REVIEW

α-Oxy sulfones and sulfoximines: versatile intermediates

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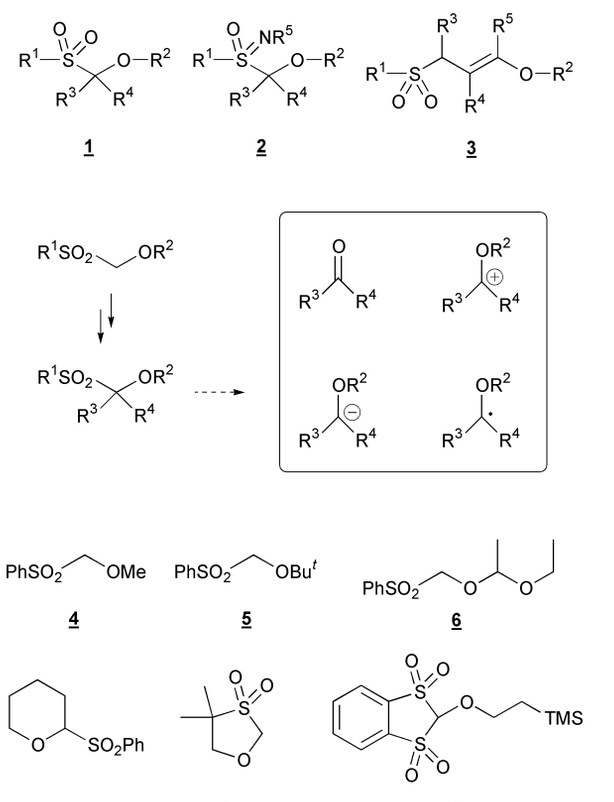
Covering: Literature up to 2000.

1 Introduction

α-Oxy sulfones of the general formula **1** (Scheme 1, R^1 = alkyl, aryl, R^2 = alkyl, acyl, alkoxide, aryl…) are compounds presenting a sulfonyl moiety and an oxygen functionality (ether, ester, ketal…) located on the same carbon. The chemical behaviour of these compounds is directly related to the sulfone chemistry, which has been widely reviewed.[1] However, the presence of the oxygen functionality enhances the leaving group ability of the sulfone, and then these compounds can be considered as masked acetals or ketals. The well-known ability of the sulfonyl group to stabilize carbanions facilitates the alkylation reactions and then these compounds can be considered as Umpolung of the carbonyl moiety; finally, the sulfonyl group can be reduced, by a one-electron or two-electron process, and then they are precursors of α-oxy radicals or α-oxy carbanions.



Scheme 1

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For all these reasons, the chemistry of α-oxy sulfones presents some interesting aspects, which have been not been reviewed specifically. Actually, α-oxy sulfones, even more than sulfones themselves, can be considered as *chemical chameleons*.[2] The case of α-oxy sulfoximines **2** (Scheme 1, R^1 = alkyl, aryl, R^2 = alkyl, acyl, alkoxide, aryl…) will also been considered, although their chemistry has found very little development compared to the one of α-oxy sulfones. The chemistry of 3-alkoxyallyl sulfones **3**, which are vinylogous to α-oxy sulfones, will also be considered. On the other hand, the case of α-amino sulfones will not be considered here, although their chemistry is directly related to the one of α-oxy sulfones. We will first consider the preparation of α-oxy sulfones, and then their particular reactivity in regard to common sulfone chemistry.

Some specific α-oxy sulfones will be seen throughout this review, because they have shown particular versatility and wide use, especially as formyl and acyl anion equivalents. These α-oxy sulfones **4**–**9** are listed in the Scheme 1.

2 Synthesis of α-oxy sulfones and α-oxy sulfoximines

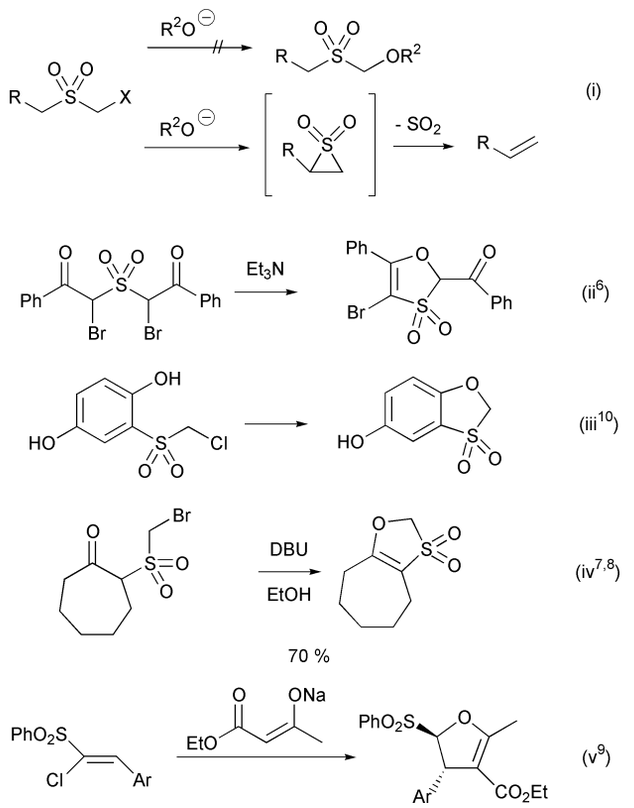
There are many different approaches for the synthesis of α-oxy sulfones. They can be prepared by nucleophilic substitution, by nucleophilic addition, by oxidation or through carbenes or sulfur dioxide insertion.

2.1 α-Oxy sulfones by nucleophilic substitution

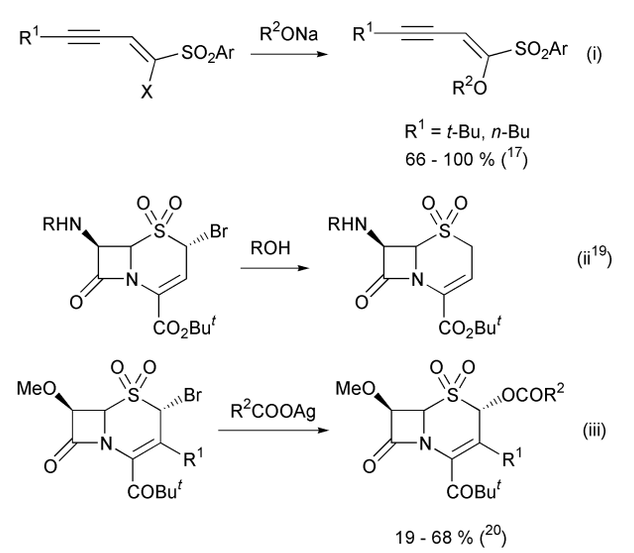
2.1.1 From α-halogenated sulfones

The substitution reaction of the halogen moiety of an α-halogenated sulfone by an alkoxide is conceptually possible, but actually very few synthetic methods based on this scheme have been developed. The main reaction is the deprotonation of the α-halogenated sulfone by the alkoxide, followed by an intramolecular substitution, leading to an episulfone; this episulfone is generally unstable, and gives the corresponding alkene through SO_2 extrusion (the Ramberg–Bäcklund reaction,[3,4] Scheme 2, eqn. (i)). However, the substitution reaction can be observed in some particular intramolecular cases.[5–12] Some examples are listed in Scheme 2, eqns. (ii)–(v). Sometimes, besides the desired Ramberg–Bäcklund reaction, due to important ring strain, the substitution of the halogen moiety by an alkoxide has been observed.[13–16] When the α-halo sulfonyl pattern is a part of a vinylic moiety, the substitution reaction with an alkoxide takes place, leading to the corresponding vinylic α-alkoxy sulfone[17] (Scheme 3, eqn. (i)). This reaction occurs with a high stereospecificity. In the carbapenem series, substitution of a bromine atom by an alkoxide has been described to be impossible under standard conditions. Elimination or reduction occur instead of substitution[18,19] (Scheme 3, eqn. (ii)). However, silver carboxylates undergo the substitution reaction with retention of the configuration[19,20] (Scheme 3, eqn. (iii)).

However, there is an important case where the substitution of a halogen moiety by an alkoxide is involved is the one-pot formation of epoxy sulfones from α-halogenated sulfones and carbonyl compounds[21–25] (Scheme 4, eqn. (i)). A sulfonium group instead of the halogen has been used.[26] The same methodology has been applied[27] for the preparation of epoxy sulfoximines, with variable diastereoselectivities (Scheme 4, eqn. (ii)). This reaction can be realized under phase-transfer conditions.[28–32] Very few results are reported concerning the use of chiral phase-transfer agents. The use of polymer-bounded *N*-alkyl-*N*-methylephedrinium halides as catalysts leads to low asymmetric induction[33] and substrate-dependent results; enantiomeric excesses up to 23% are obtained, but with a low stereoselectivity (Scheme 4 eqn. (iii)). By contrast, the use of a quinine-derived phase transfer catalyst leads to good enantiomeric excesses[34] (up to 81%, Scheme 4, eqn. (iv)).



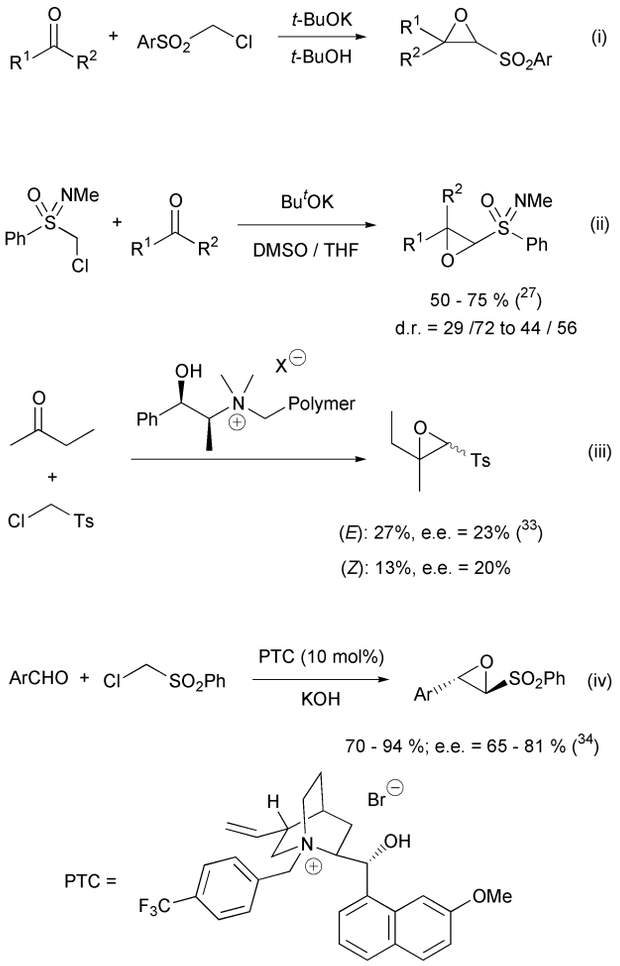
Scheme 2 Intramolecular reactions of alcoholates on α-halo sulfones.



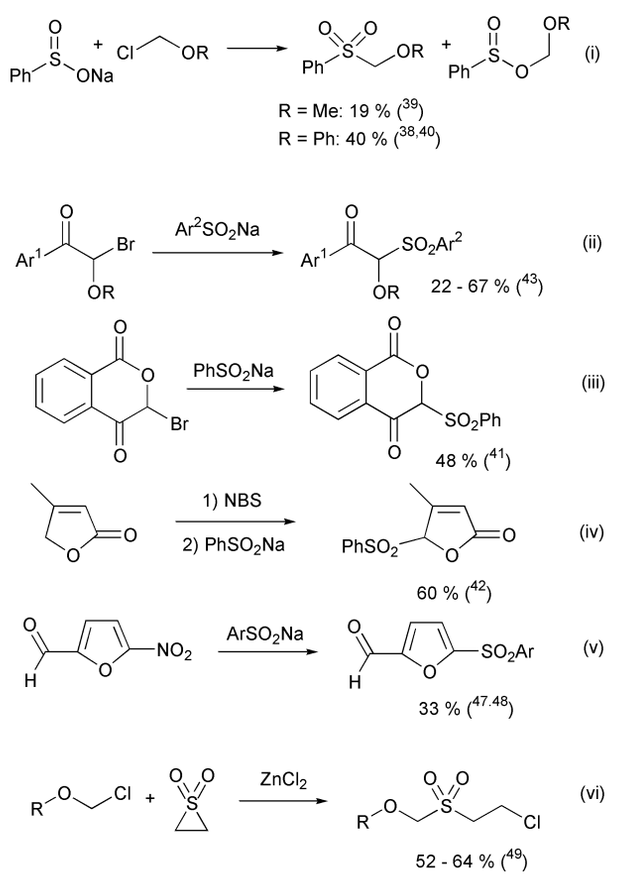
Scheme 3 Intermolecular reactions of oxygen-centered nucleophiles on α-halo sulfones.

2.1.2 From α-halo ethers

The substitution reaction of an α-halo ether by a sulfinate anion is not the best route to α-oxy sulfones. This reaction gives in most cases the desired compound, but the product resulting from the O-alkylation of the sulfinate is also obtained in variable yields as a side product.[35–37] For this reason, the yields of α-oxy sulfone is generally fair or low[38–43] (Scheme 5 eqns. (i)–(iv)). Yields are better under phase transfer conditions,[44] although O-alkylation has also been reported.[45] By this way, α-alkoxy-α-chloro sulfones can be prepared.[46] In some special cases, a nitro group has been used as a leaving group instead of the halogen[47,48] (Scheme 5, eqn. (v)). Another interesting method is the reaction of α-halo ethers with episulfone in the presence of a Lewis acid (Scheme 5, eqn. (vi)).[49]



Scheme 4 Reaction of α-halo sulfones with carbonyl compounds.



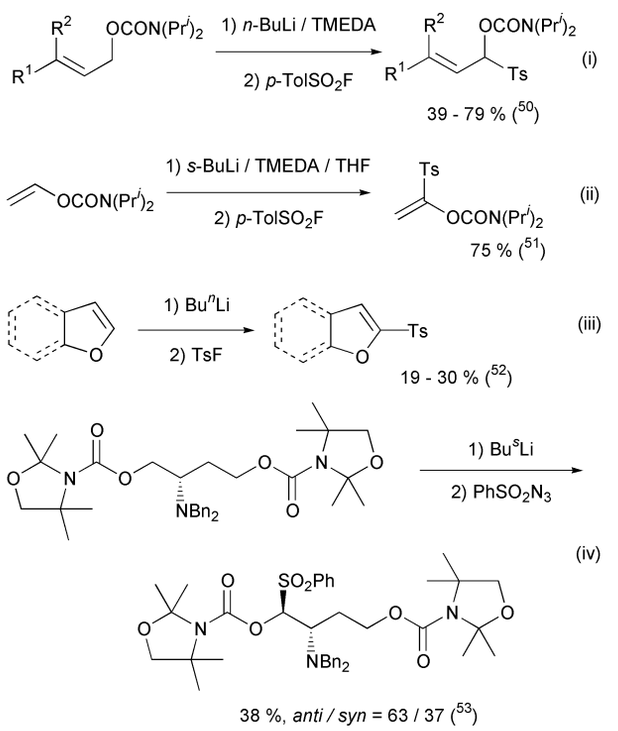
Scheme 5 Reactions of sulfinate salts with haloethers and related compounds.

2.1.3 From α-hydroxy sulfones

This synthetic method will be discussed in Section 2.2.1.

2.1.4 From α-oxy carbanions

There are few examples of preparation of α-oxy sulfones through sulfonation of an α-oxy carbanion. However, this methodology has been applied efficiently in the synthesis of allylic α-oxy sulfones[50] with good control of the regiochemistry (Scheme 6, eqn. (i)). The sulfonation agent is $ArSO_2F$, which is generally used for the sulfone formation.[1] Another recent example (Scheme 6, eqn. (ii)) is the preparation of vinylic α-carbamoyl sulfones through deprotonation of enol carbamates and reaction with $ArSO_2F$.[51] The same reagent has been used for the preparation of 2-sulfonylfurans,[52] although yields are low (Scheme 6, eqn. (iii)). Another possible reagent is benzenesulfonyl azide, which has been reported to react with lithiated enol carbamates in fair yield (Scheme 6, eqn. (iv)).[53] In this case, the lack of stereoselectivity was attributed to an epimerization through a deprotonation–protonation process.



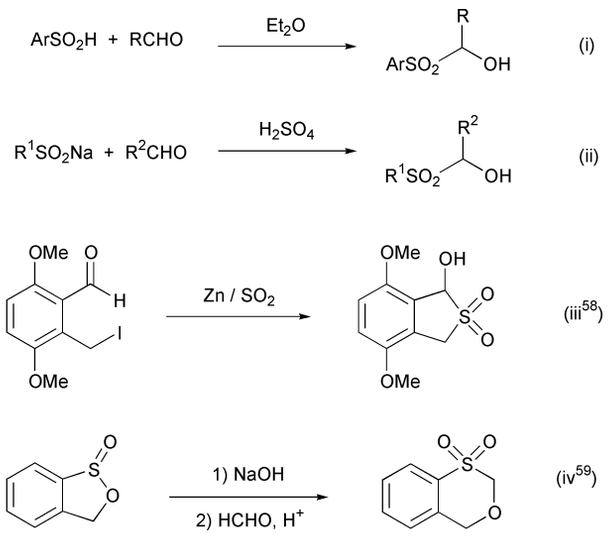
Scheme 6 Sulfonation of α-oxy carbanions.

2.2 Preparation of α-oxy sulfones by nucleophilic addition

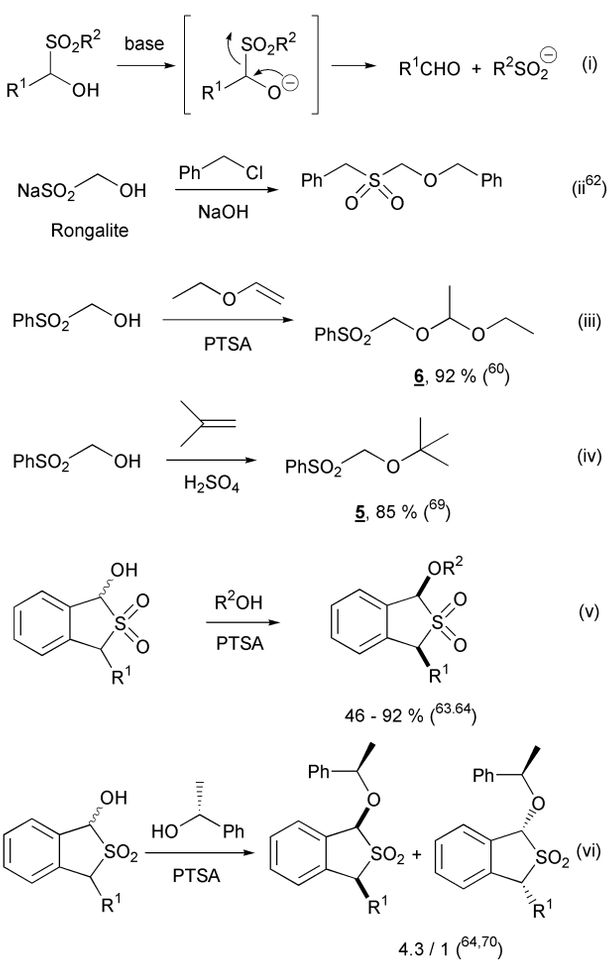
2.2.1 From sulfinic acids and carbonyl compounds: synthesis of α-hydroxy sulfones

Sulfinic acids react readily with carbonyl compounds under acidic conditions to give α-hydroxy sulfones in good yields[54–57] (Scheme 7, eqns. (i) and (ii)). The sulfinic moiety can be prepared from the more stable sulfinate salt by acidic treatment, or prepared *in situ* by insertion of Zn into a benzylic iodide and reaction with SO_2[58] (Scheme 7, eqn. (iii)). Alternatively, it is possible to formylate a sulfinate prepared *in situ* from a sultine (Scheme 7, eqn. (iv)).[59]

These α-hydroxy sulfones are generally unstable in a basic medium.[23,29,57,60,61] They undergo a retrocondensation reaction to the parent carbonyl compound and sulfinate (Scheme 8, eqn. (i)). This process, by which an α-hydroxy- (or an α-oxy-) sulfone can be transformed into a carbonyl moiety, is one of the most interesting features of α-oxy sulfones and will be exemplified further in Section 3. An exception is the bleaching agent "rongalite". This compound can be alkylated twice under basic conditions (Scheme 8, eqn. (ii)).[62]



Scheme 7 Preparation of α-hydroxy sulfones.



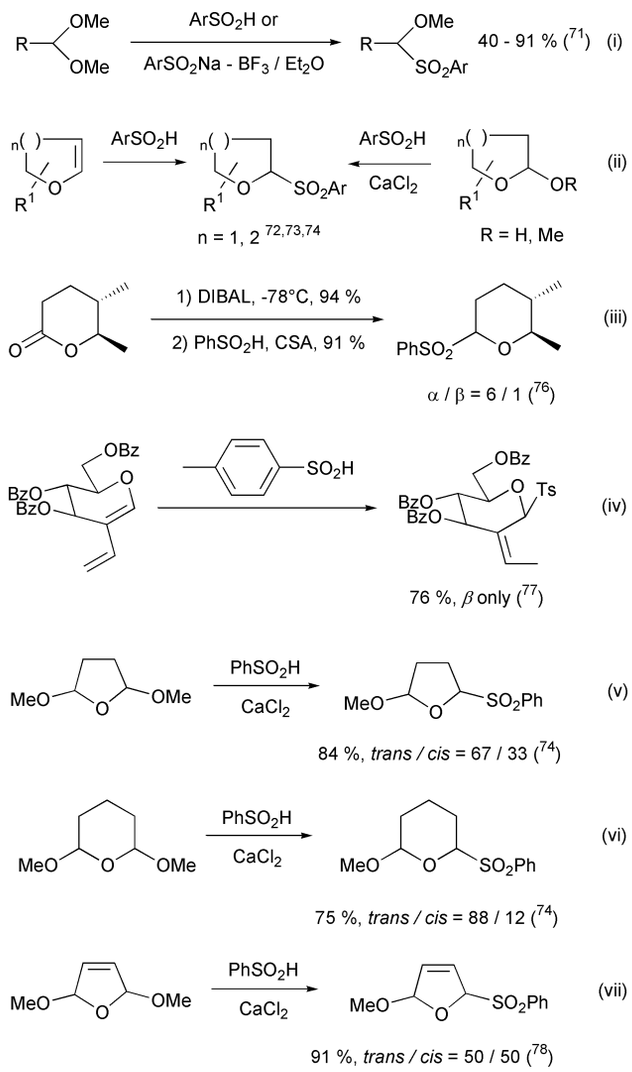
Scheme 8 Reactions of α-hydroxy sulfones.

On the other hand, α-hydroxy sulfones can be readily tosylated, benzoylated[38] or acetylated.[63–68] They can react with alkenes under acidic catalysis.[60,69] By this way the useful sulfones **5** and **6** are prepared (Scheme 8, eqns. (iii) and (iv)).

The etherification of hydroxybenzothiophene *S*,*S*-dioxides has been realized with alcohols.[63–67] The mechanism of this reaction involves ring opening of the cyclic sulfone, formation of the hemiacetal of the obtained aldehyde and ring closure.[65,67] The resulting α-oxy sulfone is obtained in main cases with a good diastereoselectivity in favor of the *syn* product (Scheme 8, eqn. (v)). When homochiral α-methylbenzyl alcohol is used, good asymmetric induction occurs as one major isomer is obtained (Scheme 8, eqn. (vi)).[64,70]

2.2.2 From sulfinic acids and enol ethers or acetals

A sulfinic acid reacts with an acetal or a hemiacetal, sometimes under Lewis acid activation. With an enol ether, this activation is not necessary. This is the best way to prepare α-methoxy sulfones as **4**[71] or 2-tetrahydrofuranyl or -pyranyl sulfones[72–74] as **7** (Scheme 9, eqns. (i) and (ii)). However, this method is not always successful.[75]

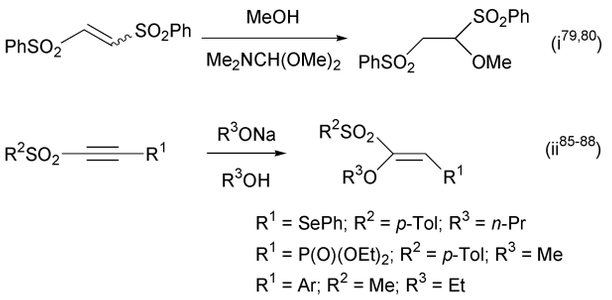


Scheme 9

If a substituent is present on the tetrahydropyranyl or tetrahydrofuranyl ring, the stereoselectivity in the sulfone formation is in most cases low,[74] but some examples are reported where good diastereoselectivities can be achieved (Scheme 9, eqns. (iii) and (iv)).[76,77] When a cyclic diacetal is used, it is possible to transform only one of the two possible acetal moieties (Scheme 9, eqns. (v)–(vii)).[74,78] Starting from a β-halo acetal, the α-oxy sulfone intermediate can undergo a base-induced elimination to give a vinylic α-oxy sulfone[71] (see Section 3.1.7).

2.2.3 From unsaturated sulfones

Some very reactive vinyl sulfones are able to react with alcohols to give the corresponding α-oxy sulfone through an addition reaction[79,80] (Scheme 10, eqn. (i)). The addition reaction of an acid has also been reported.[81] Addition of alcohols, alkoxides or acids on acetylenic disulfones produces the corresponding vinylic α-oxy sulfone generally as an isomeric mixture.[82–84]



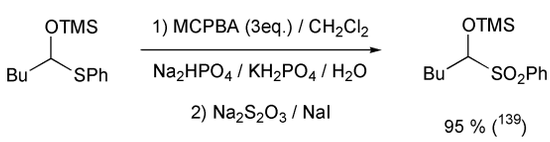
Scheme 10

Anti-Michael additions of sodium alkoxides have been observed for acetylenic sulfones bearing another activating group on the acetylenic position (Scheme 10, eqn. (ii)).[85–88]

2.3 Preparation of α-oxy sulfones by oxidation reactions

2.3.1 From α-oxy sulfides

α-Oxy sulfides are very easy to prepare[89] through reaction of aldehydes or acetals with thiols or by a Pummerer rearrangement. They can be readily oxidized into α-oxy sulfones *via* the corresponding sulfoxides. Various reagents have been described for this oxidation. MCPBA[21,61,90–102] and H_2O_2[41,100,103–114] are the mainly used oxidizing agents; potassium permanganate has also been used,[115–120] as well as *tert*-butyl hydroperoxide,[121–123] ozone,[124] monoperphthalic acid[103,125] (or more frequently its magnesium salt[126–130]), peracetic acid,[125,129,130] oxone,[131,132] dimethyldioxirane in acetone,[133] osmium tetraoxide–NMO,[134,135] HOF–CH_3CN[136] and the MoO_5–Pyridin–HMPA complex [MoOPh].[137] In several cases, no reaction or degradation has been reported. This seems to be due to the instability of the resulting α-oxy sulfone under the oxidation reactions.[75,95] Addition of inorganic bases such as $NaHCO_3$ or Na_2CO_3 can avoid the degradations or rearrangements induced by the acidic conditions of oxidations (for example with MCPBA[138]). In some extreme cases, such as in the case of very unstable substituted α-trimethylsilyloxy sulfones (Scheme 11), the use of a buffered two-phase system oxidation medium can limit the degradation reactions.[139a]



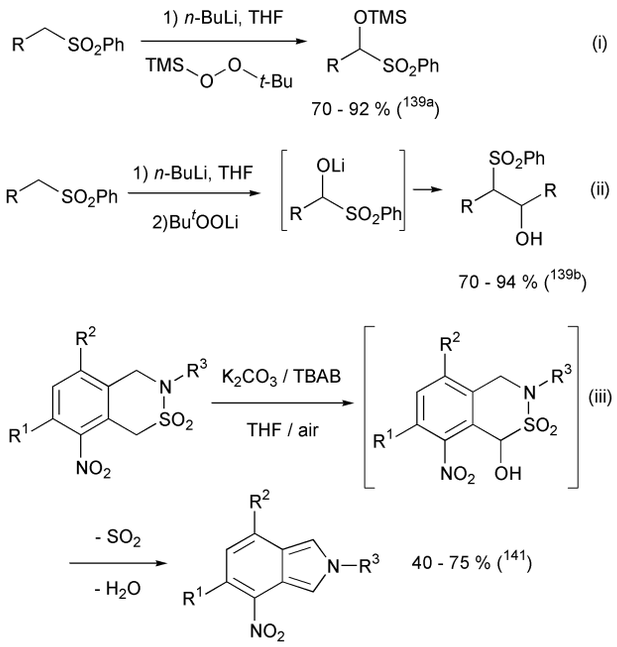
Scheme 11

2.3.2 From α-sulfonyl carbanions

α-Sulfonyl carbanions have been oxidized into α-trimethylsilyloxy sulfones by the means of the *tert*-butyl trimethylsilyl peroxide[139a] (Scheme 12, eqn. (i)). These very unstable compounds undergo readily hydrolytic cleavage into aldehydes. α-Trimethylsilyloxy sulfones have also been envisioned as intermediate products in the oxidation reaction of α-sulfonyl carbanions by bis(trimethylsilyl) peroxide;[140] however, further studies seem to disprove this assumption.[139] When α-sulfonyl carbanions are oxidized with lithiated *tert*-butyl hydroperoxide, the resulting α-hydroxy sulfone undergoes retrocondensation to aldehyde, which is quenched by the starting sulfonyl anion to yield symmetrical β-hydroxy sulfones (Scheme 12, eqn. (ii)).[139b] Finally, the strange aerobic oxidation of a benzylic sultam under phase transfer conditions has also been reported (Scheme 12, eqn. (iii)).[141]

2.3.3 From vinylic sulfones

A very efficient method to obtain epoxy sulfones is the epoxidation of vinylic sulfones. This oxidation reaction has been



Scheme 12 Oxidation of sulfonyl carbanions.

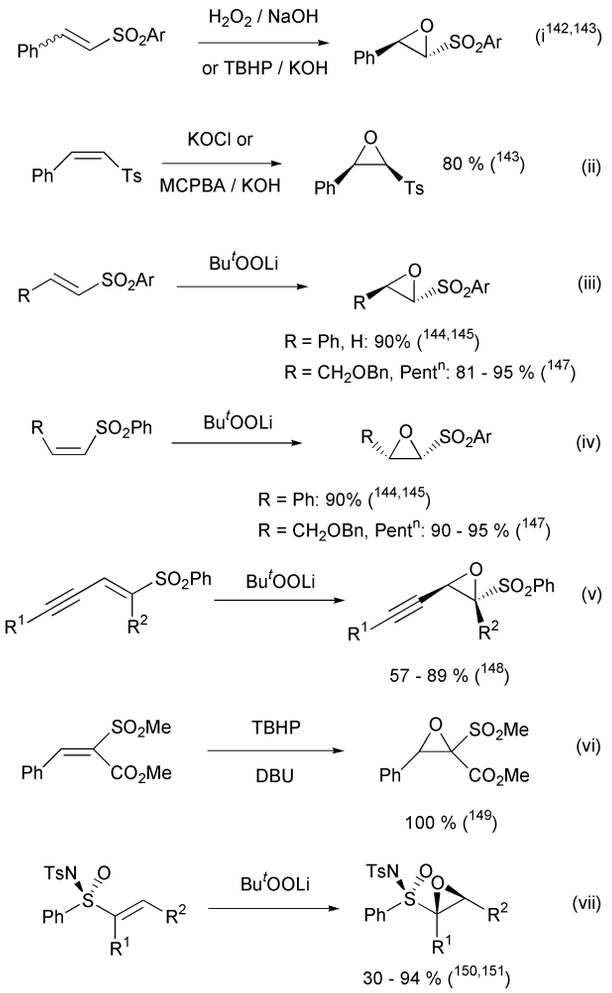
conducted in good yields with several reagents: H_2O_2–NaOH,[142] MCPBA,[143] NaOCl[143] and *tert*-BuOOLi,[144–148] the two latter being the more stereospecific. Some examples are depicted in Scheme 13, eqns. (i)–(v). The use of *tert*-butyl hydroperoxide in conjunction with DBU as a base has been proven to be efficient with electron-deficient α,β-unsaturated sulfones (Scheme 13, eqn. (vi)).[149] However, this methodology gives no result with common α,β-unsaturated sulfones. Epoxidation of vinylic sulfoximines with Bu^{t}OOLi is both stereoselective and stereospecific (Scheme 13, eqn. (vii)).[145,150–152] The stereoselectivity was proven through X-ray structure analysis,[150–152] and is governed by a possible chelation of the lithium salt to the oxygen of the sulfoximino moiety.[150] Epoxidation of 1,2-disubstituted vinylsulfoximines is rather slow and gives only fair yields of the sulfoximinooxirane.[151] By contrast to Bu^{t}OOLi, epoxidation with H_2O_2–NaOH shows no stereoselectivity.[151]

The stereoselectivity of the epoxidation reaction on α-(1-hydroxyalkyl)-α,β-unsaturated sulfones and β-(1-hydroxyalkyl)-α,β-unsaturated sulfones has been studied. In the cases of α-(1-hydroxyalkyl)-α,β-unsaturated sulfones, diastereoselectivities are good,[153,154] depending on the unsaturated sulfone structure and on the protecting group on the alcohol moiety. By contrast, in the cases of β-(1-hydroxyalkyl)-α,β-unsaturated sulfones, diastereoselectivities are much lower.[155,156] Some of the best examples are depicted in Scheme 14, eqns. (i) and (ii). The influence of the protecting group on the alcohol moiety has been evidenced nicely in sugar derivatives (Scheme 14, eqns. (iii) and (iv)).[157] The use of potassium salts of hydroperoxides sometimes enhances the stereoselectivity (Scheme 14, eqns. (v) and (vi)).[158–160] Oxidation of both vinylic and sulfur centers on α-(1-hydroxyalkyl)-α,β-unsaturated sulfoxides can be performed in one step[161] with an excellent stereoselectivity (Scheme 14, eqn. (vii)). Finally, excellent stereoselectivities have been achieved with α,β-unsaturated sulfoximines derived from isopropylideneglyceraldehyde,[158,159] apparently without any *matched–mismatched* effect (Scheme 14, eqns. (viii) and (ix)).

2.4 Miscellaneous methods

2.4.1 From carbene insertions

The first synthesis of α-oxy sulfones in the literature was realized through the reaction of α-diazo sulfones with alcohols.[162–165] The real reacting species is the carbene formed upon irradiation (Scheme 15, eqn. (i)). The carbene insertion



Scheme 13 Oxidation of vinyl sulfones and sulfoximines.

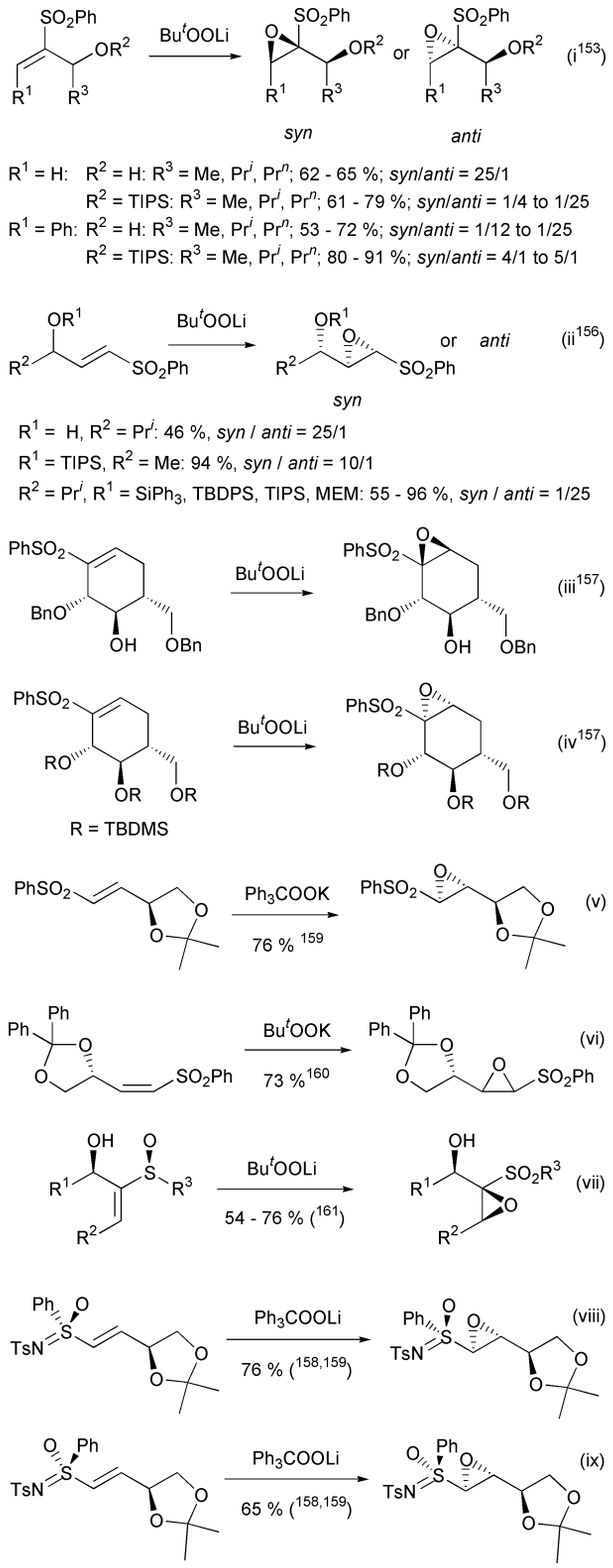
into the O–H bond could also been realized under acidic conditions (Scheme 15, eqns. (ii) and (iii)),[162,164,166,167] with copper catalysis[166] or with rhodium acetate under smooth conditions (Scheme 15, eqns. (iv) and (v)).[168–172] A diazo sulfone has been reported to react intramolecularly with the enol form of a ketone.[173] By this type of carbene insertion, α-alkoxy-α-chloro sulfones have been prepared.[174,175] Finally, it has been reported[176–179] that α-alkoxy carbenes can react with sodium benzenesulfinate to give an α-oxy sulfone.

2.4.2 From sulfur dioxide insertions

Cyclic α-silyloxy sulfones have been prepared by insertion of SO_2 into a benzocyclobutene.[63] SO_2 has been widely used by the same authors[63–68,70] as a dienophile for the preparation of cyclic α-hydroxy sulfones (Scheme 16). This process may be a stepwise process, with the initial formation of a sultine and further thermal rearrangement.[65] As it has been seen in Section 2.2.1, these α-hydroxy sulfones can be readily transformed into α-oxy sulfones by treatment with alcohols. It should be noted that the conceptually possible [4 + 2]-cycloaddition reaction of 1-alkoxy dienes with SO_2 leads to the corresponding sultines instead of the α-oxy sulfones.[180–182]

2.4.3 Through elimination reactions

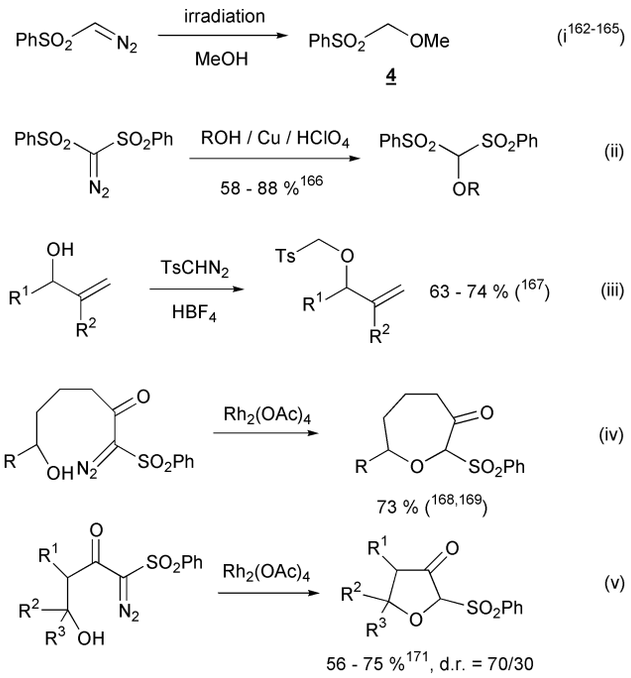
γ-Oxy allyl sulfones are the reagents vinylogous to α-oxy sulfones, and have found very little use in organic chemistry. They can be prepared[183] easily in two steps in stereochemically pure form by elimination reaction from propargyl bromide (Scheme 17, eqn. (i)) or 2,3-epoxy-1-phenylsulfonylpropane (Scheme 17, eqn. (ii)). Cyclic examples of γ-oxy allyl sulfones are also reported[184–186] (Scheme 17, eqns. (iii) and (iv)).



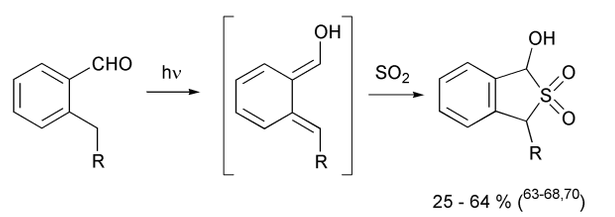
Scheme 14 Diastereoselectivity in the oxidation of vinyl sulfones and sulfoximines.

2.4.4 Through cycloaddition reactions

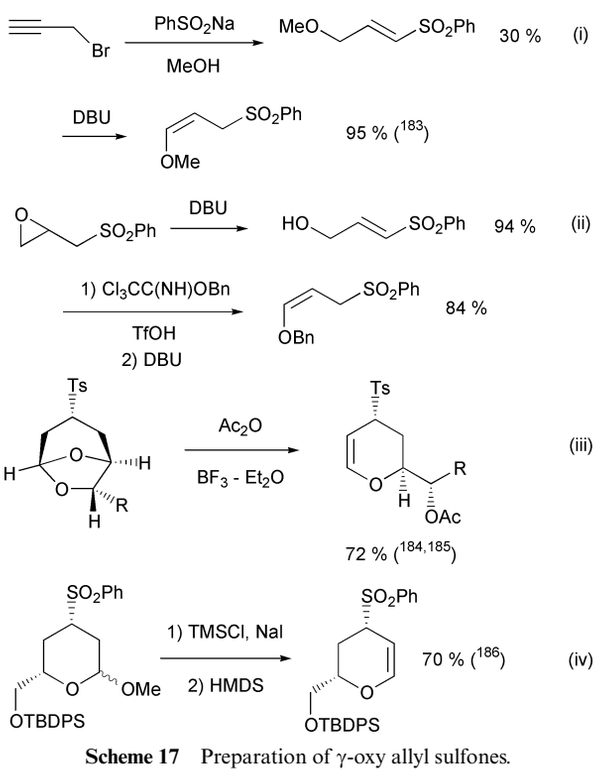
As unsaturated sulfones are good dipolarophiles,[187] some α-oxy sulfones have been prepared through [3 + 2]-cycloadditions. Reactions of vinylic or acetylenic sulfones with nitrile oxides (Scheme 18, eqns. (i) and (ii)),[188–193] nitrones (Scheme 18, eqns. (iii) and (iv))[194–197] and acrolein (Scheme 18, eqn. (v))[198] are reported, as well as the reaction of 5-sulfonyl-2(5*H*)-furanones with diazo compounds.[199] Some representative examples are listed in the Scheme 18. The reaction of sulfenes with furans[200] or bismuthonium ylides[201] can also be pointed out.



Scheme 15 Formation of α-oxy sulfones through carbene insertions.



Scheme 16 Preparation of hydroxybenzothiophene *S*,*S*-dioxides.



Scheme 17 Preparation of γ-oxy allyl sulfones.

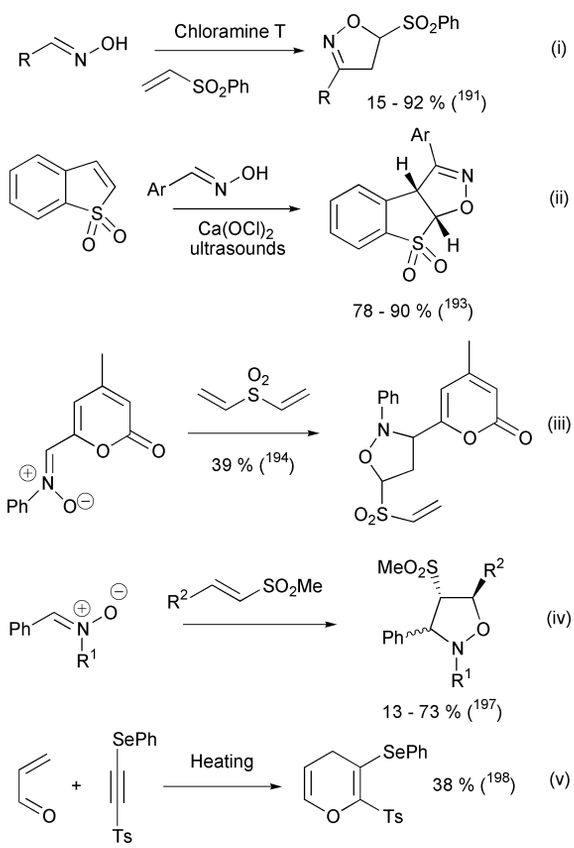
3 Reactions of α-oxy sulfones

3.1 Through α-oxy sulfonyl carbanions

Since the early work of K. Schank,[202–206] the major synthetic applications of α-oxy sulfones commence by the deprotonation in the α-position of the sulfonyl moiety and reaction with electrophiles. These reactions are often coupled with solvolytic displacement of the sulfonyl group or retrocondensation reaction to regenerate the parent carbonyl functionality.

Table 1 pK_A of $PhSO_2$-CH_2-R (measured in DMSO)

R	pK_A
Bu^t	31.2
Me	31
MeO	30.7
H	29
PhO	27.9
MeS	23.4
PhS	20.5
Ph_2P	20.2
Me_3N	19.4
MeCO	12.5
$PhSO_2$	12.1
CN	12

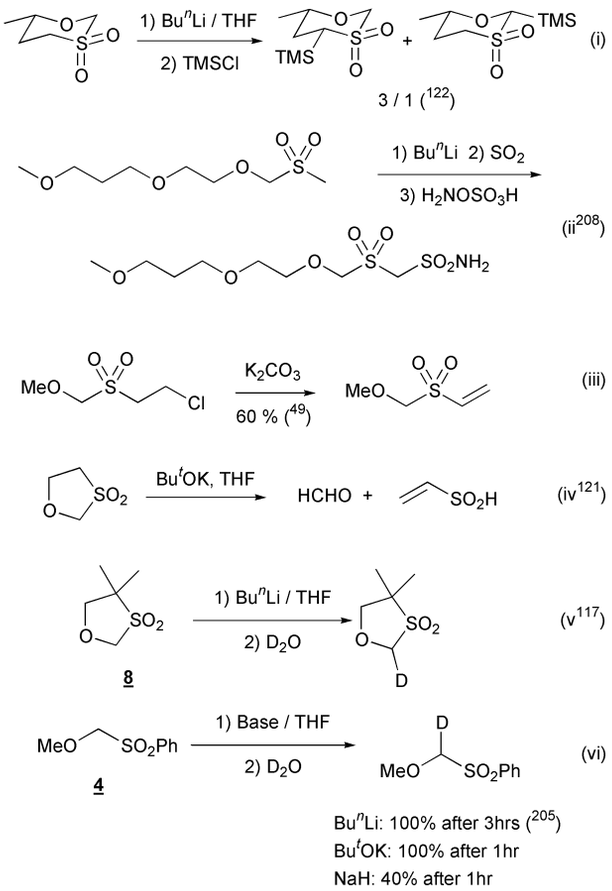


Scheme 18 Formation of α-oxy sulfones through cycloaddition reactions.

3.1.1 Deprotonation of α-oxy sulfones

α-Oxy sulfones, as sulfones themselves, can be readily deprotonated by bases. pK_A measurements have shown that the presence of the oxygen atom α to the sulfonyl group has little effect on the thermodynamic acidity (Table 1).[207]

From the kinetic point of view, however, it has been shown from studies on 1,3-oxathiane 1,1-dioxides that deprotonation of α-oxy sulfones is slower than deprotonation of sulfones[122] (Scheme 19, eqn. (i)). Another example is the regioselective deprotonation of a polyether sulfone on the α′ position (Scheme 19, eqn. (ii)).[208] This ease in deprotonation at the α′ position to the sulfonyl group is problematic, especially in the case when there is a leaving group in the β′-position. However, it has been used for the synthesis of vinylic α-oxy sulfones (Scheme 19, eqn. (iii)).[49] This problem can be avoided



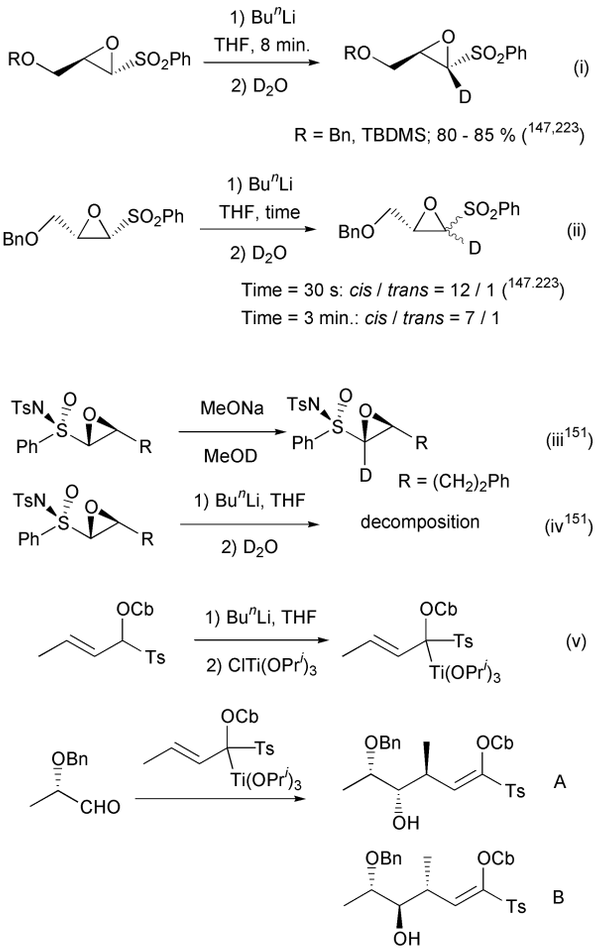
Scheme 19 α *versus* α′ deprotonations.

by blocking the α′ position[117] (compare eqns. (iv) and (v) in Scheme 19) or by using arenesulfonyl groups in the case of acyclic α-oxy sulfones.

Different bases can achieve deprotonation. Bu^{n}Li or LDA are the most frequently used. Early work by Schank[202–206] showed that in the case of methoxymethyl phenyl sulfone **4**, Bu^{t}OK in THF is the best reagent (Scheme 19, eqn. (vi)). In the case of benzylic α-oxy sulfones, Bu^{t}OLi has been widely used.[209–216] Deprotonation with Bu^{t}OK in liquid ammonia has also been reported.[217] For α-oxy β-keto sulfones, a tertiary amine can be used,[218,219] as well as inorganic bases (caesium carbonate) in the case of α-oxy disulfones.[137] The formation of the dianion of **4** by using an excess of base has been applied in dialkylation[60] (see Section 3.1.3) and Wittig-type reaction[220] (see Section 3.1.4). Carbanions derived from epoxy sulfones have shown a limited thermal stability, generally undergoing decomposition at temperatures higher than −100 °C.[146,221]

3.1.2 Stereochemistry of α-oxy sulfonyl carbanions

No general study concerning the configurational stability of α-oxy sulfonyl carbanions has been reported to date. However, since the pioneering work of Eisch[222] and Jackson,[145,221,223,224] several synthetic applications[123,147,160,225–230] have shown that the carbanion derived from the deprotonation of an epoxy sulfone reacts with retention of configuration, regardless of the initial stereochemistry of the epoxy sulfone. The carbanion derived from an (*E*)-epoxy sulfone is reasonably configurationally stable at −95 °C. By contrast, the carbanion derived from a (*Z*)-epoxy sulfone is much less configurationally stable, beginning to isomerize within 3 minutes[223] at −100 °C to the more stable (*E*) isomer (Scheme 20, eqn. (i)). However, carrying out the deprotonation at −100 °C under Barbier conditions can circumvent this isomerization (and degradation, Scheme 20, eqn. (ii)).[147,223]



Scheme 20 Stereochemistry of α-oxy sulfonyl carbanions.

Treatment of sulfoximinooxiranes with MeOLi in MeOD results in H–D exchange with retention of configuration. However, all attempts to achieve deprotonation of these sulfoximinooxiranes using the same conditions as sulfonyloxiranes lead only to decomposition products[151] (Scheme 20, eqns. (iii) and (iv)).

Allyltitanium carbanions derived from allylic α-carbamoyl sulfones were found[50] to be configurationally unstable by application of Hoffmann's test based on the two reactions of the chiral racemic carbanion with a chiral aldehyde, first racemic and then enantiomerically pure.[231] When the reaction of the organotitanium reagent with the chiral racemic aldehyde gave the two diastereomers in 23% and 51% yield respectively, the same reaction performed with the enantiomerically pure aldehyde gave the same diastereomers, but in a similar ratio (Scheme 20, eqn. (v)). These two parallel experiments show the configurational unstability of the starting carbanion on the time-scale of the addition on the aldehyde.

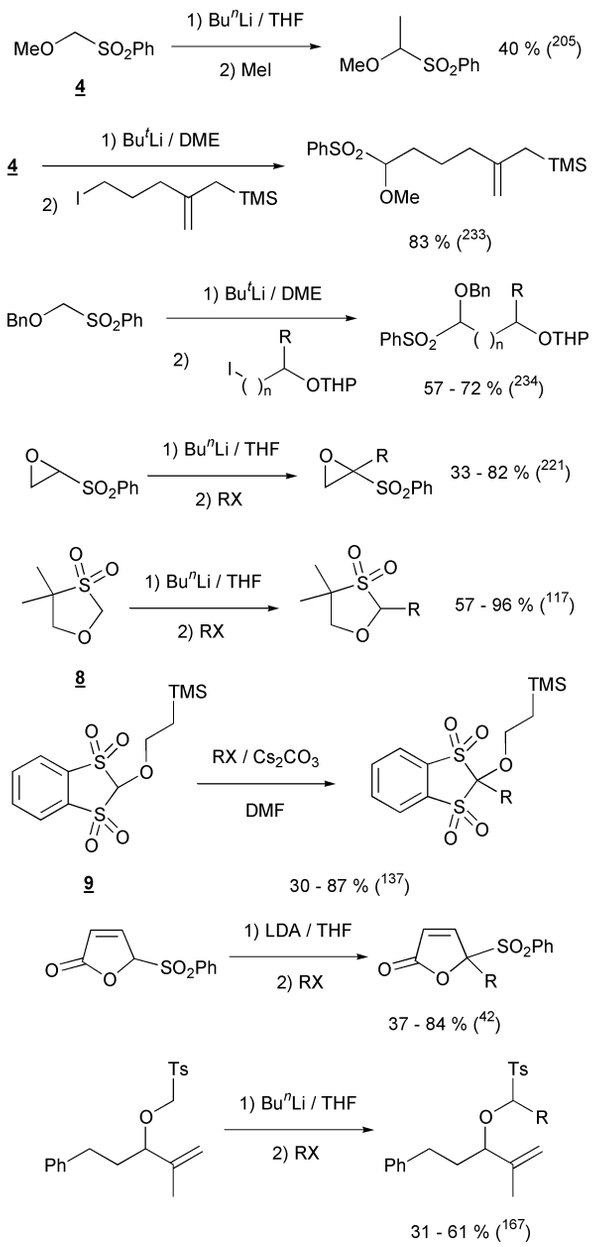
In the case of glycosyl sulfones, deprotonation on the anomeric position[232] leads, after deuterolysis, to a 4:1 mixture

of the two anomers,[45] the α-sulfonyl anomer being preponderant regardless of the stereochemistry of the starting sulfone (Scheme 20, eqn. (vi)). This is reflecting the preference of the C–Li bond to take the equatorial position (anti-anomeric effect).

Substituted dihydrofuranyl sulfone has been shown to epimerize readily to the more stable *trans* stereoisomer under basic conditions (Scheme 20, eqn. (vii)).[78]

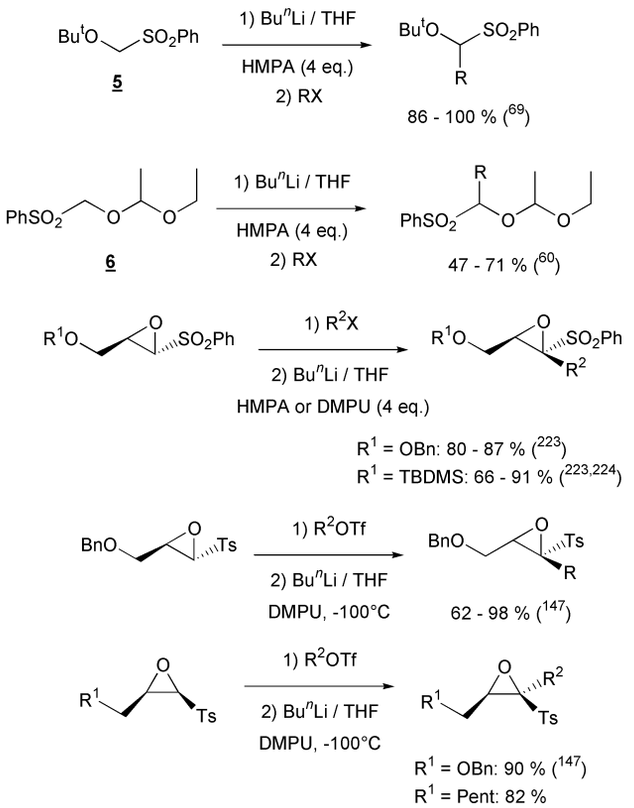
3.1.3 Reactions with alkylating agents

Alkylation of α-oxy sulfonyl carbanions is generally achieved with alkyl iodides or alkyl triflates. In general, yields are slightly lower than the corresponding reactions with simple sulfone carbanions. Several representative examples[42,117,137,167,205,221,233,234] are depicted in Scheme 21.



Scheme 21 Alkylation of α-oxy sulfones.

Adding HMPA or DMPU † can raise the yields. The influence of this cosolvent can be explained by the possible chelation of the lithium cation to the oxygen atom of the α-oxy sulfone, which lowers its reactivity.[60] Some examples[60,69,147,223,224] are listed in Scheme 22.



Scheme 22 Alkylation in the presence of HMPA or DMPU.

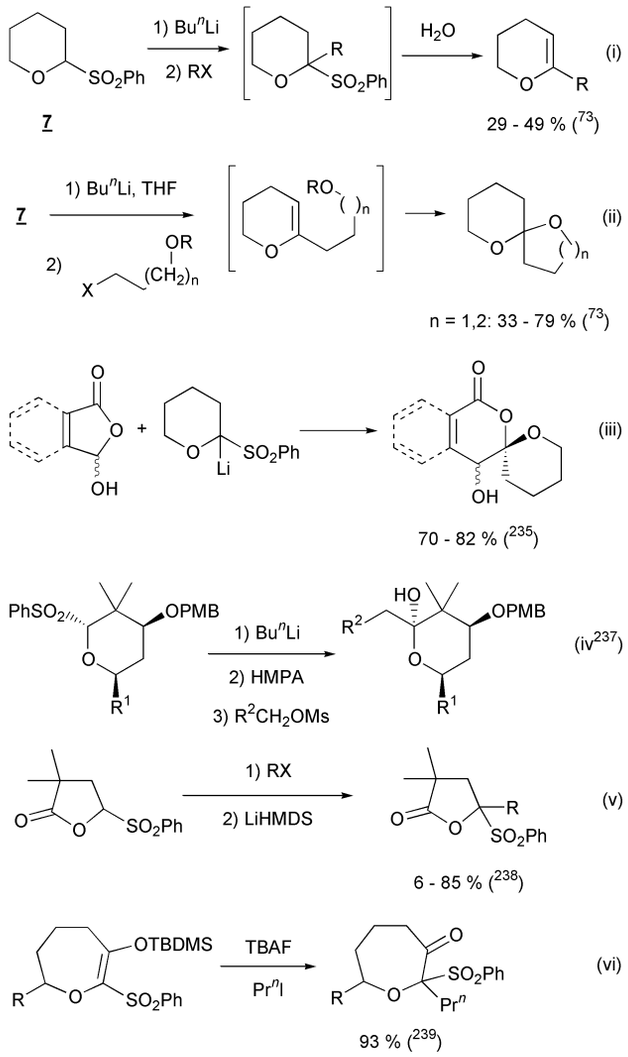
In the case of tetrahydropyranyl sulfones, the tertiary sulfone resulting from the alkylation reaction is not stable.[73] It undergoes sulfinate elimination upon hydrolysis to give the corresponding substituted dihydropyran (Scheme 23, eqn. (i)). The formed dihydropyran undergoes cyclization to a spiroketal[73] if the alkylating agent is presenting the properly masked alcohol functionality on the right position (Scheme 23, eqn. (ii)). This cyclization can be achieved in the same pot, thus avoiding the isolation of the dihydropyran intermediate. Several spiroketal systems have been prepared by following this procedure. The intramolecular displacement of the sulfinate group by a carboxylate species has also been reported (Scheme 23, eqn. (iii)).[235] This methodology has been applied in the total synthesis of the ionophore antibiotic routiennocin.[236]

If, because of the structure of the resulting substituted tetrahydropyranyl sulfone, the elimination of sulfinate is impossible, hydrolysis yields the tertiary lactol upon substitution of the sulfinate moiety by water. This has been used as a key step in the total synthesis of bryostatin 2 (Scheme 23, eqn. (iv)).[237] By contrast, alkylation products derived from 2-sulfonyl-γ-lactones undergo no elimination of sulfinate (Scheme 23, eqn. (v)).[238] Thus the tertiary sulfones are stable, presumably because of the more important steric hindrance to elimination or the lower donor ability of the oxygen atom α to the sulfone. In the case of α-oxy-β-keto sulfones, an enolization–alkylation sequence through the silyl enolate has been described (Scheme 23, eqn. (vi)).[239]

3.1.4 Reactions with epoxides

α-Oxy sulfonyl carbanions react with epoxides with or without Lewis acid activation. This methodology has been seldom used. The product α-oxy sulfone can be functionalized (Scheme 24, eqn. (i)).[240] Here again, in the case of tetrahydropyranyl sulfones, the resulting tertiary sulfone undergoes sulfinate elimination to the corresponding substituted dihydropyran.

† DMPU = 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one.



Scheme 23 Alkylation of cyclic α-oxy sulfones.

This product can be isolated and derivatized[241] (Scheme 24, eqn. (ii)). Alternatively, it can cyclize to the spiroketal unit[76,242] with an alcohol moiety properly placed on the epoxide structure (Scheme 24, eqn. (iii)). This methodology has found a major synthetic application in Ley's total synthesis of (+)-milbemycin β_1 (Scheme 24, eqn. (iv)).[76]

Finally, there has been a recent report of an intramolecular ring opening of an oxirane by an α-oxy sulfonyl carbanion, followed by a Graub-type fragmentation to yield substituted 3-arylbenzofurans (Scheme 24, eqn. (v)).[243] This synthesis of 3-substituted benzofurans has been achieved in solution and in solid-phase.

3.1.5 Reactions with carbonyl compounds

α-Oxy sulfonyl carbanions react smoothly with aldehydes and ketones. Yields are generally higher than the reaction with alkylating agents. This reaction, coupled with hydrolysis of α-oxy sulfones into carbonyl compounds, gives a straightforward access to α-hydroxy aldehydes.[69,117] The tertiary alcohol resulting from the reaction with ketones can be utilised for ring expansion[124,244,245] (see Section 3.2.3). Diastereoselectivities are generally low; reaction with α,β-unsaturated aldehydes or ketones occurs in a 1,2-fashion.[72,73,244] Some representative examples are given in the Scheme 25. In the case of β-keto-α-oxy sulfones developed by Schank, the product alkoxide can induce a fragmentation to the vinyl α-oxy sulfone (Scheme 25, eqn. (vii)).[203,204,246] The same author has also described a Peterson-type olefination reaction by using α-methoxy-α-trimethylsilyl sulfones (Scheme 25, eqn. (viii)).[206]

In the case of tetrahydropyranyl sulfones, as for alkylation reactions, the reaction with aldehydes or ketones is followed immediately by elimination of sulfinic acid to give the corresponding dihydropyran derivative[72,73] (Scheme 26, eqn. (i)).

Carbanions derived from allylic α-carbamoyloxy sulfones react with α-stereogenic aldehydes to give α-carbamoyloxy allylic ketones[50,247,248] These products are formed through addition of the allylic carbanion to aldehyde, followed by migration of the carbamoyloxy group and retrocondensation of the resulting α-oxy sulfone into ketone (Scheme 26, eqn. (ii)). The stereoselectivity of the reaction is excellent, indicating thus the configurational instability of the starting carbanion.

Reactions of α-oxy sulfonyl carbanions with acid derivatives give the corresponding α-oxy α-keto sulfones or α-oxy α-carbalkoxy sulfones.[126,202,223,224,233,249,250] Yields are generally good, and no further reaction is normally observed. Some representative examples are listed in Scheme 27. It should be noted that in the case of tetrahydropyranyl sulfones, contrary to the other examples depicted above, the resulting 2-sulfonyl-2-carbalkoxytetrahydropyran is stable and can be isolated without any sulfinic acid elimination (Scheme 27, eqns. (iv)–(vi)).[73] In the case of hindered and base-sensitive acyl compounds, the benzotriazolyl derivative can be useful. This was demonstrated[251,252] in a total synthesis of spongistatin 2 (Scheme 27, eqn. (vii)).

3.1.6 Michael reactions

Since the early work of Hauser,[92,209,212,214–216,253,254] α-oxy sulfonyl carbanions are known to react with Michael acceptors such as cyclic or acyclic α,β-unsaturated esters. This reaction has been widely used in the case of phthaloyl sulfones or analogues to give a straightforward access to anthra- and naphthaquinones. The overall process is depicted in Scheme 28.

By this methodology, a number of natural products and analogues have been prepared, including kidamycinone,[254] aklavinones,[255] daunomycinones,[209,256–258] nanaomycin and kalafungin,[259] isokalafungin,[260] adriamycinones,[214] citromycinone,[212] aklavinone,[215] pigment G2N,[216] proposed structure for prekinamycin,[261] kinafluorenone scaffolds,[262,263] shinkonin and alkannin,[264] methyl rishiliride B,[265] biphyscion,[266] radermachol,[267] aquayamycin[268] and vitamins K[269] as well as models for fredericamycin,[210] anthracyclines,[270] heteroanthracyclines[188] and benz[*a*]anthraquinones.[271] It should be noted that in some cases, the overall process described in Scheme 28 can be stopped after the Michael addition and the resulting tertiary α-oxy sulfone isolated.[272]

The Michael addition of the α-oxy disulfone **9** under nickel catalysis has also been described.[137]

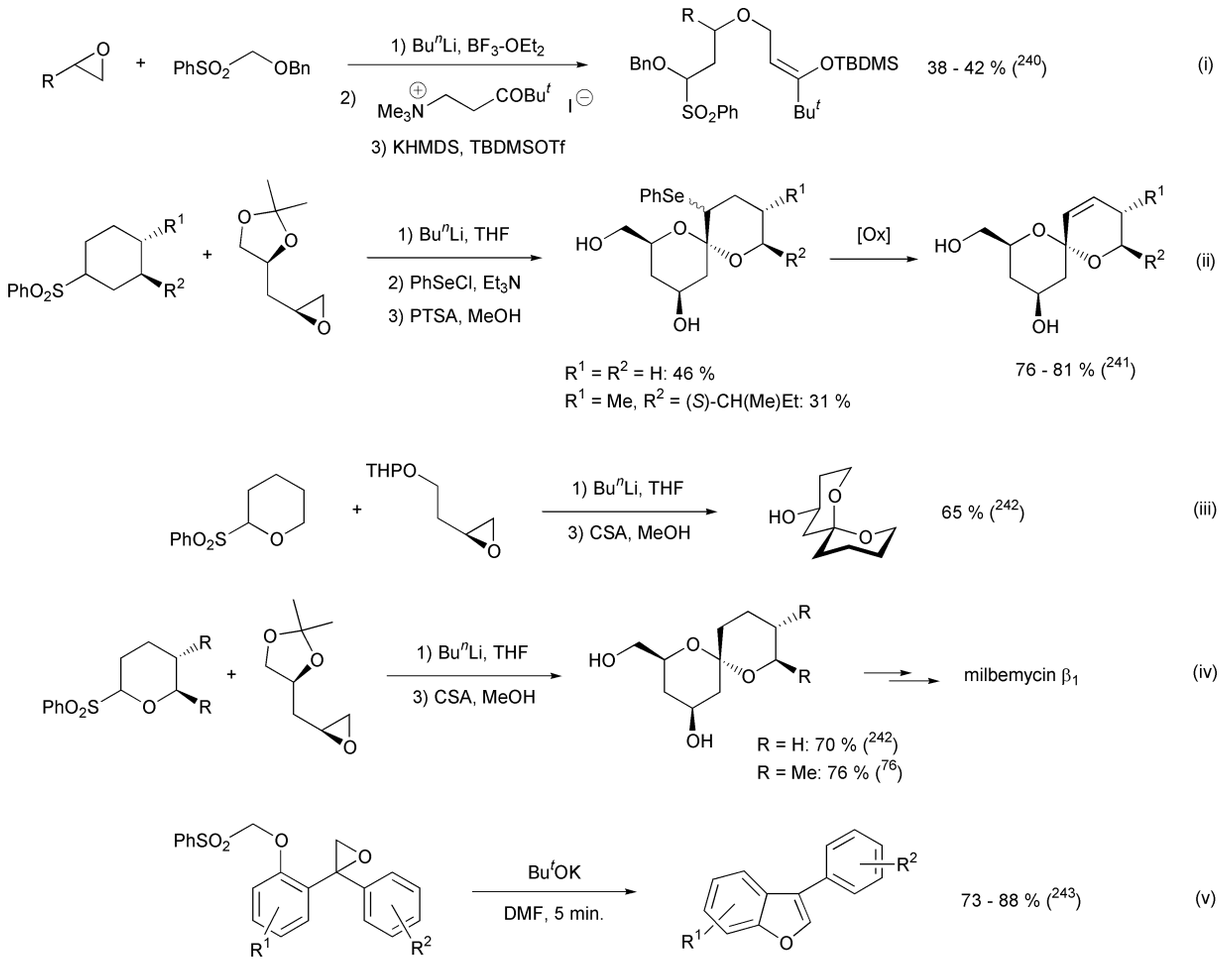
3.1.7 Elimination reactions

When a potential leaving group is present in the β-position of the α-oxy sulfone, β-elimination can occur to give the corresponding vinylic α-oxy sulfone.[93] This methodology has found little use in acyclic series. The α-oxy sulfones formed through nucleophilic substitution of β-halo acetals undergo readily a base-induced elimination to give vinylic α-oxy sulfones,[71] compounds which are somewhat difficult to prepare by other ways (Scheme 29).

On the other hand, this method has found a wide range of applications in carbohydrate chemistry,[232] because of its efficiency in forming 1-sulfonyl glycals. The general course of the reaction can be found in Scheme 30. Several leaving group have been used: OBn,[273–275] OMe,[276] ketals.[277,278] Yields are good when a strong base is used (LDA,[273,274] Bu^{n}Li,[275,276,278] MeLi[277]).

3.1.8 Ramberg–Bäcklund reactions

Recently the Ramberg–Bäcklund reaction (see Section 2.1.1) has found considerable interest for the synthesis of *exo*-glycals.[232] Several diversely substituted *exo*-glycals have been



Scheme 24 Reaction of metalated α-oxy sulfones with epoxides.

synthesized[279,280] by following the general synthetic pathway depicted in Scheme 31. It should be pointed out that although β-elimination occurs rapidly in the case of glycosyl sulfones (Section 3.1.7), this reaction works well with glycosyl sulfones bearing a leaving group (OBn or OTBDMS) in the β-position. It has been shown[279] that bromination occurs exclusively in the α′ position of the sulfone (see Section 3.1.1), and these results indicate that formation of the episulfone moiety occurs at a faster rate than the β-elimination process. Further research is needed to rationalize the exact mechanism.

This reaction, followed by hydrogenation of the resulting double bond, has been applied in the synthesis of benzylic C-glycosides,[281] C-linked disaccharides,[282] C-linked glycosyl amino acids[283] as well as C-glycolipids.[284]

Another recent development of the Ramberg–Bäcklund reaction involves epoxy sulfones.[285] Deprotonation in the α′-position of an epoxy sulfone is followed by an intramolecular ring opening of the oxirane to episulfone and subsequent SO_2 extrusion to yield allylic alcohols in fair to good yields (Scheme 32).

3.1.9 Miscellaneous reactions of α-oxy sulfonyl carbanions

Brückner has demonstrated the possibility of α-allyloxy sulfones to undergo metalation followed by a [2,3]-Wittig rearrangement.[61,167] The overall course of the reaction is depicted in Scheme 33. This reaction has been used for the stereocontrolled synthesis of the C_{14}–C_{20} fragment of amphotericin B.[61]

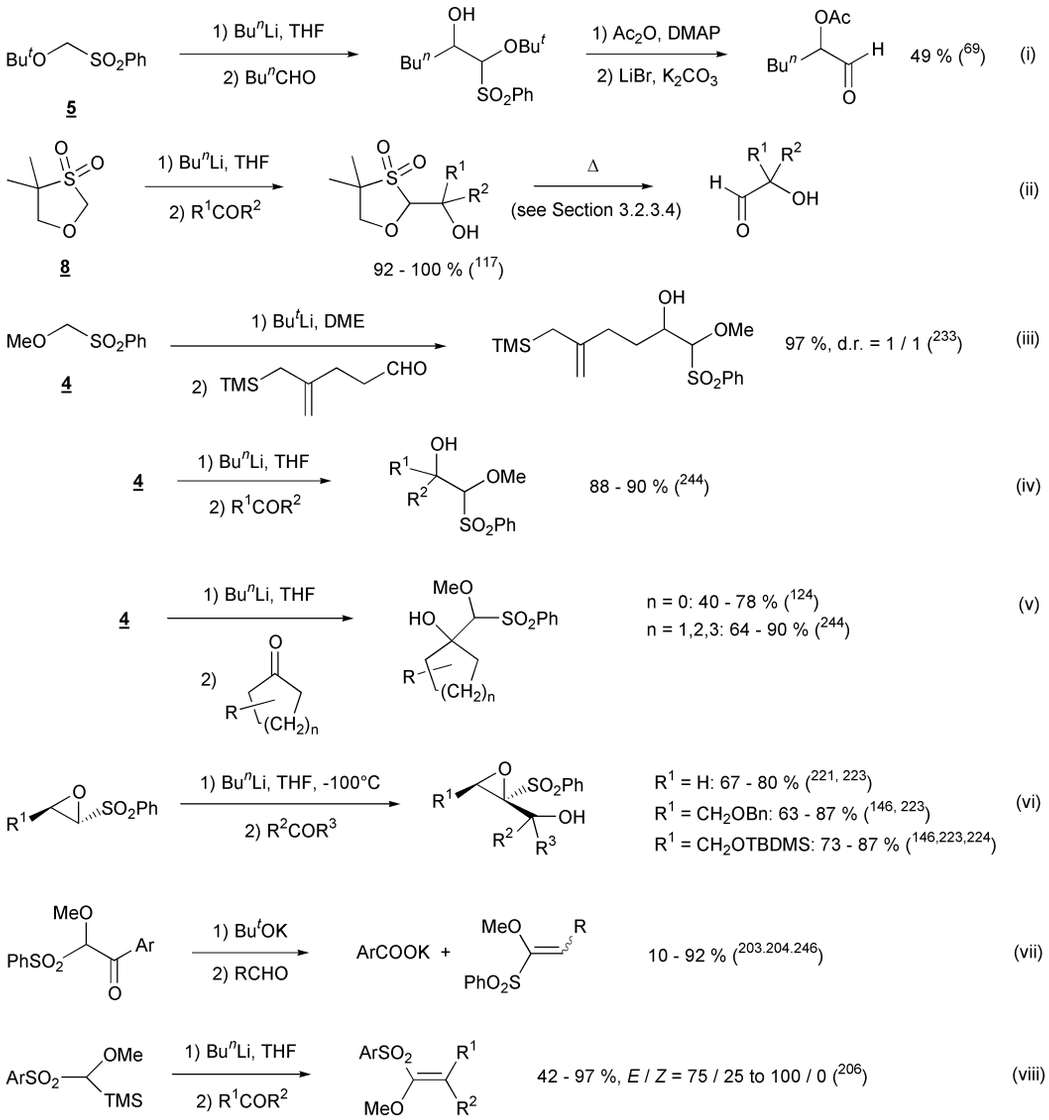
Reaction of α-oxy sulfonyl carbanions of epoxy sulfones with disulfides[286a,287] provides a good entry to epoxy-*S*,*S*-dioxythioketals (Scheme 34, eqn. (i)). Reaction with TMSCl has also been reported.[286b] Halogenation of α-oxy sulfonyl carbanions can be realized[287,288] by sulfuryl chloride or bromine (Scheme 34, eqns. (ii) and (iii)). Reactions of α-oxy sulfonyl carbanions derived from dihydropyrans with Bu_3SnCl give the corresponding α-oxy α-tributylstannyl sulfones. Upon treatment with base, they undergo elimination of the sulfinate group to give a rapid access to 2-tributylstannyldihydropyrans (Scheme 34, eqn. (iv)).[289–292] Base-induced elimination of sulfinate from alkylated α-methoxy-α-*tert*-butoxy sulfones to give methyl and *tert*-butyl vinyl ethers have also been achieved in good yields and with a moderate to good *E*/*Z* selectivity.[293,294] (*Z*)-Vinyl ethers are obtained as major products for alkyl α-oxy sulfones, whereas (*E*)-vinyl ethers are predominant starting from allylic and benzylic α-oxy sulfones (Scheme 34, eqn. (v)).

Dianions of sulfone **4** react[220] sequentially with diethylchlorophosphonate, then with aldehydes to give an access to vinylic α-oxy sulfones with a good stereoselectivity in the case of aromatic aldehydes (Scheme 34, eqn. (v)). The α-oxy-α-sulfonyl phosphonate intermediate can also be prepared through Rh(II)-catalysed insertion of α-sulfonyl diazophosphonates into alcohols[172] (see Section 2.4.1).

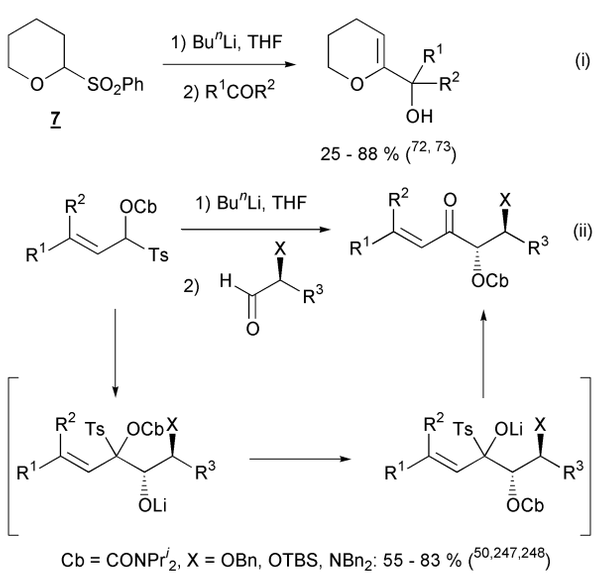
The reaction of a cyclic α-oxy sulfone with an electrophilic carbenoid has been reported[295] for the preparation of an exocyclic enol ether (Scheme 34, eqn. (vii)). This reaction has been applied to the synthesis of a phorboxazole fragment.

3.2 Through nucleophilic displacement of the sulfonyl group

The sulfonyl group of an α-oxy sulfone can be easily displaced by a nucleophile. The exact mechanism is not known, but it can be assimilated in most cases to an S_N1 reaction as, for example, substitution of the sulfonyl group in a diastereoisomeric mixture of tetrahydropyranyl sulfones gives substitution products in a diastereoisomeric ratio which is not related to that of the starting materials. In most cases, a Lewis acid activates the



Scheme 25 Reaction of metalated α-oxy sulfones with aldehydes or ketones.



Scheme 26

substitution reaction, and the general mechanism can be envisioned as depicted in Scheme 35.

This overview will be divided into two main parts: nucleophilic substitution with heteroatom-centered nucleophiles and nucleophilic substitution with carbon-centered nucleophiles.

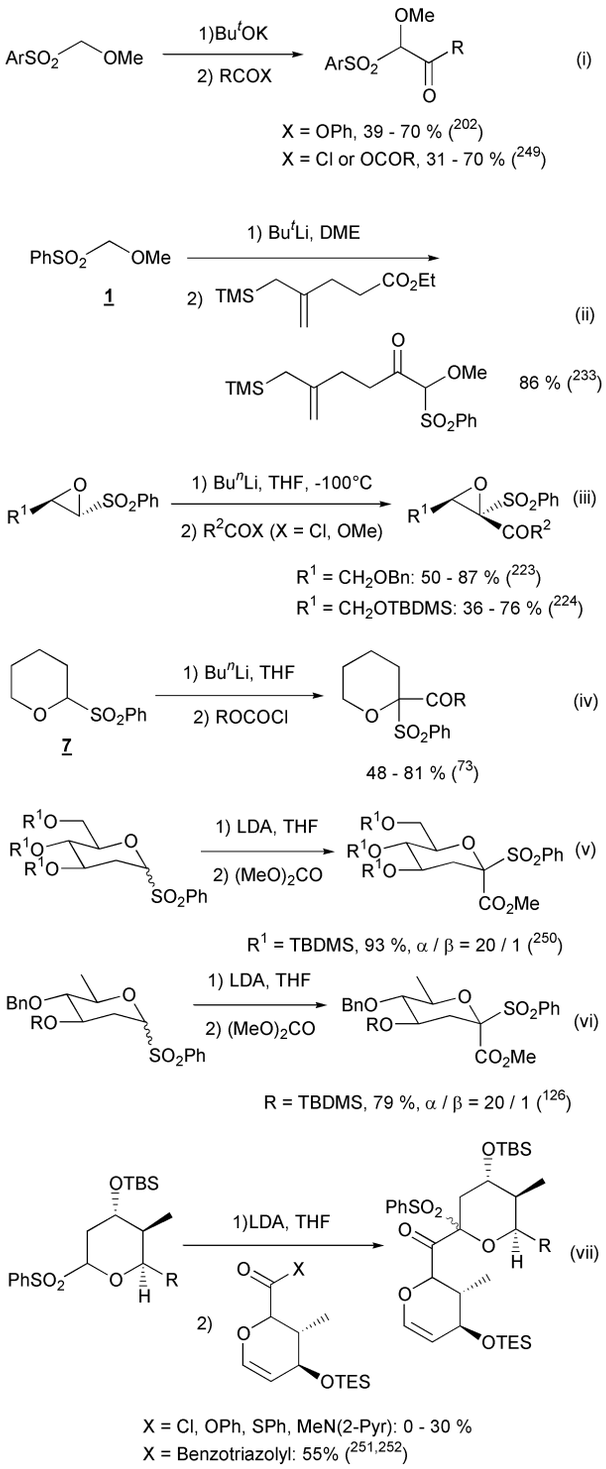
3.2.1 With heteroatom nucleophiles

3.2.1.1 Oxygen-centered nucleophiles

It has been shown that solvolytic displacement of the sulfonyl group in α-methoxy sulfones and α-*tert*-butoxy sulfones by alcohols can be achieved in good yields to give the corresponding mixed acetals or ketals. For α-methoxy sulfones, the reaction occurs under somewhat harsh conditions[294] (catalytic PTSA in refluxing methanol, Scheme 36, eqn. (i)), when for α-*tert*-butoxy sulfones,[296] the solvolytic displacement occurs under slightly basic conditions at room temperature (Scheme 36, eqn. (ii)). The parent α-*tert*-butoxy sulfone **5** itself has been developed as a *tert*-butoxymethyl protecting group donor (Scheme 36, eqn. (iii)).[296]

Displacement of the sulfonyl group in tetrahydrofuranyl and tetrahydropyranyl sulfones by alcohols has been achieved in good yields.[297,298] Here again, activation with a Lewis acid is necessary under slightly basic conditions (Scheme 36, eqn. (iv)). As stated above, the reaction is not stereospecific. This methodology has been applied in an intramolecular fashion (Scheme 36, eqn. (v)).[299] Related to that is the *in situ* spiroketal synthesis mentioned above (see Sections 3.1.3 and 3.1.4). On the other hand, the same type of reaction on sulfones in the butenolide series has been reported to fail.[300]

Some examples are reported in intramolecular[113] and intermolecular[301] glycosylation reactions (Scheme 36, eqns. (vi) and (vii)). Related to that is the impossibility, reported by

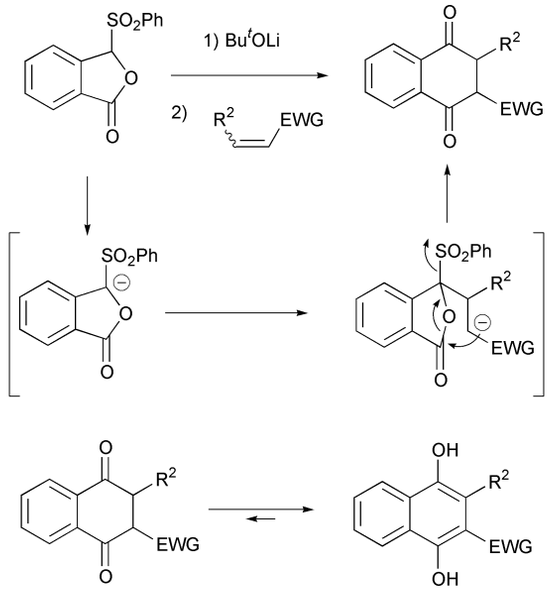


Scheme 27 Reactions of metalated α-oxy sulfones with acyl derivatives.

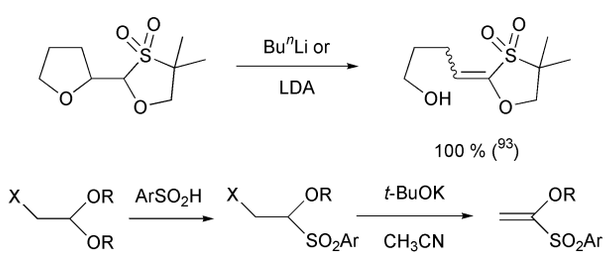
Beau and coworkers,[302] to oxidize anomeric sulfides in the β-galactosamine series, although a possible rearrangement of the sulfoxide intermediate into sulfenate[303] can be also envisioned. The nucleophilic displacement of the sulfonyl group in the chromone series has been reported (Scheme 36, eqn. (viii)).[304]

It has been shown that alkylated disulfones derived from the disulfone **9** can be transformed into esters by treatment with methanol in the presence of boron trifluoride etherate.[137] The sulfone **9** behaves thus as a methoxycarbonyl anion equivalent (Scheme 36, eqn. (ix)).

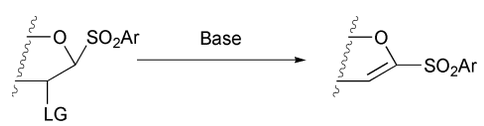
Finally, the reaction of α-acyl-α-halo-α-methoxy sulfones with alkoxides is reported to follow a retrocondensation pathway (Scheme 36, eqn. (x)); surprisingly neither the sulfonyl group nor the halogen moiety is substituted in these conditions.[288]



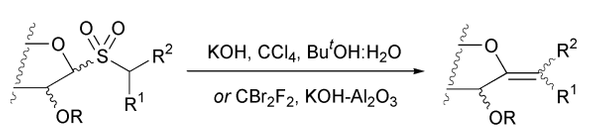
Scheme 28 Synthesis of naphtha- and anthraquinones.



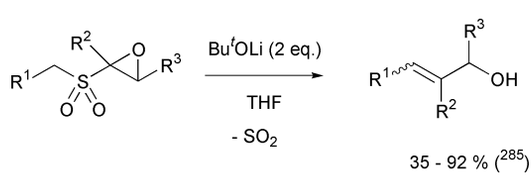
Scheme 29 Elimination reactions of metalated α-oxy sulfones.



Scheme 30 Synthesis of glycals.



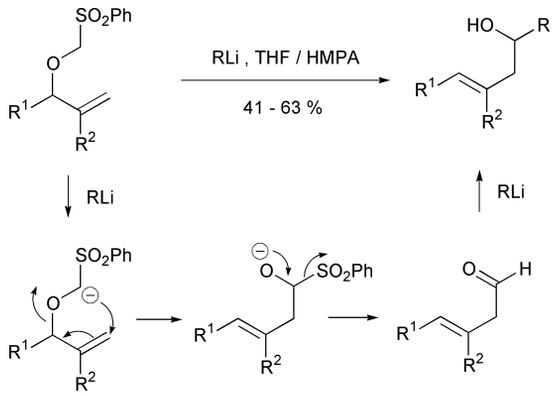
Scheme 31 *exo*-Glycals by Ramberg–Bäcklund reaction.



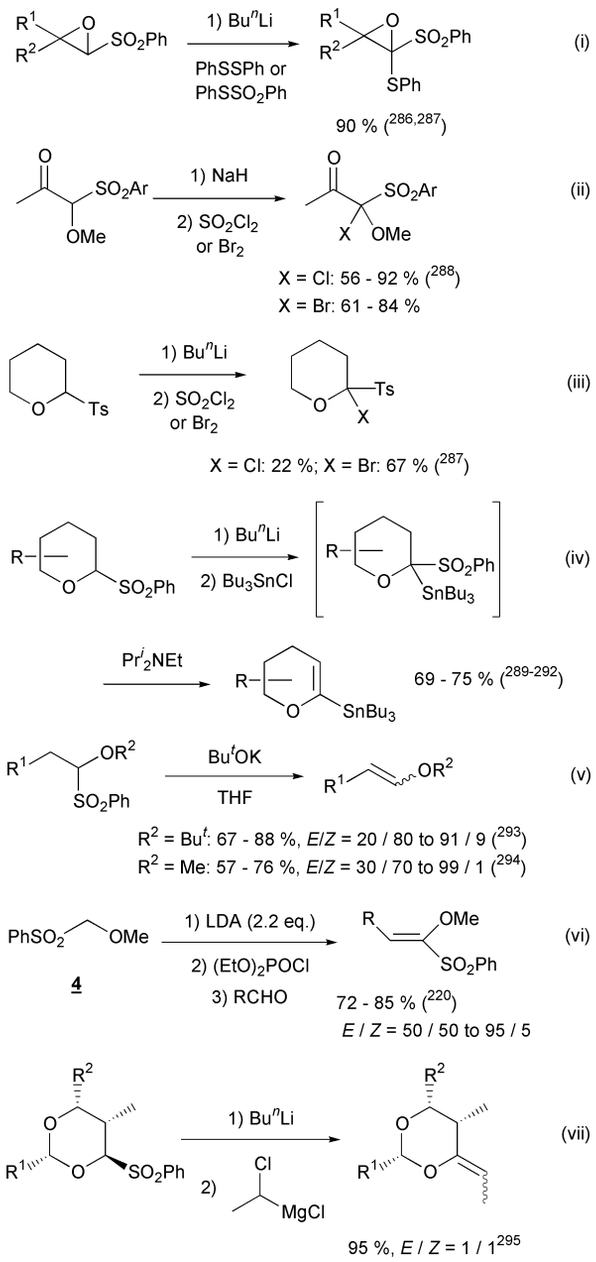
Scheme 32 Allyl alcohols by Ramberg–Bäcklund reaction.

3.2.1.2 Nitrogen-centered nucleophiles

Sulfones in the 2-position of a furan,[305–309] 1,3,4-oxadiazole[310] or chromone[311] ring have been shown to be displaced easily by amines (Scheme 37).



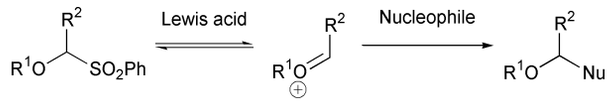
Scheme 33 [1,3]-Wittig rearrangement.



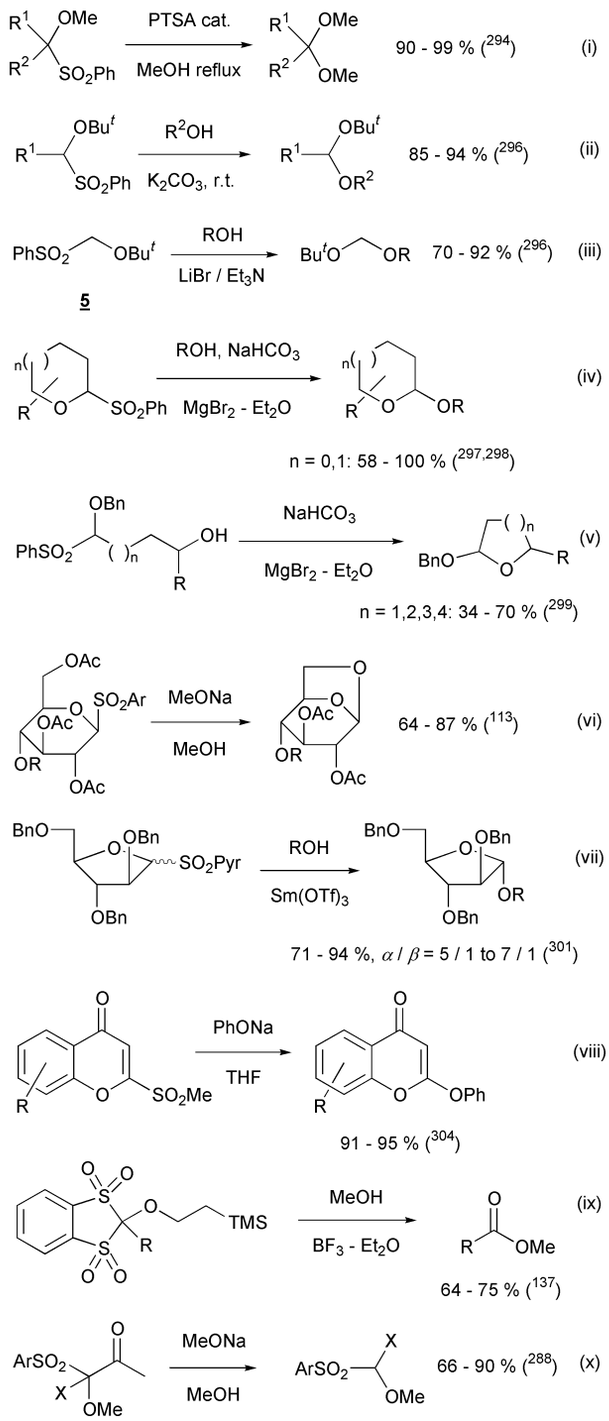
Scheme 34 Reactions of metalated α-oxy sulfones with various electrophiles.

3.2.1.3 Other heteroatom-centered nucleophiles

The reduction of α-*tert*-butoxy sulfones by hydrides has also been realized in good yields [312] (Scheme 38, eqn. (i)). Some other substitution reactions with phosphorus-centered nucleophiles [313] and sulfur-centered nucleophiles [311] (Scheme 38, eqns. (ii) and (iii)) are reported. The reaction of the anion derived from 2-tosyl tetrahydropyran with phenyl disulfide is reported [287] to give 2,2-di(phenylthio)tetrahydropyran through substitution of the sulfonyl moiety by phenylthiolate in the 2-phenylthio-2-tosyltetrahydropyran intermediate (Scheme 38, eqn. (iv)).



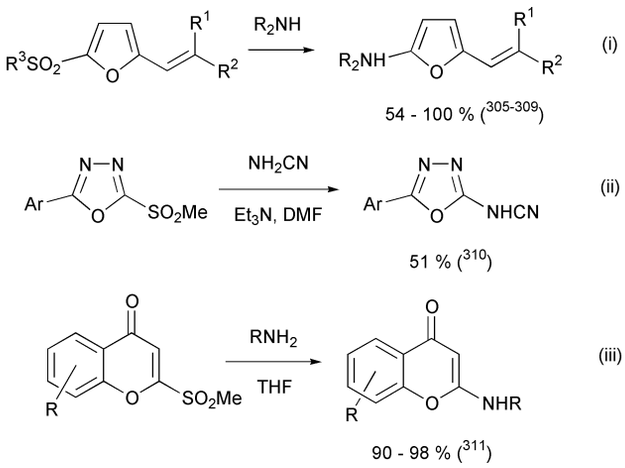
Scheme 35 Nucleophilic displacement of the sulfonyl group.



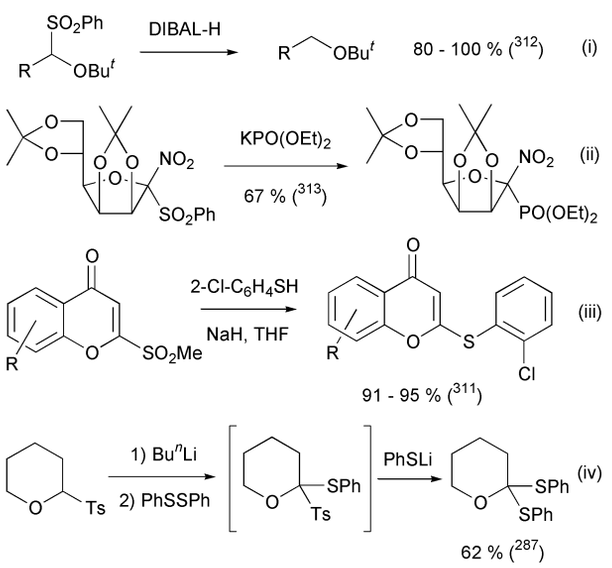
Scheme 36 Reactions with oxygen-centered nucleophiles.

3.2.2 With carbon nucleophiles

The sulfonyl group of an α-oxy sulfone can be readily displaced by carbon-centered nucleophiles. This displacement can be



Scheme 37 Reactions with nitrogen-centered nucleophiles.



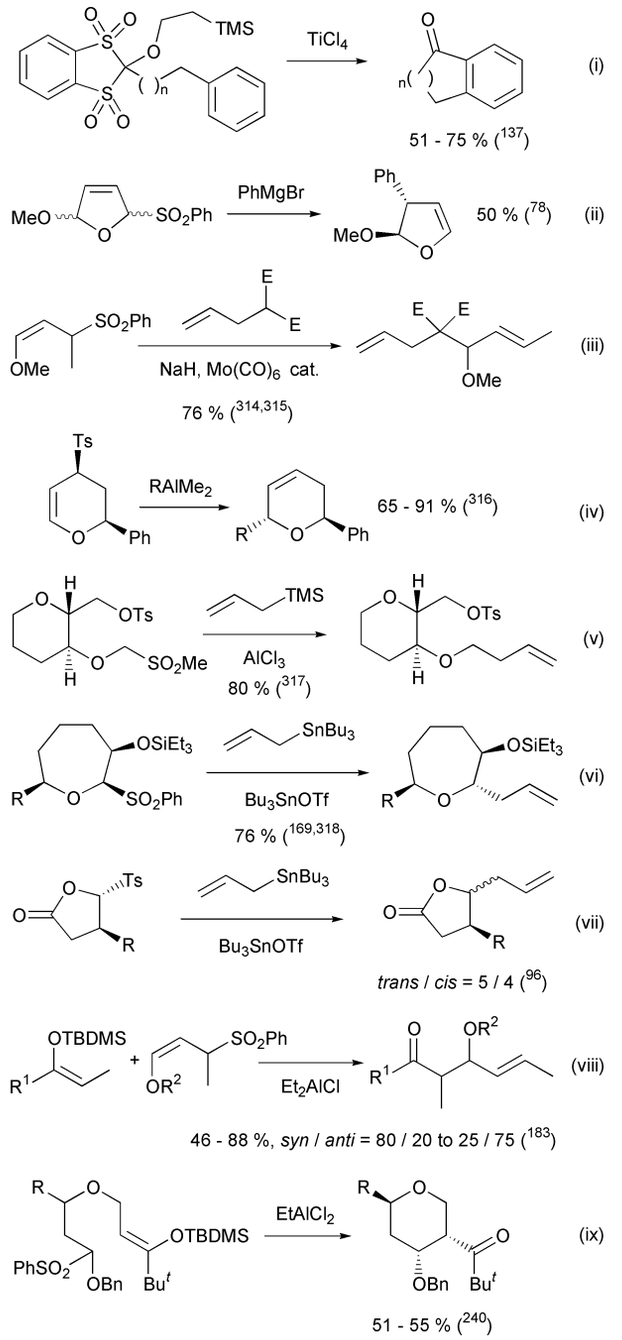
Scheme 38 Reactions with various nucleophiles.

achieved by various nucleophiles (Grignard reagents, allylsilanes, silicon enolates) and has been particularly studied and developed in the case of cyclic α-oxy sulfones.

Reaction of alkylation products derived from the disulfone **9** and bearing an aromatic ring in the right position can undergo a Friedel–Crafts-type reaction to give aromatic ketones[137] (Scheme 39, eqn. (i)). The sulfonyl group, in these substitution reactions, is generally a better leaving group than the ether moiety. This is exemplified in the the reactions depicted in Scheme 39. Nucleophiles include Grignard reagents[78] (Scheme 39, eqn. (ii)), malonates[314,315] (Scheme 39, eqn. (iii)), aluminium reagents[316] (Scheme 39, eqn. (iv)), allylsilanes[317] (Scheme 39, eqn. (v)), allylstannanes[96,169,318] (Scheme 39, eqns. (vi) and (vii)) as well as silicon enolates in an intermolecular[183] and intramolecular[240] fashion (Scheme 39, eqns. (viii) and (ix)).

Nucleophilic displacement of the sulfonyl group of tetrahydrofuranyl- and tetrahydropyranyl sulfones can be achieved in good yields by Grignard reagents in the presence of zinc(II) salts.[74,319] This methodology has been extensively studied and applied in total synthesis. The stereoselectivity of the substitution is in general excellent in the THP series, but lower in the THF series. Some representative examples[74,320–322] are given in Scheme 40. This reaction has been used in the total synthesis of tetronasin,[323,324] okadaic acid[325] and the anti-asthmatic CMI-977.[326] By this way it is possible to obtain fused oxetanes.[327,328]

When the α-oxy sulfone is bearing an allylsilane moiety in the proper position, a direct Sakurai-type cyclization reaction can occur between this allylsilane moiety and the *in situ* formed oxonium ion.[329] Surprisingly the stereochemistry of the cyclized

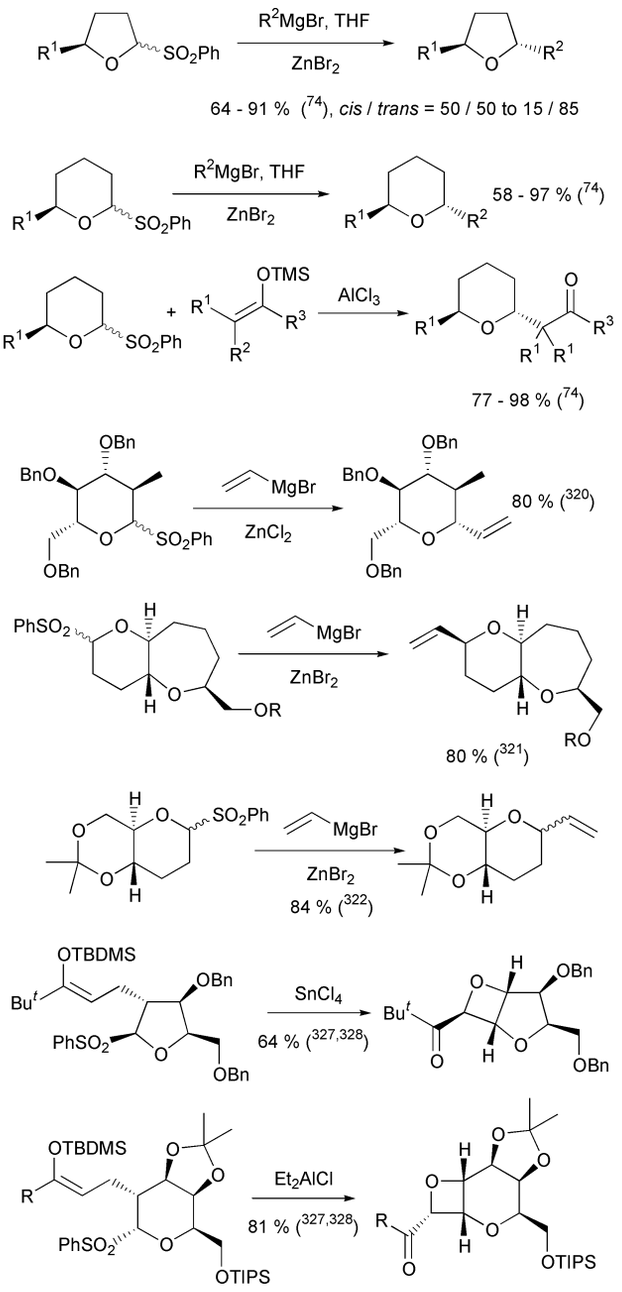


Scheme 39 Reactions with carbon-centered nucleophiles.

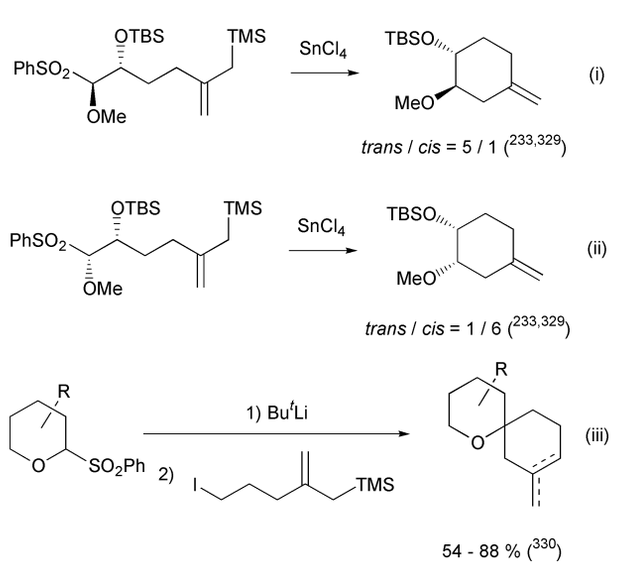
product is directly related to the one of the starting α-oxy sulfone[233] (Scheme 41, eqns. (i) and (ii)). This was attributed to a slow oxonium equilibration compared to the reaction rate, rather than an S_N2-type reaction. When the allylsilane is introduced through alkylation of a tetrahydropyranyl sulfone, cyclization occurs in the same pot without the need of a Lewis acid, presumably through the corresponding substituted dihydropyran. The stereochemistry of this cyclization, which depends on the substituents on the tetrahydropyranyl ring, has been studied in detail (Scheme 41, eqn. (iii)).[330]

3.2.3 Rearrangement reactions

This section deals with rearrangement reactions of α-oxy sulfones. Four different types of rearrangement can be considered. The first one is concerning all reactions in which a *retrocondensation of an α-sulfonyl alkoxide into aldehyde* is involved. The second one is concerning *sulfonyl group migration*, and the third *carbon–carbon bond migration* with sulfinate expulsion. The fourth one is concerning all *SO_2-extrusions*.



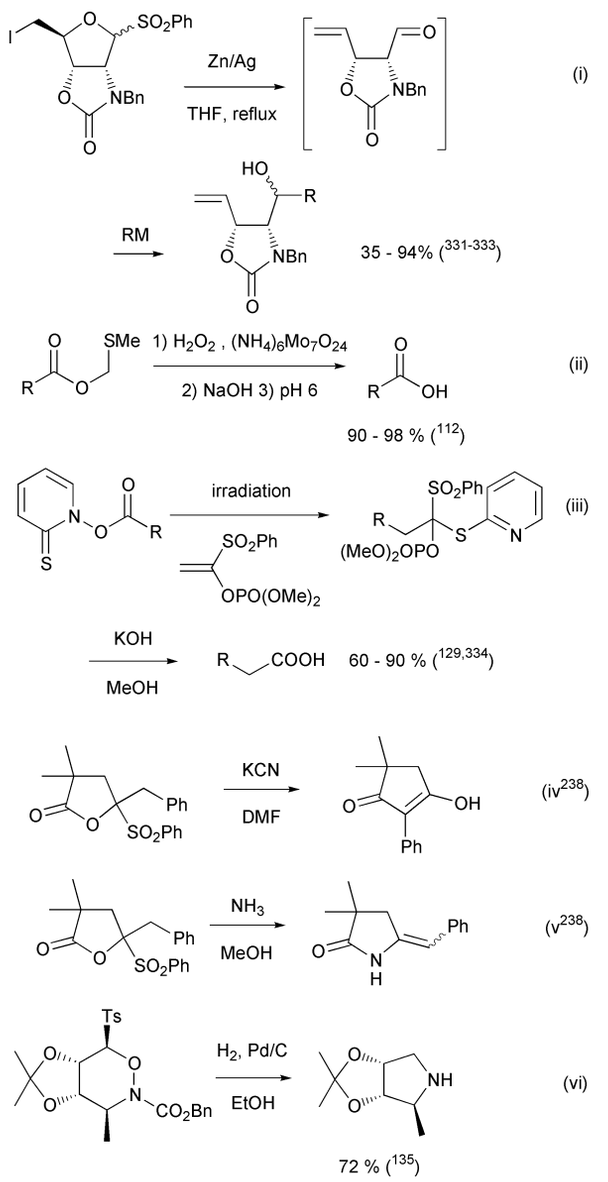
Scheme 40 Reactions of cyclic α-oxy sulfones with carbon-centered nucleophiles.



Scheme 41 Intramolecular Sakurai cyclizations of α-oxy sulfones.

3.2.3.1 Retrocondensation of an α-sulfonyl alkoxide into aldehyde

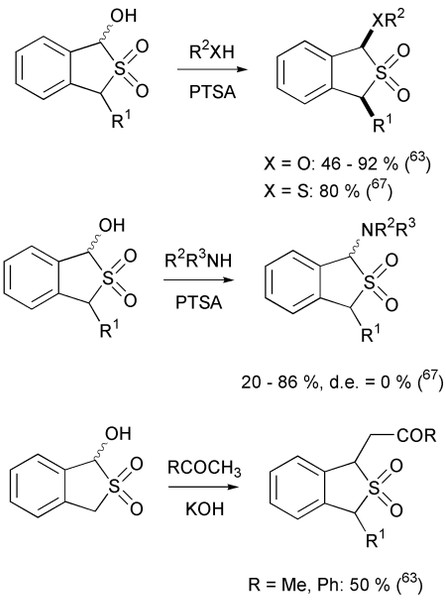
It has been mentioned above (see Section 2.2.1) that α-hydroxy sulfones are unstable in a basic medium and undergo retrocondensation to aldehydes with sulfinate elimination. This feature is a part of the interest of α-oxy sulfones as formyl, acyl and alkoxycarbonyl equivalents (see Section 3.1.5). Some examples have already been mentioned above: rearrangement of the product derived from the condensation of α-carbamoyloxy allyl sulfones[50,247,248] (see Section 3.1.5), retrocondensation during the [2,3]-Wittig rearrangement of α-allyloxy sulfones[61,167] (see Section 3.1.9). and of course sulfinate elimination in the naphthaquinones and anthraquinones through phthaloyl sulfones (see Section 3.1.6). This feature has been used for example for the *in-situ* preparation and uses of unstable aldehydes[331–333] (Scheme 42, eqn. (i)), oxidative deprotection of methylthiomethyl esters (Scheme 42, eqn. (ii)),[112] and in a nice method of one-carbon homologation of carboxylic acids (Scheme 42, eqn. (iii)).[129,334] Some other examples[135,238] can also be found in Scheme 42 (eqns. (iv)–(vi)).



Scheme 42 Reactions involving retrocondensation of α-oxy sulfones into carbonyl compounds.

The conversion of hydroxybenzothiophene *S*,*S*-dioxides into alkoxybenzothiophene *S*,*S*-dioxides by treatment with an alcohol has been mentioned above. This process also involves

retrocondensation of a α-hydroxy sulfone into an aldehyde. The same reaction can be carried out with thiols or amines,[67] giving the corresponding thiobenzothiophene *S*,*S*-dioxides and aminobenzothiophene *S*,*S*-dioxides (Scheme 43).



Scheme 43 Preparation of diversely substituted benzothiophene *S*,*S*-dioxides.

The use of α-hydroxy sulfones as carbonyl precursors has featured particularly in the nucleophilic ring opening of epoxy sulfones. Due to steric and field effects,[335] the sulfonyl group deactivates the α-carbon, and thus nucleophilic attack occurs on the carbon β- to the sulfonyl group. The resulting α-hydroxy sulfone is then transformed into a carbonyl group (Scheme 44, eqn. (i)). This general way has been widely used, and some representative examples, including oxygen-centered nucleophiles (Scheme 44, eqn. (ii)),[336] nitrogen-centered nucleophiles (Scheme 44, eqns. (ii)–(v)),[23,336–338] phosphorus-centered nucleophiles[339] (Scheme 44, eqn. (vi)) and some others[336] (Scheme 44, eqn. (ii)) are listed here.

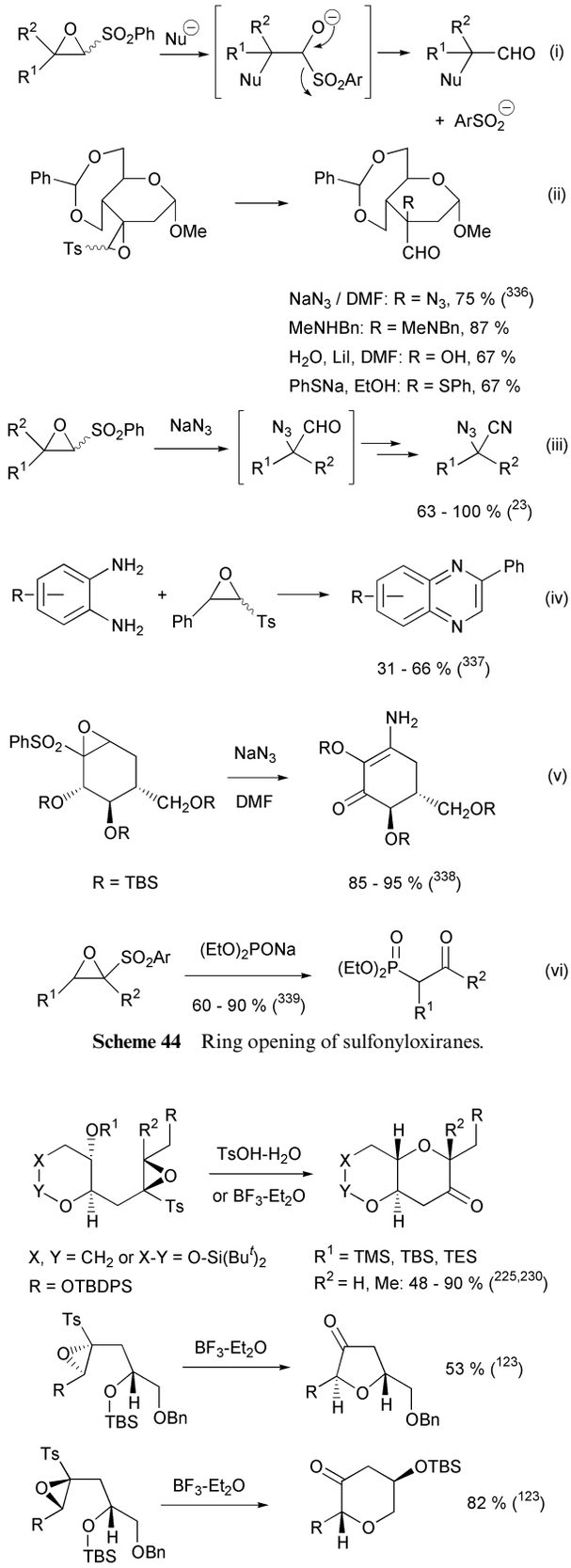
Intramolecular ring opening of epoxy sulfones by oxygen-centered nucleophiles has been reported. In this case, use of a Bn-,[123] TMS-,[230] TES-[230] or TBS-[123,160,225,230] protected alcohol implied the necessity of activation by a Lewis or Bronstëdt acid. This methodology, joined to the epoxy sulfone carbanion methodology, has been applied in a very nice iterative formal total synthesis of hemibrevetoxin.[226,228] However, depending on the substitution of the nucleophile and the acid used, competition between the nucleophilic ring-opening and the rearrangement with sulfinate migration (see Section 3.2.3.2) can occur.[230] Some of these results are listed in Scheme 45.

The ring opening of epoxy sulfones by halide ions[29,30] giving α-halo carbonyl compounds has been particularly studied. The reaction is stereospecific[157,229] and has been applied to a wide range of epoxy sulfones.[29,30,157,223,224,229,286] In the case of optically pure epoxysulfoximines, as the epoxydation reaction is also largely stereospecific, the corresponding α-halo ketones are obtained in a good enantiomeric excess.[159,340,341] Some of these results are reported in Scheme 46.

By contrast, some examples are reported where the regioselectivity of the nucleophilic attack is the opposite of the common one; ring opening occurs on the carbon bearing the sulfonyl moiety. These examples[25,336] are listed in Scheme 47. No explanation to date has been proposed for this unusual behaviour, but it could be related to steric hindrance.

3.2.3.2 Rearrangements with sulfonyl migration.

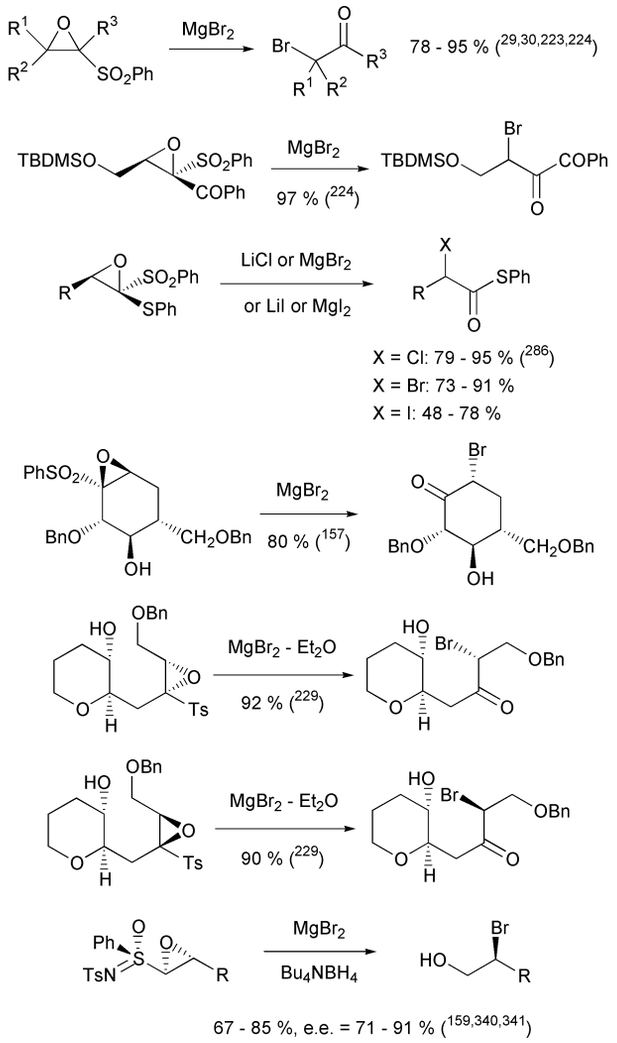
Upon treatment with BF_3–Et_2O[30,230,342,343] or upon heating,[30,342,343] epoxy sulfones undergo rearrangement with



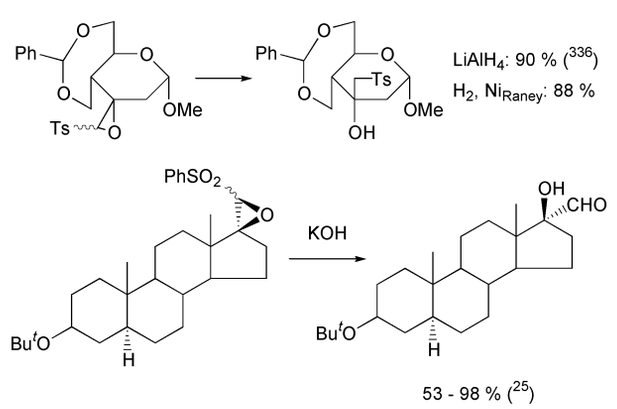
Scheme 44 Ring opening of sulfonyloxiranes.

Scheme 45 Intramolecular ring opening of sulfonyloxiranes by oxygen-centered nucleophiles.

sulfinate rearrangement. The mechanism (Scheme 48, eqn. (i)) is proposed to be cationic, as sometimes competitive 1,2-hydride shift occurs.[30] This has been applied in a nice ring-expansion of cyclic sulfones (Scheme 48, eqn. (ii)),[30] in a synthesis of β-sulfonylenamines[31] (Scheme 48, eqn. (iii)) and in a synthesis of substituted pipecolic acid derivatives[344] (Scheme 48,



Scheme 46 Ring opening of sulfonyloxiranes by halide nucleophiles.

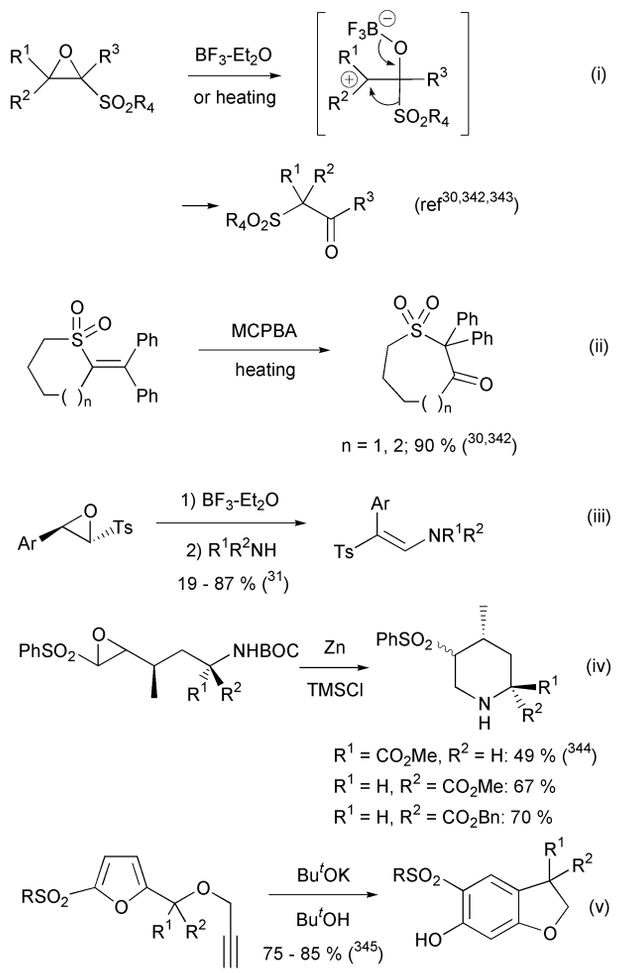


Scheme 47

eqn. (iv)). Finally, a strange rearrangement of 2-sulfonyl-5-propargyloxymethylfurans (Scheme 48, eqn. (v)) involving sulfinate migration has been reported.[345]

3.2.3.3 Rearrangements with carbon–carbon bond migration

The possibility of a one carbon ring expansion of cyclobutanones and cyclopentanones mediated by aluminium Lewis acids was first demonstrated by Trost and Mikhaïl.[245] The reaction is regioselective, following the trend of the more substituted carbon undergoing preferential migration, but shows little stereoselectivity in favor of the thermodynamically more stable diastereomer.[124] Although yields are only fair, and



Scheme 48 Rearrangements with sulfinate migration.

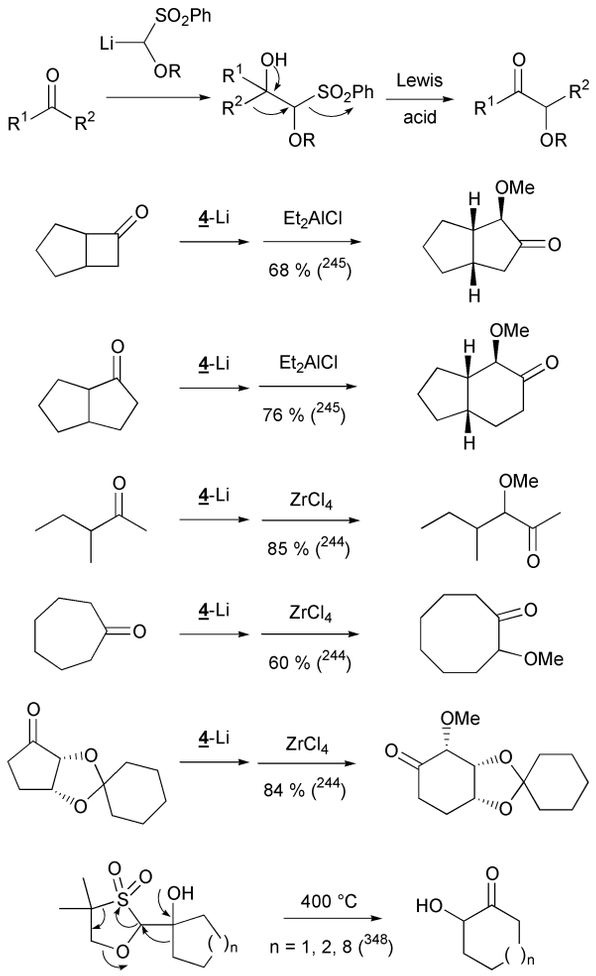
the reaction limited to four- and five-membered rings as starting materials,[124,245] it was applied in prostaglandin synthesis.[346] However, use of zirconium tetrachloride as activator enhanced yields and the reaction was then efficient also for six- and seven-membered rings as starting materials, as well as in acyclic series.[244] This methodology was applied to conduritol synthesis.[347] The generally accepted mechanism and some representative examples are listed in Scheme 49. A similar, but more complex rearrangement has been observed in the hydroxyoxathiolane *S*,*S*-dioxide series.[348]

3.2.3.4 Rearrangements with sulfur dioxide extrusion

Thermal extrusion of sulfur dioxide from substituted benzothiophene *S*,*S*-dioxides results in the formation of *ortho*-quinodimethanes through a disrotatory process.[65] These *ortho*-quinodimethanes have been trapped with various dienophiles[63,65,349,350] to give substituted benzocyclohexanes in a stereoselective fashion. Use of homochiral benzothiophene *S*,*S*-dioxides results in the formation of homochiral substituted benzocyclohexanes;[64,70,351] this has been applied in the asymmetric synthesis of isolariciresinol dimethyl ether[66] and podophyllotoxin analogues.[68] Some selected representative examples are listed in Scheme 50. Related to this sulfur dioxide extrusion is the transformation of α-oxy sulfones derived from the sulfone **8** into carbonyl compounds, under somewhat harsh conditions.[117]

3.3 Through reduction of the sulfonyl group

Several different methods have been used for the reduction of α-oxy sulfones: sodium amalgam, tin hydride, lithium naphthalenide, titanium(II) and samarium diodide reductions have been reported. As the products as well as the stereo-



Scheme 49 Rearrangements with carbon-carbon bond migration.

chemical outcome of the reductions is highly dependent on the conditions and the substrates, these methods will be reviewed separately.

3.3.1 Reductions with sodium amalgam

Reductive dimerization by sodium amalgam of α-alkoxy sulfones into polyethers has been reported [312] (Scheme 51, eqn. (i)). This method has been applied to the synthesis of crown ethers.

3.3.2 Tin hydride-mediated reductions

It is possible to reduce α-oxy sulfones into ethers with tributyltin hydride under radical conditions. This method has been mainly used in 2-sulfonylfuran and benzofuran series,[52] as well as in the sulfonylglycal series [275,352–354] (Scheme 51, eqn. (ii)) to give, upon sulfonyl–tin exchange, 1-tributylstannylglycals which are interesting precursors of 1-metalated glycals.[232] Reduction of tertiary α-oxy sulfones in the same conditions leads to the corresponding ether upon sulfonyl-H exchange [42,239] (Scheme 51, eqns. (iii) and (iv)). This method has been applied in the total synthesis of papulacandins.[276]

3.3.3 Lithium naphthalenide mediated reductions

The reduction of α-oxy sulfones with lithium naphthalenide leads to α-oxygenated lithium species. This methodology has been applied to induce [2,3]-Wittig rearrangements,[355] but the most important field is the formation of glycosyl anions. Since the initial applications of this methodology in tetrahydropyran [73] and glycosyl [356] series, a number of applications have been published. As this chemistry has already been reviewed recently,[232] just general trends will be mentioned here.

The presence of a leaving group in the β-position gives rise to β-elimination reaction to form glycals (Scheme 52, eqn. (i)). The same behaviour has been observed through titanium-catalysed reduction of a glycosyl-2-pyridyl sulfone.[357] When there is no leaving group in the β-position, the resulting lithium carbanion adopts an axial configuration, due to the preferentially axially oriented radical intermediate (Scheme 52, eqn. (ii)). This trend is reversed when the α-oxy sulfone also bears a carbonyl moiety in the α-position. Several one pot transformations of α-oxy sulfones involving 1) deprotonation 2) reaction with electrophile 3) lithium naphtalenide reduction (Scheme 52, eqns. (iii) and (iv)) have been reported, and applied for example in the synthesis of spongistatins.[358] However, due to side reactions (for example dimerization [359]) and the limitation to have no leaving group in the β-position, attention turned recently to the samarium diiodide-induced reduction.

3.3.4 Samarium diiodide-induced reductions

Samarium diiodide-induced reduction of glycosyl 2-pyridyl sulfones has received wide interest in the last few years.[232] Its great advantage over lithium naphthalenide reductions is that the carbanion resulting from the reduction is less basic than its lithium counterpart, and also less prone to β-elimination. This has been particularly demonstrated in the *manno*-pyrannosyl [360–365] (Scheme 53, eqn. (i)) and *N*-acyl galactosamine [366,367] (Scheme 53, eqn. (ii)) series. Under Barbier conditions, the resulting α-directed samarium(III) anion has been quenched by a variety of electrophiles, with few elimination products. On the other hand, Sm(III) anions derived from glucosyl and galactosyl pyridyl sulfones give β-directed samarium(III) anions, which can also react with electrophiles, but are much more prone to β-elimination (Scheme 53, eqn. (iii)).[360,363] This last process can be seriously diminished under nickel iodide catalysis (Scheme 53, eqn. (iv)).[368] Actually, all seems to indicate that glycosyl Sm(III) anions are more prone to *syn*-elimination than *anti*-elimination.[363] The α or β stereoselectivity is not related to the stereochemistry of the starting sulfone, but has been attributed to the initial formation of an axially oriented anomeric glycosyl samarium(III) compound. This kinetic product reacts in the *manno* series on the α-orientation, but undergoes a configurational change to the thermoynamically favoured equatorial Sm(III) intermediate in the *gluco* and *galacto* series to react in the β-orientation with an important part of β-elimination.[363] Elimination becomes the major pathway if a benzenesulfonyl group is used instead of a 2-pyridylsulfonyl group,[369,370] or by addition of HMPA, together with reductive dimerization.[371]

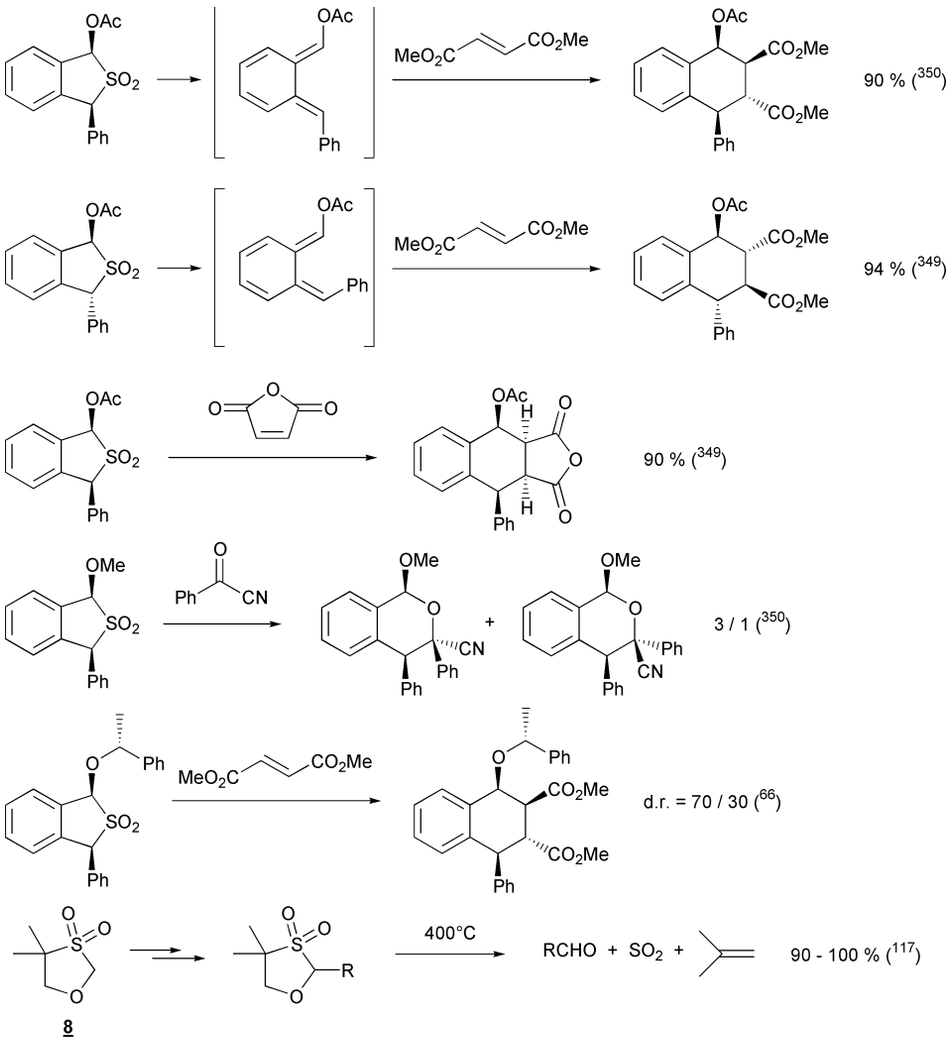
When the β-substitutent of a glycosyl pyridyl sulfone bears an unsaturated silicon moiety, the glycosyl radical formed by reduction with SmI_2 can cyclize before being further reduced to give C-glycosides. This tethered approach has been recently used for the synthesis of 1,2-*cis*-C-glycosides [372,373] (Scheme 54).

3.4 Through carbenoid reactions

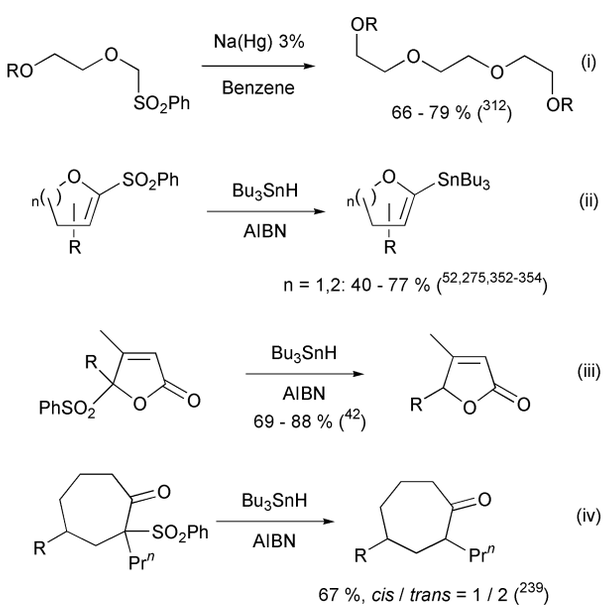
Very few studies have been done concerning the possible carbenoid behaviour of α-oxy sulfonyl carbanions. α-Methoxy-α-halo sulfones have been shown to be a possible source of singlet carbenes upon treatment with bases.[374] These carbenes have been engaged in cyclopropanation reactions (Scheme 55, eqn. (i)). On the other hand, lithiated α-*tert*-butoxy sulfones have been shown to behave as electrophiles towards lithiated sulfones to give a good access to *tert*-butyl vinyl ethers (Scheme 55, eqn. (iii)).[293,375]

4 Conclusion and perspectives

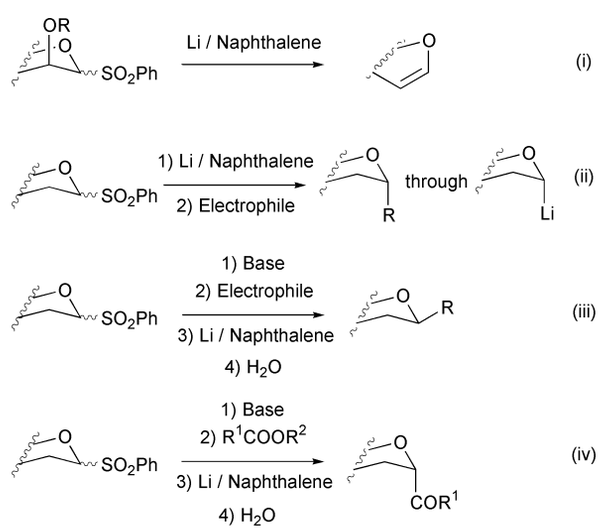
As it can be seen throughout this review, the chemistry of α-oxy sulfones presents all the features of the simple sulfones, enriched by other very important features related to the



Scheme 50 Rearrangements with SO_2 extrusions.

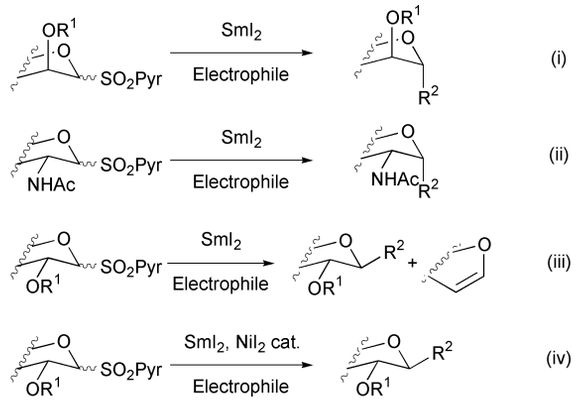


Scheme 51 Radical mediated reductions.

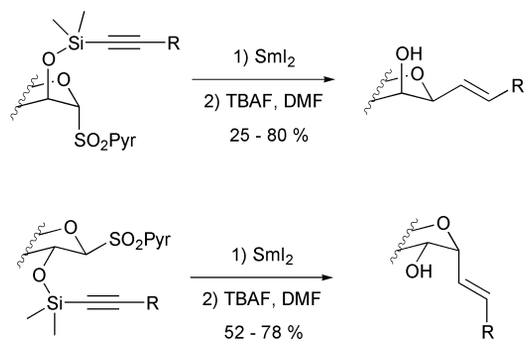


Scheme 52 Reductions of glycosyl sulfones.

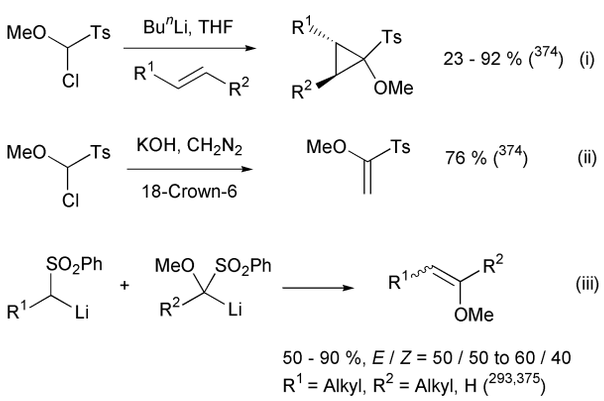
excellent leaving group ability of the sulfonyl group. After the seminal works of K. Schank in the seventies and F. M. Hauser in the beginning of the eighties, this chemistry has entered into its adulthood with the works of S. V. Ley, R. F. W. Jackson, J.-M. Beau, R. J. K. Taylor and many others. Synthetic applications are growing more and more numerous, especially concerning the tetrahydropyranyl sulfones and glycosyl sulfones chemistry. On the other hand, the potential of α-oxy sulfones as formyl, acyl and alkoxycarbonyl anions equivalents has been more rarely applied. This is rather surprising, in view of their simplicity. Some fields remained rather unexplored, especially the one of carbenoid reactions. However, undoubtedly, the chemistry of α-oxy sulfones has shown its



Scheme 53 SmI_2 mediated reductions of glycosyl sulfones.



Scheme 54 Formation of C-glycosides through SmI_2 reductions.



Scheme 55 Carbenoid-type reactions of α-oxy sulfones.

versatility and their transformations have entered into the group of synthetic methodologies a chemist should remember in his every day work.

5 Acknowledgements

Thanks are due to my friend Da Zhang, who gave me several years ago the courage to undertake this review.

6 References

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