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The chemistry of sulfinyl and sulfonyl enones

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1. Introduction

This review is devoted to the chemistry of unsaturated sulfones and sulfoxides bearing a carbonyl group in the α- or β-position. The structural types of sulfones and sulfoxides

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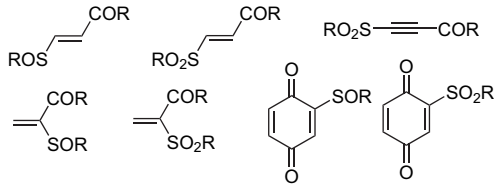
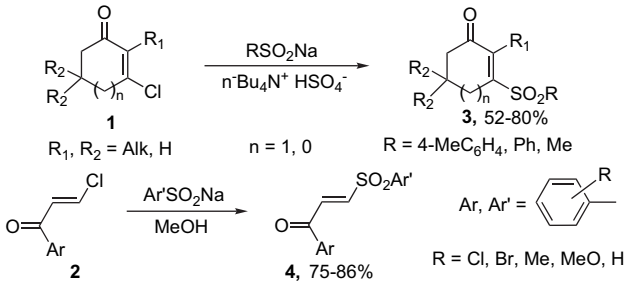
are shown below. Only the corresponding aldehydes, ketones, and also quinones are reviewed in order to restrict the literature. Derivatives of sulfinyl- and sulfonyl-substituted acids, e.g., esters, as well as structures where the double bond is a part of an aromatic or heteroaromatic system, are not topics of this review. The review covers the literature up to May 2006.



Sulfonyl and sulfinyl enones are useful reagents in modern organic synthesis. The reaction ability of these compounds is connected with the presence of two electron-withdrawing substituents at the same double bond. The multifunctional nature of these compounds results in broad synthetic possibilities. Due to the presence of two EWGs at the same double bond, sulfonyl and sulfinyl enones react easily with various nucleophiles. This reaction can proceed as a Michael addition, as well as a formal nucleophilic substitution of the sulfinyl or sulfonyl group, to form a broad variety of the functionalized alkenes. They are also very active dienophiles and dipolarophiles. Moreover, these compounds can serve as carbonyl compounds, e.g., in the synthesis of heterocyclic compounds. The presence in a molecule of sulfonyl and sulfinyl enones of good leaving groups RSO_2– or RSO– opens also additional possibilities for the synthesis of a variety of classes of organic compounds. As a rule, sulfonyl and sulfinyl groups play the role of activating an auxiliary, and often these groups are not present in the final target molecules. In recent years, significant attention has been paid to the synthesis of chiral unsaturated sulfoxides. Several books[1] and excellent reviews[2] including a very new article[3] are available. These compounds are important building blocks for the construction of many valuable optically active molecules including natural and important physiologically active compounds.



Scheme 1.

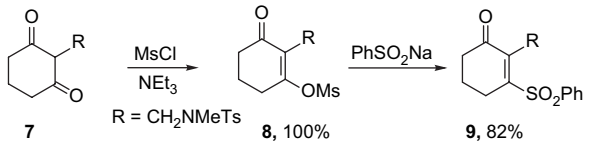
2. Synthesis of sulfonyl and sulfinyl enones

2.1. Ionic and radical additions to enones and acetylenic ketones

A broadly applicable strategy for the preparation of sulfonyl and sulfinyl enones involves ionic and radical additions and substitutions to enones and acetylenic derivatives. The reaction of cyclic and open-chain chlorovinyl ketones **1** and **2** with sodium sulfinates provided the preparation of β-sulfonyl enones **3** and **4** in good yields.[4–6] The best results were obtained using phase-transfer catalysis (Scheme 1).[7]

In addition, the preparation of interesting divinyl sulfones **6** from the corresponding 1-aroyl-2-chloroethenes **5** using the reaction with an unsaturated sodium sulfinate was reported (Scheme 2).[8]

A similar methodology—nucleophilic substitution with sodium phenylsulfinate—was used for the preparation of β-sulfonyl enone **9**. The conversion of 1,3-dione **7** into enol mesylate **8** followed by treatment with sodium benzenesulfinate in NMP leads to sulfonyl enone **9** in high yield (Scheme 3).[9]

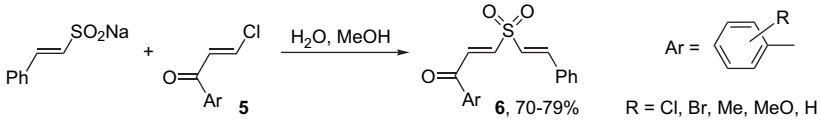


Scheme 3.

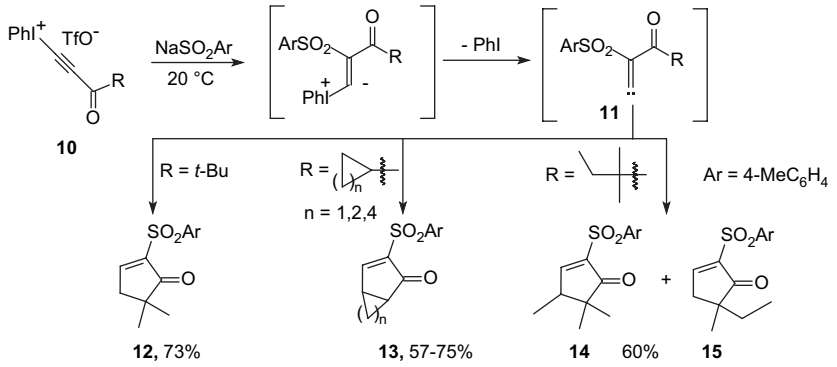
Some 2-sulfonyl cyclopentenones **12–15** were prepared in good yields by the reaction of ethynyliodonium salts **10** with anhydrous sodium *p*-tolylsulfinate. The intermediate alkylidene carbenes **11** undergo CH-bond insertion to give α-sulfonyl vinyl ketones **12–15** (Scheme 4).[10]

Several alternative methods are available for the synthesis of intermediate β-hetero-substituted sulfones or sulfoxides, which involve ionic or radical additions of CF_3SO_2X (X= SPh or SePh) to alkenes,[11] e.g., selenosulfonation of enones can be carried out under electrophilic conditions. The reaction of $PhSeSO_2CF_3$ with cyclopentenone **16** proceeds 100% regio- and stereoselectively to give the adduct **17** of conjugate addition. A subsequent oxidation with MCPBA or hydrogen peroxide provides the β-sulfonyl enone **18** in good yield via a spontaneous elimination of the selenium moiety (Scheme 5).[11]

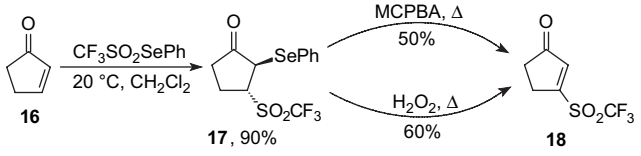
Recently, a novel DABCO (30%)-catalyzed addition of selenosulfonates to a variety of α,β-unsaturated ketones was described.[12] The authors proposed that the reaction proceeds in a similar manner to the Baylis–Hillman reaction. α,β-Unsaturated ketones **19** react with DABCO to give the



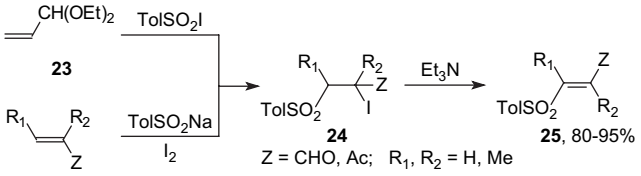
Scheme 2.



Scheme 4.



Scheme 5.

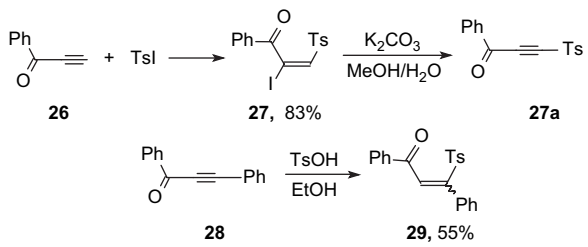


Scheme 7.

intermediate enolates **20** that react with selenosulfonate to form the adducts **21** in good-to-high yields. The reaction proceeds within a short reaction time under mild conditions. Subsequent oxidation with hydrogen peroxide provides a facile route to the stereoselective synthesis of (*E*)-β-phenylsulfonyl enones **22** (Scheme 6).

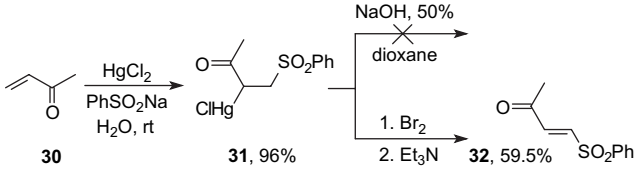
Using sulfonyl iodides instead of selenides allows the application of toxic and expensive selenides to be avoided, e.g., the radical addition of $TolSO_2I$ to acrolein diethyl acetal **23**. Similar results can be obtained using a convenient system $TolSO_2Na/I_2$, which presumably forms in situ the somewhat unstable $TolSO_2I$.[13] After treatment of the adducts **24** with TEA, the target sulfones **25** were prepared in high yield (Scheme 7).

p-Toluenesulfonyl iodide has been found to add readily and stereoselectively to ethynyl phenyl ketone **26** with the formation of an iodo-substituted sulfone **27**.[14] Attempts to dehydroiodinate the sulfone **27** met with only limited success. The crude product **27a** was detected by its IR spectrum, but the pure acetylenic sulfone could not be isolated, and the spectral evidence indicated the presence of varying amounts of the products resulting from methoxide and hydroxide displacements on the vinyl iodide.[14] The reaction of acetylenic ketone **28** with *p*-toluenesulfinic acid afforded a mixture of the (*Z*)- and (*E*)-isomer of sulfone **29**. The cis-isomer of **29** isomerized to the trans-isomer upon standing in AcOH solution overnight (Scheme 8).[15]

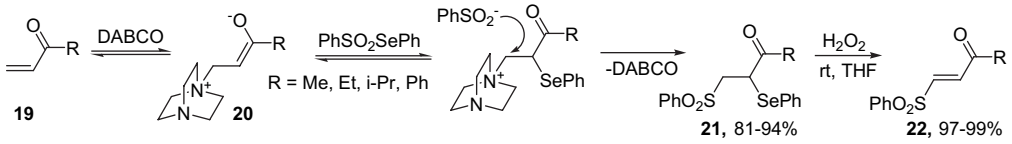


Scheme 8.

The reaction of methyl vinyl kenone **30** with $HgCl_2$ in the presence of $NaSO_2Ph$ results in the formation of an arenesulfonyl mercury intermediate **31**. However, this intermediate cannot be transformed into alkene **32** by standard techniques under basic conditions.[16] The elimination was performed by bromination of the mercury derivative **31** followed by treatment with triethylamine (Scheme 9).[17]

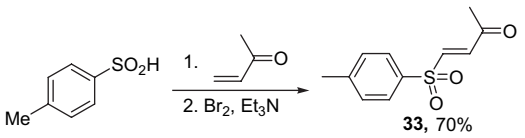


Scheme 9.



Scheme 6.

The crystalline sulfone **33** was prepared by the reaction of 4-tosyl-2-butanone (obtained by the addition of *p*-toluenesulfonic acid to methyl vinyl ketone) with bromine and subsequent elimination of HBr with triethylamine (Scheme 10).[18]



Scheme 10.

An interesting process utilizes enedione **34**, which reacts with arylsulfinic acids to form the adducts **35** (Scheme 11). Subsequent treatment of the sulfones **35** with Br_2 or NBS under photolytic conditions results in the formation of the unsaturated sulfones **36**.[19] Unfortunately, no yields are given in the article.

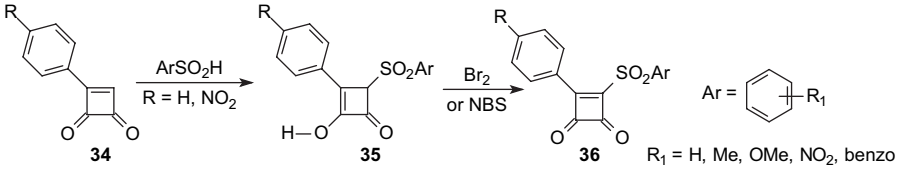
A versatile approach involving Li–Br exchange of protected α-bromo enones **37** followed by reaction with chiral sulfinates as electrophiles has been used to prepare a variety of chiral cyclic sulfoxides **38** (Scheme 12). Deprotection of the carbonyl group was carried out using both sulfuric acid on SiO_2 and $CuSO_4$ in acetone. The target chiral sulfoxides **38** were prepared in good yields and high ees.[20–24]

A very interesting and efficient methodology for the synthesis of sulfinyl-substituted α,β-unsaturated ketones was elaborated recently. The addition of sulfenic acids to acetylenic ketones leads to the formation of α- or β-sulfoxides. Chiral sulfenic acids **39** were generated in situ by thermolysis of suitable precursors **40** and trapped by acetylenic ketones **41**, affording (R_S,*E*)- and (S_S,*E*)-sulfoxides **42** and **43** in good yields and in enantiomerically pure form after simple column chromathography.[25,26] Bornyl- and isoborneol-substituted derivatives were studied as chiral auxiliaries (Scheme 13).

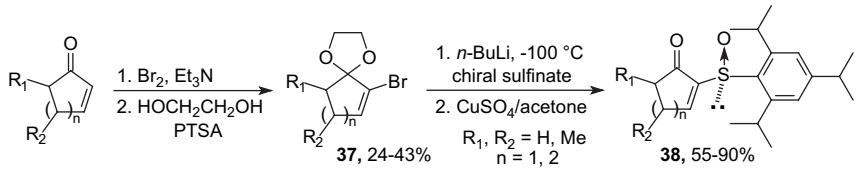
2.2. Reactions using sulfone- or sulfoxide-stabilized carbanions

Many syntheses of sulfonyl and sulfinyl enones **44** are based on the addition of an α-sulfone- or α-sulfoxide-stabilized carbanions **45** to a carbonyl compound followed by the elimination of water or $(EtO)_2(O)POH$. In the simplest case (X=H), dehydration of the intermediate hydroxy sulfone (or its derivatives) is necessary, usually in a separate step (Scheme 14).

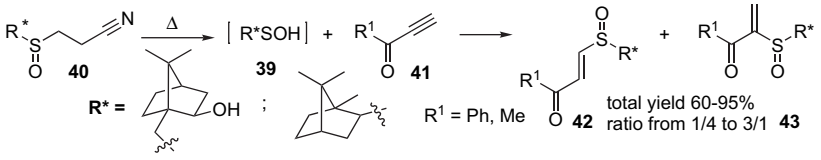
Thus, a variety of sulfonyl and sulfinyl enones were prepared by a Knoevenagel reaction that includes condensation of aldehydes with activated methylene compounds **46**. It should be noted that the sulfonyl enones **47** were obtained usually



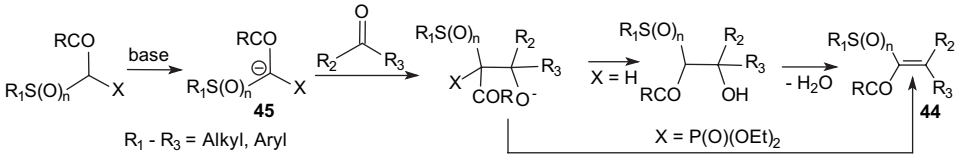
Scheme 11.



Scheme 12.

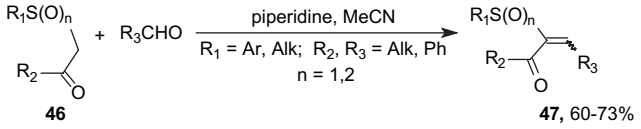


Scheme 13.



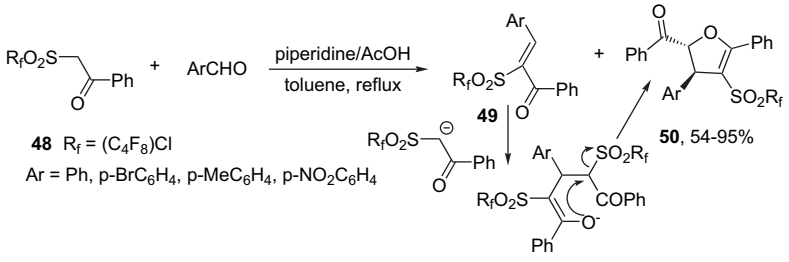
Scheme 14.

as a mixture of (*E*)- and (*Z*)-isomers.[27] When the initial compound was a sulfoxide, the reaction gave the (*E*)-isomer of the desired sulfinyl enones **47** (Scheme 15).[28–30]



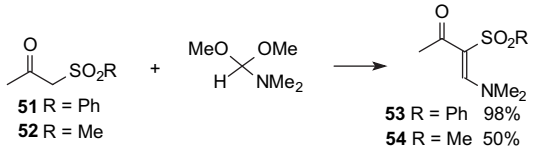
Scheme 15.

An unusual type of Knoevenagel condensation reaction was demonstrated for β-keto polyfluoroalkanesulfones such as **48**. The reaction with aldehydes proceeds via the initial condensation products **49** to provide an efficient and novel method for the stereoselective synthesis of fluorine-containing tetrasubstituted *trans*-2,3-dihydrofurans **50**. The intermediate alkenes **49** could not be fully separated due to their similar polarity.[31] The formation of furan derivatives is explained by the addition of a second molecule of the starting β-keto polyfluoroalkanesulfone **48** to the intermediate Knoevenagel product **49** followed by cyclization and elimination of an $R_fSO_2^-$ anion (Scheme 16).



Scheme 16.

α-Sulfonyl-substituted acetones **51** and **52** react with dimethylformamide dimethyl acetal in THF, giving dimethylaminobutenones **53** and **54** in good yields (Scheme 17).[32]



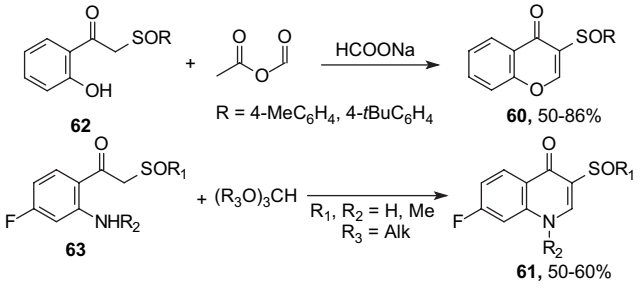
Scheme 17.

Another strategy for the preparation of enamines is based on the condensation of lactams **55** with ketomethylenesulfones **56**. This reaction leads to the stereoselective synthesis of the corresponding enamines **57** in low yields. The main product is the vinylogous sulfone **58** without an acetyl group. It should be noted that only the formation of the (*E*)-isomers takes place. The acetyl group can be easily removed by treatment with TFA. These sulfones **58** can be used for the synthesis of unsaturated keto sulfones having an indolizine skeleton **59**. Cyclization proceeds through the intermediate formation of a mixed anhydride (Scheme 18).[33]

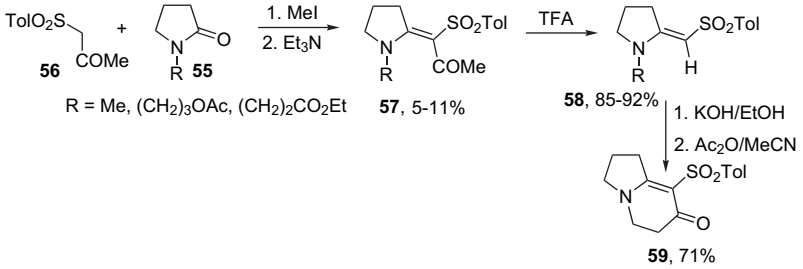
Some interesting related processes, which lead after intramolecular cyclization to sulfinyl enones are shown below. Both acetyl formate[34,35] and trialkyl orthoformate[36] were used as a source of carbonyl groups in these reactions. These transformations are valuable for the synthesis of chromones **60** and quinolones **61** bearing a sulfoxide moiety, starting from 2-hydroxy-substituted keto sulfoxides **62** and 2-amino-substituted keto sulfoxides **63** (Scheme 19).

The condensation reaction with carbonyl compounds can also be accompanied by the elimination of an acyl group. Unfortunately, in the case of condensation of arylglyoxals **64** with sulfones **65**, a mixture of diastereomeric sulfones **66** was formed (Scheme 20).[37]

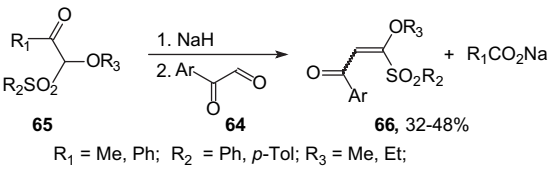
Sulfone-stabilized carbanions generated from the keto sulfone **67** could be alkylated followed by a subsequent



Scheme 19.

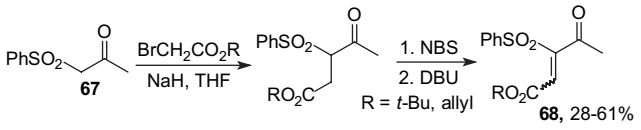


Scheme 18.



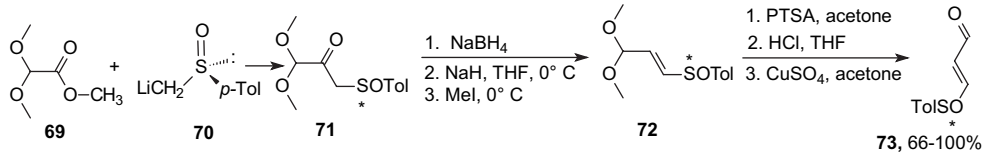
Scheme 20.

bromination–dehydrobromination procedure leading to α-sulfonyl enones **68** having an additional functional group such as an ester functionality (Scheme 21).[38]



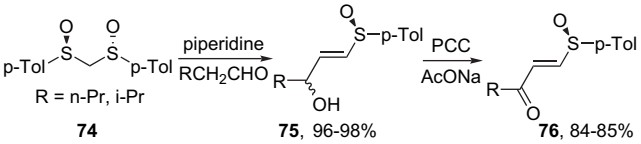
Scheme 21.

The original approach to the synthesis of a chiral β-sulfinyl vinyl aldehyde **73** was carried out by the reaction of a deprotonated chiral sulfoxide **70** with methyl dimethoxyacetate **69**. However, all attempts to deprotect the polyfunctional acetal **71** to prepare the corresponding aldehyde without the loss of chirality failed.[39] The target alkene **73** was prepared in up to quantitative yield (Scheme 22).



Scheme 22.

The synthesis of chiral (*E*)-keto sulfoxides **76** has been proposed recently. The corresponding precursors **75**, the allylic alcohols bearing a *p*-tolylsulfoxide group, were obtained in excellent chemical yield by condensation of enantiomerically pure (*S*,*S*)-bis-*p*-tolylsulfinyl methane **74** with enolizable aldehydes in the presence of piperidine as base. The process involves a Knoevenagel condensation between the aldehyde and the methylene-active bis-sulfoxide **74**, in tandem with an allylic sulfoxide–sulfenate rearrangement and hydrolysis of the sulfenate ester promoted by piperidine. (*E*)-γ-Hydroxysulfoxides **75** were oxidized with PCC and sodium acetate in dichloromethane at room temperature to afford enantiomerically pure (*E*)-γ-keto-α,β-unsaturated *p*-tolylsulfoxides **76** in high chemical yields and high optical purity (Scheme 23).[40]



Scheme 23.

2.3. Oxidation of vinyl sulfides

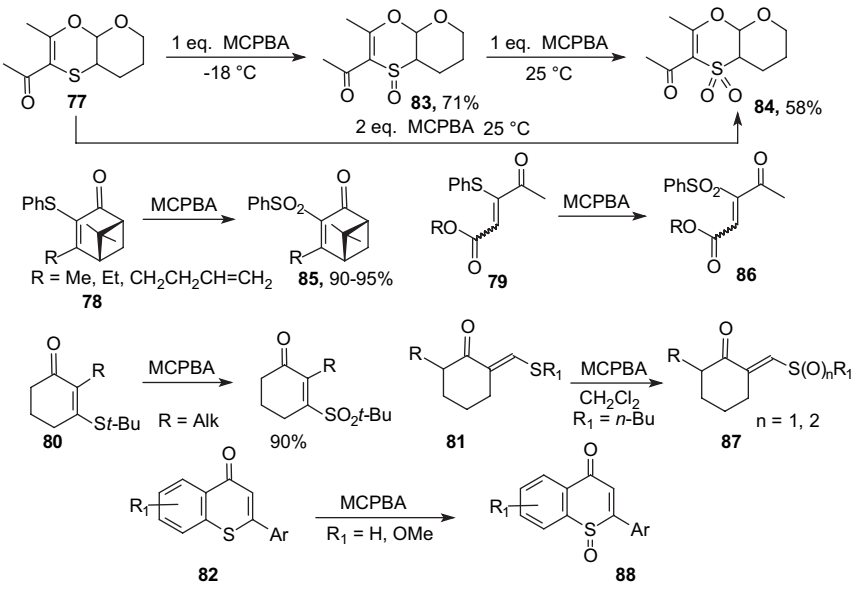
In all probability, the oxidation of ketovinyl sulfides to the corresponding sulfoxides and sulfones is the most useful and practical method for the preparation of this type of compounds. There are many methods available for the oxidation of sulfides to the corresponding sulfoxides and sulfones. This transformation can now be considered in most cases to be trivial.[41] However, only some of these methods are used for the preparation of sulfonyl and sulfinyl enones from the corresponding sulfides. Perhaps, the most commonly used reagent for the oxidation of sulfides to sulfones or sulfoxides is MCPBA. Some examples of the preparation of sulfonyl and sulfinyl enones **83–88** from the corresponding sulfides **77–82** incorporating MCPBA oxidation are highlighted below. It should be noted that both α-sulfides[35,42–47] and β-sulfides[10,48–50] can be oxidized in similar conditions. Moreover, obtaining the sulfoxides or sulfones in most cases simply depends on the quantity of MCPBA as oxidizing agent (Scheme 24).[38,46]

Some sulfanyl ketones being oxidized by MCPBA could give considerable amount of byproducts such as the corresponding oxiranes. $NaIO_4$ is a mild and selective reagent for the oxidation of sulfides to sulfoxides. Attempts to oxidize **89** chemoselectively to the corresponding sulfones **91** were unsuccessful. Exposure with MCPBA led also to partial epoxidation. However, after oxidation of **89** to the sulfoxides **90**, the double bond became less prone to oxidation and subsequent exposure with MCPBA afforded the desired unsaturated keto sulfones **91** (Scheme 25).[51,52]

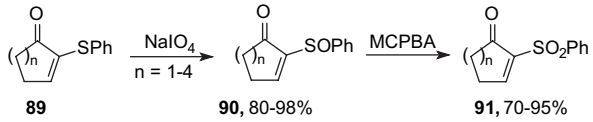
However, the oxidation of more electron-deficient β-ketovinyl sulfides **92** by $NaIO_4$ is not as successful as by MCPBA. Much better yields were observed for MCPBA oxidation, whereas oxidation with $NaIO_4$ gave a very low yield of the corresponding sulfoxide **93** (Scheme 26).[53,54]

A rare example of the synthesis of an acetylenic acyl sulfone has been described in the literature. At the final step of the synthesis, the target sulfone moiety was prepared using MCPBA oxidation. The ethynyl sulfide precursor was prepared from the THP-protected propargylic alcohol **94**, which was metalated with BuLi and the carbanion formed then reacted with diphenyl disulfide and the hydroxy group was deprotected before Swern oxidation by PTSA in methanol. The yield of the final keto sulfone **97** was not given, due to the unstability of the product and its tendency to polymerize. Nevertheless, it can be used directly as a potent useful dienophile (Scheme 27).[55]

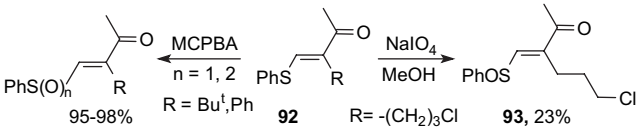
Peracetic acid generated in situ from hydrogen peroxide is a very popular choice for the oxidation of sulfides. In these reactions, the first oxidation step to form the sulfoxide is much less rapid than the second oxidation step to form the sulfone. This is why $NaIO_4$ has been used for the oxidation of ketovinyl sulfides **98** to the corresponding sulfoxides **100** and peracetic acid in order to prepare sulfones **99**.[56,57] Nevertheless, peracetic acid could also be successfully used for the preparation of both sulfones and sulfoxides,[58,59] e.g.,



Scheme 24.



Scheme 25.

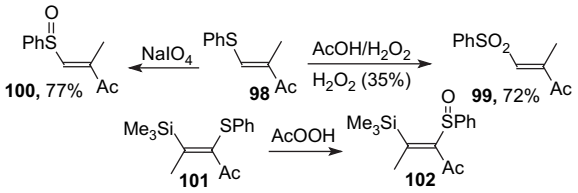


Scheme 26.

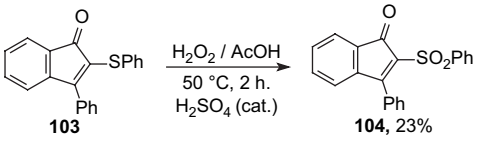
oxidation of the TMS-substituted sulfide **101** proceeds with preservation of the TMS group in the molecule to form the sulfoxides **102** (Scheme 28).

Often an excess of H_2O_2 is required and prolonged reaction times and/or heating may be needed to complete the reaction. Acidic catalysis, e.g., using H_2SO_4, of the reaction is possible. Thus, the reaction of sulfide **103** with hydrogen peroxide in glacial acetic acid in the presence of catalytic amounts of H_2SO_4 leads to the corresponding sulfone **104**.[60] Unfortunately, the yield of **104** is low (Scheme 29).

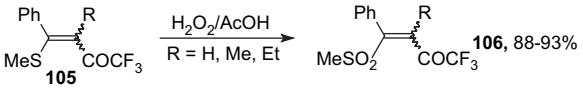
A series of CF_3-enones bearing a sulfonyl group were also synthesized via oxidation of the corresponding sulfides by peracetic acid.[61] Due to the presence of a strong electron-withdrawing group (CF_3CO) in the structure of the starting sulfides **105**, the oxidation demands heating under reflux, but, nevertheless, the yields of the target sulfones **106** are almost quantitative (Scheme 30).



Scheme 28.

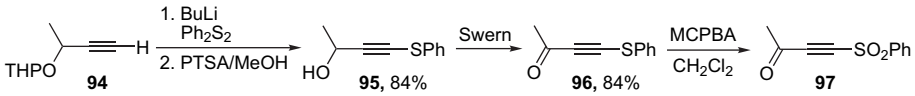


Scheme 29.



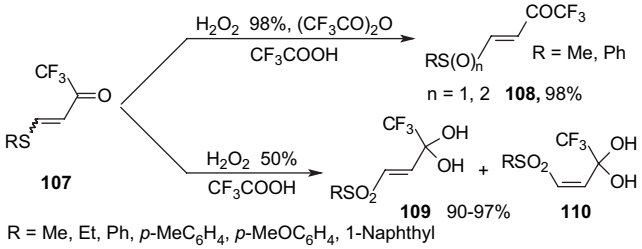
Scheme 30.

However, in the case of oxidation of the analogous unsubstituted trifluoroacetylvinyl sulfides **107** using the H_2O_2/AcOH system at room temperature no reaction proceeds, whereas an attempt to elevate the temperature resulted in complete resinification of the reaction mixture. A stronger oxidant—trifluoroperacetic acid—allows for the oxidation to be carried out under mild conditions. This reaction gives rise to the corresponding sulfones or sulfoxides **108**. It should be noted that trifluoroperacetic acid prepared from 50% hydrogen peroxide and CF_3COOH (1/1) afforded the corresponding diastereomeric diols **109** and **110**. Exclusive formation



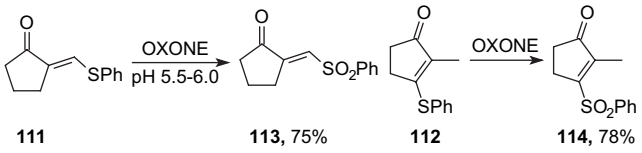
Scheme 27.

of the (*E*)-isomers of the ketones **108** was observed in the absence of water using anhydrous trifluoroperacetic acid prepared from TFAA and highly concentrated H_2O_2.[62] Moreover, the corresponding sulfoxides **108** could also be obtained by treatment with anhydrous trifluoroperacetic acid.[63] Probably, trifluoroperacetic acid is the best reagent for the oxidation of the sulfides, due to high yields, mild reaction conditions, and simplicity of the procedure (Scheme 31).



Scheme 31.

Oxone ($2KHSO_5/KHSO_4/K_2SO_4$) is a safe commercially available oxidant, which has become widely accepted for the oxidation of sulfides to sulfones. The reagent is usually employed in an aqueous alcoholic solvent, in which it forms an acidic solution (pH 2–3). Buffering of the solution, e.g., with borate, enables oxidations to be performed at about pH 5 for acid-sensitive substrates. As an example, using Oxone, the corresponding derivatives of cyclopentanones **111** and **112** were oxidized to the sulfones **113** and **114** (Scheme 32).[64]



Scheme 32.

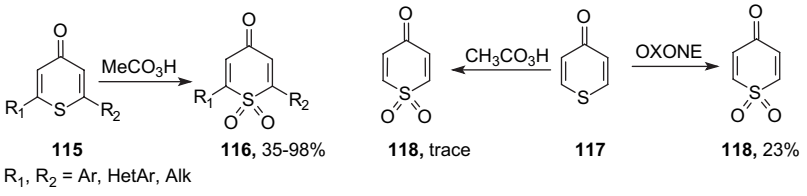
Substituted thiopyrans **115** were oxidized to the corresponding sulfones **116** by peracetic acid in good yields. In the case of parent unsubstituted thiopyran **117**, however, oxidation with peracetic acid gives only traces of the desired product **118**, whereas aplication of Oxone in methanol gives better results. Nevertheless, the target sulfone **118** was prepared in low yield (Scheme 33).[65]

Potassium permanganate is not applicable as rule for the preparation of the sulfonyl enones from the corresponding sulfides. This is connected with the possibility of double-bond oxidation. Only one example of the application of this oxidizing agent has been presented in the literature. Oxidation of the sulfide **119** with $KMnO_4$ leads to the sulfone **120** in poor yield.[66] The reaction of $Fe_2(CO)_9$ with the sulfoxide prepared from **119** by oxidation with $NaIO_4$ afforded dinuclear Fe(0) complexes **119a**, the structures of which were established by X-ray diffraction analysis (Scheme 34).[67]

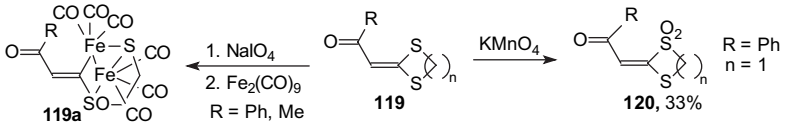
The application of 30% hydrogen peroxide in the presence of ammonium molybdate could be used as a successful alternative to MCPBA. Thus, oxidation of sulfide **121** with MCPBA gives only 26% yield of the corresponding sulfone **122**, whereas the use of the hydrogen peroxide/ammonium molybdate system gives a 60% yield of the polyunsaturated sulfone **122** (Scheme 35).[49]

2.4. Oxidation of allylic alcohols

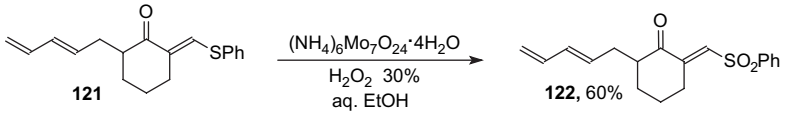
Another approach for the preparation of sulfonyl and sulfinyl enones is also based on the oxidation reaction. This method involves the oxidation of allylic alcohols bearing sulfonyl or sulfinyl substituents. The oxidation of β-sulfonyl allylic alcohols was carried out with different oxidizing agents, such as a $DMSO/SO_3/Py$ complex, PCC/SiO_2, and NiO_2, but the best results were obtained when a Dess–Martin reagent was used. Dess–Martin periodinate is a mild and convenient reagent for the transformation of allylic alcohols **123** and **124** to the corresponding carbonyl compounds **125** and



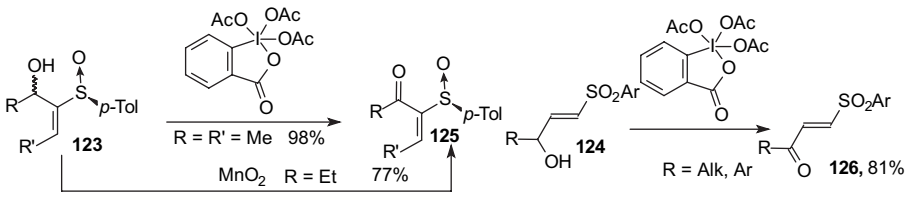
Scheme 33.



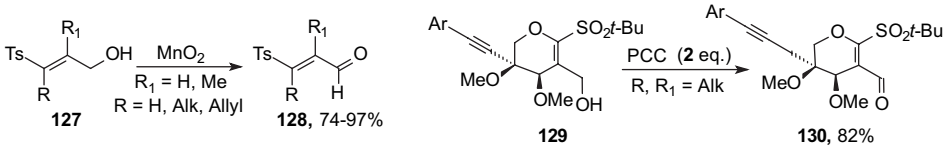
Scheme 34.



Scheme 35.



Scheme 36.

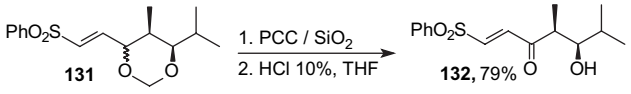


Scheme 37.

126. MnO_2 could be also used, but the yields of the target products are lower (Scheme 36).[68–72]

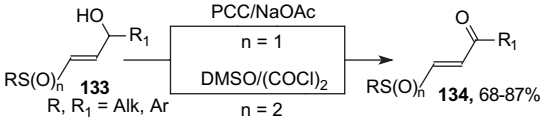
However, MnO_2 gives better yields in the case of oxidation of primary allylic alcohols **127** to the corresponding α,β-unsaturated aldehydes **128**.[73] Similarly, α,β-unsaturated aldehydes with a sulfonyl substituent **130** can be prepared in good yields by oxidation of the corresponding alcohols **129** with PCC in AcOH (Scheme 37).[74]

The oxidation of protected diol **131** with PCC/silica gel under sonication and subsequent hydrolysis of the ketal moiety in the presence of acid led to ketone **132** (Scheme 38).[75]



Scheme 38.

A successful alternative to oxidation using PCC is Swern oxidation. In all cases, the desired sulfones and sulfoxides **134** were obtained from **133** in good yields (Scheme 39).[76–78]

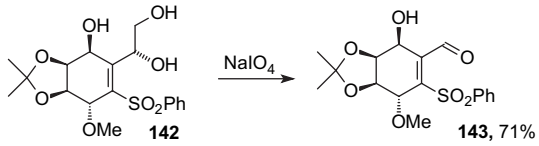


Scheme 39.

A widely used oxidizing agent is CrO_3 in acidic conditions, e.g., alcohol **135** was oxidized successfully at −78 °C by CrO_3 with subsequent warming to 0 °C to form the sulfone **136** and in some cases, enal **137** as byproduct is formed.[79]

Moreover, CrO_3 has also been used for the preparation of the corresponding α-sulfinyl enones **140** from **139**.[80] Oxidation of β-sulfonyl-substituted allyl alcohols **139** by CrO_3 also leads to β-sulfonyl enones **141** in excellent yields (Scheme 40).[81]

It is well known that vicinal diols can be oxidized by sodium periodate with the destruction of the C–C bond and the subsequent formation of a carbonyl group, e.g., oxidation of diol **142** was carried out by sodium periodate to give the corresponding β-sulfonyl vinyl aldehyde **143** (Scheme 41).[82,83]

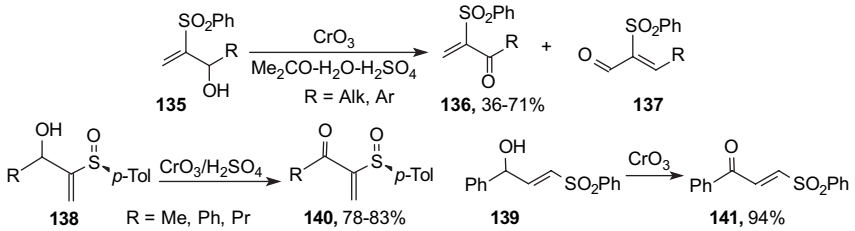


Scheme 41.

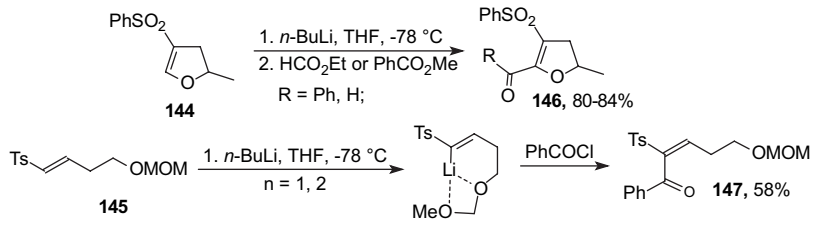
2.5. From unsaturated sulfones and sulfoxides

The discovery that simple vinyl sulfones can be deprotonated to give the corresponding vinylic anions opened up new and attractive possibilities for the direct synthesis of highly substituted vinyl sulfones **146** and **147**.[84] The reaction of both esters[85] and chloro anhydrides of carboxylic acids[86] with metalated vinyl sulfones **144** and **145** was carried out in good yields. In the case of the vinyl sulfones **145**, α-metalation took place, due to the chelate effect of the MOM group (Scheme 42).

It is not possible to form such a vinylic anion from the parent unsubstituted vinyl sulfone or sulfoxide, due to its rapid polymerization. This problem can be overcome by using

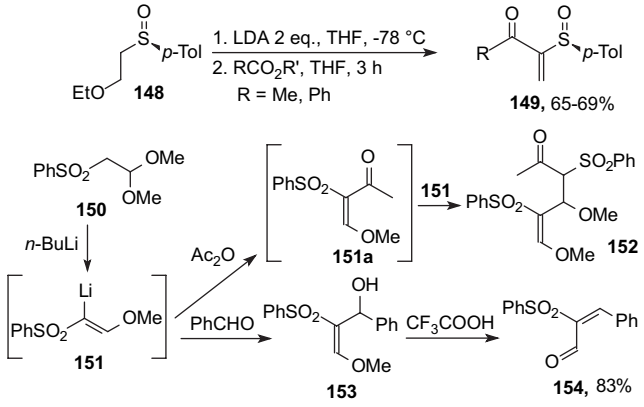


Scheme 40.



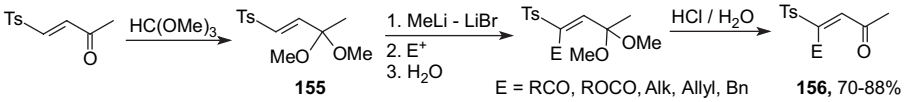
Scheme 42.

suitably derived sulfones or sulfoxides as masked vinyl sulfones or sulfoxides, e.g., β-ethoxysulfoxide **148** was transformed to **149**.[87] In the second sequence, the α-lithiated vinyl sulfone **151** was obtained in situ by treatment of *n*-BuLi with 1,1-dimethoxy-2-(phenylsulfonyl)ethane **150**.[88] However, the desired vinyl sulfone **151a** reacts easily with the starting α-lithiated vinyl sulfone **151** to form dimer **152**. The stable allyl alcohol **153**, which can be prepared by the reaction of α-lithiated vinyl sulfone **151** with benzaldehyde, undergoes a rearrangement in CF_3COOH to give the α-sulfonyl-substituted cinnamaldehyde **154** (Scheme 43).



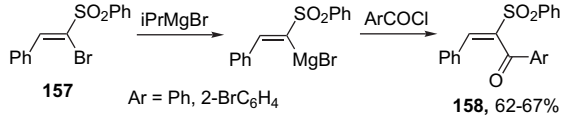
Scheme 43.

Sulfonyl enones protected at the carbonyl group can be deprotonated to form the corresponding vinyl anions. This has allowed the synthesis of a wide variety of substituted sulfonyl enones. Metalation of the ketal **155** leads to a β-ketovinyl anion. Treatment of the anion with various electrophiles followed by hydrolysis gives the modified derivatives **156** (Scheme 44).[89]



Scheme 44.

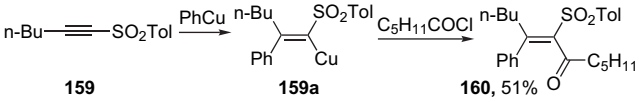
Bromine–magnesium exchange using *i*-PrMgBr permits the preparation of Grignard reagents from vinyl sulfones **157**



Scheme 45.

(and some other functionalized alkenes bearing also CN, CO_2Et, $CONR_2$ groups). Application of acyl chlorides as electrophiles allows the preparation of unsaturated sulfonyl ketones **158** (Scheme 45).[90]

Similar vinylcopper organometallics such as **159a** can also be prepared from ethynyl sulfone **159** by the addition of phenylcopper. The intermediate organocopper derivative of vinyl sulfone **159a** can be acylated with acyl chlorides, e.g., tetrasubstituted sulfonyl ketone **160** was prepared stereoselectively in 51% yield (Scheme 46).[91]



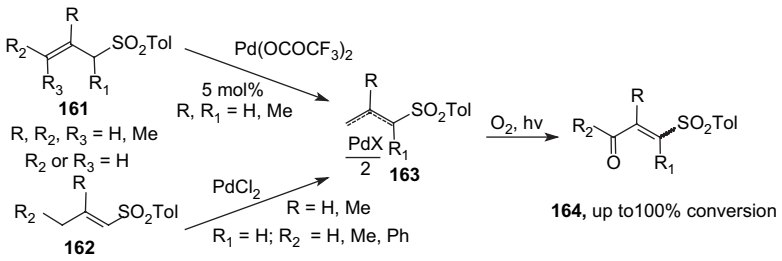
Scheme 46.

A general method for the synthesis of sulfonyl enones **163** from allyl sulfones **161** or vinyl sulfones **162** is based on catalytic oxidation in the presence of a Pd or a Cu catalyst. The best results were attained using Pd(II)[92] and Cu(II) trifluoroacetates.[93] Both allyl and vinyl sulfones can be involved in this reaction. The main drawbacks of this approach are the formation of an *E*/*Z* isomeric mixture **164** (Scheme 47).[94,95]

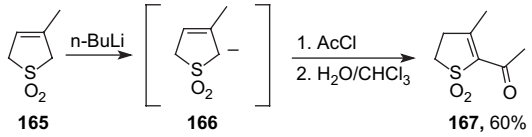
Allyl sulfones can be deprotonated easily, opening up a straightforward method for the synthesis of α-sulfonyl enones. Thus, sulfolene **165** was deprotonated with *n*-BuLi to give the sulfolene carbanion **166**. Acetyl chloride (0.33 equiv) was added to the solution of the carbanion **166** at −105 °C to give the product **167** with migration of the double bond (Scheme 48).[96]

Direct acylation also took place in the case of electron-donating vinyl sulfones, but the yields of the desired product were average,[97] e.g., acylation of enaminosulfone **168** with AcCl results in acyl sulfone **169** in 43% yield (Scheme 49).

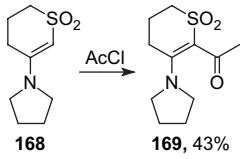
A number of substituted sulfones can be prepared by the reaction of vinyl sulfones **170** with aldehydes on irradiation.[98] Various ketovinyl sulfones **173** were prepared after



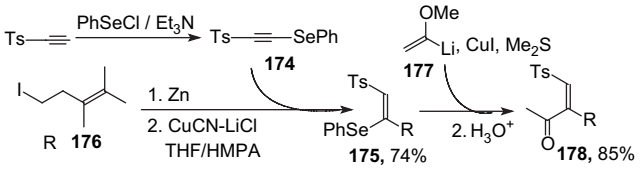
Scheme 47.



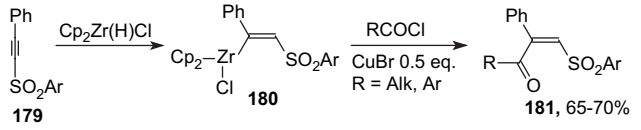
Scheme 48.



Scheme 49.



Scheme 51.



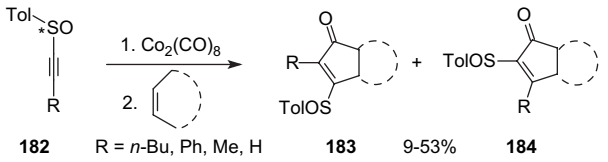
Scheme 52.

oxidation of the methylsulfanyl group in **171** to form **172** and subsequent thermal elimination of methylsulfenic acid. The main drawback of this method is the formation of *E*/*Z* isomers of sulfones **173** (Scheme 50).

There are some methods to prepare sulfonyl and sulfinyl enones by reactions of the corresponding acetylenic sulfones and sulfoxides. As an example, in a sequence of reactions, Back et al. converted selenylacetylene **174** to vinylselenosulfone **175** bearing a substituent R by reaction with organometallics formed from **176**. The last step of the sequence is substitution of the PhSe group with the synthetic equivalent of acyl anion **177** to form **178** (Scheme 51).[99]

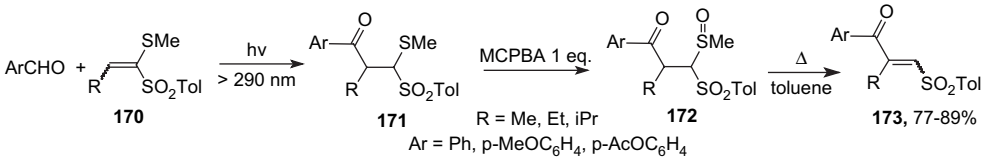
A more convenient and versatile approach, which allowed the avoidance of toxic selenium-containing compounds, deals with organozirconium compounds. Thus, acetylenic sulfones **179** easily react with $Cp_2Zr(H)Cl$ at room temperature and lead to the corresponding β-zirconium-substituted vinyl sulfones **180** that can be coverted into a number of β-sulfonyl enones **181** by reaction with acyl chlorides in the presence of CuBr (Scheme 52).[100]

The scope and limitation of the Pauson–Khand reactions of chiral alkynyl sulfoxides **182** with alkenes (norbornene, norbornadiene, bicyclo[3,2,0]hept-6-ene) have been studied thoroughly.[101] The observed loss of enantiomeric excess in diastereomerically pure Pauson–Khand adducts **183** and **184** arising from enantiomerically pure sulfoxides was explained by an extremely easy racemization of the dicobalt hexacarbonyl complexes of alkynyl sulfoxides. Moreover, the reaction is sensitive to steric factors, the best results being obtained in the case when R=Me in the initial sulfoxide **182** (Scheme 53).



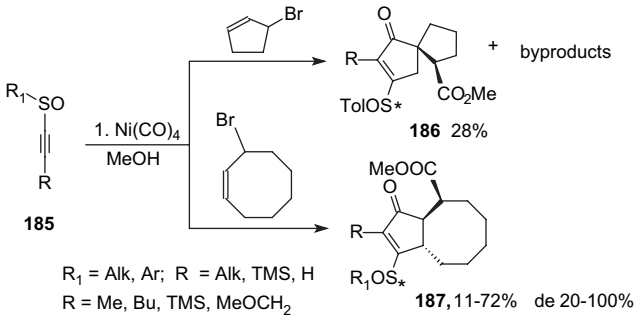
Scheme 53.

Similar syntheses of fused and spirocyclopentenones **186** and **187** have been elaborated on the basis of $Ni(CO)_4$-induced alkyne–allyl halide cyclization–carbonylation.[102] The target products were obtained in moderate to good yields by means of acetylenic sulfoxides **185** as auxiliaries. The *p*-tolylsulfoxide group has proved to be a suitable auxiliary for the effective diastereocontrol of the cyclization. The



Scheme 50.

prepared diastereomeric cycloadducts **186** and **187** can be separated by flash chromatography (Scheme 54).



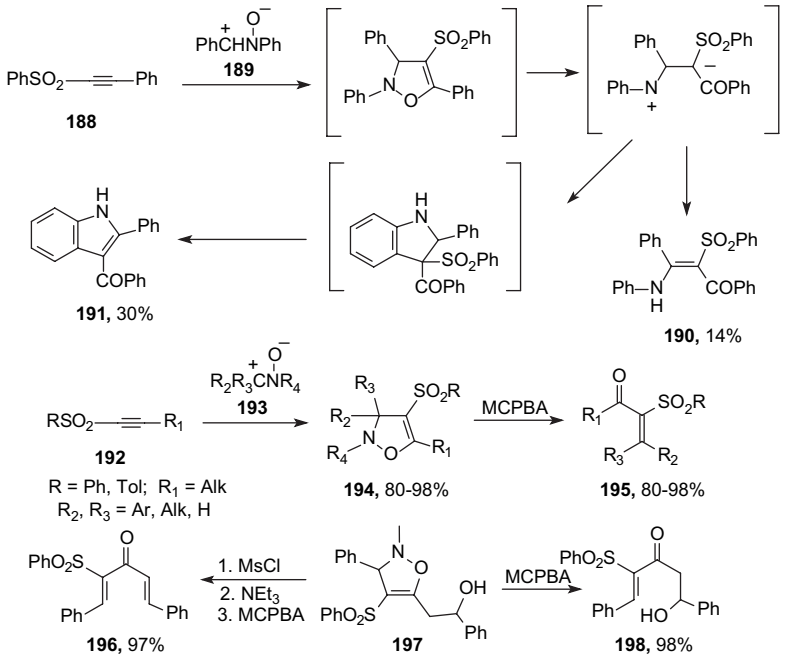
Scheme 54.

An unstable isoxazoline formed in the reaction of sulfone **188** and nitrone **189** gives a mixture of products—vinyl sulfone **190** and indole **191**.[103] In the case of reaction of **192** with disubstituted nitrones **193** stable isoxazolines **194** were obtained which were oxidized to ketovinyl sulfones **195** in excellent yield by MCPBA.[104] This approach has also allowed the preparation of interesting divinyl ketones **196** and β-hydroxy ketones **198** , starting from **197** (Scheme 55).[105]

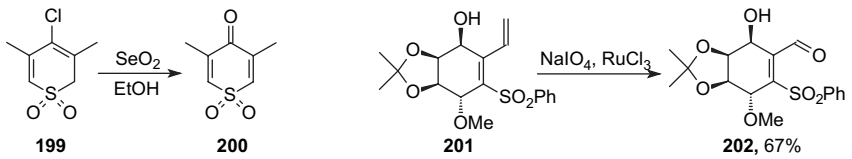
It has been reported that oxidation of the sulfone **199** by SeO_2 leads to the corresponding 4*H*-thiopyranone-1,1-dioxide **200**.[106] In the case of the sulfonyl diene **201**, oxidation with sodium periodate in the presence of ruthenium chloride was carried out with cleavage of the C–C bond to give β-sulfonyl vinyl aldehyde **202** (Scheme 56).[82,83]

Other examples of the oxidation of diene systems, viz. thiophene dioxides **203**, were reported in literature. Thus, treatment of **203** with alkaline hydrogen peroxide in EtOH at room temperature afforded the crystalline hydroperoxide **204**. The reaction produced the ring-opened products **205** and **206** at 50–60 °C. The hydroperoxide **204** on heating above its melting point decomposes in a manner typical of hydroperoxides to give the ketone **207** quantitatively. Reductive cleavage of the O–O bond produced the alcohol **206**. Interestingly, treatment of **204** with aqueous $NaHSO_3$ afforded the ketone **207**, but not the alcohol **206**. Reflux of **204** in ethanolic sodium hydroxide afforded another type of sulfonyl enone **205**. Under the same conditions, alcohol **206** also gives rise to **205** by a retro-aldol-type cleavage.[107] A similar product **208** was obtained in good yield by oxidation of 3-methoxythiophene by dimethyloxirane (Scheme 57).[108]

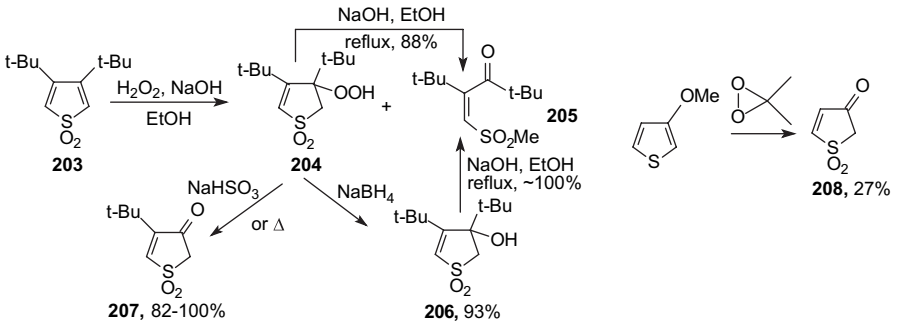
An example of the functionalization of an acyl moiety by the oxidation of sulfonyl enones **209** is also interesting.



Scheme 55.

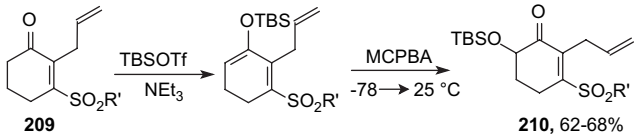


Scheme 56.



Scheme 57.

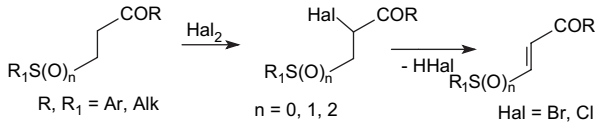
Thus, silyl ether **210** prepared from cyclic sulfone **209** was oxidized by MCPBA into α-silyloxy ketone **210** (Scheme 58).[7,9]



Scheme 58.

2.6. Creation of a double bond to form acylsulfones and acylsulfoxides

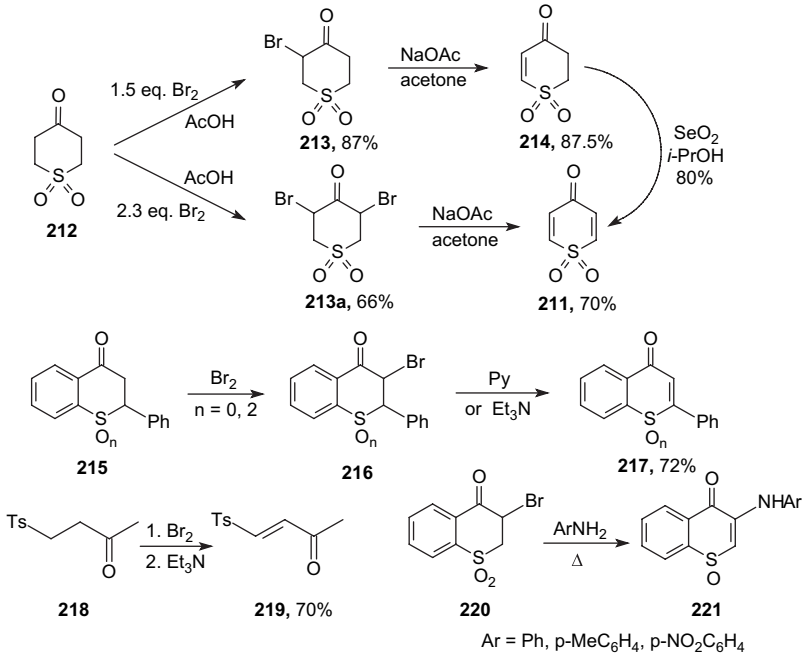
A useful method for the preparation of sulfonyl and sulfinyl enones is the creation of a double bond in ketones having either sulfonyl or sulfinyl groups. In most cases, it is a two-step procedure, which includes a halogenation–dehydrohalogenation sequence (Scheme 59).



Scheme 59.

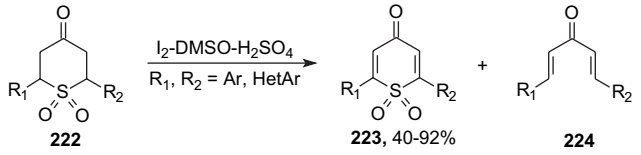
Two different synthetic routes to the unsubstituted 4*H*-thiopyran-4-one-1,1-dioxide **211** were investigated. Sulfone **212** was brominated in acetic acid to form monoadduct **213** or diadduct **213a**, depending on the bromine quantity. Dehydrobromination was successfully achived by sodium acetate in acetone to form **214** or **211**. Although the route through SeO_2 oxidation incorporates one additional step the overall yield in this case is higher.[65,109,110] An analogous approach was used for the preparation of cyclic sulfone **217**[111] and linear sulfone **219**. It was shown that triethylamine or pyridine was the most convenient bases for dehydrobromination (Scheme 60). It was also shown that using anilines for the dehydrobromination of sulfone **220** instead of triethylamine led to the formation of substituted unsaturated sulfoxides **221**.[65]

The iodine/DMSO/sulfuric acid system is the reagent of choice for large-scale reactions for one-pot conversion of saturated sulfones **222** into thiopyran-4-one-1,1-



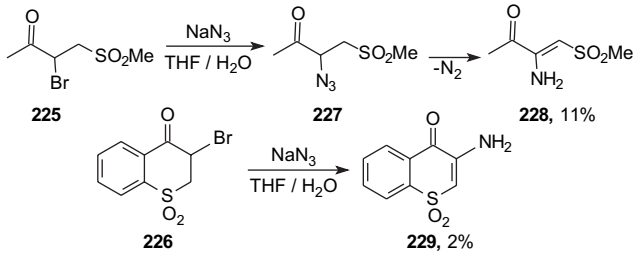
Scheme 60.

dioxides **223**, although small amounts of 1,4-pentadien-3-ones **224** were also detected as byproducts (Scheme 61).[65]



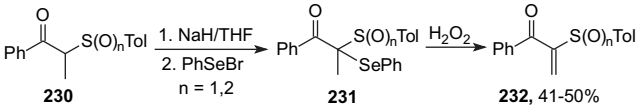
Scheme 61.

The next sequence of reactions is very interesting from a synthetic point of view. Treatment of the bromides **225** and **226** with sodium azide in aqueous THF converted them into the corresponding amino ketones **228** and **229**. Not only a double bond was formed, but also an amino group was introduced in the molecule via elimination of N_2.[112,113] As a result, the corresponding enamino ketones bearing a sulfonyl group were obtained, but the yields are very low (Scheme 62).

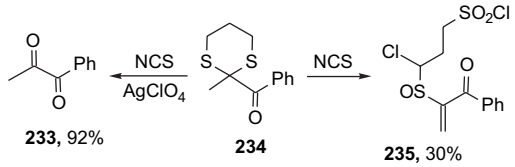


Scheme 62.

Only one method for the preparation of α-keto sulfones or α-keto sulfoxides from the corresponding saturated compounds **230** was described in the literature. Thus, enones **232** were obtained by conversion of **230** to the corresponding selenides **231** followed by oxidative elimination of PhSe group (Scheme 63).[114,115]



Scheme 63.



Scheme 64.

2.7. Miscellaneous

There are some methods to synthesize sulfones and sulfoxides that have not been included in the above-mentioned approaches. However, these methods are important in order to prepare more complex and some unusual products. Reaction of *N*-chlorosuccinimide (NCS) with 2-benzoyl-2-methyl-1,3-dithiane **234** yields α-dione **233** in high yield, especially in the presence of silver(I) perchlorate. The application of NCS alone or with cadmium nitrate or cupric chloride furnished only moderate yields of the α-dione **233**; the major byproduct (30% yield) was the highly functionalized α-chloro sulfoxide **235** (Scheme 64).[116]

Treatment of diazo sulfones **236** with Rh(II) acetate at 80 °C gave the sulfoxides **237**. This oxygen-transfer reaction can be rationalized by a sulfone oxygen attack onto the vinyl carbenoid **238**, producing the dipolar species **239**. Subsequent collapse of this intermediate affords the sulfoxide **237** (Scheme 65).[117,118]

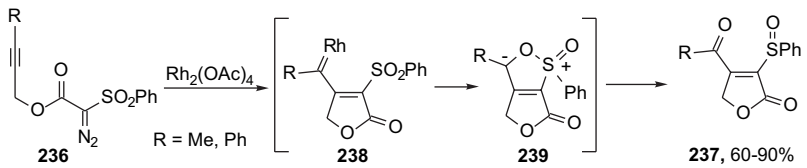
Cycloaddition of the vinylketene acetal **240** with diazo ketone **241** in the presence of rhodium(II) pivalate in pentane results in the formation of the cycloheptadiene **242**, which is formally a [3+4] cycloadduct. Further hydrolysis of **242** in acidic media followed by oxidation with DDQ leads to the tropone **243** having an α-sulfonyl vinyl fragment (Scheme 66).[119]

A versatile approach for the preparation of (*Z*)-isomers of β-sulfonyl enones exclusively is connected with the use of organochromium compounds. Thus, sulfonyl-substituted ylides of phosphorous **244** react easily with chromium alkoxycarbenoid complexes **245** to form unstable intermediate sulfonyl allenes **246**, which, on treatment with HCl, give rise to the corresponding (*Z*)-ketovinyl sulfones **247** in good yield (Scheme 67).[120]

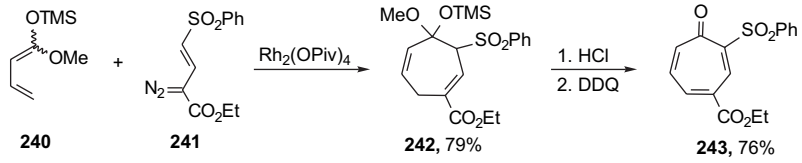
The intramolecular cyclization of aminocinnamates **248** by treatment with PPA in diphenyl ether under reflux gives fluoroquinolones **249** bearing a sulfonyl group in the 3-position in good yields. However, mixtures of regioisomers of **249** were obtained (Scheme 68).[36]

The regioselective radical addition of *p*-TsBr to α-allenic alcohols **250** in the presence of AIBN gives the products of addition to the terminal double bond **251** as (*E*)-diastereomers. Subsequent base-promoted 1,4-elimination of the resulting allylic bromides affords the β-Ts-substituted α,β-unsaturated ketones **252**. The best yield of the target ketones was obtained using Et_3N as a base in THF (Scheme 69).[121]

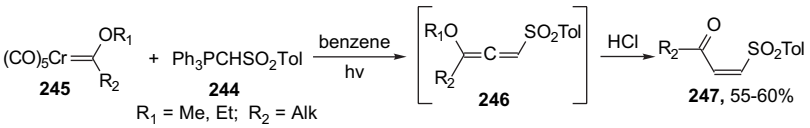
The reaction of enaminones such as **253** with mesyl azide leads either to triazoles or to sulfone **254** formation. It was



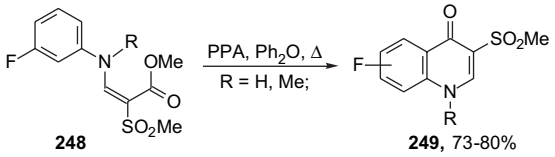
Scheme 65.



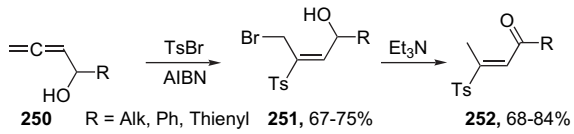
Scheme 66.



Scheme 67.

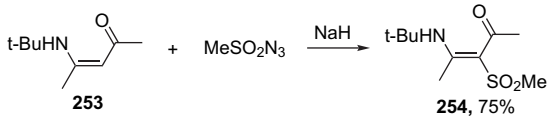


Scheme 68.



Scheme 69.

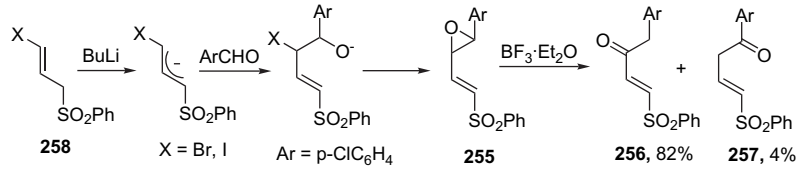
shown that in the case of a bulky *t*-Bu group at the enaminone nitrogen, the formation of the sulfone **254** proceeds in 75% yield (Scheme 70).[122]



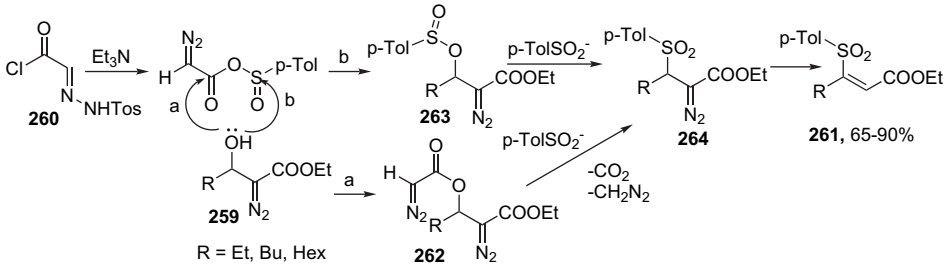
Scheme 70.

Treatment of epoxide **255** with BF_3/Et_2O afforded isomerization to a mixture consisting largely of the ketone **256** together with a small amount of **257** (ca. 4%). Epoxides **255** were prepared by lithiation of bromo(iodo)allylsulfones **258** followed by reaction with aldehydes (Scheme 71).[123]

The unexpected reaction of β-hydroxy-α-diazocarbonyl compounds **259** with tosyl hydrazone of glyoxyl chloride **260**/Et_3N system gave β-(*p*-tolylsulfonyl)-α,β-unsaturated carbonyl compounds **261**.[124] The authors proposed a mechanism for this unusual reaction. The reaction of β-hydroxy diazo compound **259** with the TsNHN=CHCOCl/Et_3N system gave bis-diazo ester **262** (path a) together with *p*-toluenesulfinate ester **263** (path b). The *p*-toluenesulfinate group in **263** is a good leaving group, which is easily replaced by the *p*-toluenesulfinyl anion through the attack of the more nucleophilic sulfur. The diazo ester group in **262**, on the other hand, may also be easily replaced by the *p*-toluenesulfinyl anion after protonation. The S_N2-type nucleophilic substitution gives β-(*p*-tolylsulfonyl)-α-diazo ester **264**. When R of **264** is an aryl group, the diazo decomposition occurs under the reaction conditions to give the 1,2-hydride shift product **261**. The yields of keto sulfones **261** are high, but the generality of the method is not discussed (Scheme 72).



Scheme 71.



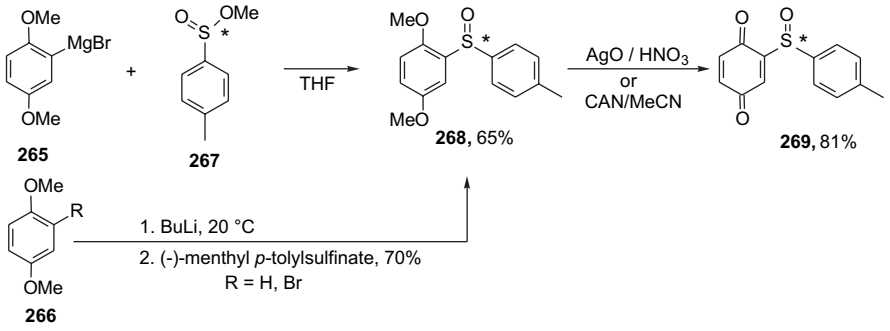
Scheme 72.

3. Synthesis of sulfonyl and sulfinyl quinones

A very important class of ketovinyl sulfones and sulfoxides is sulfonyl and sulfinyl quinones. The chemistry of these types of compounds has been thoroughly investigated and the approaches to the preparation of sulfonyl and sulfinyl quinones are sometimes very specific. This is why the synthesis of these compounds is discussed in a separate section.

3.1. Synthesis from phenols

The most general approach to the synthesis of sulfonyl quinones is based on the reaction of lithium or magnesium derivatives of *p*-dimethoxybenzenes with sulfinates. The obtained diaryl sulfoxides were then oxidized to the desired quinines, e.g., the chiral sulfinyl quinone **269** was obtained by the reaction of Grignard reagent **265** with *S*-(−)-*p*-tolylmethylsulfinate **267** in THF with subsequent oxidation of **268** by AgO in nitric acid.[125] The first stage can be also carried out by the reaction of lithiated 1,4-dimethoxybenzene **266** with (−)-menthyl *p*-tolylsulfinate.[126,127] The same approach was used for the preparation of the analogous naphthoquinones, but, in this case, cerium ammonium nitrate in acetonitrile was used in the oxidation stage (Scheme 73).[128–130]

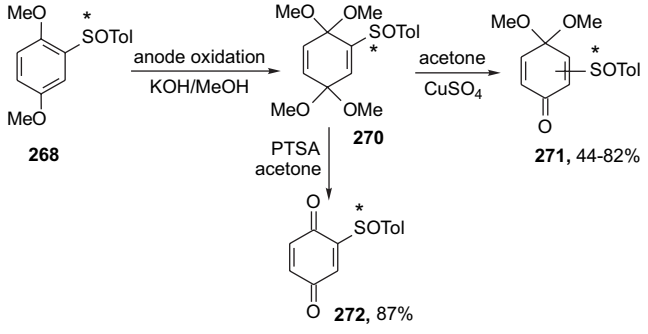


Scheme 73.

Another method to oxidize dimethoxyphenyl sulfoxides to quinones is anode oxidation. As an example, **268** can be converted by this method into the corresponding diacetal **270** in a KOH/methanol system. Acetal **270** under treatment with $CuSO_4$ gives mixture of isomeric α- and β-sulfinyl enones **271**, which are the products of partial deprotection of the carbonyl group. Application of PTSA in acetone was more successful and led to the pure sulfinyl quinone **272** in good yield (Scheme 74).[127,131]

N-Boc-protected imine **273** of sulfinyl quinone **272** was also synthesized. The first stage in this case was the preparation of the precursor. The corresponding aryl sulfide **274** was prepared from **275** using orthometalation directed to the NHBoc group with *t*-BuLi followed by reaction with ditolyl disulfide. The corresponding aryl sulfoxide was prepared by MCPBA oxidation. The final step was oxidation to azaquinone **273** by lead tetraacetate (Scheme 75).[132]

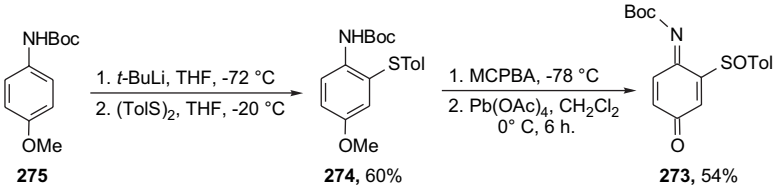
A general and convenient method for the preparation of sulfonyl and sulfinyl naphthoquinones deals with the reaction of metalated amides of benzoic acid **276** with β-phenylsulfanylacroleins. The obtained product **277** could be cyclized by treatment with BuLi to form the naphthoquinones **277a** bearing a PhS group. Subsequent oxidation with MCPBA gives rise to the corresponding sulfinyl naphthoquinones **278**. The distinguishing peculiarity of this approach is the construction of a quinone nucleus in the reaction process, but not by the oxidation of hydroquinone (Scheme 76).[133]



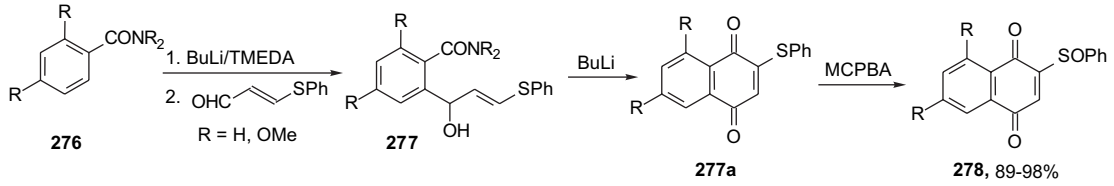
Scheme 74.

3.2. Synthesis from quinones

Sulfinic acids react readily with *p*-benzoquinones, e.g., the reaction of phenylsulfinic acid with activated quinone **279** leads to mono-substituted hydroquinone **280** and disulfonyl-substituted hydroquinone **281**. Sulfone **282** can be obtained by treatment of hydroquinone **280** with nitrogen

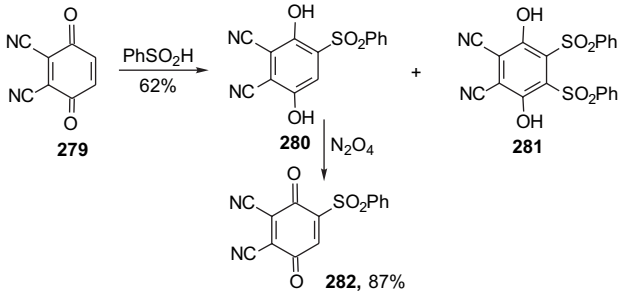


Scheme 75.



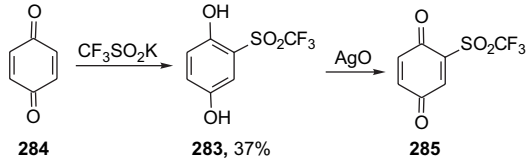
Scheme 76.

tetroxide. However, the more electron-deficient hydroquinone **281** cannot be oxidized with N_2O_4 (Scheme 77).



Scheme 77.

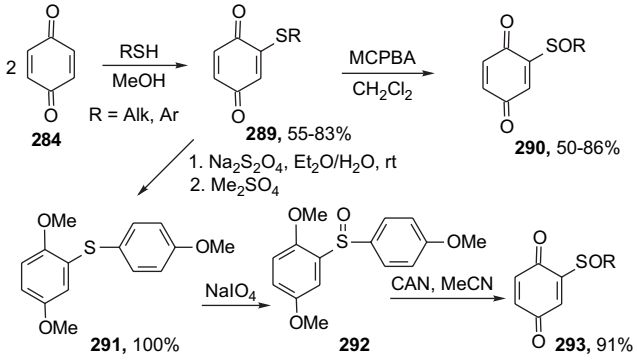
The same approach to the synthesis of sulfonyl quinones has been succesfully employed for the preparation of a CF_3SO_2-substituted quinone **285**. Thus, CF_3SO_2K in ethanol adds easily to *p*-benzoquinone **284** with the formation of hydroquinone **283**. This product was oxidized by silver oxide to the corresponding quinone **285** (Scheme 78).[134]



Scheme 78.

In fact, sulfinic acid could also react with non-activated unsymmetrical quinones like phenylbenzoquinone **286**. A two-step procedure was described to afford the sulfone **288**. The reaction of sodium *p*-tolylsulfinate with **286** followed by oxidation of the obtained hydroquinone **287** by *o*-chloroanil in acetone affords the corresponding sulfonyl quinone **288** as the only isomer (Scheme 79).[135]

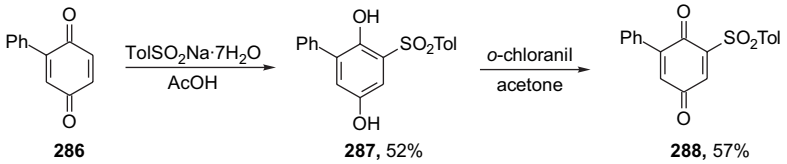
Another convenient method for the preparation of sulfonyl and sulfinyl quinones deals with the addition of thiols to benzoquinones followed by oxidation to the corresponding sulfonyl or sulfinyl quinones. Thus, benzoquinone **284** reacts easily with various thiols to form sulfanyl quinones **289**, which were oxidized by MCPBA at the room temperature to sulfinyl quinones **290**.[125,129,136] In the case of electron-rich thiols, a four-stage procedure for the oxidation of sulfide **289** to sulfoxide **291** was used, because direct oxidation by MCPBA failed.[136] Quinone **289** was converted quantitatively into the reduced dimethoxyphenyl sulfide by treatment with $Na_2S_2O_4$ followed by methylation with dimethyl sulfate. The stepwise oxidation of **291** with sodium periodate and CAN gave the target **293**, via **292** in high yield (Scheme 80).



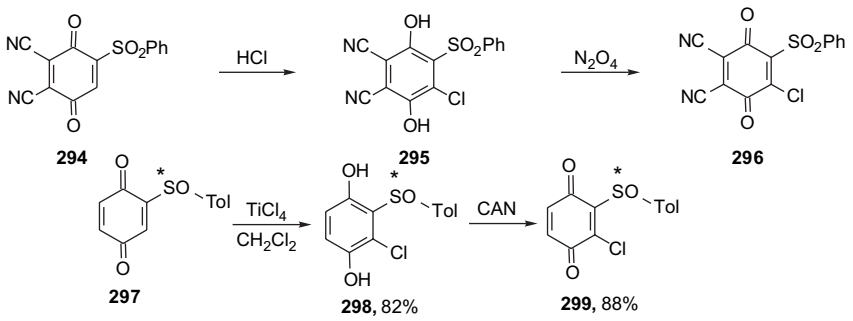
Scheme 80.

3.3. Modification of simplest sulfonyl and sulfinyl quinones

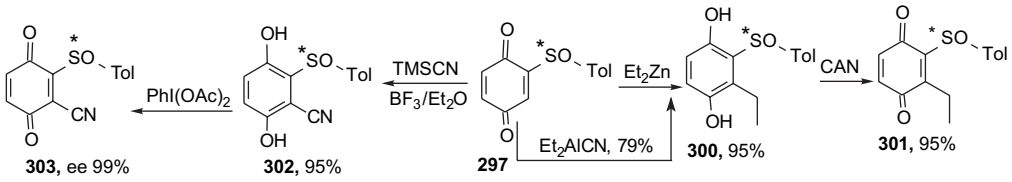
Both sulfonyl and sulfinyl quinones could be modified in the β-position to sulfur fragment via the intermediate formation of hydroquinones. In one example, anhydrous hydrogen chloride in benzene was added to quinone **294** to afford 2,3-dicyano-5-chloro-6-phenylsulfonyl hydroquinone **295** in moderate yield (Scheme 81). Oxidation of **295** with nitrogen tetroxide in methylene chloride under strictly anhydrous conditions gave the quinone **296**, which was found to be a very strong oxidant and π-acid.[134] An alternative method includes the treatment of sufinyl quinone **297** with $TiCl_4$ in methylene chloride. In this case, cerium ammonium nitrate was successfully used for the oxidation of hydroquinone **298** to form **299** (Scheme 81).[137]



Scheme 79.



Scheme 81.



Scheme 82.

It was also shown that organozinc compounds react with sulfinyl quinone **297** to give products of alkyl group addition in excellent yields.[137] The reaction takes place on the more electrophilic double bond and the only isomer of hydroquinone **300** is formed. Similarly, ethylation proceeds under treatment of **297** with Et_2AlCN to give **301**, whereas cyanation of **297** was performed using TMSCN in the presence of BF_3 etherate. After oxidation of the intermediate hydroquinone **302**, the corresponding enantiopure quinone **303** was prepared (Scheme 82).[138]

In conclusion, the methods described above allow the synthesis of a large variety of sulfonyl and sulfinyl enones, but, nonetheless, the search for new more simple and effective approaches to the preparation of these compounds (particularly chiral derivatives) is an ongoing process.

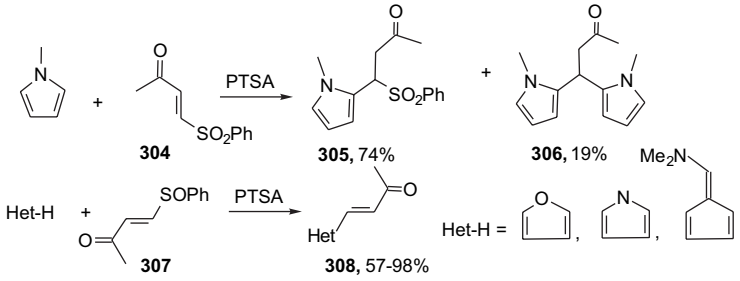
4. Reactions of sulfonyl and sulfinyl enones

4.1. Reactions with double bonds

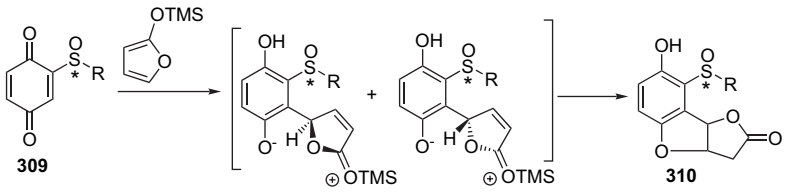
4.1.1. Reactions with *C*-nucleophiles. The most investigated reaction of unsaturated keto sulfones and sulfoxides is the nucleophilic addition reaction (Michael addition) to the double bond. This was caused by two electron-withdrawing groups at this double bond. *C*-, *S*-, *O*-, and *N*-Nucleophile could be used in this reaction. In most cases, elimination of sulfinic (sulfenic) acid after the addition of nucleophiles was observed. A number of electron-rich aromatic and heteroaromatic compounds react with sulfones and sulfoxides as Michael acceptors. Thus, the reaction of *N*-methylpyrrole with sulfone **304** leads to a mixure of the mono-Michael adduct **305** and di-Michael adduct **306**.[139] This is why the authors have used the reaction successfully for the preparation of the monoadducts **308** from the corresponding sulfoxide **307** (Scheme 83).

In the case of the reaction of sulfinyl quinones **309** with 2-trimethylsiloxyfuran as a nucleophile, furobenzofurans **310** were obtained. The mechanism of the transformation involved the addition of 2-TMSO-furan to **309** followed by intramolecular cyclization to the corresponding 3a,8b-dihydro-7-hydroxy-8-(arylsulfinyl)furo[3,2-*b*]benzofuran-2(3*H*)-ones **310**. The diastereomeric excesses ranged between 60 and 80% for *p*-tolyl and 2-methoxynaphthyl sulfoxides, but increased up to 96% with the bulky *tert*-butylsulfinyl group (Scheme 84).[126,129,140–142]

A similar reaction of 2-(arylsulfinyl)-1,4-benzoquinones **311** with *N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)pyrrole has been studied under different catalytic

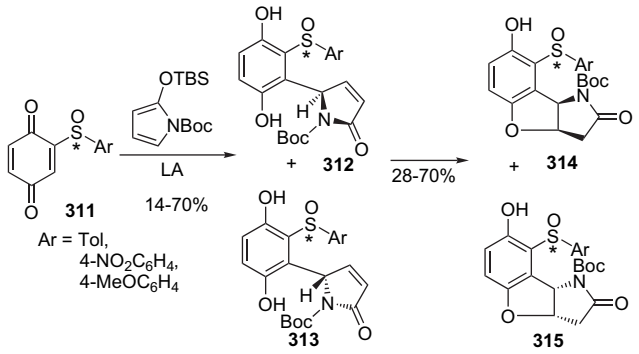


Scheme 83.



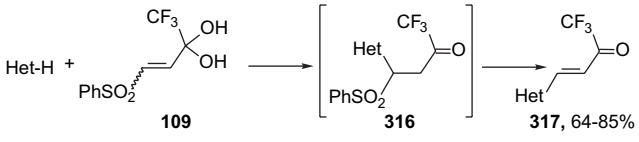
Scheme 84.

conditions. Under $BF_3 \cdot OEt_2$ catalysis, the reactions were completely stereoselective leading to the Michael-type adducts **312**, whereas in the presence of $SnCl_4$, diastereomeric mixtures of pyrrolo[3,2-*b*]benzofurans **314** and **315** were obtained in up to 70% yield. The latter products result from a tandem process involving the Michael reaction followed by an intramolecular cyclization of the intermediates **312** and **313** (Scheme 85).[143]



Scheme 85.

The reaction of a CF_3-containing sulfone existing in the hydrated form as diol **109** (R=Ph) with various electron-rich heteroaromatics such as furans, pyrroles, and indoles was also investigated. The addition–elimination reaction proceeds under mild conditions 100% stereoselectively and permits a one-step procedure for the preparation of CF_3-enones **317** bearing a heterocyclic moiety in high yield. In all cases, only the (*E*)-isomers of the unsaturated CF_3-ketones **317** were obtained.[63] It should be noted that a study of the reaction mechanism shows that the reaction proceeds only with the keto form of the sulfone **316** formed in situ (Scheme 86).



Scheme 86.

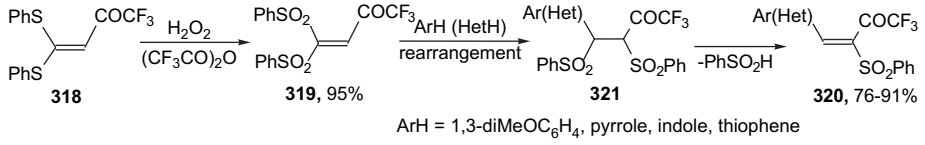
A new highly reactive electrophile—β-trifluoroacetylketene diphenyldithioacetal tetroxide **319**—was easily prepared by oxidation of the corresponding sulfide **318** with trifluoroperacetic acid. Michael addition reactions with electron-rich aromatics and heteroaromatics permit access to various 1,1,1-trifluoro-4-aryl-3-(phenylsulfonyl)but-3-en-2-ones **320** in good yields. In some cases, the formation of an intermediate product **321** was observed. Treatment of this product **321** with triethylamine permits the stereoselective preparation of **320**. The tetroxide **319** was proved to be a good synthetic equivalent of the 1,1,1-trifluoro-3-(phenylsulfonyl)but-3-en-2-one cation in reactions with electron-rich aromatics. The procedure is extremely simple and can be easily scaled up (Scheme 87).[144]

As a rule, α-sulfonyl enones are much more reactive in this type of reaction than their β-substituted counterparts, e.g., both furan (to give **323**) and anisole react with α-sulfonyl enone **322** without any catalysts. However, less nucleophilic aromatic compounds such as *tert*-butylbenzene did not react with the sulfone **322**.[79] The regioselectivity of the reaction with anisole is not very high. *para*-Adduct **324** is formed preferentially over the *ortho*-adduct **325** (Scheme 88).

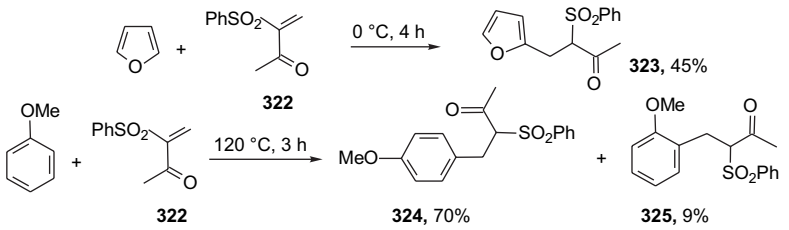
Intramolecular cyclization of **326** that is a nucleophilic addition of the aromatic nucleus to the double bond of β-sulfonyl enones **326** is catalyzed by TfOH and leads to the stereoselective formation of indanones **327** (Scheme 89).[98]

Another example of intramolecular cyclization is the formation of indole ring **328**. Cyclization of **329** proceeds to benzene ring into the *ortho*-position to amino group. Aromatization after elimination of sulfinic acid leads to the formation of indole **328**. As a byproduct, vinyl sulfone **330** was isolated in the case of methylation of enamino ketone **329** in the presence of sodium hydride as a base (Scheme 90).[103]

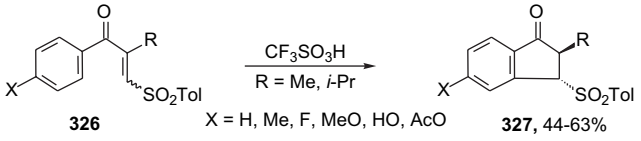
Electron-rich alkenes also react easily with sulfonyl enones. Thus, enamines **329** react with ketone **330** in THF and gave 1,5-diketones **331** after aqueous workup. The least reactive enamine, i.e., cyclohexenyl derivatives **329**, gave the highest yield in this reaction. No formation of [2+2] or [2+4] cycloadducts was observed. However, the reaction with



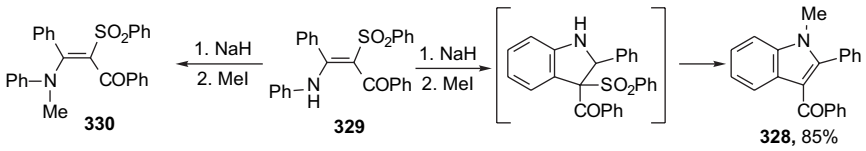
Scheme 87.



Scheme 88.



Scheme 89.



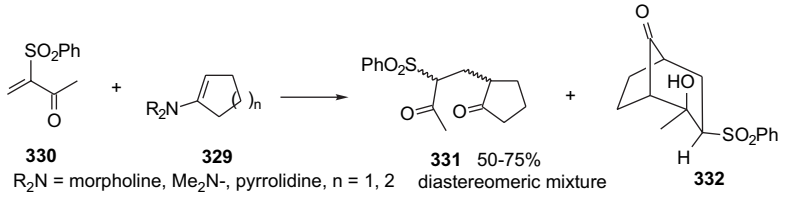
Scheme 90.

morpholinocyclopentene gives also [3.2.1]bicycle **332** as byproduct (Scheme 91).[79]

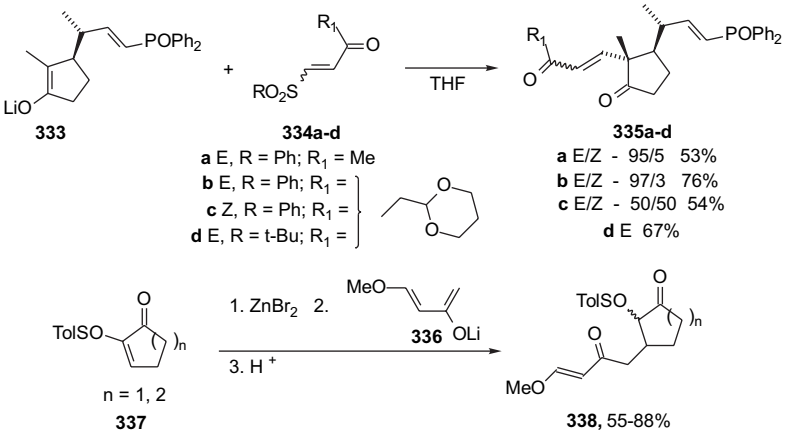
Li-enolates also participate in the reaction with sulfonyl enones. Enolate **333** reacts with β-sulfonyl enones **334a–d** to generate the unsaturated diketones **335a–d** in good yields.[145] The same approach was also used for the addition of enolate **336** to cyclic keto sulfoxides **337** to give the diketones **338** (Scheme 92).[146]

The reaction of the enolate prepared from **339** with the sulfonyl enone **340** is the key step in the synthesis of shahamin K **342** through the preparation of sulfonyl ketone **341**. This natural substance **342** was isolated from the skin extracts of a dorid nudibranch *Chromodoris gleniei* found in the coastal waters of Sri Lanka (Scheme 93).[147]

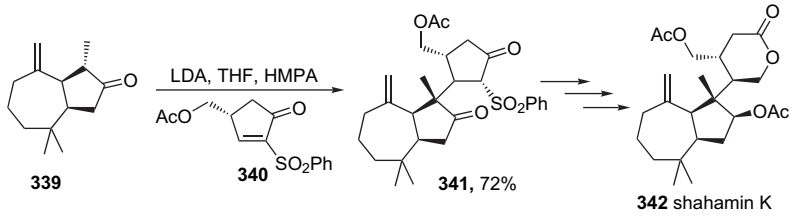
Addition of *n*-hexyllithium to the double bond of sulfanyl enone **343** leads to the formation of the enolate, which reacts with the more powerful electrophile, keto sulfoxide **344**. As



Scheme 91.

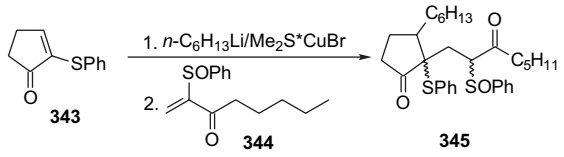


Scheme 92.



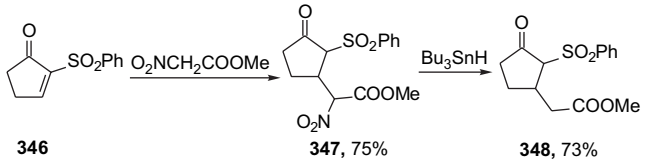
Scheme 93.

a result, two new C–C bonds are formed; however, a mixture of diastereomers of **345** was obtained (Scheme 94).[148]



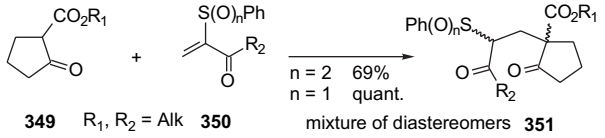
Scheme 94.

CH-acids are a very important type of *C*-nucleophiles that could react with sulfonyl and sulfinyl enones via addition to the double bond. If the CH-acid has two electron-withdrawing groups, the reaction does not demand additional activation and catalysis. As an example, Michael addition of methyl nitroacetate to the cyclic sulfone **346** followed by reductive denitration of **347** provides a new method for the conjugate addition of methyl acetate to electron-deficient olefins.[149] However, the stereochemistry of the obtained product **348** was not established (Scheme 95).



Scheme 95.

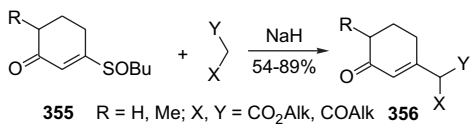
In a similar manner, β-keto esters **349** react easily with both sulfoxides[150,151] and sulfones **350** to give the adducts **351** containing a quaternary carbon atom. The mild neutral conditions ensure that **351** suffers neither a retro-Michael nor an intramolecular aldol reaction. It should be noted that, in the case of the sulfoxides **350**, the reactions took place in quantitative yields (Scheme 96).



Scheme 96.

When the CH-acids are less sterically hindered, e.g., esters of acetylacetic or malonic acids, a mixture of the monoadduct **352** and diadduct **353** can be obtained from **354** (Scheme 97).[150]

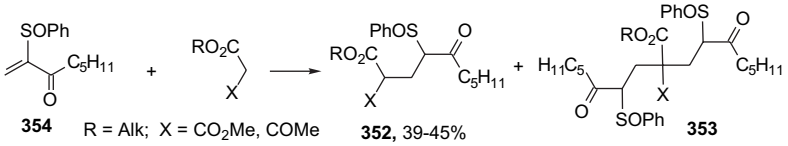
However, this phenomenon could be observed only in the case of very active electrophiles viz. α-sulfinyl enones. Thus, β-keto sulfoxides **355** react with CH-acids to form exclusively the monoadducts **356** and, moreover, activation by sodium hydride was needed (Scheme 98).[152]



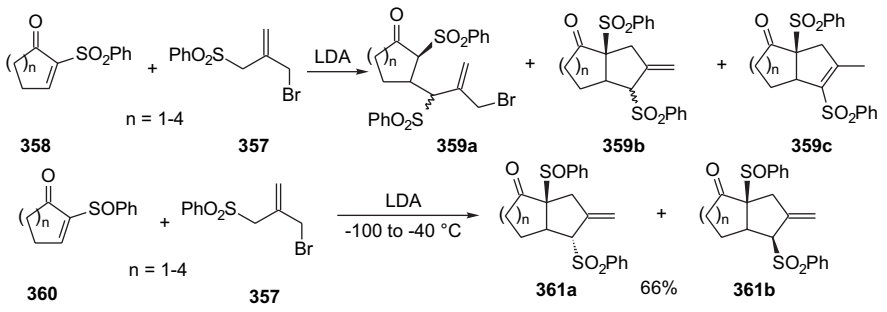
Scheme 98.

Base-induced reactions of allyl sulfone **357** with cycloalkenones **358** were investigated with the ultimate purpose of developing a route leading to the bicyclic sulfones **359b**. Low-temperature fast-quenched reactions led generally to the open-chain adducts **359a**, while an increase of temperature and the addition of HMPA resulted in subsequent ring closure to **359b** and isomer **359c**.[51] Treatment of the sulfoxides **360** with LDA and **357** gave a mixture of stereoisomers **361a** and **361b** in a 14/86 ratio, resulting from a subsequent ring closure by a tandem Michael process (Scheme 99).

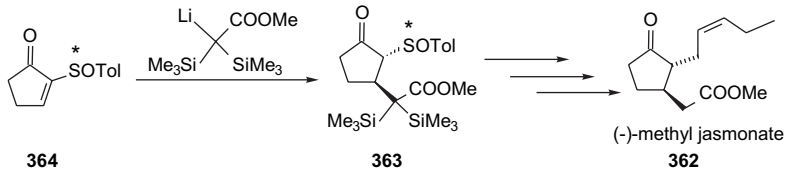
A short and effective asymmetric synthesis of natural (−)-methyl jasmonate **362**—a very desirable perfume constituent and insect sex-attractant pheromone—has been reported. The critical asymmetric synthetic step involves carbon–carbon bond formation for **363**, which was directly used in the next step without further purification. Conjugate addition of an α-lithioacetate unit to doubly activated, enantiomerically pure, Michael acceptor (*R*)-(−)-**364** opens up a new route to target molecule.[153] α-Metalated derivatives of acetic acid esters were also used in this reaction. The



Scheme 97.



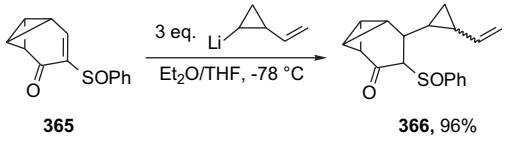
Scheme 99.



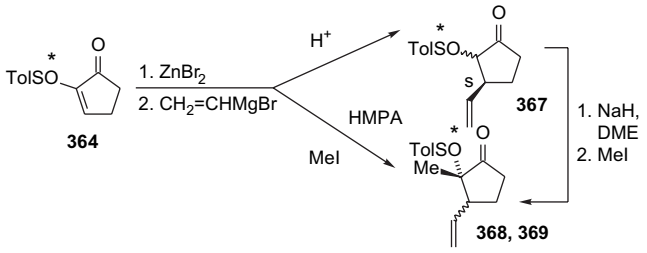
Scheme 100.

best results (ee 70%) were obtained in the case of lithium phenylsulfonyl acetate (Scheme 100).[154]

An interesting example is the addition of 2-vinylcyclopropyllithium to the sulfoxide **365**. This example also demonstrates the broad application and universality of this method, permitting the preparation of the target product **366** in quantitative yield (Scheme 101).[44]



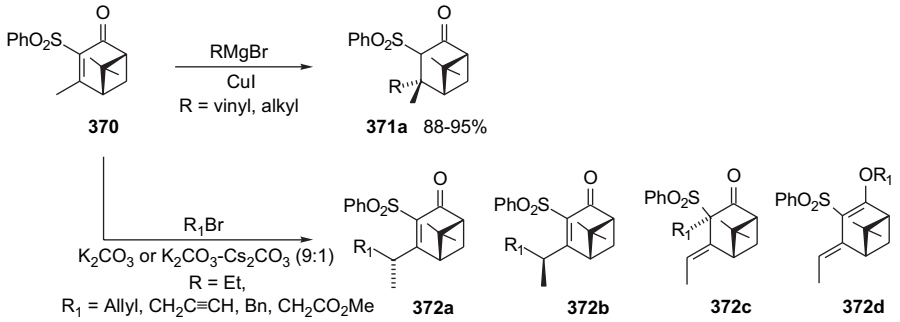
Scheme 101.



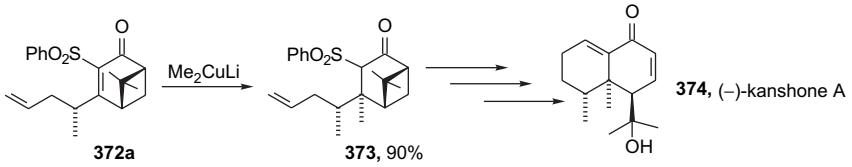
Scheme 102.

Some reactions of vinylmagnesium or vinylcopper derivatives with sulfinyl enones are described in the literature. Optically pure cyclopentenone sulfoxide (*S*)-(+)-**364** was treated firstly with zinc dibromide to preform an activated chelate complex and then with vinylmagnesium bromide. Conjugate addition led to the cyclopentanone **367** in quantitative yield. The intermediate enolate can also be methylated to produce 2,2,3-trisubstituted cyclopentanones **368** and **369** in approximately equal amounts. Cyclopentanones **368** and **369** are precursors for the preparation of optically pure estrone derivatives.[155] The divinylmagnesium derivative and mixed cuprates could also be successfully participated in this reaction (Scheme 102).[156,157]

The conjugate addition reactions of **370**, prepared from (+)-nopinone, with some Grignard reagents in the presence of copper(I) iodide were examined (Scheme 103). All conjugate addition reactions proceed smoothly to give the adducts **371a** in high yields, and no formation of stereoisomers **371a** at the C-4 position was detected.[46] Alkylation reactions of **370** with alkyl bromides in the presence of K_2CO_3 in MeCN proceeded in a regio- and extracyclic stereocontrolled fashion to give, as the major product, mixtures of γ-alkylated products **372a** and **372b** with great predominance of isomers **372a** and α-alkylated products **372c** and *O*-alkylated products **372d** on reactions with allyl bromide.



Scheme 103.

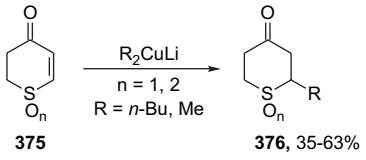


Scheme 104.

Reaction of **370** with methyl bromoacetate provided **372a** as the sole product.[47]

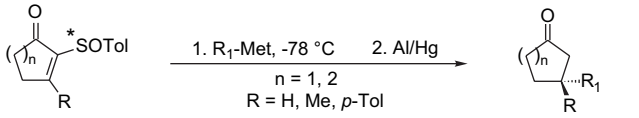
The application of **372a** (R_1=allyl) as a synthetic intermediate for the asymmetric synthesis of (−)-kanshone A **374**, a nardosinane sesquiterpene, was studied. Conjugate addition of Me_2CuLi to **372a** in THF/ether solution leads to the formation of sulfone **373**, a precursor for the (−)-kanshone A synthesis (Scheme 104).[158]

A model example of lithium alkylcuprate additions to the cyclic derivatives **375** was investigated.[159] It should be noted that, in all cases, the reactions proceed 100% regioselectively with the formation of the β-substituted ketones **376** (Scheme 105).



Scheme 105.

Addition of both organomagnesium and organocopper compounds to the cyclic keto sulfoxides **377** to form **379** was thoroughly investigated.[34,35,156,160] It was shown that, in the case of organomagnesium compounds, the best results were obtained for diphenylmagnesium (ee >98%). Moreover, the addition of 18-crown-6 increased the enantioselectivity for more than 20% as a general rule. From a range of cuprates, *p*-Tol_2CuLi and *n*-Bu(PhS)CuMgCl gave the best results.[160] The presence of catalytic amounts of Zn, Ni, Co, Pd, and Mg dibromides was shown to improve the yield of the reaction (Scheme 106).[22,23]



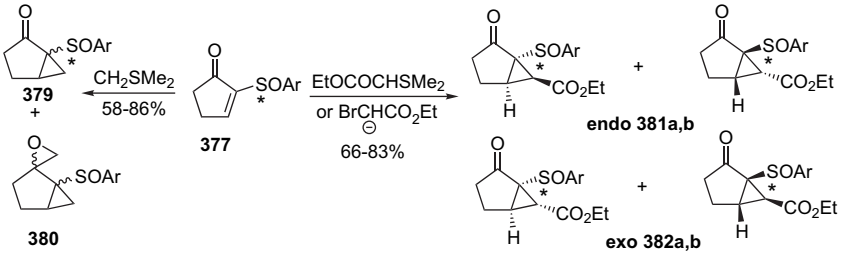
Scheme 106.

The cyclopropanation of (*S*)-**377** with various sulfur ylides has been examined. The reaction with methylenesulfonium ylides gave the corresponding cyclopropanes **379** with low diastereoselectivity (from a 1/1 to 1/3 ratio). The formation of oxirane **380** arising from the subsequent methylenation of the carbonyl group was also observed. A clean cyclopropanation of (*S*)-**377** took place with ethyl (dimethylsulfanylidene)acetate affording the cyclopropanes **381a**,**b** and **382a**,**b** with high π-facial selectivity, but low *endo*/*exo* ratio. A high *endo*/*exo* selectivity but low π-facial selectivity was observed in the reaction of (*S*)-**377** with (2-ethoxy-2-oxoethyl)(diphenyl)sulfonium tetrafluoroborate. The use of the α-bromoacetate carbanion as the cyclopropanation reagent resulted in the formation of **381a** with high facial and *endo*/*exo* selectivity. In a proposed explanation of the stereochemical outcome of the cyclopropanations investigated, the ground-state conformation of the sulfoxide **377** and the transition-state structure of the initial addition step were taken into account (Scheme 107).[161]

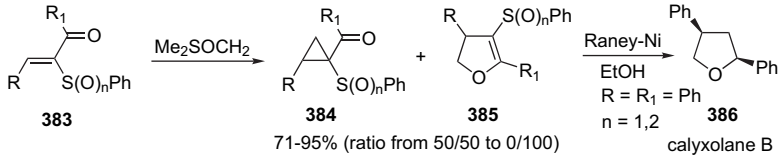
The reaction of sulfonyl and sulfinyl enones **383** with dimethylsulfoxonium methylide leads to the formation of a mixture of cyclopropane **384** and dihydrofuran **385** in a ratio from 50/50 to 0/100. This synthetic approach was used for the preparation of the natural product, calyxolane B **386**, isolated from a marine sponge. The product was prepared by the reduction of **385** with Raney Ni (no yield was given) (Scheme 108).[162]

The exclusive formation of dihydrofurans **387** was observed in the case of a similar reaction of α,β-unsaturated sulfones **388** with arsonium bromides **389** in the presence of potassium carbonate at room temperature through addition of the in situ generated arsonium ylide. The reaction proceeds stereoselectively and only the trans-isomer is formed (Scheme 109).[163]

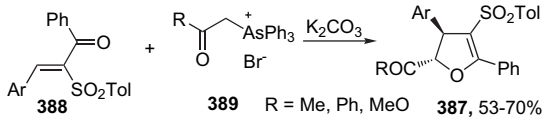
Michael addition of the dianion prepared from *N*-Boc-anilines **390** in the presence of CuCN and LiCl with the unsaturated sulfonyl ketones **391** generates the 1,4-adducts **392**, which, after deprotection of the Boc group and thermal elimination of the tolylsulfinic acid, provide the quinolines **393**. The four-step synthesis of the trisubstituted quinolines **393**, from the readily available bromomethyl or chloromethyl



Scheme 107.



Scheme 108.



Scheme 109.

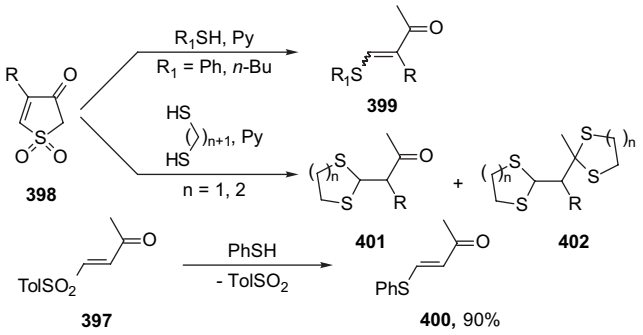
ketones, aldehydes, and *N*-Boc-anilines, proceeds in overall yields of 23–50% (Scheme 110).[164]

In the case of less active nucleophiles, catalysis by a Lewis acid was needed. The interaction of allylsilanes **395** with cyclic sulfoxide **394** was activated by titanium(IV) chloride or boron trifluoride.[165] The dependence of the diastereomeric ratio of **396a**,**b** on the reaction conditions was thoroughly investigated, but no pure diastereomers were obtained. The reaction, however, was *erythro*-stereoselective in the case of (*E*)-crotylsilanes and *threo*-stereoselective in the case of (*Z*)-crotylsilanes (no yields were given) (Scheme 111).

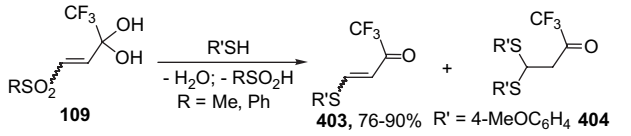
4.1.2. Reactions with *S*- and *O*-nucleophile. Both open-chain sulfonyl enone **397**[13] and cyclic sulfonyl enone **398**[105] react easily with various thiols to afford the β-sulfanyl-substituted ketones **399** and **400**. In the case of the reaction with dithiols, monoadducts **401** and diadducts **402** could be obtained (Scheme 112).

The same approach was used for the preparation of β-trifluoroacetylvinyl sulfides **403**. A number of thiols, even the weakly nucleophilic, *p*-nitrothiophenol, could enter into the reaction with the diol form **109**. As a rule, the target products can be prepared in very high yields. The ratio of isomers in the desired product depends upon the character of the thiol substituent. In the case of the more active *S*-nucleophile, *p*-methoxythiophenol, a mixture of the monoadducts **403** or diadducts **404** was obtained (Scheme 113).[62]

Alcohols react only with the most active keto sulfones and sulfoxides, e.g., α-acyl vinyl sulfones **405**. Thus, Michael

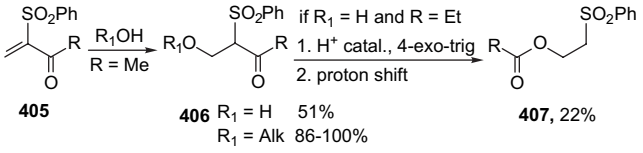


Scheme 112.

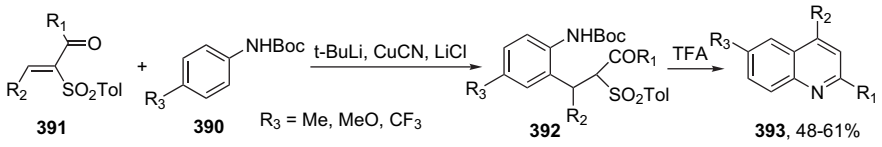


Scheme 113.

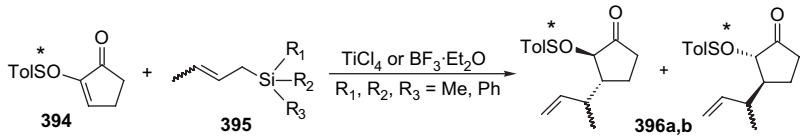
addition with alcohols under neutral conditions afforded functionalized ethers **406** in high yields. In the case of reaction with water the addition was rather slow and compound **406** (R_1=H) was found to be unstable. Rearrangement of this product **406** in acidic conditions at room temperature leads to the formation of the ester **407** (Scheme 114).[79]



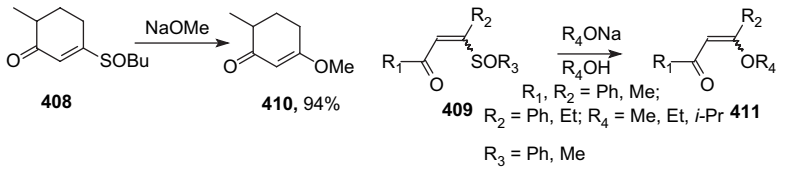
Scheme 114.



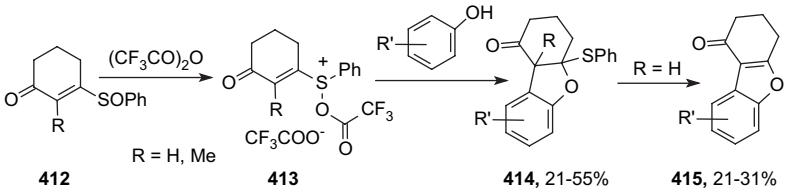
Scheme 110.



Scheme 111.



Scheme 115.

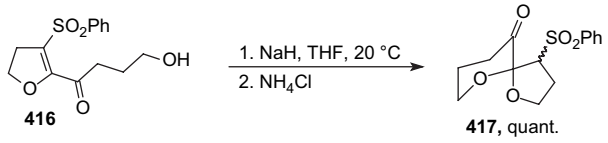


Scheme 116.

The less reactive β-sulfonyl and β-sulfinyl enones do not react with alcohols directly. However, the reaction takes place with alcoholates or in the presence of activating agents. β-Alkoxy enones **410** and **411** were successfully prepared by the reaction of sulfoxides **408** and **409** both with primary and secondary alcohols (Scheme 115).[166]

Activation of sulfoxides **412** can be achieved by treatment with trifluoroacetic anhydride. Further reaction of phenols with the double bond of the intermediate sulfonium salts **413** leads via **414** to the formation of substituted benzofurans **415** (Scheme 116).[167]

An example of intramolecular nucleophilic addition of *O*-nucleophiles has also been described. Hydroxy ketone **416** deprotonated by reaction with sodium hydride afforded an intramolecular cyclization to give the bicycle **417** in quantitative yield.[85] It is interesting that the cyclization leads to the product without substitution of the sulfonyl group (Scheme 117).

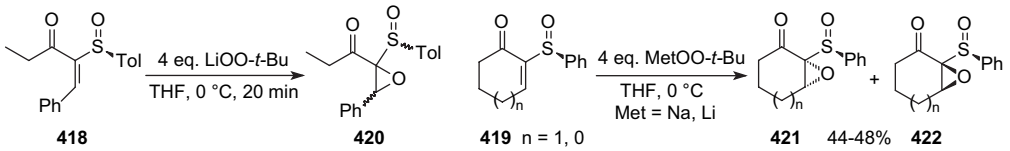


Scheme 117.

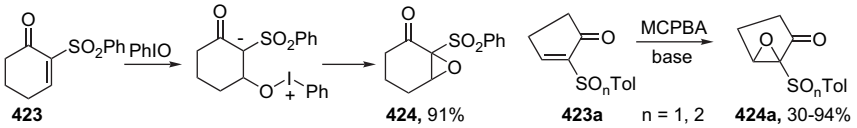
Nucleophilic epoxidation of open-chain sulfoxide **418** and cyclic sulfoxide **419** and the influence of the counterion in hydroperoxides were thorougly investigated. The reaction of sulfoxide **418** with LiOO-*t*-Bu proceeds with low selectivity and leads to a mixture of four diastereomers of the epoxy sulfoxides **420**, presumably, geometric and facial isomers.[168] Moreover, in all cases of the epoxidation of cyclic sulfoxides **419**, a mixture of diastereomers **421** and **422** was also obtained (Scheme 118).[169]

The *m*-chloroperoxybenzoate anion (generated from MCPBA and bases such as K_2CO_3 or KOH) was found to be a highly efficient nucleophilic epoxidizing reagent for sulfonyl and sulfinyl enones **423a** opening up an effective route to the epoxides **424a**. This reaction works only in the case of alkenes containing two electron-withdrawing groups at the same carbon and under mild conditions, which affect neither the other double bonds nor the electrophilic oxidizable centers such as sulfoxides.[170,171] PhIO was also used for the epoxidation of electron-deficient olefins, such as the sulfonyl enone **423** to **424** (Scheme 119).[172]

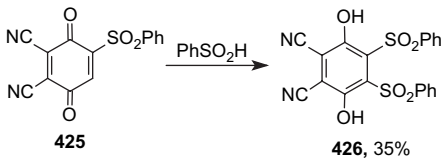
Addition of phenylsulfinic acid to the highly reactive sulfonyl quinone **425** led to the hydroquinone **426** having four electron-withdrawing groups (Scheme 120).[134]



Scheme 118.

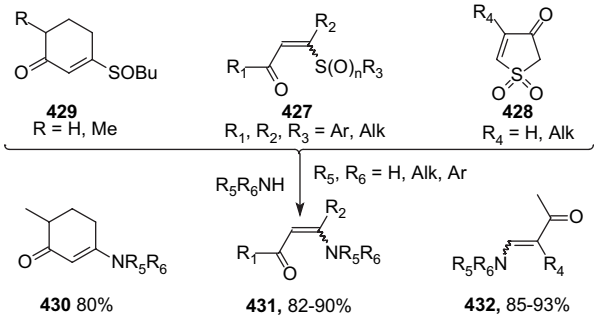


Scheme 119.

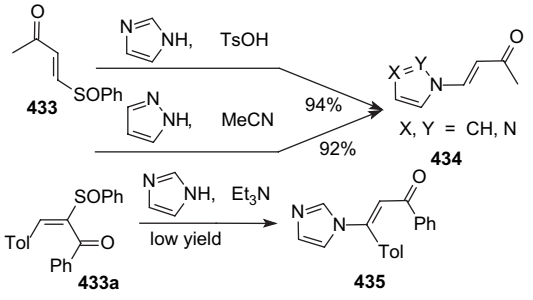


Scheme 120.

4.1.3. Reactions with *N*-nucleophiles. Amines and anilines react easily with sulfonyl enones **427** and **428** and sulfinyl enones **427** and **429** without additional activation to give the corresponding enamino ketones **430–432** (Scheme 121).[13,108,152,173,174]



Scheme 121.



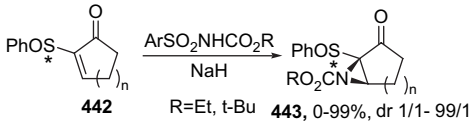
Scheme 122.

Nucleophilic substitution of the sulfoxide group in α-keto sulfoxide **433**[175] and β-keto sulfoxide **433a**[139] with imidazole and pyrazole leads to β-azolyl enones **434** and **435**. It should be noted that in the case of **434**, pure (*E*)-diastereomers of the desired products **434** were obtained that could be explained by steric hindrance at the β-carbon (Scheme 122).

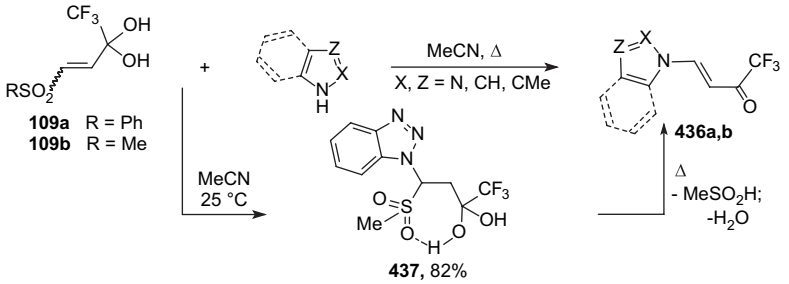
The reaction of β-sulfonyl trifluoromethyl enones **109a**,**b** as the hydrated diol form with various azoles such as pyrazole, imidazole, triazole, and its benzo analogues was also investigated. The addition–elimination reaction proceeds under mild conditions stereoselectively and permits a one-step preparation of CF_3-containing β-azolyl-substituted enones **436a**,**b** in high yield. In all cases, only the (*E*)-isomers of the unsaturated CF_3-ketones were obtained. In the case of the reaction with benzotriazole, the abnormal adduct **437** was isolated. This product has a non-eliminated $MeSO_2$ group and can be converted into the β-azolyl-substituted enone **436b** by heating that confirms an addition–elimination mechanism in this reaction (Scheme 123).[176]

The reaction of sodium azide with a strong Michael acceptor sulfone **438** afforded the azide **439** in 71% yield. Compound **439** was found to be fairly stable on storage in a refrigerator, but, on heating in chloroform or under UV irradiation, it underwent decomposition with the formation of bicyclic azirine **440** and amine **441** (Scheme 124).[177]

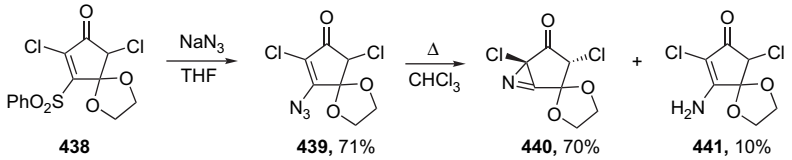
Highly functionalised aziridines **443** were easily obtained with high levels of diastereoselectivity (up to 98%) from 2-(phenylsulfinyl)-2-cycloalkenones **442** by treatment with arylsulfonyl oxycarbamates in the presence of bases under mild conditions. This use of bulky *tert*-butyl tosyloxycarbamate provided the best results in terms of both the chemical



Scheme 125.



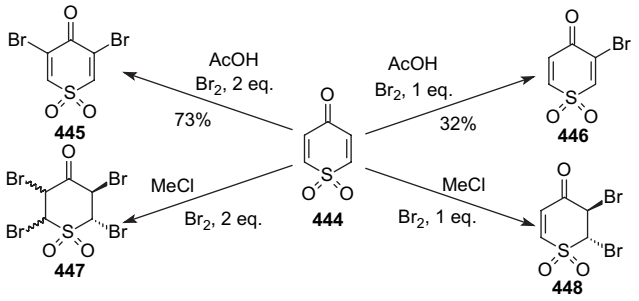
Scheme 123.



Scheme 124.

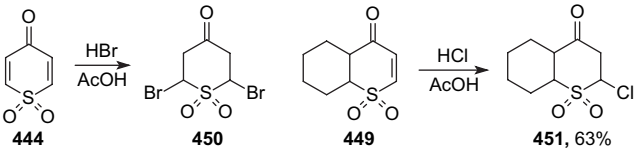
yields and the diastereomeric ratios for **443** (up to 99% and 99/1, respectively) (Scheme 125).[178]

4.1.4. Electrophilic addition. Reactions of electrophiles with sulfonyl and sulfinyl enones are rare and practically unknown, since the double bonds in these compounds are very electron deficient, because of the presence of two electron-withdrawing groups. The additions of halogens or hydrohalogens were investigated only for the most reactive cyclic sulfones. In the case of bromination of sulfone **444** in acetic acid, the corresponding vinyl bromides **445** and **446** were obtained, but, in chloroform, elimination of HBr did not take place and the reaction led to the dibromide **448** and tetrabromide **447** (Scheme 126).[109,179]



Scheme 126.

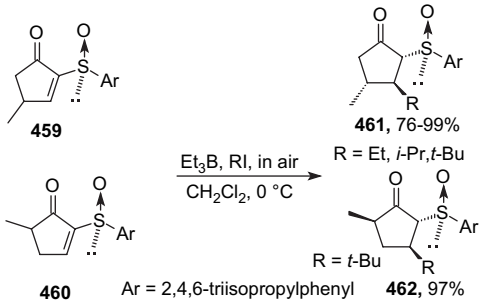
Hydrohalogenation of sulfones **444** and **449** was also carried out in acetic acid. It should be noted that, in this case, not only hydrobromination,[109] but also hydrochlorination,[110] was successfully carried out to give regioselectively β-halogenoketones **450** and **451**, because of more electron-withdrawing character of the keto group, compared to the sulfonyl group (Scheme 127).



Scheme 127.

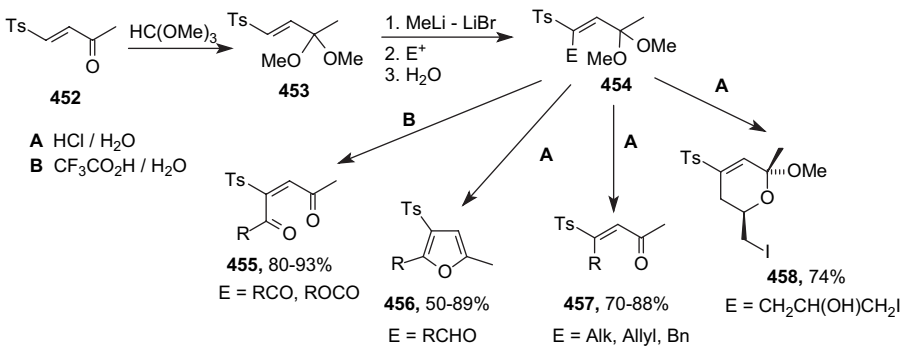
Protected keto sulfones can be metalated with strong bases. Subsequent transformation with a broad range of electrophiles opens up a valuable route to a variety of substituted derivatives. Thus, sulfone **452** was transformed into ketal **453** by treatment with trimethyl orthoformate. Lithiation of ketal **453** led to the corresponding anion (*E*)-4-lithio-4-tosylbutenone dimethyl ketal. Treatment of this intermediate with various electrophilic reagents afforded, after careful hydrolysis, the corresponding functionalized ketal derivatives **454**. When the alkylation of the anion with different alkyl halides was followed by acid hydrolysis, the expected alkylated tosyl ketones **457** were obtained directly. In the case of reaction with aldehydes in situ acid hydrolysis yielded 3-tosylfurans **456**. Monoprotected enediones and keto esters were deprotected by treatment with aqueous trifluoroacetic acid leading to cis-configurated enediones or keto esters **455**. The cyclic dihydropyran derivative **458** obtained from epichlorohydrin alkylation was isolated as the sole stereoisomer. Finally, the chlorine–iodine substitution to give **458** can be explained because the initially used methyllithium was prepared starting from methyl iodide (Scheme 128).[89]

4.1.5. Reactions with radicals. Reaction of alkyl radicals with a diastereomeric mixture of sulfoxides **459** or **460** leads to the formation of pure diastereomeric adducts **461** and **462** from the (4*R*)- and (5*R*)-isomers correspondingly, i.e., (*S*)-isomers did not react. This reaction could therefore be used for the kinetic resolution of diastereomeric sulfinyl cyclopentenones. The target products can be prepared in up to quantitative yields (Scheme 129).[20]

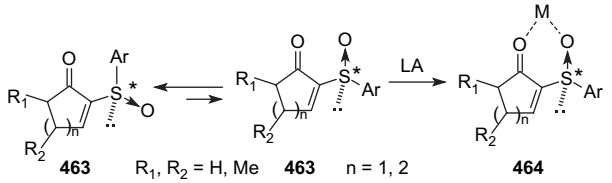


Scheme 129.

The same authors also investigated the influence of Lewis acids on the diastereomeric ratio of the products. The Lewis acid fixes the conformation in the starting sulfoxide **463** by formation of the corresponding chelate complex **464**.[21,180] In some cases, application of the Lewis acids reversed the ratio of diastereomers during the radical alkylation of keto sulfoxides (Scheme 130).

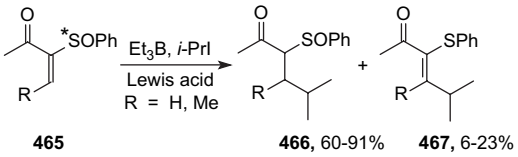


Scheme 128.



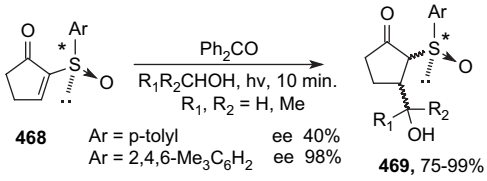
Scheme 130.

The reaction of acyclic chiral sulfoxides **465** with *iso*-propyl radicals leads to a mixture of racemic sulfoxides **466** and unsaturated sulfides **467** or simply to the racemic sulfoxides **466**. There are no studies on whether Lewis acids can improve this result (Scheme 131).[70]

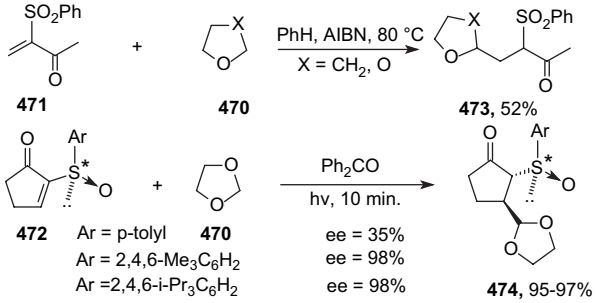


Scheme 131.

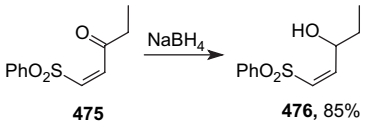
The radical photoaddition of alcohols to the chiral sulfoxides **468** affords the corresponding ketoalcohols **469** in good yields.[181] It was shown that the larger sulfinyl group leads to a better ratio of *R*/*S* isomers in the desired products **469** (Scheme 132).



Scheme 132.



Scheme 133.



Scheme 134.

THF and 1,3-dioxalane **470** could react with sulfone **471** and sulfoxides **472** in the presence of AIBN or under irradiation in a preparatively simple manner.[181] Thus, α-functionalized ethers **473** and **474** were isolated in good yields. In the case of application of chiral sulfoxides **472**, the best results (ee 98%) were obtained when the sulfinic group was sterically hindered (Scheme 133).

4.2. Reactions directed on carbonyl groups

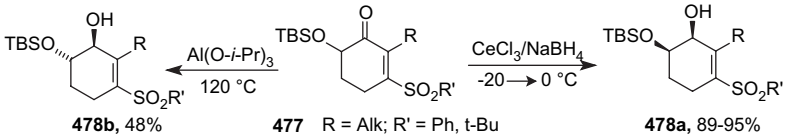
One of the most investigated reactions of the carbonyl group of sulfonyl and sulfinyl enones is the reduction to the corresponding allylic alcohols. The common non-chiral reducing agent used for this reaction is sodium borohydride in the presence of cerium(III) chloride. This reductant was successfully used for the reduction of sulfonyl ketones[64,78] and sulfonyl aldehydes[83,93] and, moreover, the formation of saturated byproducts did not occur. As an example, reduction of ketone **475** with $NaBH_4$ in methanol led to the corresponding allylic alcohol **476** (Scheme 134).[182]

An interesting example of the synthesis of different diastereomers depending on the reductant was investigated by Toth et al.[7,9] Thus, the reduction of ketones **477** by $CeCl_3$/$NaBH_4$ in MeOH/CH_2Cl_2 provided the *cis*-alcohols **478a**[7] in comparison with $Al(O\text{-}i\text{-}Pr)_3$ that provided only *trans*-**478b**,[9] which were used as precursors of *dl*-morphine (Scheme 135).

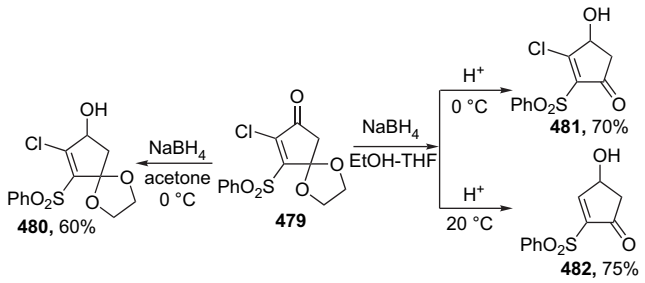
The reduction of **479** with $NaBH_4$ at 0 °C followed by quenching of the reaction mixture with water or acetone afforded the expected alcohol **480**; workup under acidic conditions furnished ketoalcohol **481**, which is the key synthon for a planned approach to prostaglandin synthesis. Sulfone **482**, the product of simultaneous reduction, dechlorination, and removal of the dioxolane protection, was obtained in 75% yield when the reaction was carried out at room temperature, and the excess of reductant was quenched with acid (Scheme 136).[183]

Reduction of the sulfone **483** could also be achieved with DIBAL-H and afforded the allylic alcohol **484** in quantitative yield.[9] In the case of reduction of ketone **485** with DIBAL in THF at −78 °C, the reaction was highly *syn*-stereoselective to give diol **486** in quantitative yield (Scheme 137).[75]

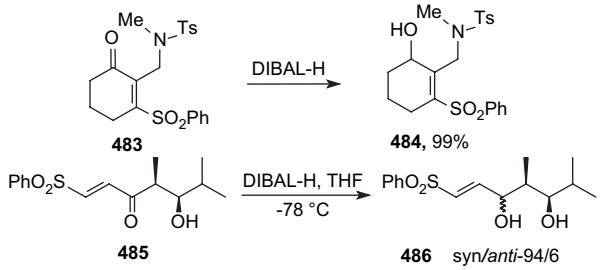
The enantioselective reduction of the carbonyl group of sulfonyl and sulfinyl enones was also studied (Scheme 138). The best results were obtained in the case of the application of catechol borane in the presence of oxazaborolidine **490**. *trans*-Ketone **487** was reduced to form **488a** in better yields



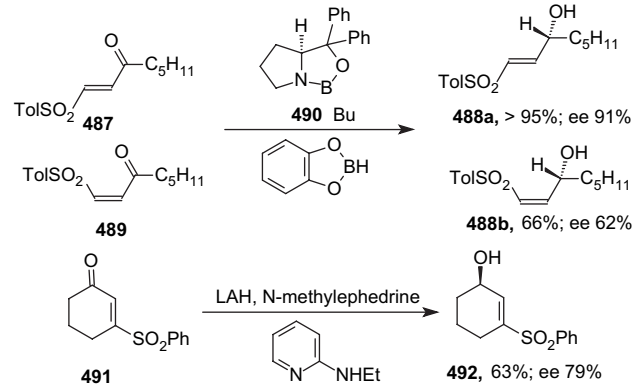
Scheme 135.



Scheme 136.



Scheme 137.

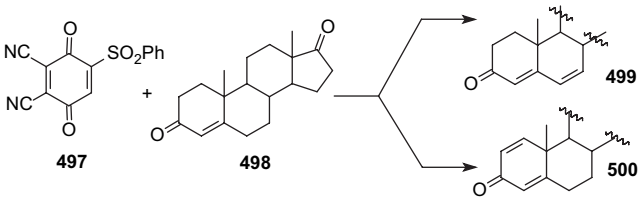


Scheme 138.

and higher enantiomeric purity than the *cis*-ketone **489** that is reduced to **488b**.[120,184] Reduction using lithium aluminum hydride in the presence of *N*-methylephedrine[64] permits the reduction of ketone **491** in moderate chemical and optical yields (**492**, 63 and 79% ee).

Fermentative reduction was also succesfully used for the enantioselective reduction of sulfonyl and sulfinyl enones. It was shown that sulfone **493** could be reduced to form the corresponding alcohol **494** in better yields and with higher enantioselectivity than sulfoxide **495** giving rise to **496** (Scheme 139).[56]

Some of the sulfinyl quinones have been used as oxidizing agents. Thus, quinone **497** in refluxing benzene reacts with



Scheme 140.

dehydrogenated 4-androstene-3,17-dione **498** to give mainly 1,4-dien-3-one **499** with a smaller amount of 4,6-dien-3-one **500**. However, even after 24 h the reaction mixture contained about 40% unchanged 4-androstene-3,17-dione **498**. Addition of *p*-toluenesulfonic acid facilitated dehydrogenation of the dione **498**, but afforded approximately equal parts of dienes **499** and **500** (Scheme 140).[134]

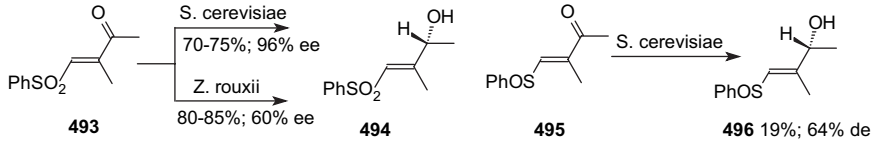
A typical property of the carbonyl group is the formation of hydrazones by reaction with different hydrazines. Thus, heating of **501** with 1 equiv of tosylhydrazide in ethanol produced a mixture of products **502** and **503**. The major component isolated was not the expected tosyl hydrazone **503**, but diazothiopyran **502**. The reaction was much cleaner when **501** was refluxed with 2 equiv of tosylhydrazide.[185] Dihydro derivative **504** produced, under the same reaction conditions, only the tosyl hydrazone **505**. The latter compound cannot readily be deprotonated and α-eliminate the toluenesulfinate to give the diazo compound under the reaction conditions (Scheme 141).[185]

Reaction of thiopyran dioxide **507** with 1 equiv of hydrazine produced only the hydrazone **508**. However, the same reaction run in the presence of 2 equiv of hydrazine gave the 2/1 adduct **506**. In Me_2SO-d_6, the diadduct **506** easily reverted to the hydrazone **508** on addition of D_2O (Scheme 142).[185]

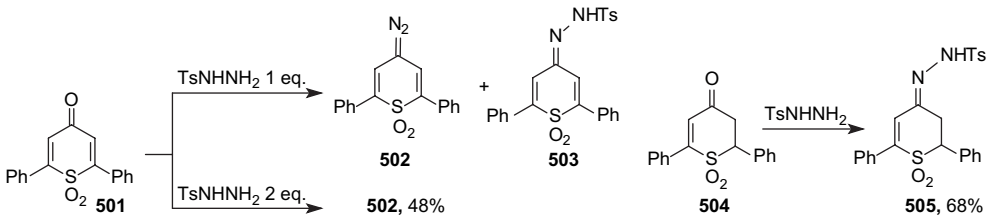
Surprisingly, the cyclic sulfone **509** did not form the corresponding heterocyclic compounds in the reactions with binucleophiles such as semicarbazide and hydroxylamine, and the reactions proceeded only on the carbonyl group to give **510** and **511**.[109] In addition, 2,4-dinitrophenylhydrazones can be prepared in quantitative yields without the formation of any byproducts (Scheme 143).[186]

In some cases, the carbonyl group of sulfonyl or sulfinyl enones must be protected for further reactions. Thus, sulfone **512** could be protected by reaction with trimethyl orthoformate to form the dimethyl acetal **513**.[89] The formation of thioacetals **516** from sulfonyl aldehydes **514** and thiol **515** was catalyzed by $BF_3 \cdot Et_2O$ (Scheme 144).[187]

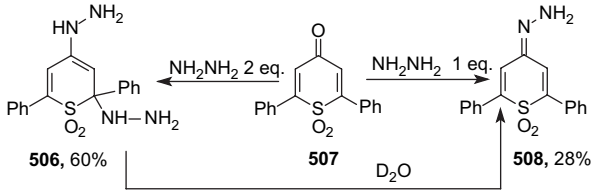
Trifluoroacetyl-containing sulfones and sulfoxides **108** are very hygroscopic and react easily with water to form the corresponding stable diols **109** as a mixture of *E*/*Z* isomers (Scheme 145).[62]



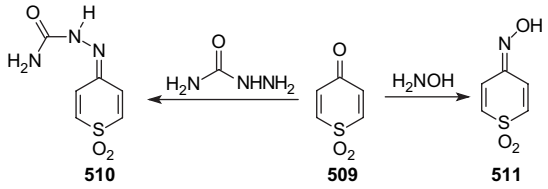
Scheme 139.



Scheme 141.



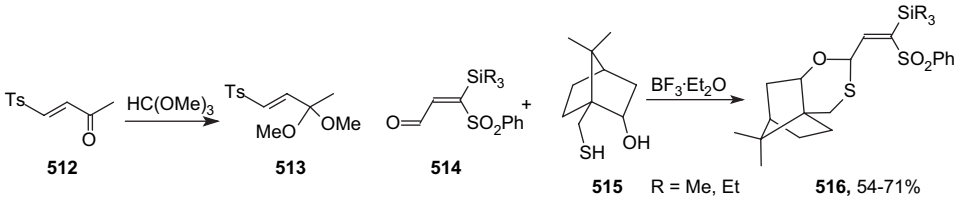
Scheme 142.



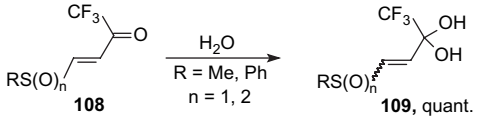
Scheme 143.

If there are two keto groups in the cis-position, an intramolecular cyclization is also possible. Treatment of enediones **517** with sodium hydroxide in ethanol yielded self-condensation to form the functionalized cyclopentenones **518**. Nucleophilic substitution of the sulfone moiety by the ethoxy group can take place either on the starting enedione **517** or following the cyclization step (Scheme 146).[89]

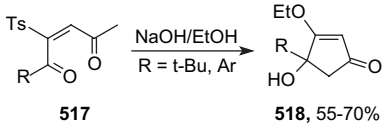
An interesting example of the preparation of a substituted chiral sulfinyl diene **520** was carried out by treatment of the starting chiral keto sulfoxide **519** with triethylamine in the presence of trimethylsilyl chloride.[188] Another synthesis of sulfinyl dienes **524** from chiral sulfinyl aldehyde **522** is based on the use of the Horner–Emmons reaction with **521** (via intermediate formation of **523**).[39] The best enantioselectivities (>98%) were obtained for X=CO_2Me and SO_2Ph (Scheme 147).



Scheme 144.



Scheme 145.

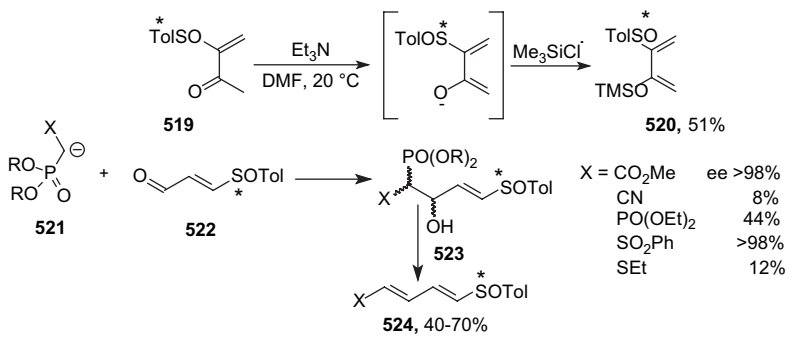


Scheme 146.

The reaction of sulfoxide **525** with phosphorous pentasulfide was investigated. Thionation of the carbonyl function was accomplished by the reduction of the sulfoxide group to the sulfide **526** (Scheme 148).[111]

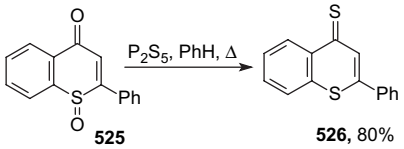
4.3. Desulfurization reactions

The most widely used reagents for the desulfurization of keto sulfoxides **527** and **529** are Raney-nickel[101] and tributyltin hydride, as a result **528** and **530** are formed.[189] The first reagent usually gives better yields and is easier to handle (Scheme 149).



Scheme 147.

The thermal elimination of PhSOTMS by heating the diastereomeric sulfoxides **531** and **532** leads to the formation

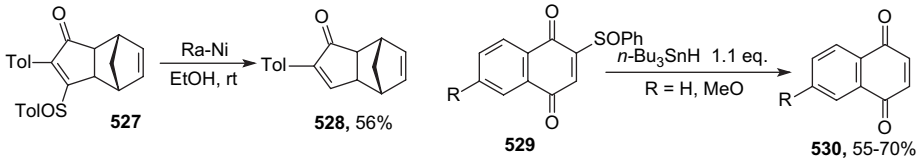


Scheme 148.

of an acetylenic ketone **533**. In the case of a cis-orientation of the trimethylsilyl and sulfinyl groups **531**, elimination proceeded at a lower temperature and gave better yields (Scheme 150).[58,190]

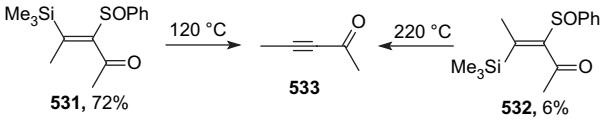
Reductive desulfinylation of cyclic keto sulfoxide **537** led to the chiral 5-methylcyclopentenone **539** through the stages of reduction of the double bond (**538**) and pyrolytic elimination of the sulfinyl group.[20] It should be noted that both steps give quantitative yields (Scheme 152).

Reductive cleavage of the sulfonyl group of sulfonyl enones **540** was achieved by initial protection of the carbonyl functionality by cyanosilylation using trimethylsilyl cyanide followed by aluminum amalgam reduction giving **542**. The overall sequence was completed by a cesium fluoride-induced desilylation reaction. Desulfonylation without protection of the carbonyl group resulted in the formation of the saturated ketone **541**.[104,105] However, the application of an aluminum amalgam reduction was successful in the



Scheme 149.

An interesting two-step procedure for the desulfurization of sulfoxides **534** has been described. Treatment of **534** with a trifluoroacetic anhydride/sodium iodide system in acetone leads to reduction of the sulfoxides to sulfides **535.** The prepared sulfides were reduced to the allylic alcohols followed by transformation to the enones **536** using mercury(II) chloride (Scheme 151).[101]

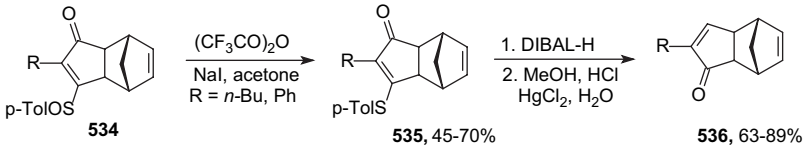


Scheme 150.

case of cyclic acyl vinyl sulfones **543** to give **544** (Scheme 153).[191]

Some examples of SO_2 extrusion reactions are also described for sulfonyl enones. In most cases, the reactions led to carbon–carbon single bond formation. Thus, pyrolysis of cyclic sulfone **545** gave the ketones **546** and **547**.[192] However, pyrolytic 1,4-elimination of SO_2 from dihydrothiophene dioxide **548** gave a reactive diene **550** via intermediate **549** that could be involved in a Diels–Alder reaction with *N*-phenylmaleimide to form the adduct **551** (Scheme 154).[193,194]

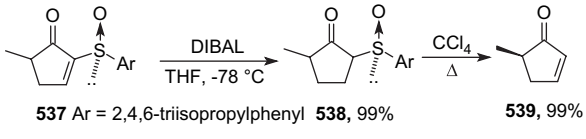
An unusual type of sulfonyl group elimination is the acid-catalyzed reaction of cyclic sulfones **552** (Scheme 155)



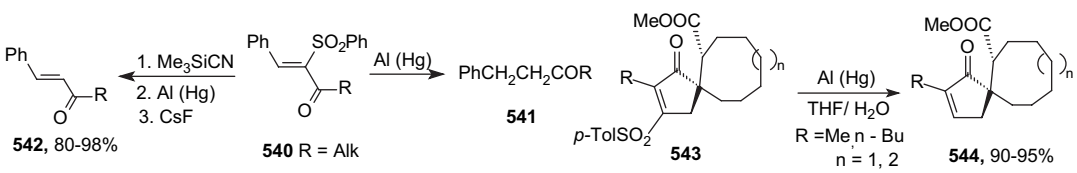
Scheme 151.

with the formation of substituted acylthioketenes **553** and **554**.[195]

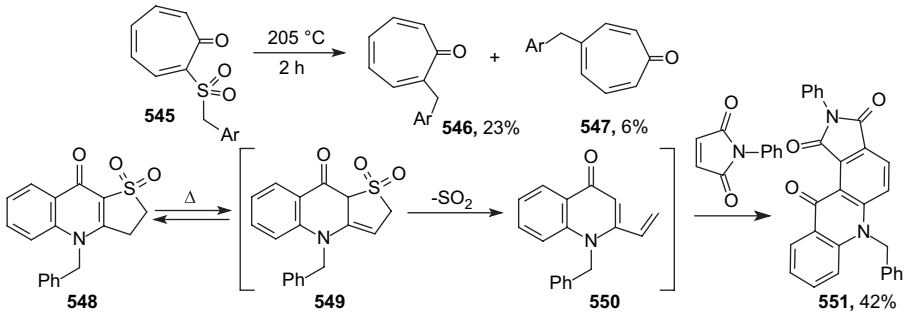
Desulfurization of a sulfonyl enone **556** (prepared from **555**) was used as a key step in the synthesis of lasubine II **557**—a quinolizidine alkaloid isolated from plants of the Lythraceae family.[196] A similar approach was used for the



Scheme 152.

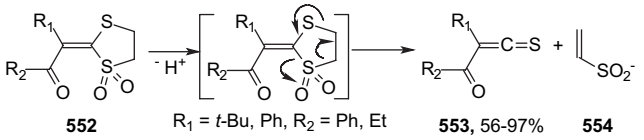


Scheme 153.



Scheme 154.

synthesis of myrtine **558**, an alkaloid found in *Vaccinium myrtillus*. In the latter case reductive desulfonylation with lithium 4,4′-di-*tert*-butylbiphenylide (LDBB) produced racemic myrtine **558** (Scheme 156).[197]



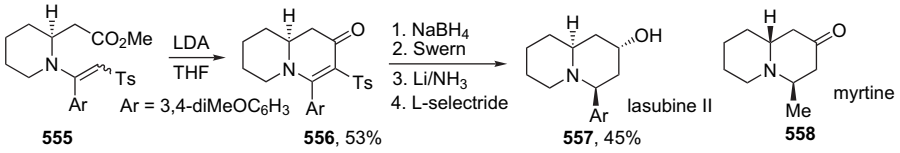
Scheme 155.

4.4. Cycloaddition reactions

4.4.1. Diels–Alder reactions. Diels–Alder and other cycloaddition reactions are probably the most effective transformations used for sulfonyl and sulfinyl enones. Two new chemical bonds are formed and much more complex molecules can be prepared, starting from simple, readily available precursors. Intensive investigations of vinyl sulfones and vinyl sulfoxides in Diels–Alder reactions began in 1980. The cycloaddition chemistry of simple vinyl sulfones and ethynyl sulfones as well as sulfoxides has been reviewed in detail by De Lucchi and Pasquato,[198] Simpkins,[199] Back,[2] and Pelissier.[3] α- and β-Sulfonyl and sulfinyl enones are very powerful dienophiles, opening up routes to various types of cyclic compounds. The Diels–Alder reaction for these dienophiles is a very popular type of transformation, due to the mild reaction conditions and also possibility of removing the sulfur fragment and constructing complex molecules including chiral derivatives. Many syntheses of natural compounds have been based on the use of this strategy.

The [4+2] cycloaddition of β-ketovinyl sulfones **559** with various dienes has been thoroughly investigated.[200,201] In some cases (R=Alk), the reaction was carried out on activated silica gel.[200] The target Diels–Alder adducts **560**, **563**, **565**, and **567** were prepared in almost quantitative yield. However, the stereoselectivity of the reaction was very low (usually, the *endo*/*exo* ratio was 1/1). The reaction with 1-methoxycyclohexa-1,3-diene shows that the regiochemistry is controlled mainly by the carbonyl group (ratio of isomers of **565** was 12/1). The sulfonyl group can be easily eliminated from the adducts with base to give **561**, **564**, **566**, and **568**. As a result, sulfonyl enones **559** behave as synthetic equivalents of acetylenic ketones (Scheme 157). In some cases aromatization to form benzene derivatives **562** or Michael addition **569** takes place.

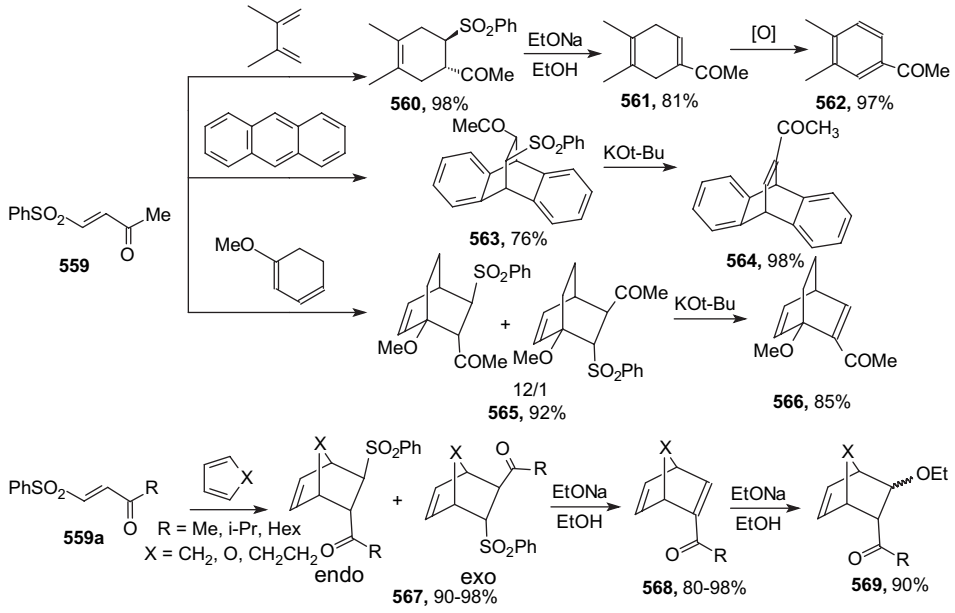
α-Ketovinyl sulfone **570** has also been applied in Diels–Alder reactions.[79] Cycloaddition reactions occurred with conjugated dienes giving [4+2] adducts **571–573** in good yields under mild conditions. In the case of cyclopentadiene and cyclohexadiene, $PhSO_2$ *endo*-adducts **571b** were formed preferentially. The formation of the *exo*-sulfonyl adduct of **571b** was detected only by NMR as a trace. Bicyclic dihydropyran **571a** is formed as a byproduct in the reaction with cyclic dienes. Its formation was explained either by cycloaddition followed by a subsequent Cope rearrangement of **571b** or by a direct hetero-Diels–Alder reaction with inverse electron demand (Scheme 158).



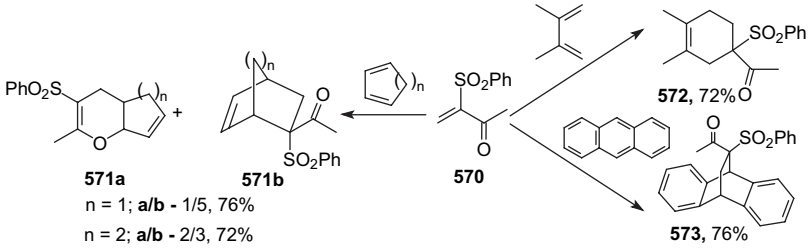
Scheme 156.

It was found that the reaction of chiral α-sulfinyl enone **574** with cyclopentadiene leads to a separable mixture of diastereomeric *endo*-Ac adducts **575a**,**b** in 94% yield. After separation of the diastereomers, oxidation of the cycloadducts with MCPBA and desulfonylation with sodium amalgam open up a simple route to both enantiomers of the bicyclic ketones **576a**,**b** and **577a**,**b** (Scheme 159).[80]

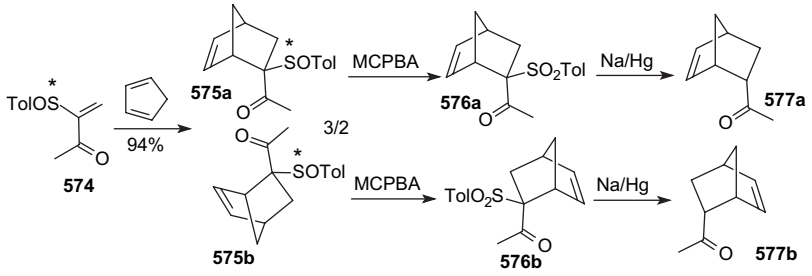
It was demonstrated that the stereoselectivity of the cycloaddition of cyclopentadiene with chiral cyclic sulfoxides **578** is low. Usually, a moderate ratio of *exo*/*endo* isomers **579a**,**b** is formed. All attempts to improve the ratio of isomers by changing the reaction conditions or by the addition of various Lewis acids failed. However, these Diels–Alder reactions are completely diastereoselective, showing an outstanding efficiency of the sulfinyl group as a chiral auxiliary (Scheme 160).[202] Subsequent reduction gave ketones **580a**,**b**.



Scheme 157.



Scheme 158.

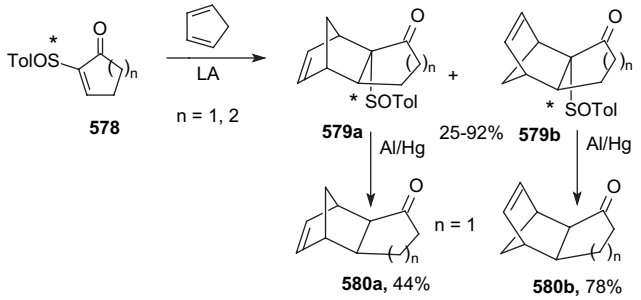


Scheme 159.

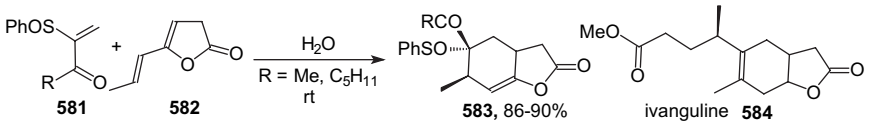
A Diels–Alder reaction of sulfinyl enones **581** with **582** was used for the synthesis of a natural sesquiterpenoid, ivanguline **584**. The formation of cycloadducts **583** proceeds stereoselectively in high yield under mild conditions (Scheme 161).[203]

In the case of the reaction of β-ketovinyl sulfoxides **585** with cyclopentadiene, a mixture of regioisomers **586a**,**b** was formed. Cycloaddition of linear dienes was accompanied by the elimination of sulfinic acid, giving 1,4-cyclohexadienes **587** that aromatized spontaneously to the corresponding aryl ketones **588** in air (Scheme 162).[204]

Later, a more detailed study of the Diels–Alder reaction of enantiomerically pure keto sulfoxides **589** with cyclopentadiene showed that the reaction leads to the formation of four easily separable diastereomers **590**. The effect of

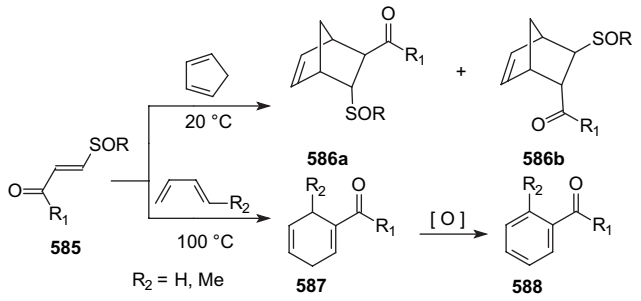


Scheme 160.

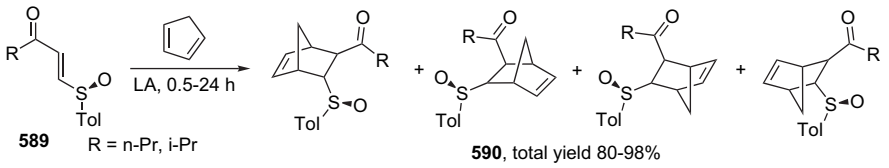


Scheme 161.

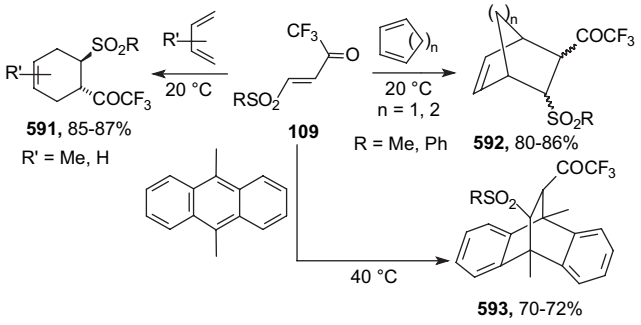
several Lewis acids on the reaction was studied, demonstrating a high *endo* selectivity with respect to the carbonyl group and a moderate diastereoselectivity using $BF_3 \cdot Et_2O$ as catalyst. The reactivity of compounds **589** and their *endo* selectivity are both higher than those observed for the corresponding (*E*)-3-sulfinyl acrylates.[40] The total yield of cycloadducts **590** is almost quantitative; although as a rule, the selectivity was not high (Scheme 163).



Scheme 162.



Scheme 163.

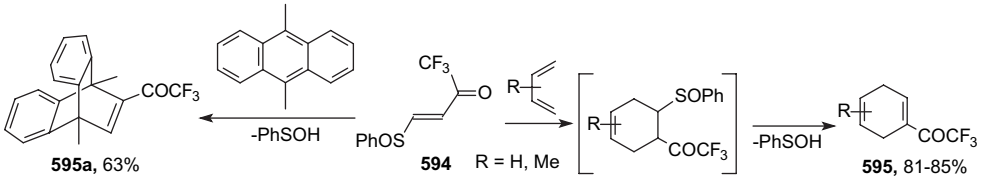


Scheme 164.

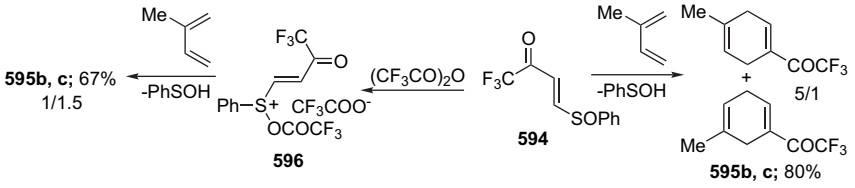
It was found that both ketovinyl sulfones **109** and the corresponding hydrates **110** are highly reactive dienophiles. Their reactions with cyclic and linear dienes proceed easily, even at room temperature in CH_2Cl_2, to form the cycloadducts **591** and **592** in high yield. Only in the case of the reaction with 9,10-dimethylanthracene a prolonged reflux in CH_2Cl_2 was required to form **593**. The reaction proceeds stereoselectively, but not regioselectively, in the case of dienes such as isoprene. The influence of a series of Lewis acids, e.g., BF_3, $TiCl_4$, $Eu(fod)_3$, and $ZnCl_2$, on the regio- and stereochemistry of the cycloaddition was also investigated. In some cases, the addition of a Lewis acid leads to an insignificant increase in the yield (5–10%), but it does not affect the regioisomeric ratio. This could be attributed to the possibility of coordination with both the carbonyl and the sulfonyl groups with a nearly equal probability, due to the low nucleophilicity of the CF_3CO carbonyl group (Scheme 164).[205]

The corresponding sulfoxide **594** was found also to be a highly active dienophile. Reaction of linear dienes with **594** results in the formation of very unstable cycloadducts. After spontaneous elimination of the sulfinyl group the corresponding α,β-unsaturated trifluoromethyl ketones **595** were obtained. In the case of reaction with 9,10-dimethylanthracene prolonged reflux in CH_2Cl_2 gave the target product **595a** in 63% yield. Probably this is connected with the low stability of the sulfoxide **594** at higher temperatures (Scheme 165).[206]

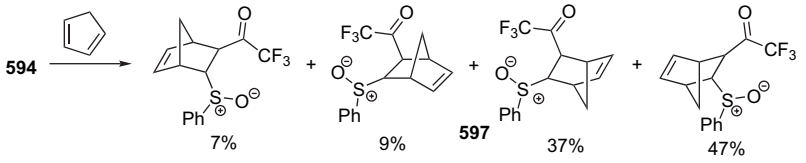
The reaction of ketone **594** with isoprene proceeds stereoselectively, forming the isomeric cycloadducts **595b**,**c** in a 5/1 ratio. Activation of **594** by treatment with TFAA leads to the more reactive dienophile—sulfonium salt **596**—which gives opposite regioselectivity, the ratio of isomers **595b**,**c** becoming 1/1.5 (Scheme 166).[206]



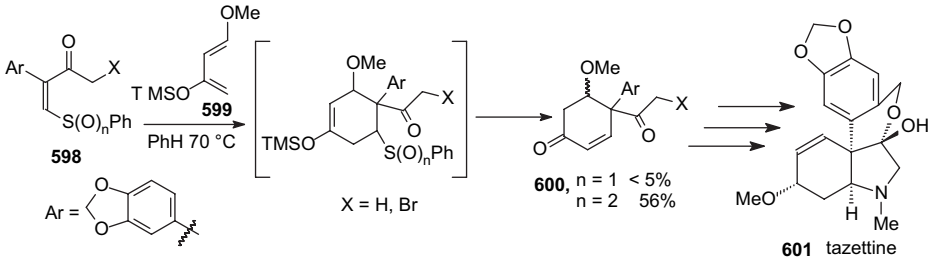
Scheme 165.



Scheme 166.



Scheme 167.



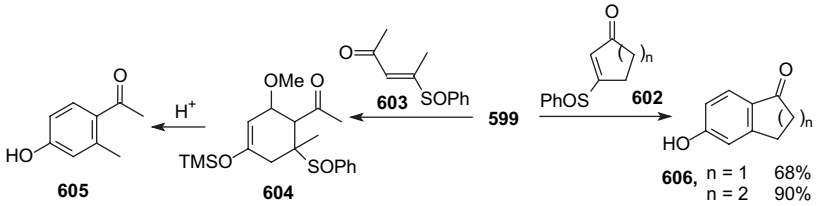
Scheme 168.

A low stereoselectivity is also observed in the case of the reaction of sulfoxide **594** with cyclopentadiene. A mixture of four isomers **597** was isolated. In this case, elimination of the sulfinyl group did not take place. Cycloadducts **597** having an *endo*-oriented $COCF_3$ group were predominant. In order to improve the stereoselectivity, reaction of the sulfoxide **594** was activated by TFAA to give the sulfonium salt **596**. Its reactions with cyclopentadiene proceeded at −35 °C in CH_2Cl_2 during 10 min. However, as in the reaction with the non-activated sulfoxide, a mixture of regioisomers **597** was obtained. An increase in the *endo*-SOPh cycloadducts **597** and equalizing of each diastereomeric pair ratio were observed, in comparison with the reaction of sulfoxide **594** (Scheme 167).[206]

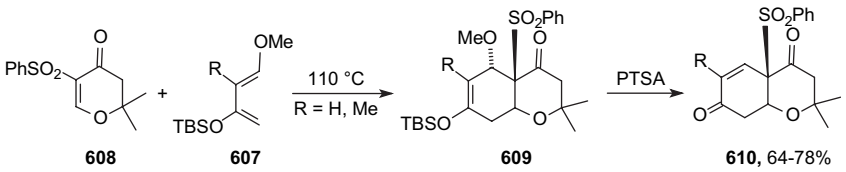
The Amaryllidaceae alkaloid tazettine **601** and its analogues have attracted much attention, due to their antitumor properties. The reaction of sulfonyl and sulfinyl enones **598** with the Danishefsky diene **599** was used as a key step for the synthesis of tazettine. The reaction was found to be highly regioselective, but the stereoselectivity of the cycloaddition is not high. Usually, a mixture of stereoisomers **600** involving the position of the methoxy group was isolated (Scheme 168).[207,208]

In the case of the cycloadducts **604** and **606** prepared from sulfoxides **602** and **603**, elimination of a methoxy group and sulfinic acid permits the synthesis of the corresponding aromatic ketones **605** and **606**. The method opens up a route to substituted phenols. An orientational dominance is exerted by the carbonyl group over the phenylsulfinyl function. Thus, sulfoxides **602** and **603** gave selectively phenols **605** and **606** after cycloaddition with diene **599** (Scheme 169).[209,210]

Another example of the reaction of silyloxy-substituted dienes **607** with sulfonyl dihydropyrone **608** was directed to the synthesis of 1-oxadecalin skeleton—the structural core of a variety of diterpenoids. [2+4] Cycloaddition was fully regioselective and almost fully stereoselective. Cycloadducts **609** were converted into the diketones **610** by hydrolysis with PTSA (Scheme 170).[211,212]

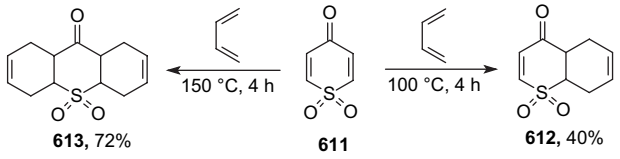


Scheme 169.



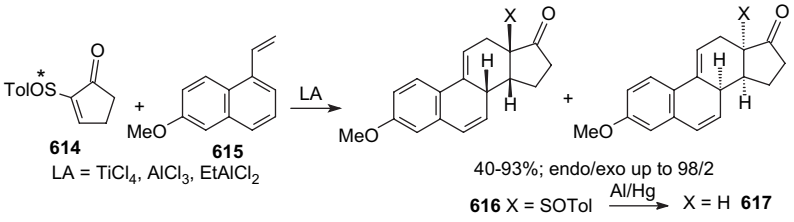
Scheme 170.

Cyclic ketovinyl sulfones, e.g., 4*H*-thiopyran-4-one-1,1-dioxide **611**,[109] react easily with 1,3-butadiene and both the monoadduct **612** and the diadduct **613** can be prepared. The preparation of the diadduct **613**, hovewer, requires a higher reaction temperature (Scheme 171).



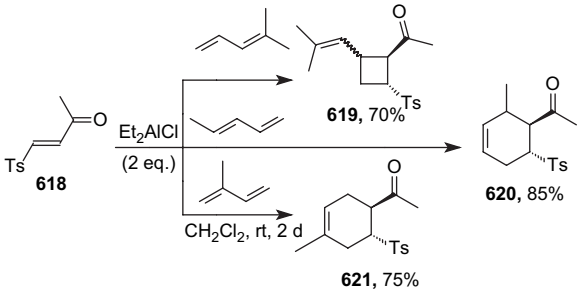
Scheme 171.

The cycloaddition of chiral sulfoxide **614** with Dane's diene **615** catalyzed by Lewis acids was studied as a straightforward approach to steroid skeletons.[213] The reaction of (*S*)-2-*p*-tolylsulfinyl-2-cyclopentenone **614** catalyzed by $EtAlCl_2$ yields *endo* selectively (controlled by the CO group) and regioselectively (controlled by the substituent at C-2 of the diene) the corresponding *endo* Diels–Alder adduct **616**. Other Lewis acids give less selective cycloaddition. After desulfonylation of the cycloadducts **616**, optically pure perhydro-cyclopenta[*a*]phenanthrenes **617** were prepared (Scheme 172).



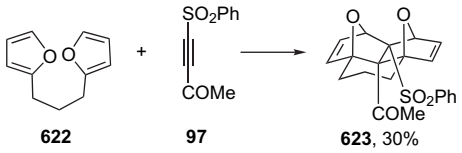
Scheme 172.

The Diels–Alder reactions of ketovinyl sulfone **618** with linear dienes in the presence of Et_2AlCl led to either [2+2] cycloadduct **619** or [2+4] cycloadducts **620** and **621**.[18] The steric size of the dienes is the determining factor that influences the ratio of products. Thus, in the case of sterically demanding dienes, e.g., 1,1-dimethylbutadiene, the [2+2] cycloaddition takes place; other dienes give the Diels–Alder cycloadducts (Scheme 173).



Scheme 173.

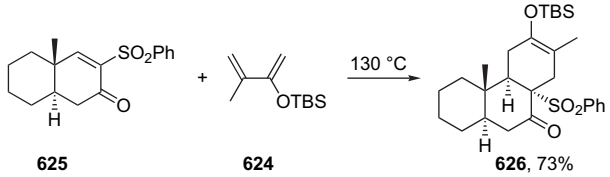
Acetylenic keto sulfone **97** behaves as an unsymmetrical diactivated dienophile, giving the *exo–exo* cycloadduct **623** as a single regioisomer in the reaction with bis-furan **622**. Keto sulfone **97** gave a low yield of the cycloadduct **623**, due to its instability and rapid polymerization (Scheme 174).[55]



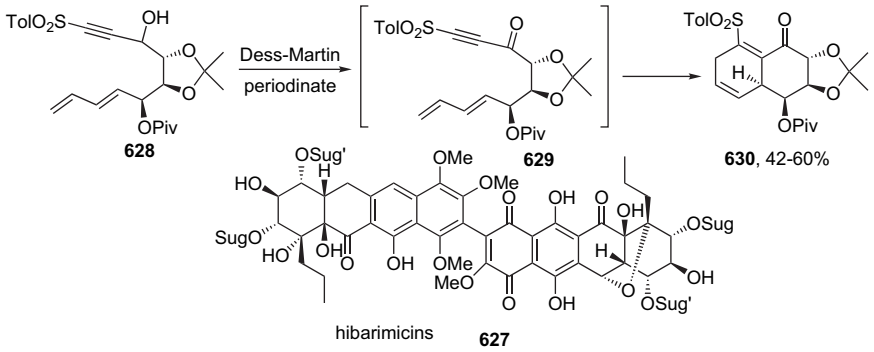
Scheme 174.

A novel and effective approach to 8,10-dimethyl *anti–syn–anti*-perhydrophenanthrene carbon skeleton beginning from the Wieland–Miescher ketone has been established.[214] As a key step, a Diels–Alder reaction of the readily accessible diene **624** with the sulfonyl enone **625** was studied. The cycloaddition proceeds fully stereo- and regioselectively to form the target adduct **626** in high yield (Scheme 175).

Hibarimicins A, B, C, D, and G **627** are among the most complex aromatic polyketide dimeric microbial secondary metabolites isolated. In addition to their unique structural features, the hibarimicins possess important biological activity, specifically inhibiting protein tyrosine kinase activity with little effect on protein kinases A and C. Cycloaddition reactions have been used to prepare the cycloadduct **630** possessing an array of four stereocenters common to the aglycon of hibarimicin **627**. Spontaneous intramolecular



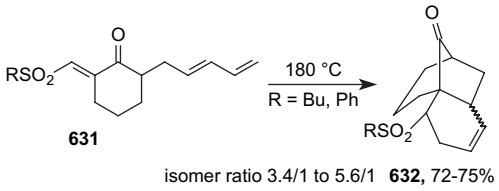
Scheme 175.



Scheme 176.

Diels–Alder cyclization of ketone **629** (prepared in situ from **628**) affords a single cycloadduct **630** in 42–60% yield (Scheme 176).[215]

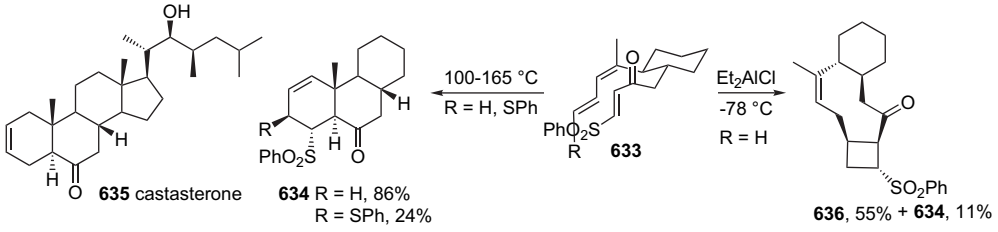
An efficient and highly stereoselective synthesis of functionalized tricyclo[6.3.1.0^{1,6}]dodec-4-enes **632**, useful synthons for constructing various natural products, has been described. The key feature of this synthesis was a stereoselective intramolecular Diels–Alder reaction of the cyclohexanone derivatives **631** bearing a sulfonyl group (Scheme 177).[49]



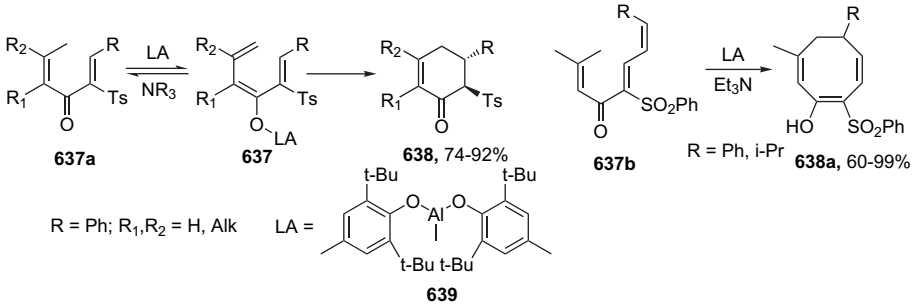
Scheme 177.

Another example of intramolecular Diels–Alder reaction with sulfonyl enones **633** was directed to the synthesis of the *trans–anti–trans* A–B–C ring system of castasterone **635**, important plant-growth-regulating steroid. The use of the sulfonyl enones **633** permits the preparations of the target cycloadducts **634** under lower temperatures and in high yields. The reaction proceeds highly selectively and the key precursor **634** for castasterone is prepared easily. The same authors showed that in the case of the use of Et_2AlCl as a Lewis acid for the activation of **633**, the main direction is not a Diels–Alder reaction, but a [2+2] cycloaddition to give **636** (Scheme 178).[216]

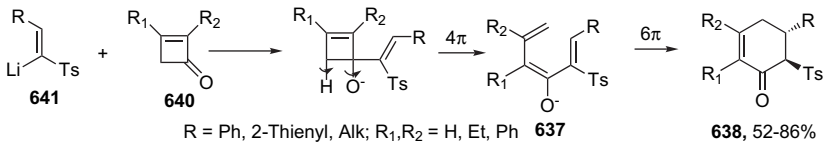
Sulfonyl-substituted enolates **637**, generated in situ by enolization of the readily available divinyl ketones **637a**, undergo an intramolecular Diels–Alder reaction leading to the functionalized cyclohexenones **638**. Generation of the extended enolates **637** from the α,β-unsaturated carbonyl compounds **637a** was accomplished by treatment with a sterically demanding aluminum Lewis acid **639** (2.0 equiv) and NEt_3 (1.1 equiv) in toluene at room temperature. Many of cycloadducts **638** were prepared in very high isolated yields. In the case of the reaction of sulfonyl-substituted trienones **637b**, the cyclization could be applied to the synthesis of cyclooctatriene derivatives **638a**. It was demonstrated that electrocyclization gives the target product **638a** in up to 99% yield (Scheme 179).[217]



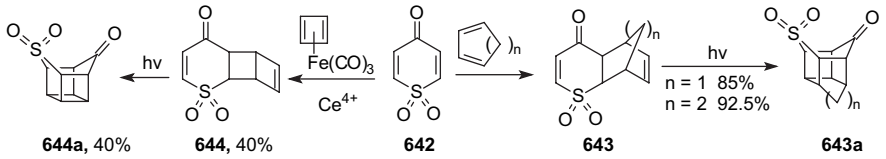
Scheme 178.



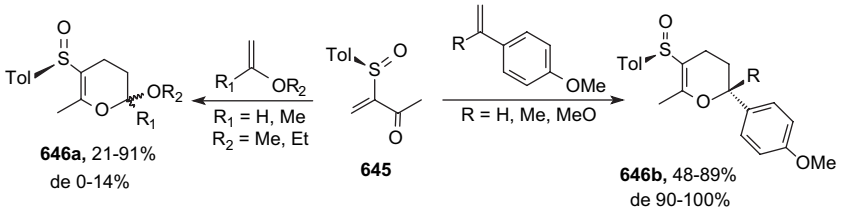
Scheme 179.



Scheme 180.



Scheme 181.



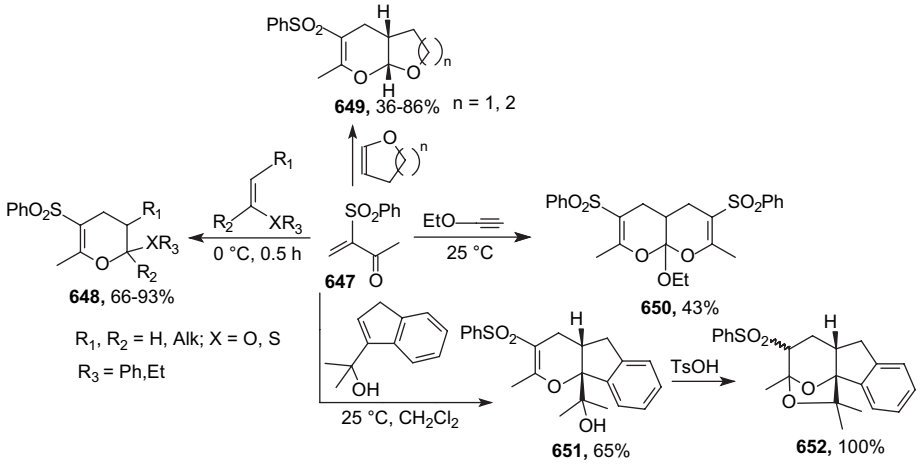
Scheme 182.

An alternative approach is based on nucleophilic addition–4π-ring opening–6π-ring closing cascade reactions between cyclobutenones **640** and *R*-lithio-α,β-unsaturated sulfones **641**. Strategic incorporation of electron-withdrawing groups at the C-2 position of the 3-oxidohexatrienes **637** significantly lowers the activation energy of the 6π-electrocyclizations, which proceed under mild conditions (Scheme 180).[218]

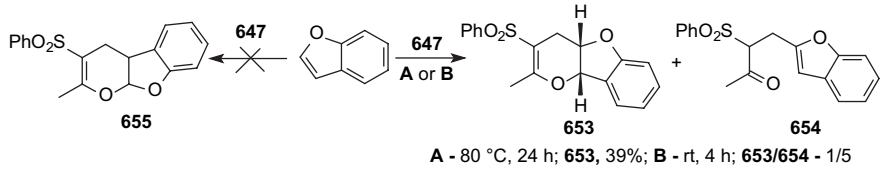
A Diels–Alder reaction of 1,4-thiapyrone-1,1-dioxide **642** with cyclopentadiene, cyclohexa-1,3-diene, and (generated in situ) cyclobutadiene was used for the preparation of some cage sulfur compounds **643a** and **644a**.[219] The reaction proceeds highly selectively to form only the *endo*-adducts. Cycloadducts were converted into the polycyclic products by irradiation (Scheme 181).

Not only can cyclohexane derivatives be prepared using a Diels–Alder strategy with α-ketovinyl sulfones[79] and α-ketovinyl sulfoxides, but they are also excellent partners for hetero-Diels–Alder reactions with inverse electron demand. Electron-rich 2π compounds such as vinyl ethers and sulfides as well as some inactivated alkenes react very easily to form substituted pyran derivatives. Heterocycloaddition of optically active (*S*)-(+)-3-*p*-tolylsulfinyl but-3-en-2-one **645** was successfully achieved with various electron-rich dienophiles in extremely mild and non-catalytic conditions. The nature of the dienophile turned out to play a critical role in the stereochemical outcome of the reaction: <14% de with vinyl ethers to form **646a** and >94% de to give **646b** with styrenes (Scheme 182).[220]

A number of alkenes as dienophiles have been studied in the hetero-Diels–Alder reactions with inverse electron demand with sulfonyl enone **647**. Electron-rich alkenes including sterically hindered alkenes react very well, usually at room temperature. The target cycloadducts **648** and **649** are



Scheme 183.

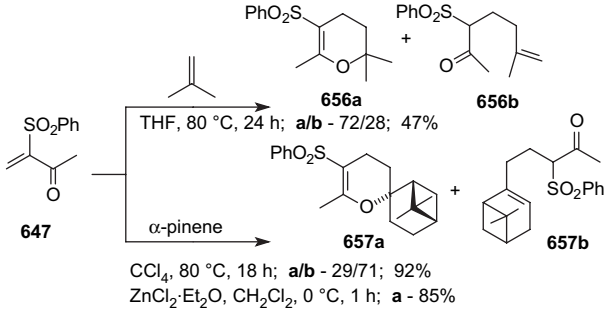


Scheme 184.

formed stereo- and regioselectively in good isolated yields, both for linear and for cyclic dienophiles. For ethoxyacetylene, only a 2/1 adduct **650** was isolated. The reaction of sulfone **647** with an indene allylic alcohol proceeds regio- and stereoselectively to form the cycloadduct **651** as the only isomer. Subsequent TsOH-promoted cyclization proceeds quantitatively to form the tetracyclic product **652** (Scheme 183).[79]

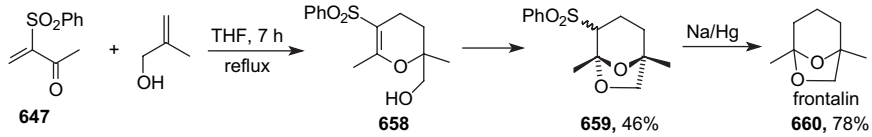
The reaction with benzofuran is of interest because the 'wrongly oriented' regioisomer **653** was isolated after comparatively forcing conditions, probably due to isomerization of the initially formed adduct **655** (thermodynamic control). In addition, the uncyclized Michael product **654** was isolated when the reaction was carried out under milder conditions (Scheme 184).[79]

A similar picture was observed for the reaction of **647** with some alkenes. Aside from the cycloadducts formed via a Diels–Alder reaction (**656a** and **657a**), the ene products **656b** and **657b** were also isolated in the reaction of sulfone **647** with isobutene and α-pinene. In the reaction with (−)-β-pinene, the ene product **657b** predominated over cycloadduct **657a** under thermal activation, but in the presence of $ZnCl_2$, cycloadduct **657a** arose as the only product in high yield. Tricycle **657a** contains part of the skeleton of robustadials A and B, which are used as antimalarial agents and isolated from the leaves of *Eucalyptus robusta* Smith (Myrtaceae) (Scheme 185).[79]



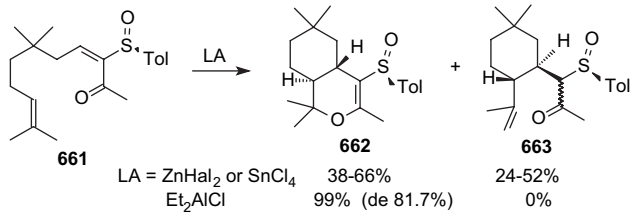
Scheme 185.

A Diels–Alder reaction followed by cyclization was used for the synthesis of an important pheromone, frontalin **660**. The sulfonyl precursor **659** was obtained by the reaction of **647** with methallyl alcohol in one pot. A mixture of *exo*- and *endo*-isomer **659** was obtained in a 1/1 ratio. Reductive desulfonylation with sodium amalgam afforded racemic frontalin **660** (Scheme 186).[79]



Scheme 186.

Intramolecular Diels–Alder reactions with inverse electron demand involving ketovinyl sulfones or ketovinyl sulfoxides are rather rare. An elegant example was carried out on **661** giving the bicyclic product **662**. Application of $ZnHal_2$ or $SnCl_4$ led to the target cycloadduct **662** and a competitive ene reaction with the formation of **663** as byproduct. The best result was obtained when Et_2AlCl had been used as the Lewis acid. In that case, exclusive formation of **662** was observed (Scheme 187).[29]

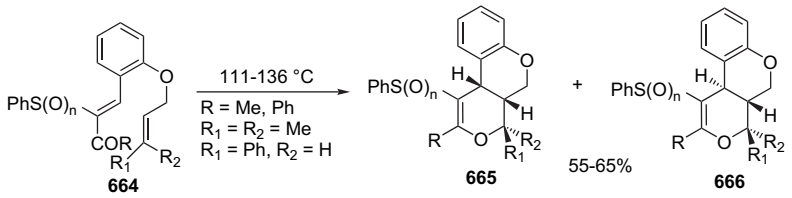


Scheme 187.

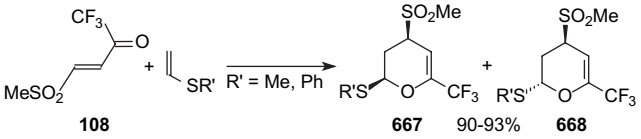
The reaction of 1-(phenylsulfinyl)- and 1-(phenylsulfonyl)-2-propanone as well as 2-(phenylsulfonyl)-acetophenone with 2-(3-methyl-2-butenyloxy)- and 2-((*E*)-3-phenyl-2-propenyloxy)-benzaldehyde yielded the corresponding Knoevenagel condensation products **664**. These compounds **664** underwent intramolecular cycloadditions, affording the *cis*-fused 2*H*-pyran derivatives **665** as the major products. Generally, the cis-diastereoisomers **665** or a mixture of cis-product **665** and trans-product **666** in which the cis-product predominates were obtained (Scheme 188).[221]

Only one example of Diels–Alder reactions with inverse electron demand with β-ketovinyl sulfones has been described in the literature. Thus, sulfone **108** reacts easily with vinyl sulfides, but the reactions with vinyl ethers lead to resinification of the reaction mixture. A mixture of stereoisomers **667** and **668** was obtained when the reaction was carried out at room temperature, but at 0 °C, the reaction gave the cycloadducts **667** stereoselectively (Scheme 189).[222]

It should be noted that sulfonyl and sulfinyl quinones can react only as dienophiles in the Diels–Alder reaction. The stereo and regiochemistries of these reactions were

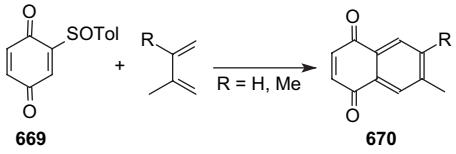


Scheme 188.



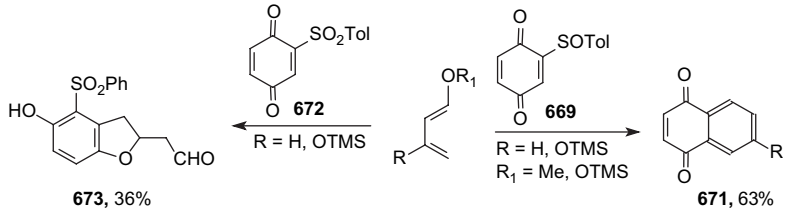
Scheme 189.

thoroughly investigated. Usually, in the case of non-cyclic dienes, the more activated double bond participates in the cycloaddition. As a rule, the formation of the corresponding naphthoquinones takes place, due to spontaneous elimination of sulfinic acid and oxidative aromatization of the primarily formed adducts, e.g., a number of substituted naphthoquinones **670** were prepared from **669** using this approach (Scheme 190).[131]



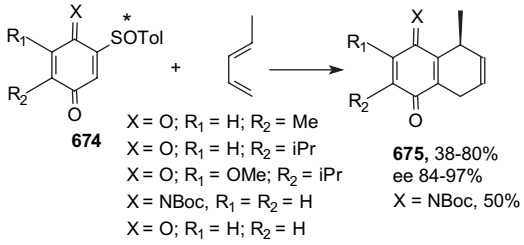
Scheme 190.

The presence in the diene of alkoxy and silyloxy groups facilitates aromatization of the cycloadducts formed. However, [2+4] cycloadducts **671** are formed in the case of sulfoxide **669**, and sulfonyl quinone **672** reacts with 1-trimethylsilyloxybuta-1,3-diene to form a benzofuran aldehyde **673** in low yield (Scheme 191).[140]



Scheme 191.

In the reactions of chiral substituted sulfinyl benzoquinones **674** with *trans*-piperylene, the non-aromatic cycloadducts **675** (after elimination of sulfinic acid) can be isolated when the reaction was catalyzed by $ZnBr_2$ and $BF_3 \cdot OEt_2$. The reaction was found to be fully regioselective and only the formation of *ortho*-adducts **675** was observed. Products **675** can be prepared in excellent enantiopurity (up to 97% ee). Only moderate yields were obtained for the cycloaddition without Lewis acids.[223] The only product was also isolated in the *ortho*-adduct in the cycloaddition with imine. The regiochemistry was controlled by the sulfoxide and/or the imine group acting in a matched way (Scheme 192).[132,224]

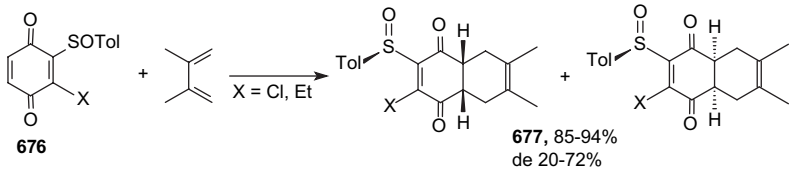


Scheme 192.

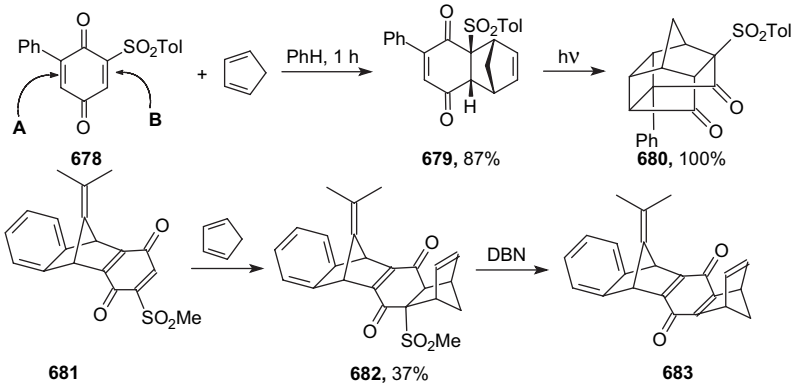
As it is sensitive to steric hindrance, the Diels–Alder reaction with sulfinyl quinones bearing additional groups near the sulfoxide moiety is directed to another double bond. As an example, the reaction of enantiopure sulfoxides **676** with 1,3-dimethylbutadiene leads to the formation of the cycloadducts **677**. Activation with $ZnBr_2$ results in a better diastereoselectivity (up to 72% de) and, therefore, remote asymmetric induction was rather effective (Scheme 193).[137]

A more complex picture is observed for the reactions with cyclopentadiene. Quinones having large substituents at the double bond **A**, e.g., **678** and **681**, react chemoselectively. Only the additionally activated sulfinyl or sulfonyl group double bond **B** reacts as a dienophile fragment.[135,225] Thus, sulfonyl quinone **678** reacts with cyclopentadiene at room temperature with the formation of the cycloadduct **679** as the only product.[135] Subsequent photocyclization confirms in addition the stereochemistry of **679**. Another sulfonyl quinone **681** gave the cycloadduct **682** with cyclopentadiene chemo- and stereoselectively by the less-hindered double bond. Sulfinic acid can be eliminated by treatment with 1,5-diazobicyclo[4.3.0]non-5-ene (DBN) to form the polycyclic quinone **683** (Scheme 194).

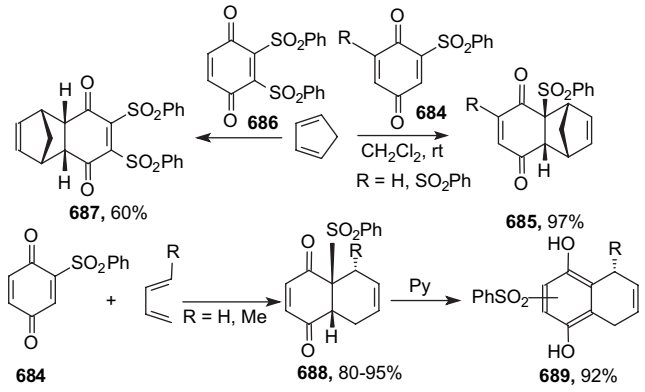
$PhSO_2$-substituted quinones **684** give the expected Diels–Alder *endo*-adducts **685**. In the bis-activated quinone **686**, cycloaddition is controlled by steric factors to form exclusively the adduct **687**. Similar naphthoquinone derivatives **688** can be prepared from butadiene and piperylene, and subsequent treatment with pyridine promotes the elimination–addition of sulfinic acid tandem to form non-selectively the products **689** (Scheme 195).[226]



Scheme 193.



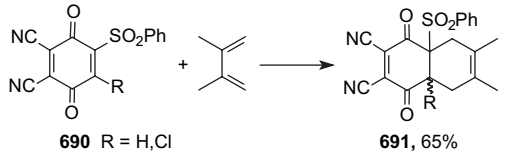
Scheme 194.



Scheme 195.

Cycloaddition of 2,3-dimethyl-1,3-butadiene to quinones **690** in benzene affords adducts, which were identified as a mixture of epimers **691**. In this case, the reaction took place also on the sulfonyl-activated double bond (Scheme 196).[134]

A detailed study of the Diels–Alder reaction of cyclopentadiene with the enantiopure sulfinyl quinone **692** shows that the reaction under thermal conditions is directed to the unsubstituted double bond to form a mixture of the two *endo*-adducts **693a**,**b** with low diastereoselectivity. At lower temperature using more polar solvents (EtOH is the solvent of choice), the diastereoselectivity can be improved up to an 86/14 ratio of **693a**,**b**. A slightly better selectivity (de 80%) is observed in the case of Lewis acid activation of the

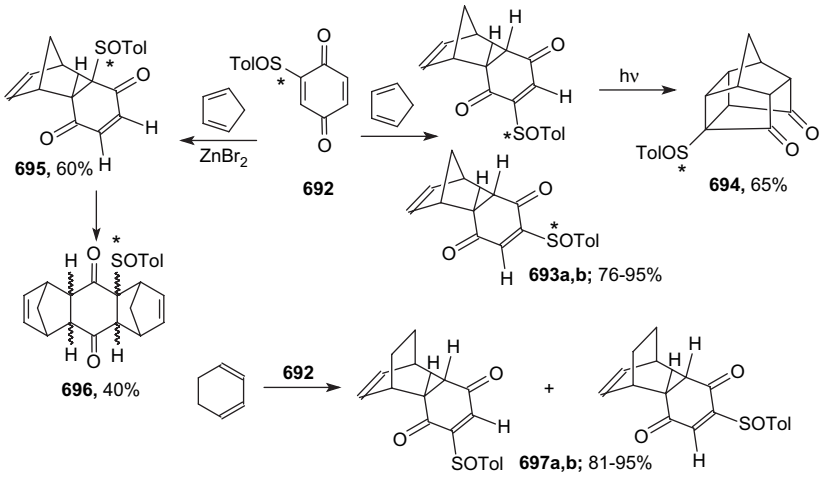


Scheme 196.

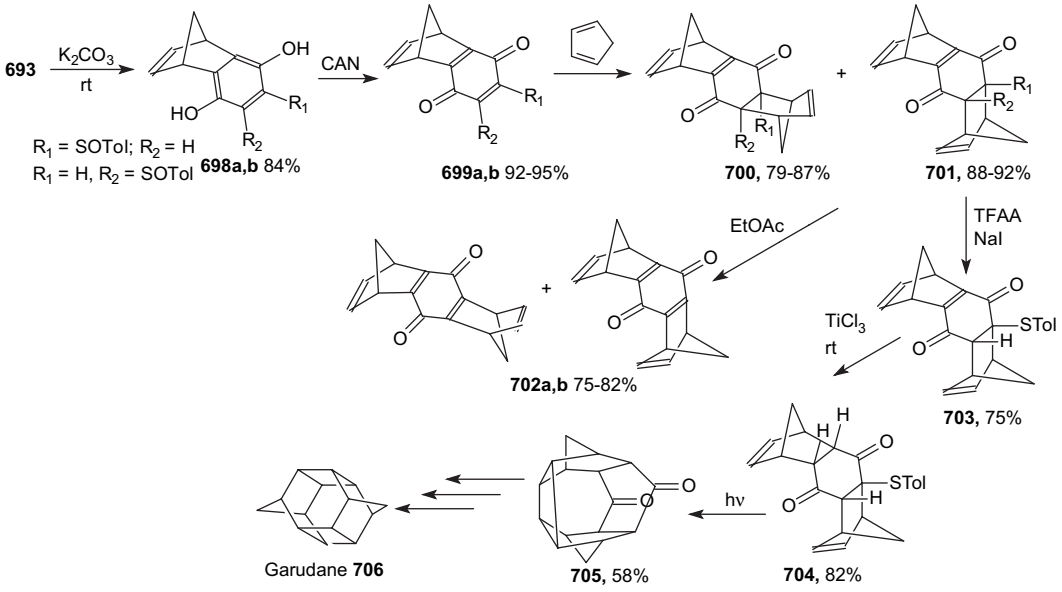
quinone with BF_3 etherate. Diastereomer **693a** was converted by photocyclization into the polycyclic chiral sulfoxide **694** confirming the *endo* configuration of **693a**. However, the cycloaddition of **692** in the presence of $ZnBr_2$ inverts the chemoselectivity permitting also a 100% diastereoselective preparation of the cycloadduct **695**. In this case, the most activated double bond reacts. It should be noted that the cycloaddition is not selective and is accomplished with the formation of the bis-adduct **696** or the cycloadducts **693a**,**b**. A similar picture is also observed for other sulfinyl quinones bearing 2-methoxynaphthyl, 2-methoxyphenyl, and 4-nitrophenyl groups.[136] In the case of 1,3-cyclohexadiene, the reaction is 100% chemoselective and up to 82% diastereoselective to give **697a**,**b** using both thermal conditions and Lewis acid activation (Scheme 197).[223,224]

The products of cycloaddition of **692** with cyclopentadiene were used for the preparation of a precursor for the synthesis of the interesting skeleton of garudane **706**. Isomerization with K_2CO_3 followed by oxidation of **698a**,**b** with CAN results in the chiral sulfinyl-substituted quinones **699a**,**b**. The subsequent Diels–Alder reaction was studied under thermal and $ZnBr_2$-catalyzed conditions (formation of **700** and **701**). This reaction proceeds highly selectively and only the *endo*-adducts are formed. Total control of the diastereoselectivity is observed for **701**. The opposite selectivity is observed when the reaction is catalyzed by $ZnBr_2$ or proceeds without an activator. Sulfenic acid can be eliminated easily by heating in EtOAc to form **702a**,**b**. Reduction of sulfoxide **701** and subsequent irradiation of **704** results in photocyclization with loss of chirality and the sulfur fragment. The cage compound **705** formed can be used for the synthesis of the symmetrical hydrocarbon, garudane **706** (Scheme 198).[227]

Compounds **693a**,**b** were found to be adequate rigid models to evaluate the ability of the sulfinyl group to control the diastereoselectivity of the [2+4] cycloadditions of cyclopentadiene on the enedione moiety. The results of thermal and



Scheme 197.

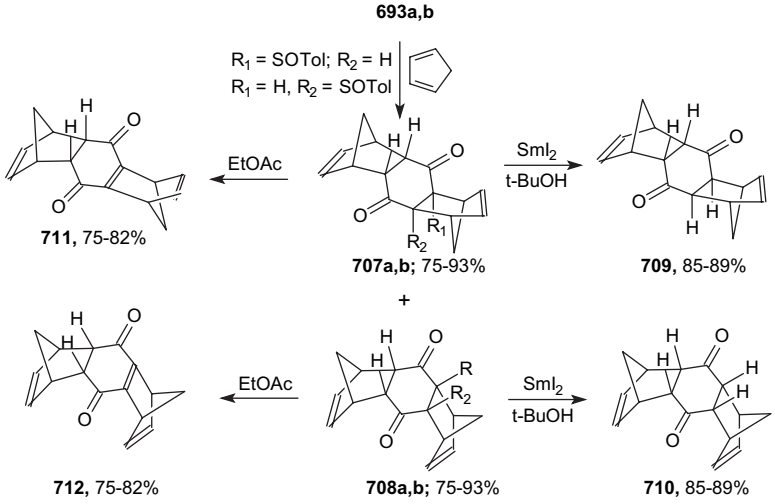


Scheme 198.

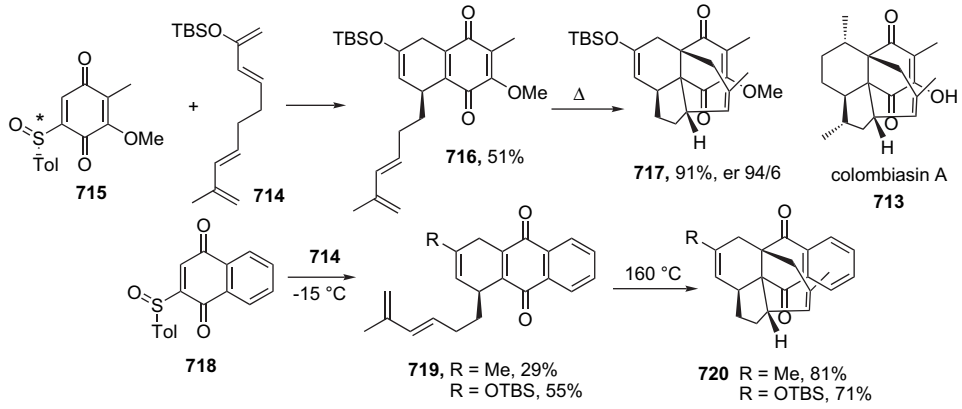
Lewis acid-catalyzed reactions established that both the reactivity and the *endo*/*exo* selectivity were modulated by the presence of the sulfinyl group, the *endo–anti–endo* or the *exo–anti–endo* bis-adducts **707a**,**b** and **708a**,**b** being obtained as the major products, depending upon the experimental conditions. The role of the association between the SOTol group and several Lewis acids ($BF_3 \cdot OEt_2$, $Eu(fod)_3$, and $ZnBr_2$) was used to explain the stereochemical course of the cycloadditions being mainly controlled by steric factors. Thermal or reductive elimination of SOTol group yielded the bis-adducts **709**–**712** (Scheme 199).[228]

The complex tetracyclic carbon skeleton of colombiasin A **713** was conveniently accessed through an enantioselective intermolecular Diels–Alder–sulfoxide elimination–intramolecular Diels–Alder sequence. The reaction of double diene **714** with dienophile **715** produced **716** in 51% yield, which underwent an intermolecular Diels–Alder reaction upon heating to give the adduct **717** in excellent yield and enantioselectivity (91% yield, er 94/6). Similarly, the racemic naphthoquinone sulfoxide **718** reacts with diene **714** to give the adducts **719** in 29 and 55% yield, respectively. Both adducts **719** were efficiently converted into the adducts **720** upon heating in toluene (Scheme 200).[229]

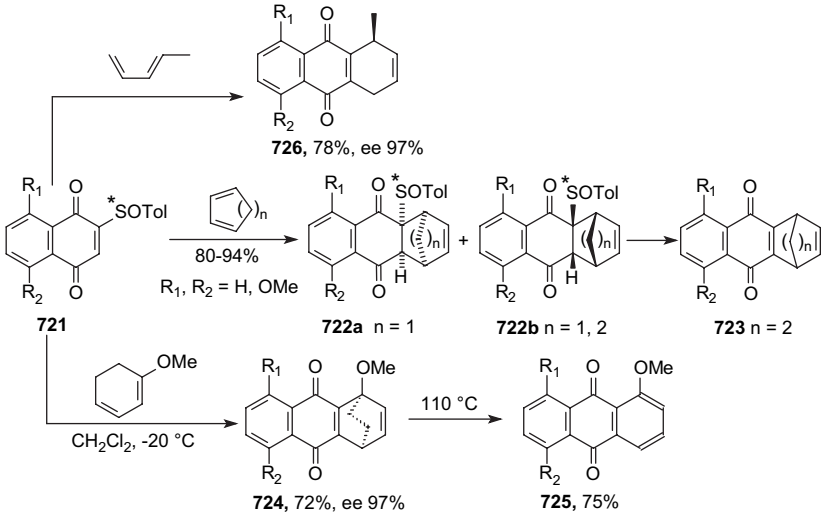
The reactions of (*S*)-2-(*p*-tolylsulfinyl)-1,4-naphthoquinones **721** with cyclic dienes afforded a mixture of the two *endo*-adducts **722a** and **722b**. Without a catalyst, **722a** was the major product, but, in the presence of $ZnBr_2$, the facial diastereoselectivity of the process was reversed. The formation of **722b** became the predominant or exclusive direction of cycloaddition. Products **723** resulting from pyrolytic elimination of the sulfinyl group from the intermediate Diels–Alder adducts were formed in the case of the reaction with 1,3-cyclohexadiene under thermal conditions. Reactions of **721** with 1-methoxy-1,3-cyclohexadiene and *trans*-piperylene also yield the products of sulfinic acid elimination **724** and **726**.[230,231] Cycloadduct **724** was also converted into substituted anthraquinones **725** by thermal aromatization (Scheme 201).



Scheme 199.

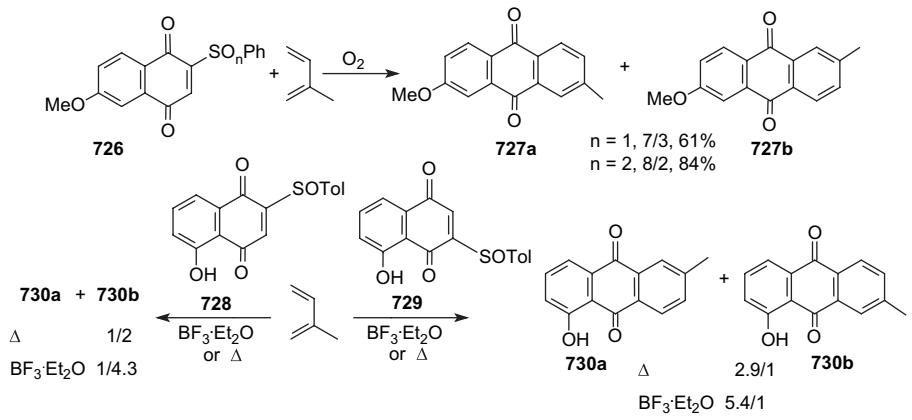


Scheme 200.



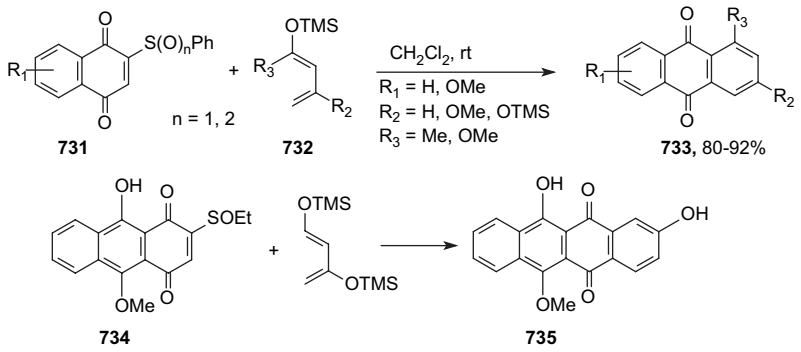
Scheme 201.

In some cases, the oxidative aromatization of the obtained cycloadducts was used for the synthesis of substituted 9,10-anthraquinones. As an example, both sulfinyl and sulfonyl naphthoquinones **726**, **728**, and **729** react with isoprene to give after elimination of the sulfur fragment and oxidation, the corresponding 9,10-anthraquinones **727a**,**b** and **730a**,**b**.[133,232,233] Unfortunately, the regioselectivity of the cycloaddition is not very high. Both thermal and BF_3 activation conditions were studied to give the target products in up to a 5.4/1 ratio (Scheme 202).



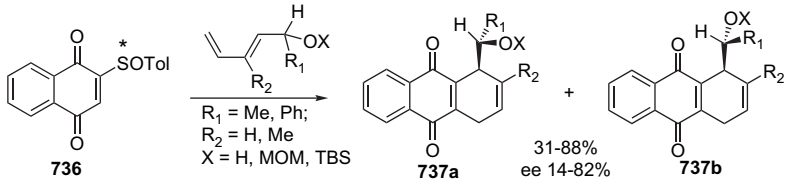
Scheme 202.

Another approach to substituted 9,10-anthraquinones was based on the cycloaddition of sulfinyl and sulfonyl naphthoquinones **731** and **734** with 1-trimethylsiloxybutadienes **732**.[133,140] Some compounds prepared (e.g., **733** and **735**) have a structural fragment of important anthracycline antibiotics such as daunomycin and adriamycin (Scheme 203).[234]



Scheme 203.

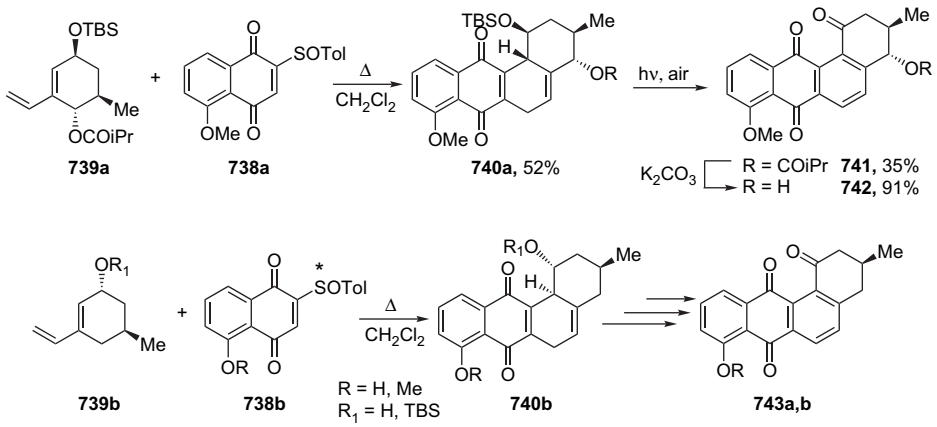
The reaction of enantiopure sulfinyl naphthoquinone **736** with racemic dienes bearing a stereogenic center proceeds through a tandem [2+4] cycloaddition followed by sulfinic acid elimination to afford optically enriched cycloadducts **737a**,**b** with good ee (up to 82%) arising from the partial kinetic resolution of the racemic dienes (Scheme 204).[235–237]



Scheme 204.

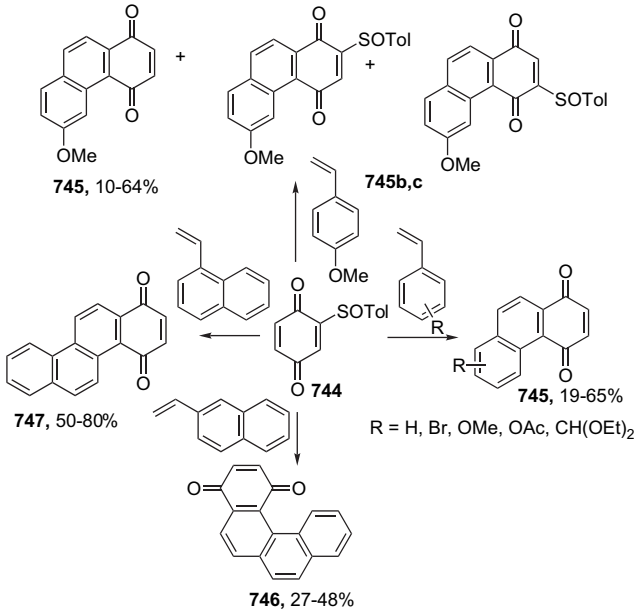
A total synthesis of the antibiotics, rubiginones A2, B2, C2, and the structurally close, ochromycinone **740**–**743** exhibiting potentiation of vincristine-induced cytotoxicity against multidrug-resistant tumor cells, was described recently. The synthesis is based on the Diels–Alder reaction of sulfinyl naphthoquinones **738a**,**b** and vinylcyclohexenes **739a**,**b**, which bear all the stereogenic centers present in the natural products. Quinones **738a**,**b** and dienes **739a**,**b** were used in the racemic or chiral forms. The corresponding precursors **740a**,**b** are formed as a result of the spontaneous elimination of the sulfoxide in the initially formed cycloadduct. Subsequent transformations of **740a**,**b** open up a simple route to **741**–**743**, e.g., exposure of **740a** to daylight under solvent-free conditions afforded natural rubiginone C2 **741** in 35% yield. Hydrolysis of the isobutyric ester afforded rubiginone A2 **742** in 91% yield (Scheme 205).[238–241]

Probably, the most spectacular application of the Diels–Alder reaction for sulfinyl quinones was the synthesis of helix-type aromatic structures. A number of illuminating articles by Carreno et al. show the power of a simple idea of transfer of chirality from the stereogenic center of sulfoxides to prepare chiral helicenes. The starting point of this investigation was the Diels–Alder reaction of sulfinyl quinonones and styrenes, opening up a convenient route to the preparation of the phenanthrene skeleton. A wide range of



Scheme 205.

substituted 1,4-phenanthrenequinones and benzo derivatives were synthesized in a one-step [2+4] cycloaddition of sulfinyl quinone **744** and various vinylarenes under thermal and high-pressure conditions.[242,243] Vinylarenes play the role of diene component and the target products **745**–**747** can be prepared in moderate yield. A detailed study of the reaction with 4-methoxystyrenes shows that the Diels–Alder reaction with **744** is not chemoselective. Polar solvents give preferentially the cycloadducts from the less activated double bond of **745b**,**c** (Scheme 206).

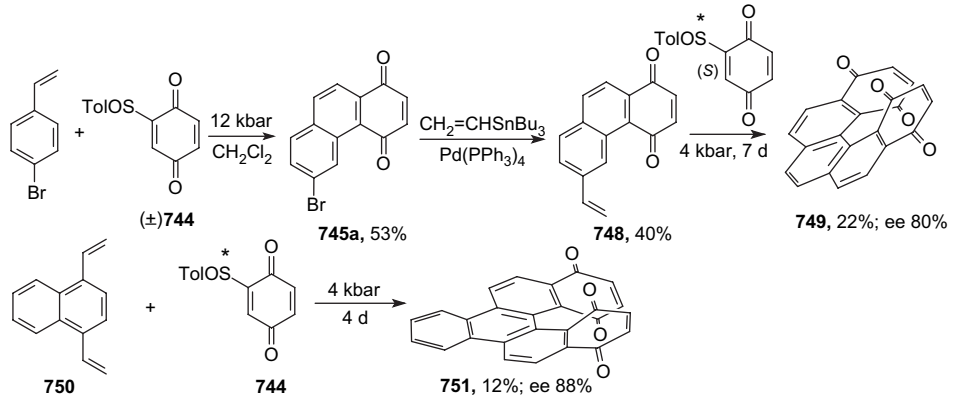


Scheme 206.

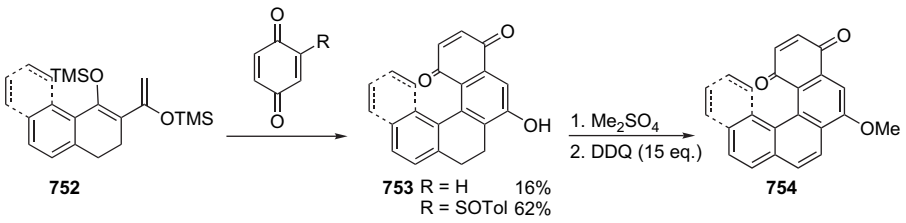
The reaction of chiral sulfinyl quinone **744** with 4-bromostyrene led to **745a** that can be converted into the vinyl-substituted quinone **748**. In the next step, the second cycloaddition with enantiopure sulfinyl quinone **744** gives the chiral spiral bis-quinone **749** in 80% ee. In both Diels–Alder reactions, the elimination of the sulfinyl group proceeded spontaneously.[244] A similar helicene **751** was prepared by the reaction of divinylnaphthalene **750** with chiral sulfoxide **744**. In spite of the yields of the target helicenes being low, the enantioselectivity is very high (Scheme 207).

The functionalized [4]helicenes and [5]helicenes **753** and **754** were synthesized in five steps from tetrahydronaphthalenone and tetrahydrophenanthrenone compounds using Diels–Alder reactions between inner–outer ring 1,3-bis-(trimethylsilyloxy)-1,3-dienes **752** and sulfinyl quinone **744**. The use of sulfinyl quinone markedly increases the Diels–Alder reactivity. Helicenes **753** and **754** were prepared in racemic form (Scheme 208).[245]

The one-pot domino cycloaddition–sulfoxide elimination–oxidation process starting from enantiopure (*SS*)-2-



Scheme 207.



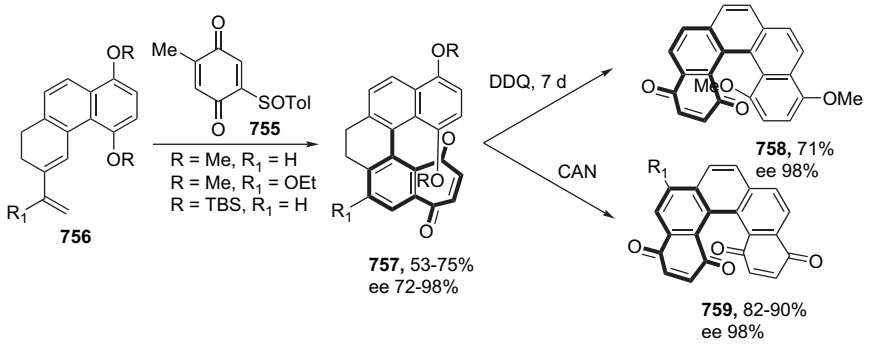
Scheme 208.

(*p*-tolylsulfinyl)-1,4-benzoquinone **755** and vinyl-dihydrophenanthrenes **756** was described as a short and versatile strategy for the enantioselective synthesis of dihydro[5]-helicenequinones **757** under very mild conditions. The (*P*) absolute configuration of all helical quinones was initially assigned considering the preferred formation of the Diels–Alder adduct resulting from the *endo* approach of dienes **756** to the lower face of sulfinyl quinone **755** adopting the *s*-trans conformation. The target helicenes **758** and **759** were prepared in good yield and very high optical purity (Scheme 209).[246]

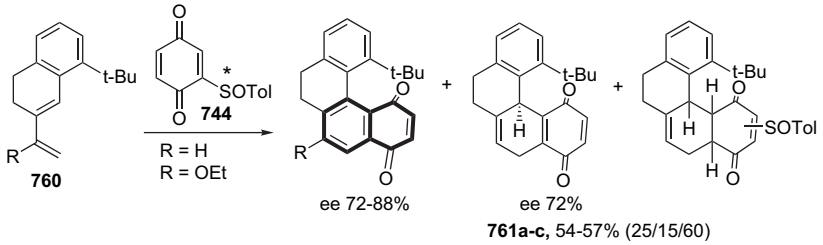
A similar enantioselective synthesis of 12-*tert*-butyl-substituted 7,8-dihydrobenzo[*c*]phenanthrene-1,4-quinones having helical chirality was achieved with good chemical and optical yields through a domino Diels–Alder reaction–sulfoxide elimination–oxidation process starting from enantiopure sulfinyl quinone **744** and 5-*tert*-butyl-substituted 3-vinyl-1,2-dihydronaphthalenes **760** as dienes. The cycloaddition at room temperature afforded a 25/15/60 mixture of **761a–c**, which could be separated by flash chromatography (54% overall yield). The (*R*) absolute configuration at C-12b, the only stereogenic center of **761**, as well as the (*P*) absolute configuration of the helical quinones was initially established considering the preferred formation of a Diels–Alder adduct resulting from the most favored *endo* approach to the lower face of **744** adopting the *s*-trans conformation (Scheme 210).[247]

The asymmetric Diels–Alder reaction between 2-((*E*)-2-acetoxyvinyl)-8-*tert*-butyl-3,4-dihydronaphthalene **762** and enantiopure **744** takes place exclusively on the unsubstituted C5–C6 double bond of **744** with a very high control of the chemo-, regio-, and diastereoselectivity of the process, affording the tetracyclic sulfinyl derivative **763** possessing five stereogenic centers. The analogous diene **764**, lacking the *tert*-butyl group, gave a less chemoselective reaction (**765**, C2–C3/C5–C6: 60/40) in favor of reaction through the sulfoxide-substituted double bond C2–C3 of **744**. Steric effects of the remote *tert*-butyl group and electronic factors due to the OAc substituent are controlling the process (Scheme 211).[248]

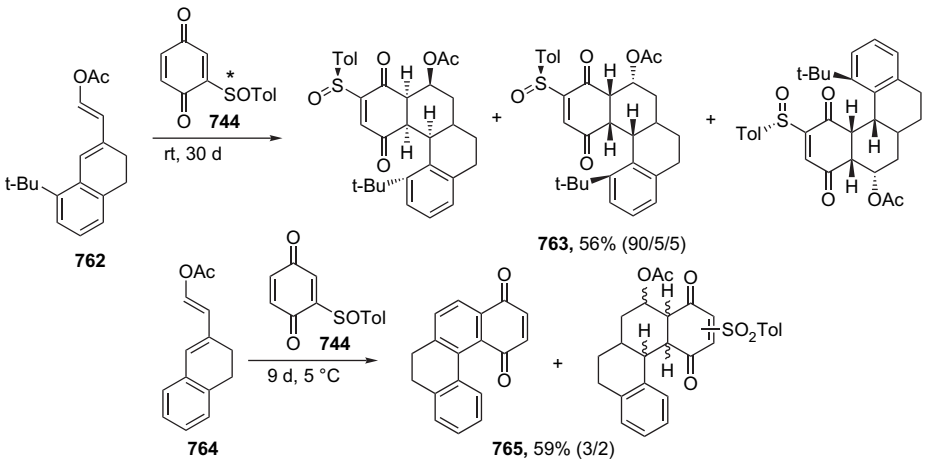
Two complementary routes to chiral dihydro[5]helicenequinones were elaborated in the group by Carreno. 1,4-Divinyl-1,3-cyclohexadiene **766** and sulfinyl quinone **744** were used as cycloaddition partners to give dihydro[5]helicene bis-quinone (*M*)-**767** in 12% yield and 50% ee and **768**. In a stepwise approach, vinyl-substituted dihydrophenanthrenequinone derivatives **769** were used as dienes to obtain dihydro[5]-helicene bis-quinone (*M*)-**767** (74% ee), dihydro[5]helicene-quinone (*P*)-**770a** (84% ee), dihydro[5]helicenequinone



Scheme 209.



Scheme 210.

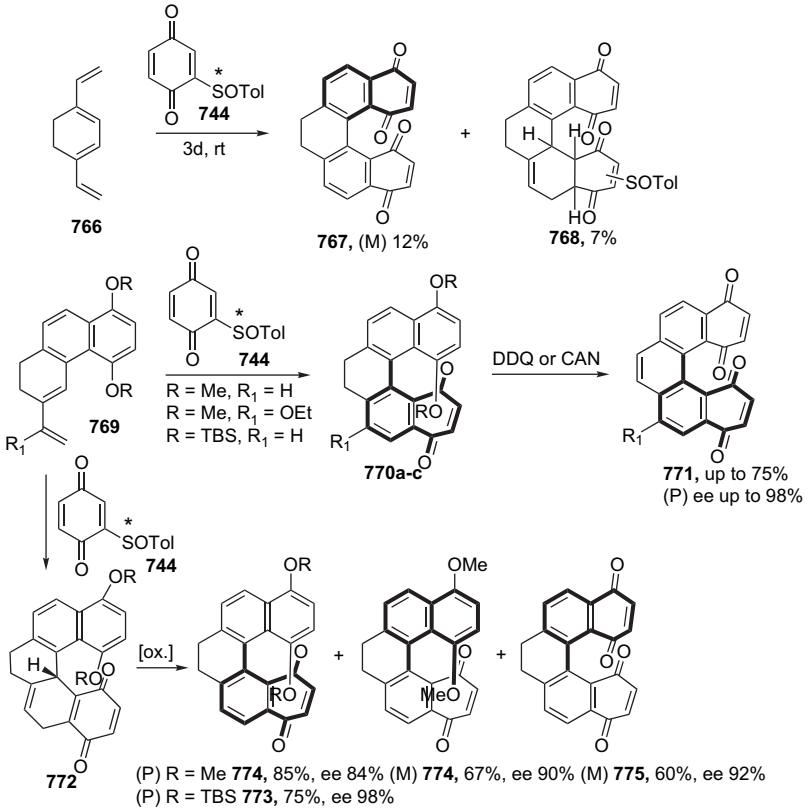


Scheme 211.

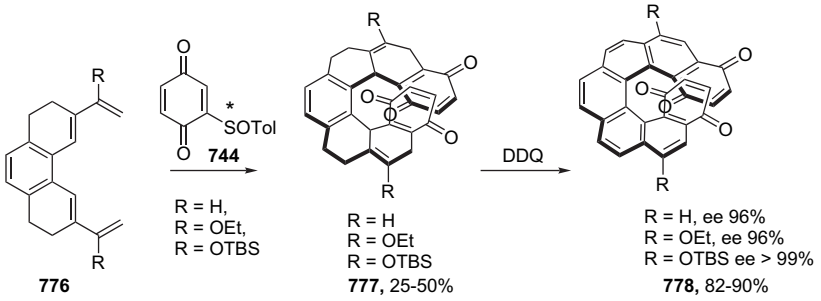
(*P*)-**770b** (92% ee), and dihydro[5]helicenequinone (*P*)-**770c** (98% ee). Fully aromatic helicene[5]bis-quinones **771** were also synthesized by oxidation of (*P*)-**770** by an excess of DDQ or CAN. This access to dihydro[5]helicenequinones allows the divergent synthesis of either *P* or *M* enantiomeric helimers by simply selecting the oxidant reagent CAN or DDQ for the oxidation of separated cycloadduct **772**. The maximum optical yield is defined in the cycloaddition step, but the absolute configuration of the helicene is selected in the oxidation step (Scheme 212).[249,250]

An analogous enantioselective approach to [7]helicene derivatives based on the reaction of 3,6-divinyl-1,2,7,8-tetrahydrophenanthrenes **776** and chiral quinone **744** has been described. Three new tetrahydro[7]helicene bis-quinones and one fully aromatized derivative were isolated with excellent optical purities (up to 99%). Dienes **776** reacted with **744** at 220 °C, giving the octahydroaromatic derivatives **777** bearing two stereogenic centers in good yield. The aromatization of the hydroaromatic B and F rings of **777** was effected by treatment with DDQ, giving rise to tetrahydro[7]helicene bis-quinones **778** in 90% yield with an excellent 96% ee (Scheme 213).[251]

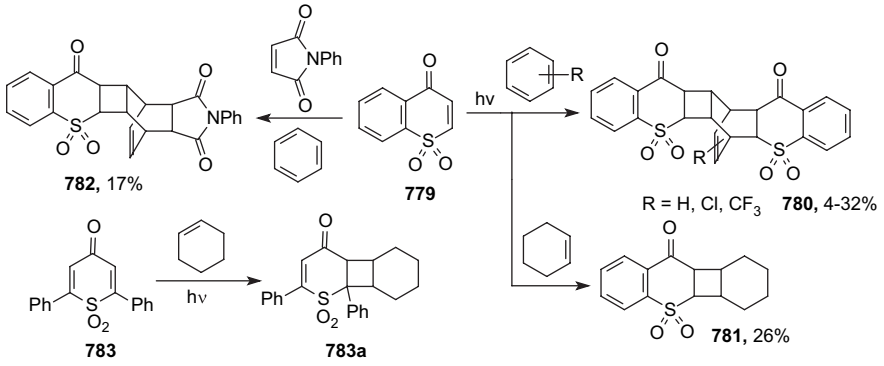
4.4.2. Light-induced cycloadditions. The [2+2] cycloaddition and other light-induced transformations of ketovinyl sulfones and sulfoxides are rather rare reactions for this class of compounds. Hovewer, some interesting reactions of this



Scheme 212.



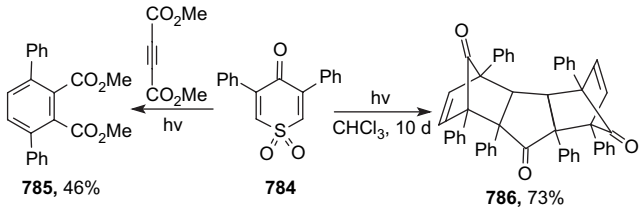
Scheme 213.



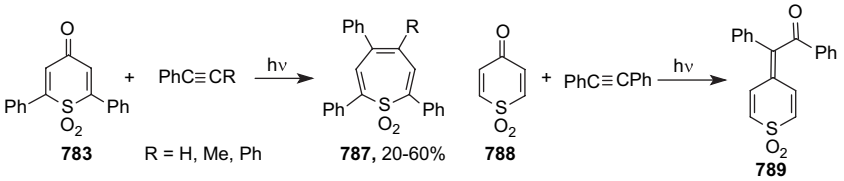
Scheme 214.

type have been described. In one example, photoaddition of thiochromone-1,1-dioxide **779** with benzene permits the constructions of polycycles **780** and **781** having a cyclobutane moiety. Moreover, trapping of the intermediate diene with *N*-phenylmaleimide led to the polycyclic product **782**. The cyclobutane derivative **783a** was prepared similarly from 2,6-diphenyl-4*H*-thiopyran-4-one-1,1-dioxide **783** (Scheme 214).[252]

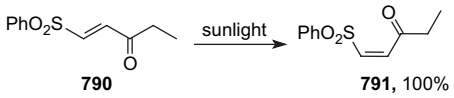
3,5-Diphenyl-4*H*-thiopyran-4-one-1,1-dioxide **784** eliminates SO_2 under irradiation to form in situ diphenylcyclopentadienone. Further reaction of the formed diene with dimethyl acetylenedicarboxylate leads to the corresponding substituted benzene **785**. If the reaction was carried out without a trapping partner, trimerization of the diene takes place to give the adduct **786** (Scheme 215).[253]



Scheme 215.



Scheme 216.

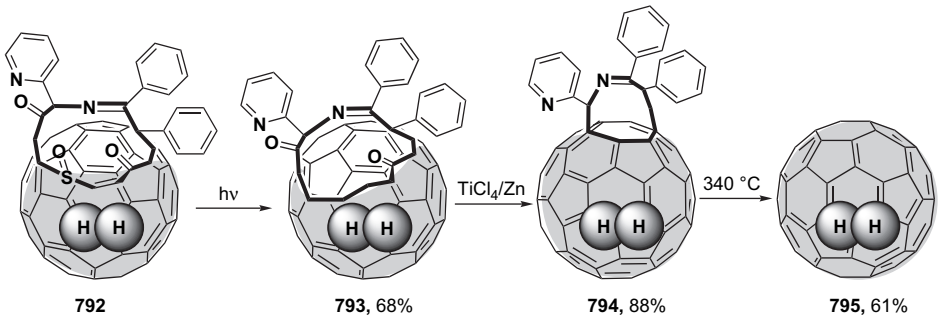


Scheme 217.

Thiepine-1,1-dioxide **787** can be prepared by photocyclization of 2,6-diphenyl-4*H*-thiopyran-4-one-1,1-dioxide **783** with arylacetylenes. However, no reaction is observed with dimethyl acetylenedicarboxylate, whereas photolysis of **783** with hexyne gave a polymeric material. It should be noted that, in the case of unsubstituted 4*H*-thiopyran-4-one-1,1-dioxide **788**, the formation of an unsaturated ketone **789** takes place (Scheme 216).[254]

(*E*)-β-Ketovinyl sulfones can be isomerized easily to the corresponding (*Z*)-isomers. Thus, (*E*)-enone **790** was converted quantitatively into the (*Z*)-form **791** by photochemical isomerization under sunlight (Scheme 217).[182]

A beatiful application of the light-induced transformation of a sulfinyl enone has been described recently. First, a chemical process to synthesize a fullerene C60 encapsulating molecular hydrogen was described. The initial step involved the preparation of a sulfoxide unit with molecular hydrogen inside the fullerene cavity. Keto sulfoxide **792** was



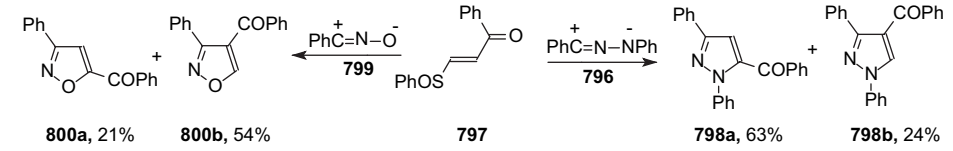
Scheme 218.

transformed by a photochemical reaction to **793**. In the next step two carbonyl groups in **793** were reductively coupled by the use of Ti(0) to give **794** with an eight-membered-ring orifice. Finally, complete closure of the orifice was achieved by heating powdery **794** in a glass tube at 340 °C for 2 h under vacuum. Cyclization to the fullerene **795** is accomplished with elimination of diphenylacetylene and 4-pyridinecarbonitrile. The desired product **795** was obtained in 61% yield (Scheme 218).[255]

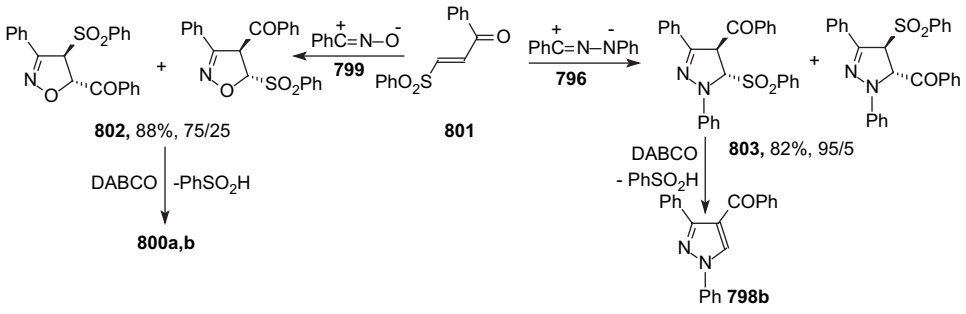
4.4.3. [2+3] Cycloadditions. Reaction of nitrilimine **796** with sulfoxide **797** yields a mixture of regioisomers **798a**,**b** of substituted pyrazole ketones. Sulfoxide **797** also reacts with nitrile oxide **799** to form a mixture of isoxazoles **800a**,**b**. Intermediate pyrazolines and isoxazolines, which are primary [2+3] adducts have never been isolated due to a facile elimination of the PhSO group with the formation of the corresponding heteroaromatic compounds **798** and **800**. Both reactions are not very selective. It is interesting to mention that in the case of the reaction with **796**, an opposite ratio of 4- and 5-substituted pyrazoles is observed, compared with the formation of isoxazoles **800a**,**b** (Scheme 219).[256]

Similar reactions with the corresponding vinyl sulfone **801** were studied. [2+3] Cycloaddition with nitrilimine **796** and nitrile oxide **799** gave stable and isolable isoxazoline and pyrazoline derivatives **802** and **803**. 4-PhCO-substituted pyrazole **798b** was isolated in a pure form after elimination of the sulfonyl group with DABCO. Similarly, isoxazoles **800a**,**b** can be prepared (Scheme 220).[256,257]

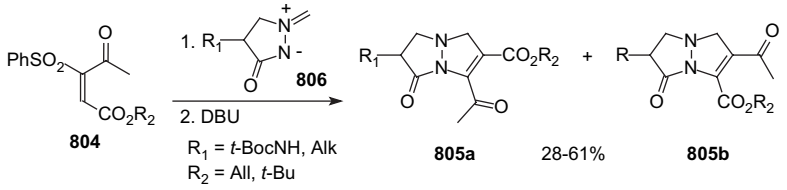
The [2+3] cycloddition of ketovinyl sulfones **804** was used for the synthesis of bicyclic pyrazolidinone analogues of carbapenems **805**. These novel compounds **805** exhibit broad-spectrum antibacterial activity against a variety of clinically important pathogens. Pyrazolidinium ylides **806** were generated in situ from the pyrazolidine precursors and formaldehyde. Subsequent 1,3-dipolar cycloaddition of ylides **806**



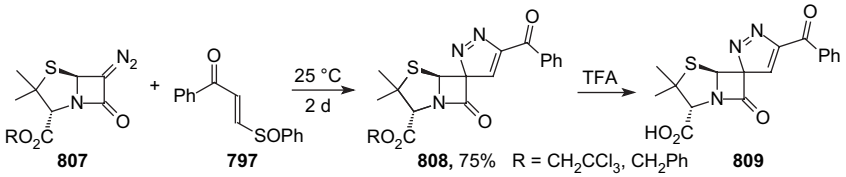
Scheme 219.



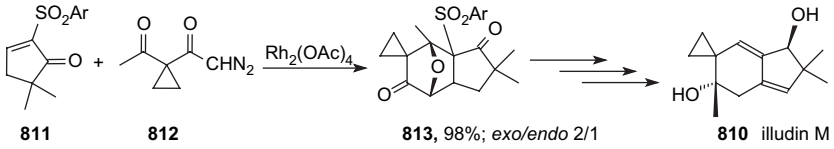
Scheme 220.



Scheme 221.



Scheme 222.



Scheme 223.

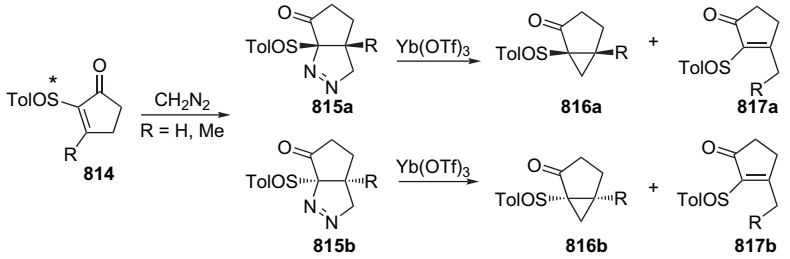
with sulfones **804** led to a mixture of pyrazolidones **805a**,**b**. Preferable formation of **805b** was observed up to exclusive formation of this regioisomer, but when R_2 was a bulky *t*-Bu group, the corresponding pyrazolidone **805a** was isolated (Scheme 221).[38,258]

β-Ketovinyl sulfoxide **797** reacted easily with esters of diazopenicillanic acids **807** with spontaneous elimination of the sulfinic group to give the cycloadducts **808**, which were converted into penicillanic acid with an additional spirocycle **809** by treatment with TFA (Scheme 222).[259]

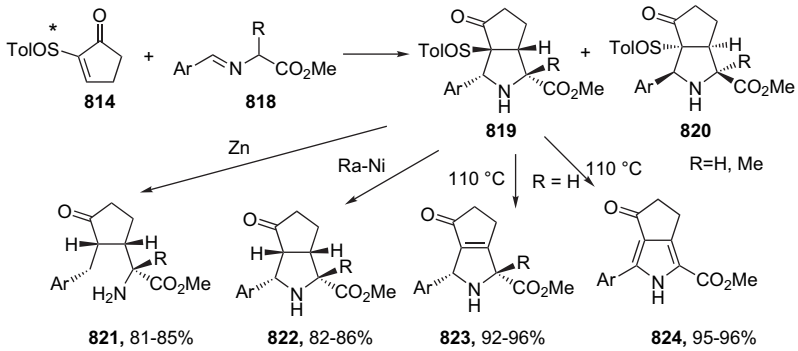
Illudin M **810** is an extremely toxic sesquiterpene produced by *Omphalotus illudens*, the jack-*o*′-lantern mushroom. The Rh(II)-catalyzed cyclization–cycloaddition methodology was used as a key step for the synthesis of illudin M **810**. Treatment of diazo ketone **812** with sulfonyl enone **811** in the presence of a catalytic amount of $Rh_2(OAc)_4$ afforded a 2/1 mixture of the *exo*- and *endo*-cycloadduct **813** in 98% yield. The two diastereomers could easily be separated by silica gel chromatography. The *exo*-isomer was used for subsequent transformation to **810** (Scheme 223).[260]

1,3-Dipolar cycloadditions of chiral 2-*p*-tolylsulfinyl cyclopentenones **814** with diazomethane were studied. The reaction affords pyrazolines **815a**,**b** in up to a 98/2 ratio in the case of R=H and 25/75 ratio for R=Me. The decomposition of pyrazolines **815a**,**b** catalyzed with $Yb(OTf)_3$ yields mixtures of cyclopropanes **816a**,**b** and olefins **817a**,**b**. When R=Me the reaction is highly chemoselective to form the cyclopropane from **815a** and the alkene from **815b** (Scheme 224).[261]

Azomethine ylides, derived from imino esters **818** and DBU in the presence of silver salts, react with (*S*)-2-*p*-tolylsulfinyl-2-cyclopentenone **814** in a completely regio- and *endo*-selective manner, but with a low facial selectivity, affording a mixture of two cycloadducts **819** and **820**. When the ylides were prepared with LHMDS, only one diastereoisomer **819** was obtained in almost quantitative yield. Compound **819** was transformed into the optically pure amino



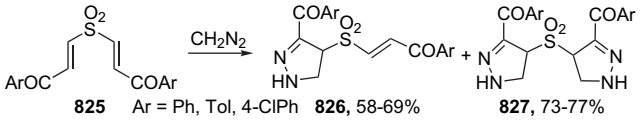
Scheme 224.



Scheme 225.

esters **821–823** and 4-oxocyclopenta[*c*]pyrrole **824** by reduction or elimination of the sulfinyl group (Scheme 225).[262]

A novel type of bis-pyrazolines has been developed from bis(1-aryl-2-propen-1-one)sulfones **825** by [2+3] cycloaddition with diazomethane. Due to the presence of two double bonds, it is difficult to control the selectivity of the reaction. Using 1 equiv of diazomethane, a mixture of the monoadduct **826** and diadduct **827** is formed. An excess of diazomethane permits the preparation of **827** selectively (Scheme 226).[263]



Scheme 226.

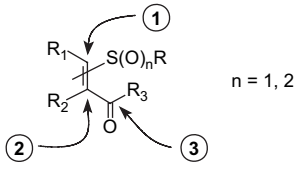
Similar reactions were also studied for sulfonyl enones **828**.[264] The bifunctional pyrazolines **829** and **830** have been prepared by reaction with diazomethane. More reactive was found double bond of sulfonyl enone **828** to form firstly **829**. Second double bond can also participate in cycloaddition leading to **830** when an excess of diazomethane was used. In addition, the pyrazoline derivatives were converted into sulfonyl-substituted cyclopropanes **831** and **832**. The same keto sulfone **828** was studied in the [2+3] cycloaddition with dipoles such as nitrile imines and nitrile oxides. The dipoles have been generated by the dehydrogenation of araldehyde phenylhydrazones and araldoximes with chloramine-T (CAT). Mono-pyrazoline and bis-pyrazolines and bis-isoxazolines **833**, **834**, **836**, and **837** were prepared by this method. The corresponding aromatic bis-heterocycles **838** and **835** were also prepared by oxidation with chloramine-T of the intermediate bis-pyrazolines and bis-isoxazolines **833**, **834**, **836**, and **837** at higher temperatures. It should be noted that the activated double bond was the more reactive dipolarophile in both cases. The target heterocycles were prepared in variable (20–78%) yields (Scheme 227).[265]

4.4.4. Cyclizations based on Michael additions. A wide variety of cyclizations are connected with the reactions of ketovinyl sulfones and sulfoxides with binucleophiles or with molecules that include both nucleophilic and electrophilic centers. It is worth mentioning that sulfinyl and sulfonyl enones have three electrophilic centers in the molecule and can react as 1,3- or 2,3-bielectrophiles in the case of reactions with binucleophiles. All these types of cyclizations have been described in the literature (Scheme 228).

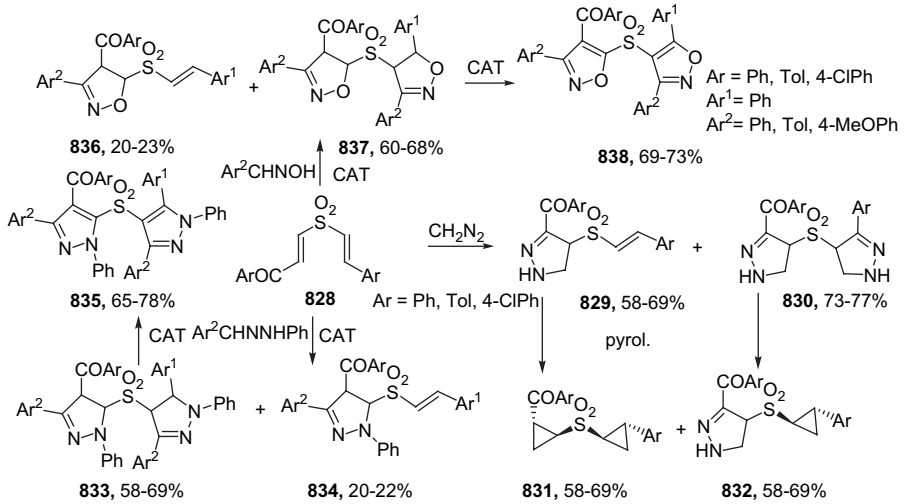
Treatment of ketovinyl sulfone **108** existing in the diol form with various 2-aminopyridines and 2-aminoquinolines in water or MeCN gave the cycloadducts **839** in 80–96% isolated yields. It is worth noting that the reaction proceeds 100% regio- and stereoselectively to form **839** as one diastereomer. Moreover, even hindered 6-substituted 2-aminopyridines react easily with sulfone **108**. The adducts formed have a highly stable semi-aminal fragment caused by the presence of the CF_3 group.[266] It should be noted that, in this case, a 2,3-type cycloaddition took place. The reaction with 5-bromo- and 5-chloropyridin-2-amine in acetic acid gave directly imidazo[1,2-*a*]pyridines **840** in good yields,but other 2-aminopyridines that were protonated in acetic acid gave a complex mixture of products (Scheme 229).[267]

Examples of 1,3-type cycloadditions are more common. Thus, the reaction of 2-amino-1*H*-benzimidazole with sulfones **108** proceeds at room temperature in acetonitrile to give **841** in high yield. Tandem elimination of water and sulfinic acid takes place under reflux in AcOH to give **842**. The one-step synthesis for the preparation of **842** was carried out under reflux in water (Scheme 230).[268]

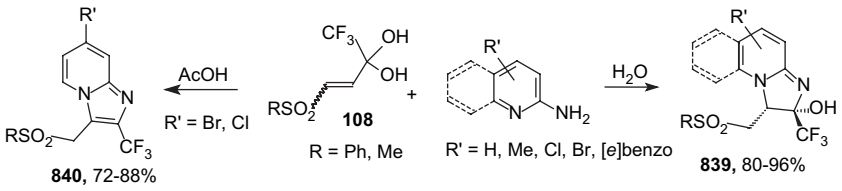
In order to extend the scope of this reaction, other condensations of **108** with various aminopyrazoles, aminotriazoles, and aminotetrazoles as binucleophiles were investigated.



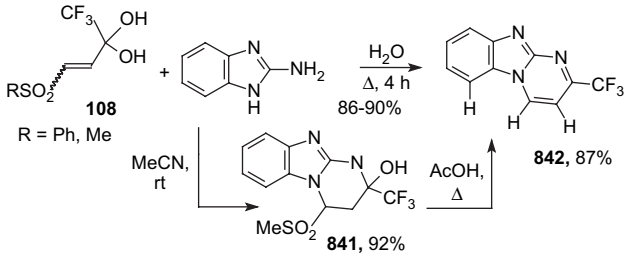
Scheme 228.



Scheme 227.



Scheme 229.

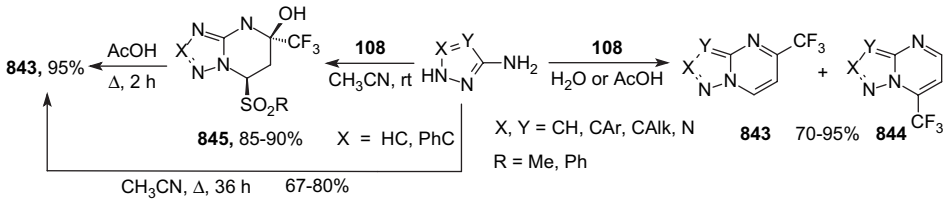


Scheme 230.

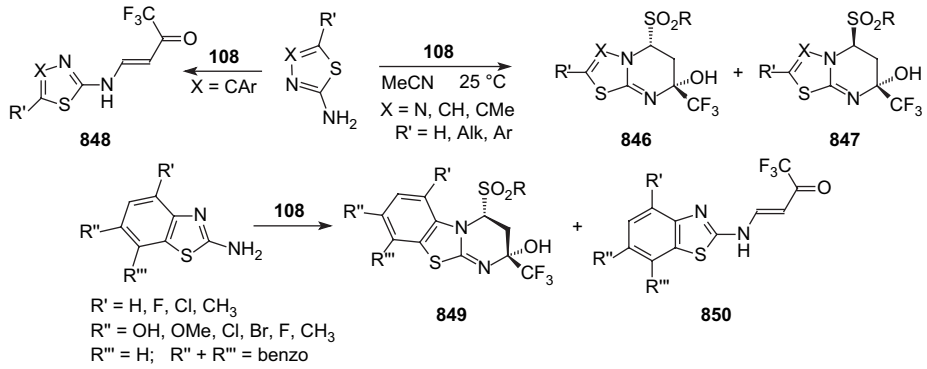
Treatment of **108** with these binucleophiles in acetic acid under reflux gave a mixture of the 7-CF_3-substituted cycloadducts **843** accompanied by the 5-CF_3 derivatives **844**. The total yields were almost quantitative. In the case of aryl-substituted aminopyrazoles, the reaction proceeds 100% regioselectively to form **844** as the only regioisomer. The reaction of the more sterically hindered phenylsulfone **108** with 5-alkyl-3-aminopyrazoles at room temperature leads to the regioselective formation of the 7-CF_3-substituted products **843** only. The reaction with aminotriazoles having both aliphatic and aromatic substituents in acetic acid or in water as a rule gives a mixture of isomeric azolopyrimidines **843** and **844**.[268,269] The reaction with aminotriazoles in acetonitrile at room temperature leads to the cycloadducts **845**. Further aromatization of **845** at reflux in acetic acid provides quantitatively the 5-CF_3-substituted triazolo[1,5-*a*]pyrimidines **843** as the only regioisomer. In acetonitrile at reflux, pure 5-CF_3-substituted azolo[1,2-*a*]pyrimidines **843** were obtained in high yields in one step (Scheme 231).

Other types of binucleophiles studied in the reaction with **108** were sulfur-containing aminoheterocycles such as aminothiazoles, aminobenzothiazoles, and aminothiadiazoles.[270,271] In the case of 2-amino-1,3,4-thiadiazoles and some 2-aminothiazoles, the formation of a mixture of stereoisomeric 6,7-dihydroderivatives **846** and **847** takes place. No heterocyclization was observed for 2-aminothiazoles bearing bulky groups. Only the corresponding enamino ketones **848** were formed. An analogous steric sensitivity was observed for the reaction of 2-amino-1,3-benzothiazoles with sulfone **108**. Only in the case of the parent 2-amino-1,3-benzothiazole was heterocyclization observed to form **849**, any substituents resulting in the formation of substituted enamino ketones **850** (Scheme 232).[271]

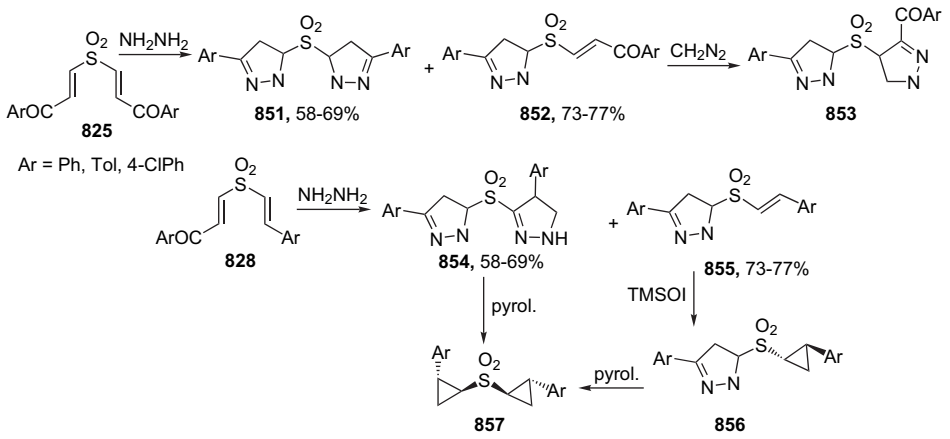
The cyclocondensation of keto sulfones **825** and **828** with hydrazine hydrate in ethanol resulted in the mono- and bis-pyrazolines **851**, **852**, **854**, and **855**. Monoadduct **852** was also converted into the isomeric bis-pyrazoline **853** by reaction with diazomethane. Further transformations of **854** and **855** to bis-cyclopropylsulfone **857** were studied. Thermolysis of **854** or cyclopropanation of the double bond of **855** with TMSOI in phase-transfer conditions gives **856**. Subsequent thermolysis permits the synthesis of biscyclopropane **857** (Scheme 233).



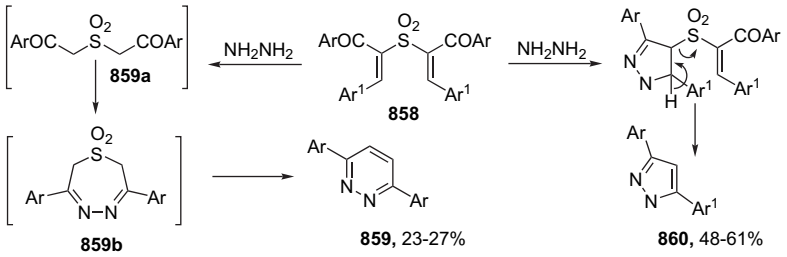
Scheme 231.



Scheme 232.



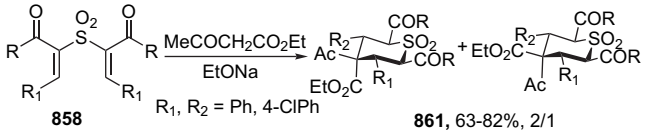
Scheme 233.



Scheme 234.

α-Sulfonyl bis-enones **858** undergo tandem reactions with hydrazine affording, unexpectedly, 3,6-diarylpyridazines **859** and 3,5-diarylpyrazoles **860**. A possible mechanism for this unusual transformation includes aromatization with elimination of the sulfur fragment in the case of the pyrazoles **860**. The formation of pyridazines **859** was explained by fragmentation of the starting ketone to form the intermediate **859a** cyclizing to the seven-membered heterocycle **859b**; after elimination of sulfur dioxide the reaction gives 3,6-diarylpyridazines **859** (Scheme 234).[272]

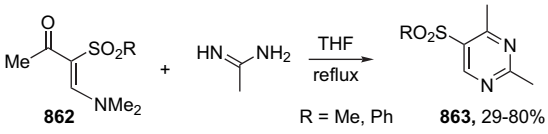
Conjugate addition of ethyl acetoacetate to 2,2-sulfonyl bis(1,3-diarylprop-2-en-1-ones) **858** afforded a diastereomeric mixture (2/1 ratio) of 4-acetyl-2,6-diaroyl-3,5-diaryl-4-ethoxycarbonyl-thiane-1,1-dioxides **861**, differing in configuration at C-4. No fragmentation is observed for this reaction (Scheme 235).[273]



Scheme 235.

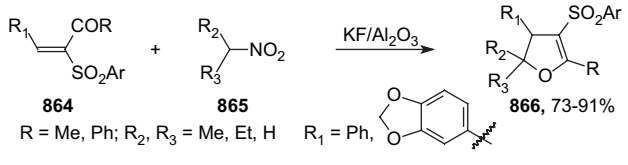
α-Sulfonyl enones react, as rule, as 1,3-bi-electrophiles. Treatment of the sulfones **862** with acetamidine acetate in refluxing THF led to the pyrimidines **863** (Scheme 236).[32]

The reaction of secondary nitroalkanes **865** with α,β-unsaturated sulfonyl ketones **864** in the presence of alumina-supported potassium fluoride in acetonitrile gave directly 4,5-dihydrofurans **866** in high yields. The first step of the



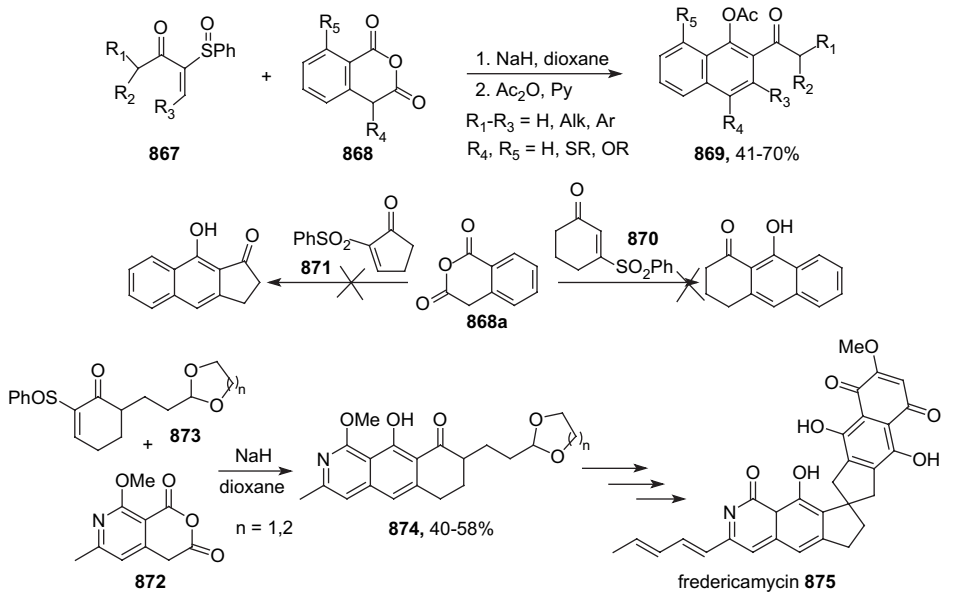
Scheme 236.

reaction is a Michael addition of the deprotonated nitroalkanes to the ketones **864** and then enolate is transformed into the furan derivatives **866** (Scheme 237).[274]

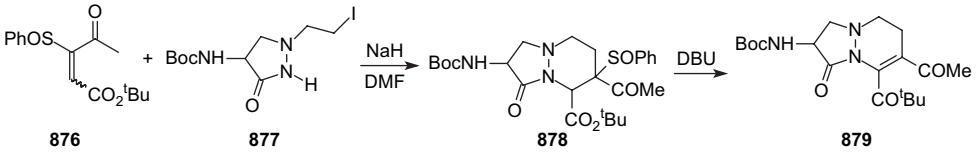


Scheme 237.

There are also some rare examples of the reaction of sulfinyl enones with molecules that have both nucleophilic and electrophilic centers. This approach was used for the synthesis of a key intermediate **874** of the polycyclic antitumor antibiotic fredericamycin A **875**.[275,276] Thus, the reaction of various sulfoxides **867** and **873** with homophthalic anhydrides **868** and **8723** in the presence of sodium hydride led to a formal 1,2-addition to form the substituted naphthalenes **869** and isoquinolines **874**. The sulfinyl group not only promotes the cycloaddition reaction, but also undergoes an in situ elimination under the reaction conditions to afford the *peri*-hydroxy aromatic compounds in a single step. Interestingly, the lithium or sodium salt of **868a** did not react with the sulfones **870** and **871** (Scheme 238).[277]



Scheme 238.



Scheme 239.

The reaction of sulfinyl enone **876** with pyrazolidinone **877** was the key stage in the synthesis of a bicyclic heterocycle with unique biological properties **879**. The reaction proceeds as a Michael addition followed by nucleophilic substitution of iodine by the intermediate anion. Cycloadduct **878** eliminates easily sulfinic acid on treatment with DBU to give **879** (Scheme 239).[278,279]

5. Conclusions

The literature data collected in this review demonstrates the high synthetic utility of sulfonyl and sulfinyl enones in modern organic chemistry. The multifunctional nature of these compounds opens up a range of fruitful approaches to some unique compounds. As a result, sulfonyl and sulfinyl enones are exceptionally valuable reagents for many purposes.

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Biographical sketch

Valentine G. Nenajdenko was born in 1967 in Ivanovo, Russia. He graduated from Moscow State University (Lomonosov) in 1991. He received his Ph.D. degree under the supervision of Professor E.S. Balenkova in 1994 researching the synthesis and application of unsaturated CF_3-ketones. In 2000 he received Dr. of Chemistry degree concerning chemistry of sulfonium and iminium salts. In 2003 he became Full Professor of Organic Chemistry at the Department of Chemistry of Moscow State University. The field of his scientific interest includes organic synthesis, asymmetric catalysis, chemistry of sulfur and fluorine-containing compounds, and chemistry of various heterocycles. He was a supervisor of nine postgraduate works. Valentine G. Nenajdenko is Head of Scientific Committee and Jury of International Mendeleev Chemistry Olympiad. He was the winner of the *Academiae Europeae* Award in 1997, the Russian President Award in 1996, the Price for the best scientific work at the Department of Chemistry of Moscow State University 2001 and 2007, Shuvalov Award 2001, the Russian President Award in 2004, Russian Science Support Foundation in 2005.

Arkady L. Krasovskiy was born in 1975 in Noginsk, Russia. He graduated from Moscow State University (Lomonosov) in 1997. He received his Ph.D. degree under the supervision of Professor E.S. Balenkova and Professor V.G. Nenajdenko in 2002 researching the synthesis and application of β-ketovinyl sulfones and sulfoxides. In 2003–2006 he worked in Professor Dr. Paul Knochel group in Munich, Germany. In 2006–2007 he worked in Professor Dr. K. C. Nicolaou group at the Institute of Chemical and Engineering Sciences, Chemical Synthesis Lab at Biopolis, Singapore. Currently he is finishing his second PostDoc under the supervision of K.C. Nicolaou in Scripps Research Institute, La Jolla, USA. Arkady L. Krasovskiy is co-author of 32 manuscripts and 6 international patents.

Elizabeth S. Balenkova was born in Moscow in 1926. She graduated from Moscow State University in 1950 and then she was a postgraduate student of the Department of Chemistry of Moscow State University. She received her Ph.D. degree under the supervision of academician B.A. Kazansky in 1953 for the research concerning medium ring hydrocarbons. Since that, she has been working at Moscow State University as a Senior Researcher (1959) and Full Professor (1986). She was a Supervisor of 27 postgraduate and 63 diploma works. Her research interests are in the area of organic synthesis, electrophilic addition reaction, and chemistry of heterocyclic and sulfur compounds.