Sulfoxonium ylides: Simple compounds with chameleonic reactivity

Sulfoxonium ylides: simple compounds, chameleonic reactivity

Giorgiana Denisa Bisag,[a] Silvia Ruggieri,[a] Mariafrancesca Fochi [a] and Luca Bernardi [*a]

Sulfur ylides first disclosed in 1930 have started to get more attention in 1960s, thanks mainly to the studies by Corey and Chaykovsky on their use for the preparation of strained rings. More recently, the chemistry of these compounds has experienced an important growth, in part due to the similarity of their reactivity with diazo compounds. This short review gives an overview on the great assortment of reactions of sulfoxonium ylides, outlining a comparison between the chemistry of these ylides and their congeners: sulfonium ylides and diazo compounds. Insertion reactions, cyclisation reactions and ring-opening reactions are highlighted, giving particular attention to catalytic asymmetric methodologies.

Introduction

Sulfur ylides are formal internal salts characterised by a carbanion flanked by a positively charged sulfur atom. These ylides can be divided into two main classes, sulfonium and sulfoxonium ylides (Figure 1), depending on sulfur oxidation state.

The first examples of sulfur ylides were reported in 1930 by Ingold and Jessop.[1] However, the synthetic prowess of these compounds was revealed later on, in the 1960s, when enlightening works by Johnson and LaCount,[2] Franzen,[3] Corey and Chaykovsky[4] showed their utility in small rings syntheses. Enantioselective implementation of this reactivity, using ylides derived from chiral sulphides, has been convincingly demonstrated in the 1990s and 2000s, providing practical platforms for enantioenriched epoxide and aziridine syntheses.[5] Conversely, the remarkable growth that the chemistry of sulfur ylides has experienced in the last years, is largely due to the similarities of their structure and reactivity with the corresponding – arguably problematic – diazo compounds (Figure 1). In fact, another historical milestone in sulfur ylide chemistry is Baldwin's disclosure on the generation and use of metal carbenoids from stabilised sulfoxonium ylides in 1993,[6] paralleling the typical reactivity of diazo compounds. Remarkably, the favourable safety and stability features of sulfoxonium ylides prompted the industrialisation of this chemistry at Merck in the 2000's.[7]

In analogy with other ylides, sulfur ylides can be "stabilised" or "unstabilised". Stabilised sulfur ylides bear an electron-withdrawing group at carbon (*e.g.* ketone, ester, amide functions, etc.), able to delocalise the electron density of the carbanion. These ylides are readily prepared and storable. On the contrary, unstabilised sulfur ylides do not present groups delocalising the anionic charge. They are thus more difficult to handle, being stable only in solution, at low temperatures, and for a fairly limited period of time. They present enhanced reactivity compared to the stabilised analogues.

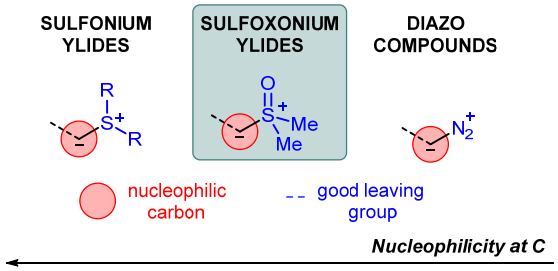


Figure 1. Sulfonium and sulfoxonium ylides, diazo compounds, and their order of nucleophilicity at carbon.

Understandably, the sulfur oxidation state influences the properties of the ylides too. The presence of the electron withdrawing oxygen at sulfur gives two important consequences on the reactivity of sulfoxonium ylides, which represent the main focus of this short review. First, these compounds are considerably more stable and less C-nucleophilic, compared to their sulfonium counterparts, thanks to a better delocalisation of the negative charge. Nevertheless, sulfoxonium ylides are more C-nucleophilic than the corresponding diazo compounds (Figure 1). Second, the oxygen atom can function as a Lewis base, coordinating a catalytic species and interfering with its action. These two aspects are very important in asymmetric catalysis. Sulfonium ylides can be easily combined with a range of chiral catalysts. Indeed, stabilised sulfonium ylides have been used with both organocatalyts[8] and Lewis acidic metal complexes,[9] in the synthesis of a range of enantioenriched products. Examples include their engagement in aminocatalytic cyclopropanation reactions,[8a] and in formal (4+1) cycloadditions driven by hydrogen bond donor catalysts.[8b] On the contrary, examples of employment of sulfoxonium ylides in asymmetric catalytic settings are less abundant, as discussed in the next sections. This is possibly due to the above-mentioned factors (*i.e.* reduced reactivity and interference of the sulfoxide oxygen with an acidic chiral catalyst).

This short review collects and discusses recent advances in sulfoxonium ylide chemistry, highlighting their utilisation in metal-free H-X insertion reactions (catalysed and uncatalysed), in formal (n + 1) cycloaddition reactions resulting in small- to medium-size rings, and in multi-step reactions showcasing different reactivity often involving a ring-opening step. A special attention is given to catalytic asymmetric methodologies. This short review intends to complement (and update) previous monographies, which cover both sulfonium and sulfoxonium ylides, but focusing on specific aspects of their reactivity, mostly

involving their combination with transition metals to form metal carbenoids as reaction intermediates.[10]

Insertion reactions of stabilised sulfoxonium ylides

Stabilised sulfoxonium ylides have been employed in a range of formal insertion reactions into X-H, C-H, C-X and X-Y bonds (Figure 2). As highlighted in the next paragraphs, these reactions are useful alternatives[11] to the more established metal catalysed insertions of diazo compounds into some of these bonds.[12,13] Such transformations are powerful tools for the preparation of numerous classes of compounds, building blocks of drugs and of natural products.

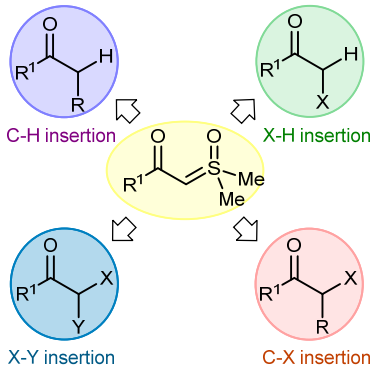
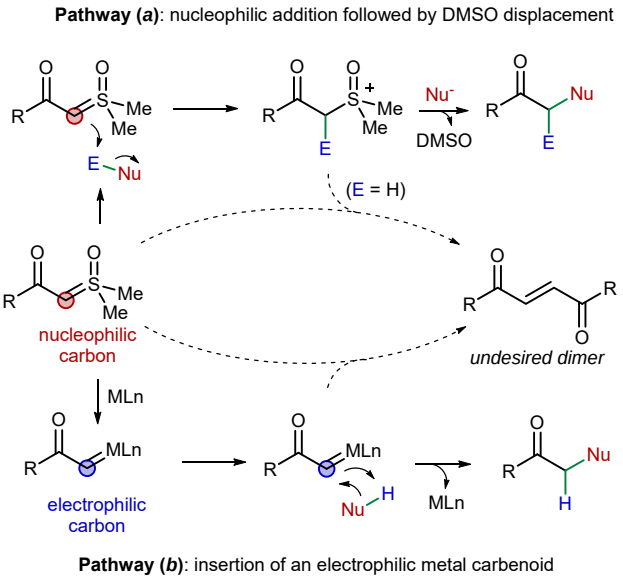


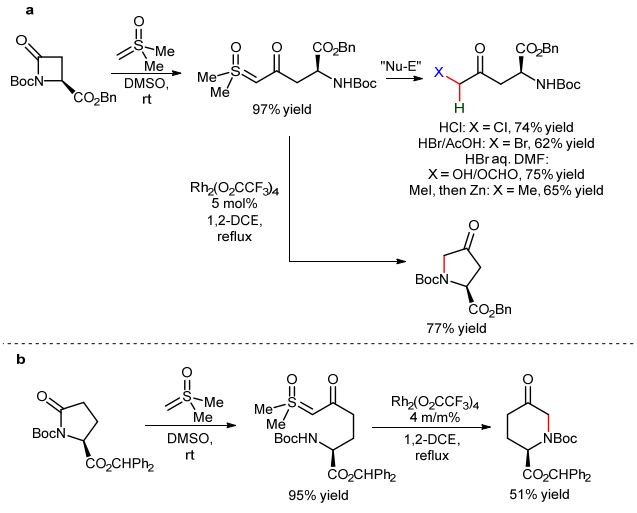
Figure 2. Formal insertion reactions of sulfoxonium ylides.

Generally speaking, sulfoxonium ylides can react with a polarised Nu–E bond by first attacking the electrophile portion with the nucleophilic carbon (Scheme 1, pathway (*a*)). DMSO displacement by the Nu follows, resulting in the formal insertion of the ylide into the Nu–E bond. The two steps can be subjected to catalytic promotion by different (acidic) species. Alternatively, sulfoxonium ylides can be combined with some transition metals to afford metal carbenoids (Scheme 1, pathway (*b*)).[14] These intermediates are electrophilic, in contrast with the starting ylides, and can thus react with a generic nucleophile Nu–H. These pathways are also typical of the chemistry of diazo compounds, which are however less nucleophilic. The higher nucleophilicity of sulfoxonium ylides might lead to the assumption that: i) pathway (*a*) is somewhat more attainable, and ii) undesired dimerization derailments through nucleophilic addition processes of the ylide can be more likely.[15]



Scheme 1. Pathways (*a*) and (*b*) in (formal) insertion reactions of sulfoxonium ylides in generic Nu-E bonds.

To place this chemistry into the right context, it is worth to mention first some early works by Baldwin and co-workers dealing with the ring-opening of *N*-Boc lactams by dimethylsulfoxonium methylide, and subsequent functionalization of the resulting β-keto sulfoxonium ylide (Scheme 2).[6,16] While the highly basic sulfonium ylide gives degradation of the starting β-lactam, its milder sulfoxonium counterpart furnishes the ring opened β-ketosulfoxonium ylide in nearly quantitative yield (Scheme 2a).

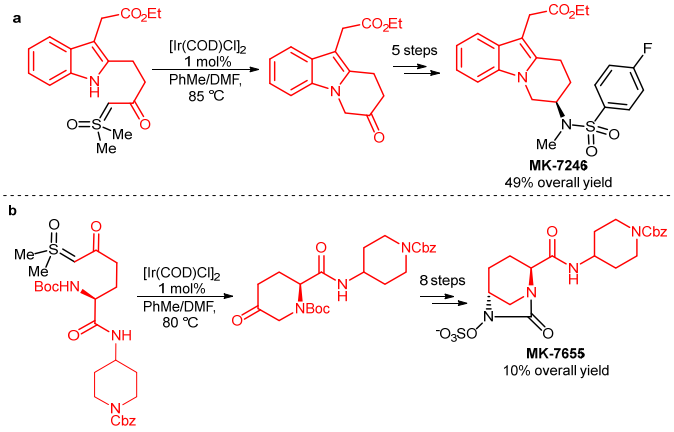


Scheme 2. Ring-opening of *N*-Boc lactams by dimethylsulfoxonium methylide, and ensuing functionalizations.

Treatment of this ylide with different H–X reagents, capable of undergoing productively formal insertions according to pathway (*a*), gives a series of functionalized products with variable results. Examples include reactions with HCl, HBr, HBr in aqueous DMF, and even MeI (followed by Zn deiodination). Conversely, to effect an intramolecular insertion into the N–H bond, the authors had to resort to a transition metal catalyst

($Rh_2(O_2CCF_3)_4$), to channel the reaction through pathway (*b*) via the formation of a metal carbenoid intermediate.[6] This was the first disclosure of a metal catalysed insertion reaction in combination with sulfoxonium ylides. The overall sequence brings about a one carbon ring expansion of a lactam. It was also applied with reasonably good results to the conversion of a pyroglutamic acid derivative into a piperidin-3-one (Scheme 2b).

Similar ring expansion strategies (γ-lactam → piperidin-3-one) were later exploited at Merck, using an iridium-based catalyst, for the synthesis of MK-7246 (Scheme 3a),[7a] a CRTH2 antagonist for respiratory disorders, and of MK-7655 (Scheme 3b),[7b] a β-lactamase inhibitor.

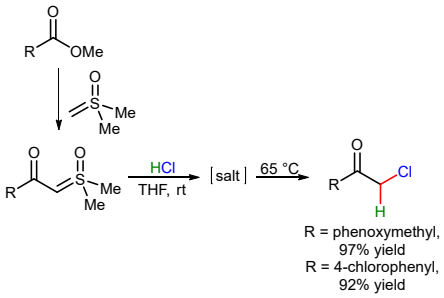


Scheme 3. Applications of the metal catalysed insertion reaction to medicinal agents.

Several features of these works are worth to be highlighted: i) the metal catalysed N-H insertion reaction allowed to overcome the unfeasibility of more conventional intramolecular nucleophilic substitutions *via* halide displacement by the amine, although recent disclosures towards MK-7655 point to an H-Cl insertion followed by S_N2 as a viable pathway if an oxime, instead of a ketone, is used;[7c] ii) a medicinal chemistry approach to a related piperidin-3-one involved an identical ring-expansion strategy, but was based on a diazo compound.[17] However, diazo compounds are generally characterized by poor thermal stability and can be explosive.[18] Process development thus resorted to sulfoxonium ylides due their inherent higher appeal for scale up (increased safety, stability, crystalline nature). iii) Industrialisation of the reaction leading to MK-7246 was carried out to produce this clinical candidate on a multi-Kg scale.

While this short review will keep the focus mostly on pathway (*a*), it is worth to mention that intermolecular insertions using sulfoxonium ylides as metal carbenoid precursors have then begun to be investigated,[11,15] with subsequent thorough studies disclosing a broad range of transformations. To gain a picture of this burgeoning field, we redirect the reader to focussed reviews.[10c,d,e] These reviews can be complemented by some very recent examples,[19] where the [Rh] catalysed aromatic C–H activation platform disclosed by Li and Aïssa in 2017[20] proved to be a truly fertile ground for the development of ingenious transformations.

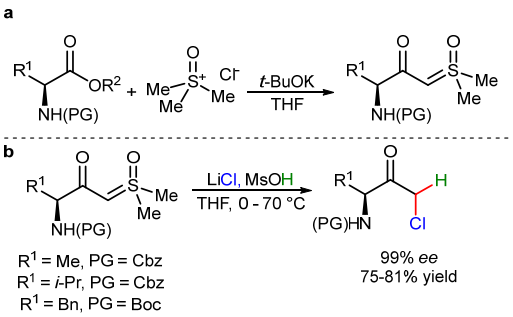
Moving back to discuss pathway (*a*), that involves formal insertion reactions of sulfoxonium ylides without metal carbenoid intervention (see also Scheme 2a), it is possible once again to trace a parallel between the chemistry of sulfoxonium ylides and the corresponding diazo compounds. In 2004, Nugent and coworkers at BMS reinvestigated the reaction of β-keto sulfoxonium ylides, prepared by reaction of esters with dimethylsulfoxonium methylide, with hydrogen chloride (Scheme 4).[21] Overall, the sequence parallels the classical diazomethane based homologation of acyl chlorides to α-chloroketones, while being considerably less hazardous. In more detail, treatment of a THF solution of β-keto sulfoxonium ylide with anhydrous hydrogen chloride results in the formation of a quite soluble salt, which is smoothly converted into the corresponding α-choloroketone upon heating.



Scheme 4. Formal insertion reaction of sulfoxonium ylide into H–Cl.

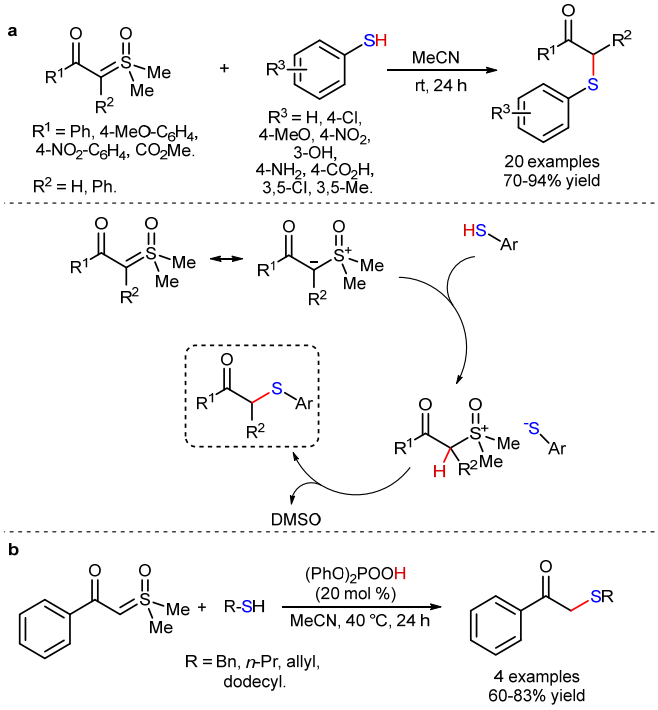
Such type of insertion reaction was then extended to sulfoxonium ylides of α-amino esters derived from *N*-Cbz protected L-alanine and L-valine, and from *N*-Boc L-phenylalanine,[21] without observable racemisation of the chiral centre, despite the basic conditions generated by the ylide (Scheme 5a). However, whereas methyl esters could be used for L-alanine and L-valine, the L-phenylalanine derivative requires a more activated ester (4-nitrophenol) to avoid racemisation. The treatment of the thus obtained *N*-protected β-keto sulfoxonium ylides with a practical source of hydrogen chloride promotes the insertion reaction into H–Cl bond in good yield and with full retention of enantiomeric excess (Scheme 5b).

This kind of reactivity was enlarged to RX–H type insertion reactions, using both aliphatic and aromatic thiols for the formation of new C–S bonds. Along the lines of the mechanism suggested by pathway (*a*), Burtoloso et al.[22] exploited the intrinsic acidity of aryl thiols (pK_a = 10 in DMSO) for the formation of an ionic pair resulting from protonation of the β-keto sulfoxonium ylide (Scheme 6a).



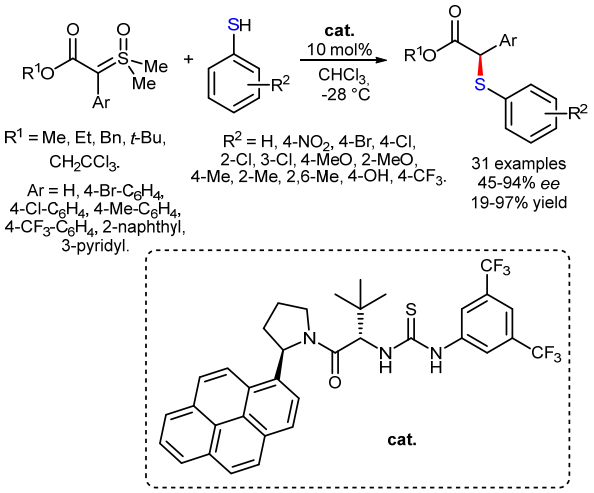
Scheme 5. Formal insertion reaction of sulfoxonium ylides derived from natural amino acids into H–Cl bond.

The freshly generated thiolate can displace DMSO generating the new C-S bond. On the contrary, the less acidic aliphatic thiols (pK_a = 17 in DMSO) are unable to protonate sulfoxonium ylides, and thus do not furnish the expected product. However, an external stronger acid catalyst, such as diphenyl phosphoric acid, could serve to protonate the ylide. In such intermediate ionic pair, the alkyl thiol displaces DMSO generating the product and regenerating the catalyst (Scheme 6b).



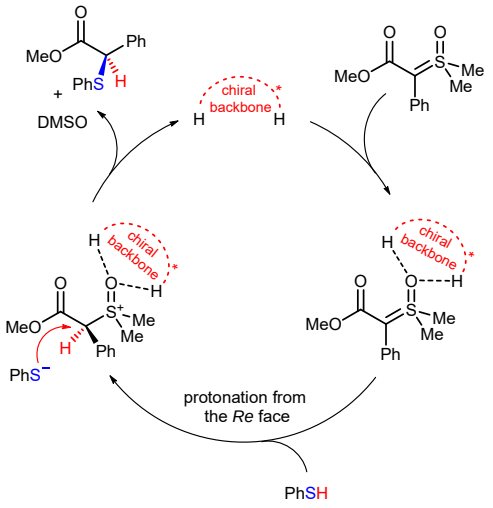
Scheme 6. Insertion reactions of sulfoxonium ylides into RS–H bond.

The enantioselective version of this reaction has been very recently reported by the same authors, in collaboration with the Mattson laboratory, using β-ester substituted sulfoxonium ylides in the presence of a Jacobsen-type thiourea (Scheme 7).[23] The reaction proceeds smoothly with a broad range of electron-rich and electron-poor arylthiols and different sulfoxonium ylides, bearing different substituents on the aryl group and on the ester moiety.



Scheme 7. Catalytic enantioselective insertions of sulfoxonium ylides into RS-H bond.

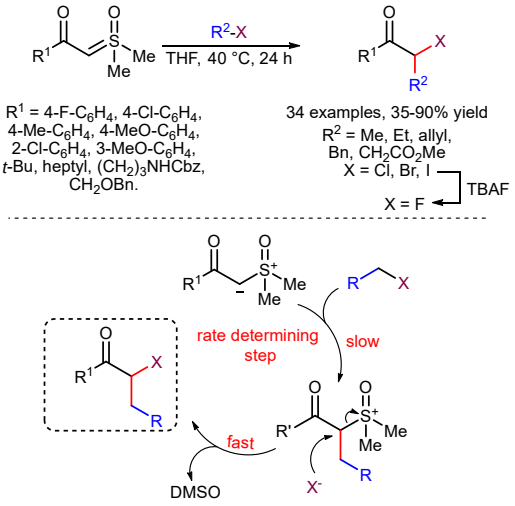
The mechanism proposed by the authors, based on computational results and NMR experiments, is reported in Scheme 8. First of all, the coordination of the sulfoxonium ylide to the chiral thiourea through hydrogen bonds consents enantioselective protonation on its Re face by the thiol, generating the chiral centre. Then, nucleophilic substitution by thiolate with displacement of DMSO generates the product in an enantioenriched fashion, releasing the catalyst for a new catalytic cycle.



Scheme 8. Proposed reaction pathway for the enantioselective insertion of sulfoxonium ylides into S-H bonds.

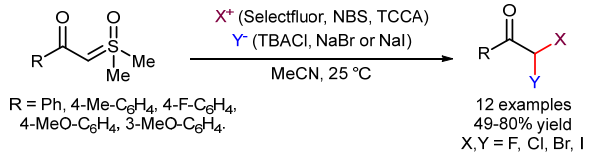
Sulfoxonium ylides can be exploited also for formal insertion reactions into C–X or X–Y bonds, for the synthesis of α-branched-α-halo carbonyl or α,α-dihalo carbonyl compounds, bifunctional intermediates capable of undertaking a broad range of subsequent transformations.[24] Burtoloso and coworkers developed two catalyst-free methodologies for these reactions.[25] The synthesis of these products is generally based on the electrophilic halogenation of carbonyl compounds using potentially dangerous reagents.[26] A safer nucleophilic

approach can be undertaken using sulfoxonium ylides and primary alkyl halides (Scheme 9). Control experiments, based on deuterium labelling on the alkyl halides, for elucidation of the geminal alkylation-halogenation reaction, suggested the formation of an ion pair, resulting from the nucleophilic attack of the ylide to the electrophilic carbon of the alkyl halides, as the rate determining step. The insertion reaction ends with the fast nucleophilic attack of the counterion of the ionic pair in conjunction with the release of DMSO as co-product of the reaction.



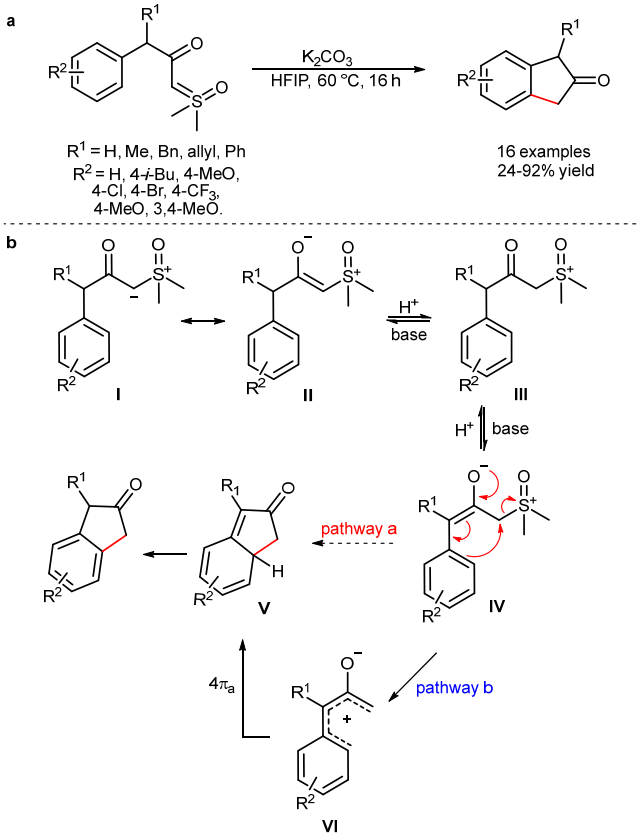
Scheme 9. Formal insertion reaction of sulfoxonium ylide into R–X bond.

This approach was extended to the preparation of α,α-dihalo carbonyl compounds, which has always been a challenge for synthetic chemists, especially with regards to the preparation of those containing two different halogens. Treating a solution of the β-keto sulfoxonium ylide in the presence of both nucleophilic and electrophilic halogens, the corresponding α,α-dihalo carbonyls can be obtained in moderate to good yields (Scheme 10).



Scheme 10. Formal insertion reaction of sulfoxonium ylide into X–Y bond.

Finally, the last type of insertion reaction we highlight in this short review is the challenging insertion of sulfoxonium ylides into aromatic C–H bonds. This type of reaction was realized through the activation of the C-H bond using a transition metal and sulfoxonium ylide as precursors of metal carbenoids.[20] However, Aïssa et al. have recently demonstrated that this reaction, in its intramolecular version, can be developed even without metal catalysts thanks to the special role played by the solvent in the reaction pathway (Scheme 11a).[27] The authors obtained a broad range of cyclic ketones performing the reaction of β-ketosulfoxonium ylide in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as solvent and using potassium carbonate as base. Under the reaction conditions, the β-keto sulfoxonium ylide, represented by resonance formulas **I** and **II**, is in equilibrium with intermediate **III**. Basic treatment affords compound **IV** ready to cyclise following pathway (*a*) into intermediate **V** which leads, after rearomatisation, to the observed product. However, a second pathway (*b*) is considered to be favoured, since the presence of a strong H-bond donor such as HFIP could encourage the departure of DMSO from intermediate **IV**. Moreover, the combination of HFIP, a base and a good leaving group is reported to promote the formation of oxy-allyl cations,[28] such as **VI**. Such species is prone to undergo an antarafacial five-centres 4π-electrocyclisation, to generate intermediate **V** and, after rearomatisation, the final product (Scheme 11b).



Scheme 11. Metal-free insertion reaction of sulfoxonium ylide into aromatic C-H bonds.

Sulfoxonium ylides and carbonyl compounds: (2 + 1) cycloadditions

Sulfoxonium ylides in combination with the π-system of carbonyl compounds (imines, saturated and unsaturated aldehydes/ketones) can generate a wide range of constricted rings such as cyclopropanes, aziridines and oxiranes (Figure 3), scaffolds often recurring in biologically active natural and unnatural compounds, as well as powerful synthetic intermediates.[29]

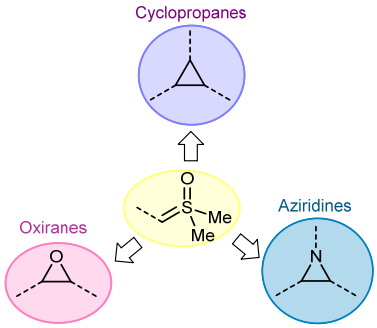
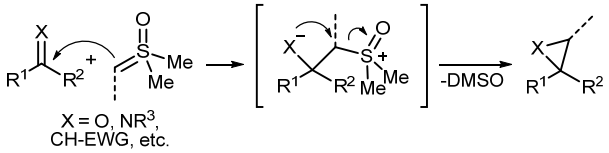


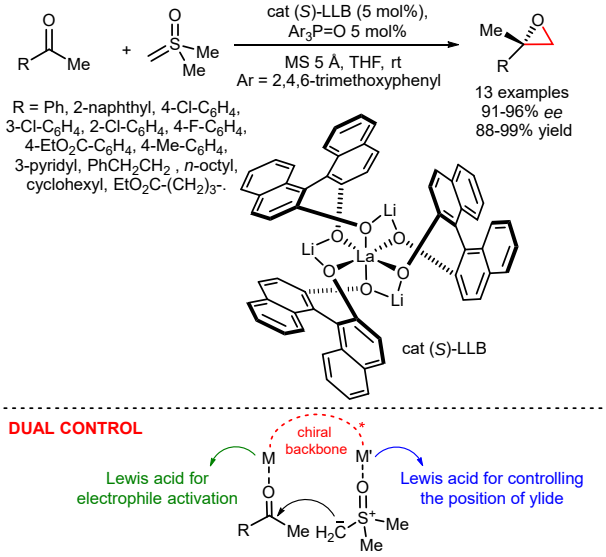
Figure 3. Constricted rings obtained from sulfoxonium ylides via (2 + 1) cycloadditions.

The formation of these rings follows a two-step pathway, involving the nucleophilic addition of the ylide to a π-acceptor C=X followed by DMSO displacement by the resulting negatively charged X atom (Scheme 12). From another perspective, the reaction can be considered as the formal insertion of the ylide into the π-bond, along the lines of a (2 + 1) cycloaddition reaction.



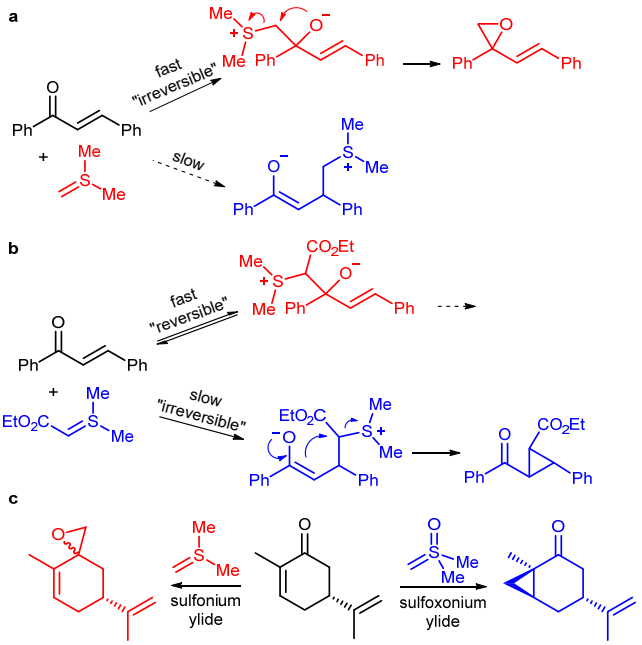
Scheme 12. Two-step pathway for the formation of constrained rings from sulfoxonium ylides.

Oxirane motifs can be obtained exploiting such reactivity of sulfoxonium ylides, as first disclosed by Johnson and LaCount[2] and then broadly investigated by Corey and Chaykovsky.[4] The enantioselective version of this type of reaction was developed in 2008 by Shibasaki and co-workers.[30] In this reaction, ketones are reacted with the unstabilised dimethylsulfoxonium methylide, under the promotion of a chiral lithium-lanthanum complex as Lewis acid, and in the presence of a phosphine oxide as additive (Scheme 13). The activation model proposed by the authors is based on a double coordination by the catalyst, one enhancing the electrophilicity of the ketone and the other one controlling the approach of the ylide. The presence of phosphine oxide as additive is crucial for high enantioselectivities. ^{31}P-NMR analysis demonstrated the coordination of the phosphine oxide to the LLB catalyst, giving an Ar_3P=O:LLB = 1:1 complex which is the active catalyst species. The resulting terminal oxiranes are obtained with outstanding results in terms of both yields and enantioselectivities.



Scheme 13. Enantioselective terminal oxirane synthesis.

When sulfur ylides, both sulfonium and sulfoxonium ones, react with α,β-unsaturated carbonyl compounds, two different products can be obtained, oxiranes or cyclopropanes, due to the two electrophilic sites present in the substrates. The kinetically favoured 1,2-addition of the ylide to the carbonyl leads to the oxirane, while the slower 1,4-addition gives the thermodynamically favoured cyclopropane. As typical textbook examples,[31] the regiodivergency of the reactions of stabilised *vs* unstabilised sulfonium ylides is rationalised considering the higher degree of reversibility in additions of stabilised ylides to carbonyls. Thus, with *unstabilised sulfonium ylides*, the 1,2-addition is a fast and irreversible process, favouring the formation of the oxirane[32] (Scheme 14a). With *stabilised sulfonium ylides*, the 1,2-addition, which is still kinetically favoured, tends to be reversible, ultimately resulting in the thermodynamic cyclopropane product[33] via the slower but irreversible 1,4-addition pathway (Scheme 14b). Similar arguments can be put forward to justify the preference of *sulfoxonium ylides* for cyclopropanes *vs* the oxiranes[34] obtained with *sulfonium ylides* (Scheme 14c). The additional oxygen of sulfoxonium ylides stabilises the anion to a sufficient extent to render the 1,2-addition reversible, even without additional electron-withdrawing groups on the ylide.



Scheme 14. Regioselectivity in the reaction of sulfur ylides with α,β-unsaturated carbonyl compounds: a) unstabilised sulfonium ylide; b) stabilised sulfonium ylide; c) sulfonium vs sulfoxonium ylide.

However, to gain a full rationalisation on the regioselectivity of these reactions, a missing piece of information is the ease by which the 1,2- and 1,4-adducts undergo displacement of dimethyl sulfide or sulfoxide, which was supposed to be inconsequential in the simplified description of the previous paragraph. In fact, several computational endeavours in reactions of sulfonium ylides showed that their overall energy profile is all but simple and obvious, and that even torsional rotation energies, arranging the intermediate in the conformation required for the displacement, cannot be neglected.[35] In contrast with these and several other studies on sulfonium ylides, computational investigations dealing with sulfoxonium ylide reactions appear to be nearly absent. One of the exceptions is a recent contribution, wherein Yu and co-workers inspected computationally the reactions of chalcone not only with the non-stabilised dimethylsulfonium methylide, but also with its sulfoxonium counterpart.[36] These reactions are known for their regiodivergent outcome (sulfonium ylide → oxirane; sulfoxonium ylide → cyclopropane). As far as the sulfonium ylide is concerned, the calculated energy profile for its reaction confirmed that both transition states for the 1,2-addition and ensuing dimethylsulfide displacement are lower in energy than the 1,4-addition. Conversely, Figure 4 illustrates the potential energy surface of the two different pathways (cyclopropanation and epoxidation) of the reaction between dimethylsulfoxonium methylide and chalcone. Both reactions begin with the formation of two different hydrogen bond complexes, **COM1** (8.1 kcal/mol) and **COM2** (6.3 kcal/mol), thanks to the interactions between ylide methyl groups and the ketone function. In the cyclopropanation pathway, **COM1** evolves to **IN1** (-2.8 kcal/mol) through **TS1** with an energy barrier of 17.5 kcal/mol. The rotation around the newly formed C-C bond gives the slightly less stable **IN2**, which generates the cyclopropane (**PR1**) overcoming the energy barrier of **TS2** (6.6 kcal/mol). Regarding the epoxidation pathway, **COM2** affords **IN3** passing through **TS3** (15.9 kcal/mol), which is favoured over **TS1** by 1.6 kcal/mol. **IN3**, which is considerably less stable than **IN1**, generates its *trans* conformer **IN4** and subsequently **PR2**, overcoming a high 23 kcal/mol barrier represented by **TS4**. Thus, despite the 1,2-addition of sulfoxonium ylide to chalcone requires less energy, 15.9 kcal/mol, in comparison with 17.5 kcal/mol of the 1,4-addition (**TS1**), the ring closure energy of **TS4** is too high, and the whole system heads for the formation of **PR1** which has **TS1** (17.5 kcal/mol) as rate determining step. While the overall scheme confirms the simplified rationalisation summarised in the previous paragraphs, these computational results well highlight the difference in the energy barriers required for DMSO displacement: 9.4 kcal/mol for the cyclopropanation (**IN1** → **TS2**), *vs* 13.5 kcal/mol for the epoxidation (**IN3** → **TS4**).

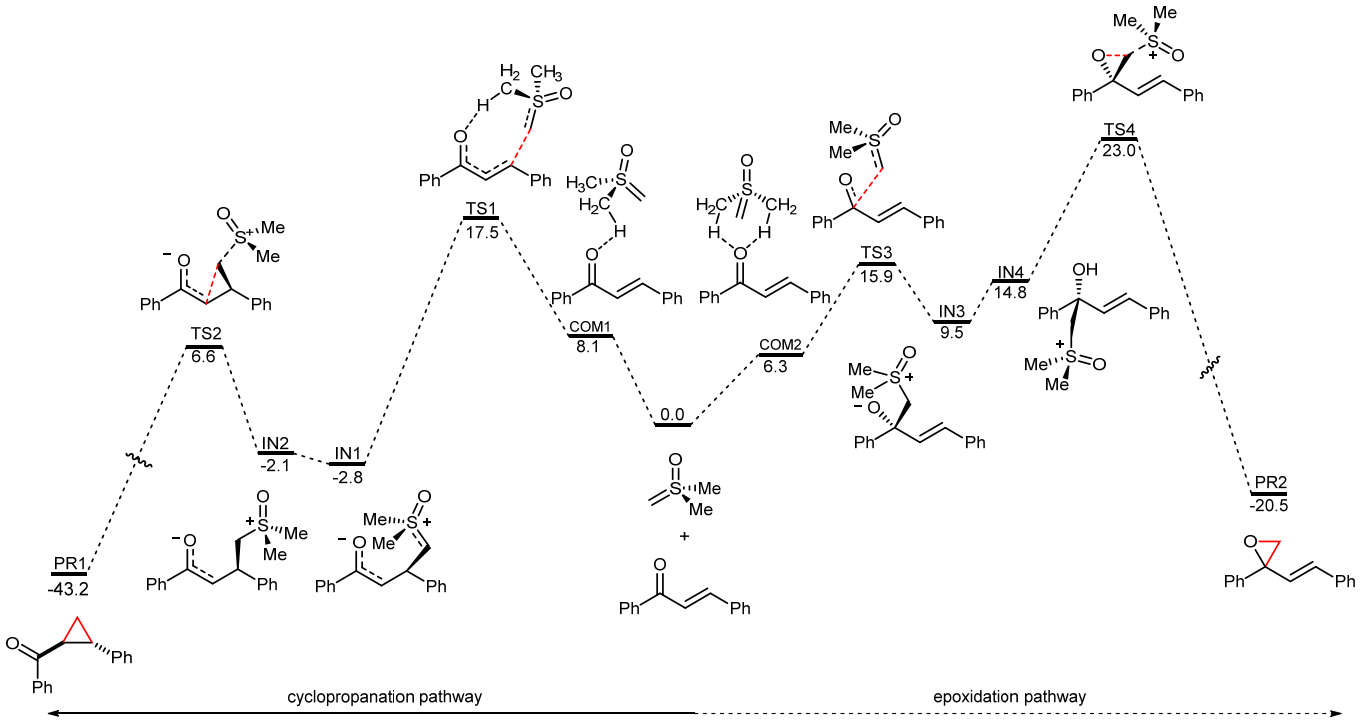
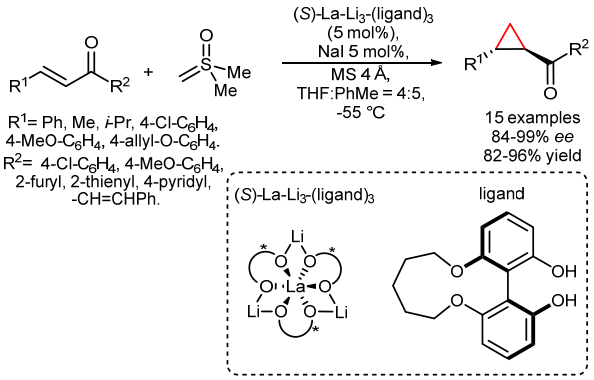


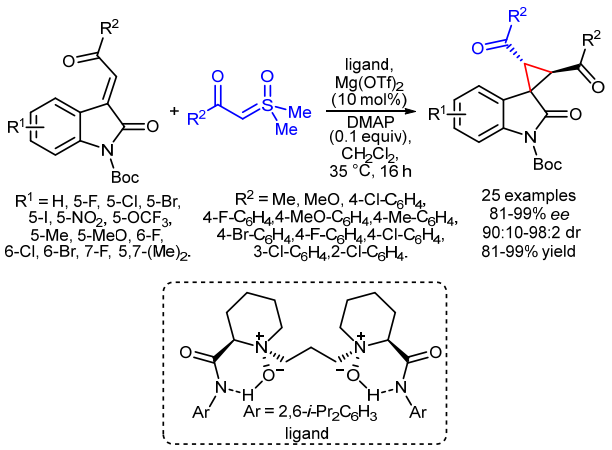
Figure 4. DFT computed energy surface for the cyclopropanation and epoxidation reactions of methylsulfoxonium methylide and chalcone.

Moving back to discuss synthetic aspects of this chemistry, α,β-unsaturated ketones in combination with sulfoxonium ylides were accordingly been successfully employed for the regioselective synthesis of 1,2-disubstitued cyclopropanes.[37] An enantioselective version of the reaction between chalcones and methylsulfoxonium methylide, which proceeds smoothly in the presence of a chiral Li-La complex related to the catalyst used for the epoxidation reaction previously mentioned in Scheme 13, was reported by Matsunaga, Shibasaki and co-workers (Scheme 15).[38] The reaction affords *trans*-1,2-disubstitued cyclopropanes with good values of yields and enantioselectivities. In this case, the presence of NaI, and in particular the presence of the iodide ion, has a key role for the enantioselectivity. Indeed, early stage investigations showed that performing the reaction from trimethylsulfoxonium chloride and iodide as ylide precursors, two different values of enantiomeric excesses were obtained, 6 and 38% respectively. While, using trimethylsulfoxonium iodide in the presence of 10 mol% of NaI, the enantiomeric excess increased up to 51%. Subsequent optimization with this ylide precursor-NaI combination led to the very good results reported in Scheme 15.



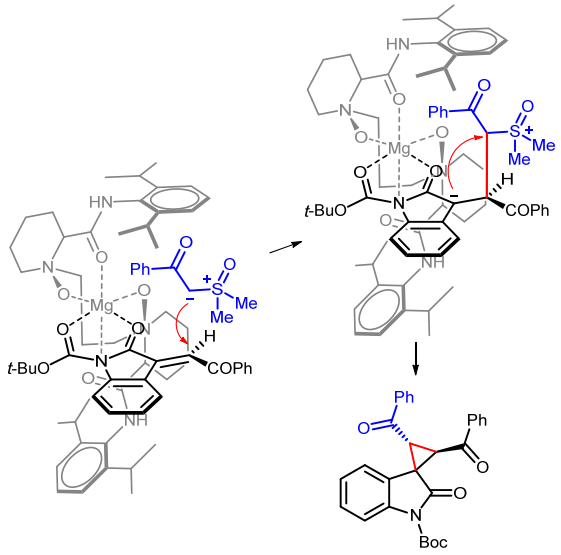
Scheme 15. Enantioselective version of cyclopropane synthesis.

Another significant example regarding asymmetric catalysis in combination with sulfoxonium ylides and carbonyl compounds was reported by Feng et al. in 2018,[39] employing 3-alkylideneoxindoles and stabilized ylides for the synthesis of spirocyclopropyl oxindoles (Scheme 16).



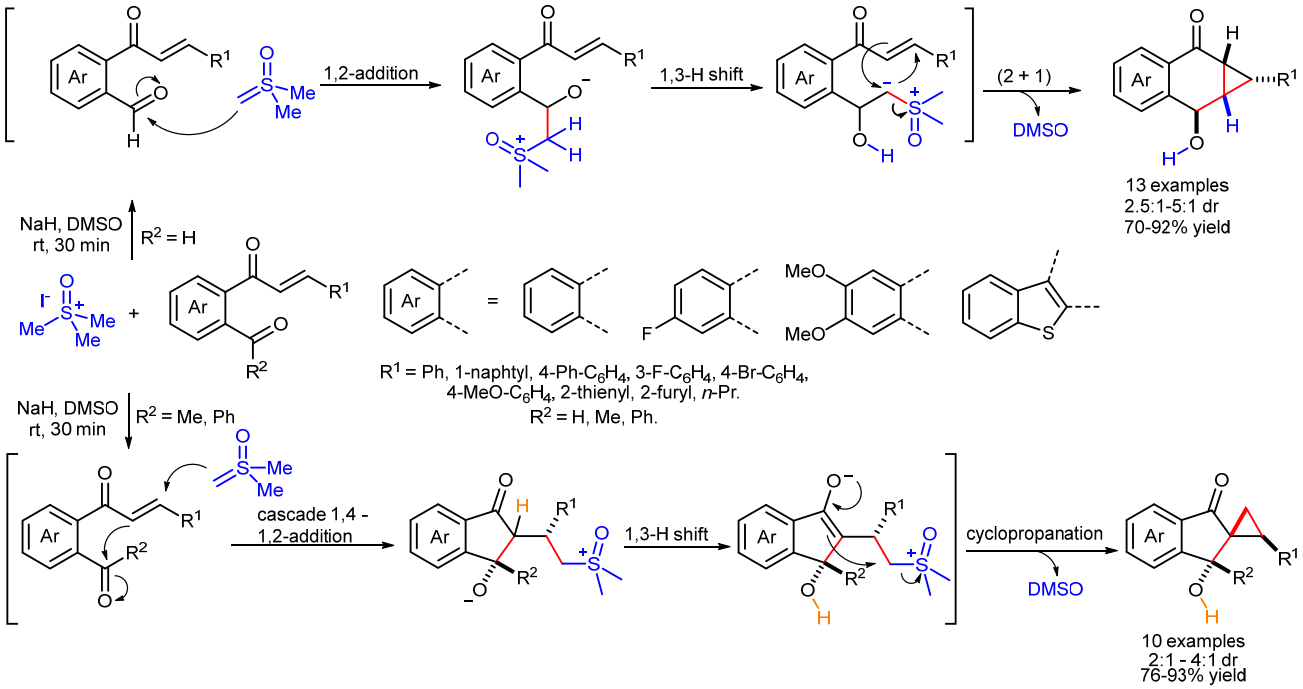
Scheme 16. Enantioselective synthesis of spiro-cyclopropyl oxindoles using stabilised sulfoxonium ylides.

The nature of the *N*-protecting group at the oxindole was found to be crucial for achieving good enantioselectivities. When using unprotected 3-phenacylideneoxindole or *N*-Bn-3-phenacylideneoxindole, instead of *N*-Boc-3-phenacylideneoxindole, the spirocyclic product is obtained without any enantioinduction, while using an acetyl moiety as *N*-protecting group the resulting product is obtained in 11% *ee.* As illustrated in Scheme 17, the triple coordination of the substrate to the catalyst, and the steric hindrance offered by the Boc moiety, force the substrate into a specific arrangement which permits a nucleophilic addition to only one of the two prochiral faces of the olefin.



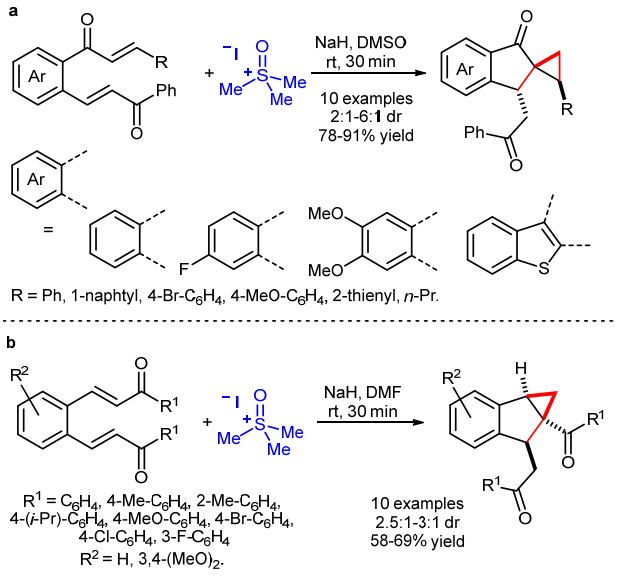
Scheme 17. Proposed model accounting for the enantioinduction in the cyclopropanation of oxindoles with stabilised sulfoxonium ylides.

In racemic versions, the reactivity of dimethylsulfoxonium methylide towards carbonyl compounds was exploited for more complex reaction cascades by Ramasastry and co-authors.[40] These authors employed a series of bifunctional aromatic substrates bearing two acceptors in *ortho*-positions. A variety of cascade processes, involving the sequential formation of three new C–C bonds, intertwined by H-shift processes, were developed, delivering polycyclic benzofused derivatives. For example (Scheme 18, top), using substrates bearing an aldehyde acceptor flanked by an unsaturated ketone, the ylide adds to the aldehyde in a 1,2-fashion, and then, instead of undergoing DMSO displacement delivering the oxirane, the alkoxide intermediate evolves *via* a 1,3-H shift, which restores the ylide functionality. An intramolecular (2 + 1) cyclopropanation reaction of this ylide with the activated olefin acceptor follows, affording a 2,3-cyclopropyl tetral-1-one. This methodology was applied to the synthesis of a series of these derivatives in good yields and moderate to good diastereoselectivities. Conversely, using a ketone as an *ortho*-substituent, instead of the aldehyde, the 1,4-addition to the Michael acceptor substituent initially prevails (Scheme 18, bottom). However, also in this case the reaction does not evolve through a simple cyclopropanation pathway. The 1,4-addition is in fact followed by an intramolecular 1,2-addition to the ketone, occurring in a cascade manner. An ensuing 1,3-H shift process generates an enolate, which ultimately displaces DMSO resulting in a spiro-cyclopropyl indan-1-one product. Also in this case, several of these derivatives could be prepared with good results in terms of yields, and moderate to good diastereoselectivities.



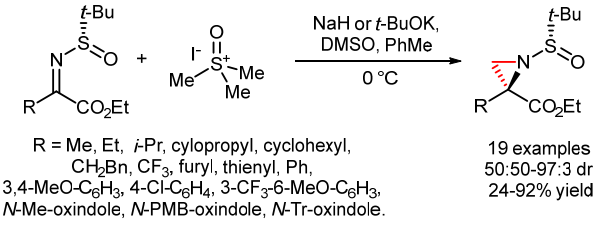
Scheme 18. Reactions of dimethylsulfoxonium methylide with arenes bearing carbonyls and Michael acceptors functionalities in ortho-positions.

In addition, substrates bearing two Michael acceptors at the ortho-positions of the arenes could undergo related sequences of cascade 1,4-additions and H-shifts events, when treated with dimethylsulfoxonium methylide (Scheme 19). These processes afford spiro-cyclopropyl indanones (Scheme 19a), or cyclopropyl fused indanes (Scheme 19b), depending on the isomeric substrate employed.



Scheme 19. (a) Spiro-cyclopropyl indanones and (b) cycloproyl fused indanes via reaction cascades between dimethylsulfoxonium methylide and 1,2-disubstituted arenes.

The last (2 + 1) cycloaddition mentioned in this section involves the reaction between sulfoxonium ylides and imines, for the synthesis of aziridines.[41] An interesting example regarding this type of reaction was reported by Stockman[42] employing chiral *N*-*t*-butanesulfinyl aldimines, and subsequently extended to *N*-*t*-butanesulfinyl ketimino esters in 2015 by Marsini and coworkers.[43] A broad range of aziridines was obtained in good yields and excellent diastereoselectivities using this methodology (Scheme 20).



Scheme 20. Aziridination reaction using a chiral auxiliary at the imine.

Miscellaneous reactivity

In addition to the classical reactivity previously described, sulfoxonium ylides can be protagonists of less common processes such as interrupted Corey-Chaykovsky reactions, ring expansions, and olefinations. These transformations lead to original syntheses of important heterocycles, for example γ-lactones, γ-lactams, tetrahydrofurans, pyrrolidines, oxetanes and dihydropyrazoles (Figure 5).

In order to underline the different reactivity of sulfonium and sulfoxonium ylides, we first highlight an oxidative copper-mediated (4 + 1) cycloaddition reaction between *N*-sulfonylhydrazones, as azoalkene precursors, and sulfur ylides, under aerobic conditions.[44]

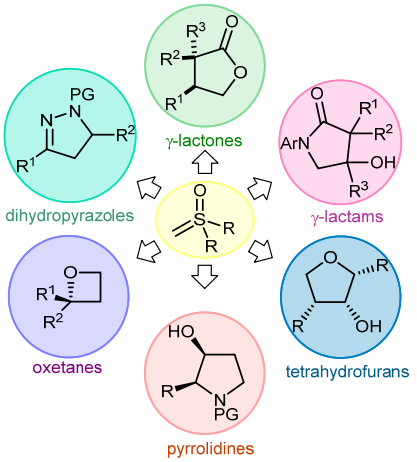
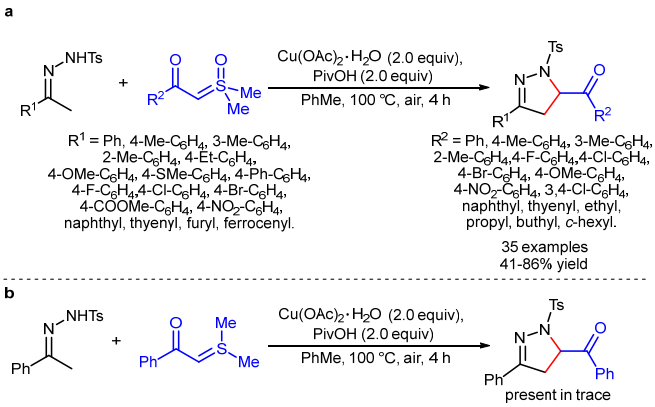


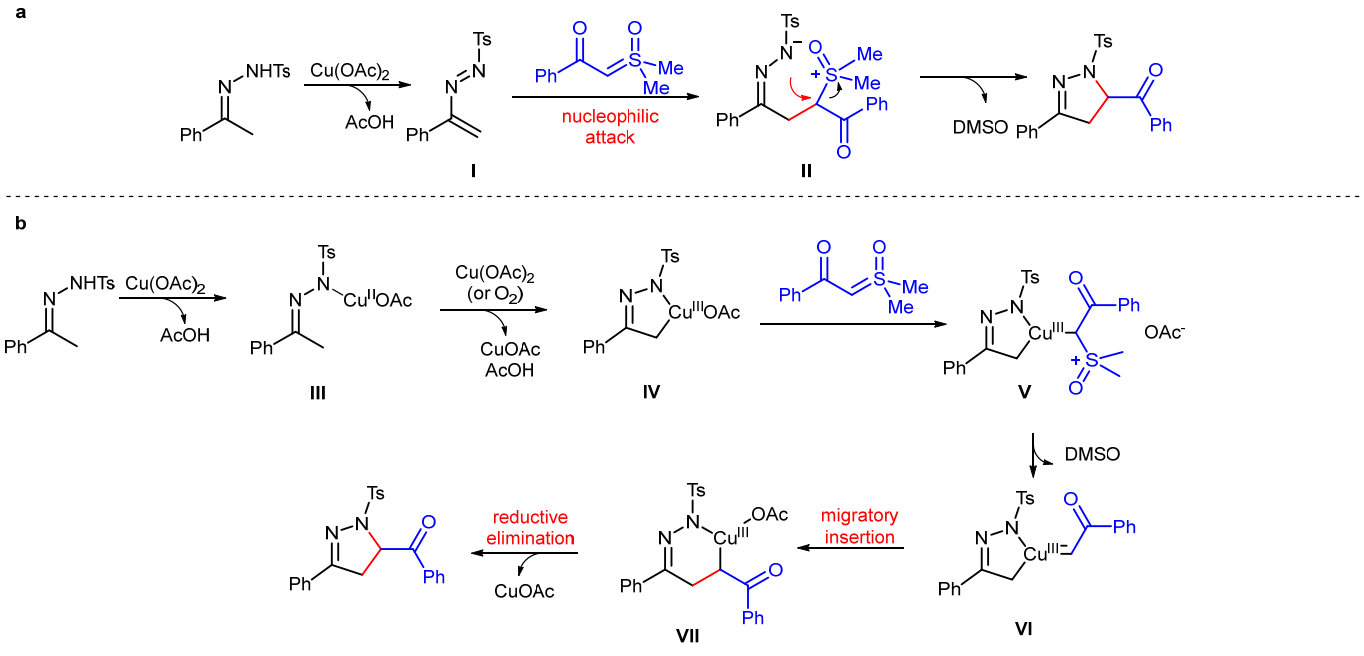
Figure 5. Examples of different heterocyclic motifs obtained employing sulfoxonium ylides.



Scheme 21. [4+1] cycloaddition reaction of N-sulfonylhydrazones and sulfonium and sulfoxonium ylides.

As illustrated in Scheme 21a, the authors obtained very good reactivity employing sulfoxonium ylides in the cycloaddition reaction. The oxidative conditions under which the reaction is carried out are necessary to obtain the product. Indeed, performing the reaction under nitrogen atmosphere, no product was obtained. Moreover, although the (4 + 1) cycloaddition between sulfonium ylides and azoalkenes is an established process,[9b] employing these ylides, only trace of the desired product is detected (Scheme 21b). Thus, only sulfoxonium ylides possess sufficient stability to survive the harsh oxidative conditions required for the reaction to occur.

Two alternative mechanisms were proposed by the authors, as represented in Scheme 22. Following the first hypothesis (Scheme 22a), the *N*-tosyl hydrazone underwent an oxidative dehydrogenation in the presence of $Cu(OAc)_2$ and pivalic acid to give intermediate **I**. Then, Michael-type addition of the sulfoxonium ylides to the azoalkene followed by DMSO elimination generates the (4 + 1) cycloadduct via zwitterion **II**. Another possible reaction pathway (Scheme 22b), involves the coordination of the *N*-tosyl-hydrazone with $Cu(OAc)_2$ to give intermediate **III**. The oxygen present in air can oxidize Cu^{II} to Cu^{III} generating intermediate **IV**. Alternatively, intermediate **IV** can be generated by disproportionation with $Cu(OAc)_2$.

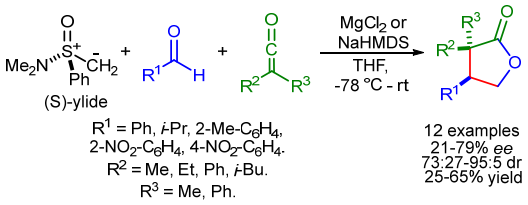


Scheme 22. Proposed possible pathways for the oxidative reaction between *N*-tosyl hydrazones and stabilized β-keto sulfoxonium ylides.

At this point, intermediate **IV** in the presence of sulfoxonium ylide gives intermediate **V**, and, after release of DMSO, compound **VI**. Subsequently, a migratory insertion giving **VII** followed by reductive elimination leads to the formation of the (4 + 1) cycloaddition product. In order to demonstrate the reaction pathways proposed, the authors monitored the reaction by LC-HRMS. During two hours

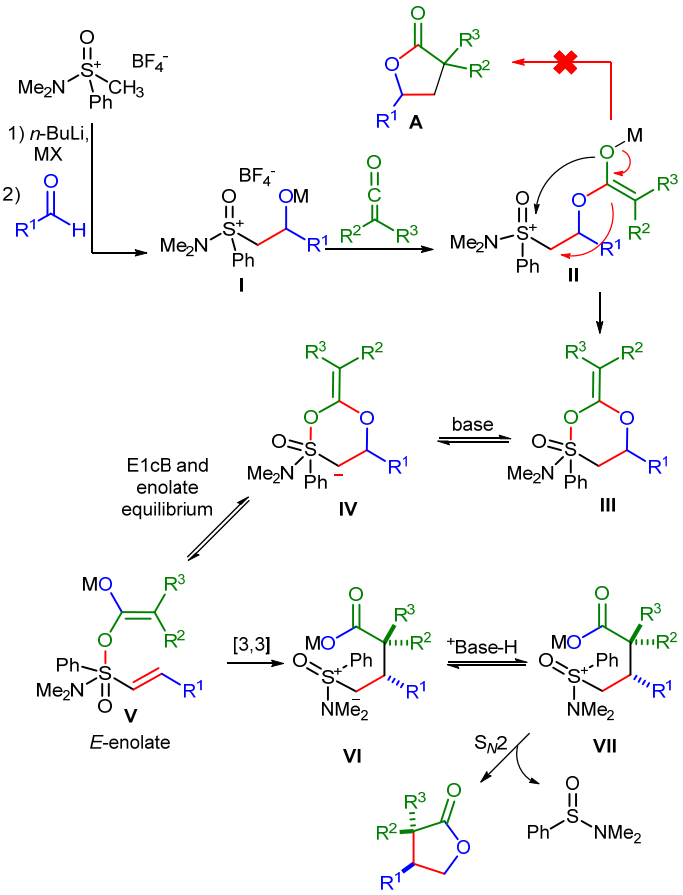
the reaction was sampled and analysed at half-hour intervals, and all intermediated **I**-**VII** were detected. Thus, both proposed mechanisms are in agreement with the experimental data.

The synthesis of γ-lactones, fundamental motifs at the base of several natural products,[45] often requires multistep methodologies, exhibits a limited substrate scope and uses expensive reagent for the obtainment of these frameworks in a stereoselective fashion. Kerrigan and coworkers developed a one pot approach for the synthesis of these scaffolds first in 2013[46] followed by the enantioselective version in 2014.[47] Their methodology is based on sulfoxonium ylide-aldehyde system but driving the reactivity towards the γ-lactone product by trapping the intermediate with ketene derivatives (Scheme 23).



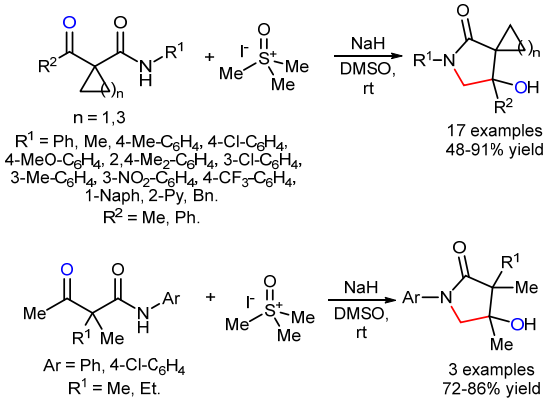
Scheme 23. Synthesis of γ-lactones by a three-component reaction between a chiral sulfoxonium ylide, aldehydes, and ketenes.

The reason of such type of reactivity and the mechanism of the reaction is explained in Scheme 24. First of all, a nucleophilic attack of the sulfoxonium methylide to the aldehyde generates intermediate **I**, which, instead of undergoing a typical ring-closure reaction giving the corresponding oxirane, is intercepted, first, by the metal ion (Na^+ or $MgCl^+$), and subsequently by the ketene, affording enolate **II**. At this point, this intermediate **II** can take two reaction pathways. The first would lead to product **A** via the displacement of the sulfur group by the enolate carbon. However, product **A** was not detected by NMR in the crude mixtures. The second pathway, accounting for the formation of the observed product, involves the formation of intermediate **III**, derived from the nucleophilic attack of the enolate oxygen to the electrophilic sulfur. Base induced deprotonation of **III** produces the anion **IV**, which evolves into enolate **V** through an E1cB elimination. A [3,3]-sigmatropic rearrangement delivers **VI**, which is quickly protonated to give **VII** which ultimately leads to the observed product via an intramolecular S_N2 substitution and release of *N*,*N*-dimethylbenzenesulfinamide as coproduct of the reaction.



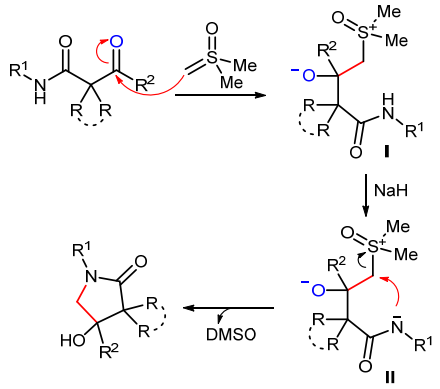
Scheme 24. Proposed mechanism for the synthesis of γ-lactones.

As γ-lactones, also γ-lactams are common scaffolds in natural products.[48] During the years, numerous synthetic routes have been developed for the construction of these scaffolds, such as C–H insertion reaction, ring expansion or cycloadditions.[49] Taking into account the ability of sulfoxonium ylides as methylene transfer agents in Corey-Chaykovsky reactions, Dong and coworkers[50] developed a new route for the synthesis of both α-branched and α-spiro γ-lactams, in good yields, from the reaction of α,α-dialkyl-β-oxo amides and trimethyl sulfoxonium iodide in the presence of NaH (Scheme 25).



Scheme 25. Synthesis of γ-lactams by reaction of trimethylsulfoxonium salts and β-keto amides.

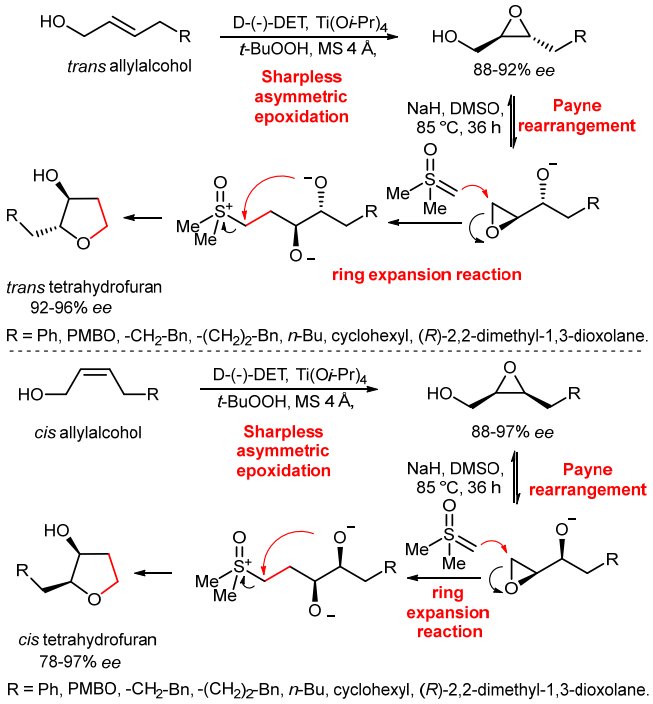
The mechanism reported by the authors is shown in Scheme 26. The nucleophilic attack of the sulfoxonium ylide to the ketone carbonyl generates zwitterion **I**, which under basic conditions forms intermediate **II**. Subsequently, the nucleophilic nitrogen of **II** undergoes an intramolecular S_N2 substitution releasing DMSO as coproduct, and the γ-lactam product after protonation.



Scheme 26. Proposed reaction pathway for γ-lactams synthesis.

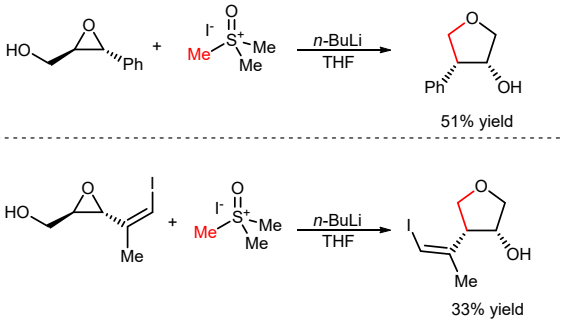
Another important chapter regarding the chemistry of sulfoxonium ylides is represented by ring-expansion reactions of strained rings (epoxides, oxetanes, aziridines). While the ability of dimethyl sulfoxonium methylide of "inserting" a methylene group in these strained rings has been known since a long time,[51] we highlight here some of its recent applications to the synthesis of 2,3- or 3,4-disubstitued tetrahydrofurans, 2,3-disubstitued pyrrolidines or 2,2-disubstitued oxetanes, both in racemic and in enantioenriched fashion.

Regarding the synthesis of 2,3- or 3,4-disubstitued tetrahydrofurans, in 2004 Borhan and coworkers[52] developed a powerful strategy based on asymmetric Sharpless epoxidation to give to 2,3-epoxy alcohols, basic treatment to promote Payne rearrangement with the subsequent formation of the terminal epoxide, and, finally, ring expansion reaction, to generate the corresponding tetrahydrofurans with complete control of the stereochemistry. As shown in Scheme 27, this methodology permits the obtainment of both *cis* and *trans* isomers starting from the two stereoisomeric allyl alcohols. Taking into consideration the stereochemistry of the reaction, good stereoselectivity is observed for *trans* epoxy alcohols during Payne rearrangement, while a wider isomeric composition can be found employing *cis* substrates. This is probably due to the interaction between C1 and C4 substituents.



Scheme 27. Synthetic sequence for the preparation of tetrahydrofurans via Payne rearrangement.

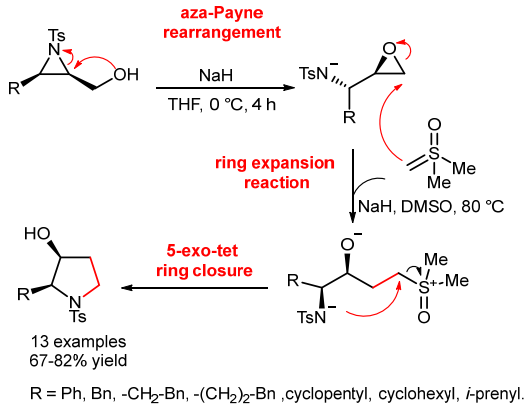
This methodology also permits the obtainment of 3,4-disubstitued tetrahydrofurans by changing the substituents on the oxirane motifs. Introducing an aryl or a vinyl group at C3 position of the epoxy alcohol, the nucleophilic addition of the ylide occurs principally at the benzylic or allylic position, giving the 3,4-disubstitued product when the reaction is carried out using *n*-BuLi as base and THF as solvent (Scheme 28).



Scheme 28. Synthesis of 3,4-disubstitued tetrahydrofurans by using 3-aryl and 3-vinyl 2,3-epoxy-1-alcohols.

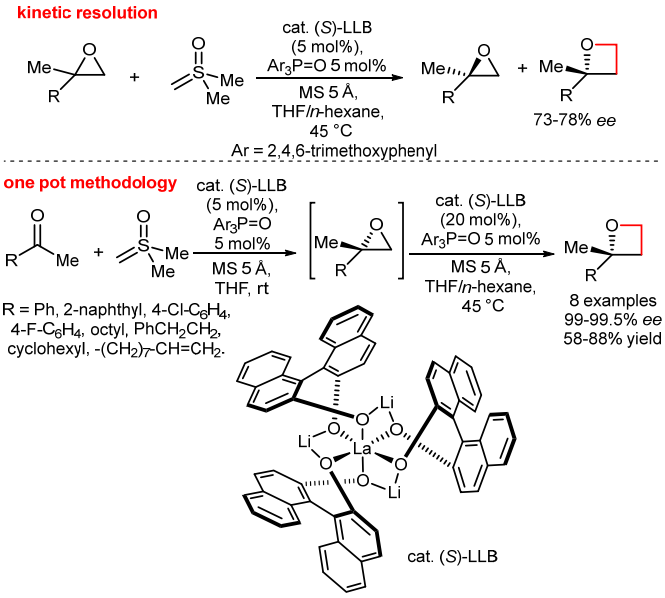
The same authors extended this approach to the synthesis of *cis* and *trans* 2,3-disubstitued pyrrolidines[53] exploiting the aza-Payne rearrangement. Similarly to the previously described 2,3-epoxy-alcohols, which under basic conditions are involved in an isomerization equilibrium to give the corresponding terminal epoxides (Payne rearrangement), also 2,3-aziridin-1-alcohols undergo the same isomerization (aza-Payne rearrangement), giving related terminal epoxides. Subsequently, treatment with methylidene sulfoxonium ylide induces ring opening reaction followed by 5-*exo*-*tet*-ring closure, affording 2,3-disubstitued

pyrrolidines (Scheme 29). Using enantiopure 2,3-aziridin-alcohols as starting materials permits the preparation of diastereomerically and enantiomerically pure 2,3-disubstitued pyrrolidines, thanks to the intrinsic stereospecificity of the involved processes.



Scheme 29. Synthetic sequence for the preparation of pyrrolidines via aza-Payne rearrangement.

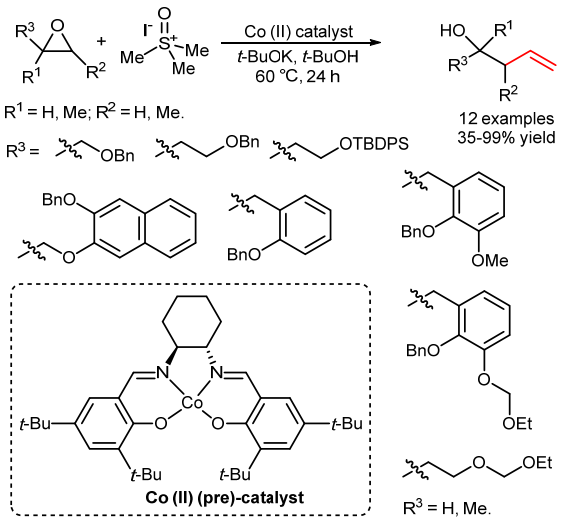
Distinct examples of ring expansion reactions triggered by dimethyl sulfoxonium methylide were reported by Matsunaga, Shibasaki and coworkers,[54] based on their mentioned approaches to the synthesis of oxirane motifs (see Scheme 13). In more detail, the authors developed two different methodologies for the synthesis of oxetanes, exploiting the sulfoxonium ylide as methylene transfer agent (Scheme 30). One of the two approaches is based on the kinetic resolution of racemic oxiranes, while the other one on a one pot process, starting from aryl or alkyl methylketones. A chiral amplification was observed during the second step. In both cases, the Lewis acid catalyst and the additives employed are the same heterobimetallic Li-La complexes used for Corey-Chaykovsky epoxidation of ketones, thanks to their ability to enhance reactivity and induce stereoselectivity at the same time. Regarding the kinetic resolution methodology, in order to improve the k_{rel} of the process, the authors carried out slight modifications to solvent and temperature. The best results were achieved employing a 1:1 mixture of THF and *n*-hexane as solvent at 45 °C, obtaining the oxetane in 43% yield and 78% *ee,* while the starting oxirane had only 65% *ee* (R = *n*-octyl). The low values of enantiomeric excess reflect a low stereoselectivity during the ring opening step.



Scheme 30. Kinetic resolution of racemic oxiranes and one pot methodology for the synthesis of oxetanes.

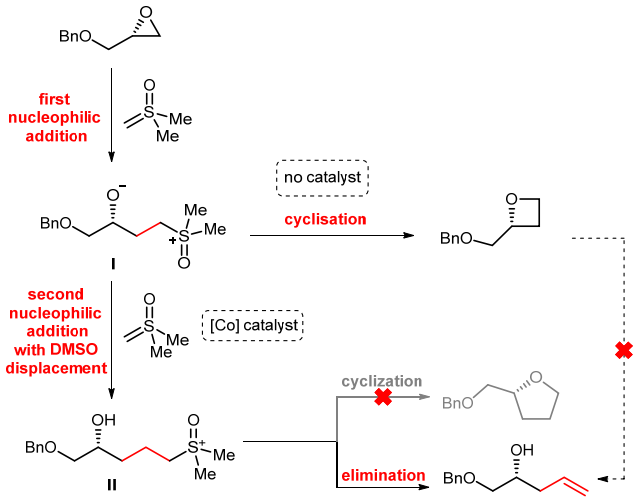
However, carrying out the same reaction on an enantioenriched substrate, a chiral amplification is observed, thanks to the moderate ability of the catalyst to discriminate between the two enantiomers of the epoxide. This approach was implemented in a one pot methodology joining the conditions of Corey-Chaykovsky epoxidation and kinetic resolution. Very good values of yields and enantiomeric excesses were achieved with a broad range of substrates employing aliphatic and electron poor/neutral aromatic methylketones.

An example showcasing the divergent reactivity of dimethyl sulfoxonium methylide with epoxides was reported by Furkert, Brimble and co-workers,[55] wherein, under the action of cobalt-SALEN catalysts, homoallylic alcohols were obtained instead of the standard ring-expansion oxetane products (Scheme 31).



Scheme 31. Synthesis of aliphatic alcohols under [Co] catalysis.

The mechanism proposed by the authors[56] is shown in Scheme 32, which takes into account the stereospecific nature of the reaction. A nucleophilic attack to the chiral oxirane generates intermediate **I** which can evolve via two different paths depending on the reaction conditions. In the absence of cobalt complexes a standard intramolecular cyclisation reaction of intermediate **I** gives an oxetane.[51] Conversely, in the presence of the cobalt catalyst, intermediate **I** suffers a second nucleophilic attack to give **II** with the concomitant release of DMSO as coproduct. At this point, two different pathways are conceivable. The first involves a cyclisation to give tetrahydrofuran motifs, which however were not detected by NMR in the crude mixture. The second, leading to the observed homoallylic alcohol product, encompasses an elimination reaction. Control experiments demonstrated that the homoallylic alcohol did not form by ring-opening of the oxetane. Interestingly, the formation of such homoallylic alcohol is a prerogative of cobalt catalysts. Other metal salts, such as $FeCl_3$ and $Sc(OTf)_3$, did not steer the reaction towards the formation of this product, affording the standard oxetane obtained in the uncatalyzed reactions. Unfortunately, the actual role of the cobalt catalysts in this reaction, accounting for such unique and peculiar selectivity, could not be clarified despite considerable investigations.



Scheme 32. Proposed mechanism.

Conclusions

By presenting recently published examples, complemented with a historical/general background, the main purpose of this short review has been to give an overview on the excellent performances of sulfoxonium ylides in insertion, cyclisation, and ring-opening reactions. All through the short review, we have tried to trace a comparison between sulfoxonium ylides and their congeners: sulfonium ylides and diazo compounds. We can conclude that, in some instances, sulfoxonium ylides can replace problematic – for safety reasons - diazo compounds. Being characterized by a remarkable safety profile and manageability, sulfoxonium ylides have been indeed useful in some insertion reactions typical of diazo compounds, under both catalysed (via metal carbenes) and uncatalysed conditions.

In addition, sulfoxonium ylides have shown in some cases synthetic opportunities beyond the reactivity of diazo compounds. It is worth to recall the smoothness of metal-free insertions of sulfoxonium ylides into RS-H, R-X and X-Y bonds, besides their more traditional (2 + 1) reactivity with π-systems. Conversely, the higher stability of sulfoxonium ylides, compared to their sulfonium counterparts, makes them tolerant to a broader range of reaction conditions and preparative protocols. This is especially true for unstabilised ylides (*i.e.* dimethylsulfoxonium methylide). On the other hand, higher stability means lower reactivity. For stabilised sulfoxonium ylides, such relatively low reactivity has perhaps hindered the development of catalytic asymmetric reactions, wherein coordination of the sulfoxide to a catalytic species might rise additional concerns. However, the few remarkable contributions highlighted in this short review show that such coordination can be overturned to become a linchpin to effect enantiocontrol.

We believe that the chemistry of sulfoxonium ylides will experience significant developments in the near future. Catalytic asymmetric insertion reactions might be flanked by the development of new cascade reactivity patterns. Following some current trends of the chemistry of diazo compounds,[57] Brønsted acid catalysis, as well as unconventional activation modes, might open unforeseen opportunities for sulfoxonium ylides.

We hope that this short review can contribute to further raise the interest in this appealing class of compounds, igniting the curiosity required for new and exciting discoveries.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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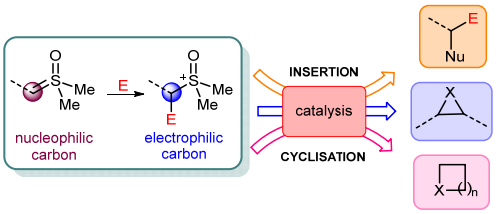
Graphic for table of contents.



Short sentence highlighting the novelty:

Sulfoxonium ylides, manageable compounds with an appealing safety profile, adapt to reaction partners like chameleons to environment, resulting in a variety of useful, and sometimes surprising and unique, reactions.