Cycloadditions and Cyclizations of Acetylenic, Allenic, and Conjugated Dienyl Sulfones†

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† Dedicated to Professor David N. Harpp, for his inspiring contributions as a teacher, mentor and scholar.

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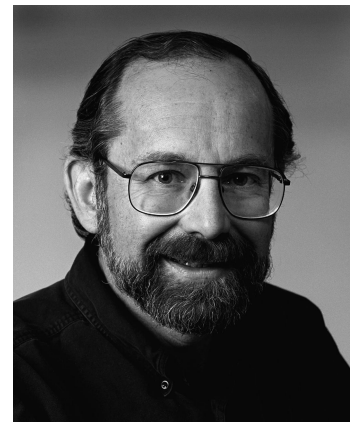
1. Introduction

Sulfones display a diverse range of behavior and possess unique features that make them valuable for numerous types of synthetic applications. As a result of their utility and versatility, sulfones have been described as "pluripotent" by Fuchs and co-workers[1] and as "chemical chameleons" by Trost.[2] Several monograms that describe the general chemistry of sulfones have appeared,[3,4] along with numerous more specialized reviews.[5−17] Unsaturated sulfones are of particular interest and their cycloadditions have been covered by previous authors.[18,19] Acetylenic,[20] allenic,[20,21] and 1,3-dienyl sulfones[22] have all been the subjects of earlier reviews, while vinyl sulfones and related species have been similarly scrutinized,[23−26] including their use as surrogates for acetylenic sulfones when suitably functionalized.[27]

The sulfone moiety has many remarkable properties. It is a strongly electron-withdrawing group that lowers the LUMO of adjacent π-bonds and allows unsaturated sulfones to behave as versatile dienophiles and dipolarophiles. On the other hand, conjugated dienyl sulfones are capable of functioning as the diene component in cycloadditions through inverse electron demand or as dienophiles by utilizing only one double bond. These and other types of cycloadditions often display high regioselectivity because of the polarizing effect of the sulfone substituent. Sulfones render the corresponding α-protons relatively acidic and stabilize adjacent carbanions. The anions can then be used in a variety of alkylations, conjugate additions, and other transformations characteristic of good nucleophiles. Furthermore, unsaturated sulfones are themselves sufficiently electrophilic to undergo conjugate additions at their β-positions with other types of nucleophiles. When such conjugate additions are used in sequence with intramolecular alkylations or other C−C bond-forming processes, they result in useful cyclization protocols. In some respects, there is a superficial resemblance between the reactions of sulfones and carbonyl compounds. However, in many synthetic applications of the latter compounds, the carbonyl group is required either intact or in modified form in the final target molecule. On the other hand, once the sulfone moiety has provided its service, it is typically cleaved by a variety of reductive, oxidative, or cross-coupling methods.[16] It also functions as a leaving group in certain elimination reactions, providing an additional means for its removal from the final product, which can thus be obtained in various oxidation states. It is noteworthy that many sulfones, particularly aryl derivatives, tend to be relatively stable, odorless, easily handled, and amenable to long-term storage. They are often solids that lend themselves to efficient purification by recrystallization, as well as to structure determination by X-ray methods when standard spectroscopic techniques prove inadequate. These features make unsaturated and other sulfones of special interest to the synthetic chemist.

This review describes the cyclizations and cycloadditions of unsaturated sulfones containing more than one carbon−carbon π-bond. Such compounds include acetylenic, cumulated, and conjugated systems, which frequently exhibit distinctive and more complex behavior than simple vinyl sulfones. The latter compounds comprise an extensive class with characteristic properties and behavior of their own, which will not be covered here. Many general methods have been developed for the synthesis of various classes of unsaturated sulfones. These were covered in previous reviews and will not be repeated here.



Tom Back was born in Prague, Czechoslovakia, and grew up in Montreal, Canada, where he attended McGill University for both his undergraduate and graduate degrees. He obtained his Ph.D. in 1974 with Professor David N. Harpp and then spent two postdoctoral years at Imperial College in London, England, with Professor Sir Derek H. R. Barton. Upon his return to Canada in 1976, he joined the Division of Biological Sciences at the National Research Council of Canada in Ottawa, where he worked in the laboratory of Dr. O. E. Edwards. In 1978 he moved to the University of Calgary and was promoted to Full Professor in 1987. Apart from a sabbatical leave with Professor Carl Djerassi at Stanford University in 1985, he has remained at the University of Calgary. He was elected a Fellow of the Chemical Institute of Canada in 1990, was the 2006 recipient of the Faculty of Science Research Excellence Award, and in 2008 received the Alfred Bader Award from the Canadian Society for Chemistry. When not on campus, he enjoys mountaineering and ice climbing in the Canadian Rockies.

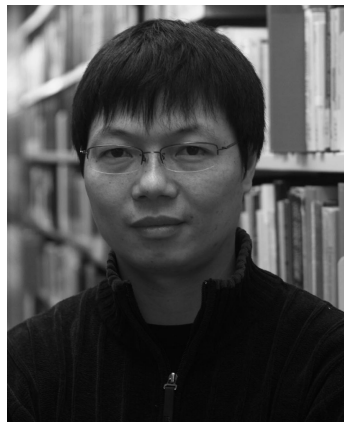
Kristen Clary was born in Kamloops, BC, Canada, in 1984. She obtained her B.Sc. Degree from the University of Calgary in 2006. She is currently a Ph.D. candidate under the direction of Professor Tom Back. Her research focuses on the vinylogous aza-Morita−Baylis−Hillman reaction and its application to the total synthesis of natural products.

2. Diels−Alder Cycloadditions

2.1. Unsaturated Sulfones as Dienophiles

2.1.1. Early Studies

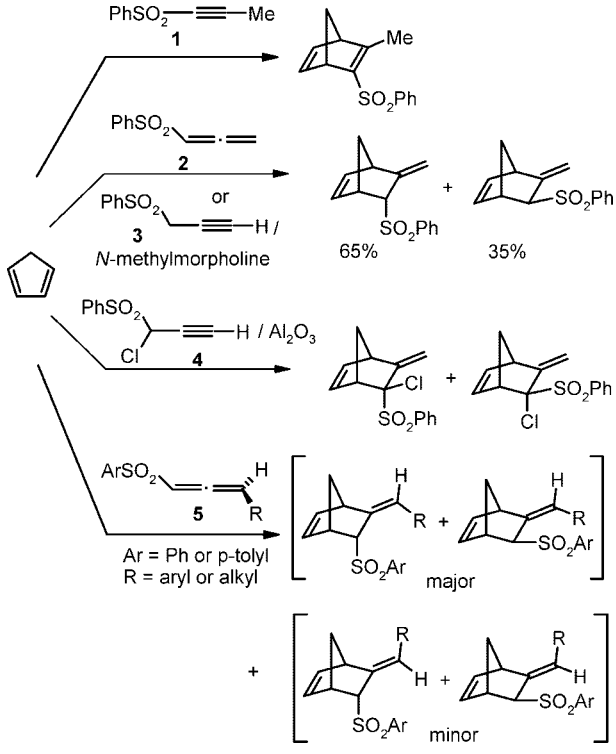
Numerous Diels−Alder reactions have been reported that successfully exploit the activating effect of the sulfone group



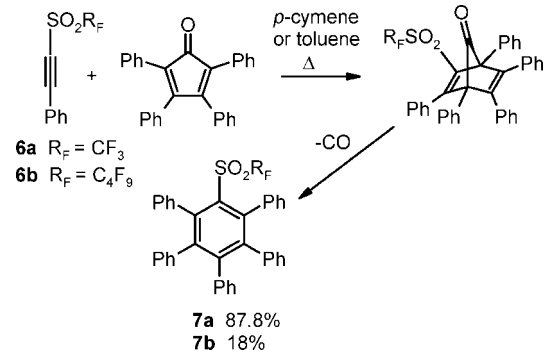
Detian Gao received his B.Eng. degree from Shenyang Pharmaceutical University (P. R. China) in 1997, followed by several years as a process chemist at The United Laboratories in China. He received his M.Sc. degree in Organic Chemistry from the University of Calgary in 2008 under the guidance of Dr. Tom Back. He is currently pursuing his Ph.D. degree in the same group. His research focuses on the application of unsaturated sulfones to the development of new methodologies for the synthesis of nitrogen heterocycles and their applications in the synthesis of natural compounds.

upon the reactivity of dienophiles in cycloadditions with normal electron demand. Several early reports from, or prior to, 1980 adumbrated synthetic opportunities that were later explored in greater detail by others. Thus, Veniard et al.[28] demonstrated that acetylenic sulfone **1**, as well as its allenic isomer **2**, reacted with cyclopentadiene to afford the corresponding [4 + 2] cycloadducts (Scheme 1). The sulfone-activated proximal double bond of allene **2** served as the dienophile and produced a mixture of *exo* and *endo* isomers, with the latter predominant. Furthermore, the propargyl sulfone **3**, in which the triple bond is not activated by the sulfone moiety, was smoothly isomerized to **2** *in situ* in the presence of *N*-methylmorpholine, resulting in the same mixture of *exo* and *endo* products. Thus, all three isomeric

Scheme 1



Scheme 2



sulfones can be employed as starting materials in Diels−Alder cycloadditions. In similar studies, Bordwell and Mecca[29] demonstrated that the chloropropargyl sulfone **4** isomerized in the presence of alumina to the corresponding allene, which was captured in a cycloaddition with cyclopentadiene, again affording a mixture of *exo* and *endo* isomers. Barbarella et al.[30] subsequently investigated the similar reactions of optically active 3-substituted allenic sulfones **5**. The products retained the enantiomeric excesses (ee) of their precursors and again exhibited *endo*-selectivity, while *exo*-selectivity was observed with 1-substituted derivatives (Scheme 1).

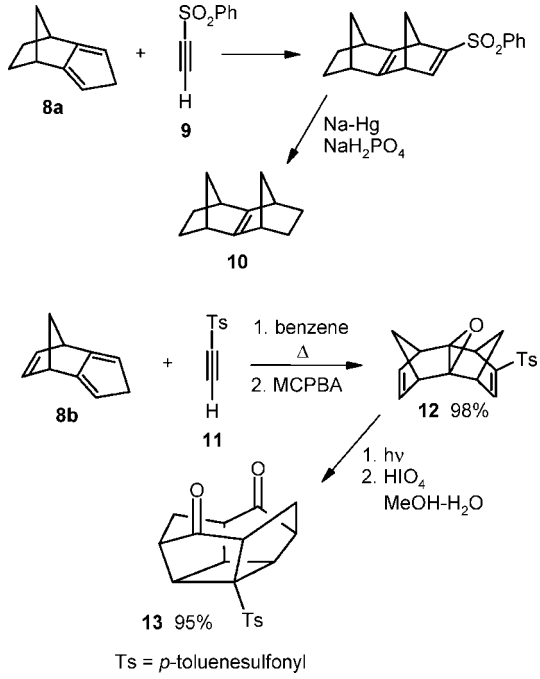
Pioneering work by Glass and Smith[31] and later by Hanack et al.[32] demonstrated the high Diels−Alder reactivity of perfluoroalkyl acetylenic sulfones. The rate constants for the reactions of the trifluoromethyl derivative **6a** with dienes were greater than for acetylenes activated by carbonyl or nitrile groups.[31] Both **6a**[31] and **6b**[32a] underwent cycloaddition with tetraphenylcyclopentadienone, followed by cheletropic extrusion of CO, to afford the corresponding arenes **7** (Scheme 2). In other work, 1-phenyl-3-(trifluoromethanesulfonyl)allene was reported to react with cyclopentadiene under mild conditions to afford the corresponding [4 + 2] cycloadduct, albeit in only 35% yield.[33]

As part of an investigation of the cycloadditions of fused ring cyclopentadienes such as **8a**, Paquette, Gleiter, and their co-workers[34] rationalized the high *endo*-selectivity of the reaction of **8a** with **9** (Scheme 3) on the basis of stereoelectronic effects (orbital tilting), which outweighed steric effects, as supported by molecular orbital calculations. Reductive desulfonylation with sodium amalgam then afforded the hydrocarbon **10**. Subsequently, the *endo* selectivity of the process was exploited by the Paquette group[35] in the preparation of **13**, a key intermediate for the synthesis of 4-peristylane, by intramolecular [2 + 2] cycloaddition of the epoxide **12** and periodate cleavage. The epoxide was in turn obtained from **8b** and acetylenic sulfone **11**, followed by peracid oxidation.

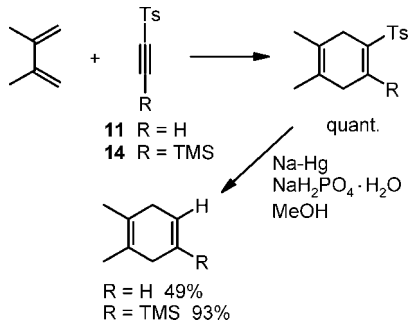
Davis and Whitham[36] demonstrated that the β-unsubstituted derivative **11**, like **9**, is a particularly effective dienophile. The cycloadducts obtained with **11** and 2,3-dimethyl-1,3-butadiene or other dienes were again readily desulfonylated with sodium amalgam, thus making **11** the synthetic equivalent of acetylene, which is a much poorer dienophile. Similarly, trimethylsilylacetylene displays low reactivity in Diels−Alder reactions, while the corresponding sulfone **14** reacted smoothly with several dienes (Scheme 4).

These early examples illustrate some of the key features and possibilities associated with the use of unsaturated sulfones as dienophiles. The sections 2.1.2−2.3.3 provide a review of more recent advances.

Scheme 3



Scheme 4

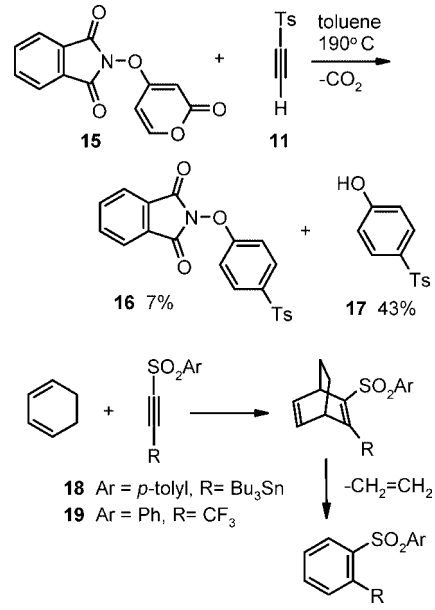


2.1.2. Aromatization of Cycloaddition Products of Acetylenic Sulfones

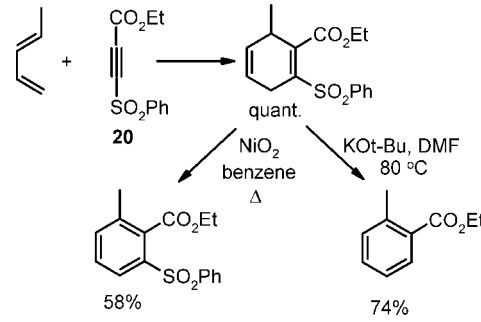
The tandem cycloaddition−cheletropic cycloreversion sequence shown in Scheme 2 has also been employed with other acetylenic sulfones,[37] while the similar cycloaddition of pyrones **15** with **11**,[38] coupled with subsequent extrusion of carbon dioxide, provided the corresponding aromatic products **16** and **17**. The Diels−Alder reactions of stannylacetylene **18**[39] and the trifluoromethyl derivative **19**[40] with 1,3-cyclohexadiene were followed by [4 + 2] cycloreversion with loss of ethylene to afford the corresponding sulfonylarenes (Scheme 5).

In another approach, Shen and Schultz[41] aromatized the cycloadduct obtained from 1,3-pentadiene and acetylenic sulfone **20** by either dehydrogenation with NiO_2 or elimination of benzenesulfinic acid (Scheme 6). It is noteworthy that **20** displayed higher reactivity than dimethyl acetylenedicarboxylate, thus demonstrating the stronger activating effect of the sulfonyl group compared with that of an ester substituent. However, the high regioselectivity of this reaction appears to be controlled by the ester group of **20**. These authors also reported that the cycloadduct from the reaction of an *N*-aminopyrrole with **20** was aromatized by the extrusion of the corresponding *N*-aminonitrene (Scheme 7). Oxidation of other cycloadducts with DDQ has been used by several groups[42−46] to effect aromatization, as in the example in Scheme 8,[43c] while a similar oxidation with potassium permanganate[46] was reported, and refluxing in the presence of air sufficed in a similar example.[47] The cycloadduct from selenoacetylene **21** and 1-acetoxy-1,3-butadiene eliminated acetic acid spontaneously (Scheme 9),[48] while elimination of fluoride ion from the fluoroalkyl substituents of cycloadducts of **22**,[44,49] as well as competing aerobic oxidation, also resulted in aromatization. Cycloadducts derived from Danishefsky's diene and the silylacetylene **23**[50] afforded arenes upon hydrolysis of the enol silyl ether moiety and elimination of methanol (Scheme 9).

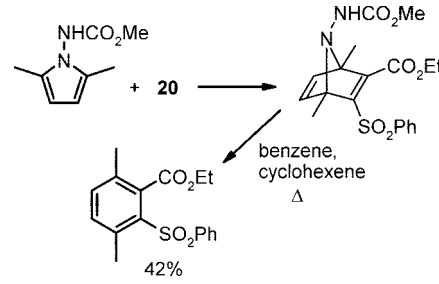
Scheme 5



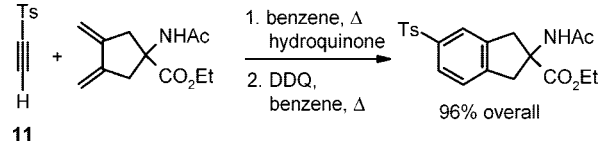
Scheme 6



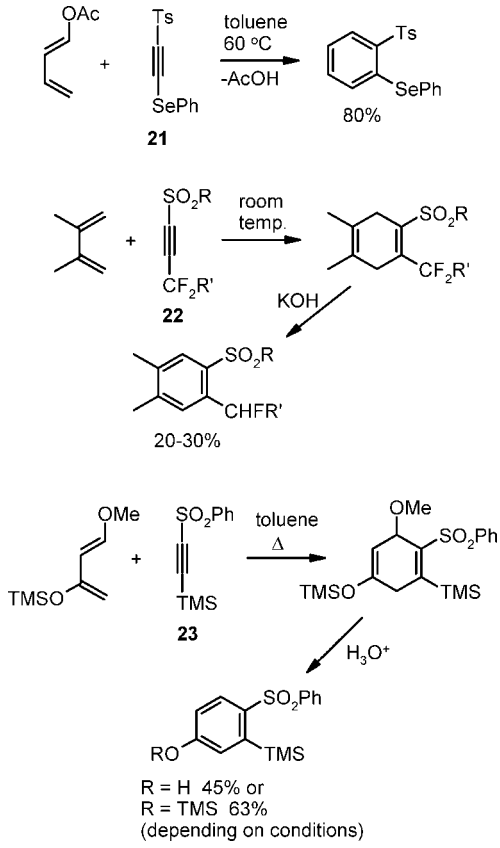
Scheme 7



Scheme 8



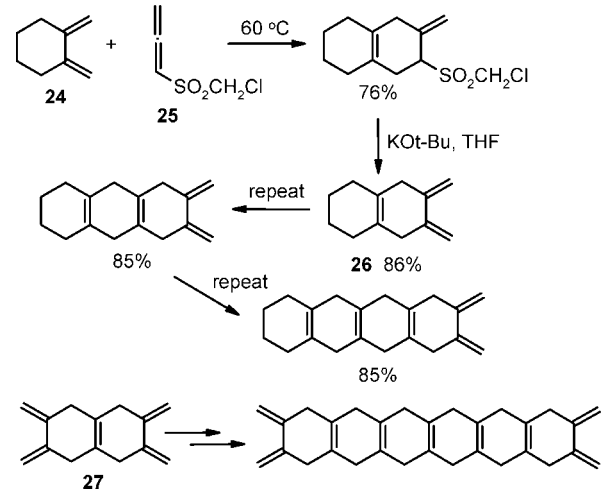
Scheme 9



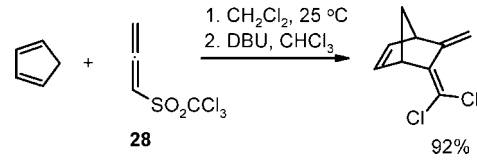
2.1.3. Iterative Diels−Alder and Ramberg−Backlund Reactions of Chloroalkylsulfonyl Allenes

The enhanced reactivity of perfluoroalkylsulfonyl acetylenes such as **6a** and **6b** in [4 + 2] cycloadditions was noted previously. Not surprisingly, chloroalkylsulfonyl allenes also display excellent reactivity as dienophiles. A remarkable tandem Diels−Alder cycloaddition−Ramberg−Backlund extrusion reaction based on the chloromethylsulfonyl allene **25** was discovered by Block and co-workers.[51] The initial cycloaddition of an exocyclic diene such as **24** was followed by base-mediated extrusion of sulfur dioxide to afford the bicyclic product **26**, containing a new exocyclic diene moiety. The process can be repeated several times, with the installation of an additional ring at each stage. An example is shown in Scheme 10. The application of this process to the synthesis of open-chain [*n*]beltenes from **27** by simultaneously elaborating both of its exocyclic diene units was reported by Graham and Paquette.[52] The reactions of **25** and its 3-substituted derivatives with various other dienes have also been investigated.[51a] The even more highly activated trichloromethylsulfonyl allene **28** was investigated by Braverman et al.[53] in Ramberg−Backlund reactions and in other applications. The authors found that it reacted smoothly with cyclopentadiene in dichloromethane at room temperature to afford a mixture of *endo* (90%) and *exo* (10%) cycloadducts.[53a] Optically active substituted derivatives of **28** produced optically active cycloadducts,[53a] while cycloadducts of **28** and its 3-phenyl analog underwent Ramberg−Backlund reactions; an example is shown in Scheme 11.[53b] The [4 + 2] cycloaddition and Ramberg−Backlund protocol has also been reported with several other unsaturated chloromethyl sulfones.[51c]

Scheme 10



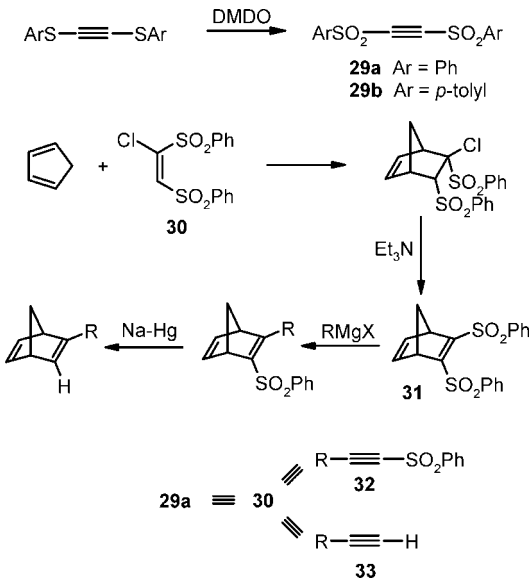
Scheme 11



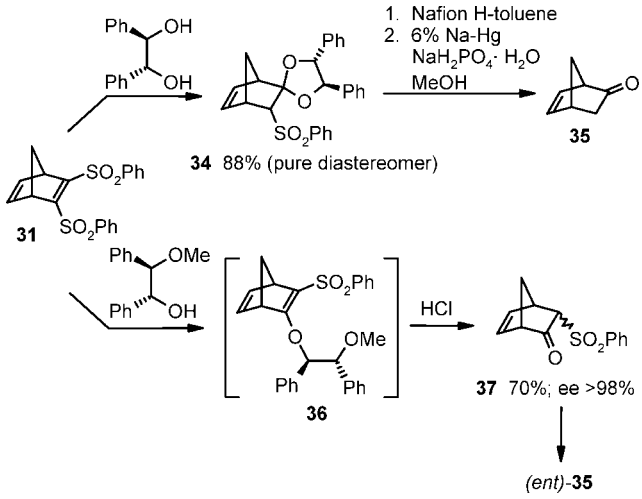
2.1.4. Diels−Alder Cycloadditions of Bis(sulfonyl)acetylenes and Their Equivalents

Doubly activated acetylenes bearing sulfonyl groups at both termini offer potential benefits from their increased reactivity as dienophiles and in other applications. However, bis(arylsulfonyl)acetylenes have limited scope for such purposes because of their instability. De Lucchi and coworkers[54] generated the phenyl and *p*-tolyl derivatives **29a** and **29b** *in situ* by the oxidation of the corresponding bis(sulfides) with dimethyldioxirane (DMDO) and trapping of the products with appropriate dienes such as cyclopentadiene, 1,3-cyclohexadiene, and anthracene in yields of 65−75%. However, a more satisfactory approach was based on the use of **30** as a surrogate for **29a** by subsequent elimination of HCl from the initial cycloadducts to afford **31**.[55] Moreover, cross-coupling of the latter with Grignard reagents rendered **30** the synthetic equivalent not only of **29a** but also of 2-substituted acetylenic sulfones **32** and of acetylenes **33** through subsequent desulfonylation (Scheme 12). While (*Z*)-**30** proved less reactive than the *E*-isomer, its corresponding cycloadducts were more easily dehydrochlorinated. Similarly, both *E* and *Z* isomers of 1,2-bis(phenylsulfonyl)ethene are isolable but function as more reactive dienophiles than the monosubstituted acetylenic sulfone **9**. They thus behave as synthetic equivalents of acetylene when reductive elimination of the two sulfone moieties from their cycloadducts is effected with sodium amalgam or as equivalents of acetylenic sulfone **9** through base-catalyzed elimination of a single sulfone group.[56] The enantioselective transformation of **31** and of similar products from other cyclic dienes to chiral ketones such as **35** was achieved by conjugate addition−elimination of chiral diols, followed by hydrolysis and reductive desulfonylation of the corresponding cyclic ketals **34**,[57] as in the example shown in Scheme 13. An interesting switch in enantioselectivity was observed when the monomethyl ether was employed instead of the chiral diol, resulting in the diastereoselective formation of the corresponding enol ether **36**, and ultimately (*ent*)-**35**.[57b]

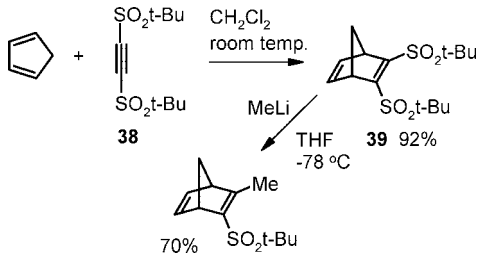
Scheme 12



Scheme 13

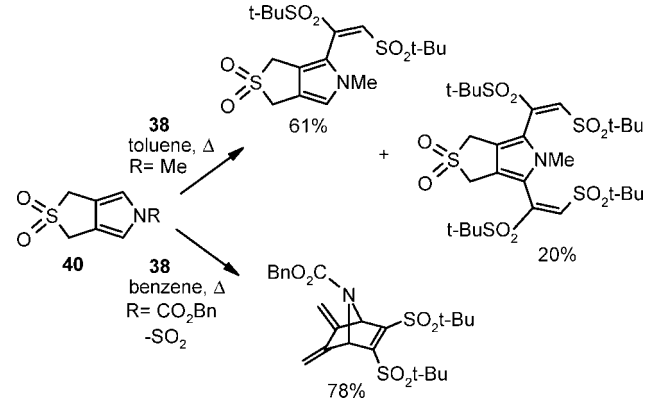


Scheme 14

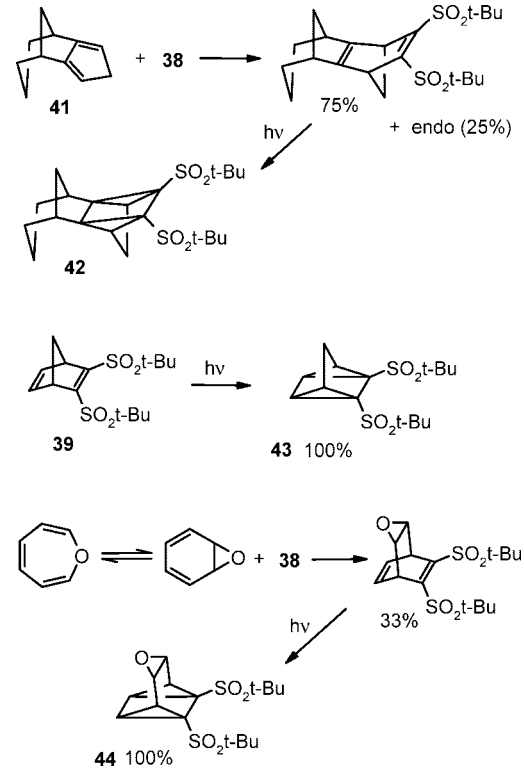


In contrast to the labile bis(arylsulfonyl)ethynes **29**, Pericás et al. demonstrated that the bis(*t*-butylsulfonyl) derivative **38** is stable and isolable. It underwent Diels−Alder cycloadditions with a variety of dienes, as well as with furans and isobenzofurans, in yields of 53−92%[58] (see also section 2.1.8) but reacted with *N*-methylpyrrole and 3-methylthiophene by conjugate addition. Cross-coupling of the cycloadduct **39** with methyllithium was reported[58] (Scheme 14), while similar cycloadducts reacted with Grignard reagents in the presence of catalytic $Pd(acac)_2$ by either cross-coupling or reductive desulfonylation.[59] A subsequent study of pyrrole derivatives **40** (see also section 2.1.7) by Takayama et al.[60] revealed that *N*-alkyl derivatives reacted by conjugate addition, while their *N*-acyl counterparts afforded the usual cycloadducts, followed by cheletropic extrusion of sulfur dioxide[60] (Scheme 15).

Scheme 15



Scheme 16

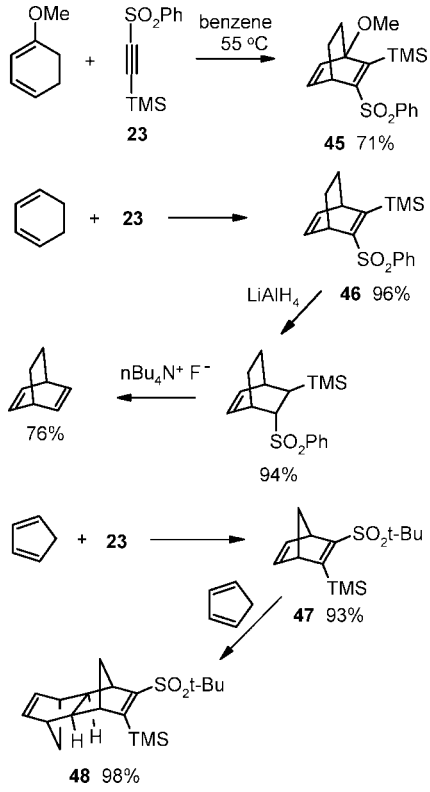


Bis(sulfonyl)acetylene **38** was also employed in further studies of the facial selectivity of diene **8a** and its homologues.[61] Thus, **8a** again showed preferential *endo* cyclization (as in Scheme 3), while the homologue **41** reacted *exo*-selectively (Scheme 16). Paquette and Hickey[61,62] and, independently, Gleiter and Ohlbach[63] reported the further conversion of bicyclic [4 + 2] cycloadducts of **38** to the corresponding quadricyclanes, such as **42**,[61,62] **43**,[63] and **44**[63b] by photocyclization. These examples are shown in Scheme 16. Double Diels−Alder cycloadditions of **38** to **27**[52] have also been employed in the synthesis of open chain [*n*]beltenes, as in the case of allene **25** (see Scheme 10).

2.1.5. Diels−Alder Cycloadditions of Acetylenic Sulfones Containing Heteroatom Substituents

A variety of other acetylenic sulfones containing heteroatoms in the 2-position serve as dienophiles in [4 + 2]

Scheme 17

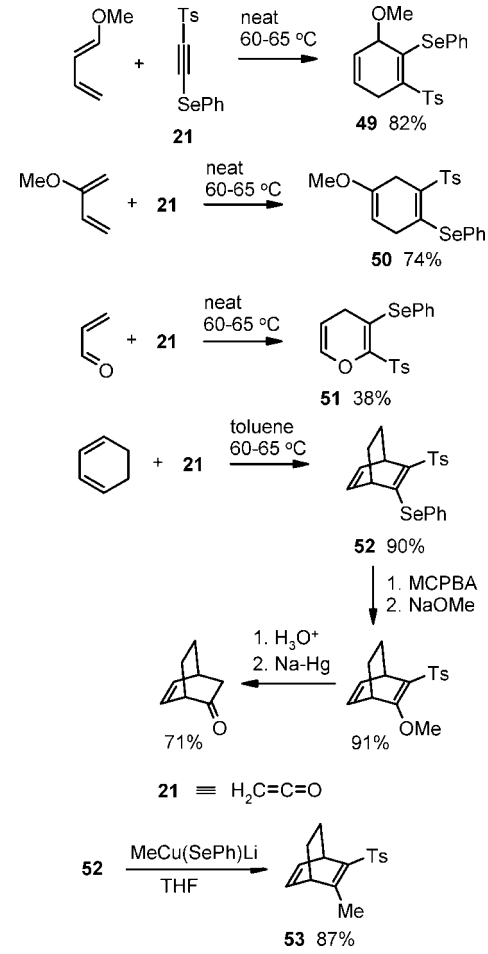


cycloadditions. In addition to the earlier studies of silylated acetylenic sulfones **14**[36] and **23**[50] shown in Schemes 4 and 9, respectively, Williams and co-workers[64] reported several additional cycloaddition studies of **23**. In contrast to the example in Scheme 9, the silyl group of **23** can sometimes overrule the sulfone moiety in controlling the regiochemistry, as in the formation of **45** in Scheme 17.[64b] Furthermore, reduction of cycloadducts such as **46** with lithium aluminum hydride, followed by elimination with fluoride ion, afforded the corresponding dienes,[64] thereby again enabling **23** to function as the synthetic equivalent of acetylene. Acetylenic sulfone **23** also underwent sequential cycloadditions with cyclopentadiene, in which the unactivated but less hindered double bond of the initial product **47** reacted preferentially in a second Diels−Alder step to produce **48** as the sole regio- and diastereoisomer.[64a] The furan analog of **40** reacted with silylacetylene **14** via [4 + 2] cycloaddition and extrusion of sulfur dioxide,[65] as in the case of the *N*-acylpyrrole in Scheme 15.

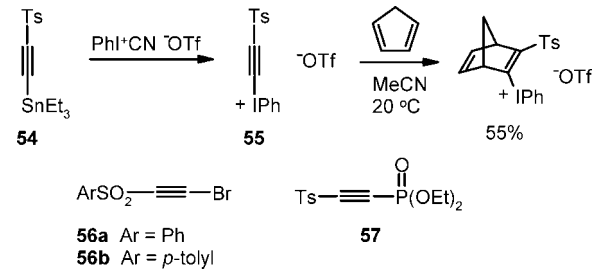
In addition to silyl groups, other heteroatoms have also been incorporated into the β-position of acetylenic sulfones. The β-phenylseleno derivative **21**,[48,66] introduced in Scheme 9, reacted with a series of other cyclic and acyclic dienes, affording [4 + 2] cycloadducts such as **49** and **50**, with the opposite regiochemistry to that expected with simple acetylenic sulfones. It also underwent a hetero-Diels−Alder reaction with acrolein to afford **51** and served as the synthetic equivalent of ketene upon oxidation, hydrolysis, and desulfonylation of cycloadducts like **52**. Cross-coupling of the selenide moiety of **52** with a cuprate to produce **53** was also observed (Scheme 18).

An example of the cycloaddition of stannylacetylene **18**[39] was shown in Scheme 5. The related triethylstannyl derivative **54** was converted into the iodonium species **55**, which also proved to be an effective dienophile (Scheme 19).[67] The alkynyl bromides **56**[68] and phosphonate **57**[69] have also been employed in Diels−Alder reactions with various dienes.

Scheme 18



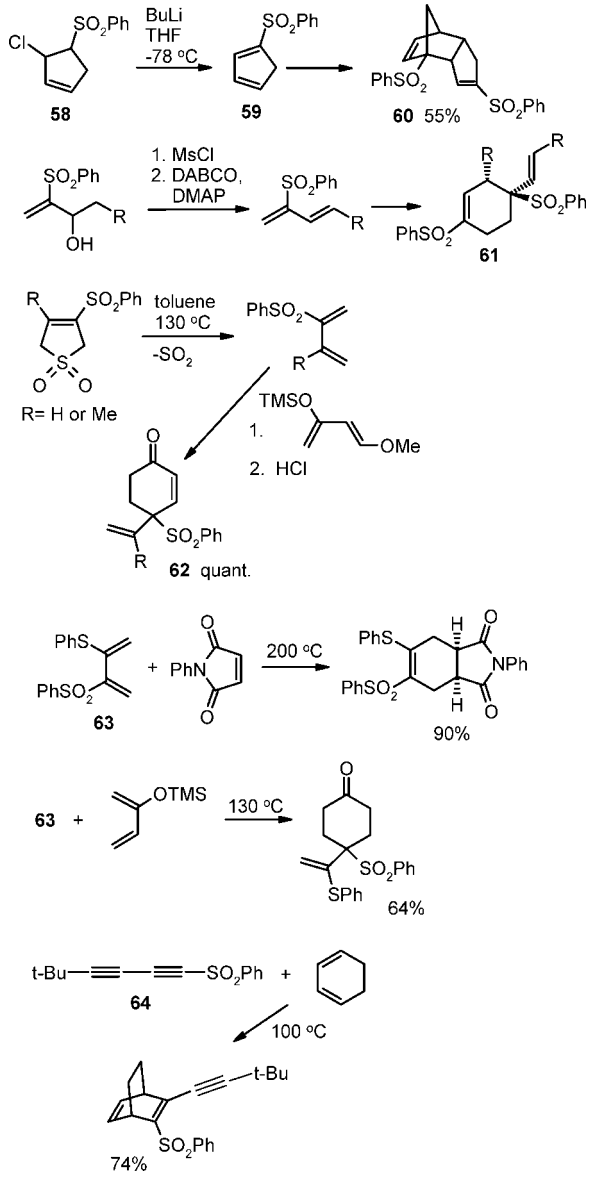
Scheme 19



2.1.6. Diels−Alder Reactions of Dienyl Sulfones as Dienophiles

The majority of [4 + 2] cycloadditions of acetylenic or allenic sulfones involve their reactions as dienophiles with various comparatively electron-rich dienes by normal electron demand. In contrast, conjugated dienyl sulfones can react with both electron-rich and electron-poor dienophiles (see also section 2.2) or assume the role of dienophiles themselves by contributing one double bond as the 2π-electron component in [4 + 2] cycloadditions with other dienes. Since they tend to be unstable, dienyl sulfones are often formed *in situ*. For example, Hartke et al.[70] and Bridges and Fischer[71] noted that cyclopentadienyl sulfones such as **59**, generated by elimination of HCl from **58**, dimerized spontaneously to afford the *endo* Diels−Alder product **60**. Evidently, one

Scheme 20



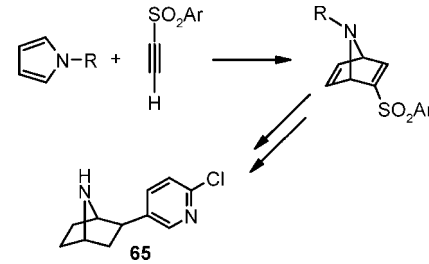
molecule of **59** functioned as the diene component, while the distal double bond of the other acted as the dienophile. Unstable bis(sulfonyl)cyclopentadienes also formed dimeric products.[70c] A similar dimerization of a sulfonyl-substituted quinodimethane was observed by Lenihan and Shechter,[72] although such species also reacted as more conventional dienes with other dienophiles (e.g., see Scheme 36). On the other hand, dimerization of a series of acyclic 2-sulfonyl-1,3-dienes involved the proximal double bond of the dienophile component, again with *endo*-selectivity, to provide bis(sulfones) **61**.[73] Dienyl sulfones behaving as dienophiles have also been trapped with Danishefsky's diene[74] or other dienes,[74,75] as in the case of cycloadduct **62**,[74] while the phenylthio derivative **63** functioned as the diene when reacting with electron-deficient dienophiles such as *N*-phenylmaleimide but acted as the dienophile with electron-rich dienes such as 2-trimethylsilyloxy-1,3-butadiene.[76] Several diynyl sulfones such as **64** afforded the corresponding cycloadducts with several typical dienes.[77] Examples are provided in Scheme 20.

2.1.7. Diels–Alder Reactions of Unsaturated Sulfones with Pyrroles

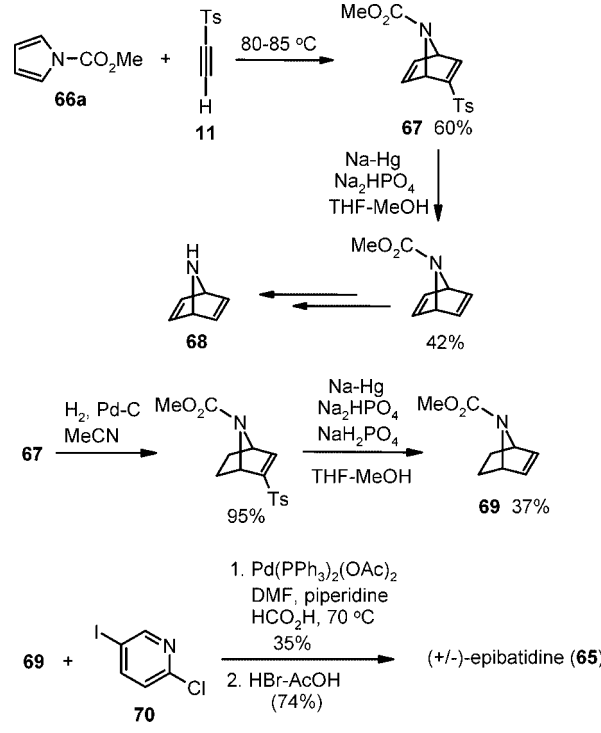
The cycloadditions of pyrroles with acetylenic and allenic sulfones have been the subject of intense investigation, largely because the resulting functionalized 7-azanorbornadienes comprise useful key intermediates for the synthesis of epibatidine (**65**, Scheme 21), a dendrobatid alkaloid with potent analgesic activity that was first isolated in minute amounts from the poison frog *Epipedobates tricolor* by Daly et al.[78] The biological activity of epibatidine and its analogs stems from its interaction with nicotinic acetylcholine receptors, and these compounds have therefore been of significant interest as lead compounds for a novel class of nonopioid analgesics.

We may recall from Scheme 15 that this approach requires an *N*-acylpyrrole in order to avoid competing conjugate additions.[60] The methyl and *t*-butyl (Boc) carbamates **66a** and **66b**, respectively, have proven particularly effective for this purpose, while (*p*-toluenesulfonyl)ethyne (**11**) has been the most frequently utilized dienophile. In earlier work, Vogel et al.[79] reported the cycloaddition, desulfonylation, and deprotection of pyrrole **66a** to afford 7-azanorbornadiene (**68**) (Scheme 22), which was the subject of photoelectron spectroscopy and MO computations.[80] The diene **67** could also be converted to **69** by selective hydrogenation and reductive desulfonylation.[80] The yield of **67** from the

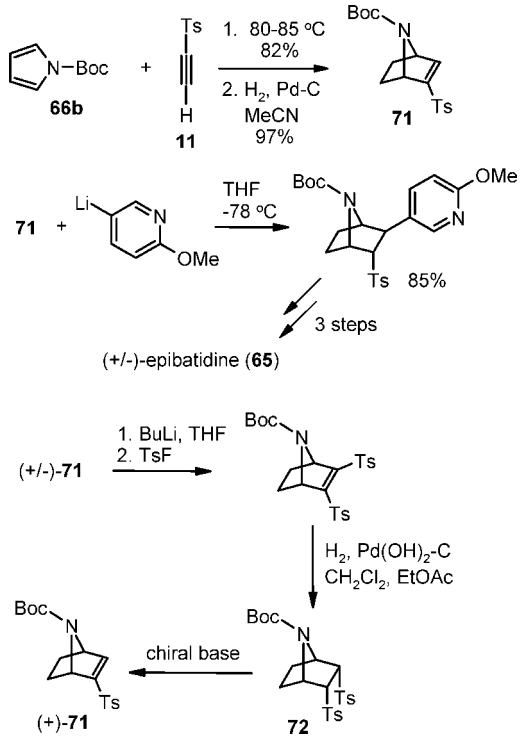
Scheme 21



Scheme 22



Scheme 23

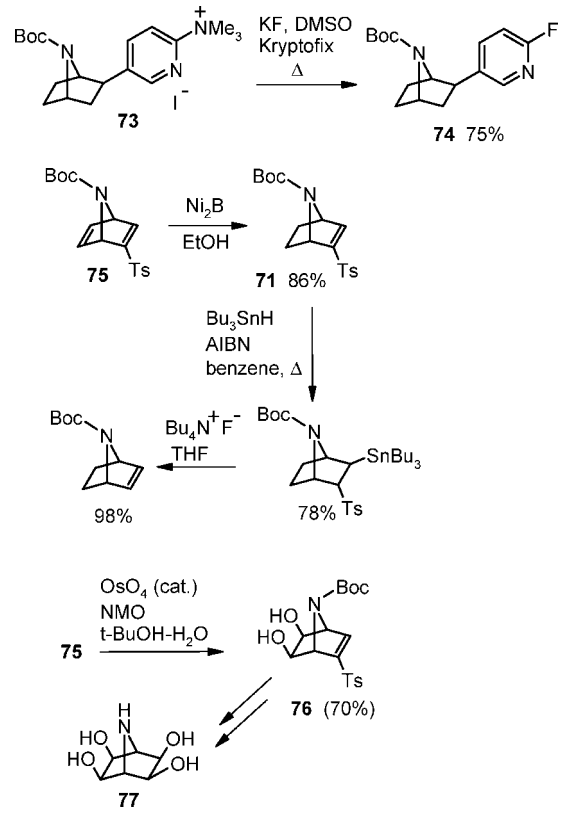


cycloaddition step was improved to 81% when the reaction was performed in dichloromethane at a pressure of 12 kbar.[81] The further conversion of azanorbornene **69** to epibatidine was later reported by Clayton and Regan,[82] who used a modified Heck reaction to install the pyridyl moiety by means of the iodide **70** (Scheme 22).

Several other groups employed the Boc pyrrole **66b** instead of **66a**, chiefly because of the milder conditions required for the cleavage of the Boc group. Thus, Simpkins and coworkers[83] obtained azanorbornene **71** by a similar cycloaddition and hydrogenation protocol, followed by the introduction of the pyridyl moiety by conjugate addition. This afforded epibatidine (**65**) in 24% overall yield in six steps (Scheme 23). These authors also developed an enantioselective synthesis of **71** by deprotonation of the racemic material[84] and tosylation of the resulting β-sulfonyl anion, followed by hydrogenation. Desymmetrization of the corresponding bis(sulfone) **72** was then achieved by elimination of one *p*-toluenesulfonyl group with various chiral bases, providing (+)-**71** with up to 60% ee.[84b]

Carroll et al.[85] prepared a series of epibatidine analogs containing other pyridine substituents in place of the chlorine atom in order to study their binding to the nicotinic acetylcholine receptor. An efficient synthesis of the fluoro derivative **74** was of special interest if it could be adapted to the corresponding ^{18}F-labeled alkaloid for positron emission tomography. Approaches based on a similar cycloaddition and Heck reaction protocol to that of Clayton and Regan[82] shown in Scheme 22 were explored. The late-stage introduction of the fluoro substituent via the trimethylammonium derivative **73** was also reported.[85a] Other innovations by Carroll et al.[85b,86] included the use of nickel boride in the hydrogenation of the initial cycloadduct **75** and a tin hydride-mediated desulfonylation procedure (Scheme 24). The ^{18}F-labeled form of **74** was prepared by Dolle et al. by nucleophilic aromatic substitution of the corresponding halo- and nitropyridine derivatives with labeled fluoride ion.[87]

Scheme 24

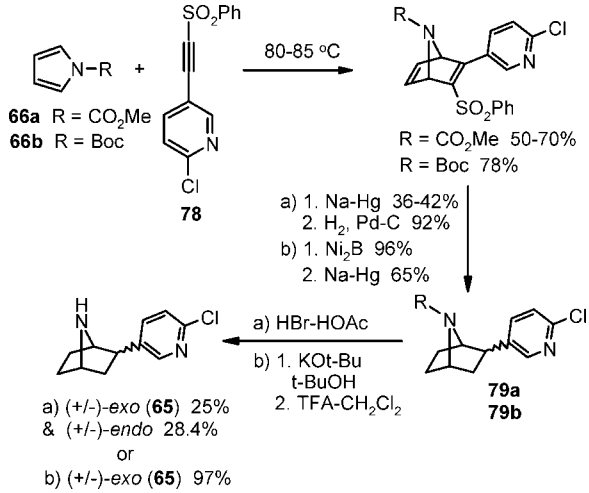


Osmium tetroxide-catalyzed oxidation of azanorbornadiene **75** afforded the *exo-cis*-diol **76**, followed by ketalization, desulfonylation, a second *exo-cis*-dihydroxylation, and deprotection to provide the tetrahydroxyazanorbornane **77**.[88] The cycloadditions of **66a** and **66b** with acetylenic sulfone **11** to afford **67** and its Boc analog, respectively, have also been exploited in a synthetic route to the conduritols and conduramines.[89]

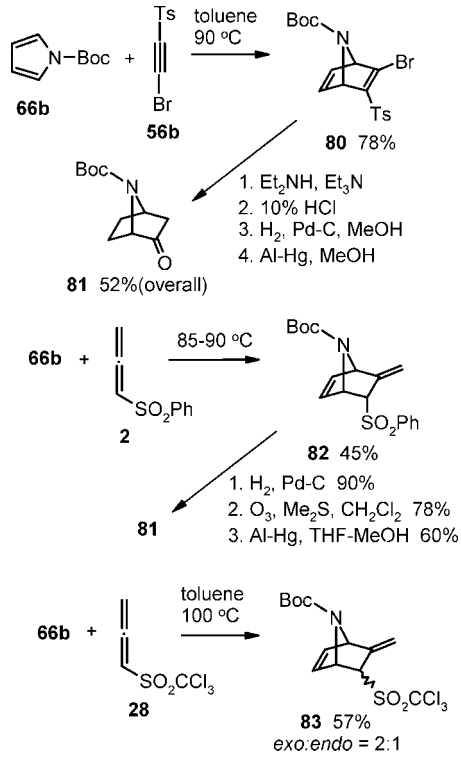
Several additional approaches to epibatidine were based on other unsaturated sulfones instead of **11**. Huang and Shen[90] and Carroll et al.[91] reported the preparation and cycloaddition of the acetylenic sulfone **78** with pyrroles **66a** and **66b**, respectively, thus incorporating the pyridyl substituent at an earlier stage. Hydrogenation and desulfonylation afforded **79a** and **79b** as mixtures of epimers, which afforded the desired *exo* isomer upon base-catalyzed equilibration. Deprotection provided (±)-epibatidine (**65**) (Scheme 25).

Trudell et al. reported several approaches to epibatidine analogs. The Diels−Alder reaction of 2-bromoacetylene **56b** with **66b** produced the expected cycloadduct **80**, which was in turn converted into the ketone **81**.[68] Alternatively, the cycloaddition of the allenic sulfone **2** with **66b** afforded **82**, which was also converted into **81**.[92] Since ketone **81** had been previously employed as a key intermediate for the preparation of epibatidine, these transformations comprised a formal synthesis of the latter compound. In an independent report, allenic sulfone **28** also reacted with **66b** to afford the corresponding cycloadduct as a mixture of *exo* and *endo* isomers **83** (Scheme 26).[93] Several substituted derivatives of pyrrole **66a** underwent cycloaddition with acetylenic sulfone **11** to afford 7-azanorbornadiene derivatives as potential intermediates for epibatidine and conduramine analogs.[94] In other work, the *N*-Boc-isoindole **84** underwent cycloaddition with acetylenic sulfone **11** to afford the benzoazanorbornene **85** (Scheme 27).[75] The furan analog of

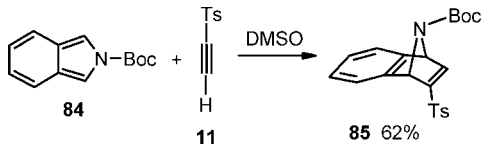
Scheme 25



Scheme 26



Scheme 27

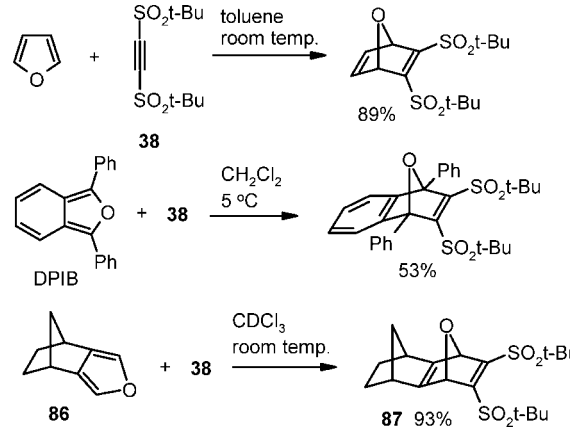


84 produced a lower yield of 30% of the corresponding bicyclic product.[75]

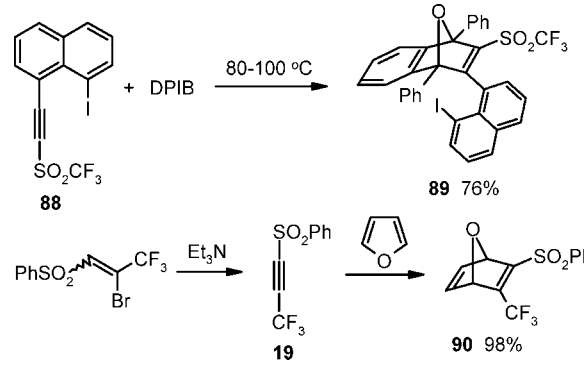
2.1.8. Diels−Alder Reactions of Unsaturated Sulfones with Furans and Isobenzofurans

A variety of acetylenic and allenic sulfones undergo [4 + 2] cycloadditions with furans and isobenzofurans. In most cases, reactions with furans have been performed with doubly activated or fluoroalkylsulfonyl dienophiles. Thus, the bis(sulfone) **38** reacted with both furan and diphenylisobenzofuran (DPIB) at room temperature,[58] as well as with **86**, the furan analog of **8a**[61] (Scheme 28). The latter reaction afforded the cycloadduct **87** in high yield as a single stereoisomer.

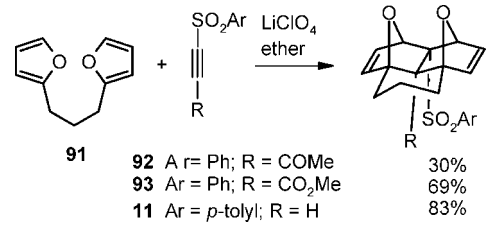
Scheme 28



Scheme 29



Scheme 30

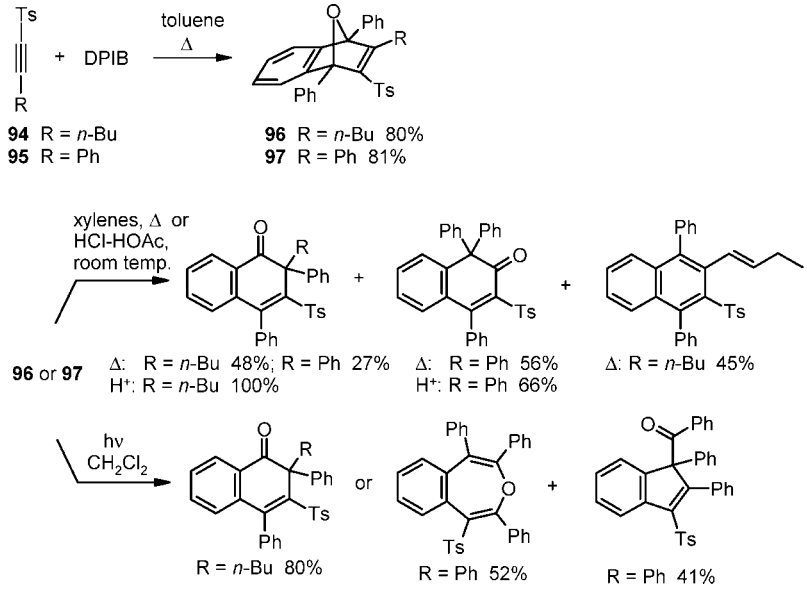


Phenyl trifluoromethylsulfonyl and perfluorobutylsulfonyl acetylenes **6a**[31] and **6b**[32a,b] reacted with DPIB to afford the corresponding cycloadducts in yields of 86% and 38%, respectively, while the acetylenic sulfone **88** reacted similarly, providing **89**[95] as shown in Scheme 29. The unstable trifluoromethyl benzenesulfonyl derivative **19** was generated *in situ* and reacted with furan, as well as with other dienes, to produce **90**[40] (Scheme 29).

An interesting "tandem pincer" Diels−Alder reaction was discovered by Lautens and Fillion,[96] in which several acetylenic sulfones reacted with the bis(furan) **91** to afford double cycloaddition products (Scheme 30) with the indicated stereochemistry. Moreover, 2-methylfuran produced only the normal 1:1 cycloadduct with the acetylene **93**. On the other hand, Plumet et al.[97] found that furan and 2-methylfuran reacted with (phenylsulfonyl)ethyne (**9**) to produce mixtures of 1:1 and 2:1 cycloadducts, whose ratios were dependent upon the conditions.

The expected products were obtained from the cycloaddition of DPIB with acetylenic sulfones **94** and **95**.[98] However, these products underwent facile rearrangements

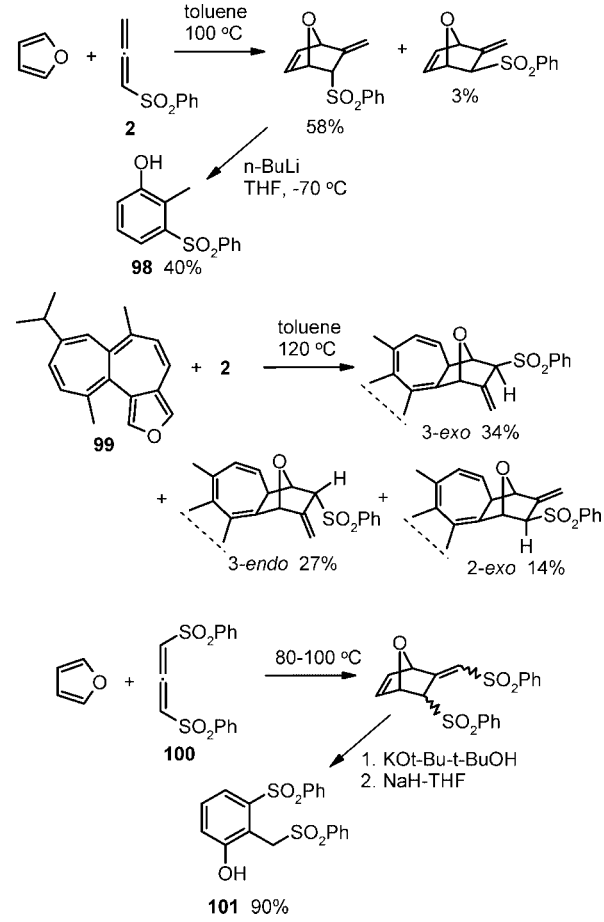
Scheme 31



upon pyrolysis, acid catalysis, or photolysis (Scheme 31). A series of carbocation rearrangements was postulated under the first two conditions, while a sequence of pericyclic reactions was invoked to rationalize the products of the photochemical process.

Allenic sulfone **2** cycloadded to furan via its proximal double bond to afford mainly the *endo* isomer, which underwent base-induced C−O cleavage to the corresponding phenol **98** (Scheme 32).[99] The *t*-butylsulfonyl analog of **2** behaved similarly, affording predominantly the *endo* isomer in a total yield of 73%,[100] while the reaction of the heptalenofuran **99** with **2** generated a complex mixture of regio- and stereoisomers, including P* and M* epimers. The products are potential intermediates for the synthesis of colchicinoids.[101] The bis(phenylsulfonyl)allene **100** produced a mixture of four isomers, which generated the phenol **101** upon treatment with base (Scheme 32).[102] Finally, the phenylseleno- and phosphonyl-substituted acetylenic sulfones **21**[48] and **57**[69] also produced [4 + 2] cycloaddition products with furan. The former product was obtained in 93% yield, while the latter was reported as being unstable.

Scheme 32

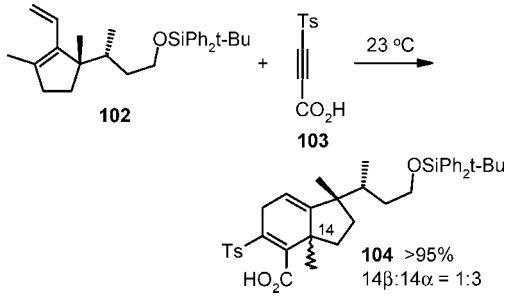


2.1.9. Miscellaneous Cycloadditions

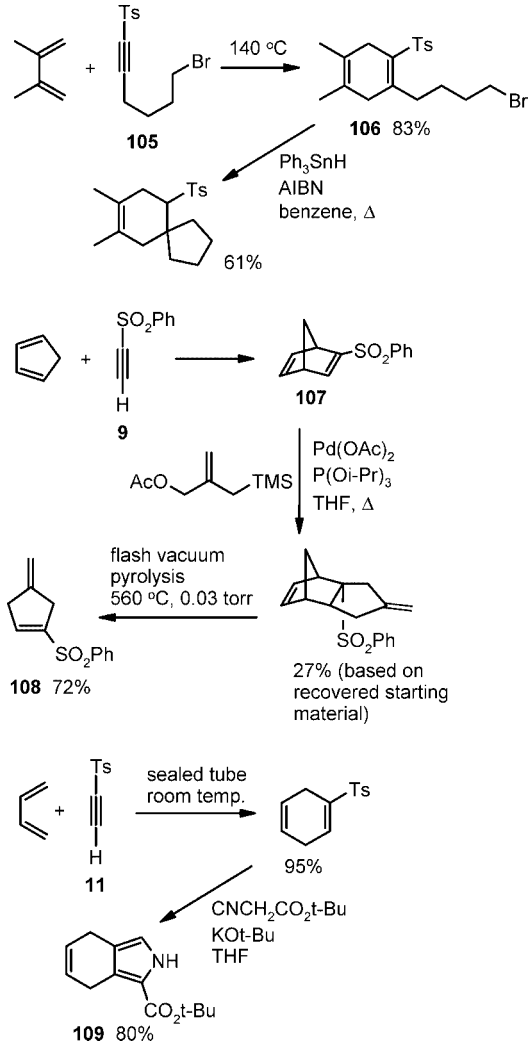
The cycloadditions of (*p*-toluenesulfonyl)ethyne (**11**) with other dienes were used in the preparation of bicyclo[2.2.2]-octadienes and octatrienes, which in turn served as precursors of barrelenes[103] and poly(1,4-phenylene vinylene).[104] Other [4 + 2] reactions of **11** were employed in the synthesis of propellenones,[105] variously substituted[106,107] and fused-ring[108] norbornadienes, 2-azabicyclo[2.2.2]octanones,[109] and naphthoxepines.[110] The doubly activated acetylene **93**, containing an ester as well as a sulfone moiety, was used in the elaboration of vinylporphyrins by Dolphin et al.,[111] while the cycloaddition of diene **102** with 3-(*p*-toluenesulfonyl)-propiolic acid (**103**) afforded **104**, an intermediate in the synthesis of glycinoeclepin A by Corey and Houpis (Scheme 33).[112] Some interesting further transformations of the cycloadducts derived from acetylenic sulfones **105**, **9**, and **11** are shown in Scheme 34. They include the radical cyclization of **106** reported by Clive and co-workers[113] and the palladium-catalyzed trimethylenemethane cycloaddition of **107** by Trost et al.[114] Elaboration of cycloadducts of **11** to the corresponding dihydroisoindole derivatives,[115,116] such as **109**,[116] was achieved by means of a modified Barton−Zard reaction.

Allenic sulfone **2** underwent *endo* selective [4 + 2] cycloadditions with cyclopentadiene[117,118] and fulvene derivatives,[117] as well as with enol silyl ethers.[117] The *t*-butylsulfonyl analog of **2** behaved similarly.[100] The cycloadducts from cyclopentadiene served as precursors of norbornenyl carbanions.[100,118] As expected, the activated proximal double bond of the allene

Scheme 33



Scheme 34

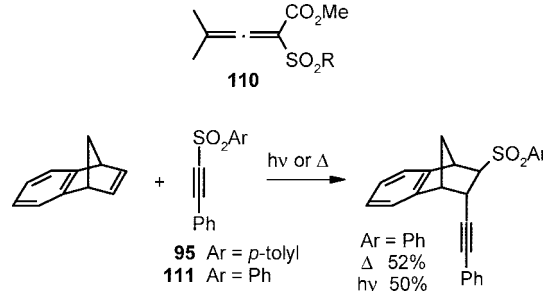


moiety reacted selectively. Captodative allenic sulfones **110** reacted similarly with cyclopentadiene, with or without added Lewis acids.[119] In related work, unusual fragmentations and 1,2-additions of acetylenic sulfones **95** and **111** to alkenes such as benzonorbornadiene were observed under either pyrolytic or photolytic conditions, presumably proceeding via radical mechanisms[120] (Scheme 35). Acetylenic sulfides, sulfoxides, and sulfones produced [4 + 2] cycloadducts with dienes under Co(I)-catalyzed conditions.[46]

2.2. Dienyl Sulfones As the Diene Components in Diels−Alder Reactions

While dienyl sulfones can behave as dienophiles (see section 2.1.6), they are more commonly employed as the

Scheme 35



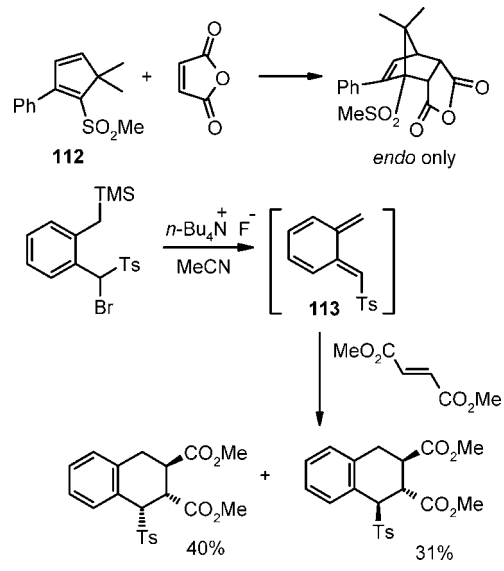
diene components of Diels−Alder cycloadditions. Both 1- and 2-sulfonyl-substituted dienes have been investigated in this context, as well as bis(sulfonyl) derivatives. A noteworthy feature of dienyl sulfones, as noted by Bäckvall et al.,[121] is their ability to display dual electron demand by reacting with both electron-rich and electron-deficient dienophiles.

2.2.1. 1-Sulfonyl Derivatives

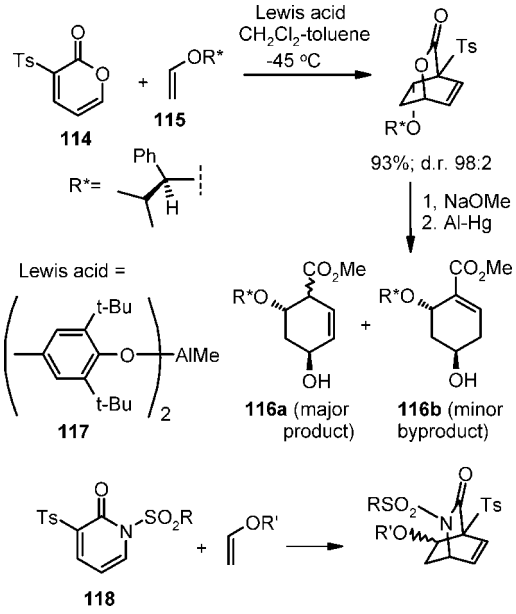
There are relatively few examples of [4 + 2] cycloadditions of conjugated dienes containing sulfonyl substituents at the 1-position, and most of these are cyclic dienes. Thus, cyclopentadienyl sulfone **112** afforded the corresponding *endo* adduct exclusively with maleic anhydride.[122] Phenyl vinyl sulfone behaved similarly, while methyl acrylate produced a mixture of both possible regioisomers. *o*-Quinodimethane **113** was generated *in situ* and trapped with dienophiles such as dimethyl fumarate (Scheme 36).[72]

On the other hand, Posner and co-workers investigated the inverse electron demand cycloadditions of sulfonylpyrones and pyridones with electron-rich enol ethers. Pyrone **114** reacted at room temperature with the (*S*)-enol ether **115** to afford the corresponding cycloadduct as a single diastereomer in 84% yield. Methanolysis, followed by desulfonylation, provided chiefly **116a**, an intermediate for the synthesis of a desired epishikimate derivative[123] and as an A-ring precursor of 1α,25-dihydroxyvitamin D_3,[124] along with a smaller amount of the conjugated isomer **116b**. The presence of the Lewis acid **117** enabled the reaction to

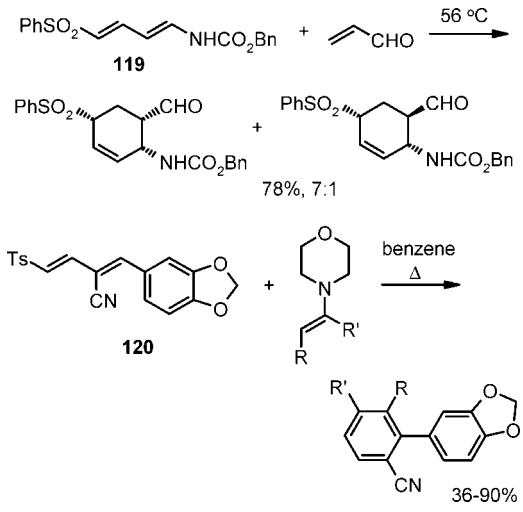
Scheme 36



Scheme 37



Scheme 38

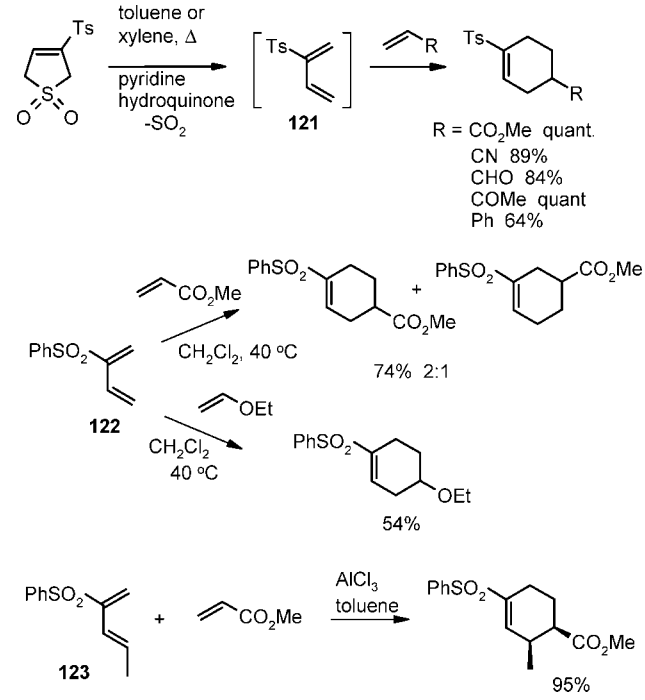


proceed at −45 °C with a yield of 93% and a ratio of 98:2 of diastereomeric *endo* isomers.[124] The related 3-sulfonylpyridones **118** reacted more sluggishly, but yields were improved at high pressure (7 kbar)[125] (Scheme 37), while a 4-sulfonylpyridone was found to react with electron-deficient dienophiles to again produce cycloadducts with the *endo* configuration.[126] A [4 + 2] cycloaddition of the acyclic dienyl sulfone **119** was reported by Overman et al.[127] and is shown in Scheme 38. Regioselectivity was controlled by the carbamate moiety, and the sulfone displayed higher *endo* selectivity than the corresponding sulfide or sulfoxide. Masuyama and co-workers[128] demonstrated that acyclic dienyl sulfone **120** produced aromatic products by formal [4 + 2] cycloaddition with enamines, followed by elimination of the amino and sulfonyl groups. The mechanism of the process is probably not concerted, and the authors referred to it as a Michael-type addition−cyclization reaction.

2.2.2. 2-Sulfonyl Derivatives

Inomata et al.[129] reported that 2-(*p*-toluenesulfonyl)-1,3-butadiene (**121**) can be produced by pyrolysis of the corresponding sulfolene but that it dimerizes similarly to

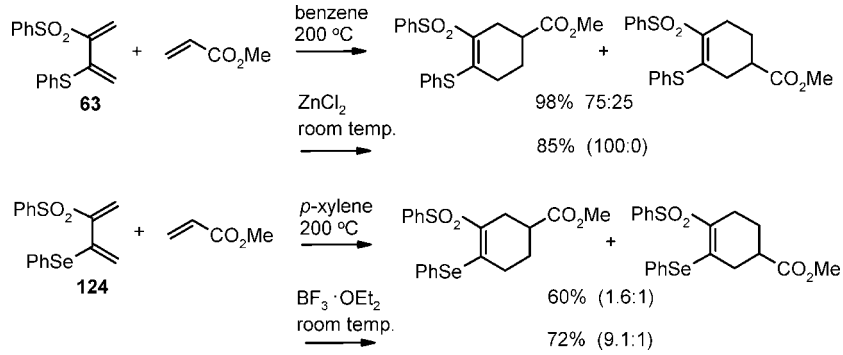
Scheme 39



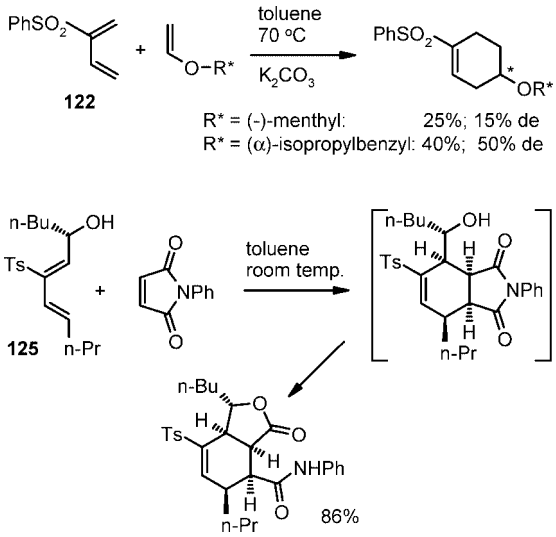
examples shown in Scheme 20. However, when the pyrolysis was performed in the presence of various dienophiles, the diene **121** was trapped as the corresponding cycloadducts, which were isolated in good to excellent yield, along with some of the dimer. With unsymmetrical dienophiles, only the 1,4-regioisomers were isolated (Scheme 39). Related work by Julia et al.[130] also showed that the reaction of **122** with methyl vinyl ketone produced chiefly the 1,4-regioisomer. Bäckvall et al.[121] demonstrated that dienyl sulfone **122** cycloadds to both electron-deficient and electron-rich dienophiles. However, clean regiochemistry was only observed with electron-rich species such as enol ethers (Scheme 39). On the other hand, the methyl derivative **123** reacted with methyl acrylate in the presence of aluminum trichloride to afford essentially a single regio- and stereoisomer[121] (Scheme 39).

As shown previously in Scheme 20, dienyl sulfone **63** reacted with the electron-poor dienophile *N*-phenylmaleimide to produce the corresponding [4 + 2] cycloadduct in high yield. Chou et al.[131] also prepared the 3-phenylthio-2-sulfoxide and 2,3-di(phenylthio) analogs of **63** from the corresponding sulfolenes[131a] and found that the sulfone **63** required the highest temperature (200 °C) for reaction with *N*-phenylmaleimide, while the 2,3-di(phenylthio) derivative reacted at 135 °C.[131b] This is consistent with normal electron demand, where rates are enhanced by a more electron-rich diene. Other dienophiles were also investigated,[131b,76] as in the case of the reaction of **63** with methyl acrylate[76] (Scheme 40). The corresponding phenylseleno analog **124** was studied independently[132] and found to react with methyl acrylate with similarly poor regioselectivity. However, addition of Lewis acids lowered the required temperature for the reaction and enhanced the regioselectivity considerably for both **63** and **124** (Scheme 40). In both the sulfide and selenide series, the normal 1,4-regiochemistry observed with dienyl sulfones **121** and **122** was reversed, with the dienophile ester substituent and the sulfonyl group now favoring a 1,3-relationship.

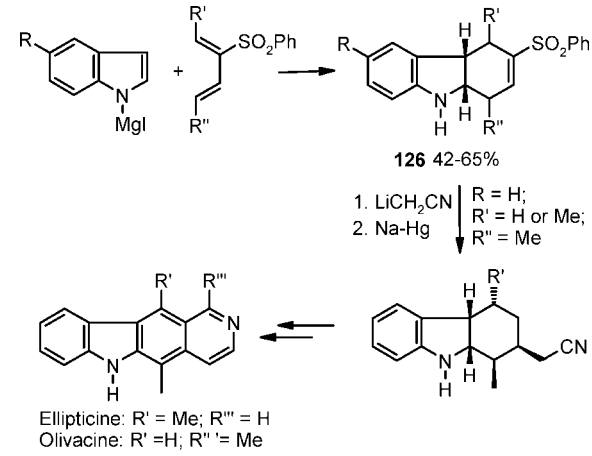
Scheme 40



Scheme 41



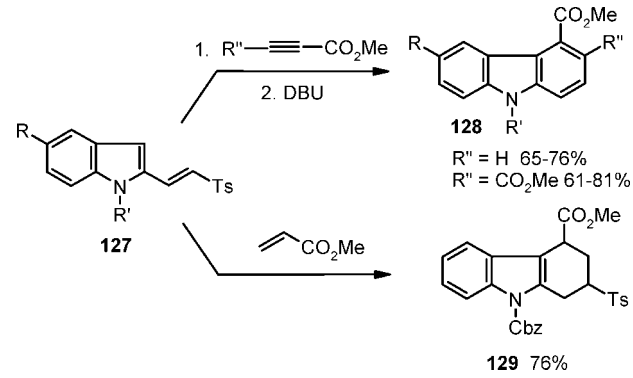
Scheme 42



Several enantioselective variations of Diels−Alder reactions of dienyl sulfones have been reported. These were effected by attaching a chiral auxiliary group to an enol ether dienophile,[133] by installing a chiral carbinol substituent at the 1-position of the dienyl sulfone,[134] or by means of a chiral alkylsulfonyl moiety at the 2-position.[135] Two examples based on dienyl sulfones **122**[133] and **125**[134b] are provided in Scheme 41. Enamines,[121,133,136,137] including several derived from chiral amines for enantioselective cycloadditions,[133,136] also furnished the corresponding [4 + 2] cycloadducts. In addition, dienyl sulfone **122** was used to functionalize a C_{60} fullerene via a [4 + 2] cycloaddition,[138] while its corresponding 1-trimethylsilyl analog reacted with *N*-phenylmaleimide to afford the corresponding *endo* cycloadduct as a single diastereomer in 84% yield.[139]

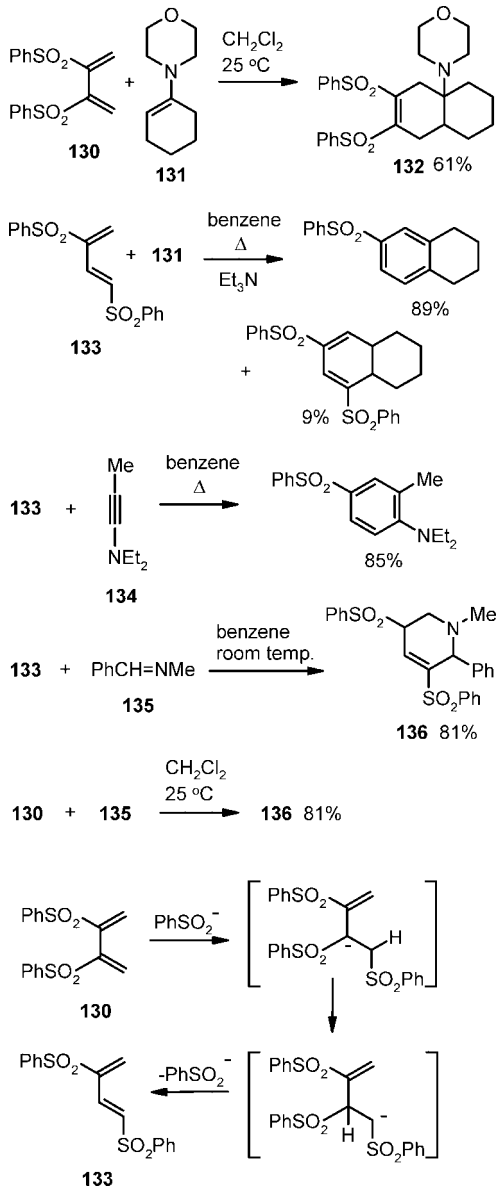
Dienyl sulfones can be employed in the elaboration of indoles to more complex structures. Bäckvall et al.[140] reported that the magnesium iodide salts of indole or its substituted derivatives reacted with a variety of dienyl sulfones to produce tetrahydrocarbazoles **126**. The lack of stereospecificity in the [4 + 2] cycloadditions of disubstituted dienyl sulfones suggests that it is not a concerted reaction. The process was applied to the synthesis of key intermediates that were required for a new route to the alkaloids ellipticine and olivacine (Scheme 42).[141] Similar examples with 2- and 3-methylindoles were later reported by Joule et al.[142] A novel synthesis of variously substituted carbazoles was based on the Diels−Alder cycloaddition of indole-based dienyl sulfones **127** that underwent subsequent base-catalyzed elimination of *p*-toluenesulfinic acid to afford the desired products **128** and **129**[143] (Scheme 43). Interestingly, the regiochemistry could be reversed by employing the corresponding sulfide analogs of **127**.[144] The dienyl sulfones **127** were in turn obtained by a palladium-catalyzed coupling reaction described in section 17.2.

Scheme 43

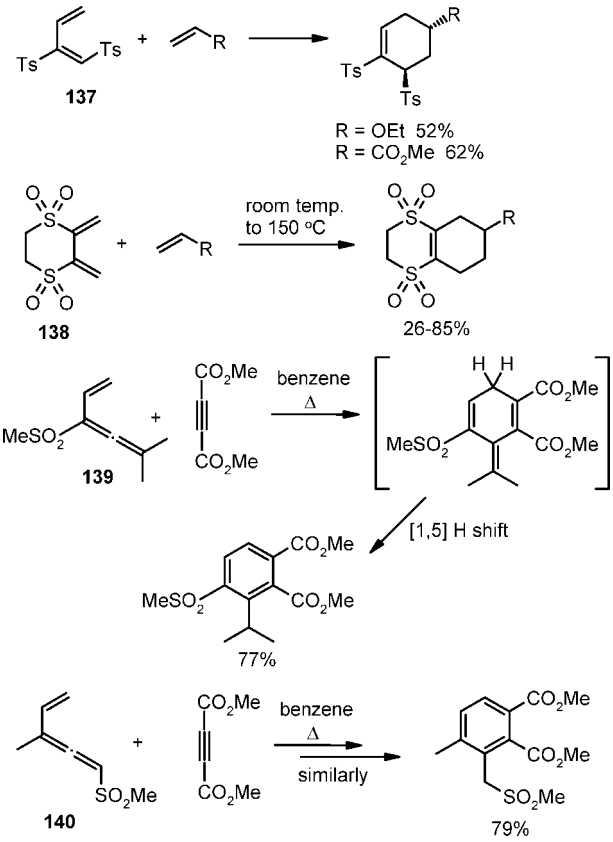


Early work by Masuyama and co-workers demonstrated that enamines are effective dienophiles for [4 + 2] cycloadditions with various 1,3-bis(sulfonyl)dienes.[145] Subsequently, the 2,3- and 1,3-bis(sulfonyl)dienes **130** and **133** and their derivatives were studied extensively by Padwa et al., who proved them to be versatile reagents for highly regioselective cycloadditions with enamines, ynamines, and imines.[137,146] The 1,3-isomer is more reactive because it possesses a lower energy LUMO for cycloadditions that proceed with inverse electron demand and because the cisoid conformation required for cycloaddition in the 2,3-derivative is strongly disfavored.[146a,b] Both of these highly

Scheme 44



Scheme 45



electron-deficient reagents, and **133** in particular, are typically generated *in situ*. The cycloadducts obtained from enamines can be isolated, as in the case of **132**,[146c] but under more forcing conditions, they are also prone to elimination and aromatization, as in the reaction of **133** with enamine **131**.[146c] Dienyl sulfone **130** produced the [2 + 2] cycloaddition product when treated with ynamine **134** (see section 4.3), but the 1,3-derivative **133** afforded the products of [4 + 2] cycloaddition, followed by elimination of *p*-toluenesulfinic acid.[146c] Imines such as **135** also reacted with **133** in a hetero-Diels−Alder reaction, followed by a [1,3] prototropic shift.[137] Surprisingly, **130** afforded the same product **136**, requiring the apparent rearrangement of a phenylsulfonyl group.[146a,b] This was rationalized by the addition−elimination of traces of sulfinate anion to **130**, resulting in its transformation to **133** prior to cycloaddition.[146a,b] Examples of these processes are provided in Scheme 44. A hetero-Diels−Alder reaction, followed by elimination of dimethylamine, was also observed when **133** reacted with *N*,*N*-dimethylthioformamide.[137]

1,2-Bis(sulfonyl)dienes such as **137** have been less studied than their 1,3- and 2,3-substituted counterparts. However, **137** behaved with dual electron demand and reacted regio- and stereoselectively with both electron-rich and electron-deficient dienophiles.[147] The cyclic 2,3-bis(sulfonyl)diene **138** was designed to overcome the lower reactivity of **130** caused by the preferred transoid conformation of the latter and also cycloadded to both types of dienophiles.[148] The α-vinyl and γ-vinyl allenic sulfones **139** and **140**, respectively, as well as their sulfoxide analogs, underwent [4 + 2] cycloadditions, followed by [1,5] hydrogen shifts to afford the corresponding arenes[149] (Scheme 45).

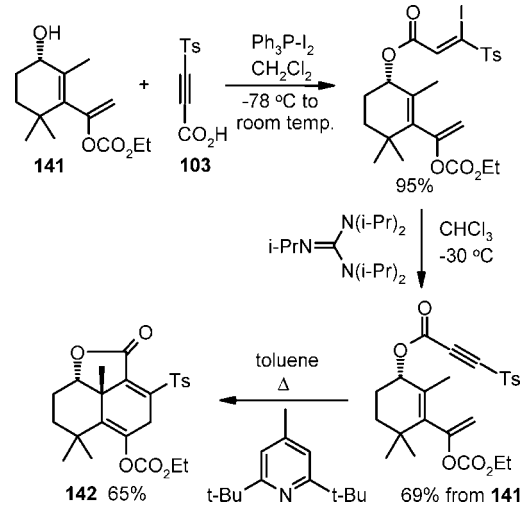
2.3. Intramolecular Diels−Alder (IMDA) Reactions of Unsaturated Sulfones

Sections 2.1 and 2.2 demonstrated that the sulfone group is very useful and versatile in activating unsaturated reactants and in directing regiocontrol of [4 + 2] cycloadditions. It is therefore no surprise that a number of intramolecular variations have been developed for synthetic applications.

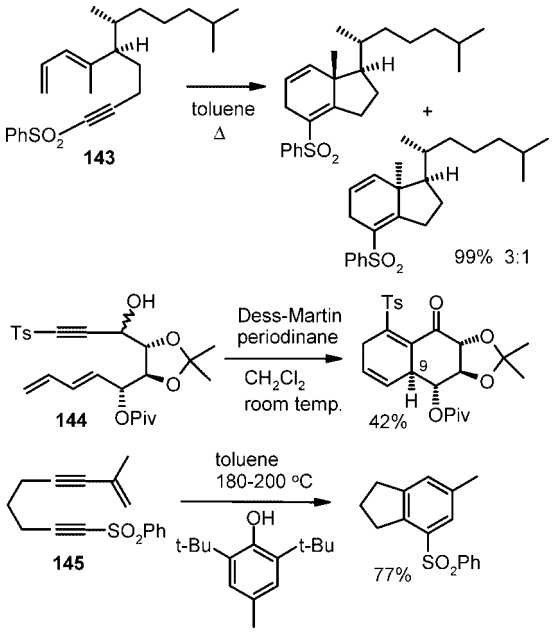
2.3.1. IMDA Reactions of Acetylenic Sulfones

The use of acetylenic sulfone **103** in the Corey synthesis of glycinoeclepin A was shown in Scheme 33. Corey and co-workers also developed an approach to forskolin based on this reagent.[150] The key intermediate **142** was obtained from alcohol **141** via esterification with **103** and iodination−elimination of HI to generate the required acetylenic sulfone moiety, followed by IMDA cycloaddition (Scheme 46). An earlier approach[151] employed the direct esterification of a similar alcohol to **141** with **103** *in situ* prior to the IMDA step but resulted in racemization. The reagent **103** is prone to decarboxylation and so must be prepared and used rapidly.

Scheme 46



Scheme 47

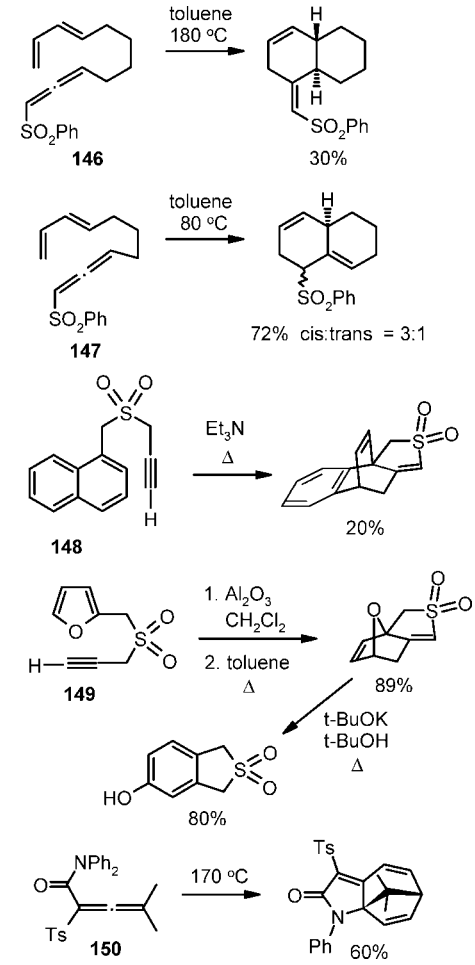


Three other examples are shown in Scheme 47. Craig et al.[152] employed the IMDA cycloaddition of **143** to construct the CD ring fragment of vitamin D_3, while Sulikowsky and co-workers[153] triggered the spontaneous IMDA reaction of **144** at room temperature by oxidation of the hydroxyl group to the corresponding ketone to produce a key fragment for the synthesis of hibarimicin HMP-Y1. Interestingly, the opposite diastereomer at C-9 was obtained when the corresponding vinyl ketone was used as the dienophile instead of the acetylenic sulfone. In the third example, Danheiser et al.[154] reported that the enyne moiety of **145** functioned as the diene component in its IMDA cyclization, affording the corresponding arene.

2.3.2. IMDA Reactions of Allenic Sulfones

Both Padwa et al.[155] and Kanematsu et al.[156] observed that [2 + 2] cycloadditions of allenic sulfones, which will be described more fully in section 4, are often competitive with IMDA reactions. When IMDA reactions predominate, it is often the unactivated distal double bond of the allenic sulfone that serves as the dienophile. For example, Bull and

Scheme 48

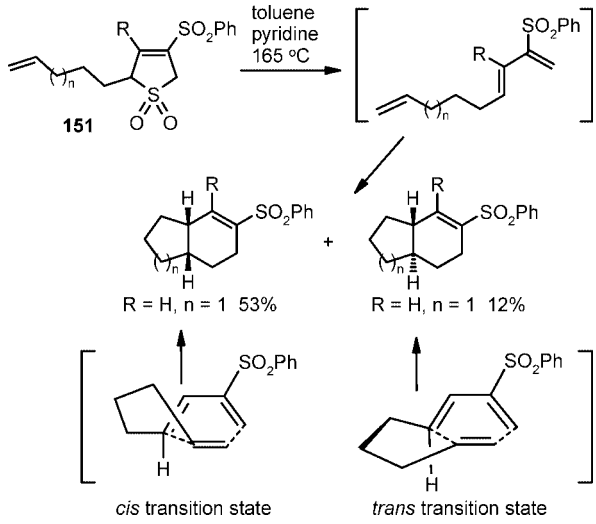


co-workers[157] noted that the distal bond reacts preferentially when the longer tether in **146** is present, while the shorter linkage in **147** afforded products of proximal attack (Scheme 48). They also found that a two-carbon tether is accompanied by exceptionally high reactivity and *exo*-selectivity. Successful IMDA reactions have been carried out with arenes such as **148**[158] and with furan derivatives[155,157b,158,159] like **149**[159] (Scheme 48). In the two latter examples, the sulfone group is part of the tether in the form of the propargyl isomer that requires prior *in situ* conversion into the corresponding allene dienophile by treatment with triethylamine or alumina. The final products in the furan series are benzosulfolenes that in turn serve as potential precursors of *o*-quinodimethanes, useful for further cycloadditions. In the case of allenic sulfone **150**, an IMDA reaction occurred with one of the *N*-phenyl substituents, followed by rearrangement.[160] Note that again the unactivated distal bonds of allenic sulfones derived from **148** and **149**, and that of allene **150**, functioned as the dienophiles.

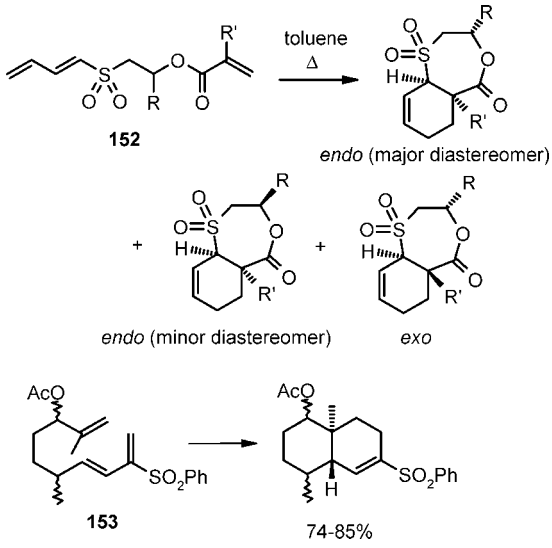
2.3.3. IMDA Reactions of Dienyl Sulfones

Just as the pyrolysis of sulfolenes was utilized in the formation of dienyl sulfones in Schemes 20 and 39, this process can also be employed to generate the activated trienes required for IMDA cycloadditions. Thus, Chou et al.[161] pyrolyzed a series of sulfolenes **151**, resulting in the liberation of the corresponding dienyl sulfones and their *in situ* IMDA reactions with the pendant alkene substituents. The reactivity was in the order of R = H > TMS > PhS, and

Scheme 49



Scheme 50



the stereochemistry was dependent upon the substituent R and the length of the tether. The example of R = H and n = 1 is shown in Scheme 49, along with the corresponding transition states leading to the principal cycloadducts. Chumachenko and co-workers[162] investigated the IMDA reactions of dienyl sulfones **152**, observing complete regioselectivity and high *endo*/*exo* ratios (Scheme 50). Weichert and Hoffmann[163] found that dienyl sulfones **153** afforded *trans*-fused products exclusively via *endo* (with respect to the olefinic methyl group) transition states (Scheme 50). The products were of interest as intermediates in eudesmane synthesis.

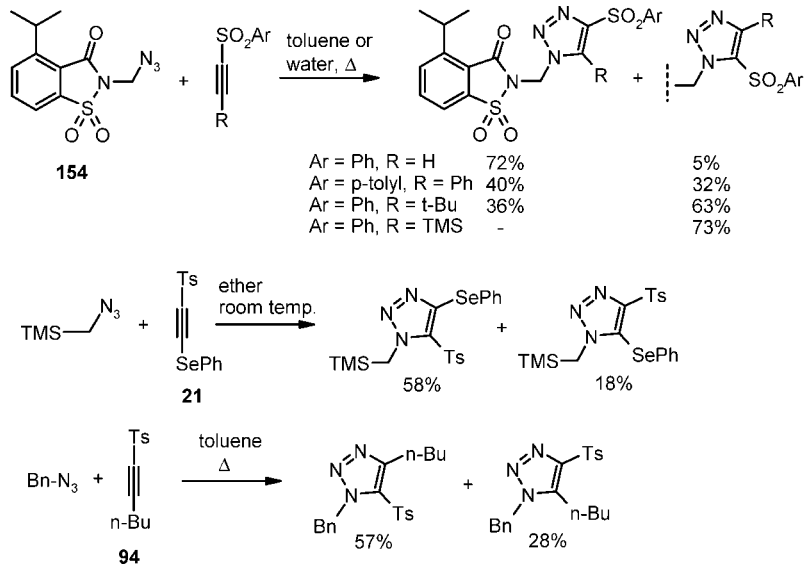
3. 1,3-Dipolar Cycloadditions

3.1. With Azides

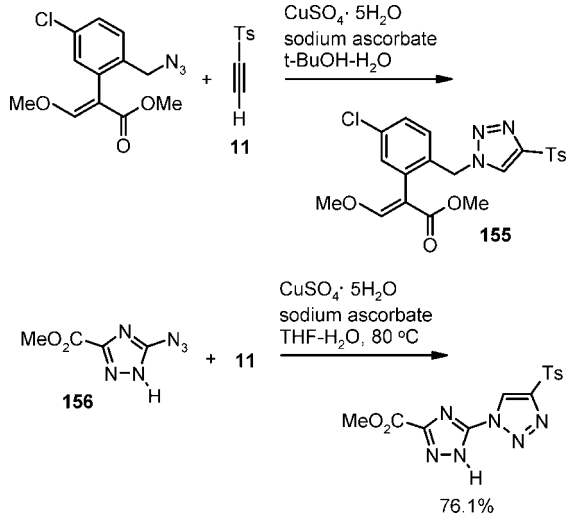
Increased interest in the cycloadditions of acetylenic sulfones with azides has been prompted by the advent of Sharpless "click chemistry" and its potential for obtaining triazoles of medicinal and other biological interest, including the generation of triazole libraries. In early work, Hlasta and Ackerman[164] employed azides **154** to produce the corresponding triazoles as potential inhibitors of human leukocyte elastase. Regioselectivity was dependent upon both the electron-withdrawing effect of the sulfone aryl group and the steric bulk of the β-substituent. The TMS substituent resulted in a clean reversal of regiochemistry compared with the corresponding terminal acetylene and likely includes an electronic as well as steric component to its effect upon the regioselectivity. The 2-phenylseleno acetylene **21** reacted with a similar reversal of regioselectivity,[66] as did the alkyl-substituted derivative **94**.[165] Examples are shown in Scheme 51.

Cycloadditions of azides to acetylenic sulfone **11** under "click conditions" have been used to contribute compounds to triazole libraries of interest as antifungal agents (e.g., **155**),[166] as protein tyrosine phosphatase inhibitors,[167] and for the glycorandomization of structures related to vancomycin.[168] A route to bistriazoles based on the cycloaddition of the 1,2,4-triazolyl azide **156** to dipolarophiles such as **11** has also been reported.[169] These reactions were performed in the presence of Cu(I) to control regioselectivity. A popular method for generating the catalyst is to reduce Cu(II) sulfate *in situ* with ascorbic acid. Two examples are shown in Scheme 52. A copper- and solvent-free method for the highly

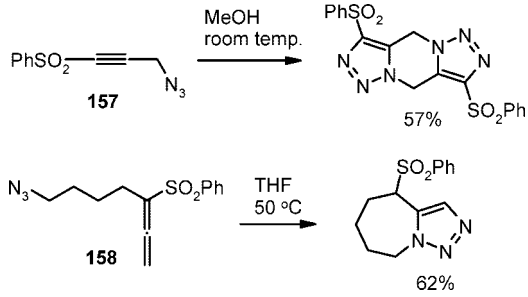
Scheme 51



Scheme 52



Scheme 53



regioselective cycloaddition of **11** with azides was also reported recently.[170]

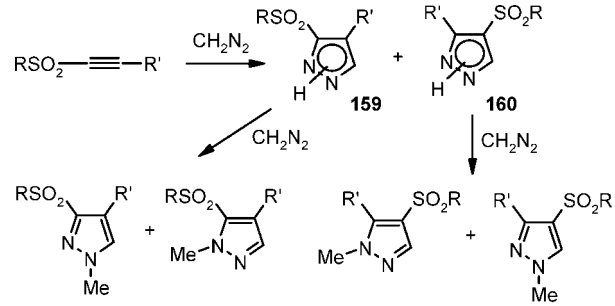
An example of the dimerization of an azide-containing acetylenic sulfone via a 1,3-dipolar cycloaddition has been reported for **157**,[171] as was the intramolecular cycloaddition of the azide-substituted allenic sulfone **158** (Scheme 53).[172] With analogs of **158** containing shorter tethers, the principal products were dihydropyrroles and tetrahydropyridines formed by loss of nitrogen.

Ley and co-workers have performed the cycloaddition of *p*-trifluoromethylbenzyl azide to acetylenic sulfone **11** in a modular flow reactor. Of additional interest was their use of a thiourea-based resin for scavenging the Cu(I) catalyst and a phosphine resin to remove excess azide. These efforts indicate that a highly automated approach to producing triazole libraries is possible.[173] Several examples of 1,3-dipolar cycloadditions of azides with acetylenic sulfones on solid supports are described in section 18.

3.2. With Diazo Compounds

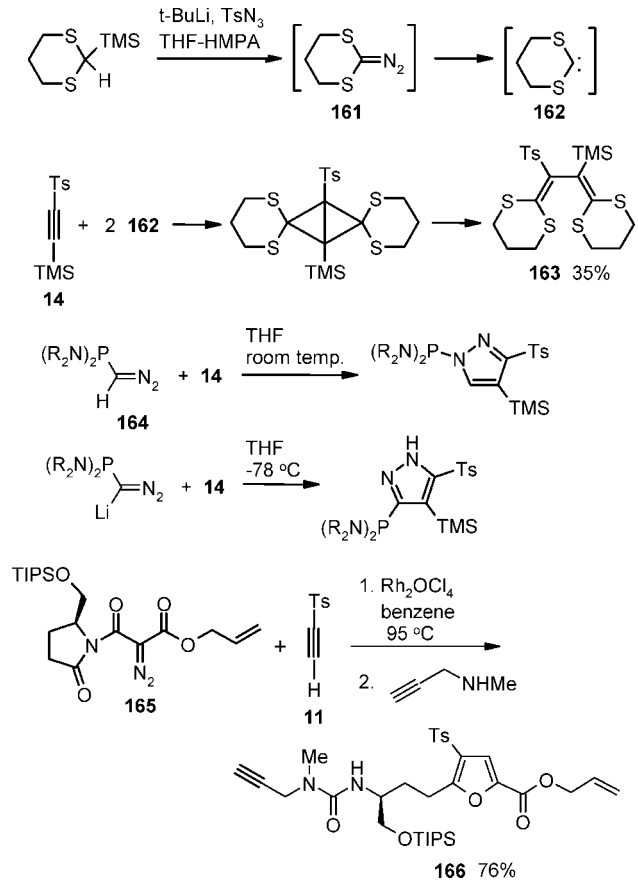
In 1973, Guillerm et al.[174] reported that the cycloadditions of diazomethane with acetylenic sulfones afforded mixtures of regioisomeric pyrazoles that undergo further *N*-methylation at either of the two nitrogen atoms. Other diazo compounds, including 2-diazopropane,[175−179] diphenyldiazomethane,[174] and ethyl diazoacetate,[165,174] have also been investigated, and the regiochemistry of the cycloadditions proved sensitive to both steric and substituent effects. The regiochemistry observed with diazomethane is illustrated in Scheme 54 and includes results from subsequent work by several other groups.

Scheme 54



R	R'	% via **159**	% via **160**	reference
Ph	Me	20	80	174
p-tolyl	Me	20	80	174
p-ClPh	Me	20	80	174
p-tolyl	TMS	-	100	175
p-tolyl	H	66	-	175
p-tolyl	SePh	-	81	66
CF_3	Ph	43	-	32b

Scheme 55

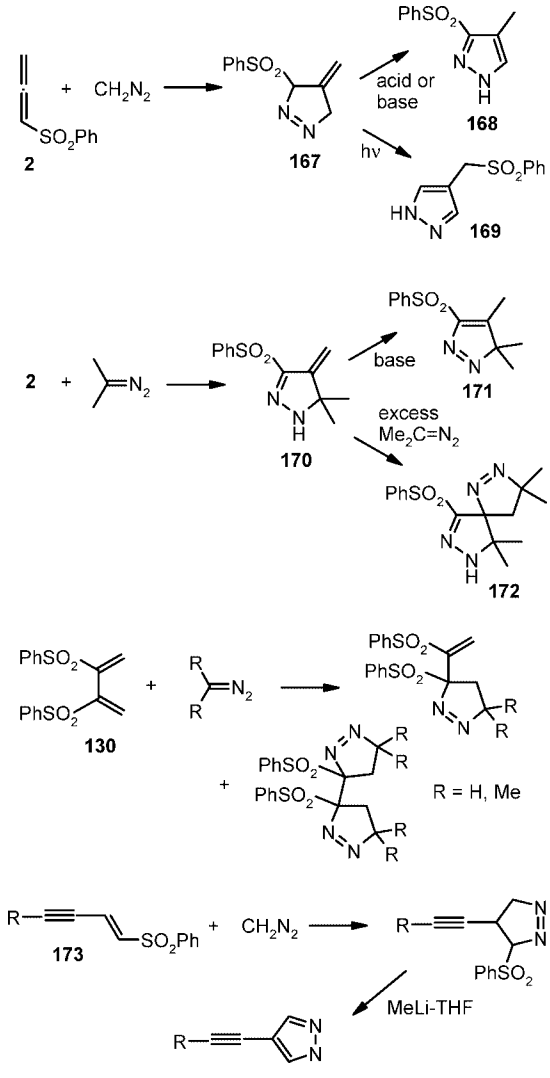


The extrusion of dinitrogen from cycloadducts of diazo compounds with acetylenic sulfones to produce cyclopropenes has been extensively studied and will be described in more detail in section 14.2. The 2-diazodithiane species **161** was formed as a transient intermediate as shown in Scheme 55. It was assumed to decompose to the corresponding carbene **162**, which either dimerized or performed a double addition to acetylenic sulfone **14**, followed by ring cleavage to ultimately afford the bis(dithiane) **163**.[180] The reactions of metalated diazo compounds can differ significantly from those of their conjugate acids, as illustrated by the example of the phosphino diazo compound **164**.[181] The latter reacted with **14** via a proposed concerted [3 + 2] dipolar cycload-

dition followed by a [1,5] migration of the phosphino substituent, while its metalated derivative was believed to effect an addition to **14**, followed by cyclization (Scheme 55). The rhodium-catalyzed decomposition of diazo compound **165** in the presence of acetylenic sulfone **11**, followed by trapping with *N*-methylpropargylamine, led to the furan **166**, required as an intermediate for the synthesis of certain macrocycles. The reaction proceeds via the [3 + 2] cycloaddition of a carbonyl ylide derived from **165** to the acetylenic sulfone, followed by [4 + 2] cycloreversion to form an isocyanate that is in turn trapped by the amine (Scheme 55).[182]

Veniard and Pourcelot reported the 1,3-dipolar cycloadditions of allenic sulfones with diazomethane and its diphenyl derivative.[183] These reactions occurred exclusively at the site of the activated double bond, with generally greater regioselectivity than observed with acetylenic sulfones. The allenic sulfones were generated *in situ* from the base-catalyzed isomerization of propargyl sulfones in the usual manner. A more detailed study of the reactions of allenic sulfone **2** with diazomethane and 2-diazopropane was later performed by Padwa and co-workers.[184] They found that the initial diazomethane cycloadduct **167** isomerized to **168** in the presence of traces of acids or bases, while a 1,3-shift of the phenylsulfonyl group was initiated by ambient light and produced **169**. With 2-diazopropane, the initial cycloadduct **170** isomerized to **171** in the presence of base or underwent a second cycloaddition to afford the spiro compound **172**. These authors also reported similar studies of bis(sulfone) **130**, which furnished normal and double cycloadducts, with the latter favored by excess diazo compound.[185] Enynes **173** were investigated by Kataoka et al.,[186] who found that the double bond is the preferred reaction site with diazomethane. Elimination of benzenesulfinic acid then afforded the corresponding alkynyl pyrazoles. These examples are provided in Scheme 56.

Scheme 56

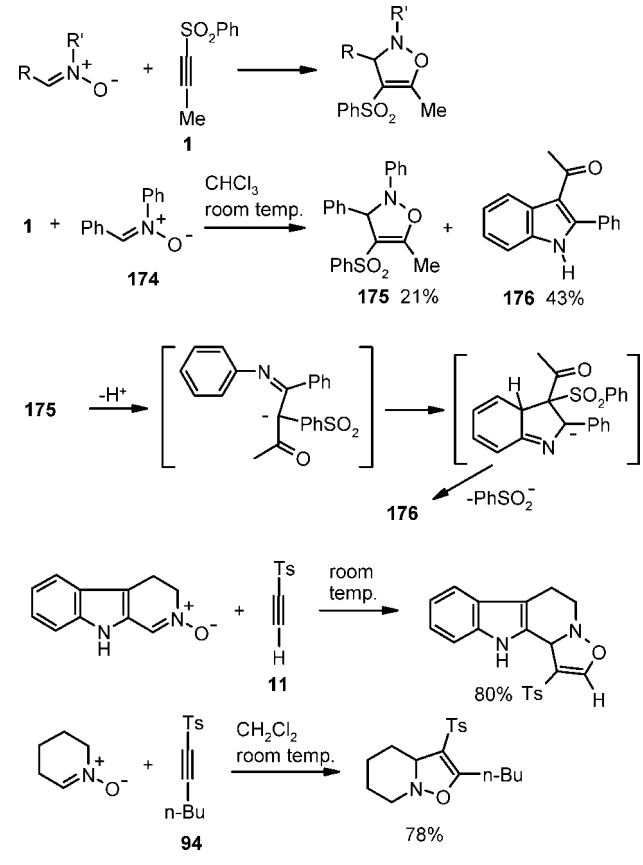


3.3. With Nitrones

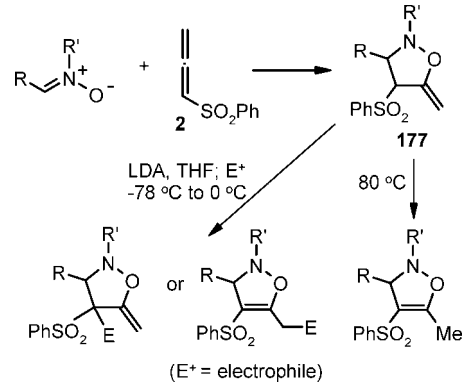
There are relatively few known examples of dipolar cycloadditions of nitrones to acetylenic sulfones.[165,187−189] During a study aimed principally at allenic sulfones (*vide infra*), Padwa et al.[187] demonstrated that the acetylenic sulfone **1** reacted with several nitrones with high regioselectivity, producing cycloadducts in which the nitrone oxygen and carbon atoms formed new bonds to the β- and α-positions, respectively, of **1** (Scheme 57). Zecchi et al.[188] reported that the dihydroisoxazole cycloadduct **175**, obtained from **1** and nitrone **174**, underwent further transformation to the corresponding 3-acylindole **176** via a proposed heterolytic O−N bond cleavage, followed by electrocyclic ring-closure. Similar products were obtained with several other acetylenic sulfones. Cycloadditions of other nitrones with acetylenic sulfones **11**[189] and **94**[165] also proceeded in good yield and afforded single regioisomers (Scheme 57).

The 1,3-dipolar cycloadditions of nitrones with allenic sulfones have been more extensively studied by several groups. Not surprisingly, the sulfone-activated double bond of allene **2** reacted exclusively with the same regiochemistry as observed with its acetylenic counter-

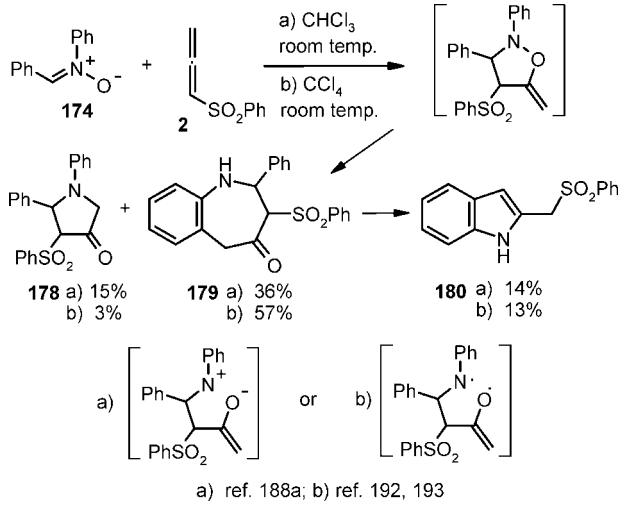
Scheme 57



Scheme 58

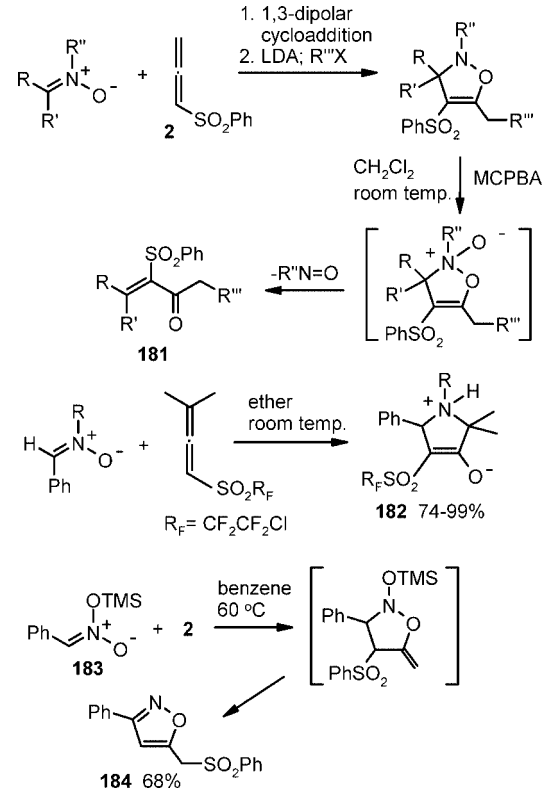


Scheme 59

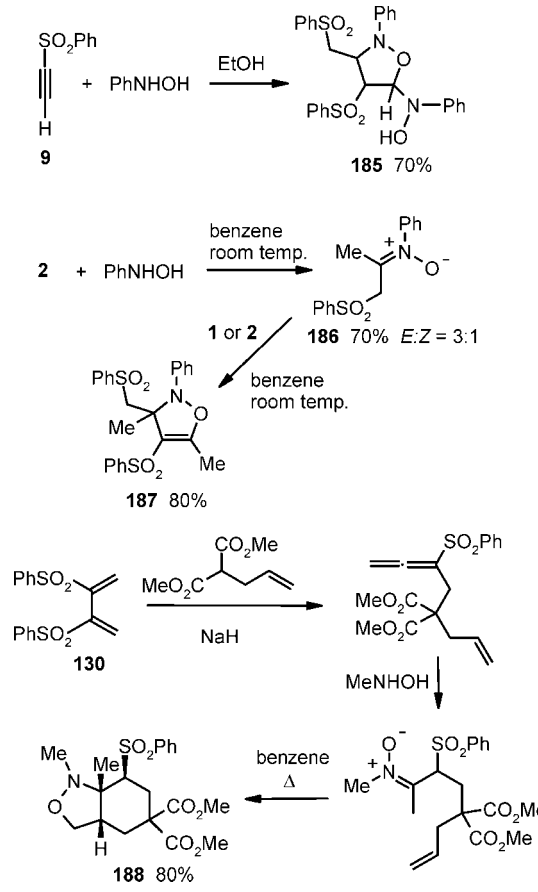


part.[187,188a,190] Padwa et al.[187] reported that upon heating, the initial cycloadduct **177** underwent migration of the exocyclic double bond to afford the same product as that obtained from the isomeric acetylenic sulfone **1**. Moreover, the sulfone-stabilized anion of **177** can be alkylated at either the α- or γ-position, with the site determined by the electrophile and a combination of steric and thermodynamic factors. Thus, methyl iodide and ethylene oxide were α-selective, while allyl or propargyl bromide, trimethylsilyl chloride, ethyl iodide, and benzaldehyde reacted preferentially or exclusively at the γ-position[187,191] (Scheme 58). Blechert,[190] Parpani and Zecchi,[188a] and Padwa et al.[192] independently observed the formation of additional products from the initial cycloadduct produced from **2** and nitrone **174**[188a,192] or its *N*-(*p*-tolyl) analog.[190] Both heterolytic[188a] and homolytic[192] dissociations of the N−O bond have been proposed to rationalize the formation of benzazepinone **179** and the pyrrolidinone **178** from the initial cycloadduct (paths a and b, respectively, in Scheme 59). A hetero-Cope rearrangement has also been suggested as a possible mechanism for the formation of the pyrrolidinone **178**.[190] The indole **180** appears to be the product of a retro-Mannich reaction of **179**, followed by hydrolysis accompanied by the formation of benzaldehyde, and recyclization, which occurs on standing in solution or upon exposure to silica gel.[192] Additional studies by Padwa and co-workers included kinetic measurements, MO computations, and the effects of allene and nitrone substituents upon product distributions, stereochemistry, and reaction rates.[193,194] These authors also reported several useful transformations of the dipolar cycloaddition products. Thus, peracid oxidation of the products obtained from the cycloaddition of nitrones to allenic sulfone **2**, followed by γ-alkylation (see Scheme 58), produced *N*-oxides that extruded the corresponding nitroso compounds

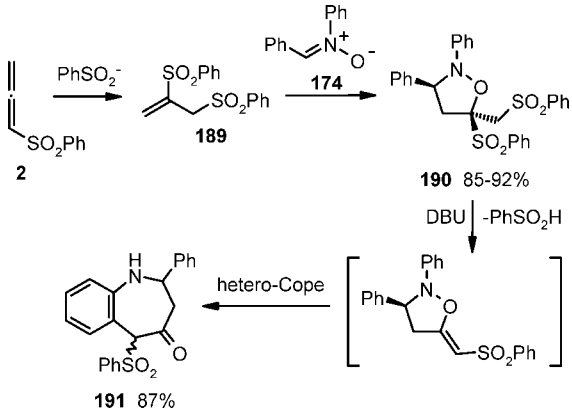
Scheme 60



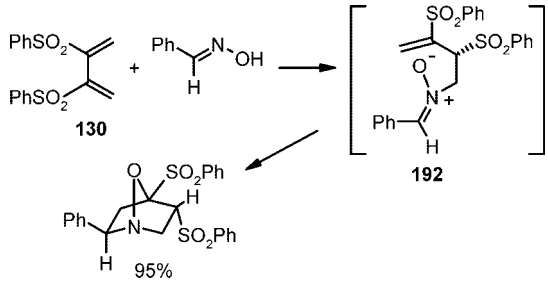
Scheme 61



Scheme 62



Scheme 63

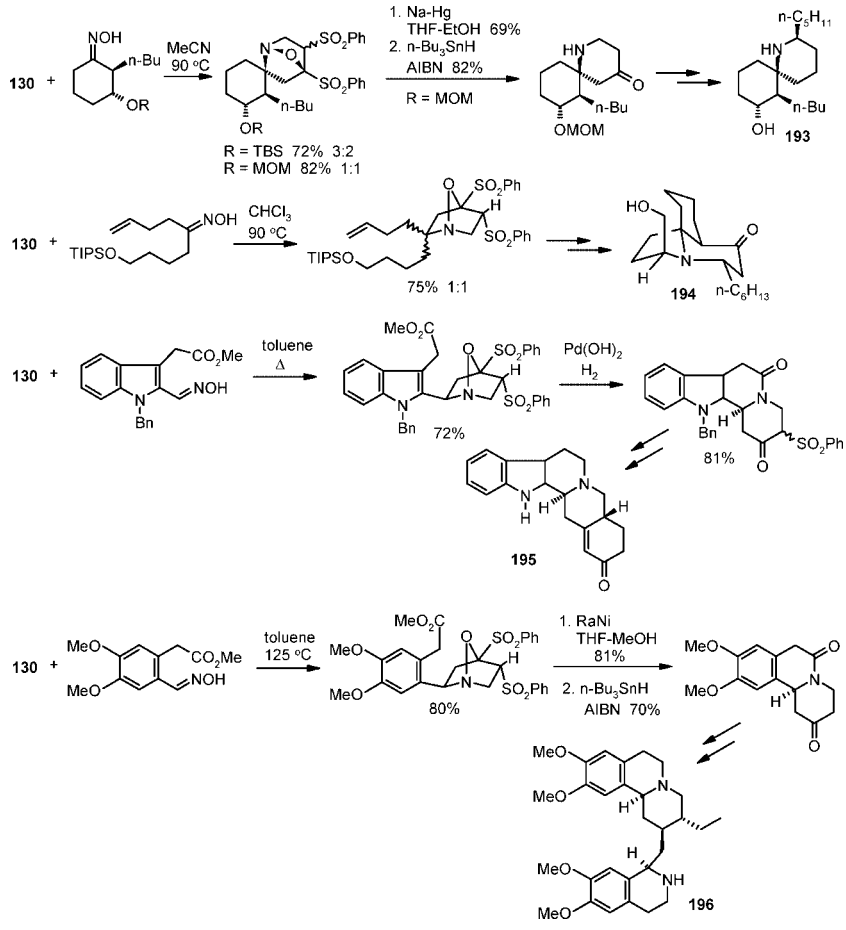


to afford sulfonylenones **181** (Scheme 60).[191b,195] Perhaloalkylsulfonyl allenes displayed increased reactivity and afforded high yields of the corresponding pyrrolidinones, which exist primarily as the corresponding ammonium enolate zwitterions **182**.[196] On the other hand, the *N*-silyloxy nitrone **183** produced the isoxazole **184** as the exclusive product via elimination of the corresponding silanol and 1,3-migration of the sulfonyl group (Scheme 60).[184a]

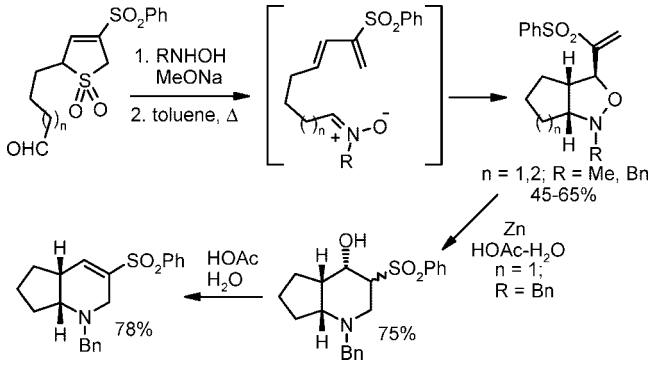
Nitrones are produced by the addition of *N*-substituted hydroxylamines to acetylenic[197] and allenic sulfones.[198] The products can then be added to a second mole of the unsaturated sulfone or to a different dipolarophile. Examples are shown in Scheme 61. In the case of **185**, a further conjugate addition of the hydroxylamine to the initially formed isoxazolidine afforded the indicated 2:2 complex.[197] The nitrone **186**, produced from allenic sulfone **2** and *N*-phenylhydroxylamine, reacted with either additional **2** or its acetylenic sulfone isomer **1** to produce the 2:1 adduct **187**.[198a] Intramolecular variations are possible, as in the preparation of **188** from dienyl sulfone **130**.[198b,199]

Padwa et al.[200a] reported an expedient method for circumventing the high selectivity for 1,3-dipolar cycloaddition to the proximal double bond of allenic sulfones. By treatment of the allenic sulfone **2** with benzenesulfinate anion, the masked allene **189** was produced. Cycloaddition of nitrone **174** to the remaining double bond (originally the unactivated double bond in **2**) of **189** afforded the corresponding isoxazolidine **190**. Elimination of benzenesulfinate anion resulted in its conversion to the benzazepinone **191** (Scheme 62) instead of to the previous isomer **179**, formed in Scheme 59. When the cycloaddition was performed under high pressure, the epimer of **190** was formed in 92% yield.

Scheme 64



Scheme 65



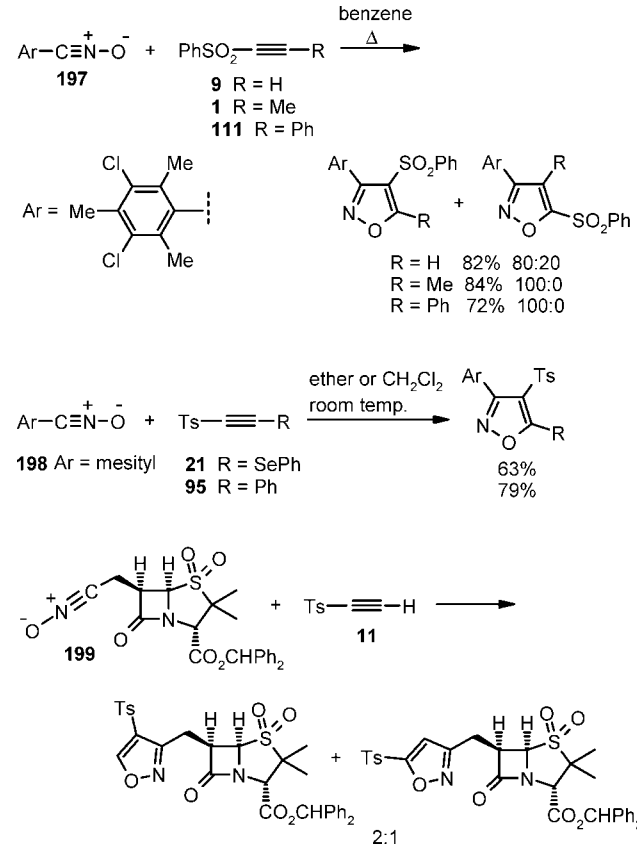
Dienyl sulfone **130** has also proved a valuable reagent for 1,3-dipolar cycloadditions. Padwa[200b] and Grigg[201] and their co-workers independently reported that the conjugate addition of oximes to **130** generated transient nitrones, resulting in highly regio- and stereoselective intramolecular cycloadditions to afford bicyclic products. In the example shown in Scheme 63,[200b,202] the *Z*-nitrone **192** was formed and reacted preferentially via *endo* addition. Variations of this methodology have been exploited by the Padwa group as the key step in the synthesis of models of perhydrohistrionicotoxin,[202] as well as in the total syntheses of (±)-2,7,8-*epi*-perhydrohistrionicotoxin (**193**),[203] (±)-cylindricine C (**194**),[204] (±)-yohimbenone (**195**),[205] and emetine (**196**),[205] as shown in Scheme 64. Chou and Yu[206] unmasked the latent dienyl sulfone moiety from the pyrolysis of suitably functionalized sulfolenes, resulting in the intramolecular cycloaddition shown in Scheme 65.

3.4. With Nitrile Oxides

The cycloadditions of nitrile oxides with unsaturated sulfones have been less frequently studied than those of azides, diazo compounds, and nitrones. Despite sometimes poor regioselectivity, these dipoles provide an alternative to nitrones as a route to substituted isoxazoles and their dihydro derivatives. The reactions of nitrile oxides **197**,[207,208] **198**,[66,165] and **199**[209] with various acetylenic sulfones are shown in Scheme 66. In general, the 4-sulfonyl regioisomer is dominant. The products derived from **199** are of interest as β-lactamase inhibitors.

1,3-Dipolar cycloadditions of nitrile oxides to allenic sulfones generally give mixtures where the dominant products appear to result from the reaction of the unactivated allene double bond. On the basis of frontier MO arguments, Padwa et al. suggested that the proximal double bond reacts with the nitrile oxide, followed by a 1,3-shift of the sulfonyl group, thus making it appear that the unactivated distal double bond had reacted.[184a] On the other hand, Zecchi et al.[210] argued that both of the allene double bonds are capable of reacting with the dipole and that the site of the reaction depends on both steric and electronic factors. Examples of cycloadditions of allenic sulfones with nitrile oxides **197**[208] and **200**[184a] are illustrated in Scheme 67. Nitrile oxides generated *in situ* from the hypochlorite oxidation of oximes reacted exclusively with the distal double bond of dienyl sulfones **201** to produce cycloadducts **202**. The regioselectivity was attributed to the difference in steric hindrance at the two available reaction sites. Subsequent annulation of the proximal double bond via the Barton−Zard reaction then afforded the corresponding pyrrole derivatives **203** (Scheme 68).[211]

Scheme 66



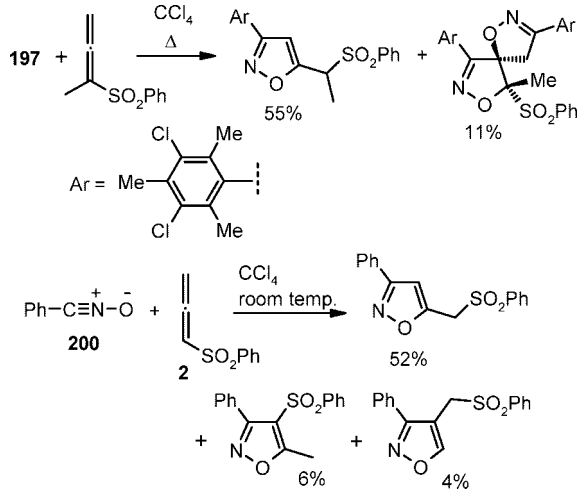
3.5. With Mesoionic Compounds

Several reports of cycloadditions of munchnones[165,212−214] and sydnones[165,207] with acetylenic sulfones have appeared. Munchnones are typically generated from the cyclization of *N*-acyl amino acids with acetic anhydride and trapped *in situ* with the dipolarophile. Extrusion of carbon dioxide from the initial cycloadducts affords the corresponding substituted pyrroles, such as **204**,[212] **205**,[165] and **206**[214] (Scheme 69). Products **206** are of interest as antifungal agents. Similarly, sydnones **207**[165] and **208**[207] reacted with acetylenic sulfones with subsequent loss of carbon dioxide to produce the corresponding pyrazoles (Scheme 70). The regioselectivity of such cycloadditions with unsymmetrically substituted munchnones and sydnones is frequently high and can be rationalized on the basis of frontier MO interactions and electrostatic interactions.[207,213]

3.6. With Other 1,3-Dipoles

The cycloadditions of several other 1,3-dipoles with acetylenic and allenic sulfones have also been investigated (Chart 1). These include nitrile imines **209**[165,207] (the hydrazonyl chloride precursor of **209** may also add directly to the allenic sulfone[184a]) and **210**,[215,216] pyridine *N*-oxides **211**,[217,218] **212**,[218] and **213**,[219] pyridine ylides **214**[69] and **215**,[69] nitrile ylides **216**,[165,220] azomethine ylides **217**[165] and **218**,[165] azomethine imine **219**,[165] and methylene methane **220**.[221] In many cases, mixtures of regioisomers were produced, along with products of subsequent prototropic or other rearrangements. Several examples where relatively high yields of cycloadducts were obtained are shown in Scheme 71.

Scheme 67



Scheme 68

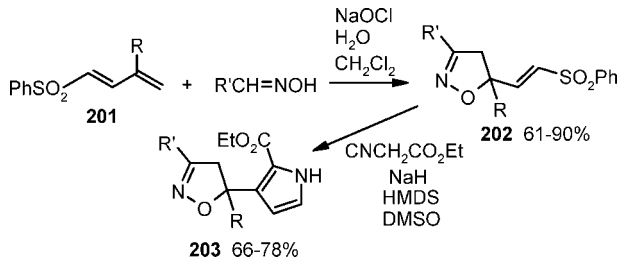
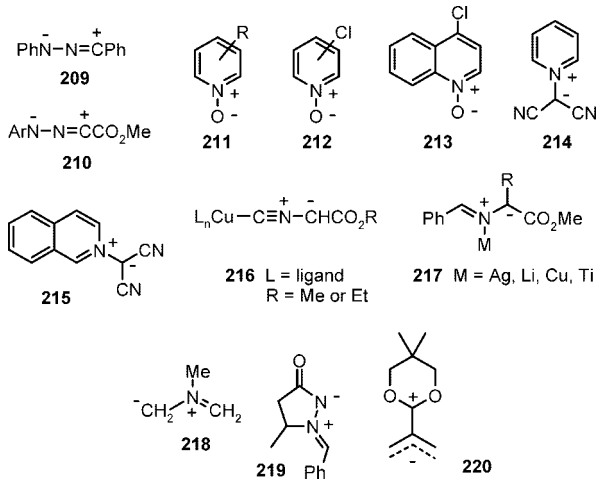


Chart 1

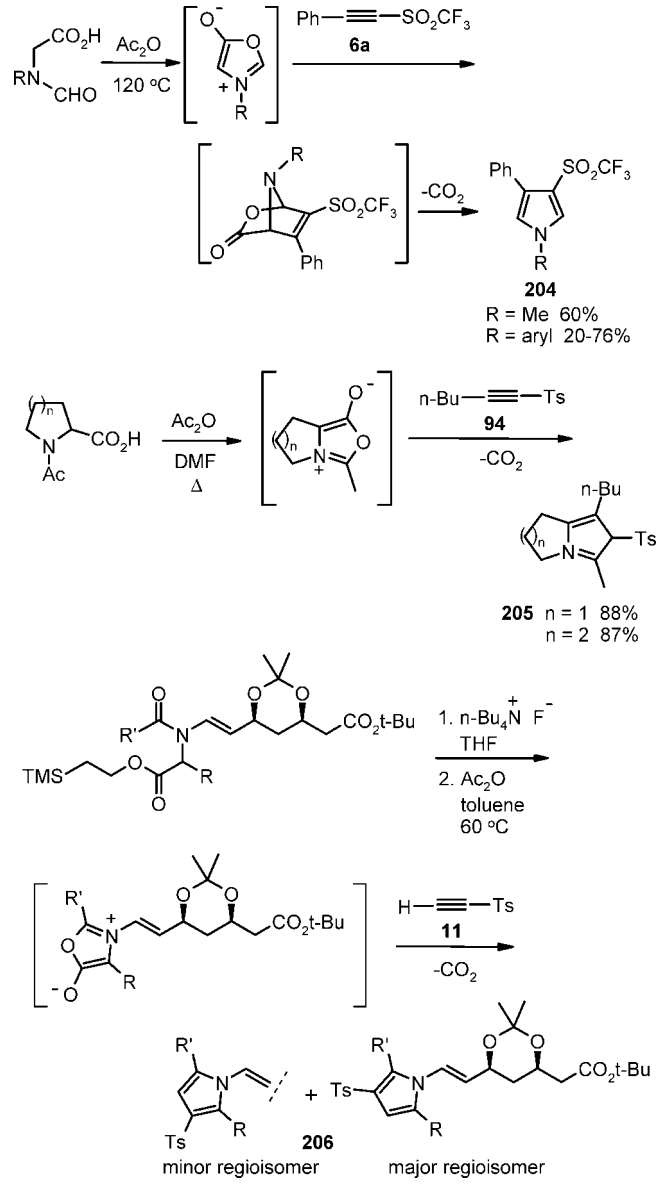


4. [2 + 2] Cycloadditions

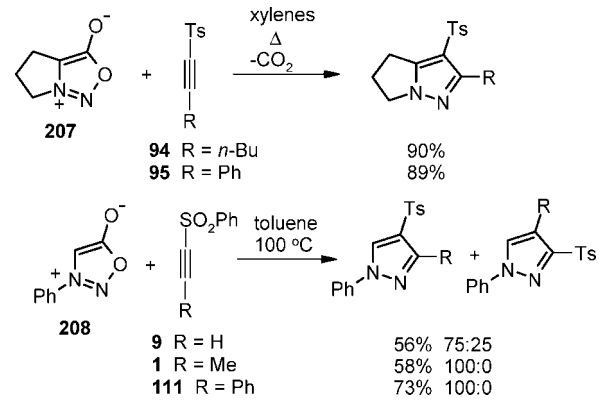
4.1. With Alkenes and Dienes

The possible competition of [2 + 2] with [4 + 2] reactions in the cycloadditions of unsaturated sulfones was noted briefly in section 2.3.2. Thus, the [4 + 2] reactions of β-aryl-substituted acetylenic sulfone **95** with cyclic conjugated dienes were accompanied by the formation of significant amounts of [2 + 2] cycloaddition products, which increased with increasing ring size of the diene.[42,120b] Fragmentation products **221**, similar to those formed in Scheme 35, were also observed with larger rings. The corresponding Dewar benzene was produced when acetylenic sulfone **11** reacted with the substituted cyclobutadiene derivative **222**.[222] In contrast to (phenylsulfonyl)allene (**2**), which strongly favored [4 + 2] cycloadditions, the more reactive bis(sulfonyl)allene

Scheme 69



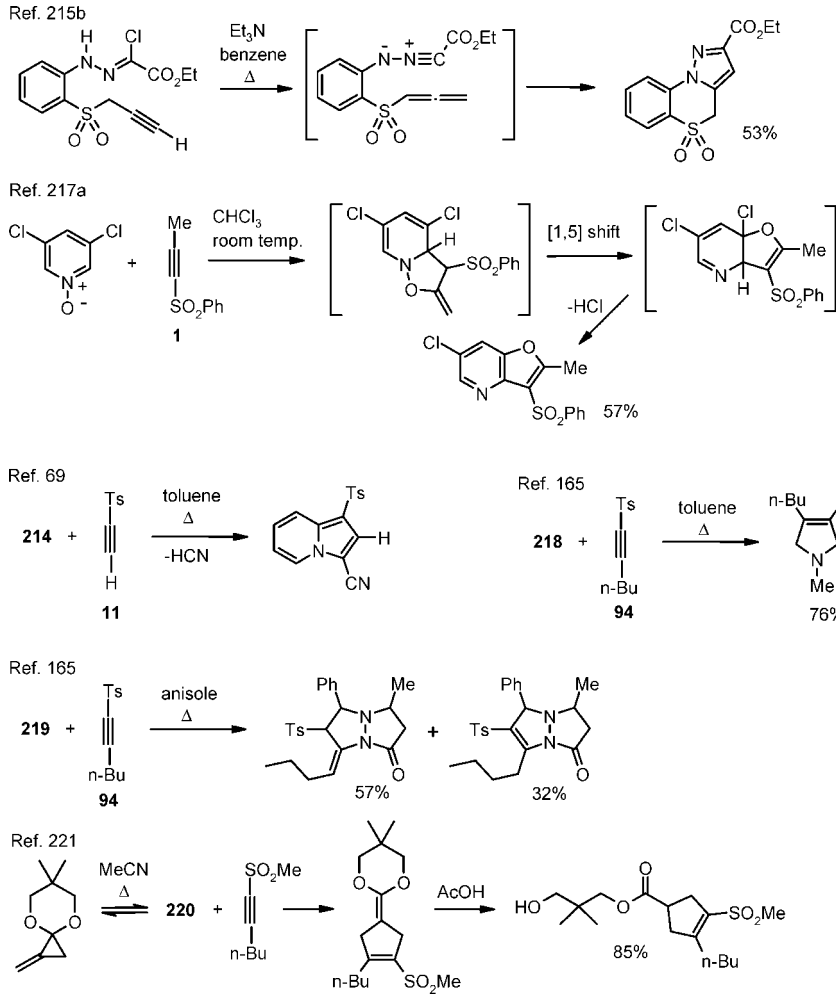
Scheme 70



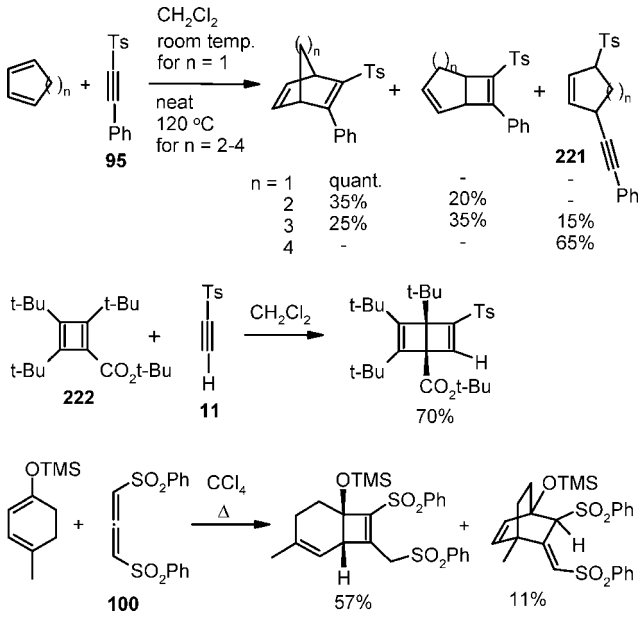
100 afforded mixtures of [4 + 2] and [2 + 2] cycloadducts.[102] These examples are shown in Scheme 72. All of these processes occurred under thermal conditions and their mechanisms are uncertain.

While there do not appear to be any examples of thermal or photochemical [2 + 2] cycloadditions of acetylenic or allenic sulfones with simple alkenes, Tam and co-workers[223]

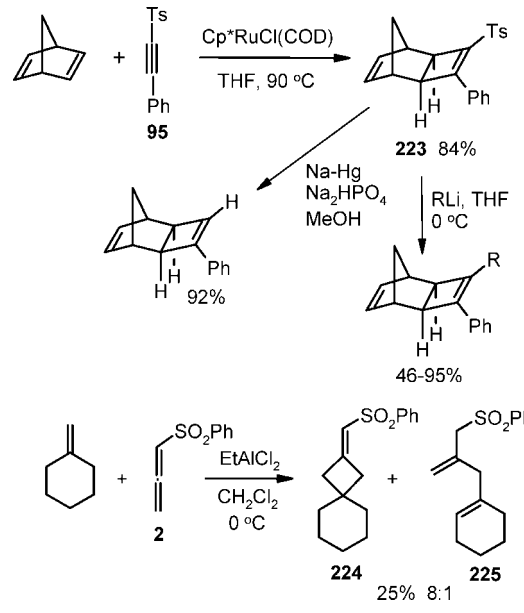
Scheme 71



Scheme 72



Scheme 73



developed a ruthenium-catalyzed method for the [2 + 2] cycloadditions of acetylenes, including acetylenic sulfones, with norbornadiene and other bicyclic alkenes. For example, norbornadiene reacted with **95**, resulting in the exclusive formation of the cyclobutene **223** (Scheme 73). Further transformations of the latter by reductive desulfonylation or cross-coupling with alkyllithiums were also reported. In the case of substituted norbornadienes, the less substituted double bond reacted preferentially. The method was successful with benzo-, 7-oxa-, and variously substituted norbornadiene derivatives. Snider and Spindell[224] found that a [2 + 2] cycloaddition could be effected with methylenecyclohexane

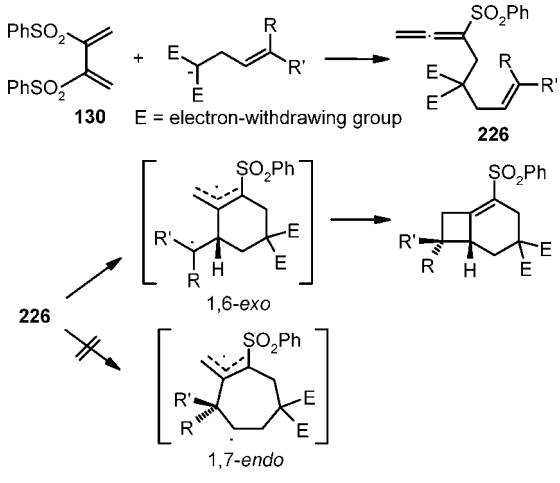
and allenic sulfone **2** in the presence of ethylaluminum dichloride to produce the corresponding spiro compound **224** in low yield, along with a trace of the corresponding ene product **225** (see also section 6).

4.2. Intramolecular [2 + 2] Cycloadditions

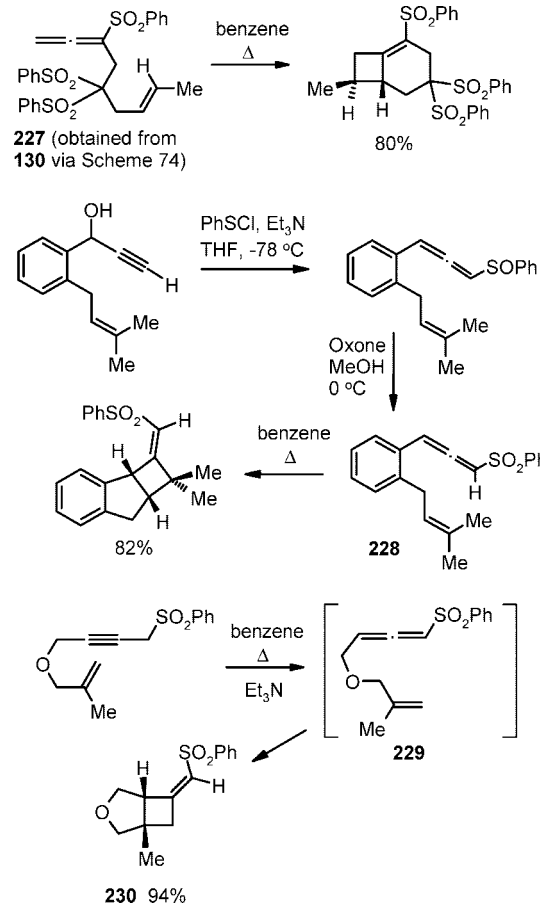
Several groups have investigated the intramolecular [2 + 2] cycloadditions of allenic sulfones tethered to alkene or acetylene moieties, which provide the means for the synthesis of fused-ring cyclobutanes. The stereo- and regiochemistry of these processes depends on whether the allenic sulfone is tethered to the alkene at its α- or γ-position, as well as by the length and nature of the tether and the position of key substituents. Padwa et al.[155] generated the α-tethered precursors **226** by the addition of stabilized homoallylic anions to dienyl sulfone **130** (see also Scheme 61), resulting in subsequent reactions via the unactivated distal double bond of the allene moiety. The cycloadditions proceeded under thermal conditions via a postulated diradical mechanism, in which 1,6-*exo-trig* closure was favored over the 1,7-*endo* mode (Scheme 74).[155,225] The high stereoselectivity of the cycloaddition with respect to the geminal alkene substituents (Me and H) is seen in the example of **227** (Scheme 75) and was attributed to slow rotation and relatively fast ring-closure of the diradical intermediate. In another example, the γ-tethered allenic sulfone functionality of **228** was introduced by the sulfenylation and [2,3]sigmatropic rearrangement of the corresponding propargyl alcohol, followed by oxidation of the intermediate allenic sulfoxide.[225,226] In this case, ring-closure occurred via a 1,7-*exo-trig* process. The base-catalyzed isomerization of the corresponding propargylic sulfone provided access to the γ-tethered allenic sulfone **229**, which cyclized to the fused tetrahydrofuran derivative **230**.[226] These examples are also shown in Scheme 75.

A series of allenynes containing α-tethered allenic sulfone groups (e.g., **231**) was studied by Mukai et al.,[227] who observed that the distal double bond was again the site of the cycloaddition, which proceeded via a similar proposed radical mechanism. In contrast, the proximal allenic double bond reacted with the alkene moiety of **232** to afford **233**, which was required as a key intermediate in the synthesis of Δ^7-protoilludine by Stenstrøm et al.[228] Allenic sulfones tethered to conjugated dienes such as **234** and **235** can, in principle, react via either [2 + 2] or [4 + 2] cycloadditions.

Scheme 74



Scheme 75



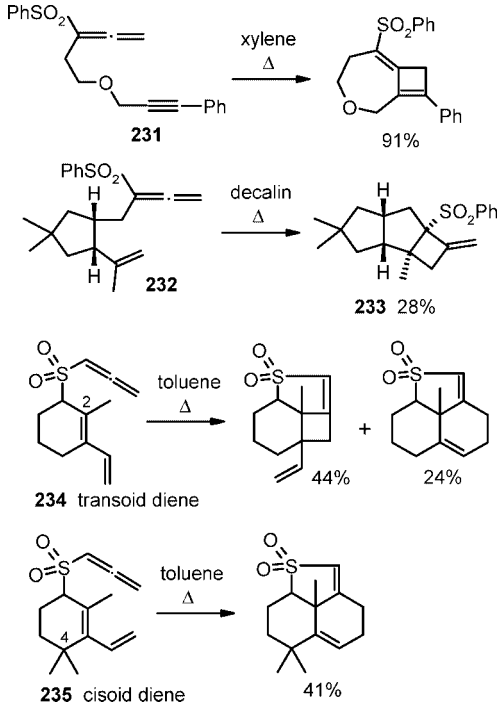
Kanematsu and co-workers[156a,b] demonstrated that substituents at C-2 (as in **234**) result in steric interactions that destabilize the cisoid conformation required for [4 + 2] cycloaddition, thereby favoring the [2 + 2] product. On the other hand, C-4 substituents (as in **235**) destabilize the transoid conformation, and [4 + 2] cycloaddition occurs preferentially. The latter effect predominates even in the presence of a C-2 substituent (Scheme 76).

4.3. With Imines, Enamines, Ynamines, And Enol Ethers

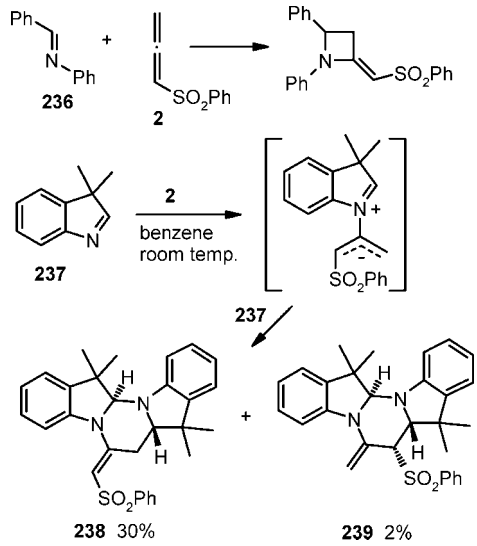
Several examples of [2 + 2] cycloadditions of imines such as **236** with allenic sulfone **2** to afford azetidines were reported by Harano et al.[217a,229] MO calculations implicated a two-step process, in which an initial conjugate addition of the imine to the allene moiety produced a zwitterion intermediate, followed by ring-closure. The isolation of 2:1 adducts such as **238** and **239** in the case of imine **237** indicated that the intermediate can be relatively long-lived (Scheme 77).[229]

Braverman et al.[230] investigated the cycloadditions of enol ethers with allenic sulfone **240** at high pressure and observed that the distal double bond of the latter reacted exclusively, affording single regio- and stereoisomers. On the other hand, the more electron-rich enamine **241** produced both possible regioisomers (Scheme 78). The authors proposed that the former process proceeds through a more concerted mechanism, whereas the latter involves ring-closure of dipolar intermediates. Furthermore, high pressure reduced the likelihood of diradical intermediates, because that pathway has a less negative volume of activation. Other enamines

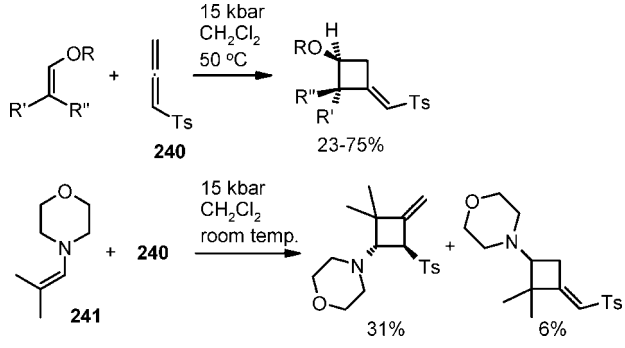
Scheme 76



Scheme 77

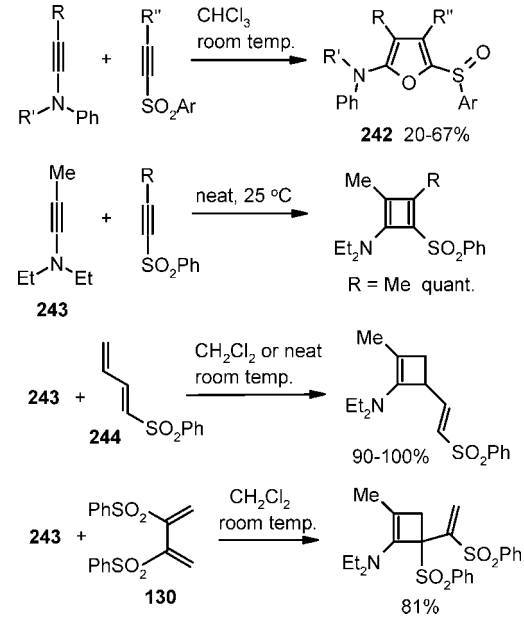


Scheme 78



that were studied earlier afforded only the products of attack upon the proximal double bond of the allenic sulfone.[231]

Scheme 79

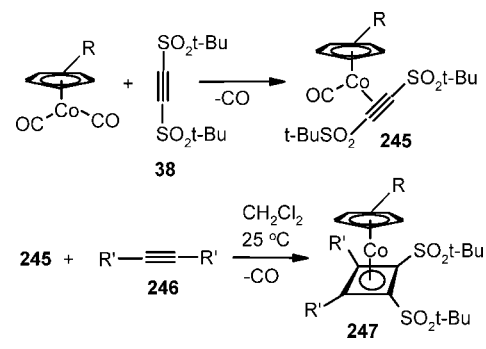


Himbert and co-workers[232] reported an unusual cycloaddition of ynamines derived from anilines with several acetylenic sulfones, which produced the corresponding furan products **242**. The formation of an expected zwitterion intermediate, followed by ring-closure via a Pummerer-like mechanism was postulated. Independent studies by Eisch et al.[233] with more nucleophilic *N*,*N*-dialkylynamines such as **243** indicated that the process involves an initial [2 + 2] cycloaddition, forming the corresponding cyclobutadiene derivatives as metastable intermediates. Other examples of the cycloadditions of ynamine **243** with dienyl sulfones **244**[233a] and **130**[146c] resulted in the preferential formation of [2 + 2] instead of [4 + 2] cycloadducts (Scheme 79).

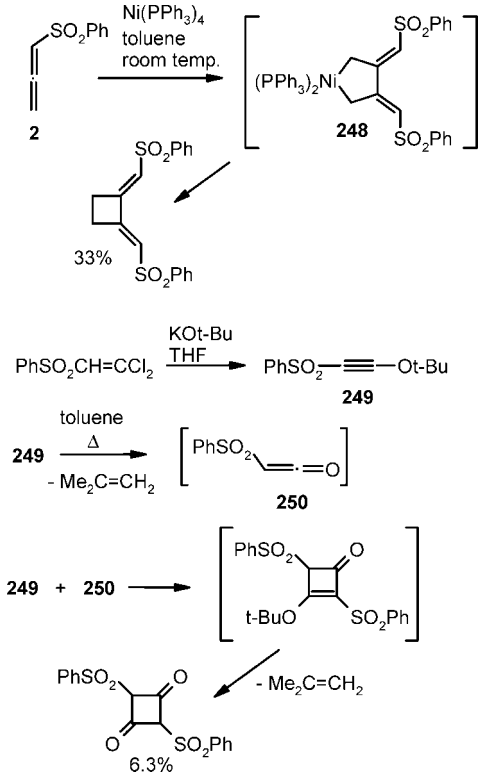
4.4. Other [2 + 2] Cycloadditions

Gleiter et al.[234] reacted the strongly electrophilic cobalt complexes **245**, derived from acetylenic sulfone **38**, with electron-rich alkynes **246**, to form the corresponding cyclobutadiene complexes **247**, as shown in Scheme 80. A broad range of alkynes proved suitable for this process, including diaryl[234b,c] and dialkyl[234b,c] derivatives, ynamines,[234d] acetylenic chalcogenides,[234c,d] tetrathiacycloalkadiynes,[234e] 1,4-di-*t*-butoxyethyne,[234a] and 1,4-di-*t*-butoxy-1,3-butadiyne.[234a] Acetylenes containing electron-withdrawing sulfone, ester, and catecholboryl substituents failed to react in this manner with **245**.

Scheme 80



Scheme 81

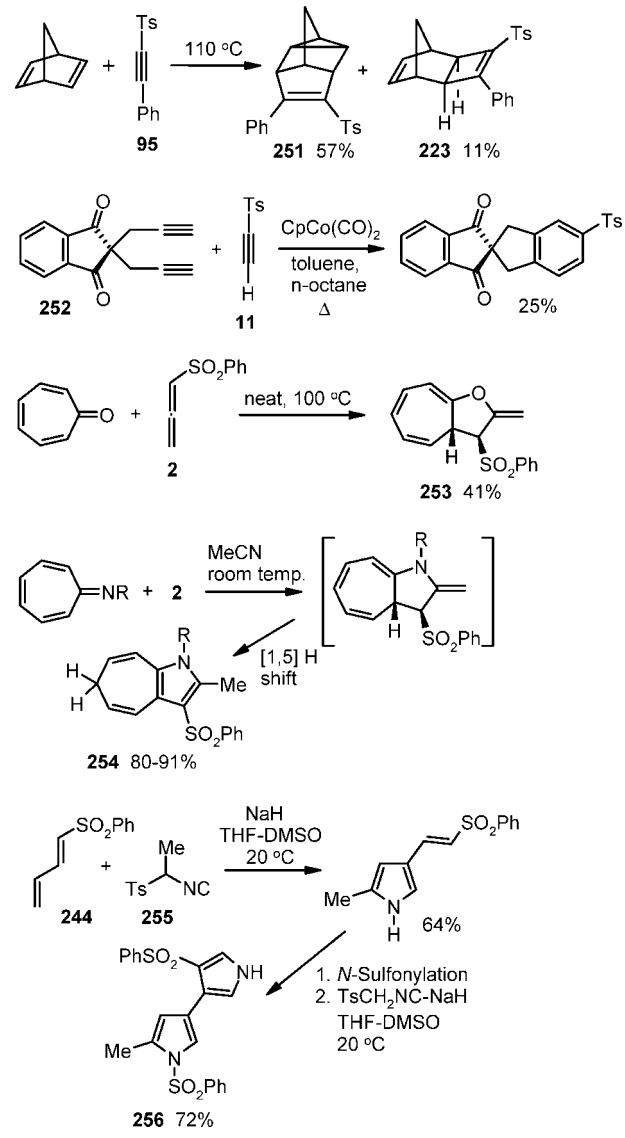


The nickel-catalyzed [2 + 2] dimerization of allenic sulfone **2** afforded the corresponding head-to-head cycloadduct as a single isomer,[235] presumably via the metallacycle **248**, followed by reductive elimination of nickel (Scheme 81). The uncatalyzed dimerization of the unstable acetylenic sulfone **249** proceeded via its decomposition to the ketene **250**, followed by [2 + 2] cycloaddition of the latter with a second mole of **249**.[236] Although the product in this case was formed in low yield, this example shows that cycloadditions of acetylenic sulfones with ketenes are feasible and may have broader applications (Scheme 81).

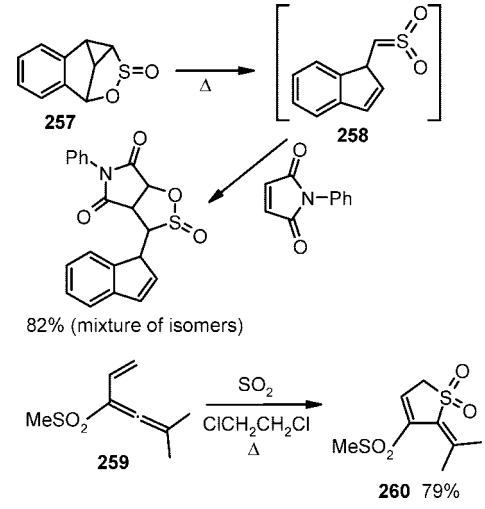
5. Miscellaneous Cycloadditions

In contrast to the Ru-catalyzed [2 + 2] cycloaddition shown in Scheme 73, norbornadiene reacted with acetylenic sulfone **95** in the absence of a catalyst to afford the [2 + 2 + 2] cycloadduct **251** as the major product, along with a small amount of the corresponding cyclobutene **223** formed by [2 + 2] cycloaddition.[42] Bis(propargyl)phthalide **252** underwent a cobalt-catalyzed [2 + 2 + 2] cycloaddition with acetylenic sulfone **11**.[47] An [8 + 2] cycloaddition of tropone with allenic sulfone **2** was observed, while a series of tropone imines reacted similarly, followed by 1,3 and 1,5 hydrogen shifts, producing **253** and **254**, respectively.[117] Dienyl sulfone **244** underwent a sequential double cycloaddition with isonitrile **255** and TosMIC ($TsCH_2NC$) in the synthesis of bispyrrole **256**, which was required as an intermediate in a new route to the antitumor agent CC-1066 (Scheme 82).[237] An unusual fragmentation−cycloaddition was observed when the pyrolysis of **257** produced sulfene **258**, which was trapped *in situ* with *N*-phenylmaleimide[238] (for cyclizations via sulfenes derived from sulfones bearing two unsaturated substituents, see section 7.3). Finally, the cheletropic cycloaddition of sulfur dioxide to α- or γ-vinyl allenic sulfones such as **259** afforded the corresponding sulfolenes **260**.[239] These reactions are illustrated in Scheme 83.

Scheme 82



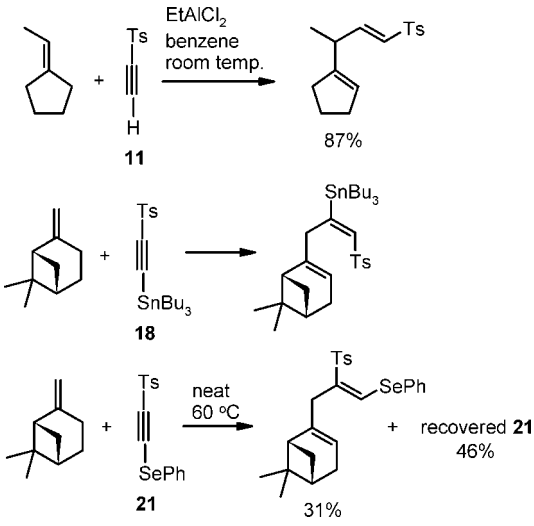
Scheme 83



6. Ene Reactions

In addition to the formation of the minor product **225** obtained together with the corresponding [2 + 2] cycloadduct from methylenecyclohexane and allenic sulfone **2** in

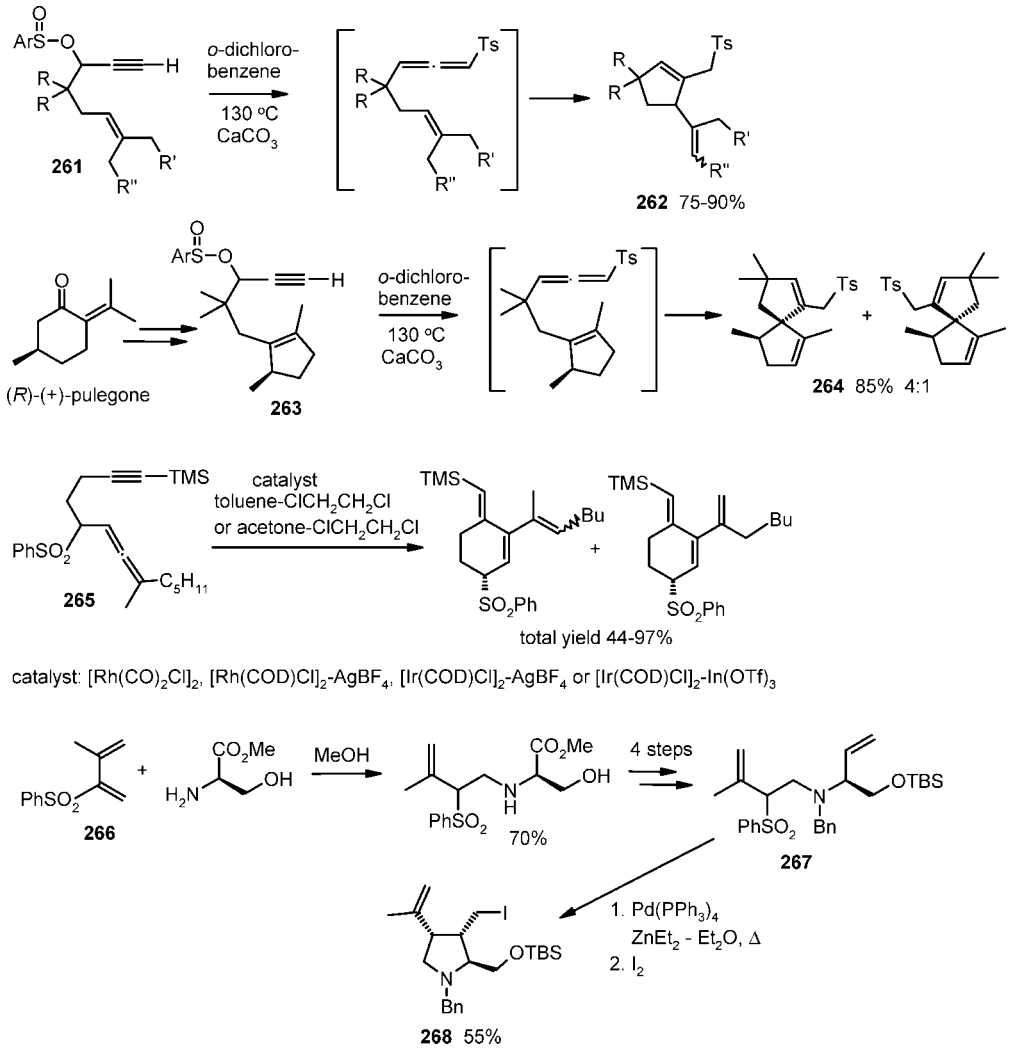
Scheme 84



Scheme 73,[224] Snider et al. also observed a series of other ene reactions when various alkenes were treated with acetylenic sulfone **11** in the presence of ethylaluminum dichloride.[240] Similarly, the tributylstannyl[39] and phenylseleno[66] derivatives **18** and **21** effected ene reactions with β-pinene in the absence of Lewis acid catalysts, with anomalous regiochemistry observed in the case of **21**. These examples are shown in Scheme 84.

Strictly speaking, the above processes are not cyclization reactions, although concerted ene reactions do proceed via a cyclic transition state. However, several examples of intramolecular ene reactions that afford cyclized products have also been reported. Thus, Uguen et al.[241] generated allenic sulfones from the [2,3]sigmatropic rearrangement of propargyl sulfinate esters **261** and **263**, followed by ene cyclization at elevated temperatures to produce the corresponding cyclopentenes **262** and spiro compounds **264**, respectively. On the other hand, Brummond and McCabe[242] reported a rhodium- or iridium-catalyzed intramolecular ene cyclization of allenes **265**, where the sulfonyl group is in the allylic position. The products were obtained as mixtures of regio- and geometrical isomers that comprise potential intermediates for the synthesis of ovalicin. An unusual example of a palladium-catalyzed "zinc−ene" reaction was employed to prepare **268** via the initial conjugate addition of the methyl ester of serine to dienyl sulfone **266**, followed by ene cyclization of the derived allyl sulfone **267**.[243] The product **268** was produced as a single stereoisomer and was a key intermediate in the synthesis of (−)-kainic acid. These examples are provided in Scheme 85.

Scheme 85



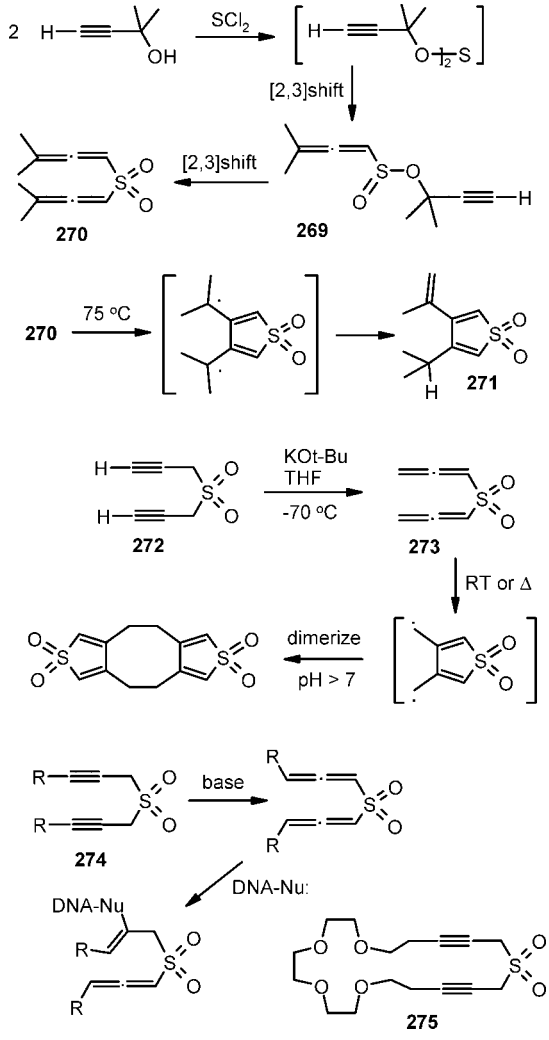
7. Cyclizations of Bis(allenic) Sulfones and Their Congeners

Bis(allenic) sulfones and congeners that contain a sulfone group flanked by an allene moiety and a second, different unsaturated sulfone substituent undergo a variety of complex and often unexpected cyclization reactions. Interest in such compounds intensified with the discovery that they exhibit potent DNA-cleaving activity, making them potentially valuable as anticancer agents.

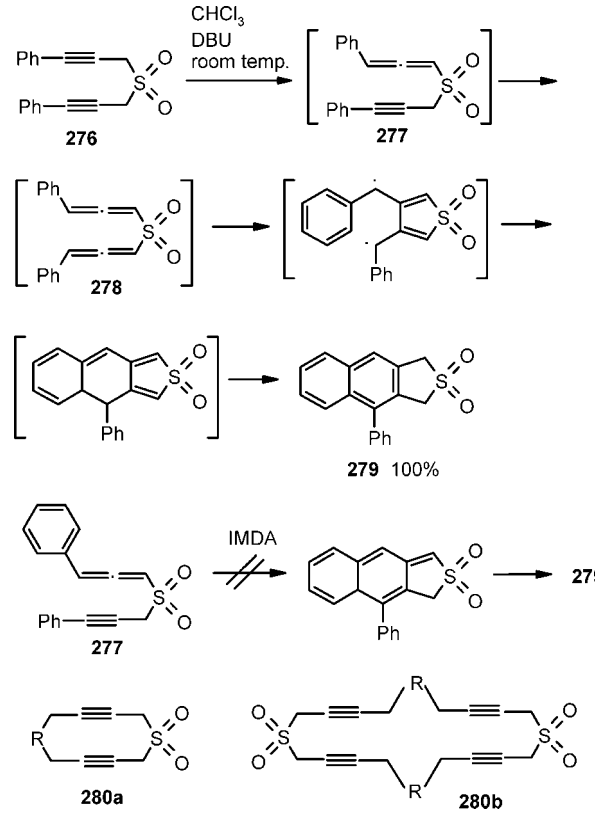
7.1. Bis(allenic) Sulfones

These compounds are typically prepared or generated *in situ* by the base-catalyzed isomerization of the corresponding propargyl isomers or by [2,3]sigmatropic rearrangement of propargyl allenesulfinates. Pioneering studies by Braverman and colleagues[244] demonstrated that sulfone **270**, obtained by the rearrangement of sulfinate ester **269**, afforded the corresponding thiophene 1,1-dioxide **271** when heated in a variety of solvents. The diradical mechanism shown in Scheme 86 was proposed for the cyclization and further experiments ruled out both an ionic mechanism on the basis of insensitivity of the rate to solvent polarity and an ene reaction from the absence of kinetic isotope effects with the corresponding hexadeuterio derivative.[245] Bis(allenes) bridged by ether, sulfide, and selenide groups also cyclized in this manner.[245,246] A similar cyclization and dimerization of bis(allenic) sulfone

Scheme 86



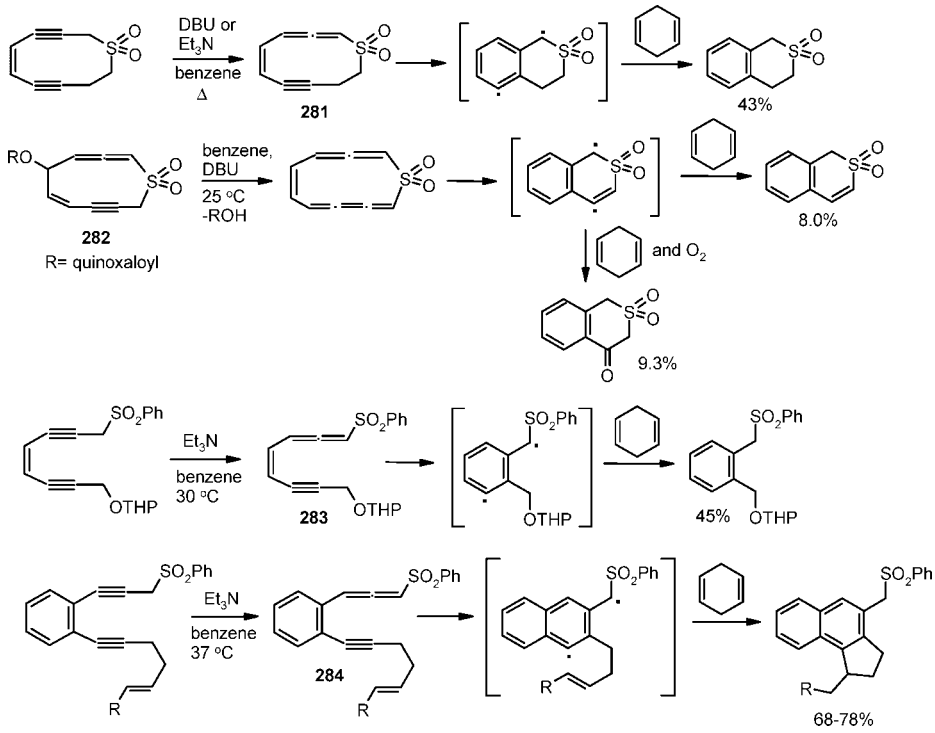
Scheme 87



273 was reported by Garratt et al., who generated it from the isomerization of the propargyl isomer **272**.[247] The diradical intermediates favored by Braverman and Garratt are reminiscent of those that are formed during the cyclizations of enediyne antibiotics. Nicolaou et al.[248] observed that several cyclic and acyclic bis(propargylic) sulfones such as **274** were capable of cleaving DNA at slightly alkaline pH. However, this was attributed to the *in situ* formation of the allenic sulfone isomer, which was in turn intercepted by nucleophilic groups in DNA through conjugate addition[249] and not via interaction with diradical intermediates of the type reported by Braverman and Garratt (Scheme 86). The alkylated DNA then underwent hydrolytic strand scission under the alkaline conditions. Similar studies of the crown ether−propargyl sulfone hybrid **275** by Kerwin[250] demonstrated that it too cleaved supercoiled DNA via conjugate addition to the corresponding allenic sulfone isomer.

Other variations of the above bis(allenic) sulfones were also reported. The introduction of amide substituents (−CONPh$_2$) in the α-position raised the temperature for the cyclization to 130 °C but still afforded the corresponding thiophene 1,1-dioxides.[251] Analogs with sulfide, selenide, and sulfoxide bridges, as well as ones with extended conjugation, were also extensively investigated by the Braverman group.[252] For example, the bis(phenyl) derivative **276** isomerized[252b] to the corresponding allene **278** and then cyclized rapidly at room temperature to produce **279** (Scheme 87). An alternative mechanism involving the IMDA reaction between the original alkyne moiety of one branch of the starting material and the isomerized phenylallene branch of **277** was ruled out in this example but could not be unequivocally excluded in some other cases. In general, compounds with sulfone bridges reacted faster than the corresponding sulfoxides or sulfides and allene formation was slower than subsequent cyclization. Out of several sulfones, sulfoxides, and sulfides

Scheme 88



assayed, only sulfone **276** proved effective at cleaving supercoiled DNA.[252b] Macrocycles such as **280** isomerized to allenes in the presence of triethylamine but failed to undergo diradical cyclization.[253]

7.2. Enynyl Allenic Sulfones

The interesting cyclization behavior and DNA-cleaving ability of bis(allenic) sulfones prompted several investigations of allenic enynes, such as **281**,[254] **282**,[255] **283**,[256] and **284**,[257] which underwent Myers cyclizations (Scheme 88) via diradical intermediates similar to those described in the previous section. As in the earlier work, it is not always clear whether DNA cleavage occurs by reaction with the diradical or through conjugate addition of nucleophilic groups to the allenic sulfone moiety. In general, the required allenes were produced by the isomerization of the corresponding acetylenes, and 1,4-cyclohexadiene was employed as a hydrogen donor to quench the intermediate diradicals. In the case of **284**, a 5-*exo* radical cyclization occurred prior to hydrogen transfer.

7.3. Cyclizations via Sulfene Intermediates

The thiolsulfonate **285** afforded a mixture of thiophene products that varied considerably in yield when heated in various solvents.[258] Their formation was rationalized by an initial [3,3]sigmatropic rearrangement to the sulfene **286**, followed by attack of the thioaldehyde sulfur atom upon the sulfene and further rearrangement of the resulting sulfinate anion. Alternatively, loss of sulfur dioxide from **286** resulted in cyclization via the carbene **287** (Scheme 89). Similar studies of the corresponding sulfinyl sulfone **288** and α-disulfone **291** suggested that transient sulfene intermediates **289** and **292** were again formed, but cyclization occurred via an intramolecular 1,3-dipolar cycloaddition of **290** in the former case, where the thiocarbonyl group served as the dipolarophile, and by an intramolecular [2 + 2] cycloaddition of **292** in the latter (Scheme 89).[259] Radical mechanisms could not be ruled out, however. The sulfene **294** was also postulated in the pyrolysis of acetylenic sulfone **293**, which was intercepted by [2 + 2] cycloaddition with alkenes, as in the examples of products **295** and **296** in Scheme 90.[260]

7.4. Anionic Cyclizations

Braverman et al. also reported an intriguing "carbanion walk" that was observed when **270** was treated with *n*-butyllithium. This consisted of four successive conjugate additions of sulfone-stabilized allenic anions to the allenic sulfone moiety of a second mole of **270** (shown for simplicity as a single step in Scheme 91), ultimately leading to the dithiaadamantane derivative **297**[245,261]

7.5. Other Cyclizations

Several other types of cyclizations have been reported with bis(allenic) sulfones. These occur via conjugate additions with amines,[262] electrocyclic ring-closures,[263] electrophilic processes,[264] and Pauson−Khand reactions[265] and are treated in sections 9.3, 12, 15.1, and 17.1, respectively.

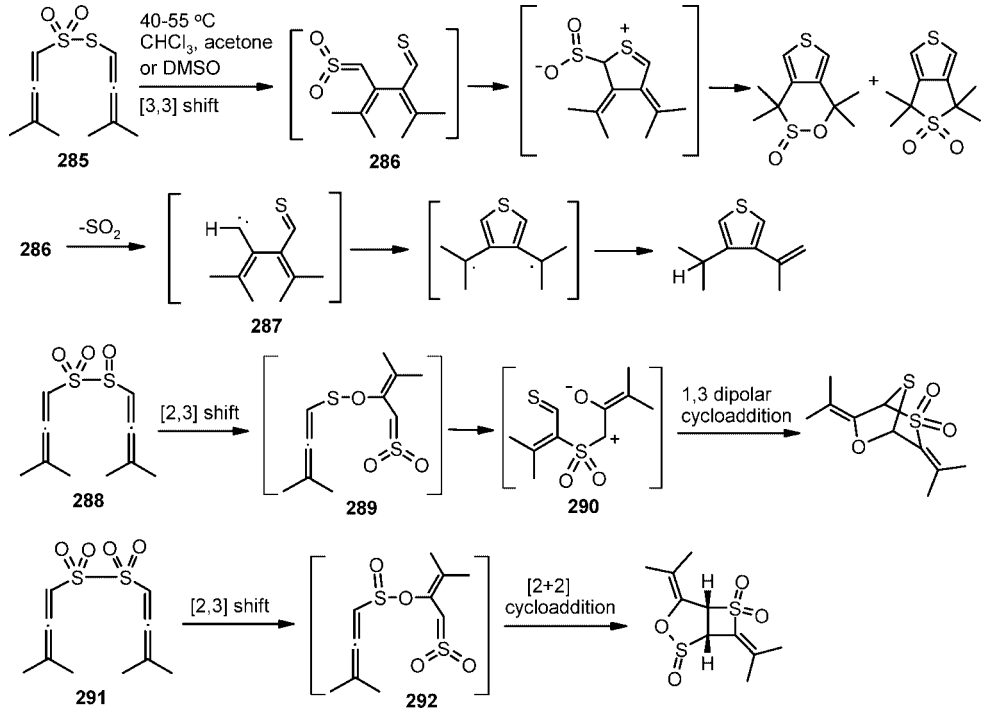
8. Intramolecular Conjugate Additions

The ability of the sulfone group to stabilize an α-anion makes unsaturated sulfones effective Michael acceptors. Thus, a variety of heterocyclic and carbocyclic products can be obtained by intramolecular conjugate additions of suitable nucleophiles tethered to the unsaturated sulfone moiety. Different ring sizes are therefore available by choosing the appropriate tether length.

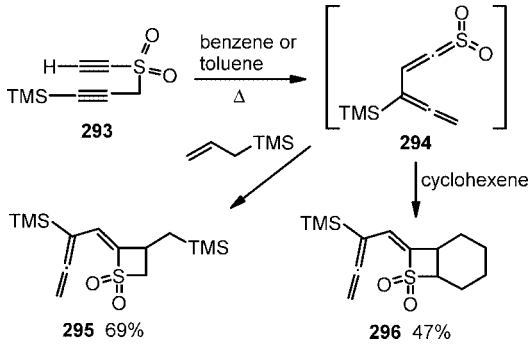
8.1. Oxygen Nucleophiles

Cyclizations of oxygen nucleophiles have been reported with acetylenic, allenic, and dienyl sulfones. Thus, acid- or

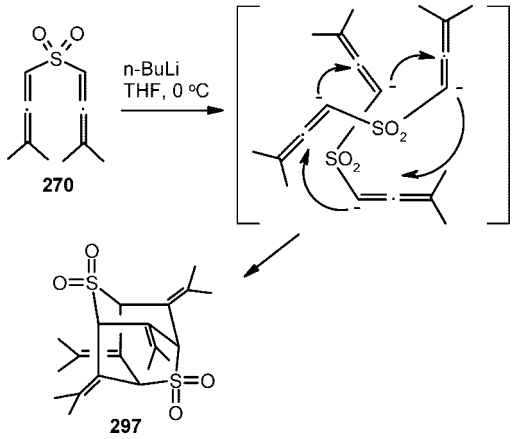
Scheme 89



Scheme 90

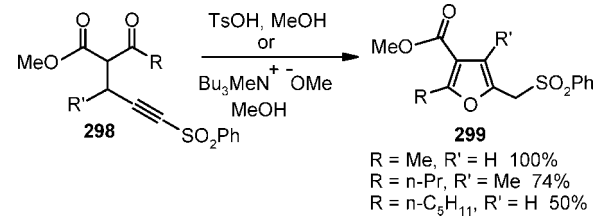


Scheme 91



base-catalyzed enolization of keto esters **298** was followed by intramolecular conjugate addition to the acetylenic sulfone moiety, resulting in the formation of furans **299** after double bond isomerization (Scheme 92).[266] The corresponding sulfoxide behaved similarly but cyclized in lower yield. The products served as key intermediates for the synthesis of calicogorgins A and C.

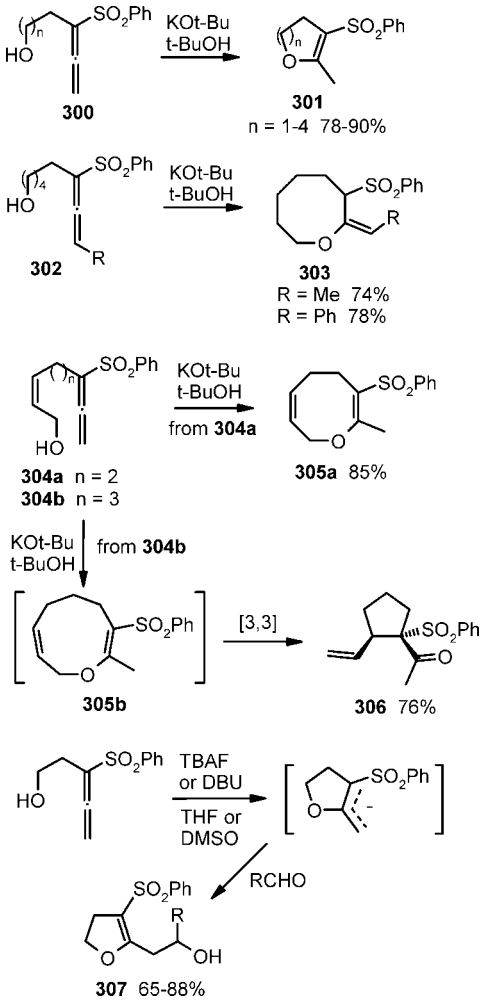
Scheme 92



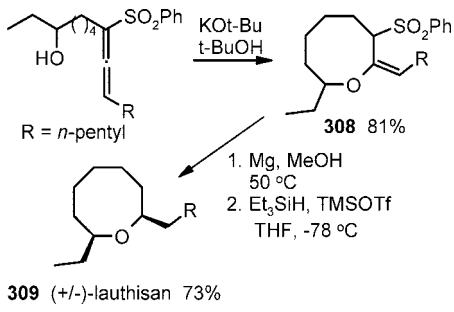
Extensive studies were reported by Mukai et al.[267] of the cyclizations of allenic sulfones (or allenes with other activating groups) containing pendant hydroxyalkyl substituents at the α-position. The formation of products with endo- or exocyclic unsaturation was possible from protonation of the intermediate sulfone-stabilized allylic anion at either the γ- or α-position, respectively, and the product distribution depended on the tether length and the presence of additional γ-substituents. For example, allenic sulfones with saturated, unsubstituted hydroxyalkyl substituents, as in **300**, produced 5−8-membered heterocycles **301**, containing endocyclic alkenes, in generally excellent yields.[267a] On the other hand, the γ-substituted derivatives **302** gave oxocanes **303** with exocyclic double bonds (Scheme 93).[267a] Similar cyclizations were observed with *cis*-allylic alcohol derivatives **304**, but while the eight-membered product **305a** was isolated in high yield, the initial nine-membered product **305b** underwent spontaneous Claisen rearrangement to afford cyclopentyl ketone **306**.[267b] The authors also demonstrated that the intermediate sulfone-stabilized anions could be trapped with aldehydes, as in the case of products **307** (Scheme 93).[267c] The usefulness of this cyclization methodology for the preparation of medium rings was further illustrated by the synthesis of (±)-lauthisan (**309**), by the further desulfonylation and double bond reduction of the oxocane **308** (Scheme 94).[267d]

In related work, allenic sulfones containing carboxylic acid substituents instead of hydroxyl groups underwent similar cyclizations to produce lactones as initial products.[267c]

Scheme 93



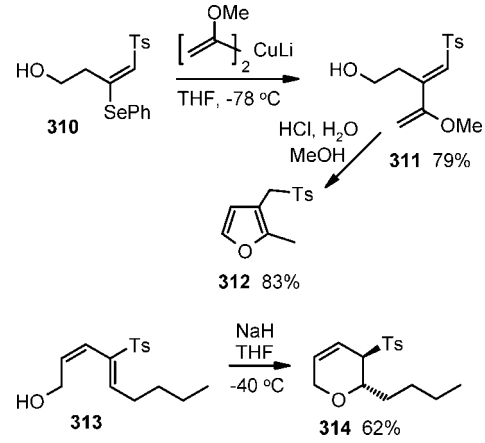
Scheme 94



Moreover, allenic sulfones containing hydroxyalkyl substituents at the γ-position were generated in situ from their propargylic sulfone isomers and cyclized readily via intramolecular conjugate additions.[268]

Several examples of alternative types of cyclizations of dienyl sulfones bearing hydroxyalkyl or carboxylic acid substituents have also been reported and are shown in Scheme 95. Dienyl sulfone **311** was obtained by cuprate substitution of the corresponding selenide **310**. Cyclization was then effected by acid-catalyzed ketalization and elimination of methanol to afford the furan **312**.[269] Cyclization of **313** was achieved via conjugate addition of the corresponding alkoxide to the dienyl sulfone function and afforded only the 2,3-*trans* isomer of the product dihydropyran **314**.[270]

Scheme 95



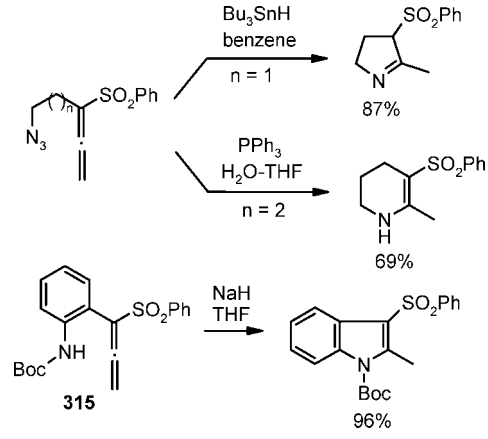
8.2. Nitrogen Nucleophiles

Several examples where ring-closure was effected directly by intramolecular conjugate addition of an amine to an allenic sulfone were reported by Mukai et al.,[172] and a few are shown in Scheme 96. In addition, analogs of compounds **315** containing homologated tethers produced the corresponding quinolines instead of indoles.

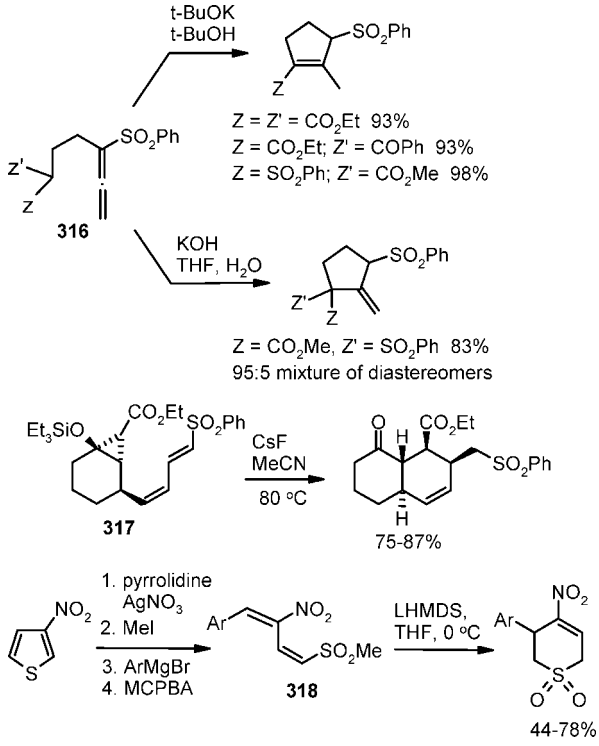
8.3. Carbon Nucleophiles

Mukai and co-workers[271] also studied the cyclization of enolates and related species tethered to allenic sulfones (e.g., **316** in Scheme 97). The products typically underwent dealkoxycarbonylation under the basic reaction conditions to afford endocyclic cyclopentenes. When conditions did not promote dealkoxycarbonylation, cyclopentanes with exocyclic double bonds were obtained. Homologues of **316** led to six- and seven-membered cyclic products. Marino and Long[272] reported the interesting cyclization of **317** in the presence of fluoride ion, which triggered the process by desilylation and liberation of the corresponding free alkoxide, followed by ketone formation and cyclopropane cleavage, with conjugate addition effected by the resulting ester enolate at the β-position of the dienyl sulfone moiety. The product was formed with complete stereoselectivity and served as an intermediate for the synthesis of dihydrocompactin. Petrillo et al.[273] developed a sulfone-based method for the ring expansion of 3-nitrothiophene to thiopyran *S*,*S*-dioxide derivatives. The required dienyl sulfone intermediates **318** were obtained from the thiophene in four

Scheme 96



Scheme 97



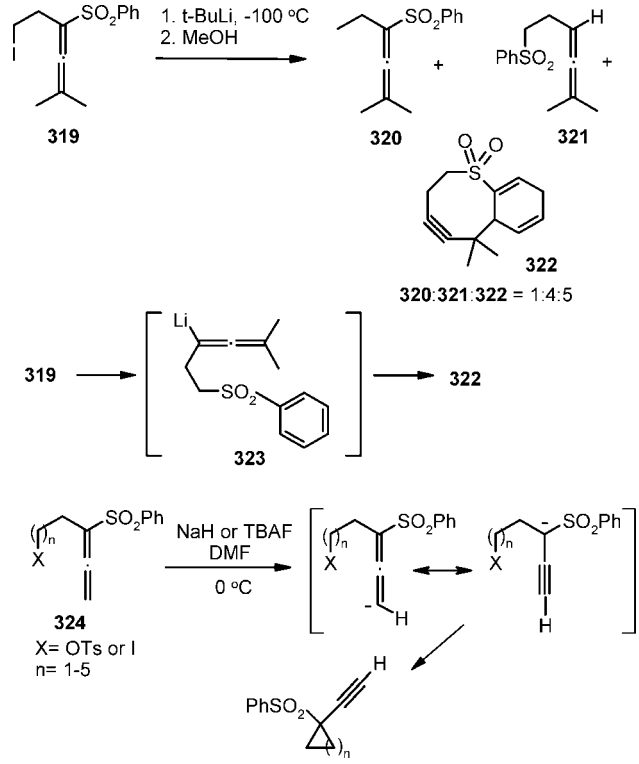
steps. The sulfone functionality then served to stabilize a nucleophilic anion produced by deprotonation of the adjacent methyl group, which performed an intramolecular conjugate addition to the δ-position of the doubly activated diene moiety that comprised the other sulfone substituent (Scheme 97).

In a different type of process, Crandall and Ayers[274] noted that treatment of the iodoethyl-substituted allenic sulfone **319** with *t*-butyllithium produced the cyclic sulfone **322**, along with the reduction product **320** and the transposed sulfone **321**. The cyclization was attributed to the intramolecular addition of the allenic anion **323** to the activated phenyl group of the phenylsulfonyl moiety. Allenic sulfones **324** containing leaving groups or other electrophiles such as aldehydes or Michael acceptors tethered to the α-position also cyclized when treated with a suitable base.[275] Examples are displayed in Scheme 98.

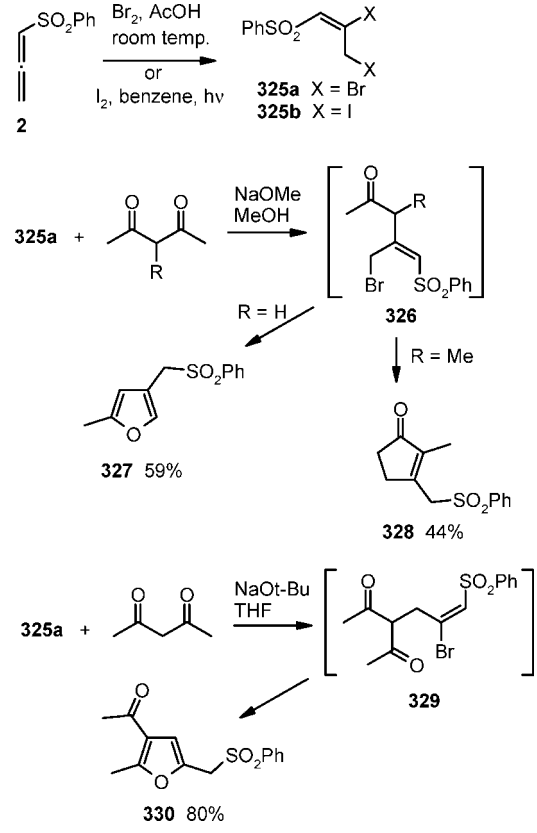
8.4. Cyclizations of 2,3-Dihalovinyl Sulfones

Padwa and co-workers[276] discovered that the conversion of allenic sulfone **2** to the 2,3-dibromo- and 2,3-diiodovinyl derivatives (**325a** and **325b**) (Scheme 99) provided several new opportunities for cyclization reactions. When enolates of 1,3-dicarbonyl compounds were generated with methanolic sodium methoxide and reacted with **325a**, the products depended on whether a 2-substituent was present in the dicarbonyl compound. In unsubstituted examples, formation of the intermediate **326** via addition−elimination of the vinylic bromide and deacetylation was followed by intramolecular O-alkylation to afford the furan **327** after isomerization of the double bond. In contrast, the presence of a 2-substituent resulted in C-alkylation by the allylic bromide to produce cyclopentenone **328**.[276a,d−f] The change in pathway was attributed to A-strain created by the 2-substituent during O-alkylation. A further variation of these cyclizations resulted from a change of base to sodium *t*-butoxide in THF. Under these conditions, the enolate reacted by substitution of the

Scheme 98



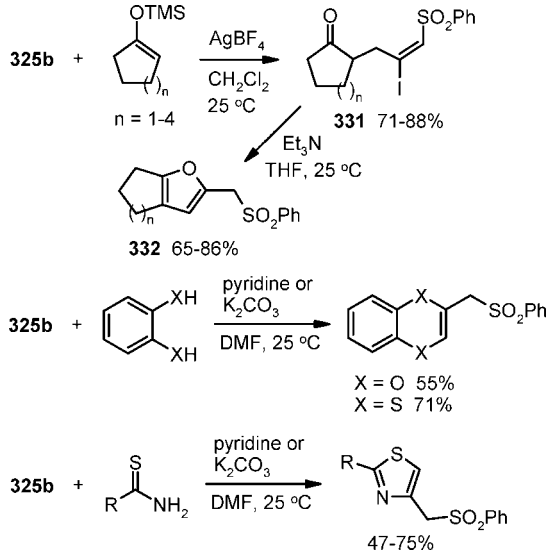
Scheme 99



allylic bromide of **325a** to furnish **329**, followed by cyclization to **330** through addition−elimination.[276b] Thus, three different products are possible, depending on the presence or absence of a 2-substituent and the choice of base and solvent, as illustrated by the examples in Scheme 99.[276a,b,d−f]

The diiodide **325b** reacted with cyclic enol silyl ethers in the presence of silver tetrafluoroborate to afford substituted

Scheme 100



cycloalkanones **331**. Cyclization by intramolecular addition−elimination then produced bicyclic furans **332**.[276c,e] These and several other examples of cyclizations achieved with **325b** and catechol,[276d] 1,2-benzenedithiol,[276d] and thioamides[276d] are shown in Scheme 100.

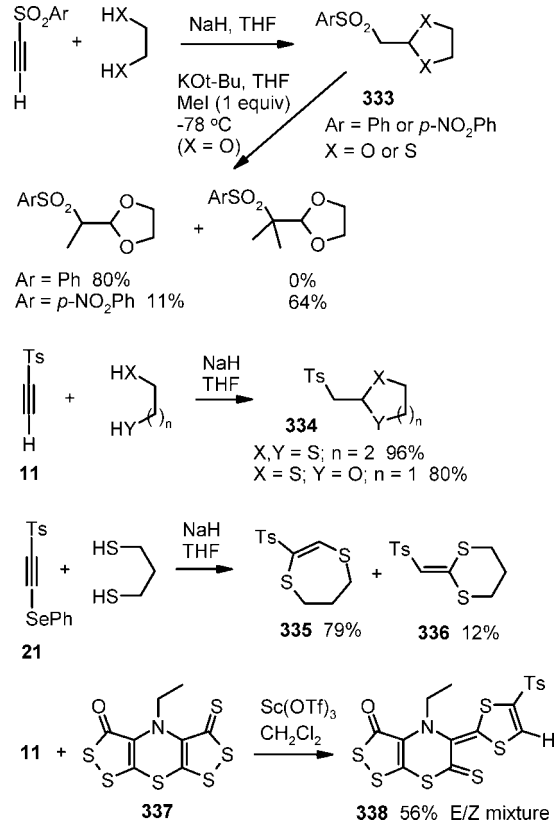
9. Tandem Conjugate Addition

In principle, the two orthogonal, cumulated, or conjugated π-bonds of acetylenic, allenic, and dienyl sulfones, respectively, can accommodate the conjugate additions of two nucleophiles. Isomerization of the remaining double bond into the α,β-position of the sulfone after the first addition has taken place may be required to activate it toward the attack of the second nucleophile (as in the case of an allenic or dienyl sulfone), but this typically occurs spontaneously under the conditions of the reaction. When the attacking molecule contains two nucleophilic functionalities or when a nucleophile capable of double conjugate additions attacks a sulfone flanked by two unsaturated groups, then tandem conjugate additions result in cyclizations.

9.1. Cyclization of Acetylenic and Allenic Sulfones with Bifunctional Nucleophiles

As expected, simple dithiols,[277−279] diols,[277,279] and hydroxy thiols[278] can perform double conjugate additions to terminal acetylenic sulfones, resulting in the formation of dithioacetals, acetals, and mixed thioacetals, respectively, as in the examples of **333**[277] and **334**[278a] (Scheme 101). Acetylenic sulfone **11** can be used as a protecting group for thiols via conjugate addition, followed by deprotection by elimination.[278] Deprotonation and alkylation of cyclic acetal products α to the sulfone group may be carried out,[277] while dithioacetals undergo prior ring-opening by elimination of thiolate followed by S-alkylation.[278a] Chiral diols were used in the preparation of acetals analogous to **333** as potential chiral synthons for further transformations.[277,279] The β-phenylseleno acetylenic sulfone **21** afforded chiefly the 1,2-addition product **335** with 1,3-propanedithiol, while the expected dithioketal **336** was formed in only a small amount (Scheme 101).[280] A possible pathway for this reaction is the conjugate addition of one thiol group to the unsaturated selenide moiety (anti-Michael to the sulfone group), followed

Scheme 101

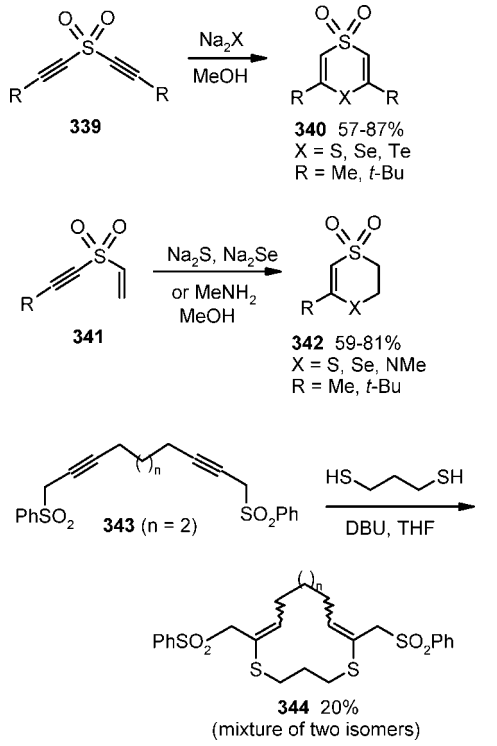


by addition−elimination of the second thiol to the resulting vinyl sulfone. Thus, the phenylseleno group of **21** competes with the sulfone group in directing conjugate additions, as well as in directing the regiochemistry of [4 + 2] cycloadditions, as was shown previously in Scheme 18. In contrast, 1,3-propanediol afforded an acyclic 1:2 anti-Michael adduct with two moles of **21** instead of cyclized products under similar conditions. In a different type of process, the dithiolothiazine **337** cyclized with acetylenic sulfone **11** in the presence of scandium triflate to produce the dithiolane **338**[281] (Scheme 101). Cyclizations of thioureas with the phosphonate-substituted acetylenic sulfone **57**[69] or with propargyl sulfones[282] (via the corresponding allene isomers) to afford thiazolidine products have also been reported.

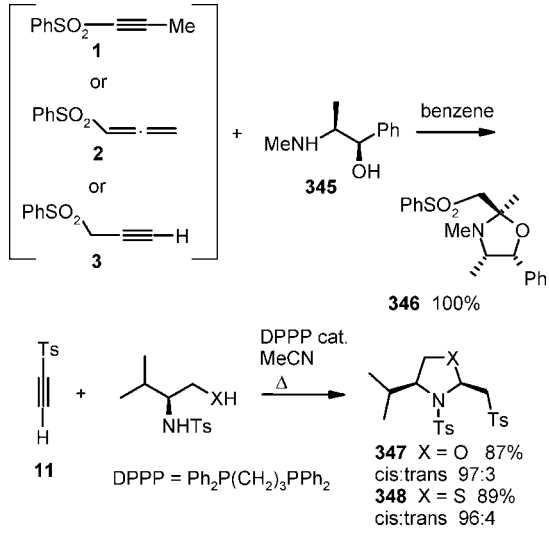
The reaction of bis(acetylenic) sulfones **339** with sodium sulfide,[283,284] selenide,[283] and telluride[283] resulted in cyclization by means of double conjugate additions, as in the examples **340**[283] shown in Scheme 102. The corresponding vinyl acetylenic sulfone **341** behaved similarly with sodium sulfide and selenide, and afforded the corresponding cyclic enamines **342** with methylamine.[285] In a related process, the double conjugate addition of 1,3-propanedithiol to the bis(propargyl) sulfone **343**, presumably via its allenic isomer, furnished the corresponding macrocycle **344** (Scheme 102).[286]

Chiral 1,3-oxazolidines were prepared enantioselectively by Cinquini et al.,[287] who treated each of the unsaturated sulfones **1**−**3** with (−)-ephedrine (**345**) to obtain the same product **346**. Similarly, Kwon and co-workers[288] effected a double conjugate addition of a valine-derived amino alcohol and thiol to acetylenic sulfone **11** in the presence of the nucleophilic catalyst DPPP to afford the respective products **347** and **348** (Scheme 103). De Lucchi et al.[289] employed the chiral camphor-based hydroxy thiol **349** to perform an

Scheme 102



Scheme 103

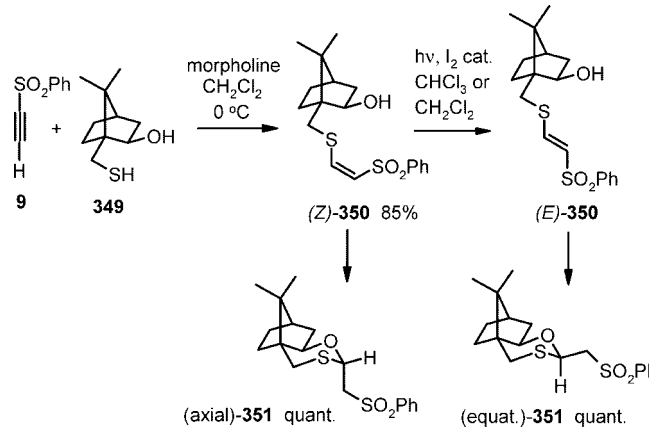


initial conjugate addition of the thiol moiety to acetylenic sulfone **9**, affording the *Z*-adduct **350** exclusively. Subsequent ring-closure by intramolecular ketalization was carried out by irradiation with sunlight in the presence of a catalytic amount of iodine. The latter process was postulated to proceed via isomerization of *Z*-**350** to *E*-**350**, with each geometrical isomer cyclizing stereospecifically to the axial and equatorial products **351**, respectively (Scheme 104). Acetylenes with other activating groups, as well as sulfoxide analogs of sulfide **350**, were also investigated.[289,290]

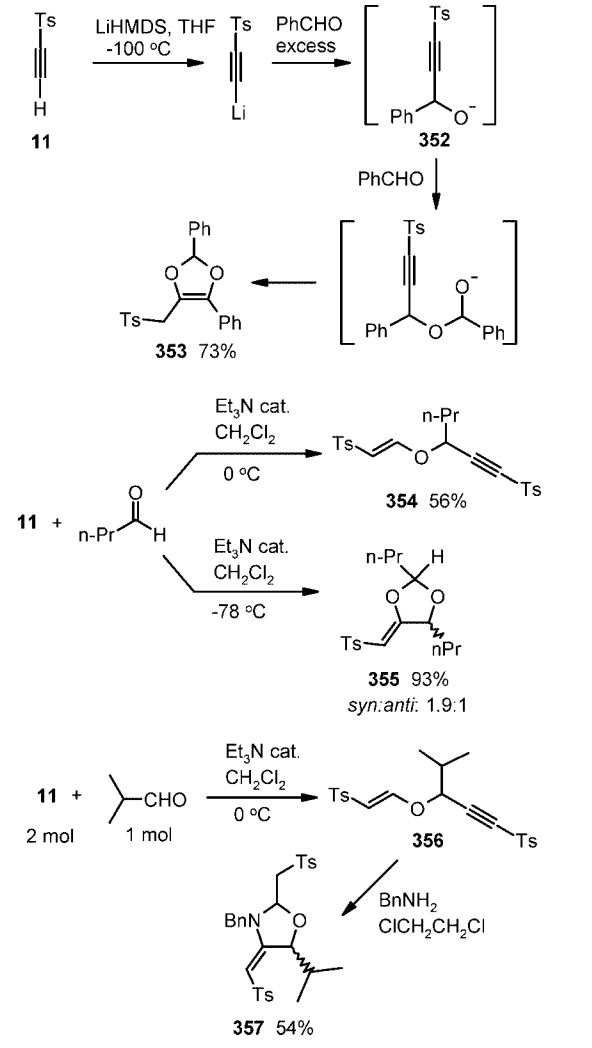
9.2. Cyclization of Acetylenic Sulfone 11 by Tandem Conjugate Addition

The acetylide anion of **11** is relatively unstable and prone to anionic polymerization. However, under carefully controlled conditions, it can be trapped by reactive electrophiles.

Scheme 104

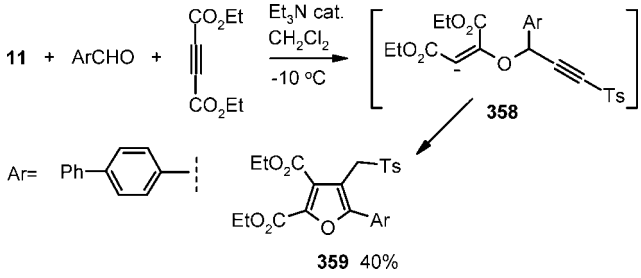


Scheme 105



This can in turn be exploited in the initiation of various cascade reactions leading to cyclic products, as shown in Scheme 105. For example, the 1:2 cyclic ketal adduct **353** was obtained by addition of the acetylide anion of **11** to benzaldehyde, followed by addition of the resulting alkoxide **352** to a second mole of aldehyde and finally by cyclization via an intramolecular conjugate addition and double bond isomerization.[291] García-Tellado and co-workers[292] investigated several similar cyclization reactions in depth with a variety of aldehydes and ketones and found that the initially formed alkoxides can attack a second mole of either **11** via

Scheme 106

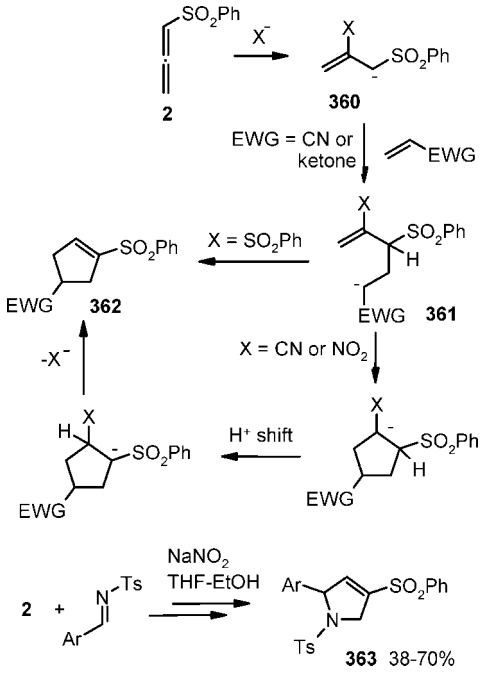


conjugate addition to produce **354** or the carbonyl compound, with subsequent cyclization leading to ketal **355**, in this case containing an exocyclic double bond. When the adduct **356** was treated with *n*-benzylamine, the oxazolidine **357** was obtained instead.[293] A related cascade reaction was reported by Wang et al.,[294] who trapped the initial alkoxide with diethyl acetylenedicarboxylate, with cyclization possibly occurring by intramolecular conjugate addition of the intermediate anion **358** to the acetylenic sulfone moiety to afford **359** (Scheme 106).

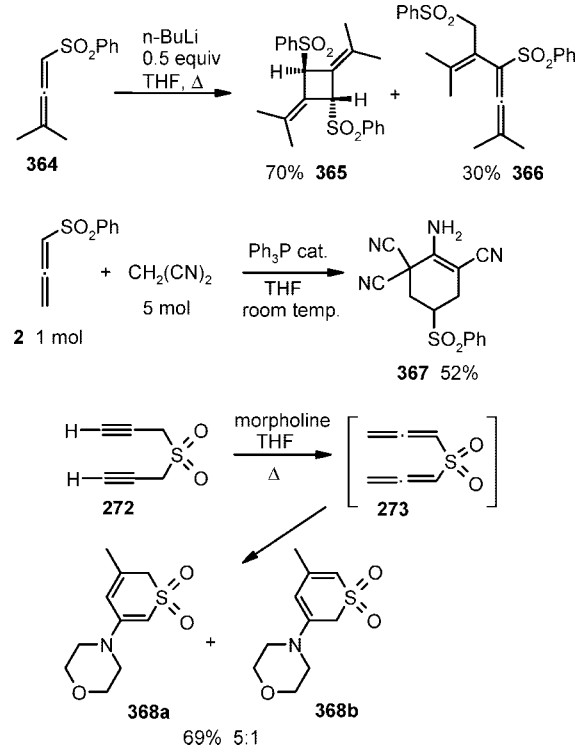
9.3. Cyclization of Allenic Sulfones by Tandem Conjugate Addition

Padwa and Yeske[295] described a formal [3 + 2] cyclization protocol based on the conjugate addition of nucleophiles such as sulfinate, cyanide, and nitrite anions to allenic sulfone **2**. The resulting sulfone-stabilized anions **360** were then captured in a second conjugate addition to acrylonitrile or an enone, followed by cyclization of **361** and elimination of the original nucleophile to afford the corresponding functionalized cyclopentene products **362**. The proposed mechanism is shown in Scheme 107. More recently, Robina et al.[296] extended the process to the [3 + 2] cyclizations of imines, which afforded 2-aryl-4-phenylsulfonyl-3-pyrrolines **363**. A complementary protocol employing allenic sulfides produced the analogous 3-phenylsulfonyl derivatives after oxidation of the sulfide group.

Scheme 107



Scheme 108

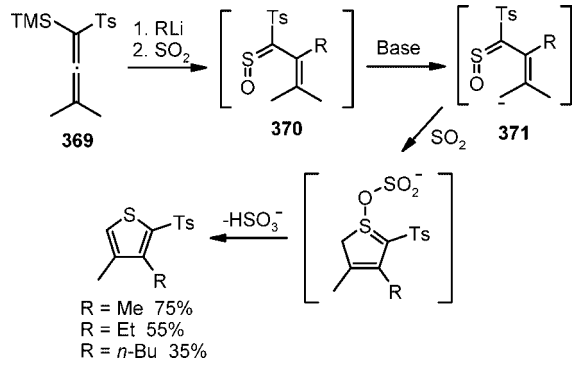


There are several other remarkable examples of cyclizations of allenic sulfones by cascades of conjugate addition reactions. Braverman and co-workers[297] reported that, in a manner reminiscent of the cyclization of bis(allenic) sulfone **270** shown in Scheme 91, the monoallene analog **364** underwent a similar mutual conjugate addition of the corresponding sulfone-stabilized vinyl anion of one molecule to the activated double bond of a second one, affording the cyclobutane **365**, along with the simple adduct **366**. The cyclization of malononitrile with allenic sulfone **2** to afford **367** by a complex cascade of conjugate additions and substitution reactions was described by Lu and Lu.[298] The bis(allenic) sulfone **273**, generated in situ from the corresponding bis(propargyl) isomer **272**, reacted with morpholine and other secondary amines to produce a mixture of double bond isomers **368a** and **368b**.[262] Presumably, the initial conjugate addition of the amine to one allenic sulfone moiety formed a sulfone-stabilized allyl anion, which then added to the remaining allenic sulfone (Scheme 108).

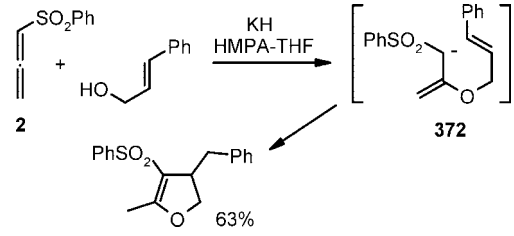
An unusual cyclization of α-silyl allenic sulfones **369** to thiophenes via their corresponding sulfine intermediates **370** was reported by Braverman et al.[299] Conjugate addition of an alkyllithium reagent to **369**, followed by trapping with sulfur dioxide and Peterson elimination, generated the postulated sulfine, which then underwent further intramolecular addition by the allyl carbanion **371** and deoxygenation with a second equivalent of sulfur dioxide (Scheme 109).

Denmark and Harmata[300] observed that the conjugate addition of cinnamyl alcohol to allenic sulfone **2** produced the vinyl ether **372**. However, instead of an expected Claisen rearrangement, the latter cyclized via a second conjugate addition of the corresponding sulfone-stabilized anion to the styryl moiety of **372** (Scheme 110).

Scheme 109



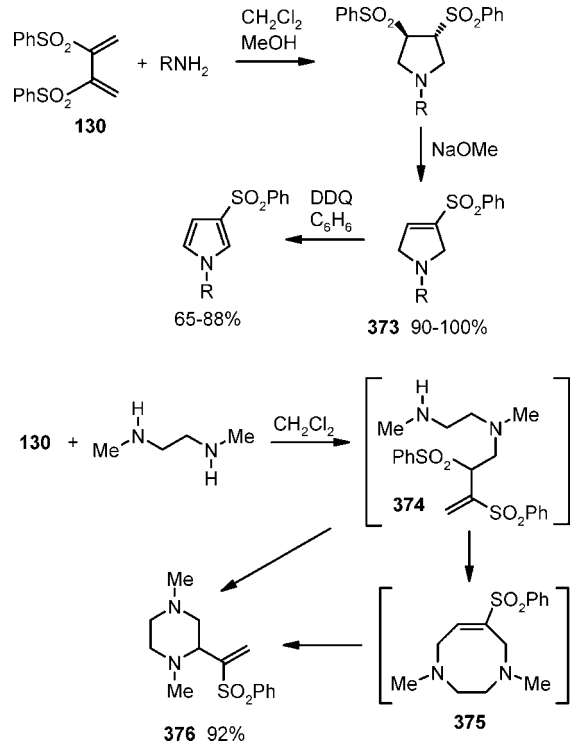
Scheme 110



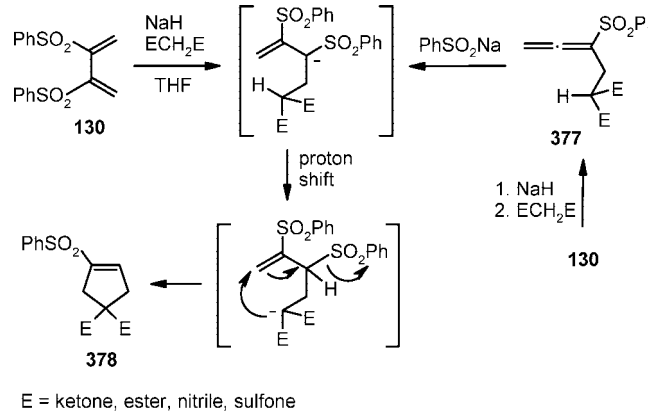
9.4. Cyclization of Dienyl Sulfones by Tandem Conjugate Addition

The double conjugate additions of primary amines to dienyl sulfone **130** were reported by Padwa et al.[301] The resulting pyrrolidines were converted to pyrrolines **373** by base-catalyzed elimination of benzenesulfinic acid, followed by DDQ oxidation to the corresponding pyrroles, while *N*,*N*′-dimethylethylenediamine afforded piperazine **376** via two competing pathways.[301b] One involved the direct formation of **376** from the initial conjugate addition product **374** by subsequent intramolecular substitution of a sulfonyl group, while the other proceeded through two successive conjugate

Scheme 111

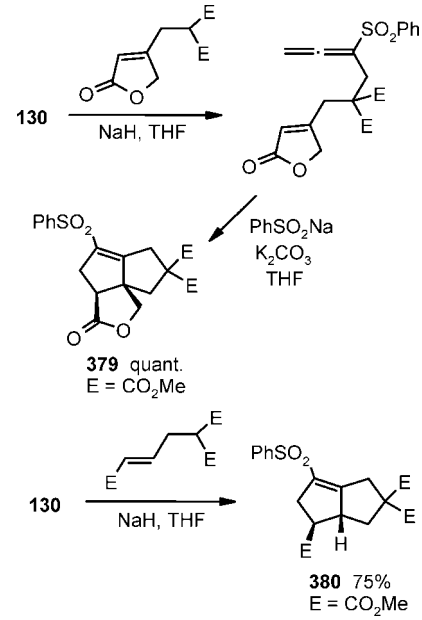


Scheme 112



E = ketone, ester, nitrile, sulfone

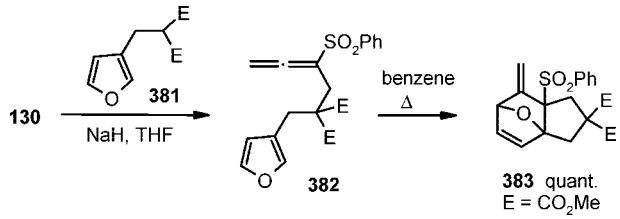
Scheme 113



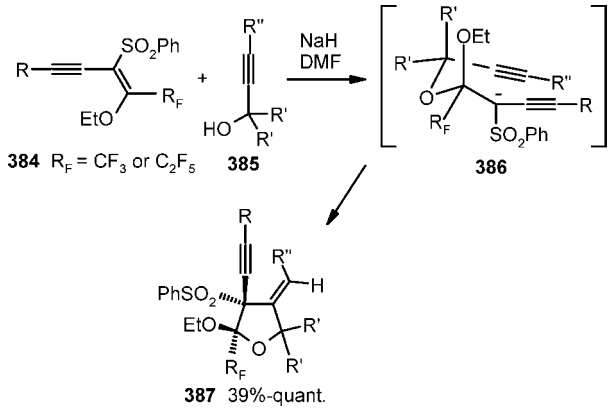
additions, followed by elimination of a sulfonyl group to produce intermediate **375** and a formal [1,3] nitrogen shift in the latter to afford the thermodynamic product **376** (Scheme 111). Similar cyclizations of primary amines with 2-acyl-3-(phenylsulfonyl)-1,3-butadiene were employed by Chou and Yuan to produce the corresponding 3-acylpyrroles.[302]

A series of double conjugate additions to **130** of various types of active methylene compounds, leading to substituted cyclopentenes **378**, was also reported by Padwa and coworkers.[303] The authors referred to these processes as anionic [4 + 1] annulations and proposed a one-pot sequence that includes initial conjugate addition, proton transfer, a second intramolecular 5-*endo-trig* addition and elimination of a sulfonyl group. Electron-withdrawing substituents on the active methylene reactant included ketone, ester, nitrile, and sulfone groups (Scheme 112). In the case of ester and sulfone groups, allenes **377** were isolated and were further converted into cyclopentenes **378** by the addition of catalytic amounts of sodium benzenesulfinate.[303a] When the active methylene reactant also contained a Michael acceptor, cyclization was possible via a further intramolecular conjugate addition, as in the case of **379**[303b,c] and **380**[303b,d] (Scheme 113). In related work, conjugate addition products derived from active

Scheme 114



Scheme 115



methylene compounds containing simple alkenyl or dienyl substituents cyclized via formal [2 + 2] cycloadditions (as shown previously in Scheme 74) or by intramolecular Diels−Alder reactions, as in the example of product **383**[155c] (Scheme 114). In the case of **383**, no competing [2 + 2] cycloaddition was observed.

Yoshimatsu and Murase[304] reacted the enynyl sulfones **384** with propargyl alcohols **385** by conjugate addition to the vinyl sulfone moiety. The resulting anions **386** then cyclized in a 5-*exo*-*dig* manner, even in the case of unactivated terminal acetylenes (R″ = H) to afford the tetrahydrofurans **387** (Scheme 115).

10. Tandem Conjugate Additions and Intramolecular Alkylations or Acylations

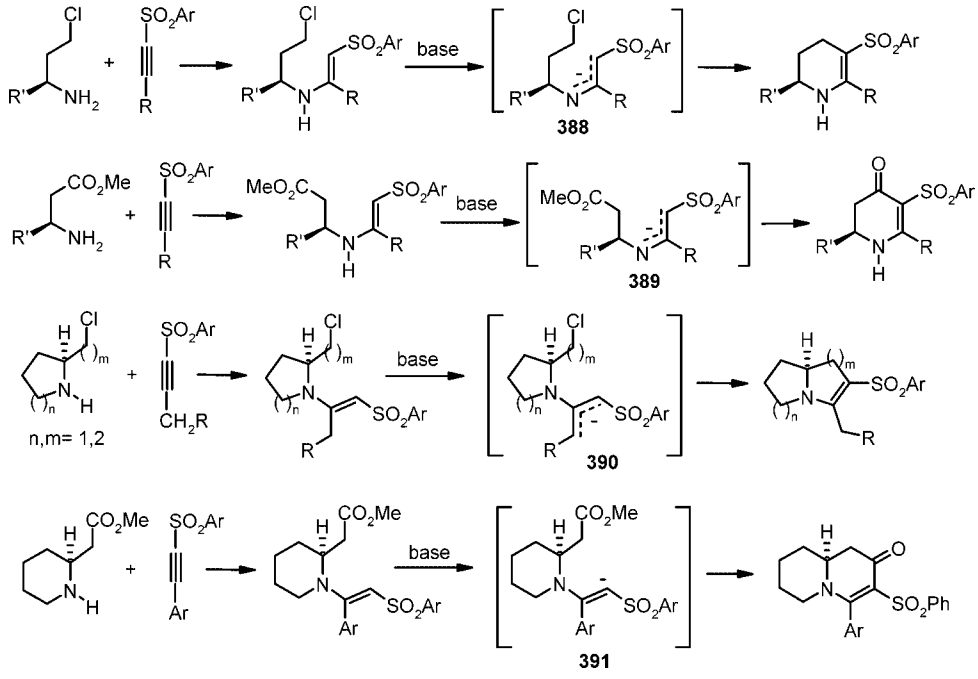
As seen in the previous section, the conjugate addition of a nucleophile to an unsaturated sulfone produces a sulfone-stabilized anion that can perform a second, intramolecular addition to a suitable Michael acceptor. Alternatively, if the nucleophile is itself tethered to a suitable electrophilic group, then the initially formed sulfone-stabilized anion may undergo cyclization through intramolecular alkylation, acylation, or similar processes.

It should also be noted that several reactions of enamines and other electron-rich alkenes with unsaturated sulfones were described in sections 2.2 and 4.3. While these processes may be considered as formal [4 + 2] or [2 + 2] cycloadditions, their concertedness is questionable and, in at least some cases, they may proceed via separate conjugate addition and intramolecular alkylation steps, thus relating them to the cyclizations described in this section.

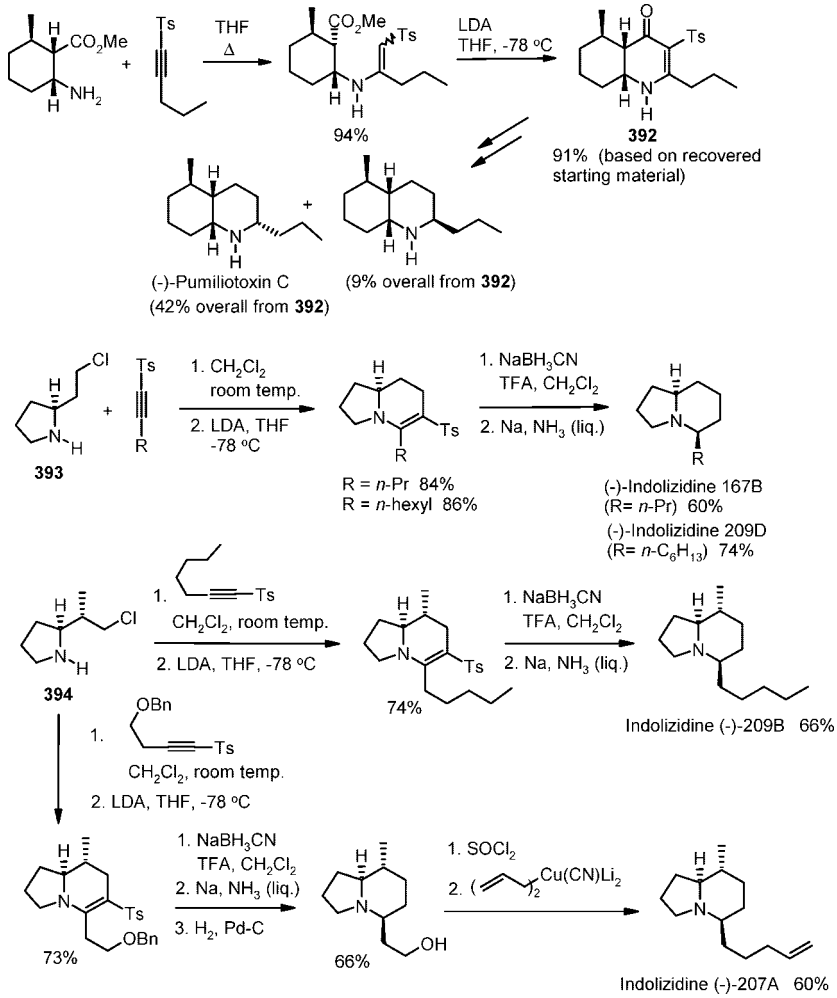
10.1. Acetylenic Sulfones

The addition of chloroalkylamines or amino esters to acetylenic sulfones affords the corresponding enamines, which can be either isolated or further transformed *in situ*. In the case of enamines derived from primary amines, treatment with a suitable base generates the anions **388** or **389** by N−H deprotonation, followed by intramolecular alkylation or acylation, respectively. When secondary amines are employed and the acetylenic substituent contains a γ-hydrogen atom, then deprotonation and alkylation of the resulting sulfone-stabilized allylic anion **390** is possible. Finally, in the absence of both N−H and γ-hydrogens, similar cyclizations may still be achieved via the corresponding vinylic anions **391**.[305] Examples are shown in Scheme 116. The products are typically subjected to reductive desulfonylation, providing access to various types of nitrogen heterocycles, including piperidines, pyrrolizidines, indolizidines, and quinolizidines.[306] Several such cyclizations have

Scheme 116



Scheme 117



been performed with acetylenic sulfones attached to solid supports,[165] as described in section 18.

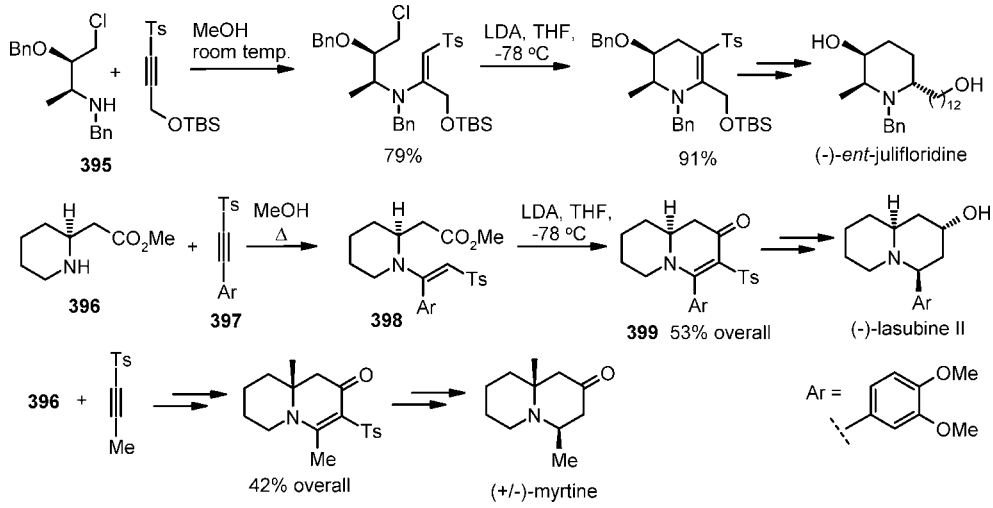
This protocol has been adapted to the total synthesis of a number of natural products. These include the dendrobatid alkaloids (−)-pumiliotoxin C,[307] as well as indolizidines (−)-**167B**, (−)-**209D**, (−)-**209B**, and (−)-**207A**[306] (Scheme 117). The lack of epimerization of the ester substituent during the formation of enaminone **392** is noteworthy and probably reflects the significantly higher acidity of the enamine sulfone moiety compared with that of the ester. The precursor chloroalkylamines for the indolizidine products were readily obtained as pure enantiomers from proline and could be stored for prolonged periods as their hydrochloride salts. The conjugate addition and cyclization steps could be performed in one pot when THF was chosen as the solvent, by simply cooling the solution prior to the addition of LDA.

In a similar fashion, chloroalkylamine **395** was obtained from L-alanine and served as an intermediate for the synthesis of 3-hydroxy-2,6-disubstituted piperidines, as illustrated by the synthesis of (−)-(*ent*)-julifloridine.[308] The homologated pipecolic acid derivative **396** underwent conjugate addition to acetylenic sulfone **397**, and the adduct **398** was successfully cyclized via intramolecular acylation of the corresponding sulfone-stabilized vinyl anion even in the presence of the enolizable ester substituent. This suggests that the vinylic proton possesses greater kinetic acidity than the ester substituent. Enaminone **399** then served as an intermediate in the synthesis of (−)-lasubine II.[309] A similar approach to racemic myrtine was also successful (Scheme 118).[309b]

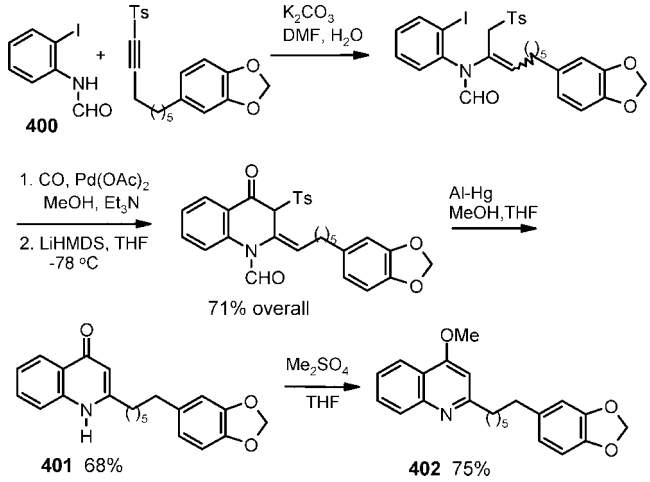
Attempts to perform tandem conjugate additions and intramolecular acylations with anthranilate esters and acetylenic sulfones gave generally poor results because of the attenuated nucleophilicity of the aniline amino group in the initial step. However, the conjugate bases of *N*-formyl-*o*-iodoanilines **400** proved superior nucleophiles and the *ortho* ester groups that were required for ring-closure were efficiently introduced by palladium-catalyzed carbonylation. This protocol provided a route to variously substituted 4-quinolones, including two alkaloids (**401** and **402**) from the medicinal plant *Ruta chalepensis*[310] (Scheme 119).

Several other examples where cyclizations were triggered by conjugate additions of amines to acetylenic sulfones but include variations in the ring-closure step are shown in Scheme 120. Thus, Degl'Innocenti et al.[311] reacted the thioformyl-substituted aminobenzofuran **403** and aminoindole **404** with excess acetylenic sulfone **11** or other activated acetylenes. Conjugate addition of the amine to **11** was followed by intramolecular addition of the resulting enamine to the thioaldehyde moiety, a second conjugate addition to **11** by the new thiol group, and spontaneous elimination of the vinyl thiolate function to afford fused pyridines **405** and **406**. Barnes and Ward[312] employed amino acetal **407** with aryl trifluoromethyl acetylenic sulfones to obtain the corresponding pyrroles **408** by means of an acid-catalyzed ring-closure, while Grigg and Savic[313] reported that the adducts of amines such as **409**, containing vinyl bromide substituents, and **11** were cyclized to pyrroles through a palladium-catalyzed process, possibly via the corresponding palladacycles.

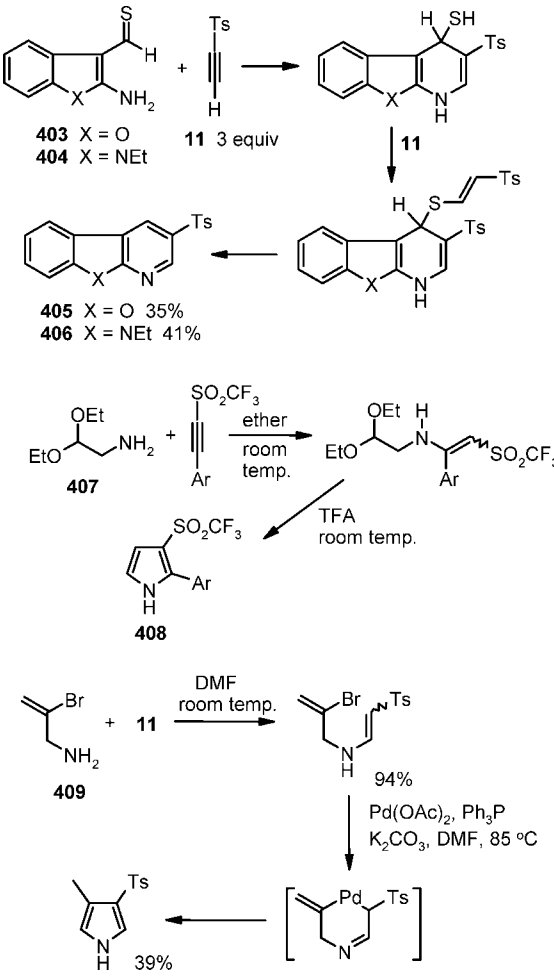
Scheme 118



Scheme 119



Scheme 120



The use of epoxy alcohols such as **410** in conjugate addition−intramolecular alkylation sequences to acetylenic sulfones was reported by Pelter et al.[314] A complication resulted from competing Michael and anti-Michael regiochemistry in the addition step, leading to mixtures of adducts **411** and **412**, but formation of the latter was suppressed by the use of electron-rich aryl substituents at the β-position of the acetylenic sulfone. The resulting dihydrofurans **413** were thus obtained enantioselectively and in good yield (Scheme 121).

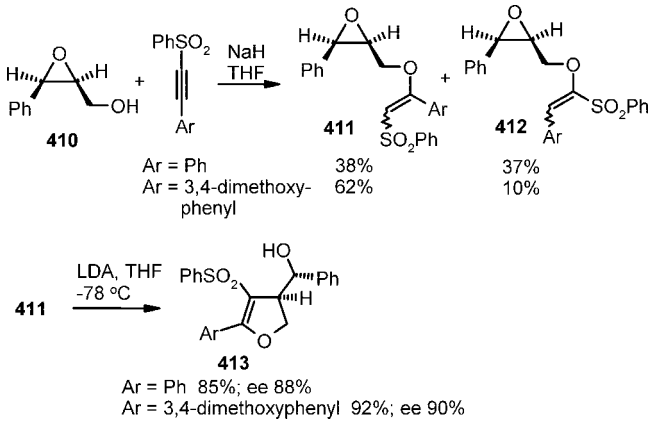
10.2. Allenic and Dienyl Sulfones

A few examples have been reported of conjugate additions to allenic and dienyl sulfones, followed by ring-closure of the resulting sulfone-stabilized anions (Scheme 122). The allene **414** was generated *in situ* and functioned as an acceptor−donor synthon when reacted with β-lactam **415**. Cyclization by intramolecular alkylation furnished the desired carbapenem **416** after sulfoxide elimination.[315] Dienyl sulfone **417**, as well as other activated dienes, underwent conjugate addition of the sulfoxonium ylide **418**, followed by intramolecular displacement of dimethyl sulfoxide, affording the corresponding cyclopentene.[316] Aldehydes can also serve as the electrophilic components in the cyclization step. Thus, conjugate additions of several imidazole and pyrrolecarbaldehydes to dienyl sulfone **419** were followed by intramolecular addition of the corresponding anions to the aldehyde groups, producing azaazulene derivatives, as in the case of imidazolecarbaldehyde **420**.[317] 2-Pyrrolecarbaldehyde afforded a mixture of three double-bond isomers, as well as products from a second conjugate addition of the initial anion to a second mole of sulfone **419**.

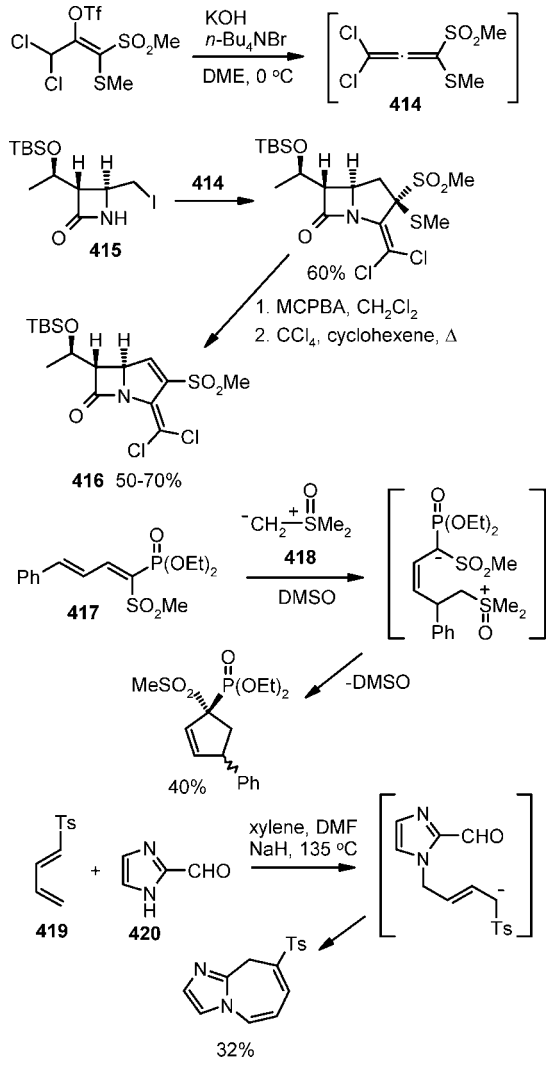
11. Aza-Cope and Related Rearrangements

Included in this section are several types of transformations that afford cyclized or ring-expanded products via

Scheme 121



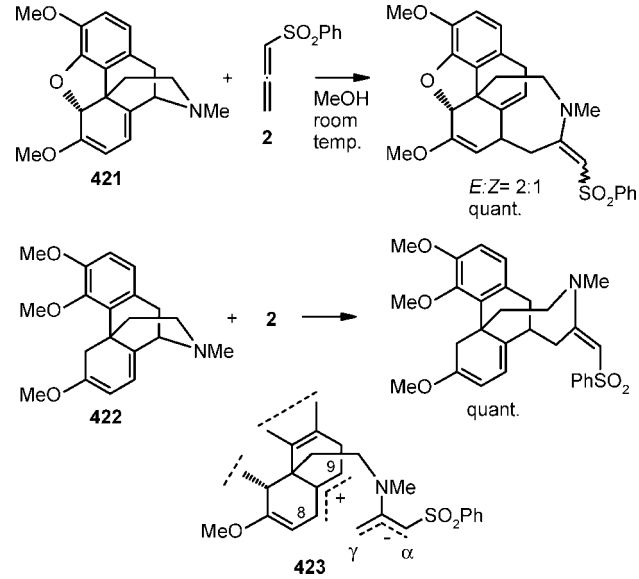
Scheme 122



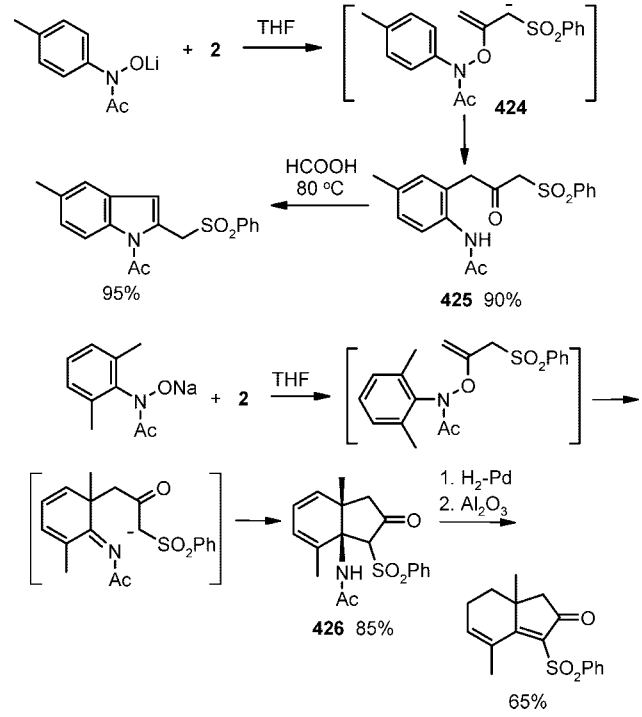
formal aza-Cope rearrangements of adducts derived from amines or hydroxylamines and allenic or acetylenic sulfones. In some examples, these processes are not necessarily concerted [3,3]sigmatropic rearrangements and may instead proceed by dissociative or intramolecular substitution mechanisms.

An early example was reported by Kanematsu et al.,[318] who found that allenic sulfone **2** reacted differently with thebaine **421** and the congener **422**. It was postulated that initial conjugate addition in both examples was followed by

Scheme 123



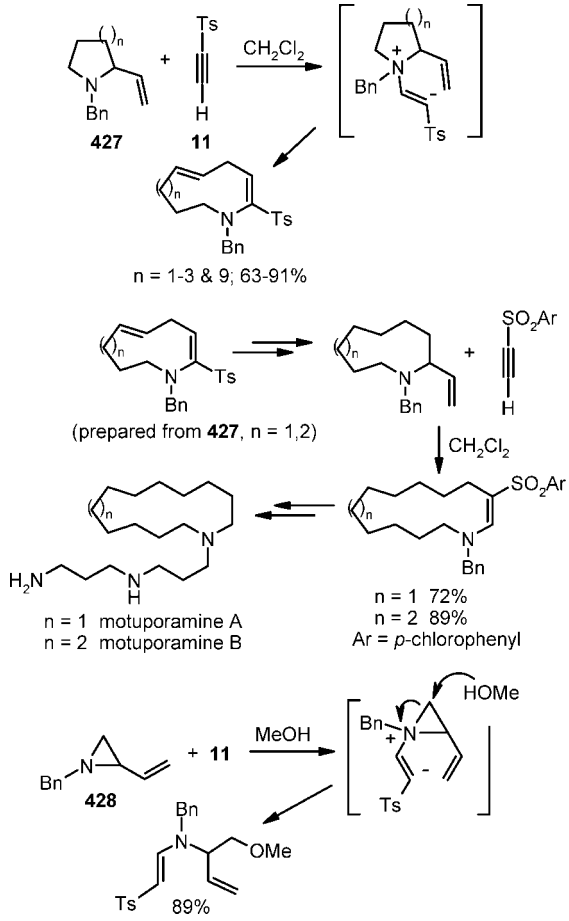
Scheme 124



a C−N bond dissociation step to produce zwitterion **423** (as opposed to [3,3] rearrangement prior to C−N bond cleavage). Thus, the product from **421** was formed by recombination of the γ-position of the allyl sulfone anion with C-8, while C-9 was the site of attack in the closure of **422** (Scheme 123). The difference in regiochemistry was attributed to conformational effects stemming from the presence or absence of the oxygen bridge in **421** and **422**, respectively.

Blechert and co-workers[319] investigated the conjugate addition and rearrangement of several arylhydroxylamines with **2** (Scheme 124). The addition step was effected by the oxyanion of the hydroxylamine, followed by rearrangement of **424** to the keto sulfone **425**. Intramolecular condensation then afforded the corresponding indole products.[319a,b] When both *ortho* positions of the hydroxylamine aryl group were substituted, indanone derivative **426** was obtained instead.[319c]

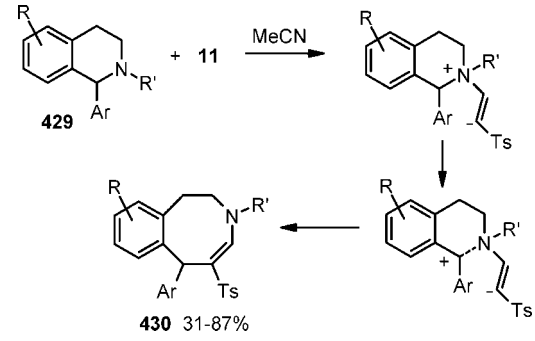
Scheme 125



Tertiary allylamines reacted with acetylenic sulfone **11** to afford zwitterions that rearranged via a formal aza-Cope process.[320] The method can be used in the ring-expansion of cyclic α-vinyl amines **427**, providing a convenient route to medium- and large-ring nitrogen heterocycles. An iterative variation that expands the original ring by four carbon atoms during each cycle was demonstrated in the synthesis of motuporamines A and B (Scheme 125).[320b] The ring expansion step may proceed via an intramolecular S_N' reaction effected by attack of the sulfone-stabilized anion of the zwitterion upon the vinyl group, with departure of the quaternary nitrogen atom, rather than by a true sigmatropic rearrangement. A dissociative mechanism was identified in cases where C−N bond cleavage was particularly facile, as in the vinylaziridine derivative **428**, or when electron-donating substituents were present to stabilize the corresponding carbocation.[320b] Kinetic evidence indicated that the conjugate addition step is rate-determining and the reactivity of the acetylenic sulfone can be modulated by the appropriate choice of *para* substituent on its aryl group, with electron-withdrawing substituents providing the most reactive acetylenic sulfones.

A different type of ring expansion was reported by Vokressensky et al., starting from α-aryltetrahydroisoquinolines **429** and **11**.[321] The formation of the corresponding zwitterion and aryl-assisted dissociation of the C−N bond was followed by an intramolecular S_N1 substitution, leading to two-carbon ring-expanded products **430** (Scheme 126). Products where the expanded ring was fused to indole[322] or thiophene[323] moieties were also accessible by this method.

Scheme 126



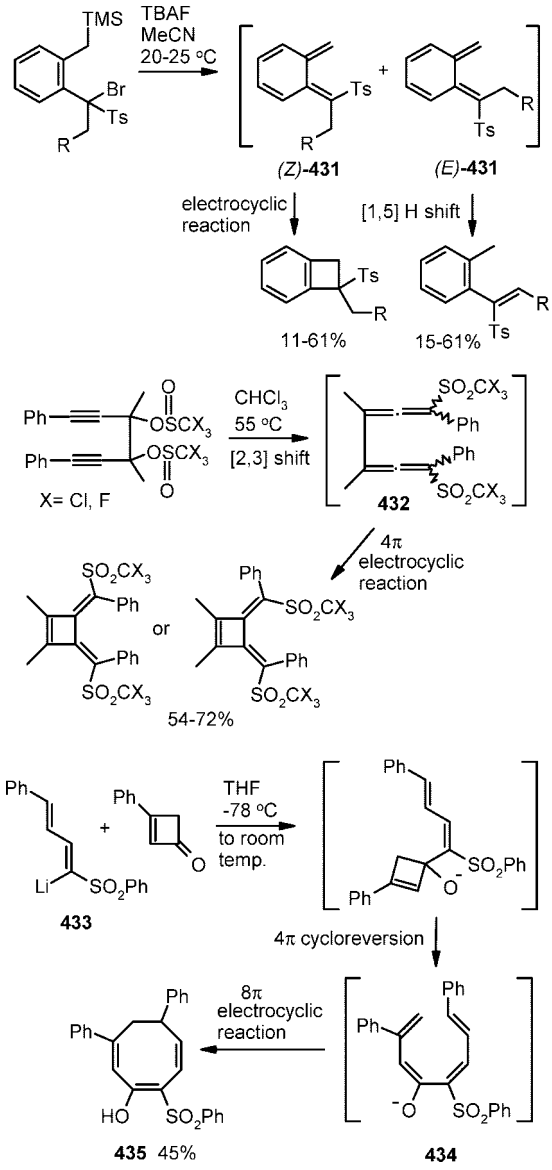
12. Electrocyclic Reactions

Several examples of electrocyclic reactions of unsaturated sulfones have been reported. Thus, Lenihan and Shechter[72] observed that the *Z*-isomer of quinodimethane **431** underwent aromatization via electrocyclization, while the *E*-isomer reacted via a [1,5] hydrogen shift. Braverman and co-workers[263] reported that the stereoisomers of bis(allenic) sulfone **432** afforded the corresponding cyclobutene products by conrotatory 4π electrocyclic ring-closure. A sequence of two electrocyclic reactions was initiated by Magomedov et al.[324] by the addition of the α-lithiated dienyl sulfone **433** to 3-phenylcyclobutenone. The resulting adduct underwent a 4π cycloreversion to produce tetraene **434**, followed by an 8π electrocyclization to afford the cyclooctatriene **435**. Similarly lithiated vinyl sulfones behaved analogously, except that a 6π electrocyclic reaction in the final step produced the corresponding cyclohexenones. Examples of these processes are shown in Scheme 127.

Electrocyclic reactions of sulfonyl-substituted trienes have been reported by several groups,[325−330] and several examples are shown in Scheme 128. Further transformations of the products are facilitated by differentiation of individual alkene moieties by the sulfone substituent.[325] A computational study of such processes by Fu et al.[326] revealed that activation energies are lowered by up to 10 kcal/mol by the presence of captodative substituents. Thus the presence of an electron-withdrawing sulfonyl substituent, along with an electron-donating enolate oxygen atom, results in especially facile cyclizations.[324,326] The same product **437** was obtained by Ogura et al.[327] via thermal disrotatory or photochemical conrotatory ring-closure of the *trans*-1-chloro and *cis*-1-chloro isomers, respectively, of the triene **436**, followed by the spontaneous elimination of HCl. These authors also reported the electrocyclization of **438** under either thermal or photochemical conditions in acetonitrile, followed by elimination of methanethiol and aromatization.[328] The presence of iodine accelerated the process, probably by promoting an electrophilic mechanism (see also section 15.1). Alternatively, the reaction could be accomplished under solvent-free conditions in the presence of solid or gaseous iodine.[329] Magomedov and co-workers[330] demonstrated that sulfonyl-substituted divinyl or vinyl dienyl ketones cyclized under modified Nazarov conditions in the presence of a Lewis acid and triethylamine, as in the example of **439**.

The tricyclic bis(sulfone) **441** was prepared by Kitagaki et al.[331] as an intermediate for steroid synthesis by means of sequential 6π electrocyclization of bis(allene) **440** and intramolecular Diels−Alder cycloaddition. This transformation required **440** at the sulfoxide oxidation state ($n = 1$), followed by oxidation to the corresponding bis(sulfone) **441**

Scheme 127

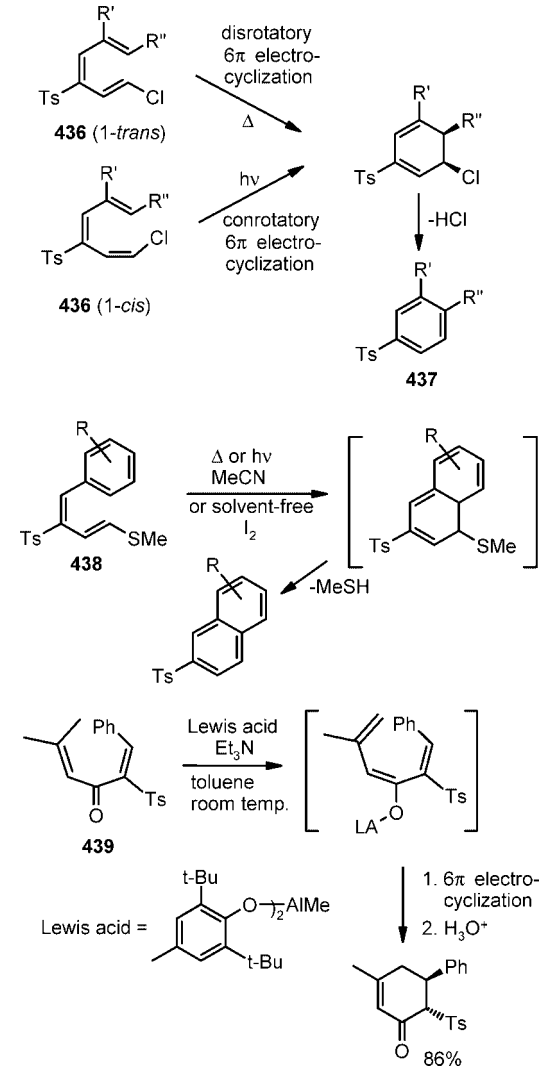


in the last step. When the bis(sulfone) derivative of **440** (*n* = 2) was employed, the IMDA step was precluded by a preferential [1,5] hydrogen shift. (Scheme 129).

13. Cyclizations Initiated by Aza-Morita−Baylis−Hillman Reactions

During an investigation of the use of activated dienes instead of alkenes in vinylogous aza-Morita−Baylis−Hillman reactions, dienyl sulfone **419** was found to produce the expected products **442**, followed by intramolecular conjugate addition to afford substituted piperidines **443**. Only the *E* isomers of **442** were capable of cyclization, but when the reaction was performed with simultaneous UV irradiation at 300 nm, facile *in situ* photoisomerization between *E*- and *Z*-**442** occurred, leading to the ultimate consumption of both geometrical isomers[332] (Scheme 130). Furthermore, the *N*-allyl derivatives of the *Z* isomers underwent intramolecular Diels−Alder cycloadditions, producing unique stereoisomers of the corresponding partially reduced isoindolines **444**.[333] Similar cyclization of analogs of **419** containing other electron-withdrawing groups were also reported.

Scheme 128

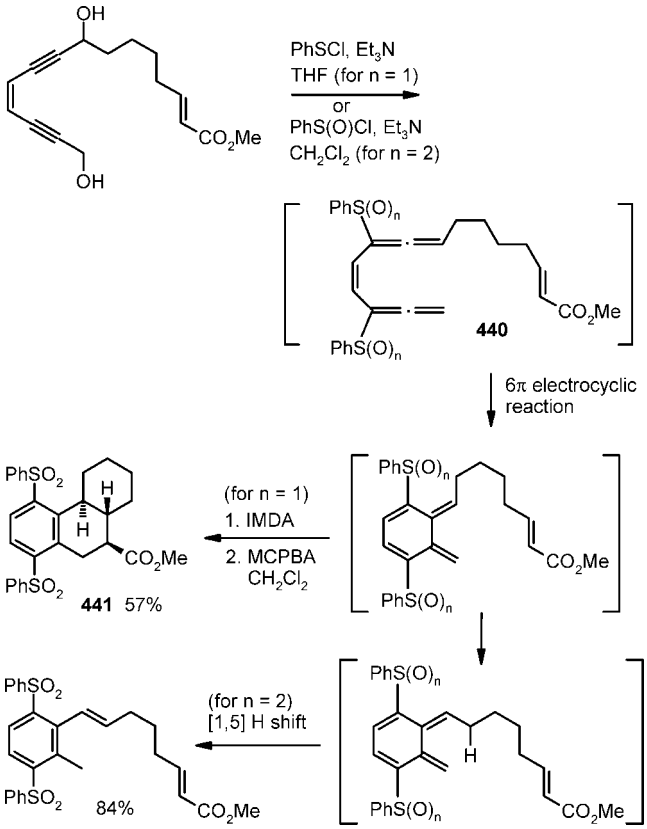


14. Synthesis of Three-Membered Rings from Unsaturated Sulfones

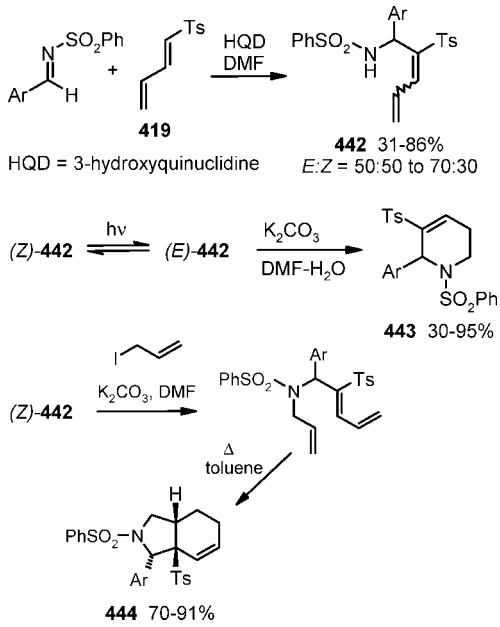
14.1. Epoxides

Numerous methods have been reported for the regio-, diastereo-, and enantioselective epoxidation of variously substituted cyclic and acyclic dienyl sulfones. As expected from the electron-withdrawing nature of the sulfone group, electrophilic reagents such as peracids[334−340] epoxidize the unactivated double bond preferentially, while nucleophilic ones such as alkaline hydrogen peroxide,[336,337] *t*-butyl hydroperoxide,[337,340−342] and *N*-methylmorpholine-*N*-oxide[343] favor the sulfone-substituted one. Enantioselective and diastereoselective epoxidations have been achieved with Jacobsen's catalyst[335,338−340,344−350] or via Sharpless asymmetric epoxidation when an allylic alcohol moiety is also present.[351,352] A comparison of the regio- and stereoselectivity of epoxidation of cycloheptatrienyl sulfones with various chiral and achiral reagents, including a dioxirane, was reported by Fuchs et al.[350] Furthermore, a very recent review by Fuchs and co-workers[1] describes numerous elegant and highly regio- and stereoselective further transformations of such epoxy sulfones, while earlier work was similarly covered in 1998 by Bäckvall et al.[22] Duplication of this material will therefore not be presented here, and the reader is directed to these prior sources for additional information.

Scheme 129



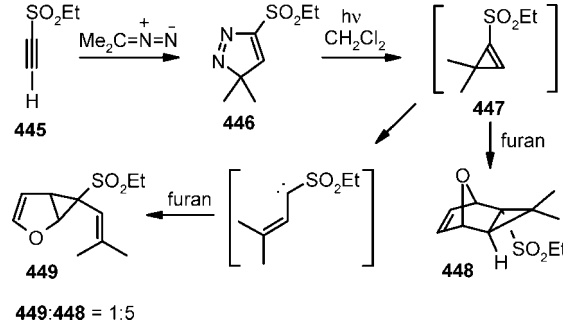
Scheme 130



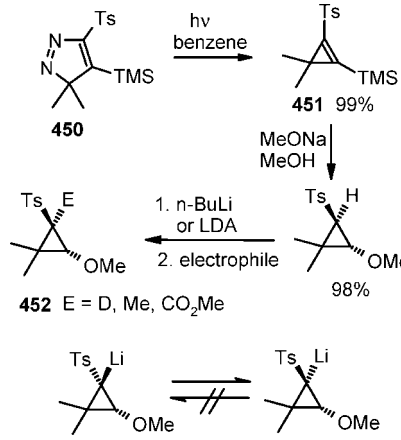
14.2. Cyclopropanes and Cyclopropenes

The 1,3-dipolar cycloaddition of diazo compounds with acetylenes produces pyrazoles, as described in section 3.2. Franck-Neumann and Lohmann[176] photolyzed the cycloadduct **446**, obtained from diazopropane and the acetylenic sulfone **445**, resulting in extrusion of nitrogen and formation of the cyclopropene **447**. In the presence of furan, both the Diels−Alder cycloadduct **448** and the vinylcyclopropane **449** were obtained, implicating the formation from **447** of the isomeric vinylcarbene as an intermediate (Scheme 131). The

Scheme 131



Scheme 132

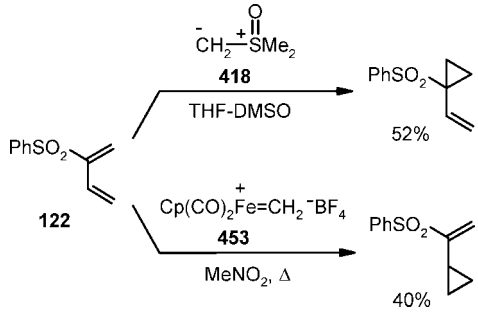


corresponding sulfoxide afforded only the analogous vinylcyclopropane via the carbene pathway.

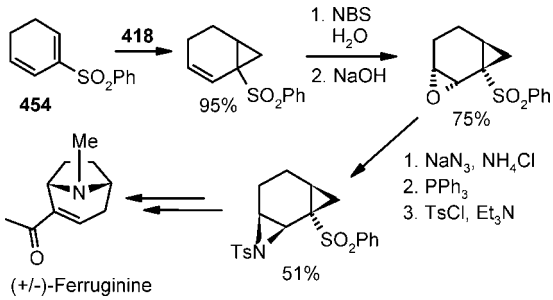
The similar photolysis of pyrazole **450**, obtained from 1-(*p*-toluenesulfonyl)-2-(trimethylsilyl)ethyne (**14**) was investigated by Padwa et al.[177−179] The cyclopropene **451** was obtained in excellent yield and converted to its methoxycyclopropane derivative as shown in Scheme 132. The corresponding anion was generated with either LDA or *n*-butyllithium and quenched with electrophiles, affording unique stereoisomers of **452**. This was attributed to chelation effects involving the lithiated cyclopropane and the methoxy group. Similarly high stereoselectivity was observed when the methoxy group was replaced with a phenylthio substituent. In this case, it was postulated that the favored carbanion was stabilized by an anomeric effect resulting from its interaction with the σ^* orbital of the β-substituent. The cyclopropenes derived from several other acetylenic sulfones underwent conjugate addition to the vinyl sulfone moiety with cuprates and substitution of the sulfonyl group with alkyllithiums.[353] The pyrolysis of the 1:1 cycloadducts obtained from dienyl sulfone **130** and diazo compounds (see Scheme 56) afforded vinylcyclopropanes in low yields along with ring-opened products.[185]

Just as either double bond of a dienyl sulfone can be epoxidized selectively by the appropriate choice of a nucleophilic or electrophilic reagent, so too complementary cyclopropanation is possible. Bäckvall et al.[354] demonstrated that dienyl sulfone **122** reacted with the sulfoxonium ylide **418** exclusively at the activated 1,2-double bond, while the iron carbenoid **453** cyclopropanated the 3,4-position with equal selectivity (Scheme 133). Higher yields were generally observed with cyclic dienyl sulfones. Regioselective combinations of epoxidation[355] or aziridination[356] with cyclopropanation were also reported, and the methodology was

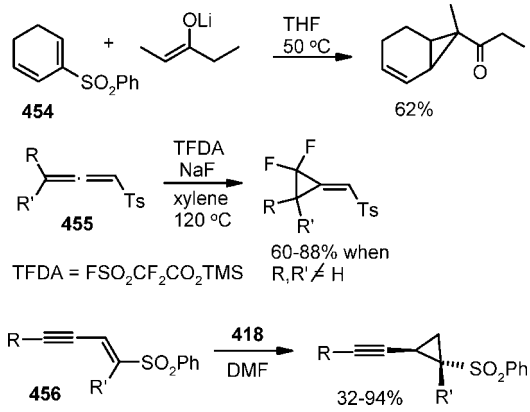
Scheme 133



Scheme 134



Scheme 135

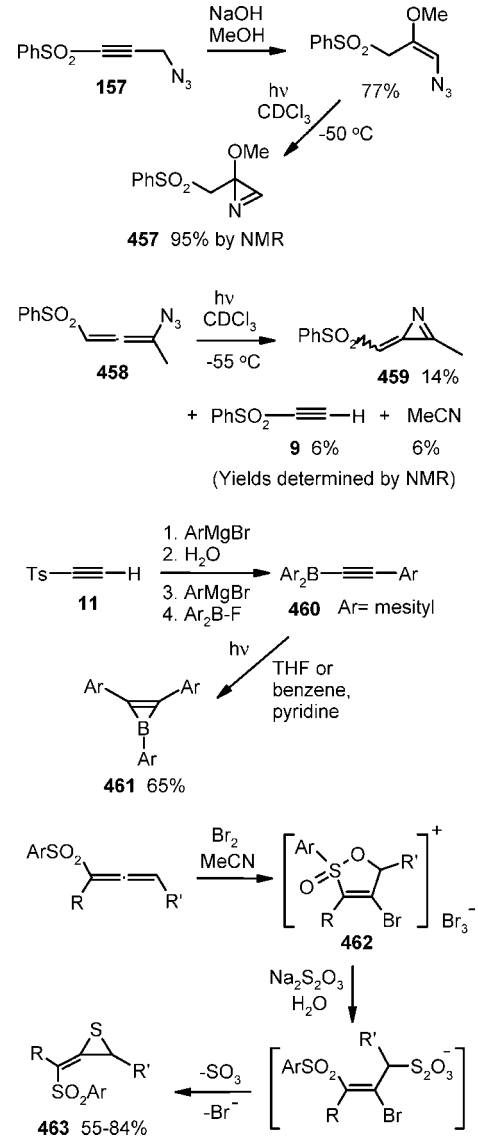


applied to the synthesis of the neurotoxin ferruginine from dienyl sulfone **454**[357] (Scheme 134). Other methods for the cyclopropanation of unsaturated sulfones include the additions of enolates to dienyl sulfones such as **454**, followed by proton transfer and substitution of the sulfonyl moiety,[358] and the addition of difluorocarbene to allenic sulfones **455**.[359] The sulfoxonium ylide **418** was also employed in the cyclopropanation of enynyl sulfones **456**[341] (Scheme 135).

14.3. Azirines, Borirenes, and Thiiranes

Fotsing and Banert[171] reported that the azido-substituted acetylenic sulfone **157** underwent dimerization in methanol solution via [3 + 2] cycloaddition (see Scheme 53). However, in the presence of a base, conjugate addition of methanol occurred instead, affording the corresponding vinyl azide, which was photolyzed to produce the azirine **457**. The γ-methyl derivative of **157** behaved similarly,[171] while the γ-azido allenic sulfone **458** formed azirine **459** in low yield, along with products of further photolysis.[360] The unusual borirene **461** was prepared by Eisch et al.[361] from acetylenic sulfone **11**, by conversion to the ethynylborane **460**, followed by photolysis. Fu and co-workers[362] demonstrated that the addition of bromine to allenic sulfones, followed by treatment

Scheme 136



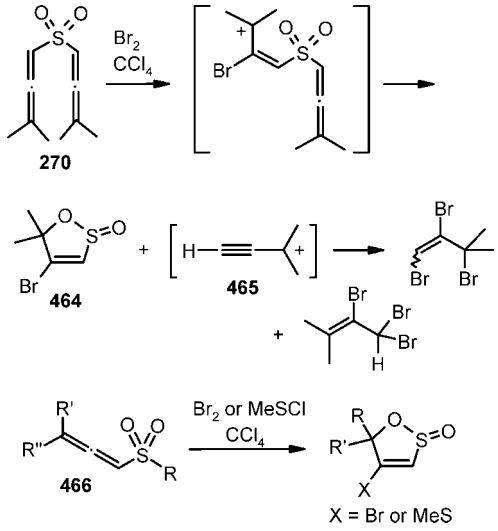
with sodium thiosulfate, occurred with neighboring group participation by the sulfone moiety via intermediate **462**. The initial cyclization step leading to **462** is a variation of earlier work by Braverman and co-workers that is described in section 15.1. Subsequent loss of sulfur trioxide, followed by intramolecular addition−elimination provided thiiranes **463**. The mechanism is supported by the observation that optically active allenic sulfones produced thiiranes with retention of configuration in enantiomeric excesses of 96−99% and by the isolation and X-ray structure determination of one such product, **463**, where R = H, R′ = Me, and Ar = *p*-bromophenyl. These processes are summarized in Scheme 136.

15. Electrophilic Cyclizations

15.1. With Halogens, Bronsted Acids, and Sulfenyl or Selenenyl Chlorides

The electrophilic cyclizations of bis(allenic) sulfone **270** were investigated by Braverman et al.[245,264,363,364] In the presence of bromine, sultine **464** was formed with accompanying cleavage of one of the allenic substituents to the corresponding carbocation **465**, which reacted with bromide anion

Scheme 137



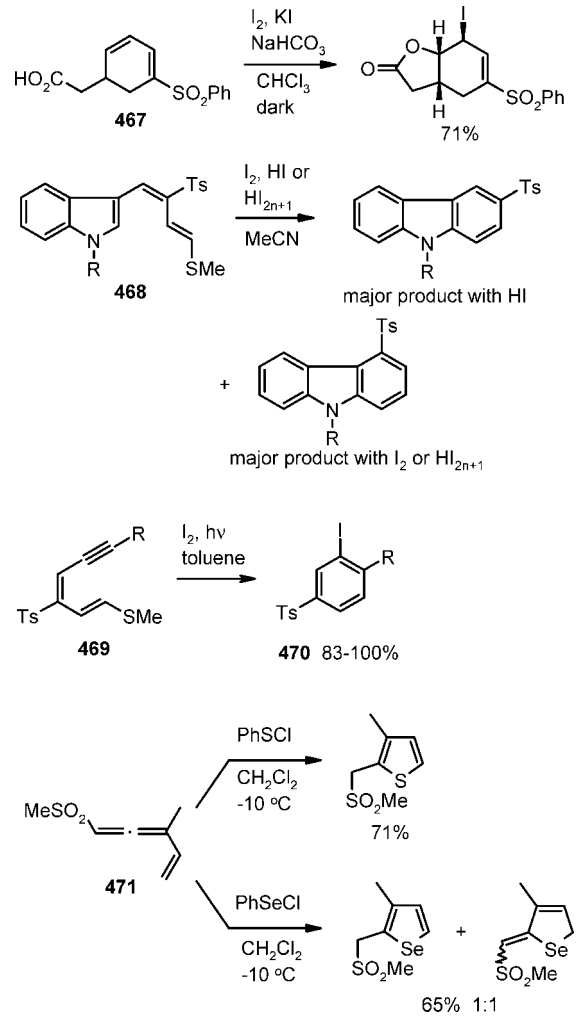
and additional bromine to produce isomeric tribrominated byproducts[264,363] (Scheme 137). The cleavage and cyclization of **270** was also induced with TFA.[264] Monoallenic sulfones **466** were similarly cyclized to their respective sultines with bromine[364] or methanesulfenyl chloride,[364] provided that the carbocation R^+ was relatively stable. The cyclization is stereospecific, as evidenced by the observation that optically active allenic sulfones produced optically active sultines.[364]

Electrophilic cyclizations of dienyl sulfones **467** and **468** were effected with iodine[365] or HI,[366] respectively. The use of iodine or hydrogen polyiodides in the latter case promoted a migration of the sulfonyl group during the cyclization. Elimination of methanethiol then produced the indicated carbazole products. A similar cyclization of dienynyl sulfone **469** was promoted by irradiation with UV light in the presence of iodine. Following *trans* to *cis* photoisomerization of the vinyl sulfide moiety, electrophilic cyclization of the more reactive *cis* isomer and loss of the methylthio group, probably as the sulfenyl iodide, produced the aromatic product **470**.[367] Treatment of vinyl allenic sulfones such as **471** with benzenesulfenyl and selenenyl chlorides afforded the corresponding thiophenes and selenophenes, respectively.[368] Cleavage of the phenyl−chalcogen bond in this process is noteworthy and was confirmed by the isolation of chlorobenzene from these reactions. These processes are shown in Scheme 138.

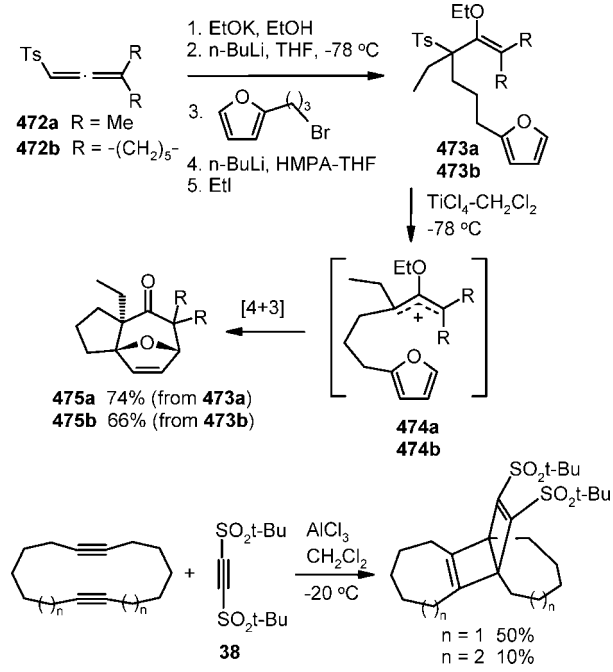
15.2. With Lewis Acids

During an investigation of intramolecular cationic [4 + 3] cycloadditions, Harmata and co-workers[369] devised a protocol based on allenic sulfones. An example is shown in Scheme 139, where allenic sulfones **472** were first converted into the allylic sulfones **473**, followed by treatment with titanium tetrachloride to generate the desulfonylated cations **474**. Cyclization of the latter with the pendant furan moiety then afforded the corresponding tricyclic products **475**. (Trimethylsilyl)methyl allylic derivatives cyclized similarly in the presence of trimethylaluminum.[369c] An investigation into asymmetric induction during the reaction revealed the importance of allylic cation stereochemistry and of the relative rates of *E*/*Z* interchange vs the rate of ring-closure in establishing the stereochemistry of the products.[369d] A subsequent photochemical variation was also reported.[370] Gleiter et al.[371] employed aluminum trichloride as the Lewis acid to synthesize Dewar benzenes and bridged prismanes from the cyclization of the doubly activated acetylenic sulfone **38** with a series of macrocyclic diynes. The sulfonyl

Scheme 138



Scheme 139

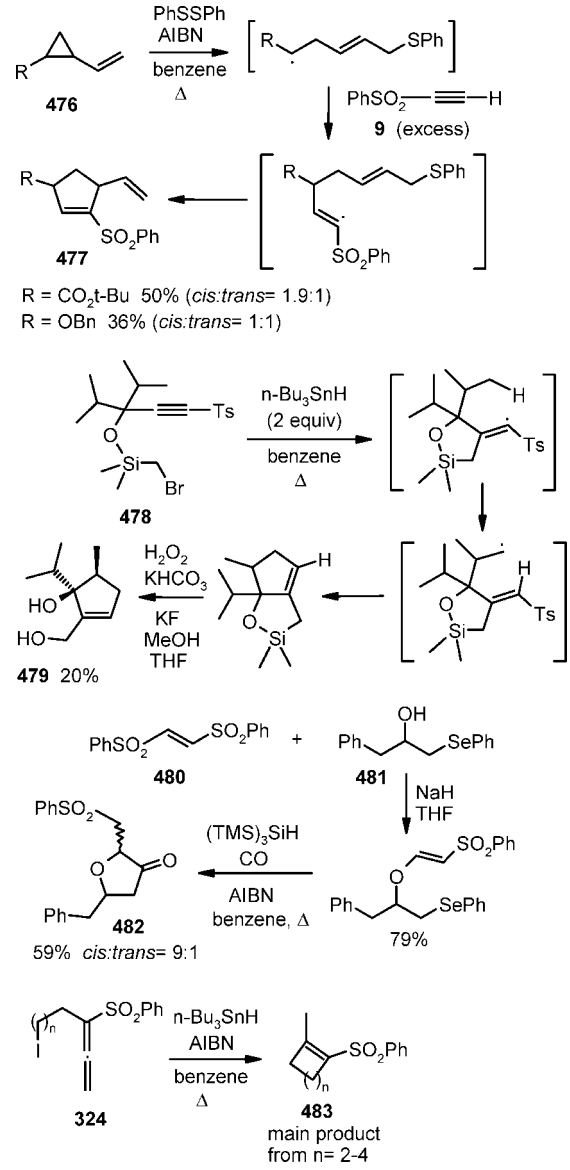


substituents were further subjected to reductive desulfonylation with samarium iodide or substitution with organolithium or Grignard reagents (Scheme 139).

16. Radical Cyclizations

The cyclization of bis(allenic) sulfones and related compounds via diradical intermediates was described in section 7. Several more conventional forms of radical cyclization have also been reported. A [3 + 2] cyclization observed by Feldman et al.[372] was based on the ring-opening of vinyl cyclopropanes **476** with phenylsulfanyl radicals generated from the homolytic cleavage of diphenyl disulfide. A sequence of inter- and intramolecular radical addition steps with acetylenic sulfone **9** then afforded the corresponding cyclopentenes **477**. The bromomethylsilyl ether tethered to the acetylenic sulfone moiety of **478** was employed by Malacria et al.[373] as a trigger for a 5-*exo-dig* cyclization, presumably followed by an intramolecular hydrogen shift and a second 5-*endo-trig* cyclization. The diol **479** was then obtained by a Tamao oxidation. In a third approach, Engman and co-workers[374] used **480** as a surrogate for acetylenic sulfone **9**. Addition−elimination of the alcohol **481** to **480** was followed by homolytic cleavage of the selenide function, carbonylation, and cyclization to produce **482**. In addition to the anionic cyclizations reported by Crandall and Ayers (see Scheme 98), these authors also noted that radical cyclizations of iodoalkyl-substituted allenic sulfones **324** (X = I) were also possible, affording cycloalkenyl sulfones **483**, along with acyclic and regioisomeric products, depending on the ring size.[375] These processes are shown in Scheme 140.

Scheme 140



17. Transition-Metal Catalyzed Cyclizations

While transition metal catalysts have played roles in some of the cycloadditions and other processes described in previous sections (e.g., see sections 4.1, 4.4, and 5), other transformations of a more unique nature will be described here.

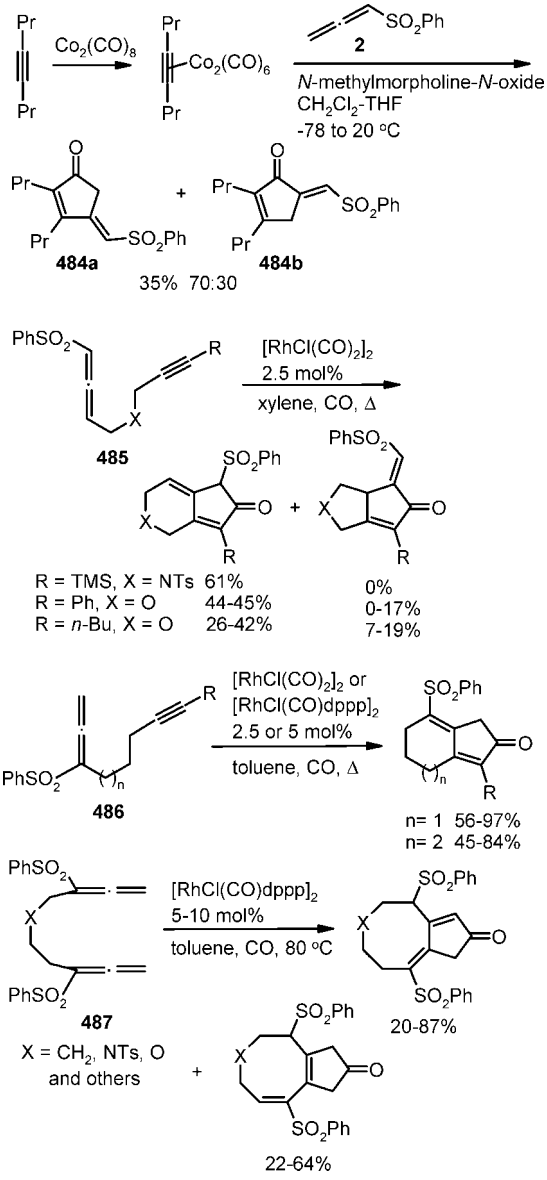
17.1. Pauson−Khand Reactions

During a study of Pauson−Khand cyclizations of activated allenes with acetylenes, Cazes et al.[376] discovered that allenic sulfone **2** reacted with the hexacarbonyldicobalt complex of 4-octyne to afford regioisomers **484a** and **484b** of the *exo*-vinylidene cycloadduct in the ratio of 70:30 (Scheme 141). Similar results were obtained by Pérez-Castells[377] with 3-hexyne. Mukai and co-workers[265,378] reported that allenic sulfones tethered to acetylenes undergo intramolecular Pauson−Khand reactions. The sulfone moiety can be present at either the 1- or 3-position of the allene and the tether can include heteroatoms. Substituents are tolerated on the tether, as well as on the allene and acetylene. Although the authors relied mainly upon $[RhCl(CO)dppp]_2$ and $[RhCl(CO)_2]_2$ as catalysts in the presence of carbon monoxide, cobalt octacarbonyl, molybdenum hexacarbonyl, triruthenium dodecacarbonyl, and various iron carbonyl compounds could also be employed.[378] Examples with 1-sulfonyl-[378f] and 3-sulfonyl-substituted[378c] derivatives **485** and **486**, respectively, are shown in Scheme 141, along with the cyclization of bis(sulfones) **487**.[265]

17.2. Heck and Other Palladium-Catalyzed Coupling Reactions

The Diels−Alder cycloadditions of indole-based dienyl sulfones **127** were described in Scheme 43. The required precursors **127** were in turn obtained by the Heck-like coupling of *o*-iodoanilines with dienyl sulfones **488**, followed by aromatization with DDQ.[143,144,379] In a related process, the conjugate addition product derived from the *o*-iodobenzylamine **489** and acetylenic sulfone **11** was subjected to an intramolecular palladium-catalyzed coupling by Berteina and De Mesmaeker,[380] affording the lactam **490** after aerial oxidation. The cyclization of phenylureas such as **491**, lacking *o*-iodo substituents, with dienyl sulfone **244** through an intramolecular carboamination reaction was reported by Lloyd-Jones and co-workers.[381] The highly electrophilic species $Pd(OTs)_2$ was generated in situ and proved effective in the required *ortho*-C−H activation step, resulting in an interrupted Heck reaction. Carretero et al.[382] observed an interesting cascade process when either dienyl sulfone **244** or **492** was subjected to a single or double Heck reaction, respectively, with iodobenzene, which occurred at the 4-position of the diene to produce the diphenyl derivative

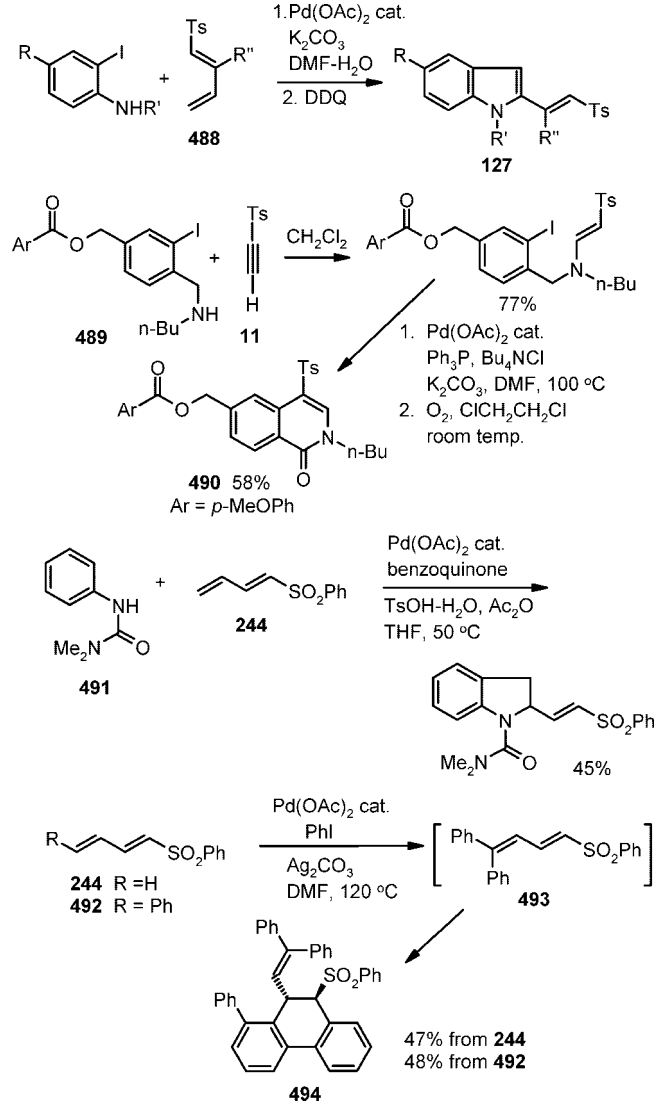
Scheme 141



493. The latter underwent further cyclization through a similar *ortho*-C−H activation step, ultimately affording the tricyclic product **494**. These processes are shown in Scheme 142.

Motherwell et al.[383] reported the palladium-catalyzed intramolecular [3 + 2] cycloaddition of the vinylidenecyclopropane and acetylenic sulfone moieties of **495**, while Trost and co-workers[384] combined two palladium-catalyzed steps in a new route to octahydroazulene derivatives **500**. The cyclization of the vinyl acetylenic sulfone **496** in the presence of the palladacycle **497** was followed by the [4 + 3] annulation of the product **498** with the masked trimethylenemethane **499**. In both cases, acetylenic esters as well as acetylenic sulfones were also investigated. Palladium complex **501** was employed by Pfeffer et al.[385] in the synthesis of indoles such as **502** from **95**, or from other activated acetylenes. Several types of sulfur heterocycles were prepared similarly.[386] Kende et al.[387] reported the palladium-catalyzed insertion of acetylenic sulfone **11** into the C−Si bond of benzosilacyclobutane **503**. These processes are shown in Scheme 143.

Scheme 142

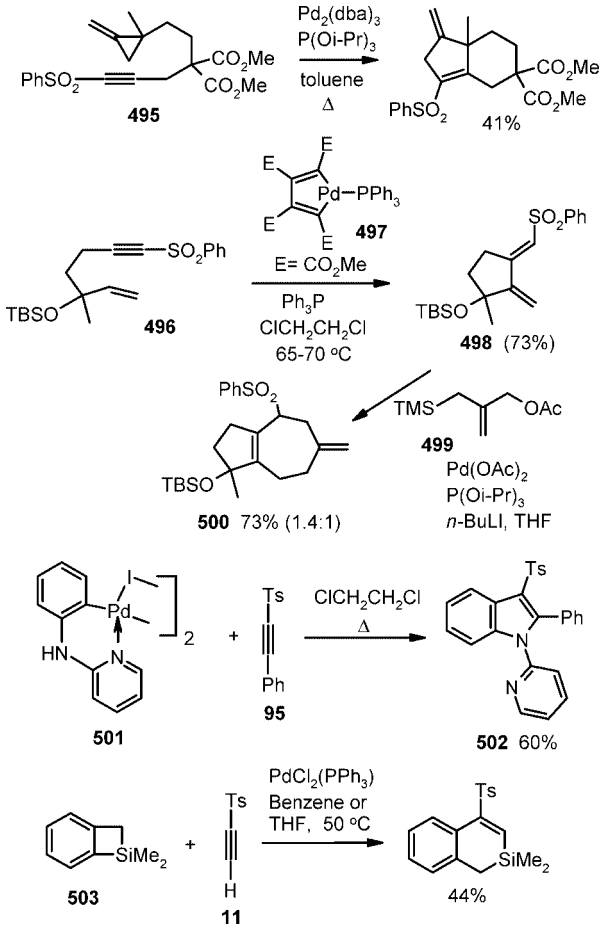


17.3. Reppe Reactions

Sato and co-workers described an enantioselective synthesis of indanols by means of Reppe reactions of preformed optically active diynes **504** with acetylenic sulfone **11**.[388] Subsequently, these authors reported a cyclotrimerization process with three different acetylenes, including **11**, that produced single isomers of the products **505**.[389] When a nitrile was substituted for one of the acetylenes, the corresponding pyridines **506** were obtained.[390] Examples are shown in Scheme 144.

Other metals apart from titanium have also been investigated in variations of the Reppe reactions of acetylenic sulfones. An iridium-catalyzed cyclotrimerization leading to aryl sulfones **507** was recently developed by Takeuchi et al.,[391] while Eisch et al.[392] reported a nickel-mediated process via the metallacycle **508**, leading to trimeric products **510** and **511**. When the acetylenic sulfone **11** and $Ni(COD)_2$ were reacted in the molar ratio of 2:1, both the nickelole **508** and the nickel acetylide **509** were produced. The major product **510** was postulated to form by a Diels−Alder reaction with inverse electron demand between these two intermediates, followed by extrusion of nickel and acid hydrolysis (Scheme 145).

Scheme 143



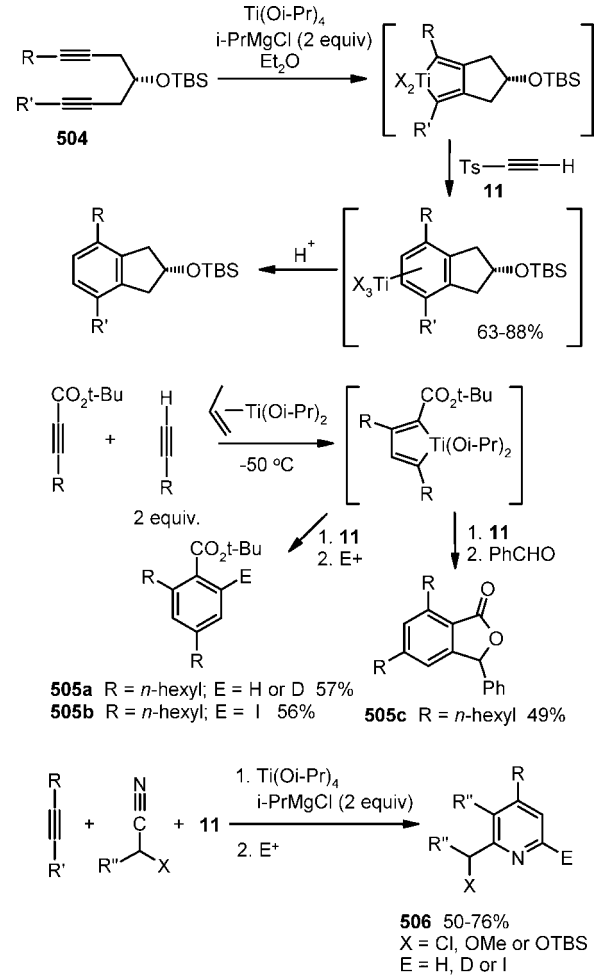
17.4. Miscellaneous Reactions

Intramolecular cyclizations of vinyl allenic sulfones **512**,[393] acetylenic sulfones **514**,[394] and bis(alkynyl) sulfone **516**[395] were catalyzed by the Grubbs' second generation catalyst **513**, the rhodium complex **515**, and the platinum complex **517**, respectively (Scheme 146). Acetylenic sulfone **1** reacted with the iron tricarbonyl complex **518**, followed by oxidation or carbonylation of the metallacycle **519**,[396] as indicated in Scheme 147. The regioisomer **520** failed to undergo these further transformations.

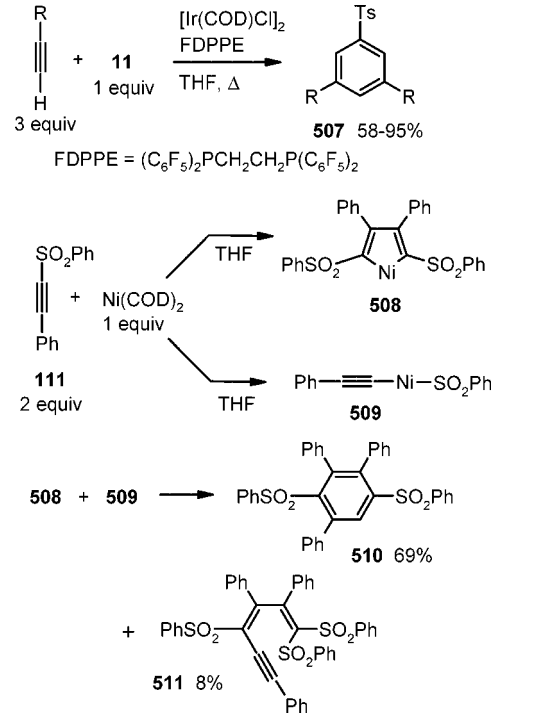
18. Cyclizations of Unsaturated Sulfones on Solid Supports

The versatility of unsaturated sulfones as reagents and starting materials in organic synthesis led several groups to investigate their cycloadditions and cyclizations on solid supports, with the ultimate objective of preparing libraries of desired products. Kurth and co-workers reported several methods[397] for utilizing dienyl sulfones on polymer supports. In one approach, sulfolene **521** was pyrolyzed to generate the corresponding dienyl sulfone, which was then trapped with *N*-phenylmaleimide and further annulated with TOSMIC or ethyl isocyanoacetate as shown in Scheme 148.[397a] Alternatively, a traceless sulfone linker approach was based on the polymer-supported dienyl sulfones **522**.[397b] The latter were subjected to 1,3-dipolar cycloadditions, followed by further annulation and cleavage with alkyl isocyanoacetates to afford a small library of isoxazolinopyrroles. In a third approach, the authors first prepared isoxazolinopyrroles containing free carboxylic acid groups in solution phase, followed by amidation with polymer-supported amines.[397c]

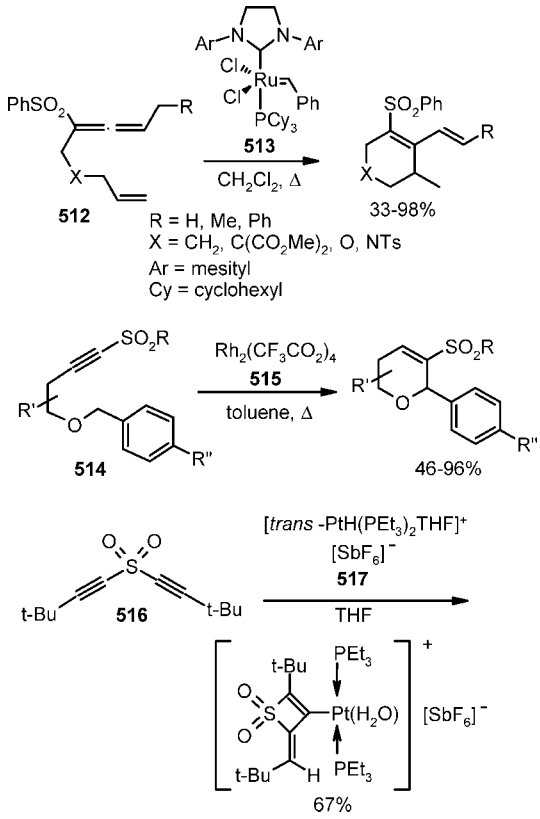
Scheme 144



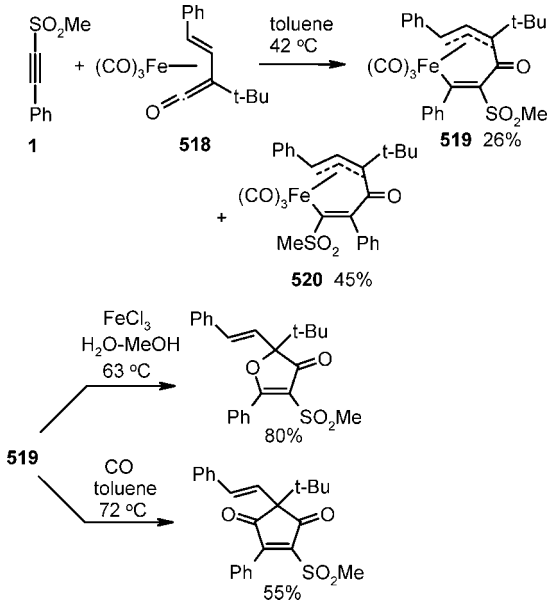
Scheme 145



Scheme 146



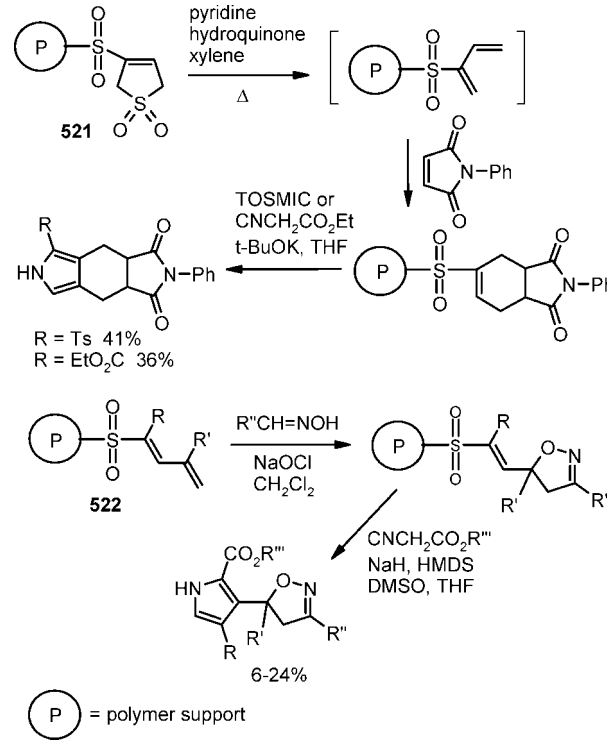
Scheme 147



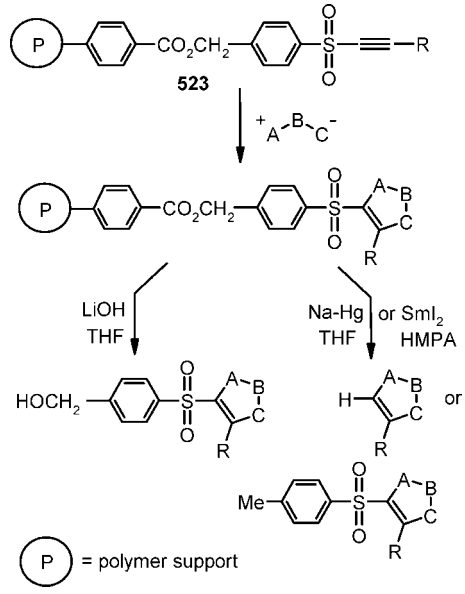
Acetylenic sulfones have been attached to polymer supports by means of ester linkers to produce **523**. The products were subjected to 1,3-dipolar cycloadditions with azides, diazo compounds, nitrile oxides, nitrile imines, nitrile ylides, nitrones, azomethine imines, azomethine ylides, munchnones, and sydnones, followed by cleavage from the support by ester hydrolysis or by reductive desulfonylation (Scheme 149).[165,398] Several Diels−Alder cycloadditions and cyclizations by conjugate addition−intramolecular alkylation were also reported.

In addition, the palladium-catalyzed intramolecular Heck reaction of **489** to give **490**, as shown in Scheme 142, was

Scheme 148



Scheme 149



also performed using polymer-supported *o*-iodobenzylamines,[399] while solid-supported azides were employed in the preparation of triazole libraries by 1,3-dipolar cycloaddition with activated acetylenes. 1-(*p*-Toluenesulfonyl)-2-(trimethylsilyl)ethyne (**14**) was investigated in a model solution reaction but was not included among acetylenes employed in the solid-phase experiments.[400]

19. Concluding Remarks

This review demonstrates that the collaboration of a sulfone group with adjacent acetylene, allene, and diene substituents produces behavior that is remarkably diverse, mechanistically complex, synthetically useful, and frequently unexpected. Although the cycloaddition and cyclization

reactions of these compounds have been extensively studied by the many researchers whose contributions are cited here, the considerable insight they have gained still leaves much room for further exploration, which we hope this review will stimulate and facilitate.

20. Acknowledgments

We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support. K.N.C. thanks NSERC and Alberta Ingenuity for postgraduate scholarships, and D.G. is the recipient of a Queen Elizabeth II scholarship.

21. Note Added in Proof

The following contributions appeared in the literature during the preparation of this review. Acetylenic sulfone **11** was employed among other alkynes in the formation of a series of triazole-substituted quinolines by dipolar cycloaddition with the corresponding azidoquinolines. The products were used as phosphorylation chemosensors.[401] A key step in a recent synthesis of the tricyclic core of halichlorine was achieved by conjugate addition of the oxime of (2-oxocyclopentyl)acetic acid to dienyl sulfone **130**, followed by intramolecular 1,3-dipolar cycloaddition.[402] The cyclization of bis(allenic) sulfones containing *o*-amidophenyl substituents at their γ-positions afforded the corresponding bis(indolyl) sulfones,[403] while several novel bis(enediynyl) bis(sulfones) underwent cycloaromatization and were able to cleave plasmid DNA.[404] A theoretical and experimental study of the mechanism of cyclization of conjugated bis(allenic) sulfones has appeared.[405] A series of 1,3-benzothiazines was prepared by the reaction of the corresponding cyclic sulfenamides with acetylenic sulfone **11** or methyl propiolate in the presence of cesium fluoride.[406] The ring-expansion protocol with **11** via the formal aza-Cope rearrangement shown in Scheme 125 was extended to the conversion of an α-vinyl azetidine to the corresponding unsaturated azocane.[407] Similarly, the conjugate addition products of *N*-oxypropargylamines to acetylenic sulfones underwent 3-aza-Cope rearrangements to produce allenes that cyclized to the corresponding pyridines.[408]

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