100** and **101** were prepared from stereospecific double conjugate additions of the camphor-derived hydroxy thiol **95** to acetylenic sulfones **19**, as shown in Scheme 61.[176] The sulfoxide **98** was also used in asymmetric cycloaddition reactions, where the camphorthio moiety acted as an effective chiral auxiliary group.[86,177]

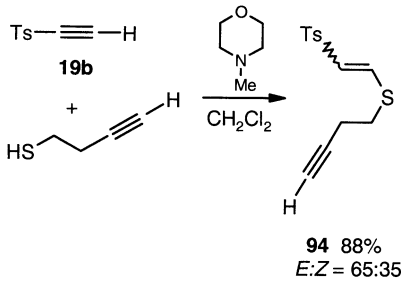
The tellurol PhTeH was produced in situ by reduction of diphenyl ditelluride with sodium borohydride and, like thiols, effected conjugate additions to acetylenic sulfones by *anti* addition.[178]

4.4. Carbon nucleophiles

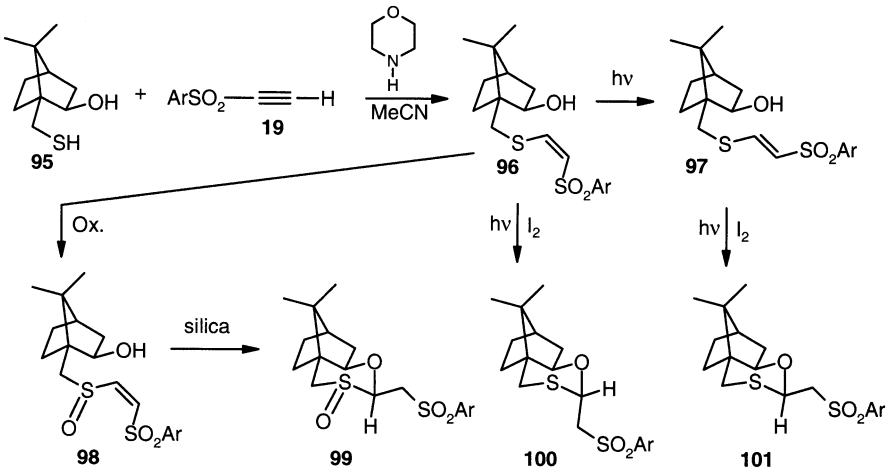
Certain organometallic reagents serve to introduce alkyl groups and other carbon substituents to the β-position of acetylenic sulfones. These additions are formally related to the conjugate additions described in earlier sections because of the overall type of transformation that is achieved, although their mechanisms tend to be more complex. Thus, as illustrated in Scheme 62, Grignard reagents with CuBr,[179] organocuprates (R_2CuLi),[180] Me_3SiCH_2Cu,[181] and diethylzinc[182] in the presence of $Cu(BF_4)_2$ all add to acetylenic sulfones predominantly by *syn* addition to afford **102**. Organocopper reagents RCu add similarly to acetylenic triflones.[183] Double additions to the terminal acetylenic sulfone **19a** were accomplished by



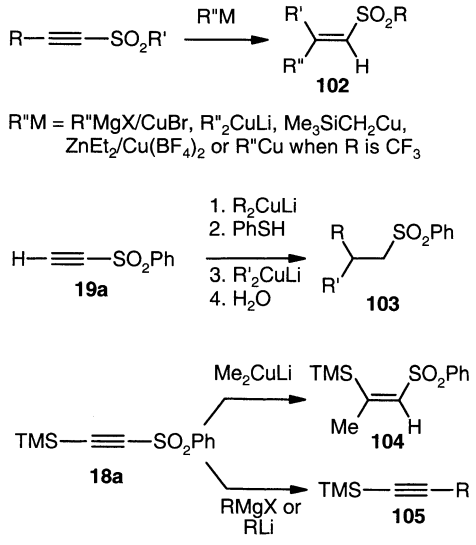
Scheme 59.



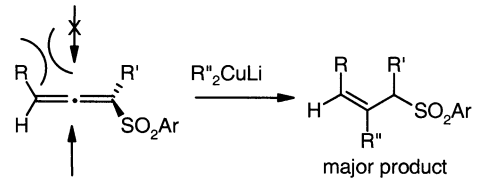
Scheme 60.



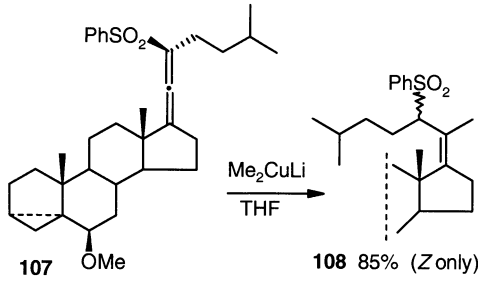
Scheme 61.



Scheme 62.



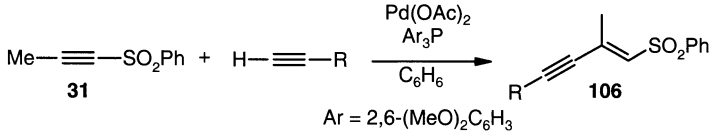
Scheme 64.



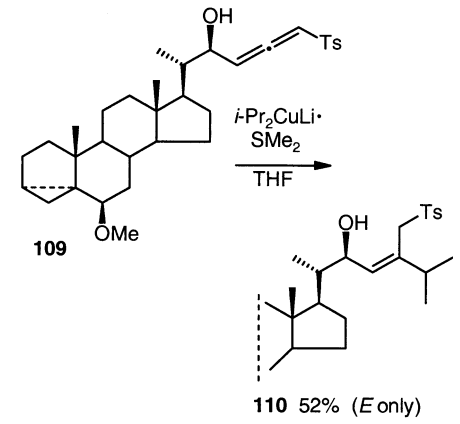
Scheme 65.

sequential addition of two cuprate reagents to produce **103**.[180] In one case, the intermediate vinyl copper species generated from the addition of Me_3SiCH_2Cu to an acetylenic sulfone was trapped in situ by quenching with allyl bromide.[181] Alternatively, the addition of RCu to acetylenic sulfoxides, followed by oxidation with MCPBA, produced the same products as obtained from similar additions directly to the corresponding sulfones.[184] The silylacetylene **18a** underwent a normal addition with Me_2CuLi to give **104**, but afforded **105**, the products of overall substitution of the sulfone moiety, with Grignard or organolithium reagents[88] (see section 6.4 for other substitution reactions). The selenoacetylene **23**, which it will be recalled reacts with heteroatom nucleophiles in a predominantly *anti*-Michael sense (see sections 4.1 and 4.2), formed adducts with normal regiochemistry with higher order and other types of cuprates (see Scheme 24).[91] The formal addition of terminal acetylenes to **31** by means of a stereoselective palladium-catalyzed coupling reaction provides entry to enynes **106** (Scheme 63).[185]

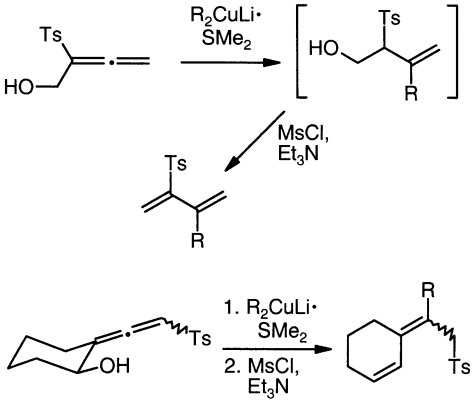
A variety of organocopper species add to allenic sulfones, including R_2CuLi, $RR'CuLi$ and R_2CuMgX,[51,186–188] as well as RCuXLi (X=I, CN, acetylide),[186b] a higher order thienyl cuprate $[i\text{-Pr(2-Th)CuCNLi}_2]$[189] and $(Me_3SiCH_2)_2CuLi$.[190] In general, attack takes place upon the activated allenic double bond from the side of the least sterically demanding γ-substituent (Scheme 64). In several cases,



Scheme 63.



Scheme 66.

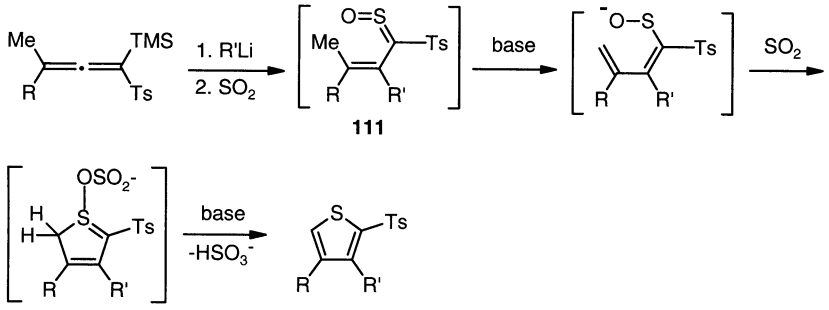


Scheme 67.

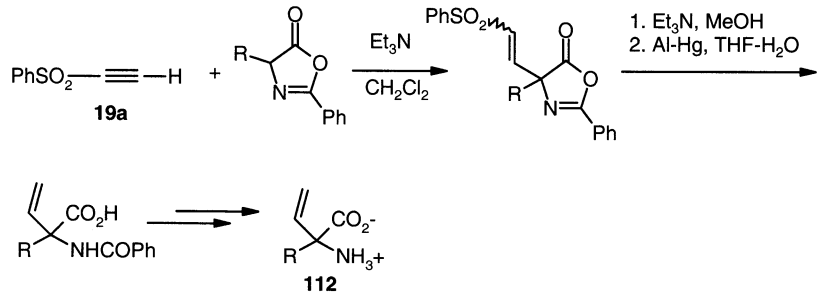
the intermediate vinyl copper species were quenched with electrophiles such as alkyl or allyl halides, or by Michael addition to enones, resulting in further substitution at the α-position.[186b] Several applications to the synthesis of steroid side chains have appeared, including preparations of vitamin D analogues (e.g. **108** in Scheme 65)[188] and intermediates of the plant growth-regulators castasterone and brassinolide (e.g. **110** in Scheme 66).[51,189] The additions of cuprates to allenic sulfones containing α-hydroxymethyl[124] or δ-hydroxy substituents,[124b] prepared via Schemes 25 and 26, respectively, provide access to various dienyl sulfones after the further transformations shown in Scheme 67. An unusual formation of substituted thiophenes was reported from the addition of organolithiums to α-silyl allenic sulfones, followed by treatment with sulfur dioxide. The reaction is believed to proceed via a Peterson elimination, leading to the sulfine intermediate **111**, and further reaction via Scheme 68.[191]

Various types of enolates have been added to terminal[88,192] or β-silyl[193,194] acetylenic sulfones. In the case of the latter compounds, it was suggested that desilylation to the corresponding terminal acetylene precedes conjugate addition under typical reaction conditions.[88] Applications include the synthesis of vinyl amino acids **112** (Scheme 69),[192] a related approach to deuterated vinylglycine,[194] and preparation of the key intermediate **113** for the synthesis of phoracantholide I (Scheme 70).[193b] Silyloxycyclopropanes function as homoenolate equivalents in the presence of $Cu(BF_4)_2$ (Scheme 71) and, like cuprates, undergo *syn* addition to acetylenic sulfones.[182]

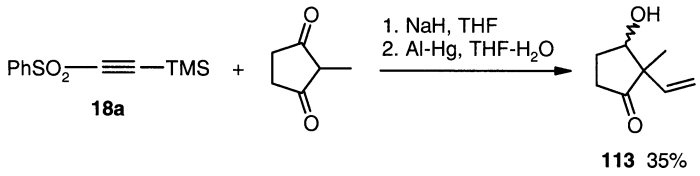
Enolate chemistry has played a role in several syntheses of substituted cyclopentenes, reported by Padwa et al.[128a,195] In one variation,[195b] conjugate addition of a sulfinate anion



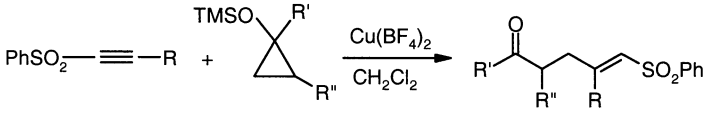
Scheme 68.



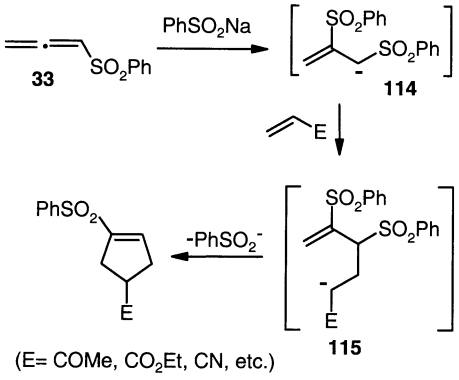
Scheme 69.



Scheme 70.

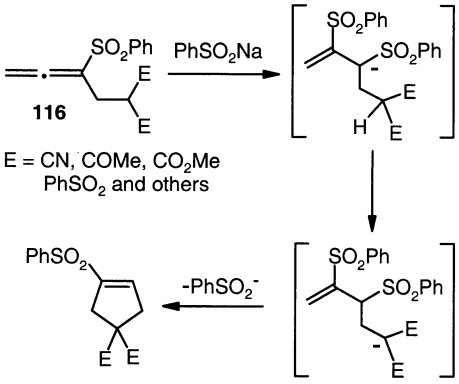


Scheme 71.



Scheme 72.

initiator (or cyanide, nitrite, etc.) to allenic sulfone **33** produced the anion **114** that was used to attack another Michael acceptor in situ. The resulting new enolate **115** cyclized via the pathway in Scheme 72, resulting in an overall [3+2] cycloaddition. In a second variation,[128a] allenic sulfones **116** were first obtained by the addition of active methylene compounds to dienyl sulfone **43** (see Scheme 28). Cyclization of **116** was again induced by the conjugate addition of sulfinate anion, as shown in Scheme 73. Numerous variations of this chemistry were also possible. Allenic sulfone **33** reacted with enamines by conjugate additon, producing chiefly δ-keto sulfones after aqueous workup (Scheme 74).[196]



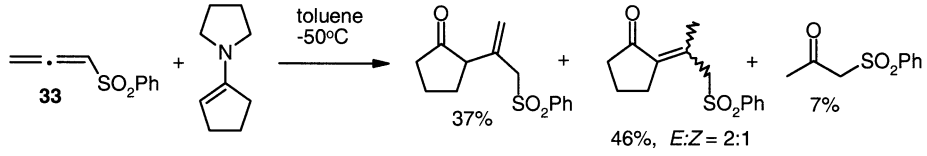
Scheme 73.

4.5. Halides

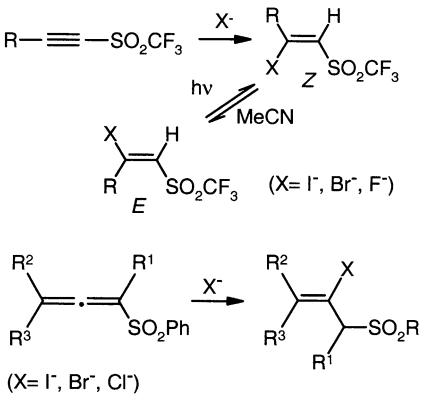
Acetylenic triflones react with LiBr in trifluoroacetic acid, LiI in acetic or with HF in pyridine to give the corresponding β-halovinyl sulfones, predominantly with the *Z*-configuration (Scheme 75).[64c,144] Photochemical isomerizations of the adducts to the *E*-form and Stille couplings of the iodo derivatives were also reported. The conjugate additions of chloride, bromide and iodide ions to variously substituted allenic sulfones in acetic acid proceed according to Scheme 75.[197] The sulfone-activated double bond reacts selectively and α- or γ-methyl substituents suppress the reaction.

4.6. Synthetic equivalents of acetylenic sulfones in conjugate additions

Vinyl sulfones **117** containing leaving groups in the β-position react with nucleophiles by overall substitution, affording similar products to those obtained from conjugate additions to acetylenic sulfones. Two possible pathways for substitution are shown in Scheme 76. In path A, base-catalyzed elimination of the leaving group generates the acetylenic sulfone in situ, followed by the usual addition of the nucleophile. In path B, conjugate addition of the nucleophile to the vinyl sulfone precedes elimination of the leaving group. Early studies by Modena and coworkers,[154,198] of β-halovinyl sulfones, and later work by others on other types of β-functionalized vinyl sulfones,[199,200] showed that the mechanism is dependent on the specific starting materials and conditions. Moreover, substitutions by organometallic reagents such as cuprates probably proceed by other mechanisms to those in Scheme



Scheme 74.



Scheme 75.

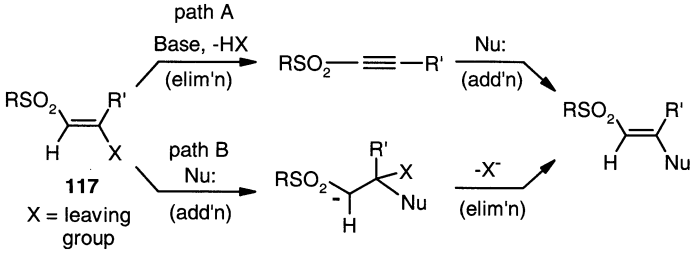
76. Regardless of the mechanism, however, appropriately β-substituted vinyl sulfones can be utilized as the synthetic equivalents of acetylenic sulfones, or as their in situ progenitors.

Thus, β-iodovinyl[184] and β-(phenylseleno)vinyl[91b,201] sulfones (**117**, X=I, SePh, respectively) react with various organocopper species with retention of configuration, while β-enol pivalates (**117**, X=OCO*t*-Bu)[202] give variable stereochemistry, depending on the type of copper reagent and conditions. An application of the selenide substitution process to the synthesis of the marine sterols 24,28-dehydroaplysterol, xestosterol and ostreasterol was reported, and an example is shown in Scheme 77.[203]

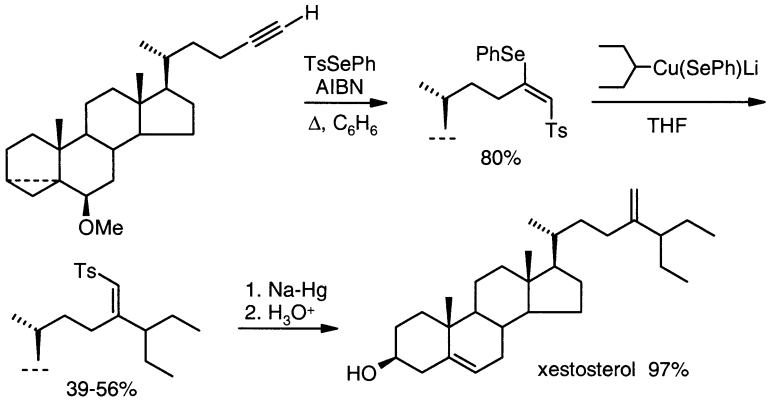
The selenides **117**, X=SePh, are too unreactive to undergo substitution with most other types of nucleophiles. However, prior oxidation to the corresponding selenoxides serves to activate them and the latter derivatives were reported to react readily with amines,[204] alkoxides,[46b] active methylene compounds,[48] 2-lithio-1,3-dithiane,[48] KCN[48]and other carbon nucleophiles.[48] In at least some cases, the selenoxide simply underwent *syn*-elimination in situ to generate the corresponding acetylene or allene, which then reacted with the nucleophile. A similar series of substitutions was also reported with the corresponding β-iodovinyl sulfone analogues.[41] Intramolecular substitutions of β-iodovinyl sulfones provided access to oxazoles,[205] thiazoles,[205] pyrroles,[43] furans[43] and cyclopentenes[43] (e.g. Scheme 78[205]). β-Chlorovinyl and β-sulfonylvinyl sulfones reacted with diols and dithiols in a similar fashion to the corresponding acetylenic sulfones to afford acetals and thioacetals by double additions of the nucleophiles.[155] In a different type of process, α-bromovinyl sulfones reacted with amines to afford enamine sulfones or α-sulfonylaziridines.[206]

5. Cycloadditions

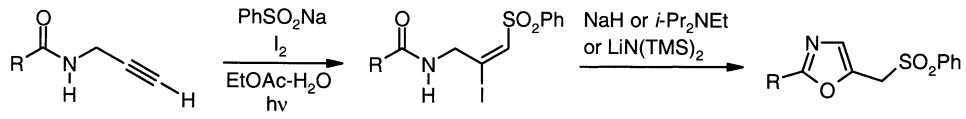
In 1968 Veniard, Benaïm and Pourcelot,[207] reported that



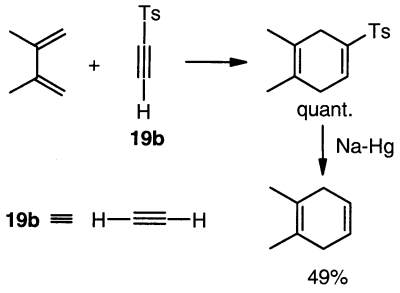
Scheme 76.



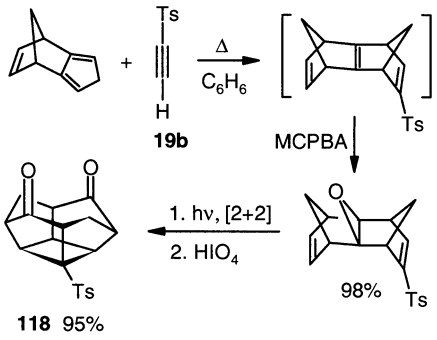
Scheme 77.



Scheme 78.



Scheme 79.

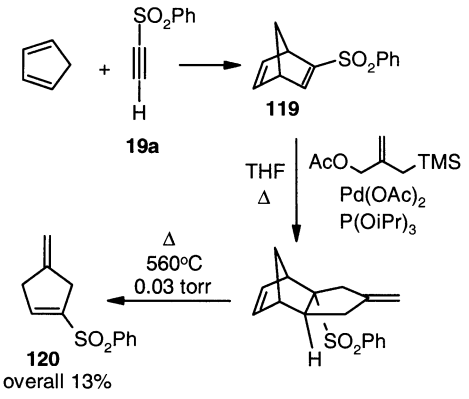


Scheme 81.

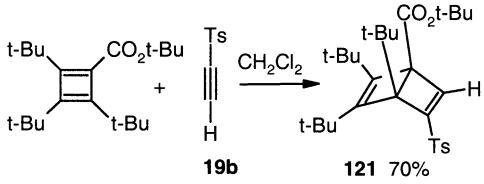
1-(phenylsulfonyl)propyne (**31**) and 1-(phenylsulfonyl)-1,2-propadiene (**33**) undergo Diels–Alder reactions with cyclopentadiene and its hexachloro derivative under relatively mild conditions. In general, acetylenes and allenes display low reactivity in Diels–Alder and related cycloadditions. However, the electron-withdrawing sulfone group increases their reactivity as dienophiles or dipolarophiles, and provides a means for controlling the regiochemistry of their cycloadditions.[208] This, as well as the numerous further transformations of the cycloadducts that are made possible by the sulfone moiety, has made acetylenic and allenic sulfones popular reagents for a variety of synthetically useful cycloadditions.

5.1. Diels–Alder reactions

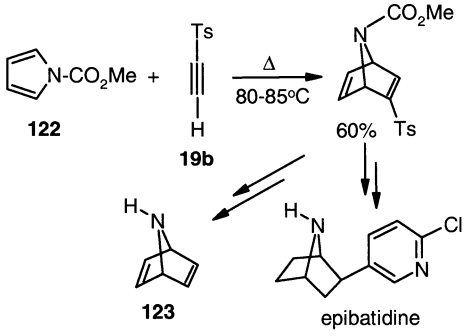
Terminal acetylenic sulfones generally react smoothly with dienes, and the Diels–Alder reactions of the phenyl and *p*-tolyl derivatives **19a** and **19b**, respectively, have been widely investigated. Davis and Whitham[209] reported that when the cycloaddition of **19b** is followed by reductive desulfonylation, the acetylenic sulfone functions as a reactive synthetic equivalent of acetylene (e.g. Scheme 79). The regiochemistry of the cycloaddition with an unsymmetrical diene is illustrated by the example in Scheme 80,[210] and is consistent with frontier MO considerations. In other applications, Paquette et al.[211] employed the reaction of **19b** with fused, polycyclic cyclopentadienes to provide the intermediate **118**, required for the synthesis of [4]peristylane, via Scheme 81, as well as related bridged polycyclic hydrocarbons. The cycloadduct **119**, obtained from **19a** and cyclopentadiene, was subjected to a palladium-catalyzed [3+2] cycloaddition, which failed with unactivated acetylenes, and a retro-Diels–Alder reaction in the synthesis of 4-methylene-1-cyclopentene **120** (Scheme 82).[212] Other activating groups, however, proved superior to the sulfone in this regard. Acetylenic sulfone **19a** reacted with either one or two moles of furan, since the initial 1:1 cycloadduct contains a vinyl sulfone moiety that is also a good dienophile.[213] The Dewar benzene **121** was obtained from the cycloaddition shown in Scheme 83.[214] In other applications, aromatization of the initial 1,4-cyclohexadiene products



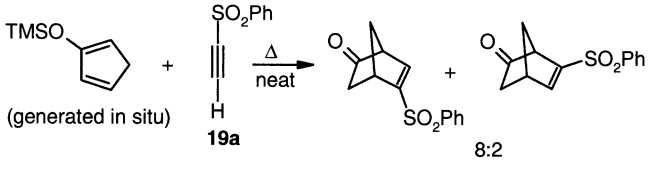
Scheme 82.



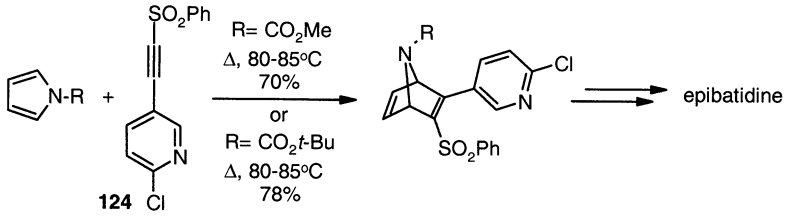
Scheme 83.



Scheme 84.



Scheme 80.

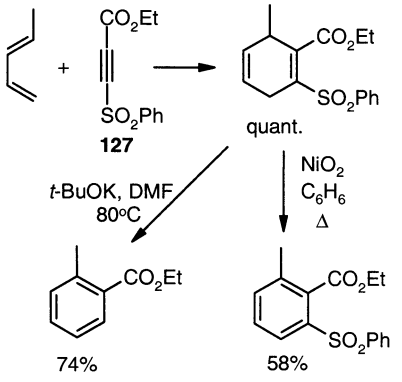


Scheme 85.

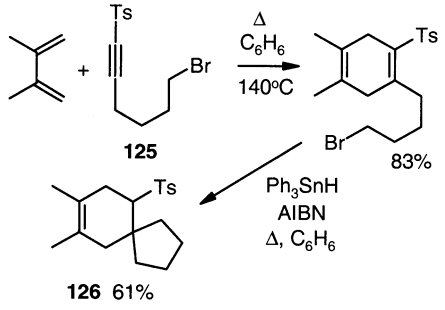
was achieved by oxidation with DDQ[215] or by extrusion of a bridging CO_2 unit from the cycloadduct obtained from a pyran-2-one diene.[216] Diels–Alder reactions of **19b** have been used in approaches to substituted barrelenes[217] and other complex polycyclic products.[218,219] The cycloaddition of *N*-protected pyrrole **122** with **19b** was used by Altenbach and Vogel[220] and their coworkers in a synthesis of 7-azanorbornadiene **123** (Scheme 84). Related reactions between pyrroles and terminal acetylenic sulfones have attracted special attention because the cycloadducts serve as key intermediates in the synthesis of the dendrobatid alkaloid epibatidine, which displays powerful analgesic activity. Many variations and improvements to this approach to epibatidine have appeared,[83,94,221–225] as well as similar routes to the conduramines.[226]

Despite the greater steric hindrance of β-aryl- and β-alkyl acetylenic sulfones, they too are capable of undergoing Diels–Alder reactions effectively. Thus, the cycloaddition in Scheme 85 employs the more highly elaborated dienophile **124**, which offers an alternative to Scheme 84 for the synthesis of epibatidine.[69,227] However, the normal Diels–Alder chemistry of β-aryl acetylenic sulfones is sometimes accompanied by competing [2+2] cycloadditions[228] (see section 5.3) or by fragmentation of the dienophile[228] (see section 6). The spiro product **126** was obtained from the Diels–Alder cycloaddition of the bromoalkyl acetylenic sulfone **125**, followed by radical cyclization (Scheme 86).[32] Intramolecular cycloadditions of acetylenic sulfones bearing dienyl[67b,67c] and enynyl[229] substituents have been reported, including an approach to the CD portion of vitamin D_3 (Scheme 87).[67b,67c] The relatively unstable trifluoromethyl acetylene **28** was generated in situ and trapped with dienes, thus providing the means for introducing the trifluromethyl substituent into the cycloadducts.[96]

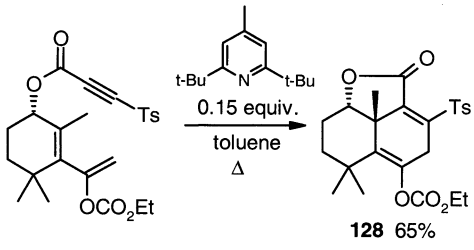
Acetylenic sulfones with β-ester substituents are doubly activated and therefore particularly reactive dienophiles. The ester group controls the regiochemistry in compounds such as **127** in Scheme 88.[31] The resulting cycloadducts can be aromatized by oxidation or elimination of sulfinic acid. Synthetic applications of ester-substituted acetylenic sulfones include approaches to **128**, an intermediate in the synthesis of forskolin, via the intramolecular cycloaddition



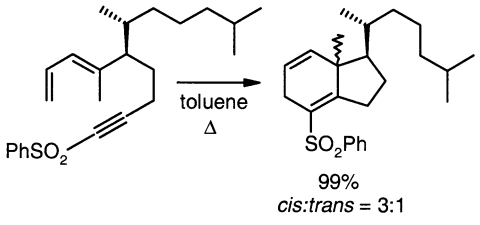
Scheme 88.



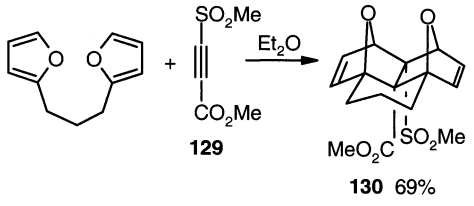
Scheme 86.



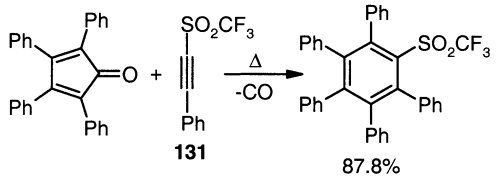
Scheme 89.



Scheme 87.



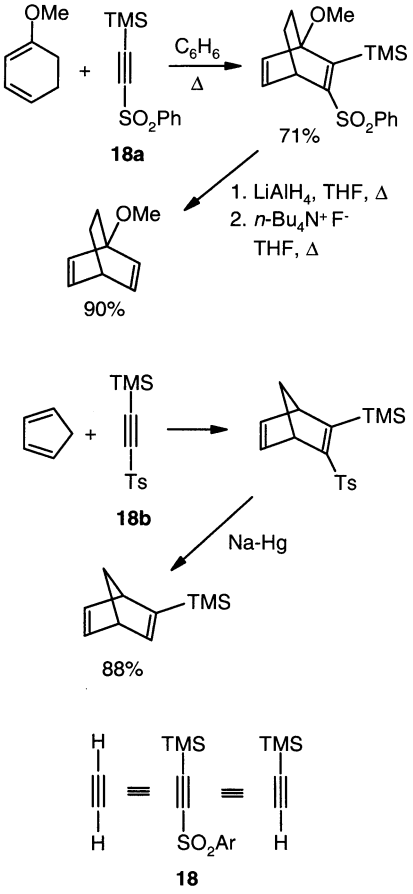
Scheme 90.



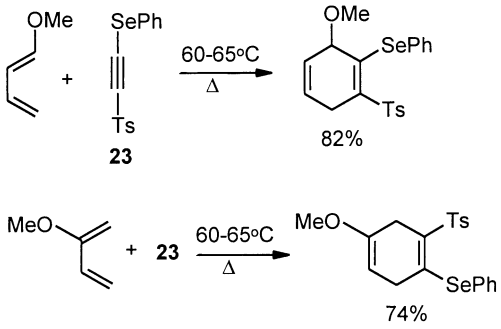
Scheme 91.

in Scheme 89.[57] The free acid **20** was employed in an intermolecular reaction in a related approach to glycinoeclepin A.[230] Other cycloadditions were used in the elaboration of porphyrins[231] and in pincer-type Diels–Alder reactions of ester **129** to give **130** (Scheme 90).[232]

Bis(*t*-butylsulfonyl)acetylene (**29**) is another doubly activated dienophile. It readily undergoes Diels–Alder reactions with, inter alia, cyclopentadiene,[97] fused cyclopentadienes related to the one in Scheme 81,[233] cyclohexadiene,[97] anthracene,[97] furans[97,233] and pyrroles,[234] and it has been employed in a synthesis of [*n*]beltenes.[235] Conjugate additions to **29** predominate over cycloadditions in the case of pyrroles[97,234] and thiophenes,[97] which attack through their 2-positions. Further transformations of the cycloadducts of **29** are possible through alkylative or reductive desulfonylation.[97,236] Bis(arylsulfonyl)acetylenes are less stable than the *t*-butyl analogue, but have been trapped as Diels–Alder cycloadducts when generated in situ in the presence of suitable dienes such as cyclopentadiene.[25]



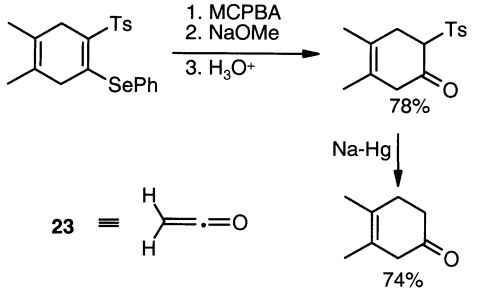
Scheme 92.



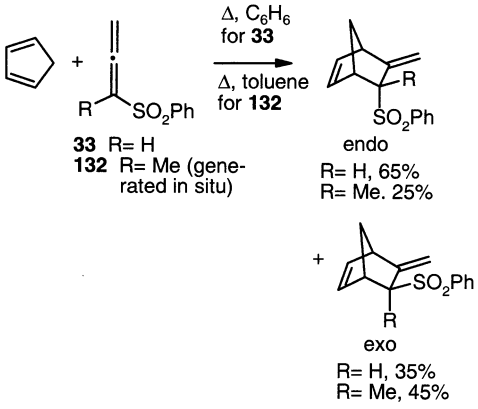
Scheme 93.

Acetylenic triflones comprise another class of highly active dienophiles. They were first studied by Glass and Smith,[59] who determined that the phenyl derivative **131** is 1.7 times more reactive than dimethyl acetylenedicarboxylate toward cyclopentadiene. On the basis of kinetic data, they also showed that the triflone group is more strongly activating than other electron-withdrawing groups such as carbonyl and nitrile. Diels–Alder reactions of acetylenic triflones[59,61,62] and other perfluoroalkyl analogues[61a,65] have been reported with a variety of dienes, including the example in Scheme 91, where the initial cycloadduct with tetraphenylcyclopentadienone loses CO to produce the corresponding aromatic product.[59] Similar cycloadditions with this diene have also been reported with other acetylenic sulfones.[61a,65,73]

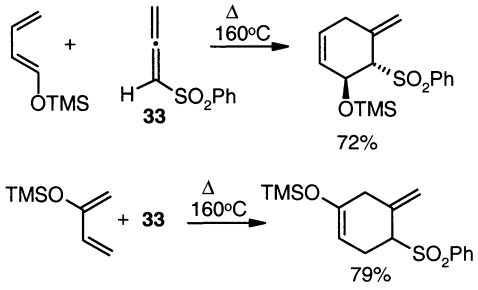
Acetylenic sulfones with a variety of β-heteroatom substituents react with dienes via [4+2] cycloadditions. Diels–Alder reactions of β-trimethylsilyl acetylenic sulfones **18** have been investigated by several groups.[209,237–239] The cycloadducts can be reduced and the silyl and sulfonyl groups removed by reductive elimination, making the acetylenic sulfone a synthetic equivalent of acetylene.[238b,238c] Alternatively, reductive desulfonylation of the cycloadduct produces the corresponding vinyl silane, thus rendering the acetylenic sulfone the equivalent of the relatively unreactive dienophile trimethylsilylacetylene.[209] In some cases, the directing effect of the silyl group appears to override that of the sulfone moiety in determining the regiochemistry of the cycloaddition.[238b] These features are illustrated by the examples in Scheme 92.[209,238b] The selenoacetylene **23**, which displayed anti-Michael behaviour in its conjugate additions (see sections 4.1 and 4.2), also reacted with anomalous regiochemistry in cycloadditions with unsymmetrical dienes such piperylene, isoprene and 1- and 2-methoxy-1,3-butadiene (e.g. Scheme 93).[240]



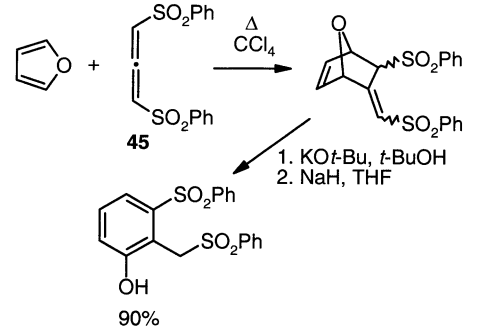
Scheme 94.



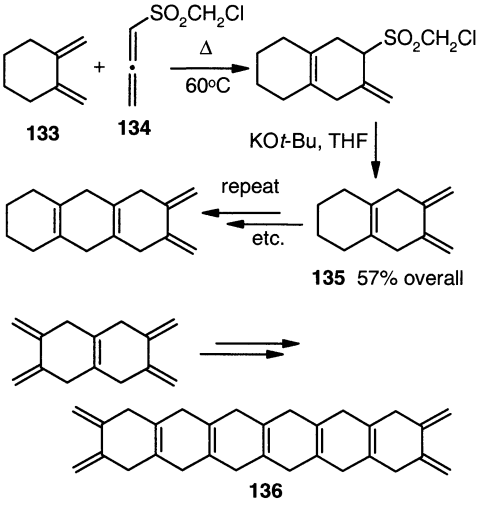
Scheme 95.



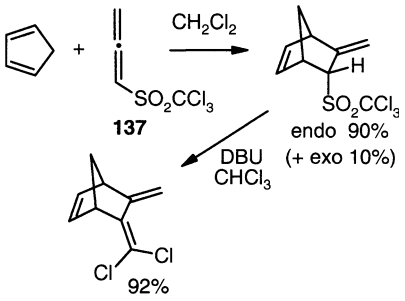
Scheme 96.



Scheme 97.



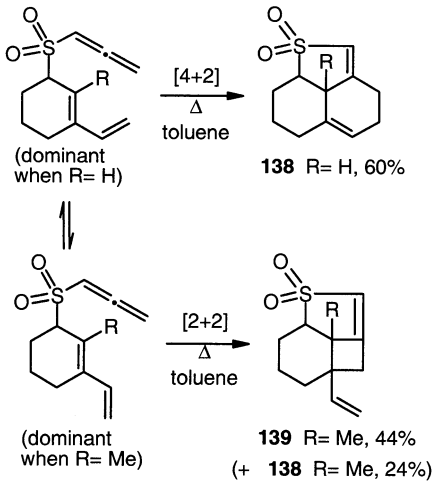
Scheme 98.



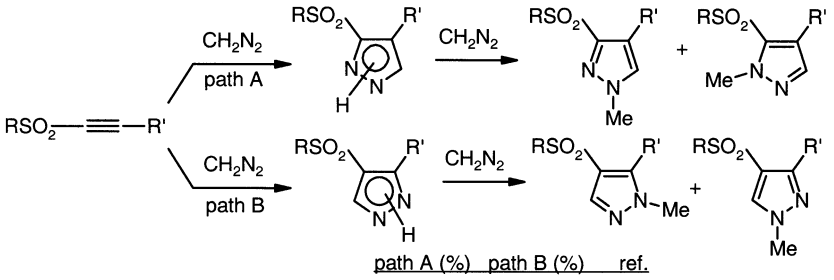
Scheme 99.

Therefore it appears that the selenide rather than the sulfone group plays the dominant role in determining regioisomer distributions, for reasons that remain poorly understood. Moreover, oxidation and hydrolysis of the vinyl selenide moiety of the products, followed by reductive desulfonylation, renders the dienophile **23** a synthetic equivalent of ketene (Scheme 94).[240] A hetero-Diels–Alder reaction of **23** with acrolein has also been reported.[240b] Other heteroatom-substituted acetylenic sulfones that undergo Diels–Alder reactions include **22**,[89,90] **25**,[93] **26**[94] and **27**.[95,95b]

As expected, allenic sulfones are also effective dienophiles. Although most of their Diels–Alder reactions occur at the sulfone-activated double bond, exceptions[241–244] are known in intramolecular processes. As in other applications, these compounds are sometimes generated in situ by isomerization of their propargylic isomers. The cycloadditions are stereochemically more complex than those of their acetylenic analogues. *endo* Products are typically favoured in intermolecular reactions, but not when the allene contains an α-alkyl substituent[207,245] (e.g. Scheme 95[207]). When optically active allenic sulfones are used, the enantiomeric excess is preserved in the cycloadduct.[245] The regiochemistry observed with unsymmetrical dienes is illustrated in Scheme 96.[246] MO calculations have been used to rationalize the Diels–Alder reactions of allenic sulfones.[246,247] Apart from unsubstituted and alkyl-substituted allenic sulfones, others containing α-chloro-,[248] α-ester[247] and α-amido[249] groups all undergo Diels–Alder reactions, as do allenic triflones[250] and 1,3-bis(phenylsulfonyl)allene (**45**).[132] Cycloadducts derived from cyclopentadiene,

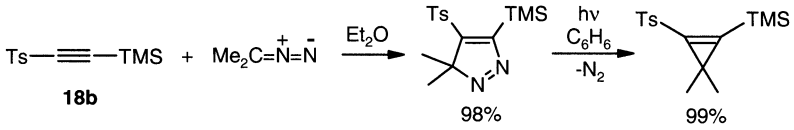


Scheme 100.



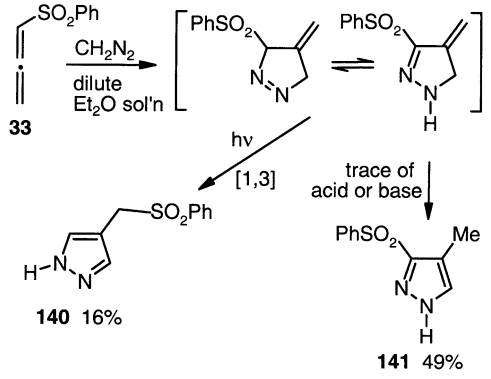
	path A (%)	path B (%)	ref.
R= Ph, R'= Me	20	80	255
R= *p*-tolyl, R'=Me	20	80	255
R= *p*-ClC$_6$H$_4$, R'= Me	20	80	255
R= *p*-tolyl, R'= TMS	-	100	256
R= *p*-tolyl, R'= H	66	-	256
R= *p*-tolyl, R'= SePh	-	81	240b
R= CF$_3$, R'= Ph	43	-	61a

Scheme 101.



Scheme 102.

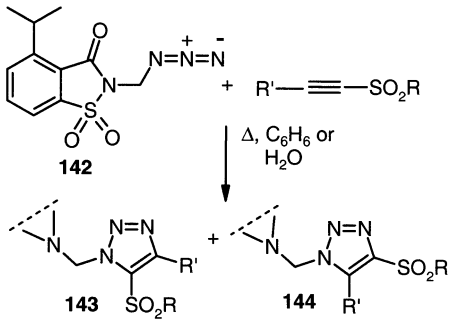
pyrroles and furan were used in the generation of norbornenyl carbanions,[251] in an alternative approach to epibatidine[252] vide supra; see Schemes 84 and 85) and for the preparation of phenols via base-mediated elimination of the oxa bridge[132,253] (e.g. Scheme 97[132]), respectively. An interesting iterative approach to the synthesis of fused 1,4-cyclohexadienes was reported by Block and Putnam,[110] based on the Diels–Alder reaction of diene **133** with (chloromethylsulfonyl)allene (**134**), followed by a Ramberg–Backlund reaction to regenerate a new diene moiety in the homologated product **135** (Scheme 98). The application of this protocol to the synthesis of [*n*]beltenes such as **136** was reported by Graham and Paquette (Scheme 98).[235] The Diels–Alder chemistry of trichloromethylsulfonyl allenes **137** has also been investigated. These allenes shows enhanced reactivity compared to arylsulfonyl analogues and transmit chirality to the cycloadducts when used in optically active form.[109] The cycloadducts also undergo Ramberg–Backlund reactions,[254] as shown in Scheme 99. Intramolecular reactions of allenic sulfones with dienes,[242,244] arenes[241,249] and furans[129a,129c,243] have also been reported. The [4+2] cycloadditions sometimes compete with [2+2] processes,[129a,129c,132,242] which are further described in section 5.3. Kanematsu et al.[242] have shown that substituent effects play an important role in the partitioning between [4+2] and [2+2] pathways (e.g. **138** vs **139** in Scheme 100).



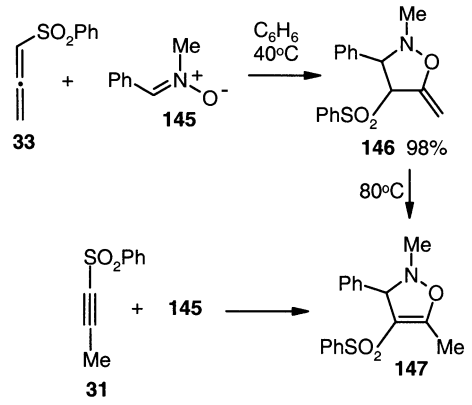
Scheme 103.

5.2. 1,3-Dipolar cycloadditions

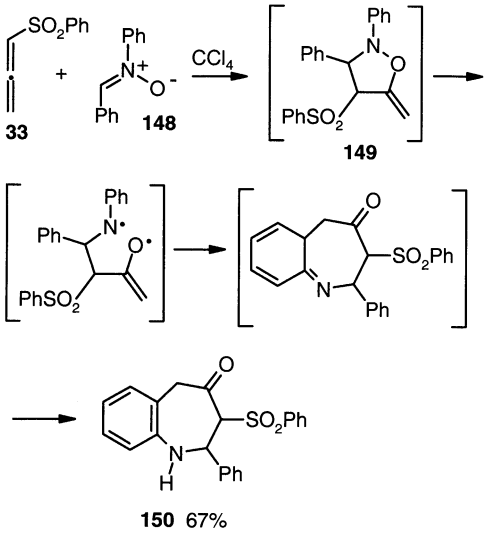
The 1,3-dipolar cycloadditions of diazo compounds with both acetylenic and allenic sulfones have been relatively widely studied. The reaction of diazomethane with acetylenic sulfones[61a,240b,255,256] is shown in Scheme 101, along with regioisomer distributions via paths A and B, respectively, for representative examples. Excess diazo compound results in *N*-methylation of the initial pyrrazole products.[61a,240b,255] Diazopropane[255–258] reacts preferentially via path A, except in the case where the acetylene bears a bulky substituent, such as a trimethylsilyl group. Other diazo compounds that have been investigated include diphenyldiazomethane,[255] ethyl diazoacetate,[255] 2-diazo-1,3-dithiane,[259] phosphinyl- and silyl-substituted diazo compounds,[92] and their lithio derivatives.[92] Acetylenic



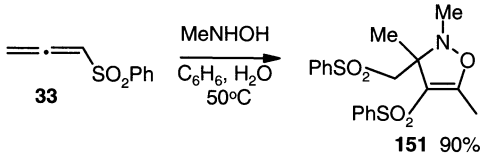
Scheme 104.



Scheme 105.



Scheme 106.

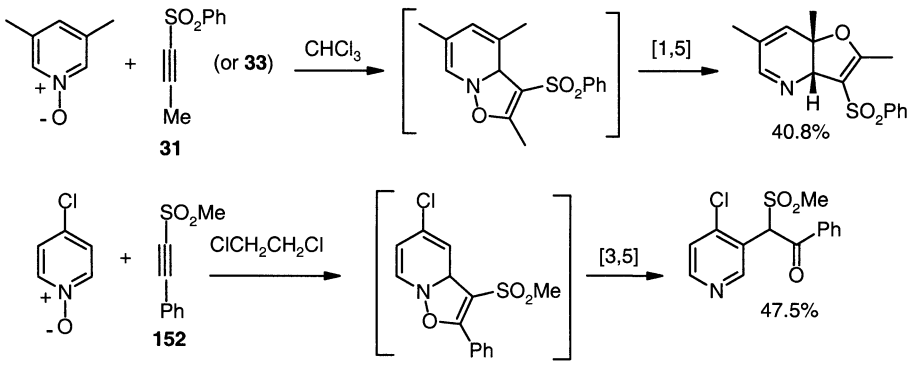


Scheme 107.

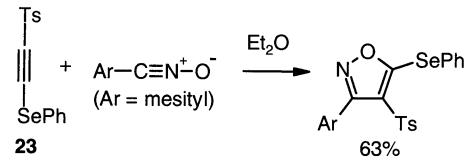
sulfones with β-silyl (**18**),[92,256,258,259] β-phenylseleno (**23**),[240b] and β-phosphinyl (**24**)[92] substituents, as well as acetylenic triflones (**6**),[61a] have been studied. Photolysis of the initially formed pyrrazole derivatives afforded sulfonylcyclopropenes[256–258,260] (e.g. Scheme 102[258b]), that were in turn employed in a large variety of further transformations. Alternatively, certain cyclopropenes were obtained by prior generation of the carbene from the diazo compound in the presence of the acetylenic sulfone.[259] Allenic sulfones react with diazomethane,[261,262] 2-diazopropane[262a] and 1,1-diphenyldiazomethane,[261] affording mainly the regioisomers where the diazo carbon atom attacks the central allene carbon and the terminal diazo nitrogen atom bonds to the α-carbon atom of the allene. In the example given in Scheme 103,[262a] **140** was formed by a subsequent 1,3-shift of the sulfonyl group in the presence of ambient light, and not by direct cycloaddition of diazomethane to the unactivated double bond of the allene.

The reactions of (trimethylsilyl)methyl azide with the selenoacetylene **23**[240b] and of azide **142** with various other acetylenic sulfones[263] afforded mixtures of the corresponding regioisomeric triazoles (e.g. **143** and **144** in Scheme 104[263]).

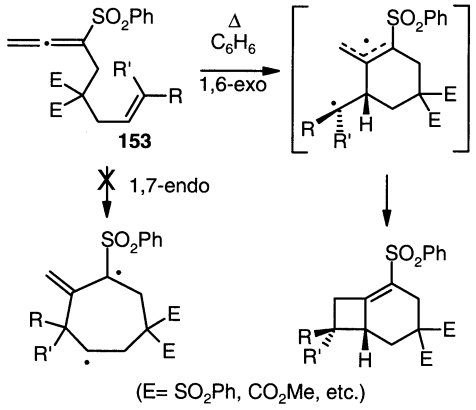
Extensive studies by Padwa and coworkers, and by several other groups, have shown that cycloadditions of nitrones to acetylenic[264–266] and allenic sulfones[264,265a,267,268] afford isoxazolines or isoxazolidines. The regiochemistry is generally characterized by new bond formation between the nitrone oxygen atom and the β-carbon of the dipolarophile, with the nitrone carbon atom bonding to the α-position. Numerous subsequent transformations of the initial cycloadducts are possible, leading to, inter alia, benzazepin-4-ones,[265a,267,268b,268c,268f] 3-acylindoles,[265] 3-pyrrolidinones,[268c] β-carbolines[266] and α,β-unsaturated carbonyl compounds.[268a,268e] For example, the *N*-methyl nitrone **145** adds to either allenic sulfone **33** or its acetylenic isomer **31** to afford **146** and **147**, respectively, with isomerization of **146** to **147** taking place upon heating (Scheme 105).[264a] Deprotonation and alkylation of the allylic sulfone moiety of **146** occurred α (e.g. with iodomethane) or γ (e.g. with allyl bromide) to the sulfone group, depending on the steric bulk of the electrophile.[264a] In contrast to the *N*-methyl derivative **146**, the *N*-phenyl analogue **149**, which was obtained similarly from the corresponding *N*-phenyl nitrone **148** and **33**,[265a,268f] underwent a radical cleavage and recombination process to afford **150** as the principal product



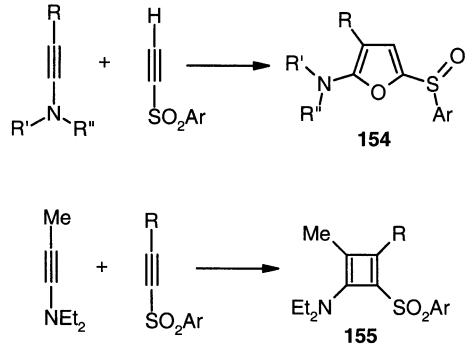
Scheme 108.



Scheme 109.



Scheme 110.



Scheme 111.

(Scheme 106[268f]). Other mechanisms have also been proposed for this transformation[265a,267] and that of other *N*-aryl nitrones.[267] An interesting variation of this chemistry consists of generating the nitrone from a hydroxylamine and an allenic sulfone, followed by its dipolar cycloaddition to another molecule of the allenic sulfone[143a] (e.g. to afford **151** in Scheme 107), or to an acetylenic sulfone.[143a] Nitrones formed in this manner also perform intramolecular cycloadditions to unactivated alkene or alkyne moieties located in pendant side chains of the original allenic sulfone.[129d,143b]

The cycloadditions of pyridine *N*-oxides to acetylenic or allenic sulfones are typically followed by [1,5][269] or [3,5]sigmatropic rearrangements[270,271] (Scheme 108). Nitrile oxides cycloadd readily to acetylenic sulfones,[240b,272] usually producing mixtures of regioisomers with the 4-sulfonyl derivative dominating. However, the selenoacetylene **23** reacted cleanly with mesitylenenitrile oxide, as in Scheme 109.[240b] Cycloadditions of nitrile oxides[272b,273] and nitrilimines[262a,274] with allenic sulfones have been reported, but tend to be complex because of competing reactions between the activated and distal allene double bonds and isomerizations of the cycloadducts. Cycloadditions of several less frequently studied 1,3-dipoles and trimethylenemethane species with acetylenic sulfones have also been reported.[93,275,276]

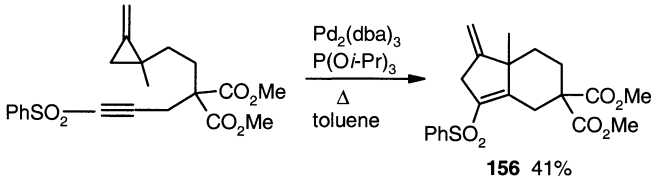
5.3. [2+2] Cycloadditions

The existence of [2+2] cycloadditions that compete with Diels–Alder reactions of acetylenic sulfones was noted in section 5.1. Moreover, Padwa and coworkers[128b,129a,129b,129c] reported a series of intramolecular [2+2] cycloadditions of allenic sulfones **153** with alkenes, which proceed via diradical intermediates. The example in Scheme 110 indicates a preferential 1,6-*exo*- vs 1,7-*endo* pathway for diradical formation, as well as stereospecific product formation attributed to rapid ring-closure of the intermediate. In other systems, where the tether between the allene and alkene moieties is based on an *o*-disubstituted aromatic ring, a 1,7-*exo* mode for diradical formation was observed.[277] The allenic sulfones **153** were readily available from the additions of enolates and sulfone-stabilized anions to diene **43** via Scheme 28.

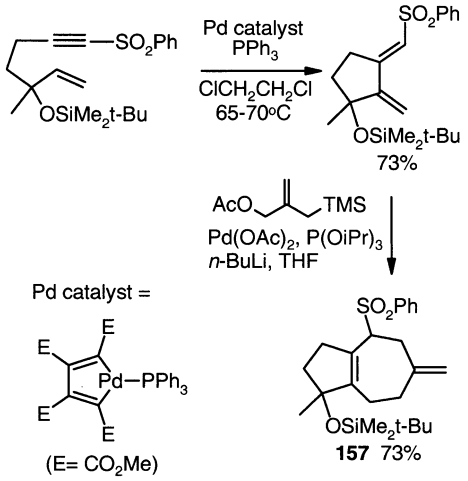
An intermolecular [2+2] cycloaddition between allenic sulfone **33** and methylenecyclohexane catalyzed by $EtAlCl_2$ was reported.[278]

The reaction of ynamines with acetylenic sulfones has aroused some debate concerning the mechanism. Thus, while Himbert et al.[279] observed the formation of furans **154** (Scheme 111) and postulated a Pummerer-type mechanism for their formation, Eisch and coworkers[280] presented evidence that the corresponding cyclobutadiene **155** is the first metastable intermediate in these reactions, which may therefore be considered to proceed via a formal [2+2] cycloaddition (Scheme 111).

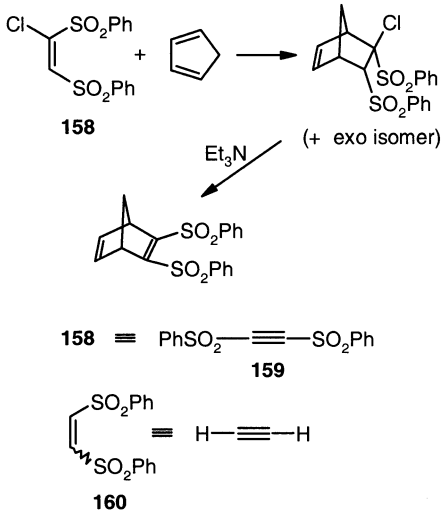
Examples of [2+2] cycloadditions between allenic sulfones and imines[281] or enamines[282] have been reported, as well as the cycloaddition of a sulfonyl ketene, generated by fragmentation of 1-*t*-butoxy-2-(phenylsulfonyl)acetylene, with a second mole of the acetylenic sulfone.[283] The formation of thietane dioxides was observed among the products of the reaction of propargylsulfonyl chloride with α-morpholinostyrene, possibly via allenic sulfone intermediates.[284]



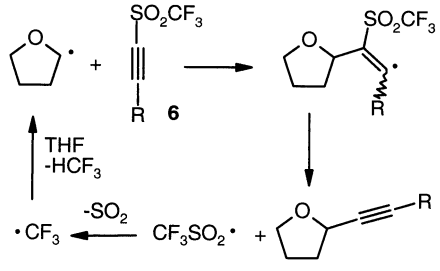
Scheme 112.



Scheme 113.



Scheme 114.



Scheme 115.

5.4. Other cycloadditions

An intramolecular palladium-catalyzed [3+2] cycloaddition between a methylenecyclopropane and an acetylenic sulfone afforded the corresponding [4.3.0]-bicylononane **156** (Scheme 112),[24] while a palladium-catalyzed [4+3]cycloaddition that produced the [5.3.0]-bicyclodecane system **157** is displayed in Scheme 113.[285] Other reported cycloadditions include those of 1-methanesulfonyl-2-phenylacetylene with ketene iron carbonyl complexes[286] and the [8+2] reactions of tropone and its imine derivatives with allene **33**.[246] Bridged prismanes were obtained by the Lewis acid-catalyzed cyclization of acetylene **29**, and other activated acetylenes, with cyclic diynes.[287]

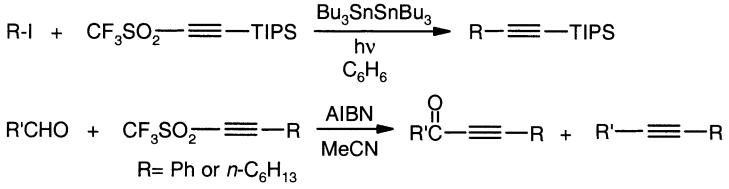
5.5. Synthetic equivalents of acetylenic sulfones and acetylenes in cycloadditions

The readily available chlorovinylbis(sulfone) **158**[288] functions as a good dienophile in Diels–Alder cycloadditions, as demonstrated by De Lucchi et al.[289] Moreover, subsequent elimination of HCl from the cycloadducts restores the double bond of the original dienophile. Although the *Z*-isomer of **158** proved the more reactive dienophile, the cycloadducts from the *E*-isomer were more readily dehydrochlorinated.[289b] The overall process (e.g. Scheme 114) therefore renders **158** the synthetic equivalent of the relatively unstable bis(phenylsulfonyl)acetylene **159**. Similarly, the vinyl bis(sulfone) **160** acts as a doubly activated equivalent of acetylene, as subsequent reductive elimination of the sulfone groups regenerates the double bond in the cycloadduct.[210,290] Various other types of unsaturated sulfones can be used as acetylene equivalents and this subject was recently reviewed.[291]

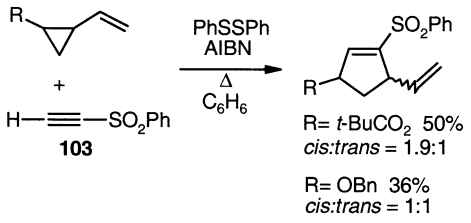
6. Radical reactions

6.1. Alkynylations with acetylenic triflones

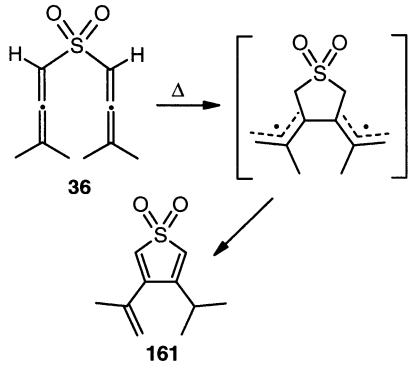
In 1996, Fuchs and coworkers[64a] discovered a remarkable alkynylation reaction of substrates such as THF with acetylenic triflones **6**. The reactions are initiated by light, AIBN or peroxides and proceed via the radical chain mechanism shown in Scheme 115. An alternative mechanism involving a carbene rearrangement was ruled out on the basis of ^{13}C-labelling and other experiments.[64b] A wide variety of substrates, including dioxane, thiophene, crown ethers, and even unactivated hydrocarbons such as cyclohexane and adamantane, reacted similarly to THF.[64a,64b,64d] The acetylenic triflone tolerates a variety of aryl, alkyl, and silyl substituents, with the triisopropylsilyl (TIPS) derivative reported to be particularly efficacious.[64d] Vinyl triflones



Scheme 116.



Scheme 117.

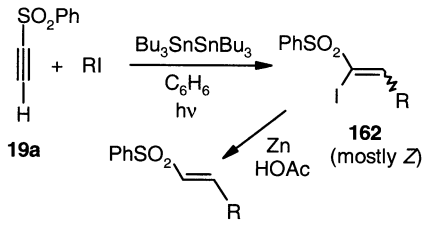


Scheme 118.

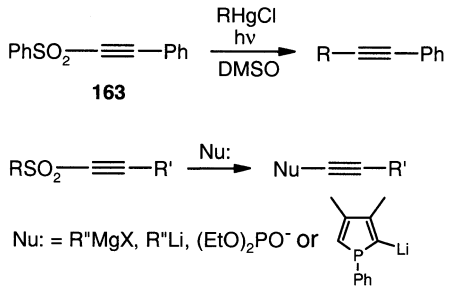
containing β-heteroatom substituents,[144] as well as allyl triflones,[292] underwent similar free radical reactions, resulting in alkenylation and allylation, respectively, of the substrates. Aldehydes reacted with acetylenic triflones to afford acetylenic ketones and/or disubstituted acetylenes from decarbonylation of acyl radical intermediates,[293] while alkyl iodides produced alkyl triisopropylsilyl acetylenes when treated with the corresponding acetylenic triflone and hexabutyldistannane.[294] The latter reactions are shown in Scheme 116.

6.2. Radical cyclizations of acetylenic and allenic sulfones

Several radical cyclizations involving radical additions to acetylenic[295,296] and allenic sulfones[297] have been reported. An example is shown in Scheme 117[295] and a tandem Diels–Alder cycloaddition-radical cyclization process was shown earlier in Scheme 86.[32] The bis(allenic) sulfone **36** cyclized under thermal conditions to the corresponding thiophene S,S-dioxide **161** (Scheme 118).[114a,114c] More complex thiophenes were prepared similarly[107,298] and mechanisms involving initial ring-closure to produce diradical intermediates, followed by disproportionation or dimerization, were implicated. A different type of [2+2] cyclization via



Scheme 119.



Scheme 120.

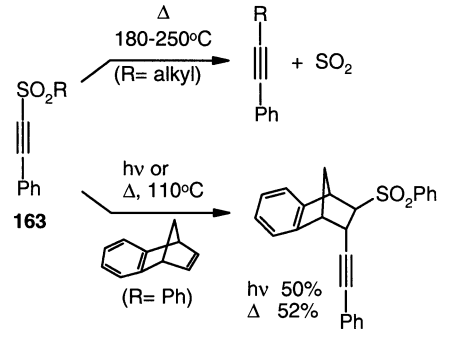
diradical intermediates was encountered earlier (Scheme 110).

6.3. Radical additions to acetylenic sulfones

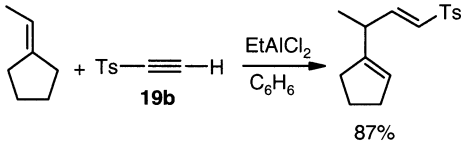
The photochemical addition of alkyl iodides to acetylenic sulfone **19a** in the presence of hexabutyldistannane afforded α-iodovinyl sulfones **162**, with the best results obtained with tertiary alkyl iodides. The adducts were then reduced to vinyl sulfones with Zn/acetic acid (Scheme 119).[299]

6.4. Radical substitutions of acetylenic sulfones

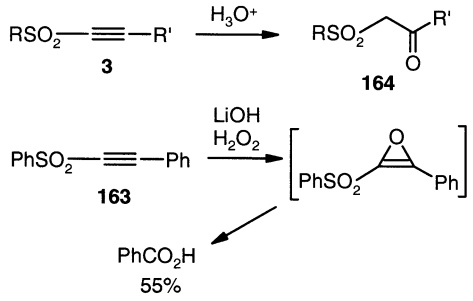
Whereas organocopper reagents typically effect additions to acetylenic sulfones (see section 4.4), acetylenic sulfone **163** undergoes photochemical radical substitutions with alkylmercury halides to produce phenyl alkyl acetylenes (Scheme 120).[300] Grignard reagents and organolithium compounds also afford substitution products with acetylenic sulfones,[82,88,300c,301,302] and mechanisms involving electron-transfer processes and radical intermediates were implicated in at least some cases.[300c,302] 2-Lithiated phospholes[303] and diethyl phosphite[300c] react with acetylenic sulfones by similar substitution of the sulfone moiety, although these reactions proceed by unspecified and ionic mechanisms, respectively. These processes, like the alkynylations with acetylenic triflones in section 6.1, all provide access to



Scheme 121.



Scheme 122.



Scheme 123.

various unsymmetrically disubstituted acetylenes (Scheme 120).

6.5. Fragmentation of acetylenic sulfones

Several fragmentation processes of acetylenic sulfones have been reported. They result in pyrolytic extrusion of SO_2 and recombination to afford the corresponding acetylenes,[39b] and the thermally or photochemically induced 1,2-additions of acetylenic sulfones to alkenes,[228b,304] as shown in Scheme 121. While there is no firm evidence for the mechanisms of these processes, radical processes are a possibility.

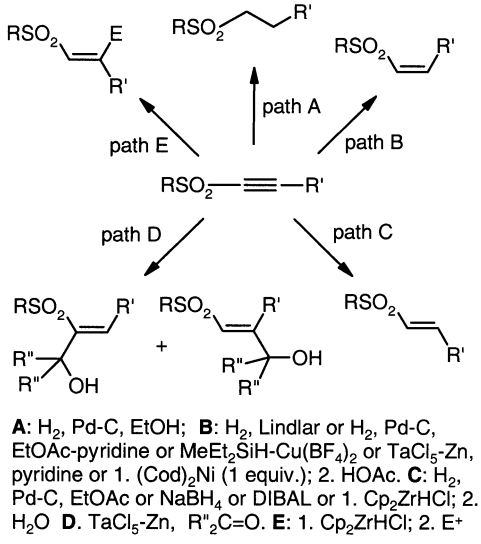
7. Miscellaneous reactions

7.1. Ene reactions of acetylenic and allenic sulfones

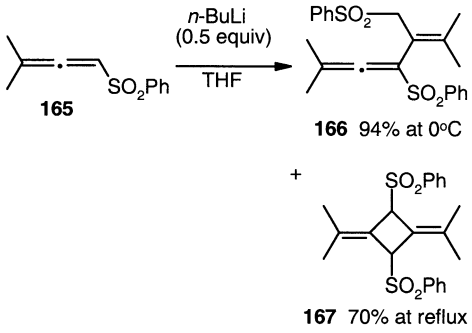
p-(Toluenesulfonyl)acetylene (**19b**) reacts with alkenes in the presence of $EtAlCl_2$ to afford ene products (e.g. Scheme 122).[85] Examples of uncatalyzed ene reactions of the β-stannyl[89] and β-phenylseleno[240b] acetylenes **22** and **23**, respectively, have also been reported, as well as several inter-[278] and intramolecular[305] ene reactions of allenic sulfones.

7.2. Hydrolysis of acetylenic and allenic sulfones

Acetylenic sulfones undergo acid-catalyzed hydrolysis to



Scheme 124.

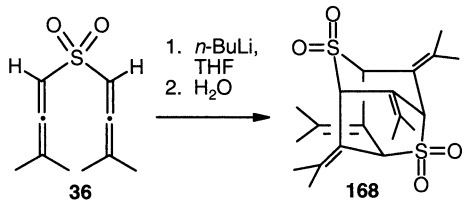


Scheme 125.

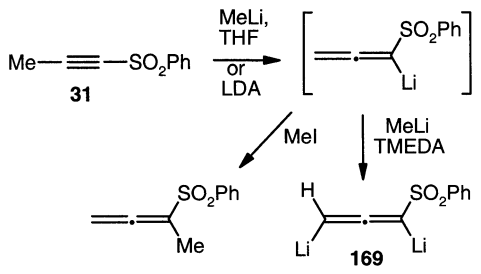
β-keto sulfones **164** (Scheme 123),[20] while acetylenic triflones[61a,61b] are similarly hydrolyzed even in the absence of a catalyst. Alternatively, prior conversion of acetylenic sulfones to their ketal,[46b] or enamine[139b] derivatives by conjugate additions of alkoxides or amines, followed by hydrolysis under milder conditions, also leads to the corresponding β-keto sulfones. A few examples of hydrolyses of allenic sulfones, which were typically generated in situ from their propargylic isomers, or of their conjugate addition products, are known. They similarly produced β-keto sulfones[125b,173,306,307] or other products such as δ-keto or unsaturated keto sulfones by more complex mechanisms.[134,307] An oxidative process that cleaved acetylenic sulfone **163** to benzoic acid, possibly via the corresponding oxirene intermediate, is also shown in Scheme 123.[308]

7.3. Reductions of acetylenic sulfones

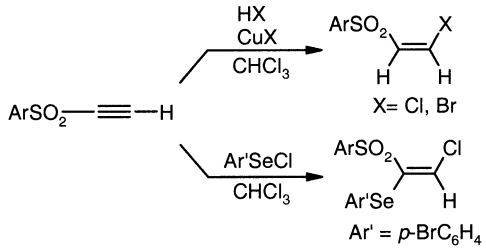
Hydrogenation of acetylenic sulfones in the presence of palladium/charcoal catalyst typically produces saturated sulfones (path A, Scheme 124),[18a,18c] whereas the use of Lindlar catalyst affords the corresponding *cis* vinyl sulfones (path B)[67c] or unreacted starting material.[18c] The trimethylsilyl acetylene **18a** was partially hydrogenated over palladium/charcoal to either the corresponding *cis*- or *trans*-vinyl sulfone by the inclusion or omission, respectively, of pyridine in the solvent.[309] Reductions of various acetylenic sulfones performed with $MeEt_2SiH/Cu(BF_4)_2$,[310] $TaCl_5/Zn$/pyridine[311] or $(Cod)_2Ni$ followed by acetic acid[88,312] produced the corresponding *cis*-vinyl sulfones (path B), whereas sodium borohydride[18c] or DIBAL[88] afforded the corresponding *trans* isomers (path C). Vinyl tantalum intermediates from the reductions with the $TaCl_5/Zn$ reagent were also intercepted by additions to the carbonyl groups of aldehydes or ketones to produce the corresponding carbinols (path D).[311] Hydrozirconation of acetylenic sulfones, followed by aqueous workup, afforded chiefly the *trans* vinyl sulfones (path C), while quenching of the vinyl zirconium intermediates with allyl or acyl halides, or with



Scheme 126.



Scheme 127.

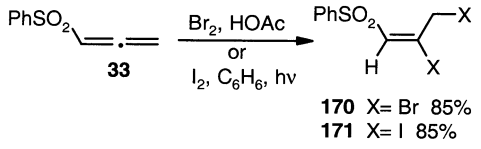


Scheme 128.

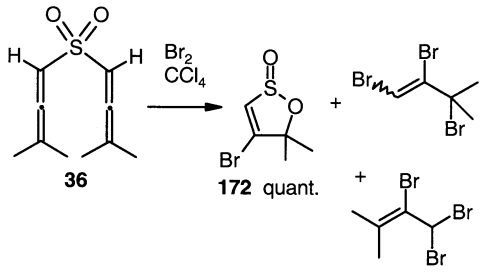
N-halosuccinimides, provided vinyl sulfones with the corresponding allyl, acyl or halo substituents in the β-position (path E).[313]

7.4. Reactions of anions of allenic sulfones

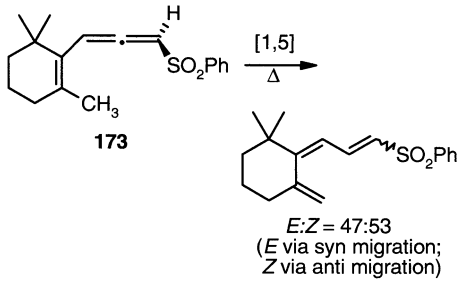
Allenic sulfones such as **165** are sufficiently acidic to form α-anions when deprotonated with *n*-butyllithium. The anions can be silylated[191] or added to a second mole of starting material[114c,262b,314] to afford the corresponding vinyl allene **166** or 1,3-dimethylenecyclobutane **167**, depending on the conditions (Scheme 125[114c,314]). In a somewhat related process discovered by Braverman et al.,[114c,315] α-deprotonation of allene **36** was followed by a remarkable sequence of four additions to the activated double bond (termed a 'carbanion walk' by the authors) that produced the dithiaadamantane **168** (Scheme 126). Alternatively, deprotonation of acetylenic sulfone **31** with LDA or methyllithium formed a sulfone-stabilized anion



Scheme 129.



Scheme 130.



Scheme 131.

that underwent methylation at the α-position.[126,302] Furthermore, double deprotonation of **31** to form the dilithiated allene **169** was achieved as shown in Scheme 127.[302] A [1,3]-shift of the sulfone moiety to a carbanion site in the side chain of an allenic sulfone has also been reported.[316]

7.5. Electrophilic additions to acetylenic and allenic sulfones

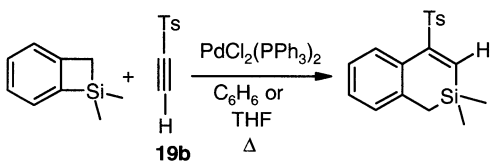
Dry HCl and HBr added to acetylenic sulfones in the presence of cuprous halides to furnish β-chloro and β-bromovinyl sulfones.[22] A selenenyl chloride added similarly[317] and both processes are regio- and stereoselective, as shown in Scheme 128. Allenic sulfone **33** reacted with bromine in acetic acid, or with iodine upon irradiation with a sunlamp, to afford the corresponding 1,2-adducts **170** and **171**.[318] The distal double bond reacted preferentially (Scheme 129). Numerous further transformations of these highly functionalized adducts were also reported, including syntheses of cyclopentenones, furans and other products.[318] More highly substituted allenic sulfones, such as **36**, reacted with bromine by other pathways, for example involving fragmentation and cyclization to sultines **172** (Scheme 130).[114b,319] A new preparation of (*E*)-β-(phenylsulfonyl)vinyl boronates was accomplished by the hydroboration of (phenylsulfonyl)acetylene (**19a**).[320]

7.6. [1,5] Hydrogen migrations in conjugated allenic sulfones

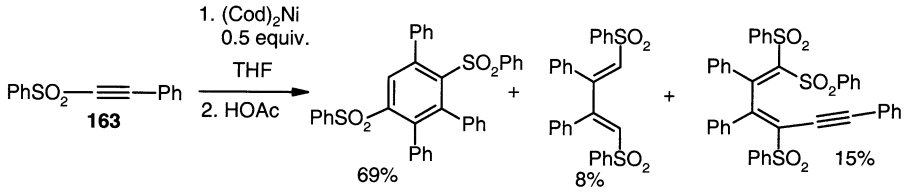
The conjugated allene **173** underwent a thermal [1,5] shift as shown in Scheme 131.[118,321] The migration is more facile than in related allenes containing sulfoxide, sulfide, alkyl or no substituents in place of the sulfone moiety.

7.7. Insertion and oligomerization reactions of acetylenic sulfones

Acetylenic sulfones react with various platinum,[322] palladium,[323,324] copper[325] and nickel[312] species, usually producing insertion products or oligomers. Two examples are shown in Schemes 132[324] and 133.[312]



Scheme 132.



Scheme 133.

8. Medicinal properties

A number of cyclic and acyclic bis(propargylic) sulfones such as **174**[326] were reported to function as DNA-cleaving agents, thus making them of potential interest as anticancer drugs.[171,326–331] Two possible mechanisms for this activity are shown in Scheme 134. In the first, prototropic isomerization to the corresponding allenic sulfone **175** is followed by alkylation of DNA via conjugate addition to the electrophilic allene moiety to form **176**. In the other, cyclization of **175** produces a diradical intermediate **177** that is responsible for the cytotoxic effects. Evidence for the conjugate addition[326,330] and diradical mechanisms[328] has been reported with different types of propargylic sulfones, and the precise pathway may depend on the specific compound and conditions under investigation. In related work, enediynes were produced by the Ramberg–Backlund reaction of α-chlorobis(propargylic) sulfones.[332,333]

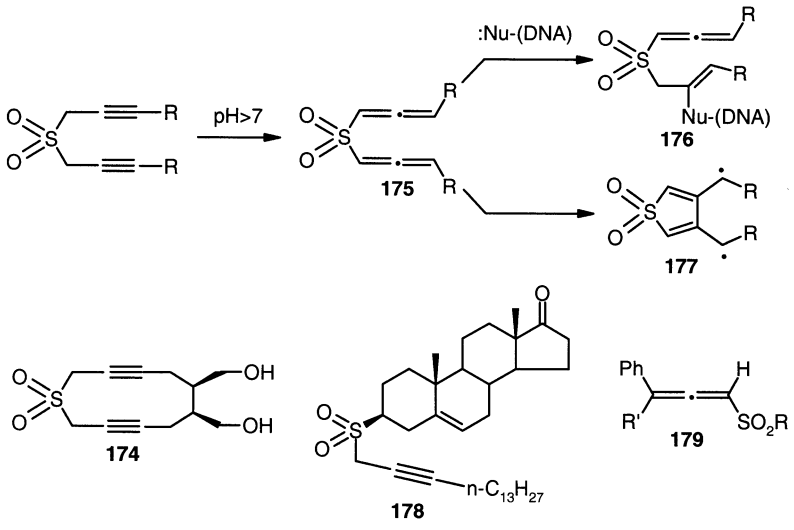
Certain steroidal propargylic sulfones (e.g. **178**) were investigated as potential inhibitors of the enzyme glucose-6-phosphate dehydrogenase (G6PDH), again with the expectation that in situ isomerization to the corresponding allenic sulfones, followed by conjugate addition by the enzyme, would result in its deactivation.[334] Lowering the levels of G6PDH is believed to have a preventive effect toward certain cancers. A series of γ,γ-disubstituted allenic sulfones **179** displayed cerebrovasodilatation activity,[335] while the triazoles **143** and **144** in Scheme 104 were reported to act as potential inhibitors of human leukocyte elastase, a mediator of pulmonary emphysema.[263]

9. Conclusions

This review shows that acetylenic and allenic sulfones are readily prepared by a variety of methods. Many of them can be isolated and are easily handled, while others are conveniently generated in situ. An added attraction to their use is that sulfones in general tend to be less malodorous than more volatile sulfur compounds such as thiols and sulfides. Acetylenic and allenic sulfones contain highly activated, electron-deficient triple and double bonds that lend themselves readily to a wide range of conjugate additions and cycloadditions. The synthetic utility of these reactions has been convincingly demonstrated in the past and invites many future applications. The free radical chemistry, as well as a variety of less thoroughly investigated reactions of acetylenic and allenic sulfones, offers considerable scope for future studies. The biological properties of these compounds have not yet been investigated in depth, but, for example, the DNA-cleaving properties of certain allenic sulfones suggest that potential medicinal applications are waiting to be discovered.

Acknowledgements

We thank the Natural Sciences and Engineering Research



Scheme 134.

Council of Canada for financial support of this area of our research.

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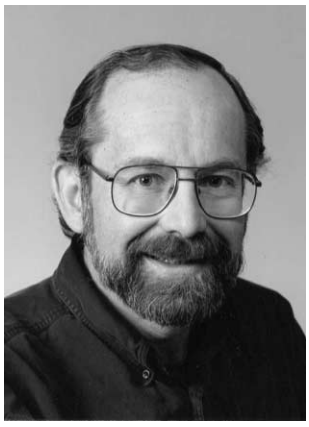
Biographical sketch



Tom Back was born in Prague, Czechoslovakia in 1947 and emigrated to Canada in 1949. He grew up in Montreal, where he attended McGill University (BSc Honours Chemistry, 1968), followed by a year in industry at Frank W. Horner Ltd (pharmaceuticals). He returned to McGill for graduate studies in 1969, obtaining his PhD with Professor David N. Harpp in 1974 for work on new sulfur-transfer reagents. This was followed by a 2 year postdoctoral fellowship with Professor Sir Derek H. R. Barton at Imperial College, London, where he worked on the chemistry of seleno-ketones and their use in the synthesis of hindered olefins by the two-fold extrusion method. In 1976, he returned to Canada to join the group of Dr O. E. Edwards at the National Research Council in Ottawa as a Research Associate, where he worked on the synthesis of maytansinoids and, independently, on various aspects of selenium chemistry. He moved to Calgary in 1978 to take up a position as Assistant Professor of Chemistry at the University of Calgary. Except for a sabbatical leave taken at Stanford University in 1985 with Professor Carl Djerassi, he has remained at the University of Calgary, where he was promoted to Full Professor in 1987. He speaks Czech and French, as well as English. He and his wife Gisèle spend most of their free time mountaineering and ice climbing in the Canadian Rockies.