The Use of Sulfonyl 1,3-Dienes in Organic Synthesis

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Contents

I. Introduction

Sulfone chemistry has been a standard part of organic chemistry for more than a century, the sulfonyl moiety being used primarily as an auxiliary group, modifying the reactivity of organic compounds. In the past decades an even more diverse range of chemistry involving the sulfone functional group has been developed.[1−6a]

A variety of versatile sulfone-containing synthons are known today, and among those, sulfonyl 1,3-dienes have attracted special attention. Such electron-deficient conjugated dienes are useful starting materials in cycloaddition reactions and in many cases they have been transformed into versatile synthetic intermediates via regioselective functionalization at each double bond. Michael-type conjugate additions to these dienes are also of particular interest since they can produce allylic sulfones, which can undergo further interesting transformations.

The present review deals with the chemistry of these sulfonyl-substituted conjugated dienes. They have been classified according to the position of the sulfonyl group relative to the 1,3-diene system, with one or two of these sulfone moieties being present. For each class of sulfonyl 1,3-diene the different methods employed for their preparation followed by the application of sulfonyl 1,3-dienes in synthetic organic transformations are presented.

II. 1-Sulfonyl 1,3-Dienes

A. Synthesis

Although a possible synthesis of sulfonyl 1,3-dienes would be the oxidation of the corresponding sulfinyl 1,3-dienes,[6b] the most general approaches to α,*β*−*γ*,*δ*-unsaturated sulfones have involved either condensation reactions between sulfones and carbonyl compounds, or elimination reactions of allyl sulfones, prepared in many cases from simple dienes. Thus, the Knoevenagel-type condensation of 4-(*p*-tolylsulfonyl)-2-butene nitrile (**1**) with aldehydes provided 3-cyano-1-(*p*-tolylsulfonyl) 1,3-dienes **2** of *E*,*Z* stereochemistry (Scheme 1).[7]

A possible route to 1-sulfonyl 1,3-dienes is also the sodium hydroxide-induced condensation of sulfones with α,*β*-unsaturated aldehydes in a two-phase system consisting of water/dichloromethane in the presence of a catalytic amount of triethylbenzylammonium chloride (TEBA). Reaction of methyl phenyl sulfone with cinnamaldehyde afforded compound **3** in moderate yield as a single isomer of which no stereochemical assignment was made (Scheme 2).[8]

The reaction of Grignard reagents **5**, prepared by adding ethylmagnesium bromide to the corresponding methyl sulfone **4**, with α,*β*-unsaturated aldehydes and ketones afforded mainly alcohols **6** from a 1,2-addition process. This sulfonyl Grignard reagent behaved differently from conventional organomagnesium compounds, which normally give large amounts of 1,4-addition products with α,*β*-unsaturated ketones. The allylic alcohols obtained were dehydrated to afford 1-sulfonyl-substituted 1,3-dienes **7** (Scheme 3).[9,10]

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Rafael Chinchilla was born in Alicante in 1959, and received his B.Sc. (1985), M.Sc. (1987), and Ph.D. (1990) degrees in Chemistry from the University of Alicante. After a period (1991–1992) at the University of Uppsala, Sweden, as a postdoctoral fellow with Professor J.-E. Bäckvall, he moved back to the University of Alicante and joined the research group of Professor C. Nájera. He recently (1997) has been appointed to Associate Professor and his current research interest include sulfone chemistry, asymmetric synthesis, amino acids, and peptide coupling reagents.

Horner−Emmons reaction of α-phosphoryl sulfones **8** with α,*β*-unsaturated aldehydes such as acrolein, methacrolein, crotonaldehyde, and cinnamaldehyde using *n*-buthyllithium to generate the phosphonate anions, allowed the preparation of the corresponding α,*β*−*γ*,*δ*-unsaturated sulfones **10**. Formation of *Z* double bonds could not be detected in the products **10** (Scheme 4). However, the use of 2-cyclohexenone in the analogous reaction afforded a 11:7 *Z*/*E* mixture of dienesulfone in 60% yield.[11a] This synthesis can be carried out following a one-pot procedue.[11b] A similar reaction has been used for the synthesis of 1-(methylsulfonyl)butadienylphosphonate **12** in good yield by condensation of diethyl phosphonate **11** with cinnamaldehyde in the presence of piperidine fol-

Carmen Nájera was graduated from the University of Zaragoza in 1973 and obtained her doctorate in chemistry from the University of Oviedo in 1979. She spent postdoctoral stays with Professor D. Seebach at the ETH (Zürich), Professor J. E. Baldwin at the Dyson Perrins Laboratory (Oxford), Professor E. J. Corey at Harvard University, and Professor J.-E. Bäckvall at Uppsala University. She became Associate Professor in 1985 at the University of Oviedo and full Professor in 1993 at the University of Alicante. She is co-author of about 100 papers and her current research interest is focused on organometallic chemistry, sulfones, amino acids, asymmetric synthesis, and peptide coupling reagents.

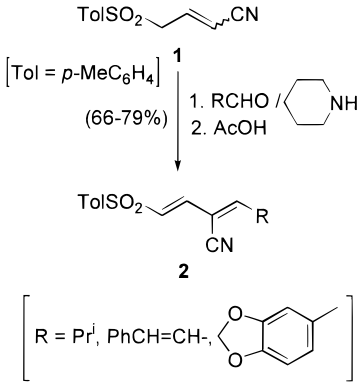
Miguel Yus was born in Zaragoza in 1947. He received the B.Sc. (1969), M.Sc. (1971), and Ph.D. (1973) degrees from the University of Zaragoza. After spending two years as a postdoc at the Max Planck Institut für Kohlenforschung in Mülheim a.d. Ruhr he returned to the University of Oviedo where he became Associate Professor in 1977, being promoted to full Professor in 1987 at the same university. In 1988 he moved to a chair in organic chemistry at the University of Alicante where he is currently the head of the Organic Chemistry Department. Professor Yus has been visiting professor at different institutions such as ETH-Zürich and the universities of Oxford, Harvard, Uppsala, Marseille, and Tucson. He is member or fellow of the chemical societies of Argentina, England, Germany, Japan, Spain, Switzerland, and United States. He is co-author of more than 200 papers mainly in the field of development of new methodologies involving organometallic intermediates. His current research interest is focused on the preparation of very reactive functionalized organolithium compounds and their use in synthetic organic chemistry.

lowed by treatment with a catalytic amount of *p*-toluenesulfonic acid (*p*TsOH) (Scheme 5).[12]

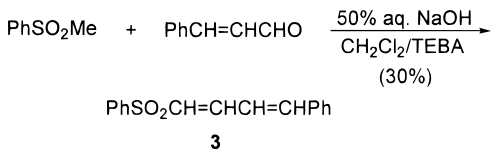
Dienyl trifluoromethanesulfones (triflones) have been prepared via halogen−metal exchange of iodotrimethylsilane (**13**) using *tert*-butyllithium, followed by addition of 0.5 equiv of triflic anhydride. The resulting anion **14** undergoes condensation reaction with α,*β*-unsaturated aldehydes allowing the stereoselective synthesis of dienyl triflones **15** (Scheme 6).[13]

The free-radical 1,4-addition of sulfonyl halides to carbon−carbon double bonds,[14] followed by base-

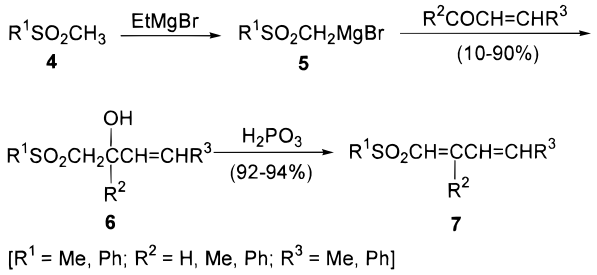
Scheme 1



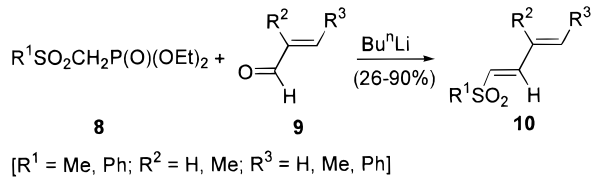
Scheme 2



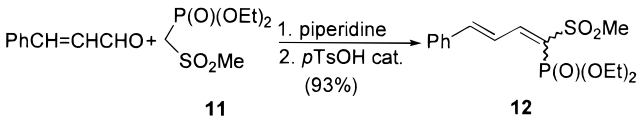
Scheme 3



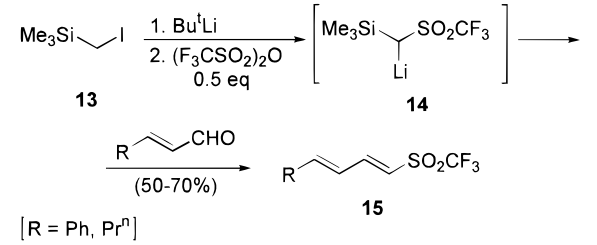
Scheme 4



Scheme 5

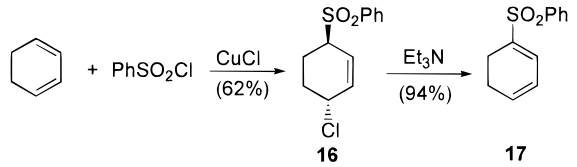


Scheme 6

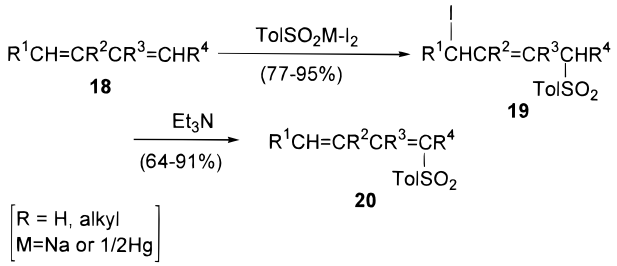


induced dehydrohalogenation constitutes one of the most efficient methods for the preparation of α,β-unsaturated sulfones. Following this synthetic route, copper-catalyzed 1,4-addition of arenesulfonyl chlorides to acyclic and cyclic conjugated dienes has been applied to the preparation of 1-sulfonyl-substituted 1,3-dienes.[15,16] The 1-sulfonyl-4-chloro-2-alkenes obtained can be dehydrohalogenated in the presence of triethylamine to the corresponding acyclic or cyclic 1-sulfonyl 1,3-dienes, as is shown in Scheme 7 for the synthesis of 1-(phenylsulfonyl)-1,3-cyclohexadiene (**17**). In the case of acyclic dienes such as isoprene *E*/*Z* mixtures are usually obtained.[17]

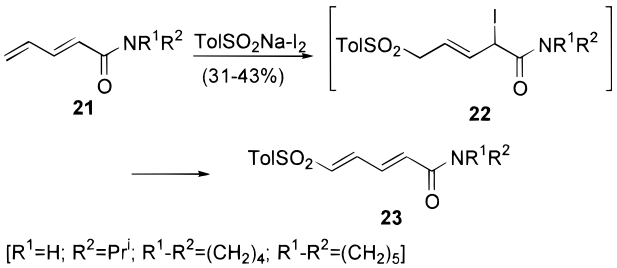
Scheme 7



Scheme 8



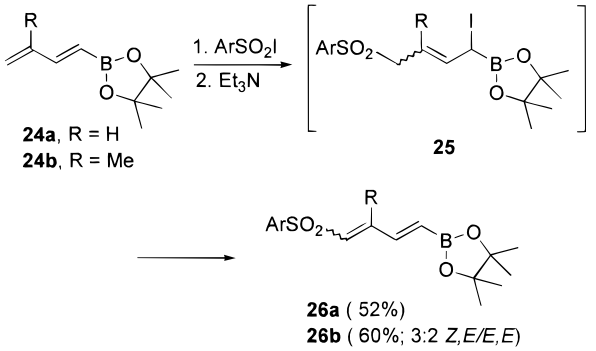
Scheme 9



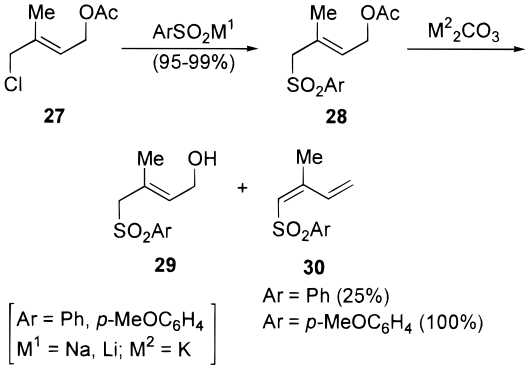
The iodosulfonylation reaction of conjugated dienes has been studied using in situ generated *p*-tolylsulfonyl iodide from sodium or mercury(II) *p*-toluenesulfinate and iodine. The δ-iodoalkenyl sulfones **19** obtained from the 1,4-addition process, undergo triethylamine-induced dehydrohalogenation to afford dienyl sulfones **20** (Scheme 8).[18] This procedure was recently applied to the stereoselective synthesis of synthetically useful (2*E*,4*E*)-5-tosyl-2,4-pentadienamides **23** from the corresponding (2*E*)-2,4-dienamides **21** (Scheme 9).[19] In this case, the iodosulfonyl intermediate **22** underwent spontaneous dehydroiodination. This iodosulfonylation−dehydroiodination procedure has also been used for the synthesis of arylsulfonyl 1,3-dienylboronates **26** from boronates **24** (Scheme 10).[20]

1-Arylsulfonyl 1,3-dienes have been obtained as byproducts in the synthesis of the allylic sulfone **29**, a starting material in a synthesis of vitamin A. Attempted hydrolysis of *trans*-acetoxy sulfones **28**, prepared by reaction of the sodium or lithium salts of sulfinic acids with isoprene hypochlorination product **27**,[21] using sodium or potassium carbonate, afforded the diene **30** together with compound **29**, with relative yields depending on the aromatic substituent (Scheme 11).[22] Also, 1-chloro-4-acetoxy-2-alkenes such as **31**, prepared from simple dienes by a palladium(II)-catalyzed chloroacetoxylation proce-

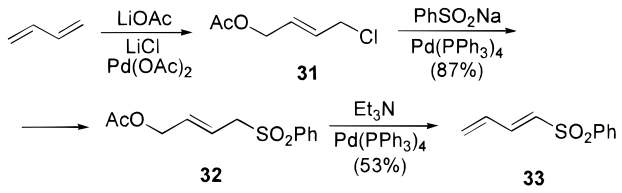
Scheme 10



Scheme 11



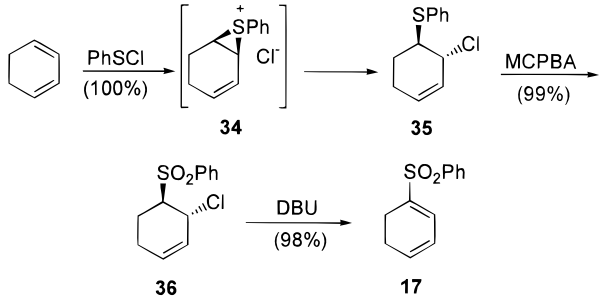
Scheme 12



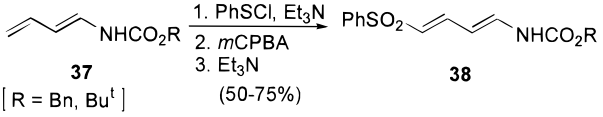
dure,[23] can be transformed into 1-phenylsulfonyl-4-acetoxy-2-alkenes such as **32** by palladium(0)-catalyzed substitution of the allylic chloro group with sodium benzenesulfinate. Further elimination of acetate is achieved by treatment with triethylamine in combination with a palladium(0) catalyst, affording 1-phenylsulfonyl 1,3-dienes such as **33** (Scheme 12).[24]

Sulfonyl dienes such as **17** have also been prepared by base-induced dehydrochlorination of *β*-chloro homoallylic sulfones. The synthetic procedure involves the well-known addition of arenesulfenyl halides to olefins, which proceeds through an episulfonium salt intermediate **34**.[25] 1,3-Cyclohexadiene produced *trans*-*β*-chlorophenyl sulfide **35**, which was oxidized to the *trans*-*β*-chloro sulfone **36** using *m*-chloroperoxybenzoic acid (*m*CPBA). Subsequent dehydrochlorination with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) afforded sulfone **17** (Scheme 13).[26] This method has been used for the direct synthesis of 4-(phenylsulfenyl)-1,3-butadiene-1-yl carbamates (1:1 mixtures of 1*E*,3*E* and 1*E*,3*Z*) by addition of phenylsulfenyl chloride to carbamates **37** at low temperature followed by warming to room temperature. Subsequent oxidation and base-catalyzed equilibration afforded highly stable (1*E*,3*E*)-4-(phenylsulfonyl)-1,3-butadiene-1-yl carbamates **38** (Scheme 14).[27]

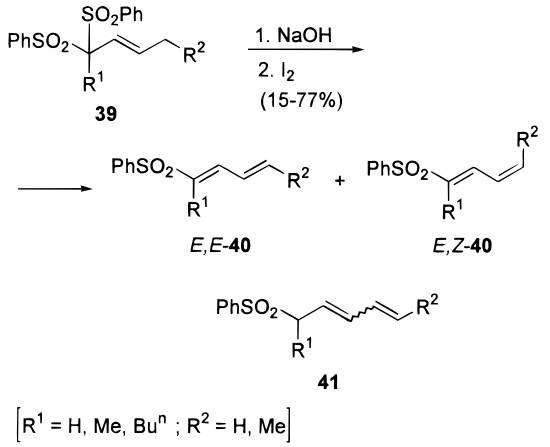
Scheme 13



Scheme 14



Scheme 15

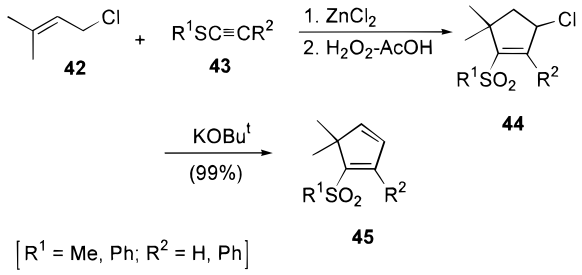


Base-induced elimination of benzenesulfinic acid from allylic 1,1-disulfones **39** furnished 1,3-dienes functionalized by the phenylsulfonyl group. Allylic 1,1-disulfones **39** (R^1 = H) were obtained by condensation of bis(phenylsulfonyl)methane with the appropriate aldehyde in the presence of piperidine acetate, whereas substituted compounds **39** (R^1 = alkyl) were prepared by metalation of the primary 1,1-disulfones with sodium hydride followed by reaction with alkyl iodides. Elimination of one of the sulfonyl groups in **39** with sodium hydroxide followed by equilibration with iodine led to a mixture of isomeric 1-(phenylsulfonyl) 1,3-dienes **40** (Scheme 15).[28,29] In this reaction it might be preferable to accept incomplete conversion since isomerization to the more stable allylic 2,4-diene sulfones **41** increases with long reaction times.

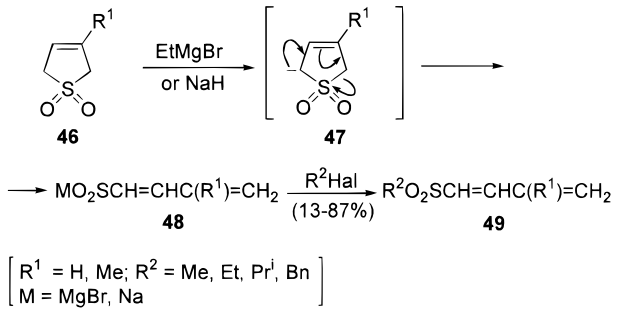
Sulfonyl-substituted cyclopentadienes have been prepared with a procedure involving a zinc chloride-induced [3+2] cycloaddition reaction between allylic chloride **42** and ethynyl sulfides **43** to give 1-sulfenyl-3-chlorocyclopentenes, which were oxidized to their corresponding sulfones **44**. Subsequent base-induced elimination afforded cyclopentadienyl sulfones **45** (Scheme 16).[30]

2,5-Dihydrothiophene 1,1-dioxides (3-sulfolenes) **46** undergo ring-opening reactions in the presence of Grignard reagents[31] or sodium hydride.[32] Alkylation of the intermediate dienesulfonyl salts **48** allows the

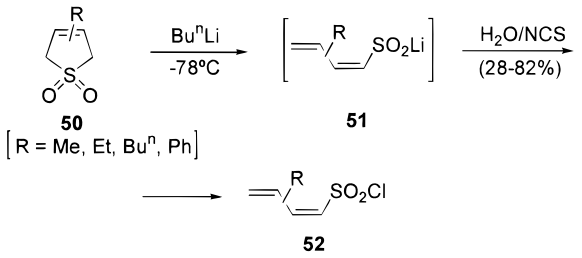
Scheme 16



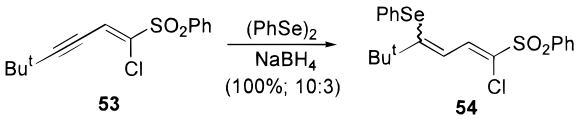
Scheme 17



Scheme 18



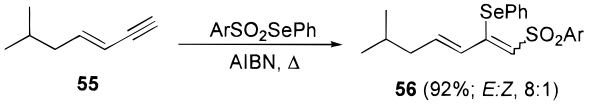
Scheme 19



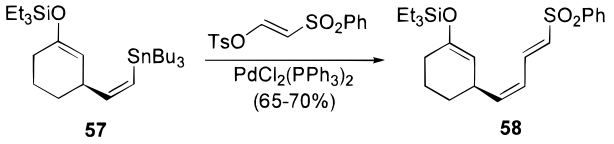
preparation of 1-(alkylsulfonyl)-1,3-butadienes **49** as pure *Z* isomers (R^2 = Me, Et) or *Z*/*E* mixtures (R^2 = Pr^i, Bn) (Scheme 17). Recently the same methodology was used for the one-pot synthesis of substituted (1,3-butadiene-1-yl)sulfonyl chlorides **52** employing *n*-butyllithium as base. Treatment of the generated sulfinate intermediates **51** with *N*-chlorosuccinimide (NCS) afforded the final products **52** (Scheme 18).[33]

Conjugate enyne sulfones such as **53**[34] undergo regio- and stereoselective addition of in situ generated sodium phenyl selenide, allowing the synthesis of the corresponding 4-(phenylseleno)-1-(phenylsulfonyl) 1,3-diene **54** (Scheme 19).[35] On the other hand, simple conjugate enynes undergo free-radical selenosulfonylation with *Se*-phenyl *p*-tolueneselenosulfonate. The reactions were performed either photochemically or thermally in the presence of azobis(isobutyronitrile) (AIBN), addition to the triple bond occurring preferentially with enynes having an acetylenic terminus affording 1,2-adducts as in the case shown is Scheme 20 for the enyne **55**.[36a] β-Selenovinyl sulfones, prepared by free-radical selenosulfonation of acetylenes, undergo substitution of the selenium moiety with vinyl cuprates affording 1-sulfonyl 1,3-dienes.[36b]

Scheme 20



Scheme 21



The Stille coupling reaction has been applied to the synthesis of the dienyl sulfone **58**, a precursor for the HMG-CoA reductase inhibitor dihydrocompactin. Reaction of vinyl stannane **57** with *trans*-(tosyloxy)-ethenyl phenyl sulfone and a Pd(II) complex afforded the product **58** (Scheme 21).[37] Also α- and β-substituted dienyl triflones have been prepared recently via this coupling reaction between iodovinyl triflones and vinyl stannanes.[38]

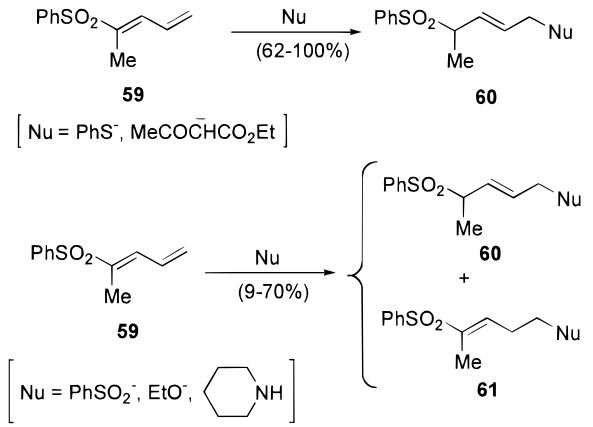
B. Reactivity

1. Conjugate Additions

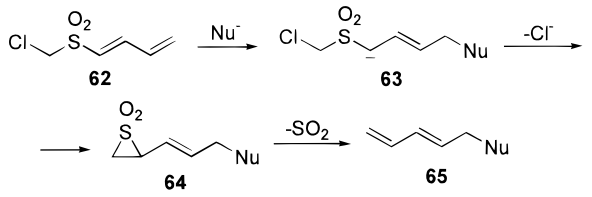
Michael addition to dienyl sulfone **59** using nucleophiles such as sodium thiophenoxide or sodium ethyl acetoacetate gave the expected 1,4-adducts **60** (Scheme 22).[29] However, nucleophiles such as piperidine, sodium sulfinate, and sodium ethoxide led to different mixtures of 3,4- and 1,4-products.[29] Dienyl sulfone **59** polymerizes under basic conditions, explaining the low yields obtained in some cases.

An approach to conjugated isoprenoid polyenes has been developed on the basis of the findings that chloromethyl butadienyl sulfone **62** reacts with nucleophiles to give an intermediate **63** that undergoes a γ-elimination of chloride followed by sulfur dioxide extrusion (Michael-induced Ramberg−Bäcklund reaction) (Scheme 23).[16] The isoprene-directed modification of this process allows the step-by-step addition of isoprene synthons in a head-to-tail (triene **68**) or tail-to-tail (triene **69**) fashion starting from a tail-functionalized isoprenoid halide **66** (Scheme 24).[39] Thus, the (*Z*)-2-methyl-1,3-butadienylsulfinate anion

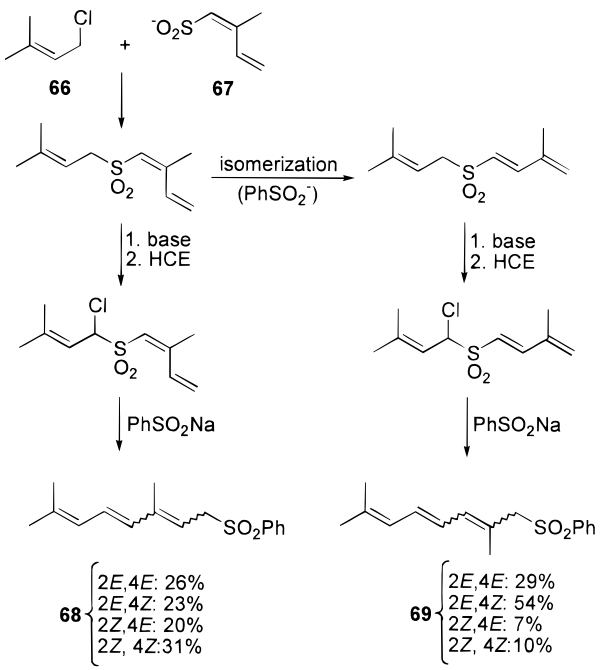
Scheme 22



Scheme 23



Scheme 24



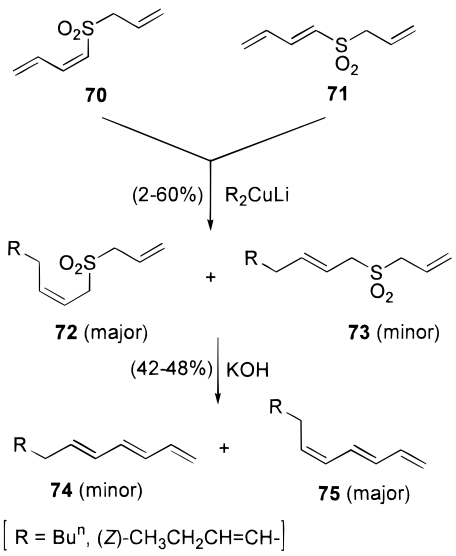
67 serves as a 5-carbon synthon and is attached to the carbon chain with its head functionality. The halogen is then reintroduced by successive reactions with base and hexachloroethane (HCE).

The Ramberg−Bäcklund sulfur dioxide extrusion has also been used for the synthesis of naturally occurring tri- and tetraenes **74** and **75** respectively, as the final step of a process involving dialkylcuprate additions either to 1,3-butadienyl 2-propenyl sulfone **70** or to its iodine-induced isomerization product **71**, both being considered as 1,3,5-heptatriene synthons (Scheme 25).[40] Also Michael additions of ethanol and ketones to allyl dienyl sulfones led to diallyl sulfones which were transformed into isoprenoid compounds by either Ramberg−Bäcklund reaction or thermolysis.[41]

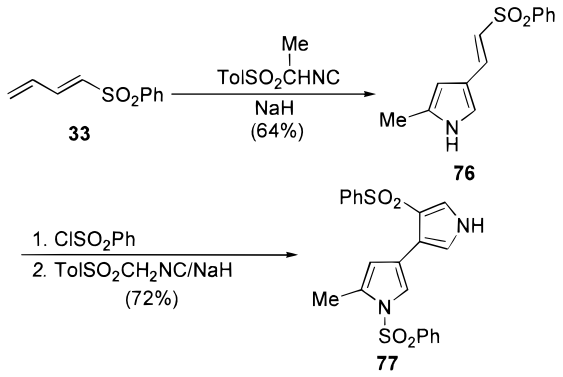
1-(Phenylsulfonyl)-1,3-butadiene can function as a viable electrophilic butadiene equivalent, as has been demonstrated in the synthesis of unsymmetrical 3,3′-bipyrroles in studies on the antitumor agent CC-1065.[42] In these studies, the sulfonyl diene was treated with $TolSO_2CHMeNC/NaH$ to give the 2,4-disubstituted pyrrole **76** in good yield despite the easy polymerization of **33** under basic conditions. The pyrrole **76** was transformed into the *N*-phenyl sulfonyl derivative and treated with $TolSO_2CH_2NC/NaH$ to give the 3,3′-pyrrole **77** (Scheme 26).

The reaction of cyclopropyl-bearing dienyl sulfone **78** with cesium fluoride in refluxing acetonitrile triggers a facile cyclopropane cleavage and subsequent Michael addition to the vinyl sulfone in a

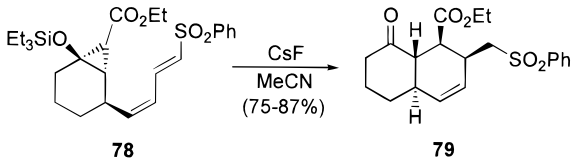
Scheme 25



Scheme 26



Scheme 27

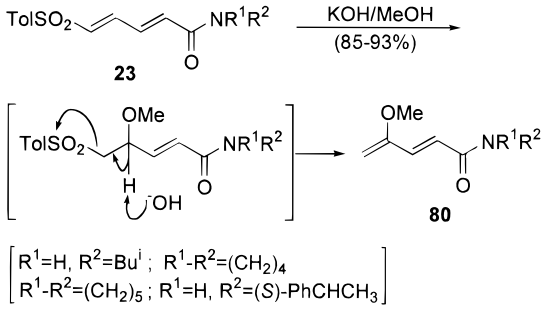


stereoselective manner to create the four contiguous chiral centers of adduct **79**, a synthon for the synthesis of dihydrocompactin (Scheme 27).[37] The high stereoselectivity achieved is presumably controlled by the *Z* carbon−carbon double bond of the dienyl sulfone and a preferred approach of the enolate to the more geometrically accessible side of the vinyl sulfone double bond.

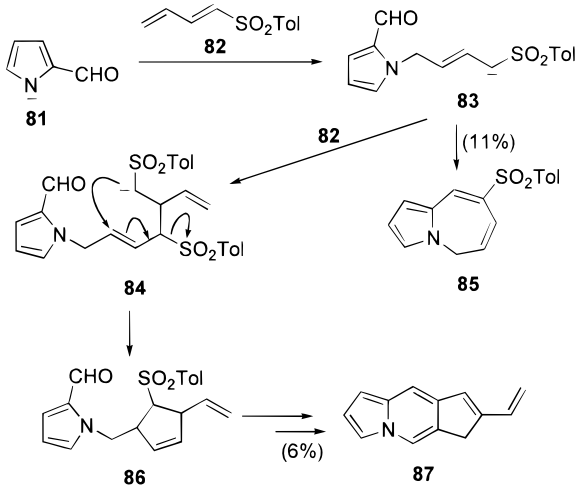
p-Toluenesulfonyl dienamides **23** react with methanolic potassium hydroxide to give (2*E*)-4-methoxy-2,4-pentadienamides **80** in good yields. The reaction proceeds via a Michael addition of the methoxide anion to the vinylic sulfone moiety followed by dehydrosulfinylation (Scheme 28).[43] These dienes were subsequently used in Diels−Alder reactions with electron-deficient alkenes affording highly substituted cycloadducts.[43]

The butadienyl sulfone **82** reacts with the anion of 2-pyrrolecarbaldehyde in a Michael addition−cyclization sequence to give azaazulene **85** together with the indolizine **87**; both compounds are formed in very low

Scheme 28



Scheme 29

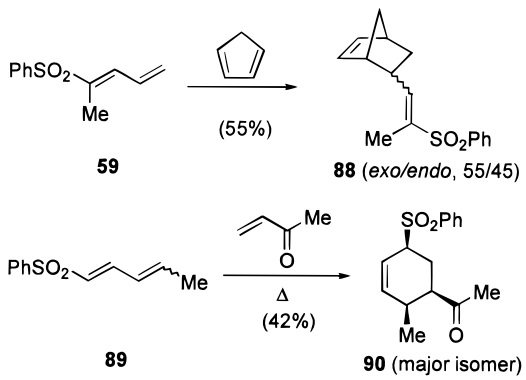


yields. The formation of **87** is explained by reaction of intermediate anion **83** with a second molecule of diene **82** followed by two cyclization steps with final elimination of the sulfone moieties (Scheme 29).[44]

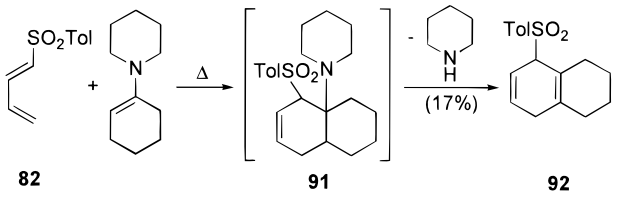
2. Cycloadditions

1-Sulfonyl 1,3-dienes can react both as dienophiles and as dienes in [4+2] cycloaddition reactions. Thus, heating sulfonyl diene **59** in toluene with cyclopentadiene led to a mixture of endo/exo cycloadducts **88** (Scheme 29), whereas no reaction was observed when diene **59** was heated in the presence of methyl vinyl ketone.[29] On the other hand, reaction of a mixture of sulfonyl dienes (*E,E*)-**89** and (*E,Z*)-**89** (ratio: 84/16) with methyl vinyl ketone yielded a mixture of cycloadducts, the major isolated isomer being compound **90** (Scheme 30).[29] The estimated stereoselectivity of the latter reaction is rather high, considering

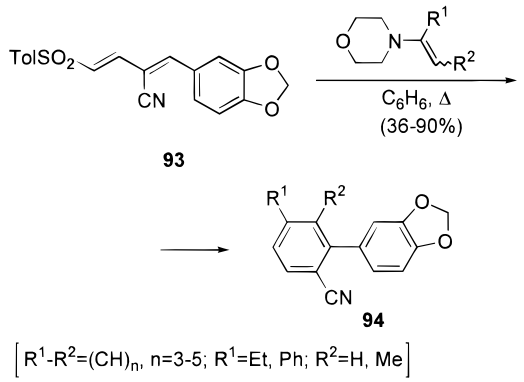
Scheme 30



Scheme 31



Scheme 32



that MO theory predicts a low stereoselectivity for dienes with electron-withdrawing substituents in the 1-position.[45]

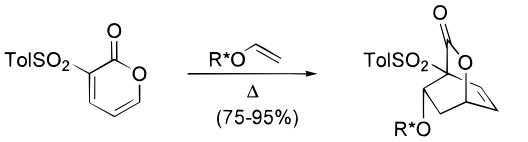
The presence of an electron-withdrawing group in the 1-position of the 1,3-diene makes these types of systems feasible for inverse electron-demand [4+2] cycloaddition reactions. Accordingly, butadienyl sulfone **82** reacted with the electron-rich olefin, *N*-(1-cyclohexenyl)piperidine, in refluxing toluene, giving the unstable cycloadduct **91** which, after elimination of piperidine, afforded the bis-allyl sulfone **92** although in low yield (Scheme 31).[44] However, highly reactive systems such as 1-(phenylsulfonyl)cyclopentadiene failed to react under "normal" or inverse electron-demand cyclization conditions and gave only dimerization products,[46] whereas other substituted 1-(phenylsulfonyl)cyclopentadienes afforded Diels–Alder cycloadducts with electron-deficient olefins.[30]

If another electron-withdrawing group is present on the sulfonyl butadiene system, the reaction with electron-rich olefins is favored. Thus, reaction of the 4-(*p*-tolylsulfonyl)-2-cyano 1,3-diene **93** with in situ generated morpholino enamines afforded benzonitriles **94** via a cycloaddition followed by elimination of morpholine and *p*-toluenesulfinic acid (Scheme 32).[7]

Asymmetric [4+2] cycloadditions of electrophilic 3-(*p*-toluenesulfonyl)-2-pyrone (**95**) with chiral alkyl vinyl ethers yielded bridged bicyclic lactone adducts **96** in good yields and diastereoselectivities (Scheme 33).[47] One of these chiral adducts has been used as starting material in the asymmetric synthesis of (−)-methyl triacetyl-4-epishikimate, an intermediate in the preparation of (−)-chorismic acid and analogues,[48] and also in the total synthesis of an A-ring precursor of the hormonally active 1α,25-dihydroxyvitamin D_3.[49]

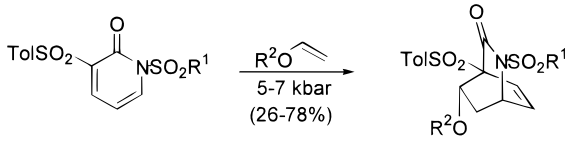
2-Pyridones have more aromatic character than 2-pyrones, and are therefore less reactive in [4+2] cycloadditions. The presence of a sulfonyl group as

Scheme 33



95 **96** (54-90% de)

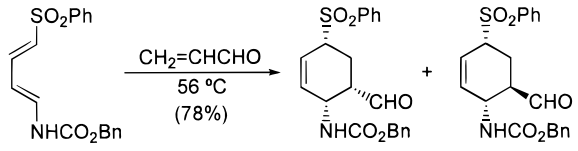
Scheme 34



97 **98**

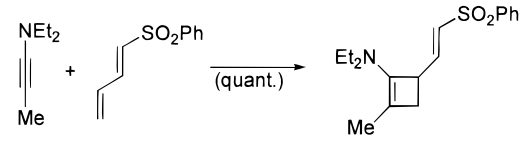
[R^1=Tol, *p*-BrC_6H_4, *p*-FC_6H_4, *p*-$NO_2C_6H_4$, C_6F_6, CF_3; R^2=Et, Bu^n]

Scheme 35



99 **100a** **100b**

Scheme 36



101 **33** **102**

substituent in the diene unit, however, makes 2-pyridones sufficiently electron deficient to react with electron-rich dienophiles in inverse electron-demand Diels−Alder cycloadditions, as shown in Scheme 34 for *N*-sulfonyl-3-(*p*-tolylsulfonyl)-2-pyridones **97**.[50]

1-Sulfonyl 1,3-dienes bearing an electron-releasing group react readily with electron-deficient olefins. Thus, the (1*E*,3*E*)-4-(phenylsulfonyl)-1,3-butadiene-1-yl carbamate **99**, reacts with acrolein to give the corresponding Diels−Alder cycloadducts **100a** and **100b** in a 7:1 endo:exo stereoselectivity (Scheme 35).[27]

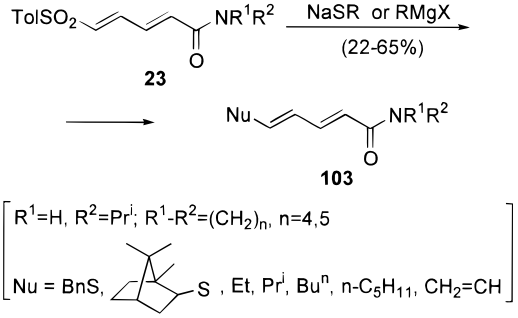
Dienyl sulfone **33** underwent a [2+2] cycloaddition with ynamine **101** to give the cycloadduct **102** (Scheme 36).[51] It is noteworthy that a [2+2] rather than a [4+2] cycloaddition takes place.

3. Miscellaneous

(2*E*,4*E*)-5-(*p*-tolylsulfonyl)pentenamides **23** act as *δ*-acyldienyl cation equivalents and undergo nucleophilic vinylic substitution of the sulfonyl group by sodium thiolates and Grignard reagents to give (2*E*,4*E*)-dienamides **103** in high regio- and stereoselectivity, probably through an addition−elimination process (Scheme 37).[19] This methodology has been applied to the synthesis of the naturally occurring unsaturated amides sarmentine [$R^1-R^2 = (CH_2)_4$, Nu = *n*-C_5H_{11}] and an Achillea amide [$R^1-R^2 = (CH_2)_5$, Nu = *n*-C_5H_{11}].

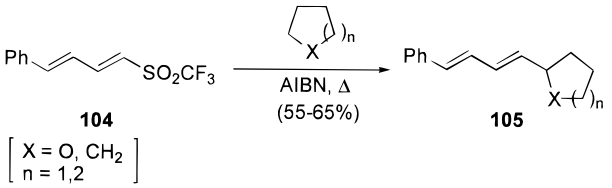
The dienyl triflone **104** provided access to substituted dienes by reaction with tetrahydrofuran or

Scheme 37



23 **103**

Scheme 38



104 **105**

cyclopentane under radical generation conditions (Scheme 38).[52] The reaction proceeds via radical C−H abstraction by the very electrophilic trifluoromethyl radical in a process involving addition of the generated alkyl radical to the α-carbon of the dienyl triflone **105** followed by elimination of trifluoromethylsulfonyl radical affording the final diene. Fragmentation of the trifluoromethylsulfonyl radical to sulfur dioxide occurs and the trifluoromethyl radical propagates the chain.

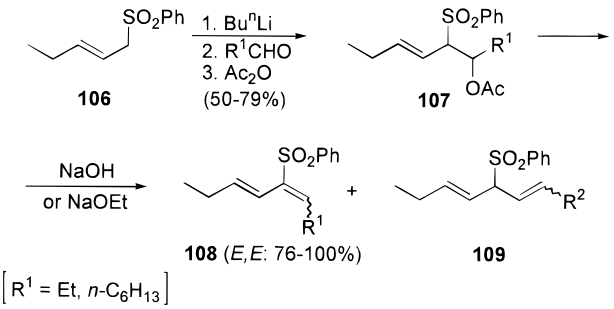
II. 2-Sulfonyl 1,3-Dienes

A. Synthesis

As in the case of the 1-sulfonyl 1,3-dienes, the 2-sulfonyl analogues have been prepared through condensation reactions using allyl or vinyl sulfones and carbonyl compounds. Another frequent synthetic method is the introduction of a sulfonyl group via metal-mediated 1,2-addition reactions to simple dienes followed by an elimination process. Methodologies based on addition to enynes, extrusion reactions, and others have also been employed.

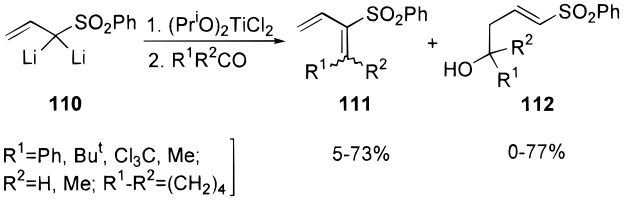
One of the general routes for the preparation of acyclic 2-arylsulfonyl 1,3-dienes from allylic sulfones and aldehydes is shown in Scheme 39.[53] Lithiation of an allyl sulfone such as **106** and reaction with an aldehyde, followed by quenching of the resulting alkoxide ion with acetic anhydride and subsequent elimination of acetic acid led mainly to the *E*,*E*

Scheme 39

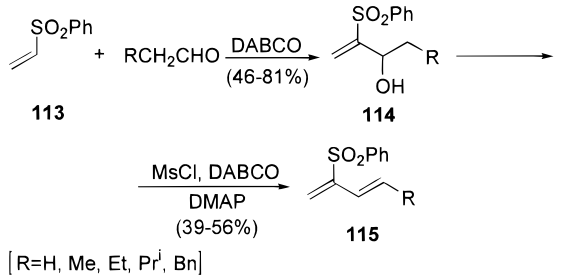


106 **107** **108** (*E*,*E*: 76-100%) **109**

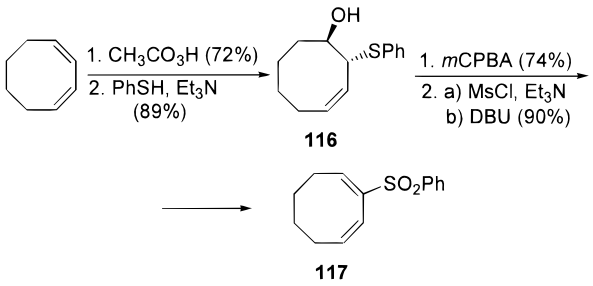
Scheme 40



Scheme 41



Scheme 42



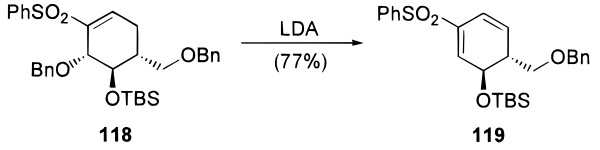
isomer of 2-(phenylsulfonyl) 1,3-dienes **108**. Small amounts of the undesired bisallyl sulfones **109** were also obtained with some aldehydes. When α,β-unsaturated aldehydes are used, conjugated homologous phenylsulfonyl trienes were stereoselectively obtained, allowing the use of this methodology for studies toward the synthesis of the triene-containing macrolides rapamycin[54] and rhizoxin.[55,56]

When the α,α-dilithiated allyl phenyl sulfone (**110**) was allowed to react with aldehydes in the presence of the $(Pr^iO)_2TiCl_2$ complex, hydroxy sulfones **112** from γ-attack were mainly obtained. However, when ketones were used as carbonyl reagents, 2-phenylsulfonyl dienes **111** were the major products (Scheme 40).[57]

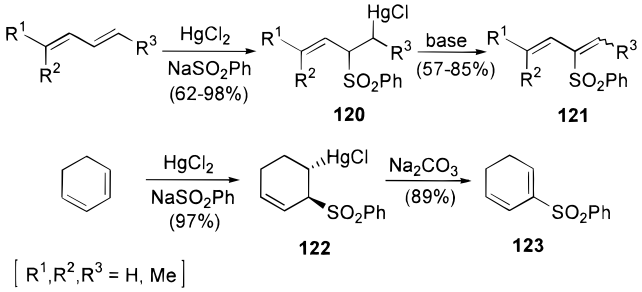
An alternative synthetic approach is based on the Baylis−Hillman coupling reaction[58] between phenyl vinyl sulfone **113** and an aldehyde in the presence of a catalytic amount of 1,4-diazabicyclo[2.2.2]octane (DABCO) followed by stereoselective dehydration.[59] Mesylation with methanesulfonyl chloride (MsCl) in the presence of DABCO and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) afforded sufonyl dienes **115** (Scheme 41).

Cyclooctadienyl phenyl sulfone **117** has been prepared from 1,3-cyclooctadiene via epoxidation with *m*-chloroperoxybenzoic acid (*m*CPBA), followed by ring opening of the epoxide by thiophenol. Subsequent oxidation (*m*CPBA) of the hydroxy sulfide **116** obtained, followed by mesylation and 1,2-elimination afforded the sulfonyl diene **117** (Scheme 42).[60] There are also examples of synthesis of cyclic sulfonyl 1,3-dienes by 1,4-elimination in β-heterosubstituted cyclic vinyl sulfones[60−63] as illustrated in Scheme 43 for the preparation of the diene **119** from sulfone **118**, an intermediate in the total synthesis of glycosidase inhibitors (±)-cyclophellitol and (1*R**,6*S**)-cyclophellitol.[63]

Scheme 43



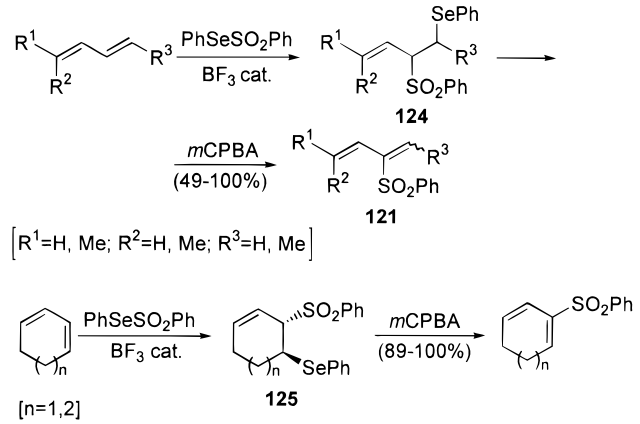
Scheme 44



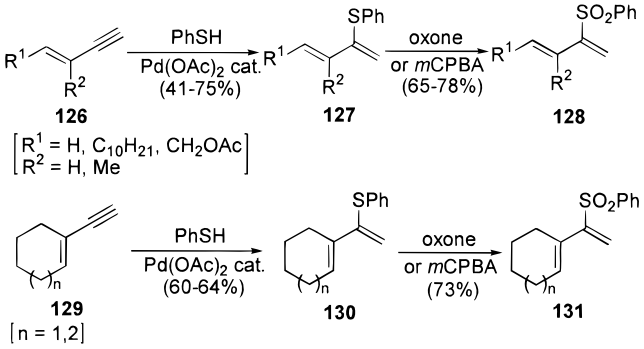
Sulfonylmercuriation−elimination of conjugated dienes constitutes a general route to both cyclic and acyclic dienyl sulfones.[64−66] The reaction is carried out by adding a preformed mercury benzenesulfinate complex, prepared by mixing mercury(II) chloride and sodium benzenesulfinate in water-dimethyl sulfoxide, to the 1,3-diene to give mercury adducts such as **120** or **122** (Scheme 44). The selectivity for 1,2-addition is usually very high although in some cases the 1,4-additions product was also obtained, for example from 1,3-cycloheptadiene (1,2:1,4 = 56:44). A reasonable explanation for the 1,2-selectivity is that sulfonylmercuriation is a kinetically controlled reaction. Elimination of mercury from adducts **120** or **122** can be performed with several bases (NaOH−Na_2CO_3, Na_2CO_3, or Et_3N), the choice depending on the substrate and the stability of the final product.[64,65] Isolation of the mercury adduct is not necessary before the elimination, allowing a one-pot procedure.

A conceptually similar approach to these systems is based on a selenosulfonylation−oxidation sequence,[67,68] a methodology originally employed for the synthesis of vinyl sulfones[67] and demonstrated to work with dienes. The synthetic utility of this approach was shown on a number of cyclic and acyclic 1,3-dienes.[68] The procedure, illustrated in Scheme 45, involves treatment of the conjugated diene with $PhSeSO_2Ph$ in the presence of a catalytic amount of boron trifluoride as a radical initiator, which led to selenosulfonated adducts **124** or **125**. The addition step can be made highly 1,2-selective in most cases (except for isoprene) by tuning the reaction conditions. For example, butadiene afforded quantitative yield of the 1,4-adduct at room temperature, but selectively gave the 1,2-adduct at 0 °C. The selenosulfonylation of cyclic dienes was stereospecific and occurred in a trans manner.[68] With this procedure 2-phenylsulfonyl-1,3-cycloheptadiene was obtained

Scheme 45



Scheme 46

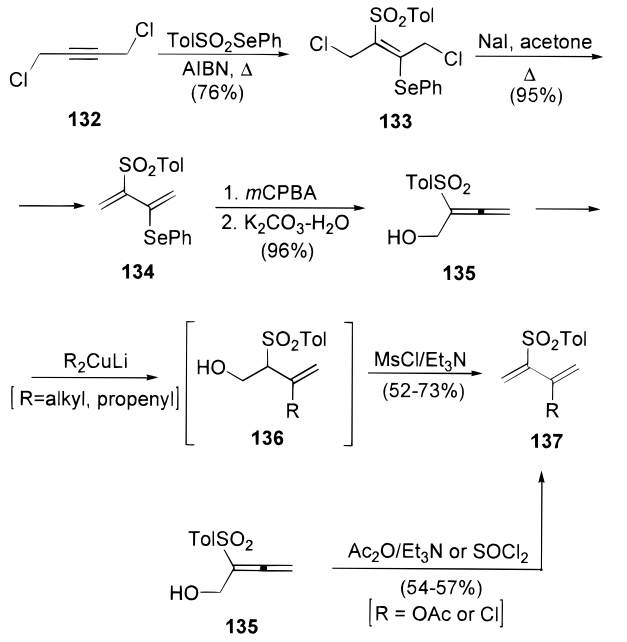


with high regioselectivity, which was not possible with the mercury-based approach. The corresponding desired 2-(phenylsulfonyl) 1,3-dienes are available by the one-pot oxidation of the crude selenosulfones using *m*-chloroperoxybenzoic acid (*m*CPBA).[68]

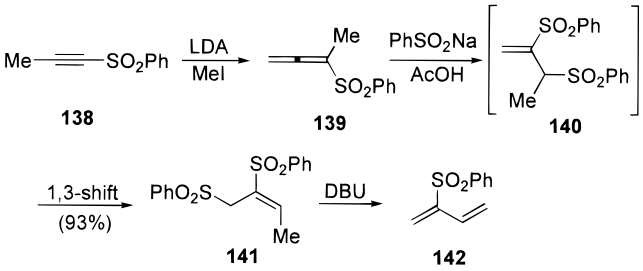
The two previously mentioned general methods for the preparation of 2-(phenylsulfonyl) 1,3-dienes involving metal-mediated (mercury or selenium) addition to conjugate dienes employ stoichiometric amounts of the metallic reagent, which has drawbacks on a large-scale synthesis. Transition metal-catalyzed additions of nucleophiles to conjugate dienes occur at the 1-position with formation of a (π-allyl)metal complex.[69] Conjugate dienes therefore seemed unsuitable as substrates for a metal-catalyzed preparation of these systems, since this approach requires addition of PhS^- or $PhSO_2^-$ to the 2-position of the diene. However, palladium-catalyzed addition of thiophenol to conjugate enynes **126** and **129** was highly regioselective, affording only the products arising from sulfur attack at carbon 2 of the 3-en-1-yne (Scheme 46).[70] Oxidation of the 2-(phenylthio) 1,3-dienes **127** or **130** to the corresponding sulfones **128** or **131** was done employing either oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) or *m*-chloroperoxybenzoic acid.[70]

A selenosulfonylation method has been applied to the synthesis of 3-(phenylseleno)-2-(*p*-toluenesulfonyl)buta-1,3-diene **134** through thermally induced free-radical selenosulfonylation of 1,4-dichloro-2-butyne **132** to adduct **133** which was reduced by elimination of chlorine (Scheme 47).[71a] Oxidation of the seleno-substituted sulfonyl diene **134** obtained, to the corresponding selenoxide, resulted in a [2,3]

Scheme 47



Scheme 48

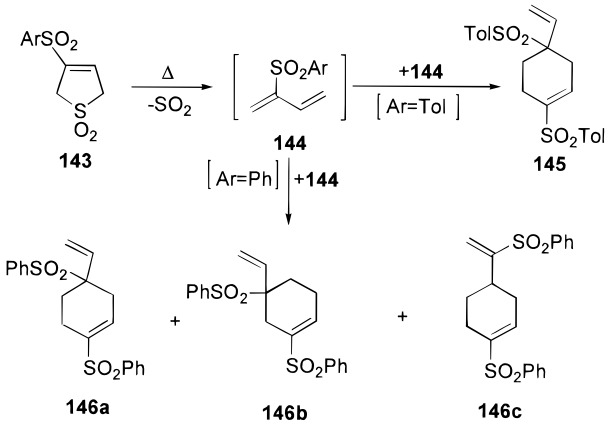


sigmatropic rearrangement to sulfonylallene **135**. After reaction with cuprates, crude product **136** was treated with mesyl chloride and triethylamine which afforded the desired 3-alkyl-substituted 2-(*p*-tolylsulfonyl)-1,3-butadienes **137** via elimination of methanesulfonic acid. Alternatively, the 3-acetoxy- and 3-chloro-substituted derivatives (R = OAc, Cl) were prepared by the reaction of allene **135** with acetic anhydride and thionyl chloride, respectively.[71a] Compound **137** (R = OTMS) has been prepared after quantitative reaction of 3-(*p*-toluenesulfinyl)-2-butanone with trimethylsilyl trifluoromethanesulfonate in the presence of diisopropylethylamine, followed by oxidation with *m*CPBA.[71b]

The preparation of 2-(phenylsulfonyl) 1,3-butadiene **142** has also been achieved starting from 1-methyl-1-(phenylsulfonyl)allene **139** (Scheme 48).[72] The activated allene was obtained by methylation of 1-(phenylsulfonyl)propyne **138** using lithium diisopropylamide (LDA) as base. Treatment of **139** with sodium benzenesulfinate in the presence of acetic acid yielded (*E*)-1,2-bis(phenylsulfonyl)-2-butene **141** after addition of the benzenesulfinate anion onto the central carbon atom of the allene and subsequent 1,3-shift of the phenylsulfonyl group. Treatment of compound **141** with DBU afforded the diene **142** which was used for further transformations without previous isolation.

The parent 2-(arylsulfonyl) 1,3-diene **144** has been quantitatively generated from 3-(arylsulfonyl)-3-sul-

Scheme 49



folene **143** by extrusion of sulfur dioxide upon thermolysis. In fact, the reaction did not give the isolated diene **144**, but quantitatively the in situ dimerization product via a Diels−Alder reaction. Thus, it was reported that compound **144** gave products **146a**:**146b**:**146c** in a ratio of 6:2:1 for Ar = Ph,[73] and only dimer **145** for Ar = Tol[74] (Scheme 49). Compound **144** must be handled in dilute solutions due to this fast dimerization which occurs even at room temperature. Other 2-(phenylsulfonyl) 1,3-butadienes bearing groups such as methyl,[75] chloro,[76] phenylthio,[76] or acetamido[77] in the 3-position have been prepared by sulfur dioxide extrusion of the corresponding 3,4-disubstituted 3-sulfolenes.

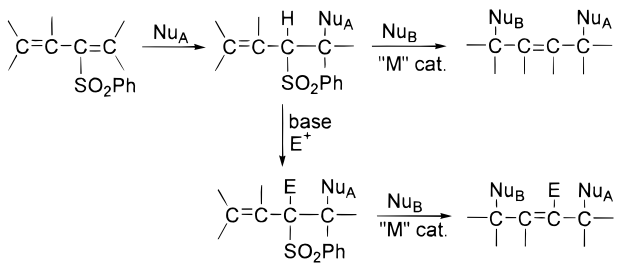
B. Reactivity

1. Conjugate Additions

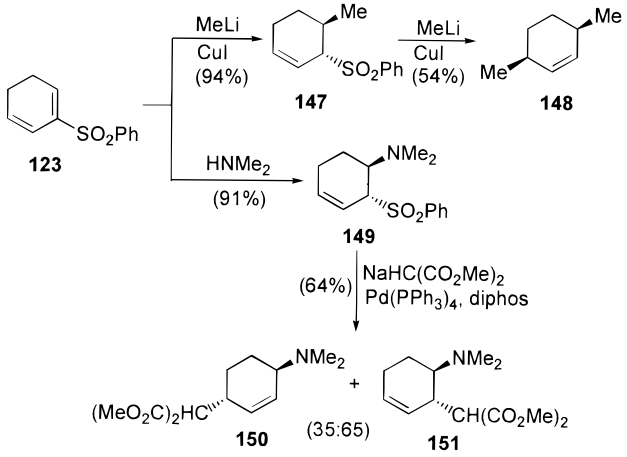
2-(Arylsulfonyl) 1,3-dienes can be functionalized by nucleophiles in a Michael-type addition fashion, leading to allylic sulfones, which can be further functionalized by both nucleophiles and electrophiles.[65,66] Thus, these dienes can react with nucleophiles in the 1- or 4-positions. In this way they constitute multicoupling reagents of high synthetic versatility. The principle for the sequential nucleophilic additions to 2-(arylsulfonyl) 1,3-dienes is shown in Scheme 50. After a Michael-type conjugate addition of the first nucleophile, the second nucleophile can substitute the allylic sulfonyl group in a copper- or palladium-catalyzed reaction.[66] As an option an electrophile can be introduced in the allyl sulfone before reaction with the second nucleophile.

The Michael addition to the sulfonyldiene **123** was found to be highly diastereoselective for all nucleophiles tried, leading preferentially to the trans isomer, in a reaction that is thermodynamically con-

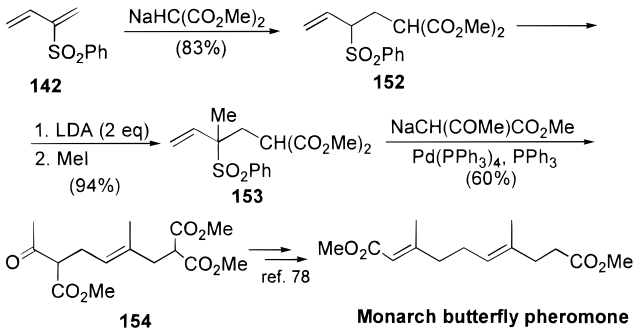
Scheme 50



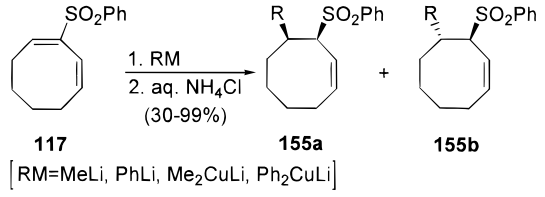
Scheme 51



Scheme 52



Scheme 53

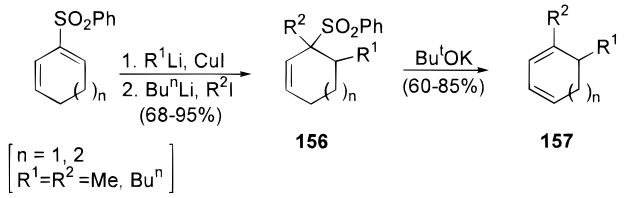


trolled. Some examples of the use of this methodology with sulfones from cyclohexadiene **123** and butadiene **142** are shown in Schemes 51 and 52.[66] Michael addition to **123** followed by a copper-catalyzed allylic displacement gave a highly regio- and stereoselective 1,4-functionalization of the diene. Palladium-catalyzed allylic substitution of the allylic sulfone obtained from the Michael addition was also stereoselective (retention) but less regioselective and produced a mixture of 1,2- and 1,4-stereoisomers **150** and **151** (Scheme 51).

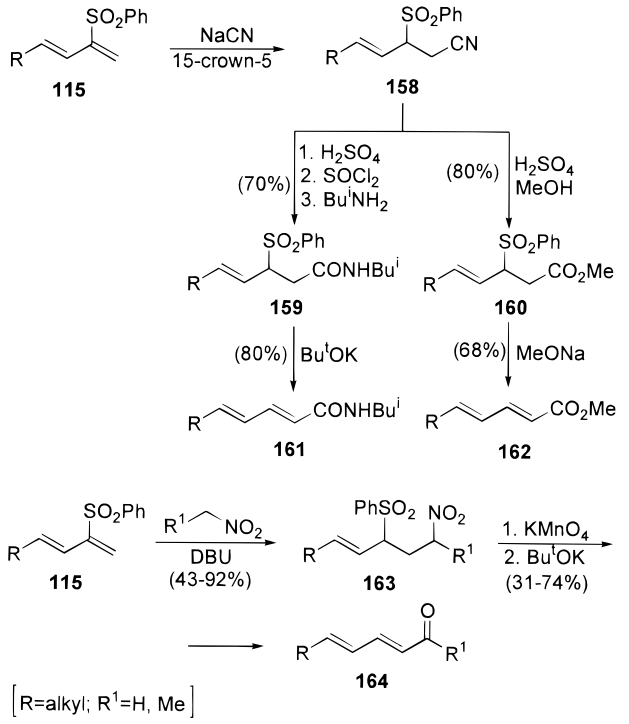
The butadiene sulfone **142** was transformed into a key intermediate for the synthesis of the Monarch butterfly pheromone. Michael addition, selective alkylation, and regioselective palladium-catalyzed allylic substitution afforded key intermediate **154**,[66] which has been previously transformed into the pheromone.[78] The sequence in Scheme 52 demonstrates the efficiency of the principle shown in Scheme 50.

In the case of the cyclooctadienyl sulfone **117**, reaction with organometallic reagents occurred at a faster rate than that of similar reactions of cyclooctenyl sulfone (Scheme 53).[60] It seems that the additional unsaturation serves to flatten the cyclooctane

Scheme 54



Scheme 55

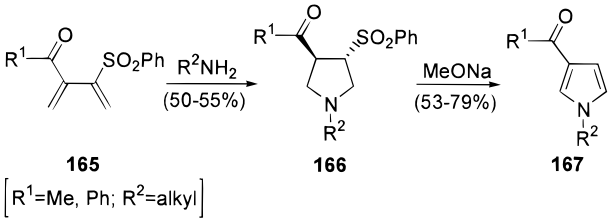


ring, thereby decreasing the degree of steric interaction. Moreover, the diastereomeric product ratios obtained upon protonation are not very different (**155a**:**155b** 70:30 maximum) showing that the faces of the intermediate allylic α-sulfonyl anion are not highly sterically differentiated.

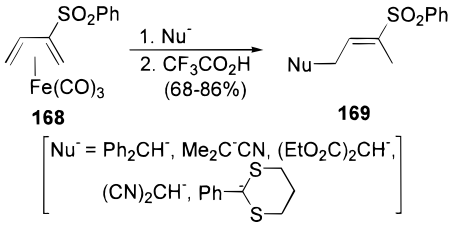
Cyclic 1,3-dienes can be prepared via selective 1,4-elimination of benzenesulfinic acid from allylic sulfones obtained from Michael addition to cyclic 2-(phenylsulfonyl) 1,3-dienes. Thus, copper-catalyzed conjugate addition of an alkyllithium to the sulfonyl diene and subsequent α-alkylation of the resulting sulfone afforded the desired disubstituted allylic sulfone **156**. Base-induced elimination of benzenesulfinic acid with potassium *tert*-butoxide gave the 1,2-disubstituted 1,3-diene **157** (Scheme 54).[79]

Michael addition of cyanide or the anion of nitroalkanes to (*E*)-2-sulfonyl dienes **115**, followed by transformation of the newly introduced group and subsequent elimination of the sulfonyl group under basic conditions, provides a synthesis of interesting naturally occurring 1-carbonyl-substituted conjugate dienes.[80,81] The use of this procedure is illustrated in Scheme 55 with the highly stereoselective preparation of (2*E*,4*E*)-dienamides **161** and dienoates **162**,[80] or (3*E*,5*E*)-dien-2-ones and dienals **164**,[81] from dienes **115**. The reactions proceed through intermediates **158**−**160** and **163** (1:1 diastereomers ratio, R^1 = Me).

Scheme 56



Scheme 57



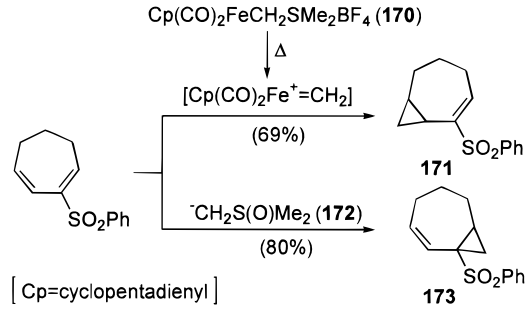
3-Acyl-substituted 2-sulfonyl dienes **165** can be transformed into 3-acyl-1-alkylpyrroles by means of two successive conjugate additions with aliphatic amines leading to *trans*-pyrrolidine intermediates **166**. These adducts undergo dehydrosulfonylation with sodium methoxide, followed by air oxidation during workup, to give pyrroles **167** (Scheme 56).[82]

Reaction of 2-(phenylsulfonyl)-1,3-butadiene tricarbonyliron(0) complex **168** with various nucleophiles gave the addition products **169** in a regio- and stereospecific manner under both kinetic and thermodynamic conditions (Scheme 57).[83] This constitutes an interesting umpolung of the sulfonyl diene. The result differs also from reports about the parent butadiene and for dienes bearing electron-donating groups, where the regiochemistry varies with the reaction temperature.[84]

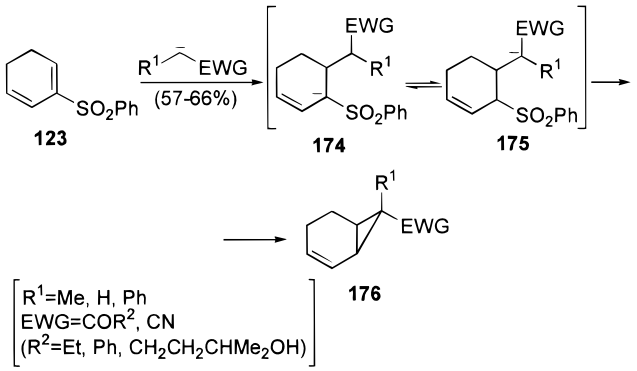
2. Cyclopropanations

Regioselective cyclopropanation of 2-(phenylsulfonyl) 1,3-dienes at each double bond can be achieved by taking advantage of their different electron density. Thus, the phenylsulfonyl-substituted double bond is electron-deficient, whereas the other is fairly electron-rich. Accordingly, a nucleophilic cyclopropanation reagent such as the sulfur ylid **172** was used for the reaction of the electron-deficient double bond leading exclusively to vinylcyclopropanes **173** (Scheme 58).[85] Regioselective cyclopropanation of the electron-rich 3,4-double bond was achieved by using reagent **170**,[86] which thermally generates in situ a reactive iron−carbene, which subsequently cyclopropanates

Scheme 58



Scheme 59



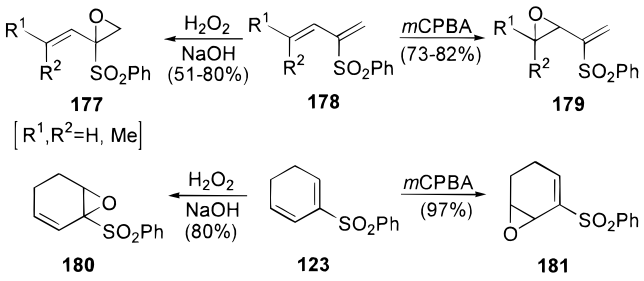
the olefin.[85] The cationic iron−carbon complex[86] has an electrophilic character and shows a complete regioselectivity (>99%) toward the 3,4 double bond.

Cyclopropanation reactions on the electron-deficient double bond of 2-(phenylsulfonyl)-1,3-cyclohexadiene (**123**) has also been achieved through Michael addition of ketone enolates or the anion of benzyl cyanide and subsequent cyclization.[87] In this process the enolate anion of the adduct **175**, in equilibrium with the intermediate **174**, displaces the allylic phenylsulfonyl group leading to compound **176** as a single diastereoisomer with the large group in the exo position (Scheme 59). This sequence was used for the attempted synthesis of sirenine and derivatives.

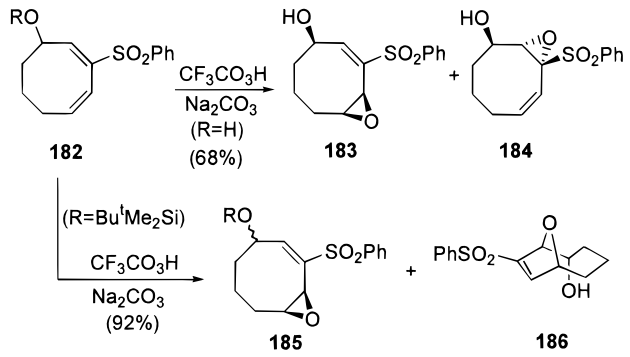
3. Epoxidations

The regioselective epoxidation of 2-(phenylsulfonyl) 1,3-dienes has been carried out considering the very different reactivity of the two double bonds toward oxidation reagents: whereas the electron-deficient double bond reacts with nucleophilic oxidants such as hydrogen peroxide under basic conditions, the electron-rich double bond undergoes epoxidation with *m*-chloroperoxybenzoic acid, yielding the corresponding 1,2- or 3,4-epoxy derivatives, respectively. These vinyl epoxides are useful building blocks due to their high functionality.[88,89] Thus, the reaction of acyclic and cyclic 2-sulfonyl 1,3-dienes **178** and **123** with *m*-chloroperoxybenzoic acid at room temperature gave the epoxides **179** and **181**, respectively, with a selectivity >95%. When the epoxidation procedure was carried out by using hydrogen peroxide and sodium hydroxide at room temperature, the corresponding epoxides **177** and **180** were formed, the regioselectivity being >99% (Scheme 60). An efficient one-pot synthesis of these epoxy(phenylsulfonyl)-alkenes starting from 1,3-dienes through a selenosulfonylation−oxidation sequence has also been developed.[89] Recently, the enantioselective epoxidation of the electron-rich double bond of 2-(phenylsulfonyl) 1,3-dienes was achieved using chiral (salen)$Mn^{III}Cl$ complexes.[90] For example, with this chiral epoxidation system epoxide **181** was obtained in 99% ee (77% yield) from diene **123**.

Scheme 60



Scheme 61

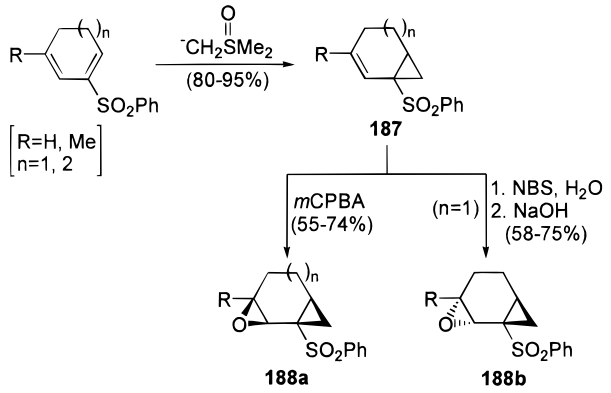


The hydroxy cyclooctadienyl sulfone **182** (R = H) was inert to *m*-chloroperoxybenzoic acid epoxidation, the use of trifluoroperacetic acid buffered with sodium carbonate being necessary. The epoxidation proceeded with low regioselectivity and gave a mixture of epoxides **183** (24%) and **184** (44%) (Scheme 61).[60] However, the regioselectivity was improved by protection of the alcohol by silylation: the silyl-protected hydroxy sulfone **182** (R = Bu^tMe_2Si) gave only the epoxide **185**. This epoxide was accompanied by compound **186** (**185**:**186**, 3.4:1 ratio), which apparently arises from an in situ transannular desilylative cyclization of *trans*-**185**.[60]

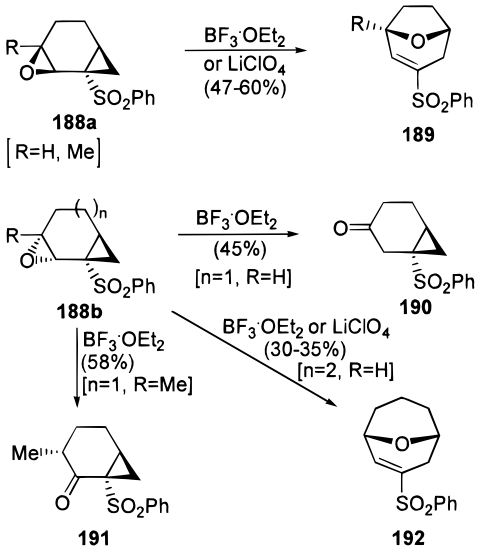
Consecutive regioselective cyclopropanation of the electron-deficient double bond of 2-(phenylsulfonyl)-1,3-cycloalkadienes using dimethyloxosulfonium methylide (vide supra), followed by epoxidation of the remaining olefinic bond with *m*-chloroperoxybenzoic acid gave access to 3,4-epoxy-1,2-methylene-2-phenylsulfonyl cycloalkanes **188a**.[91] Interestingly, the epoxidation step occurred preferentially syn to the cyclopropane group (syn:anti = 20:1 for the six-membered ring (R = H, Me); syn:anti = 3:1 for the seven-membered ring (R = H)). Apparently, the phenylsulfonyl group exerts a more powerful blocking effect toward the incoming reagents than the cyclopropane moiety. The anti isomer **188b** was synthesized via the corresponding bromohydrin (Scheme 62).[91]

The Lewis acid-catalyzed rearrangement of substrates **188a** (*n* = 1) using $BF_3{\cdot}OEt_2$ or $LiClO_4$ afforded bicyclic ethers **189** (Scheme 63).[91] The outcome of the rearrangement is dependent on the substrate stereochemistry. Thus, the isomeric compound **188b** (*n* = 1) afforded the ketones **190** (R = H) and **191** (R = Me), which are the expected products from BF_3 rearrangements of epoxides. For the seven-membered ring only the anti isomer **188b** (*n* = 2, R = H) rearranged to bicyclic compound (**192**). A mechanism involving an intermediate cyclopropyl carbinyl cation generated from Lewis acid-induced carbon−oxygen bond cleavage at the 3-position was suggested.[91] The difference in reactivity between

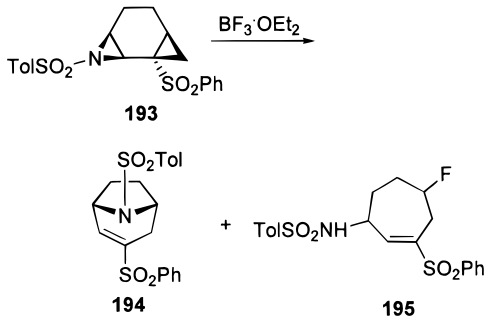
Scheme 62



Scheme 63



Scheme 64



compound **188a** (n = 1) and **188b** (n = 1) was explained by the difference in the stability of the favored conformation of the cyclopropyl carbocations necessary for ring closure.

A similar BF_3-induced rearrangement using the corresponding aziridino cyclopropanes **193**, prepared from epoxy cyclopropanes **188**, via ring opening of the epoxide by sodium azide and cyclization with triphenylphosphine followed by derivatization to *N*-tosylamide, afforded bicyclic product with tropane skeleton **194** together with fluoroamidosulfone **195** (Scheme 64).[92] The formation of this latter side product decreased with the polarity of the reaction solvent and was completely depressed using a mixture of dichloromethane and nitromethane as solvent.

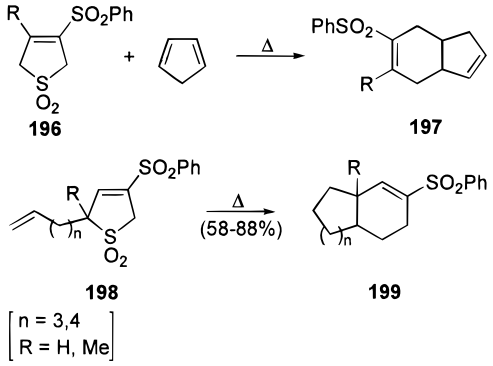
4. Diels–Alder Reactions

The 2-(arylsulfonyl) 1,3-dienes show an interesting duality in their [4+2] cycloadditions with olefins by reacting with both electron-deficient and electron-rich olefins, therefore belonging to the category of conjugated dienes with a normal and inverse electron demand. A common problem in reactions with both types of dienophiles is the fact that the diene easily forms dimers through a Diels−Alder reaction with another identical molecule, for example when obtained from thermal sulfur dioxide extrusion of 3-sulfonylated 3-sulfolenes (vide supra).[73−75] One way of avoiding this dimerization reaction is to generate the diene in the presence of the dienophile from sulfolenes such as **196** and **198**. This approach has been successfully used in inter-[75,93] and intramolecular[94] cycloaddition reactions, giving adducts **197** and **199**, respectively (Scheme 65). Recently, the intramolecular version of this synthetic methodology has been used with nitrones as 1,3-dipoles for the preparation of heterocyclic compounds.[95]

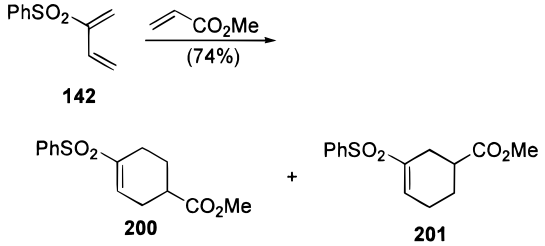
When electron-deficient dienophiles are used the regioselectivity is low for the parent 2-(phenylsulfonyl)-1,3-butadiene **142**, which on reaction with methyl acrylate afforded a mixture of regioisomers **200** and **201** in a 2:1 ratio (Scheme 66).[66] Analogously, it has been observed that reaction of 5-(phenylsulfonyl)-3,5-dodecadienene with methyl vinyl ketone also gives a mixture of regioisomers.[53] However, the reaction of pentadiene sulfone **202** with methyl acrylate in the presence of aluminum trichloride afforded mainly one stereo- and regioisomer **203** (Scheme 67);[66] this increasing regioselectivity has also been observed in the Lewis acid-catalyzed reaction of 3-(phenylsulfonyl)-2-(phenylthio)buta-1,3-dienes[93] or 3-(phenylsulfonyl)-2-(phenyseleno)buta-1,3-diene[36] with electron-deficient alkenes.

The cycloaddition of electron-rich olefins to sulfonyl 1,3-dienes usually proceeds with high regioselectivity,

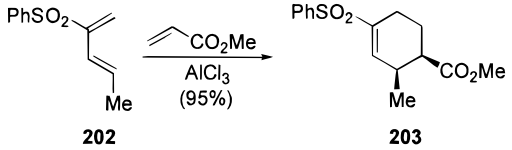
Scheme 65



Scheme 66

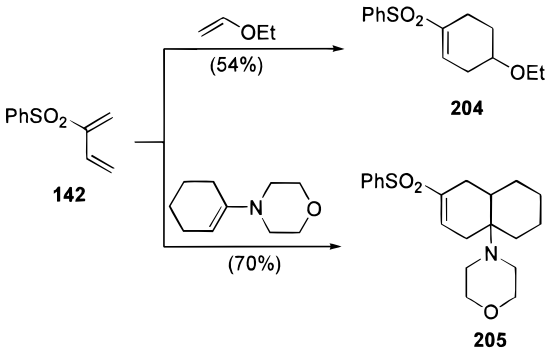


Scheme 67

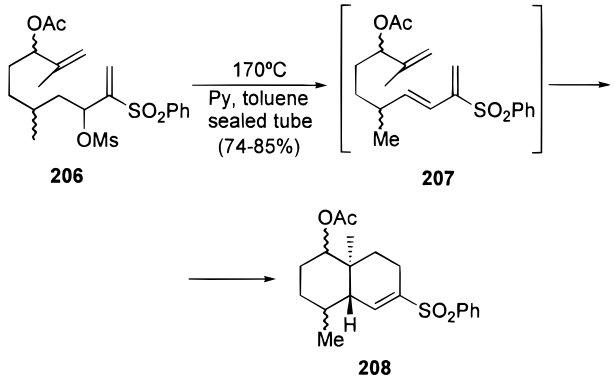


202 203

Scheme 68



Scheme 69



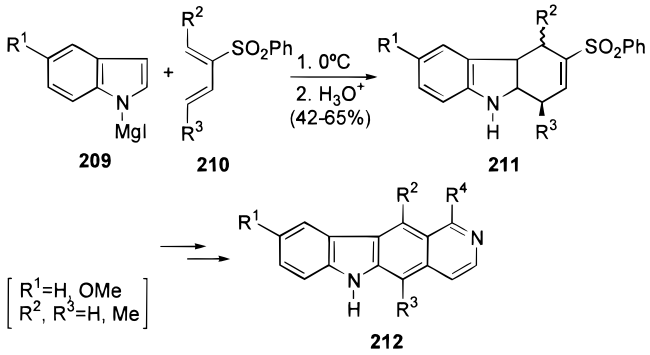
as shown in Scheme 68 for the reaction of diene **142** with ethyl vinyl ether or *N*-(1-cyclohexenyl)morpholine. In both cases only one regioisomer was obtained (**204** and **205,** respectively).[66,73] It is always uncertain whether these type of reactions follow the classical concerted Diels−Alder pathway or if they proceed via an initial Michael addition followed by ring closure of the zwitterionic intermediate.

The eudesmane precursor **208**, containing a trans ring fusion, has been prepared stereoselectively by an inverse electron-demand intramolecular cycloaddition from the in situ prepared sulfonyl diene **207** (Scheme 69).[96]

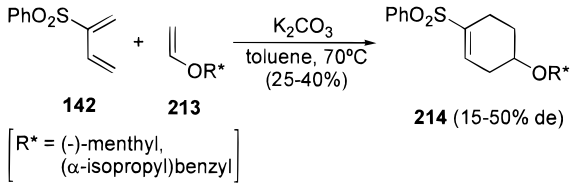
The enamine-like reactivity of indoles is increased on formation of the magnesium salt. Therefore, 1-indolylmagnesium iodides **209** react rapidly with 2-(phenylsulfonyl) 1,3-dienes to give 3-(phenylsulfonyl)-1,4,4a,9a-tetrahydrocarbazoles **211** via a formal [4+2] cycloaddition (Scheme 70).[97,98] Although a concerted pathway cannot be completely excluded, certain nonstereospecificity found in some cases suggests a two-step reaction. This methodology has been applied to the synthesis of the antitumor alkaloids ellipticine (**212**: $R^1 = R^4 = H$, $R^2 = R^3 =$ Me) and olivacine (**212**: $R^1 = R^2 = H$, $R^3 = R^4 =$ Me)[98] and recently also to the synthesis of the 5-methoxy derivatives of these alkaloids.[99]

Asymmetric inverse electron-demand Diels−Alder reactions have been achieved using chiral enol

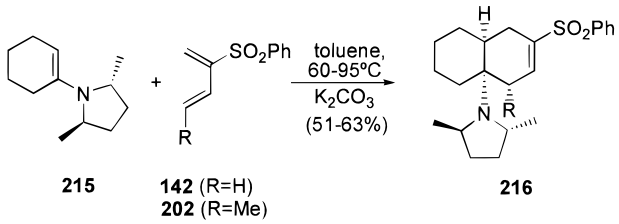
Scheme 70



Scheme 71



Scheme 72



ethers[100] and enamines.[100,101] Thus, reaction of 2-(phenylsulfonyl)-1,3-butadiene **142** with chiral (−)-menthyl or (α-isopropyl)benzyl vinyl ether **213** yielded the corresponding adducts **214** in low yields, due to dimerization, and also low de's (15 and 50% respectively) (Scheme 71).[100]

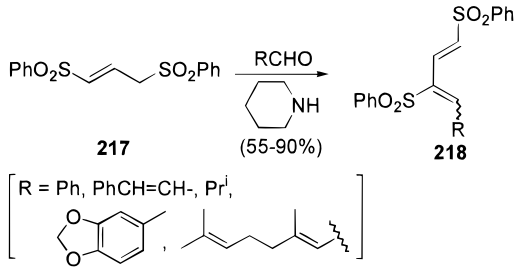
Improved levels of diastereoselectivity were obtained with chiral enamines derived from (*S*)-2-(methoxymethyl)pyrrolidine (up to 73% de)[100] and the C_2-symmetric amine (*R,R*)-2,5-dimethylpyrrolidine **215** (>99% de).[101a] In the latter case sulfonyldienes **142** and **202** afforded only one diastereoisomer **216** (R = H, Me), the stereochemistry of one of the adducts (R = H) being unequivocally determined by X-ray diffraction (Scheme 72). Recently, enantiopure 2-sulfonyl dienes bearing an allylic hydroxy group and prepared by oxidation of the corresponding sulfoxides,[101b] underwent cycloaddition with *N*-phenylmaleimide and phenyltriazolinedione affording a single diastereomer.[101c]

IV. 1,3-Bis(arylsulfonyl) 1,3-Dienes

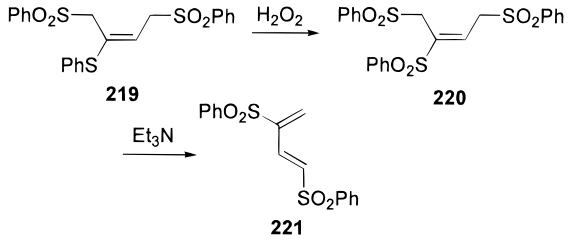
A. Synthesis

The Knoevenagel-type condensation of 1,3-bis(sulfonyl)propenes with aldehydes in the presence of piperidine is one of the available methods for the preparation of this class of systems.[102,103] This procedure is seriously affected by steric hindrance; reaction of 1,3-bis(phenylsulfonyl)propene **217** with aldehydes afforded 1,3-bis(phenylsulfonyl) 1,3-dienes

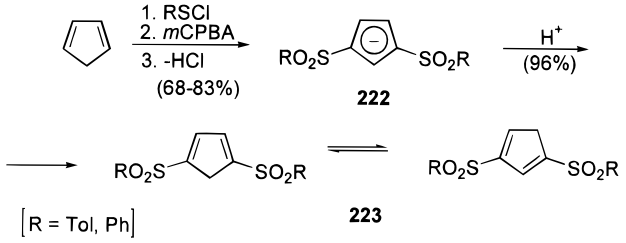
Scheme 73



Scheme 74



Scheme 75



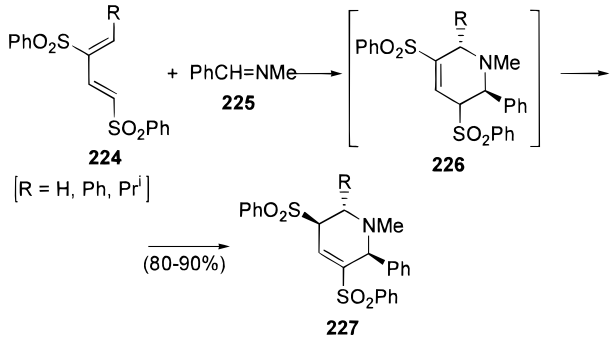
218, but no reaction occurred when ketones were employed (Scheme 73).[103] Other procedures used involve: (i) reaction of **217** with *n*-butyllithium and formaldehyde followed by dehydration[104] and, (ii) oxidation of 1,4-bis(phenylsulfonyl)-2-(phenylthio)-2-butene (**219**) to the corresponding sulfone **220** with subsequent elimination of benzenesulfinate to give the compound **221** (Scheme 74).[104]

Bis(sulfonyl)cyclopentadienes **223** have been obtained from cyclopentadiene by addition of sulfenyl chlorides followed by oxidation. Further elimination of hydrogen chloride leads to the formation of the bis(sulfonyl)cyclopentadienyl anion **222** which is protonated to give bis(sulfonyl)-substituted cyclopentadiene **223** (Scheme 75).[105]

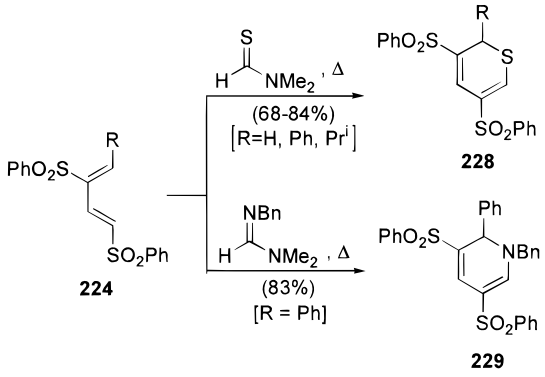
B. Reactivity

Studies on the synthetic uses of 1,3-bis(phenylsulfonyl)-1,3-butadienes have been focused on [4+2] cycloaddition reactions due to the high reaction rate of these processes. Molecular mechanics calculations indicated that the lowest energy conformer of the parent 1,3-bis(phenylsulfonyl)-1,3-butadiene corresponds to the cisoid conformation necessary for the Diels−Alder reaction.[104,106] Also, MNDO calculations showed that this diene is highly activated toward cycloaddition due to its markedly lowered LUMO energy level (−1.39 eV) compared with, for example, the 2,3-substituted isomer (−0.29 eV).[104,106] Thus, reaction of bis(sulfonyl) 1,3-dienes **224** with imine **225** readily afforded the [4+2] cycloadducts **227** after double-bond isomerization from intermediate **226**

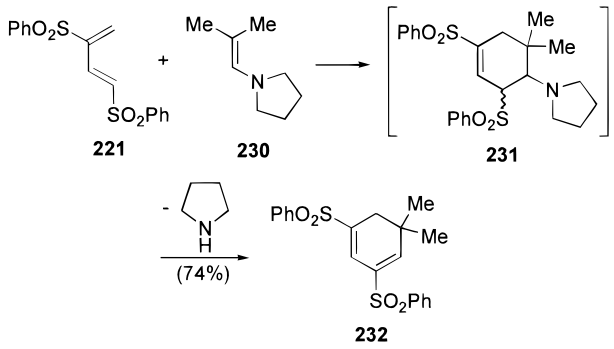
Scheme 76



Scheme 77



Scheme 78

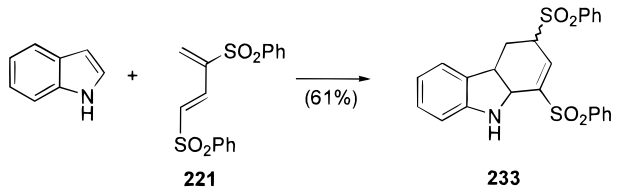


(Scheme 76).[73,104,106] [4+2] cycloadditions have also been achieved using other heterodienophiles such as thioamides or amidines to give cycloadducts **228**[73,104,107] or **229**,[107] respectively, after elimination of dimethylamine (Scheme 77).

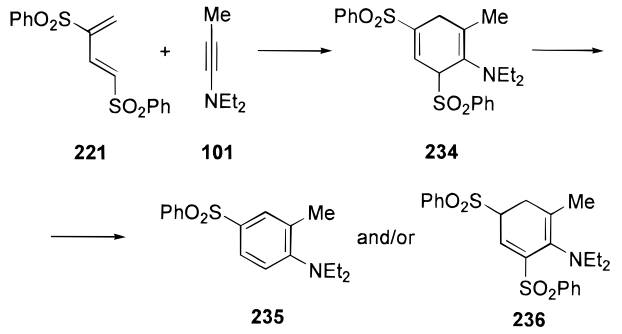
1,3-Bis(phenylsulfonyl) 1,3-dienes reacted readily with enamines to give [4+2] cycloadducts.[107] These compounds generally undergo spontaneous elimination of amine to produce bis(sulfonyl) 1,3-cyclohexadienes, as shown in Scheme 78 for the reaction of 1,3-bis(phenylsulfonyl)-1,3-butadiene (**221**) with the enamine **230,** which afforded **232** via intermediate **231**.[107] Moreover, the high reactivity of bis(sulfonyl) diene **221** is illustrated by its cycloaddition reaction with indole to afford adduct **233** (Scheme 79).[107] The second phenylsulfonyl group increases the reactivity dramatically since the corresponding 2-(phenylsulfonyl) 1,3-diene required the use of 1-indolylmagnesium bromide for the corresponding cycloaddition to occur (vide supra).[97−99]

The [4+2] cycloaddition behavior of diene **221** with an ynamine such as 1-(diethylamino)propyne (**101**)

Scheme 79



Scheme 80



has also been studied (Scheme 80).[107] When the reaction was carried out at 80 °C, cycloadduct **234** was the only isolated product (85%). However, the reaction at room temperature afforded a mixture of aromatic compounds **235** (21%) and the diene **236** (67%). The formation of **235** may proceed via an initial [4+2] cycloaddition, giving **234** followed by loss of phenylsulfinic acid. Under milder reaction conditions, the initial Diels−Alder product **234** undergoes 1,3-hydrogen shift to give **236**. Another possible explanation for the formation of diene **236** would be an initial [2+2] cycloaddition followed by consecutive electrocyclic ring opening and 6π-electrocyclization reaction.[107]

V. 1,4-Bis(arylsulfonyl) 1,3-Dienes

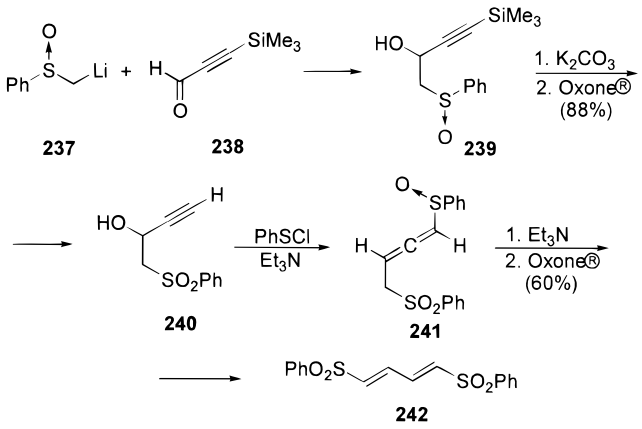
A. Synthesis

The preparation of 1,4-bis(sulfonyl)-1,3-butadienes is quite limited and there are very few reports on the subject. One strategy for the synthesis of these systems relies on the [2,3]-sigmatropic shift of propargylic sulfenates to α-allenic sulfoxides[108] followed by base-promoted isomerization and oxidation.[109,110] An example of the use of this method is the preparation of 1,4-bis(phenylsulfonyl)-1,3-butadiene (**242**) from the carbinol **240**. The latter was prepared by addition of the lithio anion of methyl phenyl sulfoxide **237** to 3-(trimethylsilyl)-2-propynal (**238**) to give the sulfoxide **239** followed by desilylation and oxidation (oxone) (Scheme 81). Further reaction of the sulfone **240** with phenylsulfenyl chloride and triethylamine afforded the allene **241** which was converted to the final diene **242** after treatment with oxone.[110]

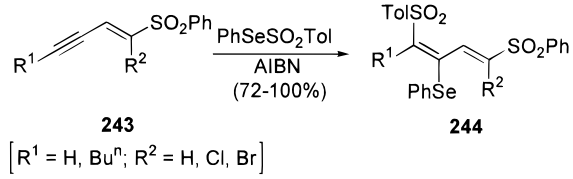
Enyne sulfones **243**[111] underwent a regioselective radical-induced selenosulfonylation to give dienes **244**. The regioselectivity of the reaction was lower starting from enyne **243** (R^1 = H, R^2 = H), which afforded a 6:1 mixture of (1*Z*,3*E*)- and (1*E*,3*E*)-2-(phenylseleno) 1,3-diene **244** (Scheme 82).[112]

Cyclization of several 1,6-heptadiynes such as **245** with *p*-tolylsulfonyl bromide under standard free-radical reaction conditions led to 1,4-bis(*p*-tolylsulfonyl) dienes such as **247** (46%) and the corresponding bromo sulfone **248** (18%), although the yield of the bis-sulfone could be optimized (91%) by changing the reaction conditions (Scheme 83).[113] The mechanism leading to the final product has been postulated as an initial addition−cyclization to an electron-deficient π-system such as the radical **246**; further addition would be disfavored due to the electrophilic nature of sulfonyl radicals.[114]

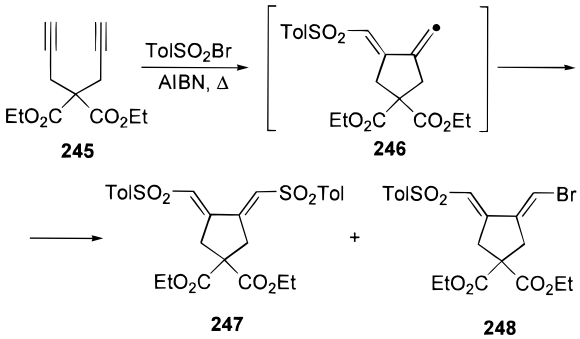
Scheme 81



Scheme 82



Scheme 83

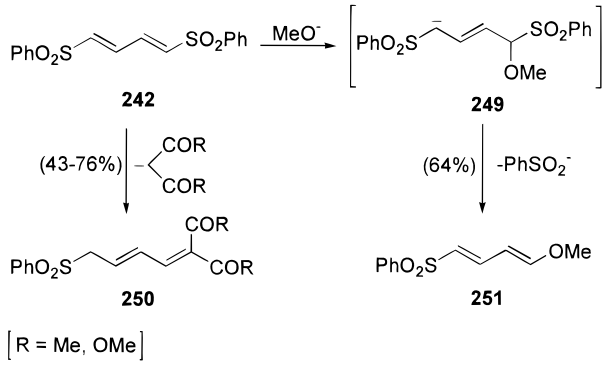


B. Reactivity

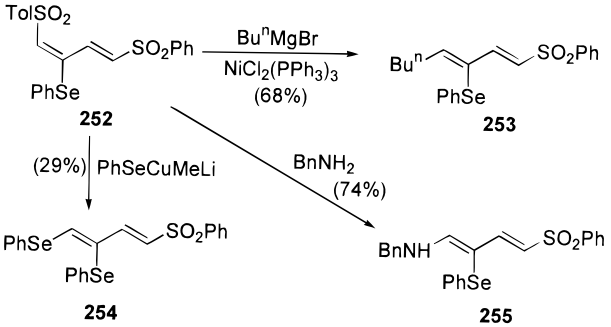
Studies on the reactivity of 1,4-bis(arylsulfonyl) 1,3-dienes have been limited to conjugate additions. Thus, reaction of diene **242** with sodium methoxide afforded product **251**, probably through a process involving Michael addition of methoxide ion to one of the terminal carbon atoms to give anion **249** followed by elimination of the benzenesulfinate group (Scheme 84).[110] The exclusive formation of **251** can be explained by the reversibility of the Michael addition of methoxide ion to the 2-position of the diene. Addition to the terminal carbon will give a stabilized allylic carbanion that gives the only observed product.

Attempted conjugate additions of enolates derived from simple ketones led only to decomposition of the

Scheme 84



Scheme 85



base-sensitive bis(phenylsulfonyl) diene.[110] However, reaction of diene **242** with the anion from dimethyl malonate or the sodium salt of 2,4-pentadienone produced compound **250**, presumably through a 1,5-sigmatropic shift of hydrogen from the initially formed diene (Scheme 84).[110]

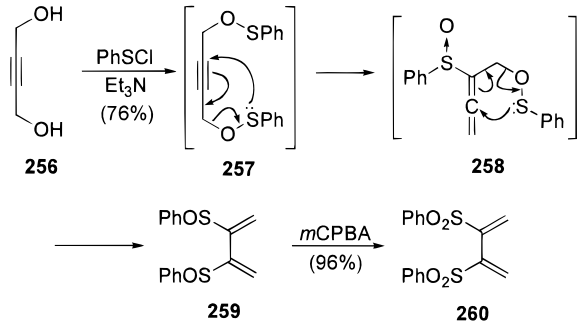
The coupling reaction of (phenylseleno)sulfonyl 1,3-butadiene **252** and Bu^{n}MgBr in the presence of a nickel(II) complex under an argon atmosphere gave 4-*n*-butyl-substituted 1,3-diene **253**, via addition of the nucleophile followed by elimination (Scheme 85).[112] Moreover, treatment of dienyl sulfone **252** with PhSeCuMeLi or benzylamine gave the corresponding addition−elimination dienes **254** and **255**.[112]

VI. 2,3-Bis(arylsulfonyl) 1,3-Dienes

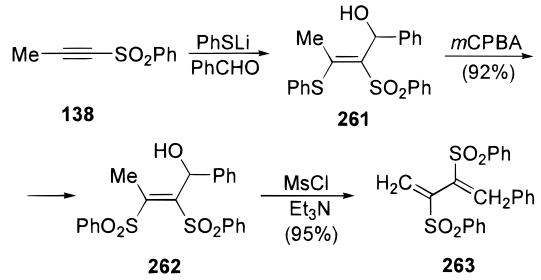
A. Synthesis

Methods for the preparation of this type of compounds have been focused mainly on the parent system 2,3-bis(arylsulfonyl)-1,3-butadiene, which has been the most frequently used for synthetic purposes. Thus, 2,3-bis(phenylsulfonyl)-1,3-butadiene (**260**) was obtained by addition of phenylsulfenyl chloride to butyne-1,4-diol (**256**) and triethylamine, which produced the disulfenate ester **257**. This transient species rapidly undergoes a [2,3]-sigmatropic propargylic rearrangement to give the allenic intermediate **258**, which subsequently undergoes a second [2,3]-sigmatropic shift affording the disulfoxide **259**. Final oxidation of this compound to bis(sulfonyl) diene **260** was achieved by the use of *m*CPBA (Scheme 86).[115,116] Other 2,3-bis(arylsulfonyl) 1,3-butadienes were prepared in the same way, by starting from the corresponding arylsulfonyl chlorides.[104]

Scheme 86



Scheme 87



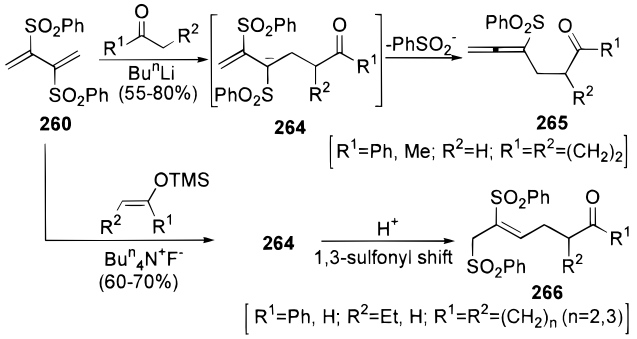
A procedure for the synthesis of 1-phenyl-2,3-bis-(phenylsulfonyl)-1,3-butadiene (**263**) from (phenylsulfonyl)-1-propyne (**138**) has also been developed (Scheme 87).[72] The synthesis involves the conjugate addition of the lithium salt of benzenethiol in the presence of benzaldehyde to give the adduct **261**, which was oxidized to the bis(sulfonyl) allyl alcohol **262**. Final reaction of this alcohol with mesyl chloride in the presence of triethylamine gave the bis-(sulfonyl) diene **263**.

B. Reactivity

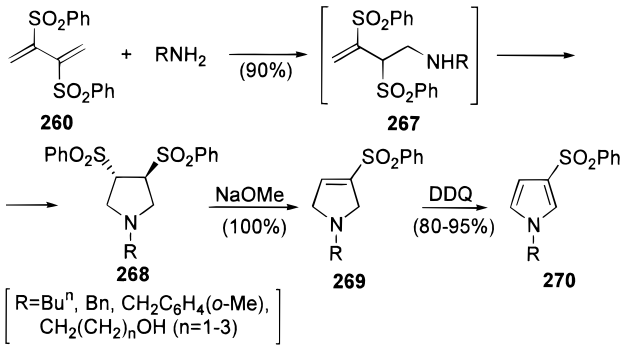
1. Conjugate Additions

The highly activated π-bond of diene **260** reacts with lithium enolates in a Michael addition fashion to give allenes **265** (Scheme 88).[117,118] The process probably proceeds via an allylic anion intermediate **264** which undergoes elimination of benzenesulfinate. However, when the enolate is generated from the silyl enol ether, the resulting products retain both phenylsulfonyl groups (Scheme 88).[117,118] The reactivity of the sulfonyl-stabilized carbanion **264** is apparently strongly dependent on the counterion. Probably the tetrabutylammonium counterion prohibits the synclinal or antiperiplanar geometry necessary for elimi-

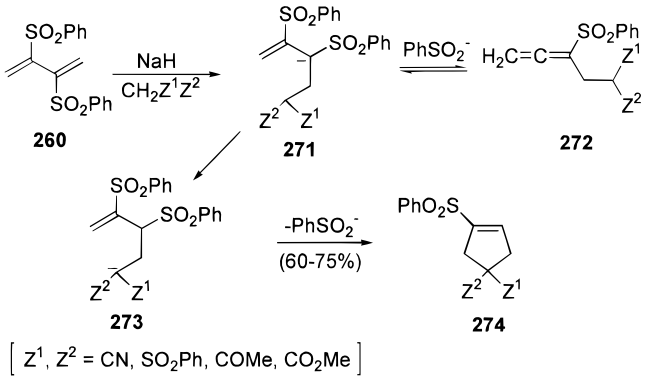
Scheme 88



Scheme 89



Scheme 90



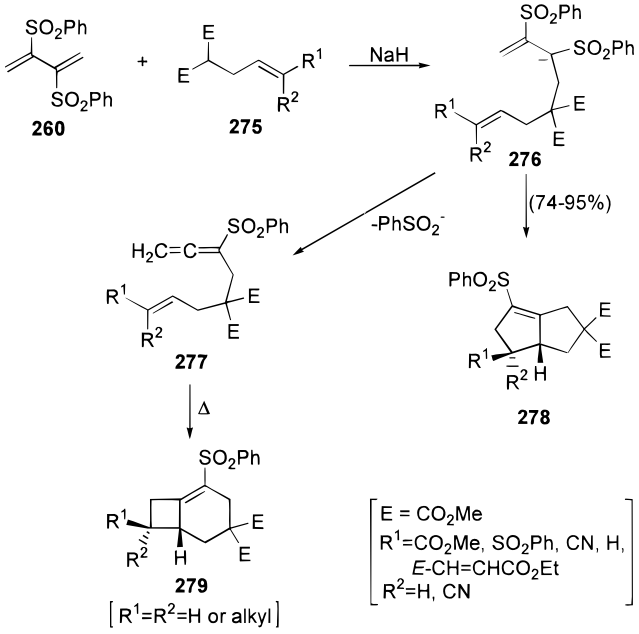
nation.[117] The carbanion is protonated in this case, giving an allylic bis-sulfone which isomerizes via a 1,3-sulfonyl shift to the observed final product **266**.

2. Cycloadditions

2,3-Bis(phenylsulfonyl)-1,3-butadiene is highly reactive toward nucleophilic addition because of its markedly lowered LUMO energy level compared to butadiene.[116] Thus, the reaction of compound **260** with primary amines afforded pyrrolines **269** as the sole product in high yields via a double Michael addition−elimination reaction sequence (Scheme 89).[116,119] After initial conjugate addition, a 5-endo-trig cyclization of the resulting amine onto the adjacent vinyl sulfone **267** takes place. Pyrrolidine **268** undergoes elimination of benzenesulfinic acid on treatment with sodium methoxide to give the 3-pyrroline ring system **269**. The latter was transformed into the corresponding pyrrole **270** by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). These pyrroles **270** can be easily lithiated at the 2-position due to the stabilizing effect of the sulfonyl group, allowing subsequent reaction with electrophiles.[116,119]

Substituted cyclopentenyl sulfones are available via [4+1] annulation of diene **260** with various stabilized carbanions.[117,118,120] The reaction involves a sequence based on a tandem addition−proton exchange−addition protocol (Scheme 90). Initial conjugate addition of the nucleophile onto the activated π-bond of diene **260** produced stabilized carbanion **271**, through the corresponding allenic system **272**, and underwent proton transfer to give the new carbanion **273**. Subsequent cyclization−elimination provided the cyclopentene derivative **274** and the

Scheme 91

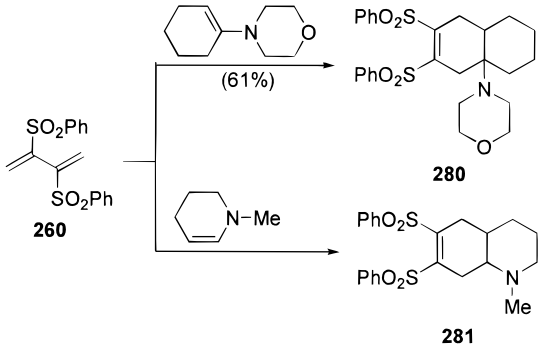


benzenesulfinate anion. It is interesting to note that the anion **271** is in equilibrium with the allene **272** via elimination−readdition of benzenesulfinate. In separate experiments the allene was in fact isolated and characterized.

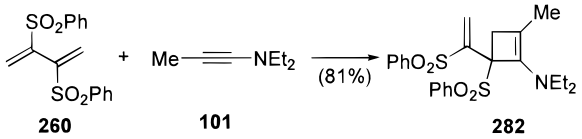
A similar strategy has been used for the synthesis of bicyclo[3.3.0]octenes **278**. Reaction of dimethyl allylmalonate **275** with 2,3-bis(phenylsulfonyl)-1,3-butadiene (**260**) afforded bicyles **278**. The reaction proceeds via the anion **276**, which undergoes a double intramolecular conjugate addition followed by elimination of benzenesulfinate (Scheme 91).[120,121] However, when R^1 or R^2 are not electron-withdrawing groups, the base-induced reaction of the allylmalonate **275** with the diene **260** afforded the allene **277**, which by subsequent thermolysis (80−120 °C) underwent a highly chemo- and stereospecific intramolecular [2+2] cycloaddition to give the cycloadduct **279**.[120,121]

There is a major problem associated with the use of 2,3-bis(phenylsulfonyl)-1,3-butadiene as the diene counterpart in Diels−Alder reactions: this diene exists exclusively in a transoid conformation due to the steric hindrance of the vicinal substituents, and has an enormous barrier (>50 kcal/mol) for the rotation about the 2,3-σ bond, as has been determined by molecular mechanics calculations.[106] However, the reaction of 2,3-bis(phenylsulfonyl)-1,3-butadiene with electron-rich dienophiles resulted in an inverse electron-demand [4+2] cycloaddition, which strongly suggests that these reactions occur in a two-step process.[107] Thus, reaction of diene **260** with 1-morpholino-2-cyclohexene or *N*-methyl-1,2,3,4-tetrahydropyridine afforded cycloadducts **280** and **281** respectively (Scheme 92).[107] Moreover, attempted [4+2] cycloaddition of 2,3-bis(sulfonyl) diene **260** with the ynamine **101** gave the [2+2] cycloaddition product **282** (Scheme 93),[107] contrary to the easy [4+2] cycloaddition reaction achieved with the 1,3-bis(sulfonyl) isomeric diene (vide supra, Scheme 80).

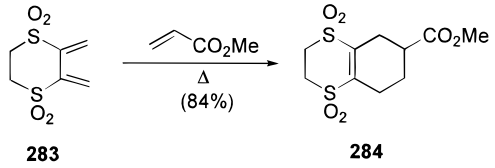
Scheme 92



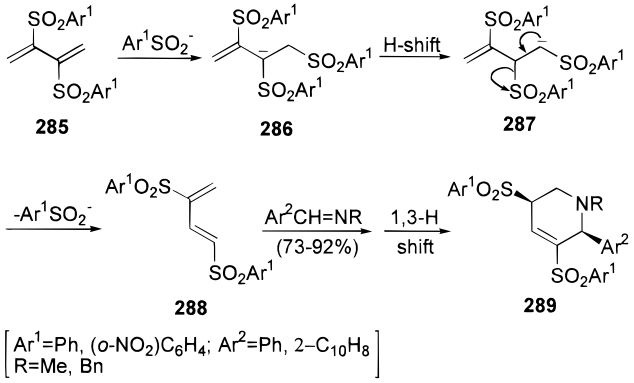
Scheme 93



Scheme 94



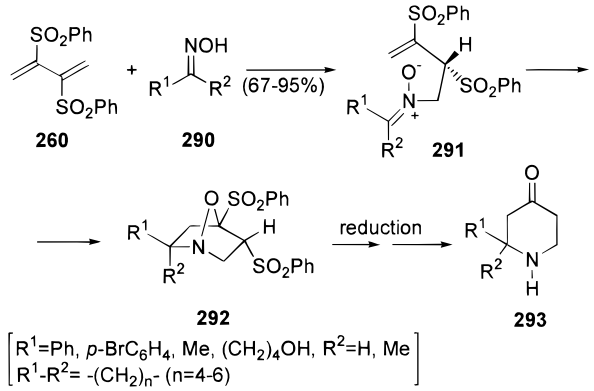
Scheme 95



The problem with the low stability of the s-cis conformation of 2,3-bis(sulfonyl) 1,3-dienes and their use in Diels−Alder reactions has been overcome by the use of the rigid bis(phenylsulfonyl) diene **283**, obtained by thermolysis of the corresponding sulfolene.[122] Thus, 2,3-bis(sulfonyl) 1,3-diene **283** showed a dual behavior and underwent [4+2] cycloaddition reactions not only with electron-rich, but also with electron-deficient olefins, such as methyl acrylate, to give the cycloadduct **284** (Scheme 94).[122]

Attempted Diels−Alder reaction of 2,3-bis(arylsulfonyl)-1,3-butadienes **285** with *N*-alkyl aryl imines as dienophiles, gave only rearranged cycloaddition products **289** in high yields (Scheme 95).[104,106] The formation of adducts **289** is explained by a mechanism involving addition of a trace of arylsulfinate anion to give the carbanion **286**, followed by proton transfer and sulfinate elimination from **287** to afford 1,3-bis(arylsulfonyl)-1,3-butadiene (**288**). The latter diene readily undergoes the cycloaddition reaction (vide supra).

Scheme 96



Oximes **290** react readily with 2,3-bis(phenylsulfonyl)-1,3-butadiene (**260**) affording 7-oxa-1-azanorbornanes **292** in high yield (Scheme 96).[123,124] The formation of the bicyclic isoxazolidine involves conjugate addition of the oxime to the diene to give a transient nitrone **291**, which undergoes an intramolecular [3+2] dipolar cycloaddition. The stereochemistry of the cycloaddition is explained in terms of an exclusive reaction of the *Z* isomer of the nitrone through an endo orientation of the reactive groups. Subsequent reductive nitrogen−oxygen bond cleavage gives 4-piperidones **293**. The bicyclic derivative obtained from cyclohexanone oxime was converted to an azaspiro[5.5]undecane ring system, which is a structural element of the perhydrohistrionicotoxin family of alkaloids.[124]

VII. Concluding Remarks

This review has summarized the methods available for the preparation and synthetic use of conjugated sulfonyl dienes. In the last 20 years, an active interest concerning these compounds has aroused, being employed in synthetic transformations and natural product synthesis. The modification of the chemical character of the diene due to the presence of the synthetically useful sulfone moiety makes these systems highly reactive toward addition or cycloaddition reactions. In some cases the two double bonds show different reactivity which allows selective epoxidations and cyclopropanations. Several dienes show a dual electron demand in Diels−Alder reactions, increasing in that way the synthetic versatility of these sulfonyl dienes. Substantially more work is warranted to fully explore and exploit the utility of these systems in organic synthesis.

VIII. Acknowledgments.

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