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Review

Recent Developments in Stereoselective Reactions of Sulfonium Ylides

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Abstract: This review describes advances in the literature since the mid-1990s in the area of reactions of sulfonium ylide chemistry, with particular attention paid to stereoselective examples. Although the chemistry of sulfonium ylides was first popularized and applied in a substantial way in the 1960s, there has been sustained interest in the chemistry of sulfonium ylides since then. Many new ways of exploiting sulfonium ylides in productive stereoselective methodologies have emerged, often taking advantage of advances in organocatalysis and transition metal catalysis, to access stereodefined structurally complex motifs. The development of many different chiral sulfides over the last 20–30 years has also played a role in accelerating their study in a variety of reaction settings. In general, formal cycloaddition reactions ([2 + 1] and [4 + 1]) of sulfonium ylides follow a similar mechanistic pathway: initial addition of the nucleophilic ylide carbanion to an electrophile to form a zwitterionic betaine intermediate, followed by cyclization of the zwitterionic intermediate to afford the desired three-membered cyclic product (e.g., epoxide, cyclopropane, or aziridine), five-membered monocyclic (e.g., oxazolidinone), or fused bicyclic product (e.g., benzofuran, indoline).

Keywords: sulfonium; ylides; conjugate addition; epoxide; cyclopropane; aziridine; asymmetric synthesis; diastereoselectivity; enantioselectivity

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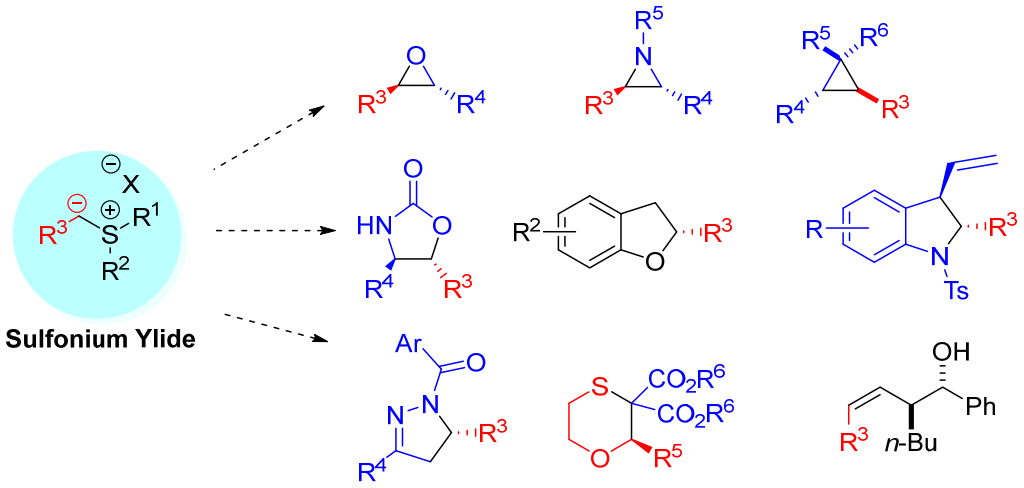
1. Introduction

Ylides were first defined in the 1920s by Staudinger as a neutral dipolar molecule containing a negatively charged atom, most often a carbanion, which is attached to a heteroatom with a formal positive charge. Although discovered by Staudinger, it was not until later in the 1950s and 1960s that their use became popularized, and in 1979 Georg Wittig won a Nobel prize for his work concerning the employment of phosphonium ylides in the synthesis of alkenes [1,2]. The chemistry of sulfur ylides, which were first discovered in 1930 by Ingold and Jessop, was later advanced significantly by A.W. Johnson, and popularized more broadly by Corey and Chaykovksy [3–5]. Their work on the use of sulfur ylides for the synthesis of epoxides, aziridines, and cyclopropanes has undoubtedly become one of the most well-known examples of the application of sulfur ylide chemistry, and a cornerstone of modern synthetic organic chemistry. Since then, the uses for these popular ylides have expanded to show their ability to act as an integral part in cycloaddition reactions, annulation reactions, and rearrangement reactions.

Sulfur ylides can be divided broadly into two main classes: sulfonium ylides and sulfoxonium ylides. The difference in reactivity between these two classes depends upon the oxidation state of the sulfur atom, with the sulfonium ylide being less stabilized and having greater nucleophilicity at the α-carbon. On the other hand, the sulfoxonium ylide displays better delocalization of the negative charge leading to lower C-nucleophilicity, but better leaving group ability for the sulfoxide group. Sulfur ylides can be further categorized as "stabilized" or "unstabilized". Stabilized ylides have an electron-withdrawing group at the nucleophilic α-carbon that can delocalize the electron density of the carbanion. These

ylides are generally bench-stable and have much longer half-lives than their unstabilized counterparts. In comparison, unstabilized sulfur ylides do not have α-groups capable of delocalizing the anionic charge and are therefore generally suited to being generated in situ and used at low temperatures. Although the latter sulfur ylides present the challenge of being more difficult to handle, their enhanced reactivity in contrast to their stabilized analogues is an important asset to synthetic chemists.

This review will highlight recent significant contributions to the literature describing stereoselective reactions of sulfonium ylides since the mid-1990s (Scheme 1), and build on and complement a number of excellent reviews describing progress in the area of sulfur ylide and sulfur salt chemistry [6–11].



Scheme 1. Stereoselective reactions of sulfonium ylides.

2. The Special Characteristics of Sulfur Ylides

The special characteristics of sulfur ylides include their relatively high stability (e.g., compared to the analogous ammonium ylides) and the superior leaving group ability associated with the weak C–S bond of the sulfur salts. It is, therefore, not surprising that the chemistry of sulfur ylides has gained considerable traction in the chemistry community, leading to many useful applications and studies [7–11].

Sulfur's ability to stabilize the adjacent (α) negatively charged carbon was originally proposed to be due to the propensity of available empty low-lying d-orbitals to enable delocalization of electron density from the filled lone pair orbital (*n*) of the carbanion [7–12]. However, since then, computational studies have illuminated our understanding of the mode of stabilization. It has become generally accepted that delocalization into d-orbitals does not play a significant role in the stabilization of sulfur ylides [7–11,13–15]. Instead, stabilization is largely attributed to electrostatic attraction, and negative hyperconjugation involving overlap between the carbanion lone pair orbital *n* and the σ* orbital of the sulfur-carbon bond [7–18]. The enhanced stability afforded by the sulfur atom in onium ylides facilitates a greater range of applications for sulfur ylides as compared to unstabilized carbanions (e.g., *n*-BuLi), which have greater nucleophilicity but also greater basicity leading to side reactions associated with said basicity.

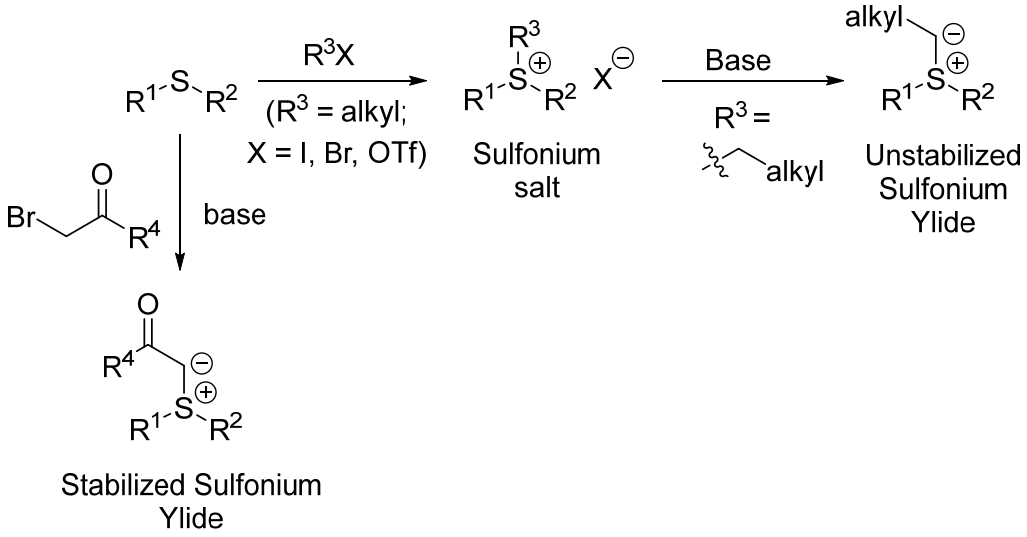
The stability of nucleophilic sulfur ylides coupled with the good leaving group ability of associated sulfides and sulfoxides has facilitated the development of an array of diverse synthetic reactions benefiting from those features. The superior leaving group ability of sulfides and sulfoxides (pKa for methyl-substituted sulfonium and sulfoxonium salts: 16–18 in DMSO), in comparison with amines and phosphines (pKa for methyl-substituted phosphonium and ammonium salts, >20 in DMSO) is especially important, and can allow 3-exo-*tet* cyclization reactions, such as epoxidation or cyclopropane formation, to proceed that will not readily occur with other classes of ylide [19]. The relatively poor leaving group ability of the phosphine (higher energy barrier to cyclization) coupled with the strength of

the P=O bond produced in the phosphine oxide byproduct of Wittig olefination means that cyclization to epoxide is disfavored [20].

3. Synthesis of Sulfonium Ylides

Synthesis of Sulfonium Salts and Ylides

Dialkyl sulfides may be readily converted to the corresponding sulfonium salts through an S_N2 alkylation reaction with alkyl iodides or triflates (Scheme 2). With less-reactive sulfides (e.g., diarylsulfides), halogen scavenging agents, such as $AgBF_4$, may be employed to accelerate the reaction with alkyl iodides and bromides [21–23]. Alternatively, reaction of alkyl Grignard reagents with alkoxy-substituted sulfonium salts provides access to *S*-(alkyl) diarylsulfonium salts. Employment of organocadium reagents, which are softer nucleophiles and less basic in comparison to Grignard reagents, has been observed to provide higher yields of the desired sulfonium salts, while racemization of enantiopure sulfoniums is reduced [24,25].

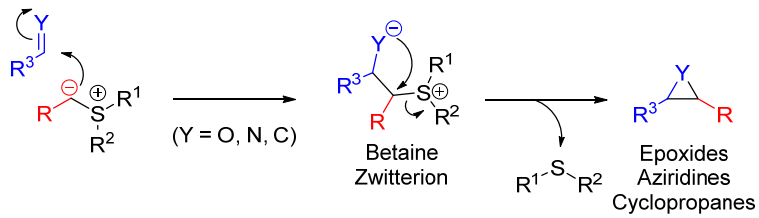


Scheme 2. Main routes to sulfonium ylides.

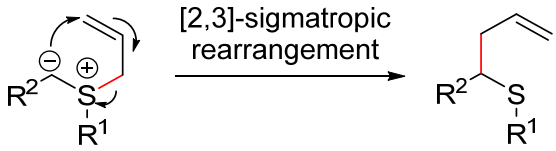
Unstabilized sulfonium ylide generation can be achieved through treatment with an appropriately strong base, such as NaH or KHMDS. Stabilized sulfonium ylides are typically prepared through reaction of a sulfide with an α-bromocarbonyl compound in the presence of a base such as K_2CO_3 or KOH.

4. Reactions of Sulfonium Ylides

The reactions of sulfonium ylides may be categorized according to reaction type (e.g., epoxidation), as we have presented in this review. Most typically involve a Johnson–Corey–Chaykovsky-type reaction mechanism (Scheme 3) leading to three-membered cyclic products, while some proceed through a formal cycloaddition mechanism (e.g., [4 + 1]-cycloaddition) to give five-membered cyclic products (monocyclic or fused bicyclic) or a [2,3]/[1,2]-rearrangement (Scheme 4) [6,26–29].

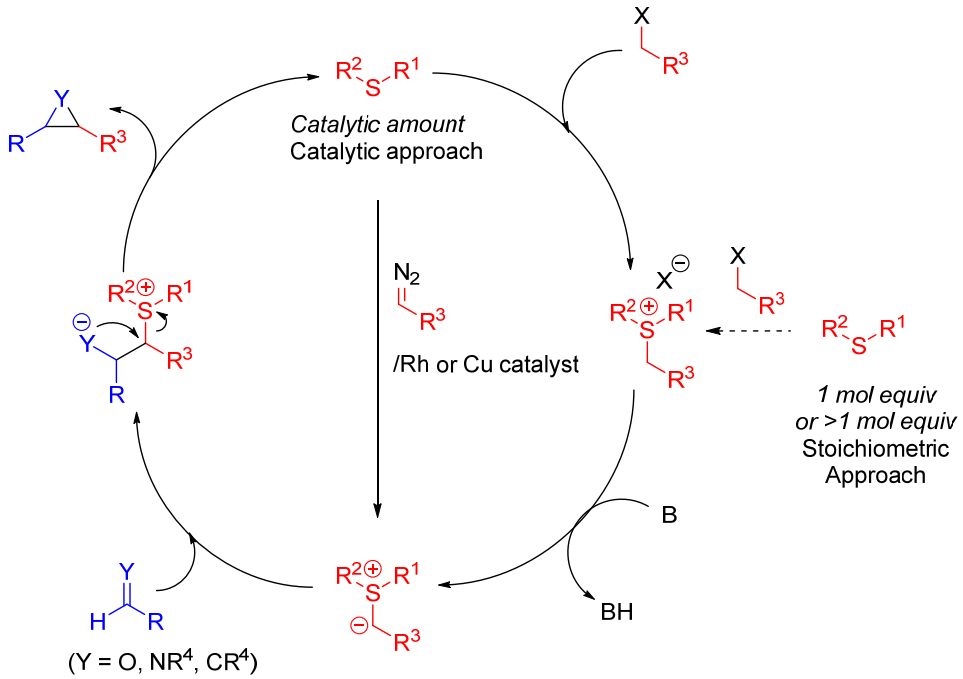


Scheme 3. Mechanism of Johnson–Corey–Chaykovsky reaction.



Scheme 4. Rearrangement mechanism.

There are two major approaches for carrying out sulfonium ylide-mediated reactions (as exemplified by epoxidation) (Scheme 5). The first approach (stoichiometric approach) involves the preparation and isolation of a sulfonium salt from a sulfide precursor, which then undergoes base-mediated generation of the sulfonium ylide, and it subsequently reacts with an unsaturated compound (e.g., carbonyl compound) to afford the desired product, e.g., epoxide [6,27–33]. In the second approach (catalytic approach), the reaction starts with a sulfide, followed by formation of a sulfonium salt, ylide formation, and finally reaction with a carbonyl compound to afford epoxide, with all steps taking place in the same pot. At the end of the cycle, the starting sulfide regenerates, and so the sulfide acts as a catalyst and can be potentially recycled [6,27–29,34–36].



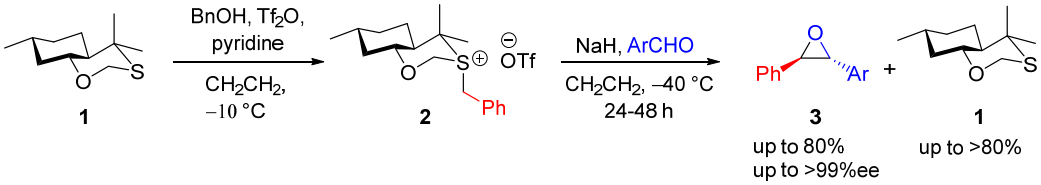
Scheme 5. Stoichiometric and catalytic variants of sulfonium ylide reactions (B = base).

4.1. Epoxidation

Epoxides, particularly enantioenriched epoxides, serve as useful intermediates and versatile building blocks in the synthesis of complex organic molecules. Due to the associated high strain of the three-membered ring system, epoxides are prone to a variety of nucleophilic ring-opening reactions. Since the discovery of the Sharpless asymmetric epoxidation, there have been many important developments in this area. With the rapid progress in the field of asymmetric organocatalysis, a wide range of organocatalysts are now available to catalyze the epoxidation of a broad class of carbonyl compounds. Ever since the discovery of the Johnson–Corey–Chaykovsky reaction, sulfur ylides have provided a unique pathway for the generation of substituted epoxides from carbonyl compounds [3–5]. As advances in the field of sulfonium ylide-mediated/catalyzed epoxidation have been summarized elsewhere in a number of excellent reviews, this review will restrict itself to a summary of some of the most important aspects of sulfonium ylide-mediated/catalyzed stereoselective epoxidation since 2000 [3–6,27–29].

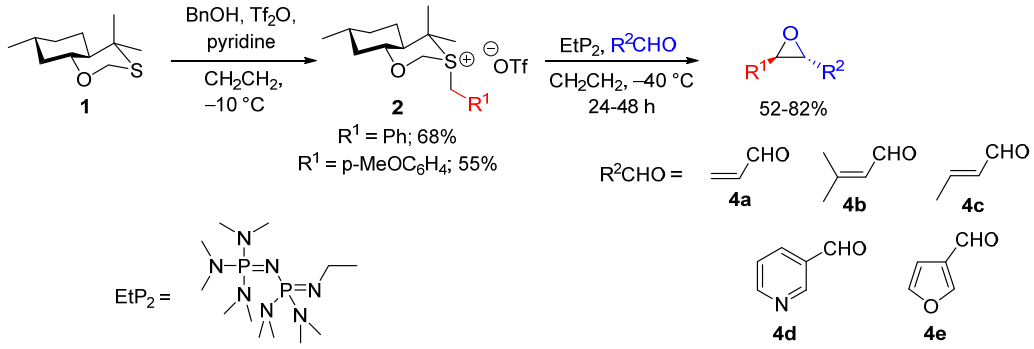
4.1.1. Stoichiometric Sulfonium Ylide-Mediated Epoxidation

Solladié-Cavallo and colleagues used oxathiane **1** (derived from pulegone) in asymmetric epoxidation (Scheme 6). This sulfide, on benzylation, formed sulfonium salt **2**, and was isolated as a single diastereomer. Sulfonium salt **2** in the presence of sodium hydride generated the ylide, which after treatment with an aromatic aldehyde furnished epoxide **3** in high yield, excellent enantioselectivity, and with recovery of the chiral sulfide **1** [32].



Scheme 6. Epoxidation using chiral sulfonium salt **2**.

By replacing the base with phosphazene, this methodology was further extended to the synthesis of aryl,vinyl-substituted epoxides with high yields, and excellent enantioselectivities and diastereoselectivities (Scheme 7) (Table 1) [32]. Although, often in the presence of an α,β-unsaturated aldehyde, there is the possibility of cyclopropanation occurring with the sulfur ylide, this reaction showed remarkable regioselectivity towards exclusive epoxidation. Heteroaryl,aryl-substituted epoxides could also be synthesized using this methodology [33].



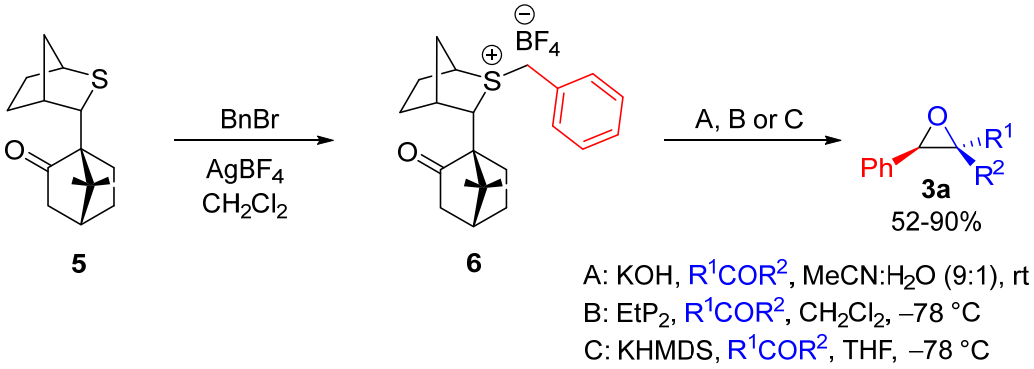
Scheme 7. Epoxidation using chiral sulfonium salt **2** and phosphazene base.

Table 1. Solladié-Cavallo asymmetric synthesis of epoxides using sulfonium salt **2** (Scheme 7).

Entry	R^1 (Ylide)	R^2CHO	Epoxide: Epoxycyclopropane: Cyclopropane.	*trans*:*cis* (Epoxide)	ee (%), *trans*-epoxide
1	Ph	**4a**	77:11:12	100:0	97
2	*p*-$MeOC_6H_4$	**4a**	100:0:0	77:23	95
3	Ph	**4b**	100:0:0	97:3	>99
4	Ph	**4c**	100:0:0	97:3	>99
5	Ph	**4d**		100:0	97
6	Ph	**4e**		100:0	>99

The Aggarwal group introduced chiral sulfonium salt **6** derived from camphorsulfonyl chloride, and applied it to the asymmetric epoxidation of various carbonyl compounds [31]. The ylides, generated from sulfonium salt in the presence of base, were treated with several carbonyl compounds to furnish epoxides in good yields, and excellent diastereoselectivities and enantioselectivities (Scheme 8) (Table 2). This method is capable of synthesizing aryl,aryl-, aryl,heteroaryl-, aryl,alkyl-, and aryl,vinyl-substituted epoxides. This was the

first example in asymmetric sulfur ylide-mediated epoxidations where the sulfonium ylide could be treated with ketones to produce trisubstituted epoxides.

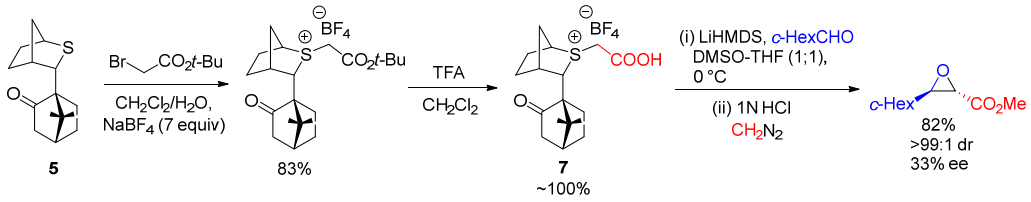


Scheme 8. Epoxidation using chiral sulfonium salt **6** and various bases.

Table 2. Aggarwal asymmetric synthesis of epoxides using sulfonium salt **6** (Scheme 8).

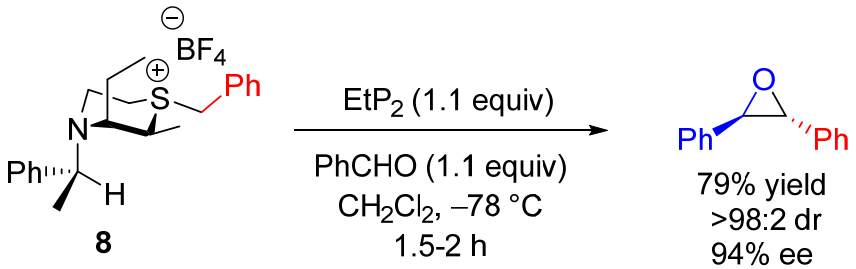
Entry	R^1COR^2	Method	Yield of 3a (%)	*trans*:*cis*	ee *trans* (%)
1	PhCHO	A	75	98:2	98
2	2-PyrCHO	B	88	98:2	99
3	n-BuCHO	C	87	90:10	>99
4	CH_2=C(Me)CHO	B	52	>99:1	95
5	I-MeCH=CH_2CHO	B	90	>99:1	95
6	Cyclohexanone	B	85	–	92
7	*p*-NO_2PhCOMe	B	73	>1:99	71
8	PhCOMe	B	77	33:67	93

Chiral sulfide **5** was further explored in carboxylate-stabilized sulfur ylide-mediated epoxidation of carbonyl compounds (Scheme 9) [37]. The reaction was investigated using **7** in the presence of different bases and solvents and, under the best conditions, *trans*-epoxide was obtained in good yield and excellent diastereoselectivity, but with poor enantioselectivity.



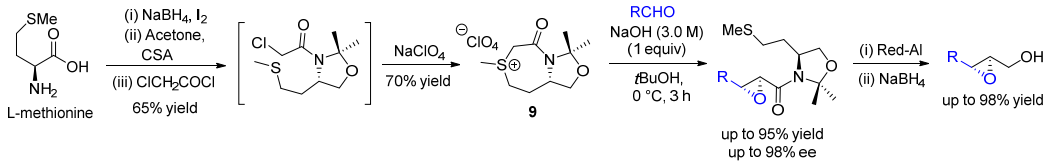
Scheme 9. Epoxidation using carboxylate-stabilized sulfonium ylide.

Aggarwal and co-workers also introduced chiral thiomorpholines synthesized from limonene or achiral alkene using α-methylbenzylamine to control absolute stereochemistry [38]. The ylide generated from these aminosulfonium salts **8** was applied to the asymmetric epoxidation of aldehydes. Excellent yields, enantioselectivities, and diastereoselectivities were achieved in these epoxidations. Significantly, the starting sulfides could be easily recovered in high yield by simple acid–base extraction (Scheme 10).



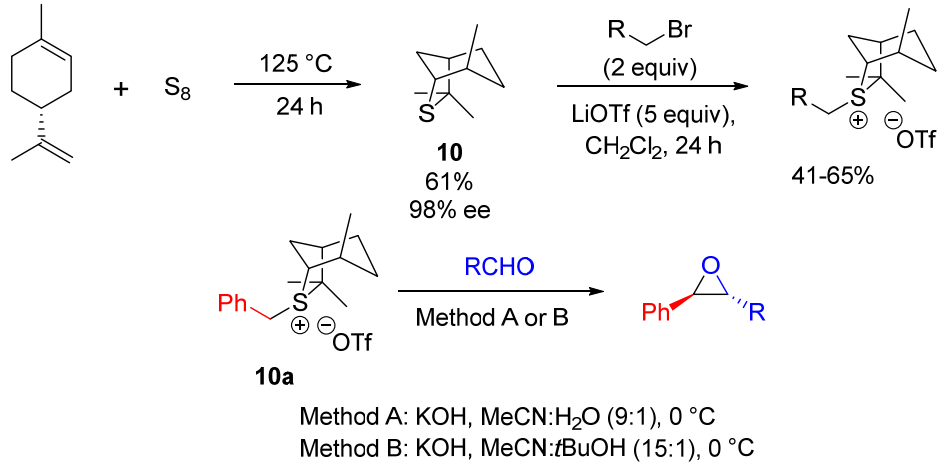
Scheme 10. Epoxidation using thiomorpholine-derived sulfonium ylide.

Sarabia et al. introduced new chiral bicyclic sulfonium salts synthesized from L- and D-methionines [39]. The stabilized ylide generated in situ from the sulfonium salt **9** reacts with aldehydes to form epoxy-amides with excellent diastereoselectivity. The epoxy-amide, on sequential reduction with Red-Al and sodium borohydride, released enantiopure epoxy-alcohols with good yields overall (Scheme 11).



Scheme 11. Epoxidation using bicyclic sulfonium ylide.

Aggarwal and co-workers introduced a novel chiral sulfide **10**, isothiocineole, synthesized from natural limonene and elemental sulfur in one-step with very good yield [40–42]. Preparation of sulfonium salt **10a** from this new chiral sulfide followed by generation of ylide in the presence of base and finally treatment with several carbonyl compounds furnished *trans*-epoxide in very good yields, with excellent diastereoselectivities (dr 91:9 to 95:5) and enantioselectivities (94–98% ee) (Scheme 12). This methodology was further explored for the asymmetric epoxidation of meroquinene aldehyde, which was utilized in quinine and quinidine synthesis.

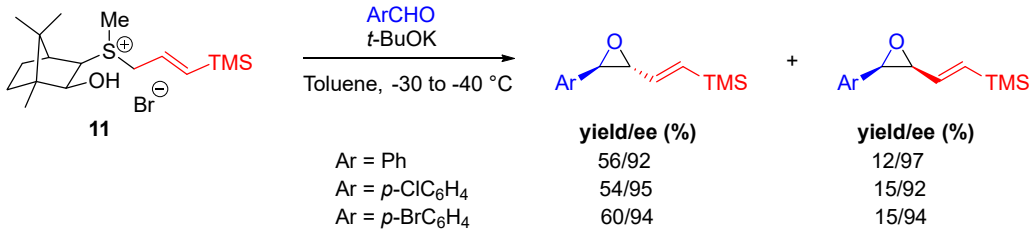


Scheme 12. Epoxidation using limonene-derived sulfonium ylide.

4.1.2. Stoichiometric Allyl Sulfonium Ylide-Mediated Epoxidation

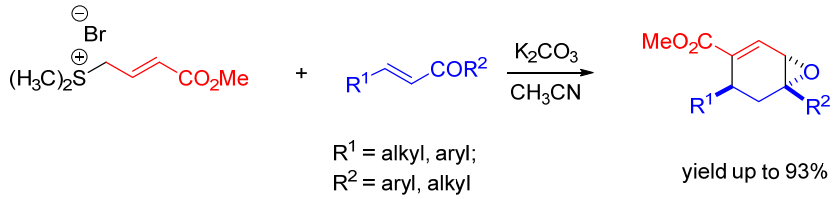
Encouraged by the high stereoselectivity observed in their cyclopropanation studies, Tang and co-workers attempted the reaction of allyl sulfoniums **11** with aldehydes [43]. Vinyl epoxides were formed with very good enantioselectivity, but with only moderate diastereoselectivity. Aromatic aldehydes worked well for this reaction. However, desired

epoxide products were not formed when less-reactive aliphatic aldehydes were employed as substrates (Scheme 13) [43].



Scheme 13. Tang's enantioselective synthesis of vinyl epoxides.

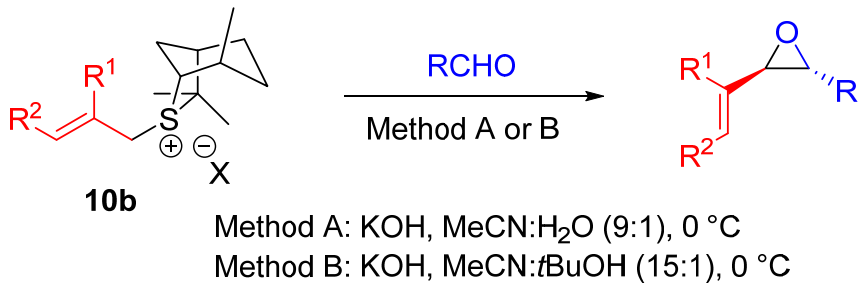
During their study of the synthesis of vinyl cyclopropanes, Tang et al. unexpectedly found that cyclohexadiene epoxides were generated through the reaction of crotonate-derived sulfonium salt with chalcones by using K_2CO_3 as a weaker base. Further experimentation showed that these reaction conditions were suitable for reaction of β-aryl- and β-alkyl-substituted α,β-unsaturated ketones. Cyclohexadiene epoxides were produced with excellent diastereoselectivity and in good yields through a tandem Michael addition/ylide epoxidation sequence (Scheme 14) [44].



Scheme 14. Tang's tandem Michael addition-ylide epoxidation.

Tricyclic cyclohexadiene epoxides could be prepared by employing an intramolecular version of this tandem reaction. While using camphor-derived chiral sulfonium salts, both intermolecular and intramolecular reactions afforded highly functionalized cyclohexadiene epoxide products in moderate-to-good yields and with greater than 91% enantiomeric excess [44]. This reaction provided a good example for remote control of enantioselectivity. The cyclohexadiene epoxides could be ring-opened by sodium methoxide with high regiospecificity or reduced using $LiBEt_3H$ with good stereospecificity [44].

Aggarwal and co-workers reported a novel chiral sulfide synthesized from limonene (as detailed earlier, Scheme 11) [40–42]. Preparation of allyl sulfonium salts **10b** from this new chiral sulfide, followed by generation of allylic ylides in the presence of base and treatment with several carbonyl compounds, furnished *trans*-epoxides in good-to-excellent yields, and with generally excellent diastereoselectivity and enantioselectivity observed (Scheme 15 and Table 3).



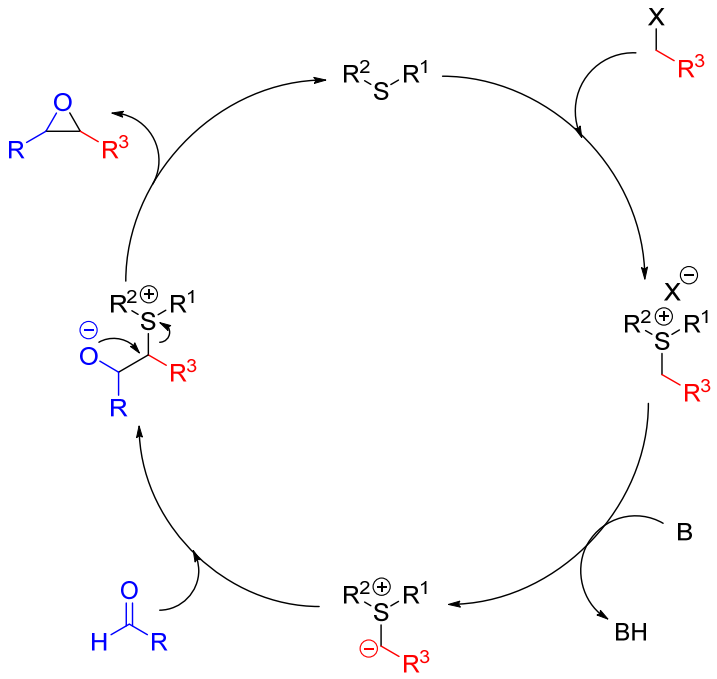
Scheme 15. Asymmetric synthesis of vinyl epoxides from chiral allyl sulfonium salt.

Table 3. Aggarwal asymmetric synthesis of vinyl epoxides using allyl sulfonium salt (Scheme 15).

Entry	X	R^1	R^2	R	Method	Yield (%)	dr (*trans*:*cis*)	ee (%)
1	BF_4	H	Ph	Ph	A	65	80:20	70
2	BF_4	Me	Ph	Ph	A	97	>95:5	98
3	OTf	Me	H	Ph	A	80	>95:5	98
4	BF_4	Me	Ph	Cy	B	77	>95:5	96
5	OTf	Me	H	Cy	B	77	>95:5	94
6	OTf	H	H	Ph	A	57	75:25	40

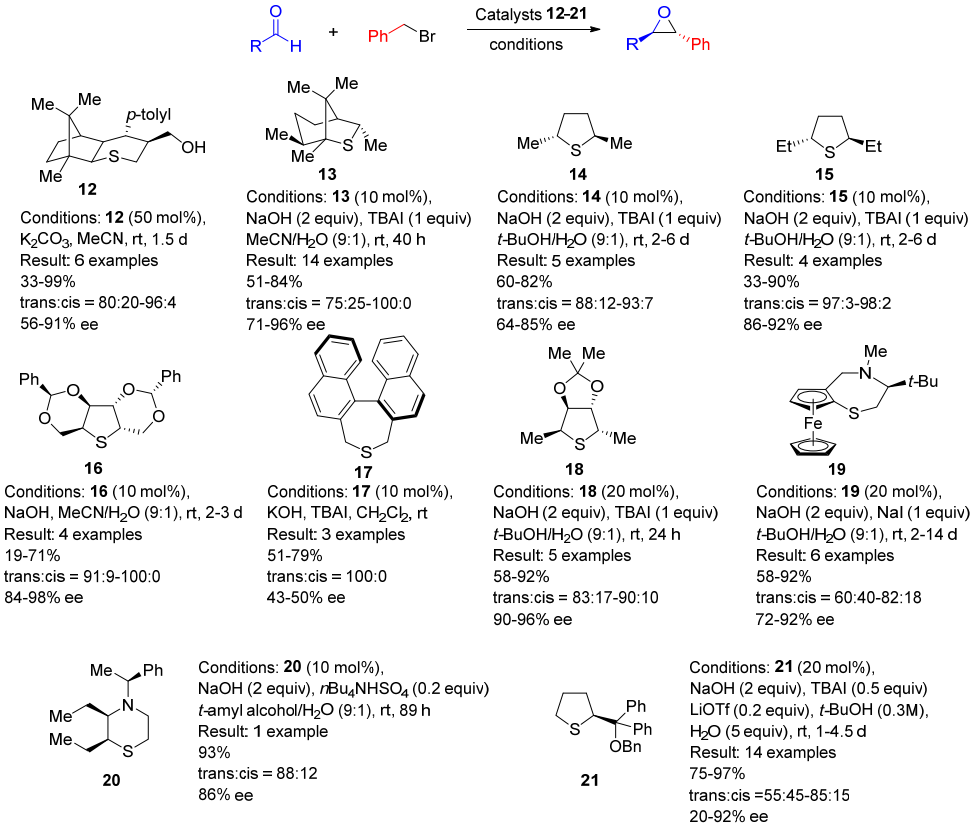
4.1.3. Catalytic Sulfonium Ylide-Mediated Epoxidation

The catalytic cycle of sulfonium ylide-mediated epoxidation involves initial alkylation of a sulfide, followed by deprotonation of the sulfonium salt to generate a sulfonium ylide. The ylide then attacks a carbonyl compound to form a new zwitterionic intermediate (betaine), which collapses to furnish epoxide product and returns sulfide into the catalytic cycle (Scheme 16).



Scheme 16. Catalytic epoxidation using catalytic amount of sulfide.

The first enantioselective sulfide-catalyzed epoxidation was reported by Furukawa et al. in 1989 [45]. The sulfide catalyst derived from camphorsulfonic acid gave oxirane in 23% yield and 31% ee. After this pioneering work, many chiral sulfide-catalyzed epoxidation reactions were developed. The chiral sulfides that have provided highest yields and enantioselectivities with a variety of carbonyl compounds are summarized in Scheme 17.



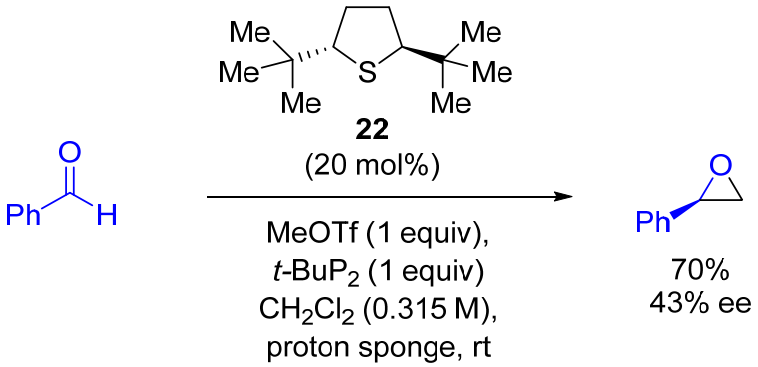
Scheme 17. Catalytic enantioselective epoxidation systems using catalytic quantity of chiral sulfides.

Saito et al. introduced the camphor-derived chiral sulfide catalyst **12**, which provided high diastereoselectivity but low enantioselectivity for substituted aromatic aldehydes [46]. Another camphor-derived chiral sulfide catalyst **13** was developed by Gui et al. and found to function well for both aliphatic and aromatic aldehydes [47]. C_2-symmetric chiral sulfide catalysts have also emerged as a promising catalyst class for asymmetric epoxidation reactions. Zanardi et al. prepared C_2-symmetric chiral sulfide catalysts **14** and **15** and they were found to catalyze epoxidation reactions of a range of aromatic, heteroaromatic, and α,β-unsaturated aldehydes with good yields, diastereoselectivity, and enantioselectivity demonstrated, but with long reaction times (up to 6 days) [48]. To enhance the reaction rate without affecting selectivity, iodide salt was introduced into the reaction mixture to convert benzyl bromide, in situ, into the more reactive benzyl iodide. Goodman and co-workers then introduced the C_2-symmetric chiral sulfide catalyst **16**, and Uemura and co-workers introduced **17** [49,50]. Both of these catalysts catalyzed the conversion of aromatic aldehydes into the corresponding *trans*-diarylepoxides. Catalyst **16** gave low yields with high diastereoselectivities and enantioselectivities, whereas catalyst **17** performed best when benzyl iodide was used as a reagent and gave epoxides in moderate yields, with high diastereoselectivity and low enantioselectivity. The C_2-symmetric chiral sulfide catalyst **14** was modified to give catalyst **18**, which provided further improvement [51]. The modified catalyst **18** gave moderate-to-good yields, good diastereoselectivities, and high enantioselectivities for various aromatic aldehydes. The increased selectivities observed with catalyst **18** arose due to the introduction of an acetal bridge, thus creating a rigid bicyclic ring system, which forced the methyl groups at the 2- and 5-positions to adopt pseudoaxial orientations.

In addition to camphor-derived and C_2-symmetric sulfide catalysts, several other catalysts have been developed and provided promising results. Metzner and co-workers introduced ferrocenyl sulfide catalyst **19**, which exhibits planar and central chiralities [52]. Asymmetric epoxidation using the ferrocenyl sulfide catalyst **19** gave moderate yields

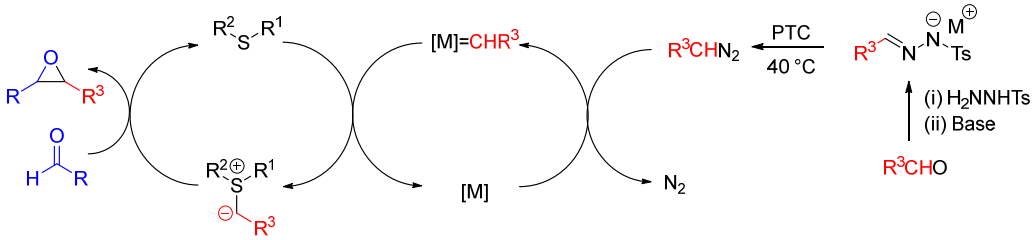
and diastereoselectivities but high enantioselectivities with aromatic, heteroaromatic, and α,β-unsaturated aldehydes. Aggarwal and co-workers introduced thiomorpholine-based chiral sulfide catalyst **20** for asymmetric epoxidation and it was demonstrated to work well with benzaldehyde, producing *trans*-stilbene oxide with high yield and good diastereo- and enantioselectivity [38]. Chein and colleagues recently introduced an efficient and promising thiolanyl-based chiral sulfide catalyst **21** for asymmetric epoxidation [53]. This catalyst is capable of delivering enantioselective sulfide-catalyzed epoxidation with several aromatic aldehydes as well as α,β-unsaturated aldehyde in good yield, and with moderate-to-high diastereo- and enantioselectivities.

Despite tremendous progress in the field of chiral sulfide-catalyzed asymmetric *trans*-epoxidation, there is only one report on catalytic asymmetric synthesis of terminal epoxides. Connon and co-workers developed a disubstituted thiolanyl-based chiral sulfide catalyst **22** for enantioselective methylene transfer to aldehydes, providing epoxides in good yield but with moderate enantiomeric excess (Scheme 18) [54].



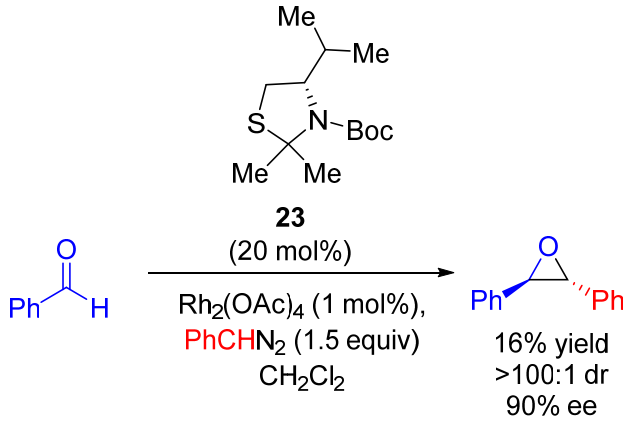
Scheme 18. Connon's catalytic enantioselective synthesis of terminal epoxides.

The conventional chiral sulfide-catalyzed asymmetric *trans*-epoxidation proceeds through an alkylation/deprotonation sequence which can limit the applicability of the reaction due to aldehyde enolization and resulting side reactions. To improve the scope of sulfide-catalyzed epoxidation, Aggarwal and co-workers introduced an innovative methodology that involved reaction of a metallocarbenoid with a sulfide to generate an ylide under neutral conditions [55]. In the catalytic cycle, a diazo compound (prepared from a carbonyl compound) underwent decomposition in the presence of an appropriate metal catalyst to form a carbenoid intermediate, which reacted with a sulfide catalyst to form a sulfonium ylide, along with regeneration of the metal catalyst. Finally, the sulfonium ylide underwent reaction with an aldehyde to produce the desired epoxide and regenerate the sulfide catalyst (Scheme 19) [56–60]. This method had several advantages over previous methods, including: (i) the method allowed use of base-sensitive substrates due to the neutral operating conditions, (ii) more-reactive carbenoid intermediates enabled easy access to the ylide intermediate, particularly when less-reactive sulfides were used as catalysts, and (iii) the method enabled the coupling of two different aldehydes together to furnish epoxides.



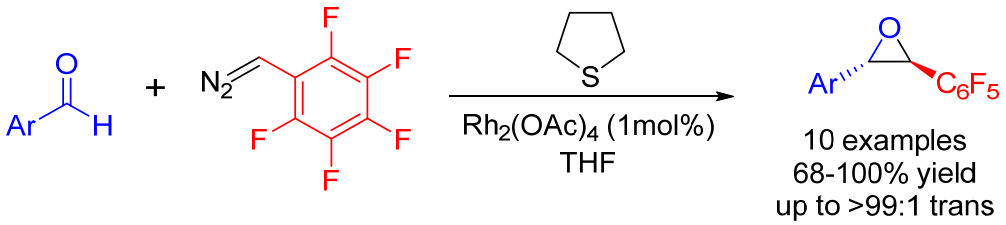
Scheme 19. Catalytic cycle for Aggarwal's catalytic epoxidation.

Koskinen and co-workers [58] introduced a thiazolidine-based chiral sulfide catalyst **23** with the aid of molecular modeling for asymmetric epoxidation of benzaldehyde with phenyl diazomethane, but the reaction proceeded with low yield, although with excellent diastereoselectivity and enantioselectivity (Scheme 20).



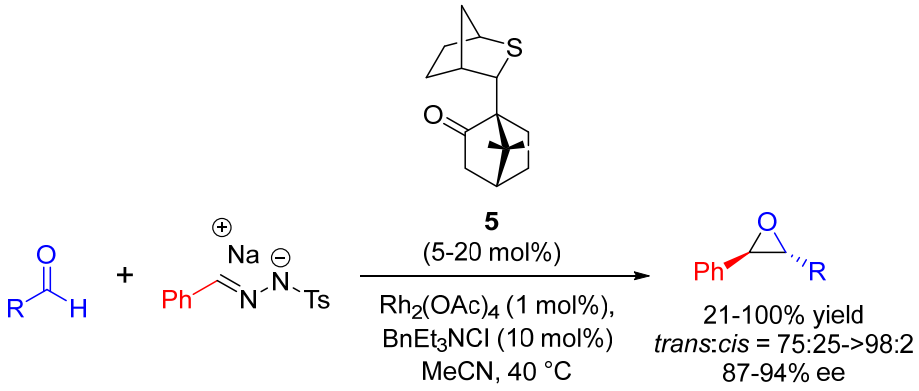
Scheme 20. Koskinen's catalytic asymmetric epoxidation.

Zhu and co-workers reported epoxidation of several aromatic, heteroaromatic, and α,β-unsaturated aldehydes with pentafluorophenyl diazomethane under $Rh_2(OAc)_4$ catalysis and with tetrahydrothiophene as the sulfide catalyst [60]. The latter methodology furnished *trans*-epoxides in moderate-to-excellent yields and with very high diastereoselectivities (Scheme 21).



Scheme 21. Zhu's catalytic diastereoselective synthesis of epoxides.

Aggarwal's group later developed a more simplified methodology for generation of chiral sulfonium ylide by reacting metalated tosylhydrazone salts, derived from benzaldehyde, with chiral sulfide catalyst **5** in the presence of $Rh_2(OAc)_4$ as metal catalyst [57]. The ylide intermediate underwent coupling with several aromatic, heteroaromatic, and α,β-unsaturated aldehydes to furnish *trans*-epoxides in moderate-to-high yields, moderate-to-excellent diastereoselectivities, and with good-to-excellent enantioselectivities (Scheme 22).



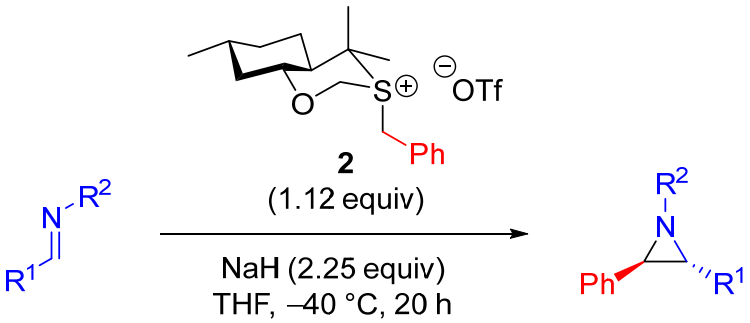
Scheme 22. Aggarwal's catalytic enantioselective synthesis of epoxides.

4.2. Aziridination

4.2.1. Stoichiometric Sulfonium Ylide-Mediated Aziridination

Aziridines are among the most fascinating heterocyclic intermediates in organic synthesis, acting as precursors of many complex bioactive and pharmaceutically important molecules, due to the strain incorporated in the three-membered ring. Since the first synthesis of an aziridine was reported by Gabriel in 1888, the synthetic scope of aziridine chemistry has developed in many directions [61–69]. Due to high ring strain energy associated with the three-membered ring, the C−N bond of the aziridine ring is vulnerable. Therefore, aziridines as nitrogen equivalents of epoxides can either undergo stereocontrolled ring cleavage reactions with a range of nucleophiles or cycloaddition reactions with dipolarophiles, providing access to a wide range of important nitrogen-containing heterocycles [70–75]. However, aziridines have been used less widely in organic synthesis than epoxides, partly because there are fewer efficient methods for enantioselective and diastereoselective aziridination relative to epoxidation. Recent advances in asymmetric aziridination have been previously reviewed in a number of articles [6,27–29,76–83]. Sulfur ylides have been widely used to achieve the efficient synthesis of aziridines from imines. Similar to epoxidation, the reaction between a sulfonium ylide and an imine forms a betaine intermediate, which undergoes ring closure to form an aziridine through elimination of the sulfide leaving group.

In 2010, Hamersak et al. reported the synthesis of a range of chiral N-protected *trans*-aziridines based on the reaction of aldimines with a chiral oxathiane-derived sulfonium salt **2** (Scheme 23) [84]. Various N−Ts, N−SES, N−Boc, and N−*o*-Ns protected chiral aziridines were synthesized in moderate-to-good yields and with remarkable enantioselectivities. The diastereoselectivities of the reactions were variable and influenced by the imine N-protecting group, the imine substituent, and the sulfide structure. By comparing the observed diastereoselectivities, the N-protecting groups were organized in the following order of decreasing *trans*-selectivity: Boc > SES > Ts > *o*-Ns. Some selected results are depicted in Table 4.



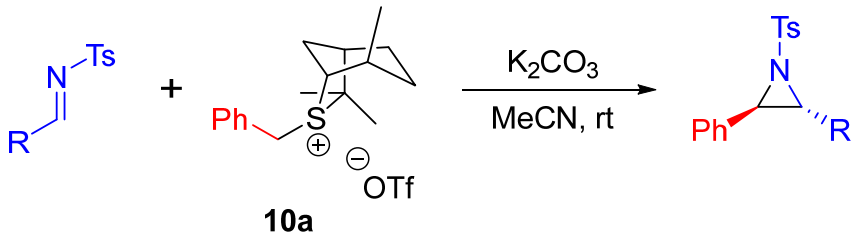
Scheme 23. Hamersak's synthesis of *trans*-aziridines.

Table 4. Substrate scope of sulfonium salt **2**-mediated aziridination (Scheme 23).

Entry	R^1	R^2	Yield (%)	*trans*:*cis*	*trans* ee (%)
1	Ph	Boc	60	90:10	97
2	PMP	Boc	31	91:9	96
3	1-Napthyl	Boc	75	98:2	96
4	*tert*-Butyl	SES	62	0:100	– (98 *cis*)
5	*tert*-Butyl	Ts	68	0:100	– (97 *cis*)
6	9-Anthryl	SES	53	91:9	98

Aggarwal and co-workers used their sulfonium salt **10a** prepared from chiral isothiocineole for asymmetric aziridination [40–42]. This chiral sulfonium salt was employed as a chiral precursor of ylides under simple reaction conditions to react with a wide range of aldimines and provide the corresponding chiral *trans*-aziridines in good yields along with

perfect enantioselectivities and diastereoselectivities [40]. They also reisolated the chiral sulfide in 95% yield (Scheme 24) (Table 5).

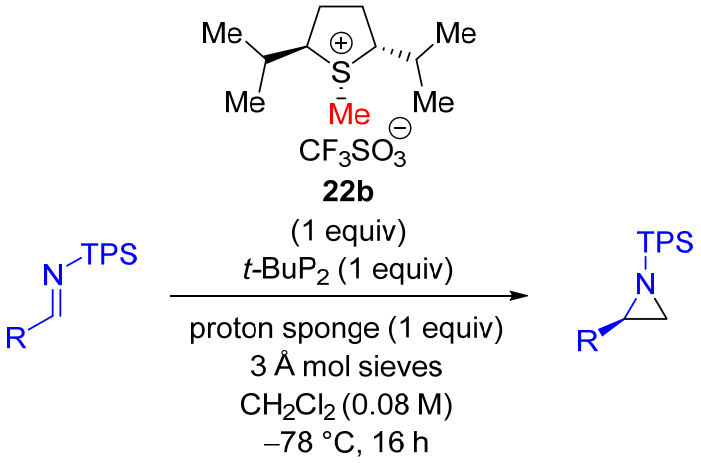


Scheme 24. Aggarwal's enantioselective aziridination.

Table 5. Scope of Aggarwal's enantioselective aziridination (Scheme 24).

Entry	R	Yield (%)	*trans*:*cis*	*trans* ee (%)
1	Ph	72	85:15	98
2	*p*-MeC_6H_4	63	86:14	98
3	*p*-ClC_6H_4	65	75:25	98
4	*p*-$MeOC_6H_4$	80	83:17	98
5	(*E*)-PhCH=CH	78	>99:1	96
6	(*E*)-TMSCH=CH	78	87:13	98

Connon and co-workers developed a simple C_2-symmetric chiral salt **22b** derived from (2*R*,5*R*)-2,5-diisopropylthiolane, and it mediated the asymmetric methylene transfer methodology for aziridination to a range of aldimines with uniformly excellent yields, albeit with low enantioselectivities (up to 30% ee) [85]. The reaction was carried out in the presence of a strong organic base and proton sponge in stoichiometric quantities and showed a quite broad scope since aromatic, aliphatic, as well as α,β-unsaturated TPS-protected aldimines gave the corresponding chiral aziridines in high yields (Scheme 25) (Table 6).

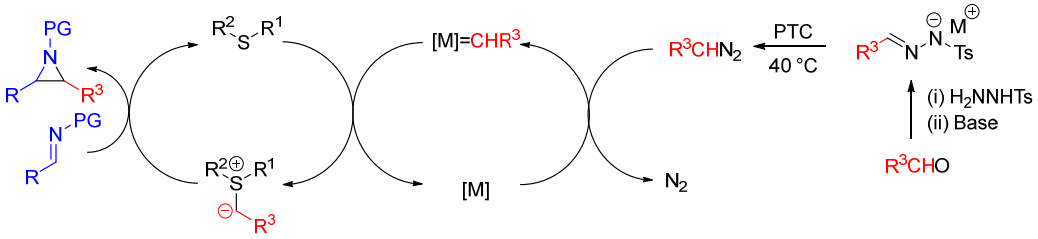


Scheme 25. Connon's enantioselective synthesis of terminal aziridines.

Table 6. Scope of Connon's enantioselective synthesis of terminal aziridines (Scheme 25).

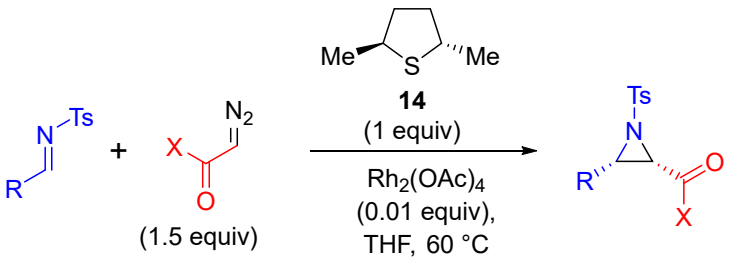
Entry	R	Yield (%)	ee (%)
1	Ph	91	23
2	*p*-ClC_6H_4	88	18
3	*p*-$MeOC_6H_4$	92	25
4	*o*-ClC_6H_4	87	30
5	2,4,6-trimethyl-C_6H_2	87	25
6	1-Naphthyl	92	23
7	Cinnamyl	92	18
8	*c*-Hex	91	20

Due to the many limitations of ylide-mediated aziridination requiring stoichiometric amounts of chiral reagents, Aggarwal and co-workers reported, in similar fashion to epoxidation, an asymmetric aziridination of imines via sulfonium ylides generated by the reaction of a metallocarbene with a sulfide (Scheme 26) [86,87]. The decomposition of a diazo compound in the presence of a suitable transition metal salt generates the carbenoid. To avoid reaction of the metallocarbene with an excess of the diazo compound, the latter reagent was added slowly to the reaction mixture over the course of the reaction.



Scheme 26. Catalytic cycle for Aggarwal's aziridination.

Aggarwal and colleagues reported a C_2-symmetric chiral sulfide **14**-mediated asymmetric aziridination of diazoesters and diazoacetamides with aromatic aldimines [87]. The corresponding ester- and amide-bearing aziridines were isolated in moderate-to-high yields with moderate enantioselectivities. The diastereoselectivities observed with ester-derived ylides were variable but favored *cis*-aziridines. Electron-poorer imines led to higher levels of *cis*-selectivity. Relatively higher temperature (60 °C) was necessary to effect diazo decomposition of the more stable diazo-precursors using this method (Scheme 27) (Table 7).

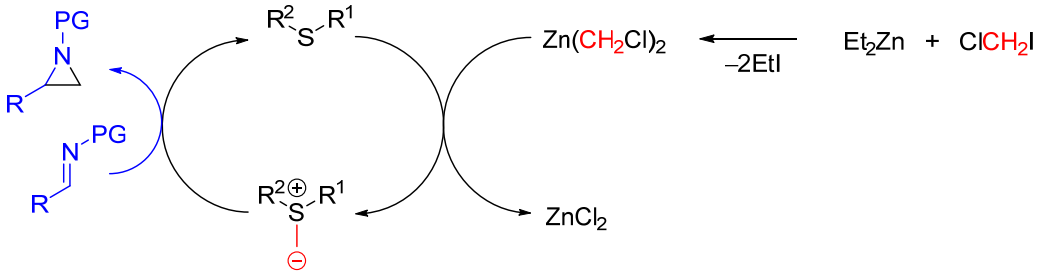


Scheme 27. Asymmetric aziridination of diazoesters and diazoacetamides.

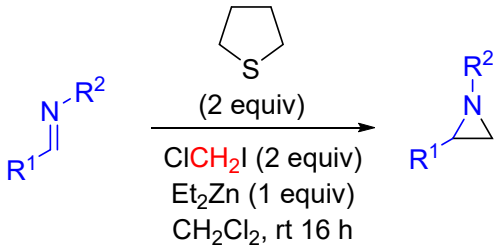
Table 7. Scope of asymmetric aziridination of diazoesters and diazoacetamides (Scheme 27).

Entry	R	X	Yield (%)	*cis*:*trans*	*cis* ee (%)
1	*p*-$MeOC_6H_4$	OEt	53	3:2	45
2	Ph	OEt	80	3:1	58
3	*p*-ClC_6H_4	OEt	72	5:1	54
4	*p*-$NO_2C_6H_4$	OEt	83	12:1	56
5	Cy	OEt	76	11:1	44
6	Ph	NEt_2	98	1:1	30

Aggarwal and co-workers further explored ylide generation by the reaction of a metallocarbene with a sulfide. They used Simmons–Smith carbenoids as a source of the metallocarbene, which on reaction with a sulfide generated sulfonium ylide in situ (Scheme 28) [88]. The ylides, generated through reaction of Simmons–Smith carbenoids and sulfides, underwent terminal aziridination with various imines derived from aromatic and aliphatic aldehydes in high yields (Scheme 29) (Table 8). Interestingly, the usual requirement in ylide aziridination for an activating electron-withdrawing group on the imine nitrogen was not found to be essential, provided the *N*-substituent had at least one possible coordinating site. It was postulated that these imines were activated through chelation with zinc(II) species. The authors' effort to induce enantioselectivity with this method was not very successful. Using C_2-symmetric chiral sulfide **14**, the best enantiomeric excess observed was only 19% (Scheme 30) [89].



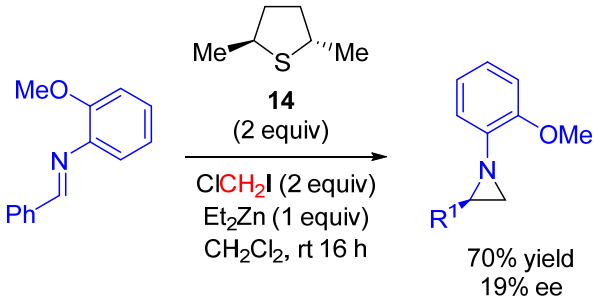
Scheme 28. Simmons–Smith carbenoid method for generation of sulfonium ylide.



Scheme 29. Simmons–Smith carbenoid method employed for synthesis of aziridines.

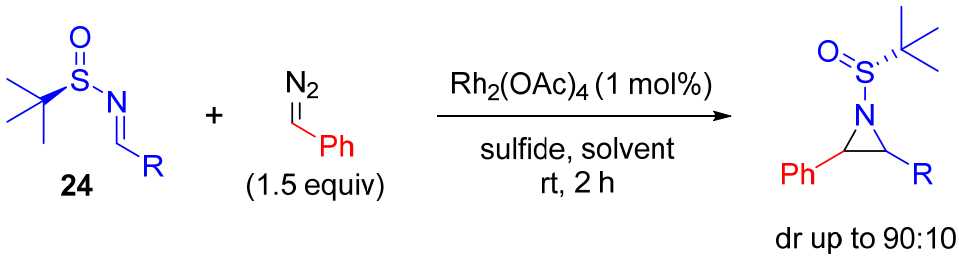
Table 8. Scope of Simmons–Smith carbenoid aziridine synthesis (Scheme 29).

Entry	R^1	R^2	Yield (%)
1	Ph	Ts	68
2	*p*-$NO_2C_6H_4$	Ts	66
3	*p*-$AcOC_6H_4$	Ts	68
4	Cy	Ts	72
5	Ph	SES	72
6	Ph	*p*-$MeOC_6H_4$	<3
7	Ph	*o*-$MeOC_6H_4$	79



Scheme 30. Enantioselectivity in Simmons–Smith carbenoid aziridine synthesis.

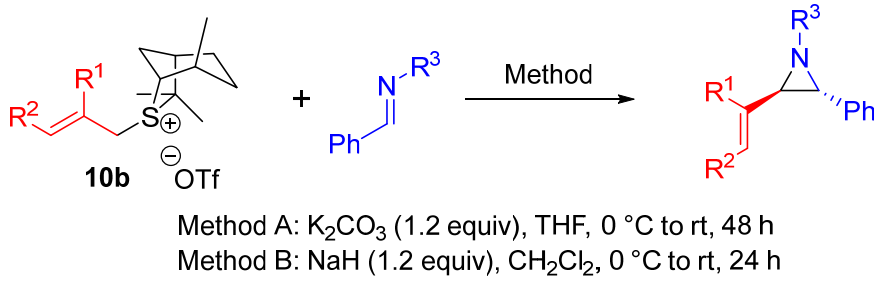
Mayer and colleagues developed a methodology for asymmetric aziridination through the reaction of chiral *N-tert*-butanesulfinyl imines **24** with benzyl-stabilized sulfonium ylides, where the ylides were generated through a rhodium-catalyzed decomposition of phenyldiazomethane in the presence of various sulfides [90]. This methodology furnished *trans*-aziridine (dr up to 90:10) predominantly in very-high-to-quantitative yields (up to 99%). The diastereoselectivity between the two *trans*-aziridines was found to vary significantly, depending upon the solvent and sulfide employed in the reaction. With most of the imines tested, toluene in combination with tetrahydrothiophene gave the highest selectivity for one of the *trans*-aziridines (de up to 71%), whereas acetonitrile used together with dibutyl sulfide selectively gave the other *trans*-aziridine (de up to 86%) (Scheme 31).



Scheme 31. Diastereoselective synthesis of aziridines through reaction of chiral *N-tert*-butanesulfinyl imines with benzyl-stabilized sulfonium ylides.

4.2.2. Stoichiometric Allyl Sulfonium Ylide-Mediated Aziridination

Later, the Aggarwal group further extended the scope of their chiral isothiocineole-enantiocontrolled aziridination synthesis methodology [42]. The use of chiral allyl sulfonium salts **10b** with benzaldehyde-derived aldimines under similar reaction conditions to before afforded the corresponding chiral *trans*-aziridines in good yields, with moderate diastereoselectivities, along with excellent enantioselectivities (Scheme 32) (Table 9). Different activating groups on the nitrogen of the imines were tolerated, such as Ts, and $P(O)Ph_2$, whereas Boc-imines were not successful.



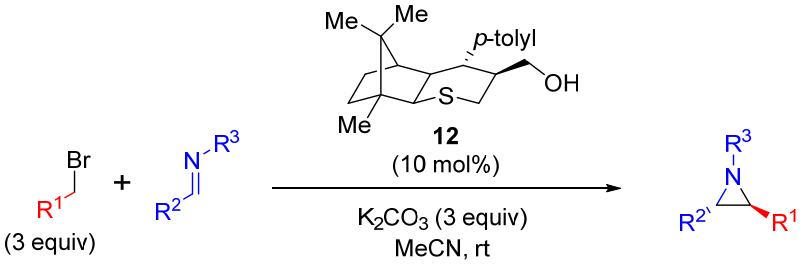
Scheme 32. Aggarwal's chiral allyl sulfonium-mediated aziridination.

Table 9. Scope of Aggarwal's chiral allyl sulfonium-mediated aziridination (Scheme 32).

Entry	R^1	R^2	R^3	Method	*trans*:*cis*	Yield (%)	*trans* ee (%)
1	Me	Ph	Ts	A	78:22	76	98
2	Me	H	Ts	A	83:17	98	98
3	H	H	Ts	A	85:15	73	88
4	H	Ph	Ts	A	80:20	81	90
5	Me	H	Ph_2PO	B	84:16	84	98
6	H	H	Ph_2PO	B	86:14	83	82

4.2.3. Catalytic Sulfonium Ylide-Mediated Aziridination

Saito et al. reported a one-pot asymmetric aziridination of imines with alkyl bromides catalyzed by camphor-derived chiral sulfide catalyst **12** (Scheme 33) [91]. Reaction of chiral sulfide **12** with excess benzyl bromide and potassium carbonate, as base, in anhydrous acetonitrile gave *trans*-aziridines, predominantly in moderate-to-excellent yields, with moderate diasteroselectivities and good-to-excellent enantioselectivities. Use of a catalytic amount of this more hindered sulfide required longer reaction times (1–4 days), even when employing a stoichiometric amount of catalyst **12**, but yields were improved and the previously competitive hydrolysis of the imine was wholly eliminated under the dry conditions employed. Increasing the temperature shortened the reaction time significantly, albeit with a small cost to enantioselectivity. However, in all cases the diastereoselectivity was quite modest, favoring the *trans*-isomer (Table 10).



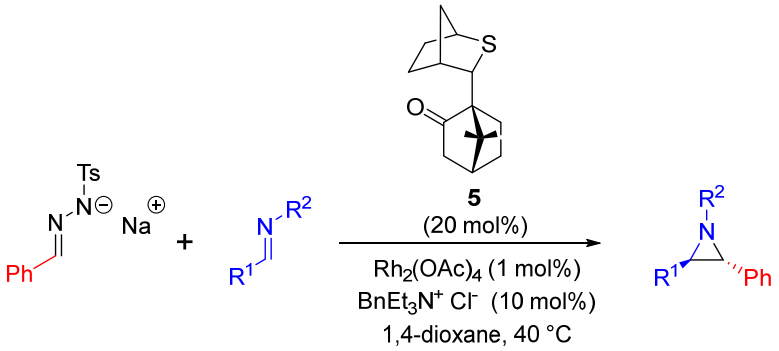
Scheme 33. Saito's catalytic enantioselective synthesis of aziridines.

Table 10. Scope of sulfide **12**-catalyzed aziridination (Scheme 33).

Entry	R^1	R^2	R^3	Yield (%)	*trans*:*cis*	*trans* ee (%)
1	Ph	Ph	Ts	>99	75:25	92
2	*p*-Tol	Ph	Ts	87	74:26	89
3	*p*-NO_2Ph	Ph	Ts	>99	65:35	98
4	Ph	*p*-Tol	Ts	>99	79:21	89
5	Ph	*p*-MeOPh	Ts	94	63:37	86
6	Ph	*p*-ClPh	Ts	86	78:22	92
7	Ph	Ph	$PhSO_2$	84	76:24	92
8	Ph	Ph	$MeSO_2$	79	67:33	92

Aggarwal and co-workers introduced camphor sulfonyl chloride-derived chiral sulfide **5** for the catalysis of an elegant asymmetric aziridination of several *N*-protected aldimines with stable phenyl *N*-tosylhydrazone salt. This methodology avoided the need to handle potentially hazardous diazo compounds by generating them slowly in situ through PTC-catalyzed decomposition of the hydrazone salts at 40 °C. Decomposition of in situ-generated diazo compounds to provide the carbenoid was catalyzed by $Rh_2(OAc)_4$ (Scheme 34) [31,86,87]. The reaction of the sodium salt of phenyl *N*-tosylhydrazone with a range of aryl, heteroaryl, cinnamyl, and aliphatic imines in the presence of catalytic amount of chiral sulfide **5** and transition metal catalyst $Rh_2(OAc)_4$ gave predominantly *trans*-aziridine in moderate-to-good yields, with excellent enantiomeric excesses, and with

diastereoselectivities that varied from poor to good (Table 11). Good yields were obtained even with sulfide loadings as low as 5 mol% (entry 3) and with no loss of enantiopurity. In addition to examples of aryl, heteroaryl, cinnamyl, and aliphatic imines as substrates, this system also allowed for the extension of the methodology to the synthesis of trisubstituted aziridines for the first time, employing an imine generated from a symmetrical ketone (Scheme 35).

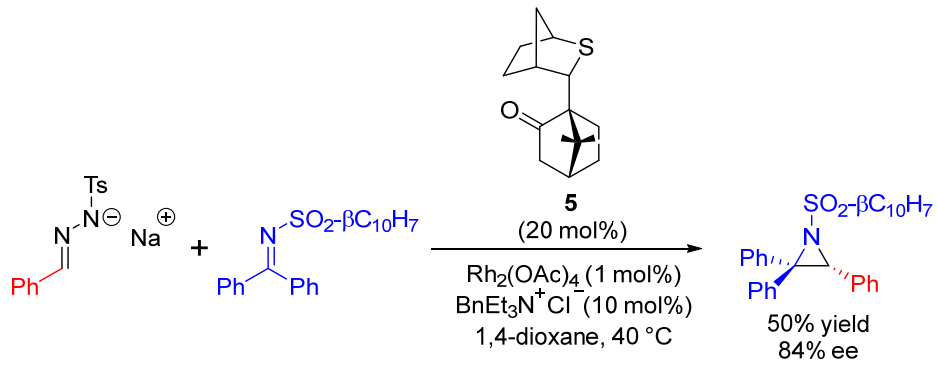


Scheme 34. Aggarwal's catalytic enantioselective synthesis of aziridines.

Table 11. Scope of Aggarwal's catalytic enantioselective synthesis of aziridines (Scheme 34).

Entry	R^1	R^2	Yield (%)	*trans*:*cis*	*trans* ee (%)
1	*p*-$MeOC_6H_4$	SES	60	2.5:1	92
2	Ph	SES	75	2.5:1	94
3 [a]	Ph	SES	66	2.5:1	95
4	*p*-ClC_6H_4	SES	82	2:1	98
5	Cy	SES	50	2.5:1	98
6	(*E*)-PhCH=CH	SES	59	8:1	94
7	3-Furfuryl	Ts	72	8:1	95
8	*t*-Bu	Ts	53	2:1	73
9	Ph	Ts	68	2.5:1	98
10	Ph	SO_2-β-$C_{10}H_7$	70	3:1	97
11	Ph	TcBoc	71	6:1	90

[a] 5 mol% sulfide used.

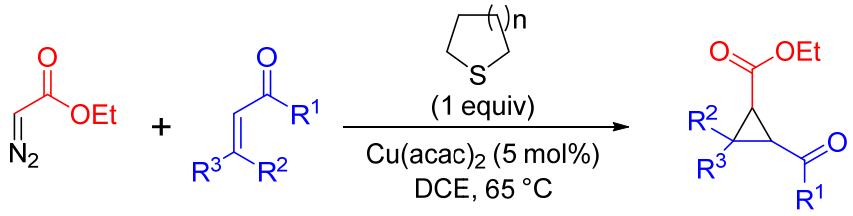


Scheme 35. Aggarwal's catalytic enantioselective synthesis of a trisubstituted aziridine.

4.3. Cyclopropanation

4.3.1. Sulfonium Ylide-Mediated Cyclopropanation

The sulfide-promoted cyclopropanation reaction of stabilized ylides worked well with both cyclic and acyclic enones to give high yields and, in some cases, excellent diastereoselectivities (Scheme 36) (Table 12) [92,93]. However, acrylates, enals, and nitrostyrene proved to be problematic substrates for this methodology.

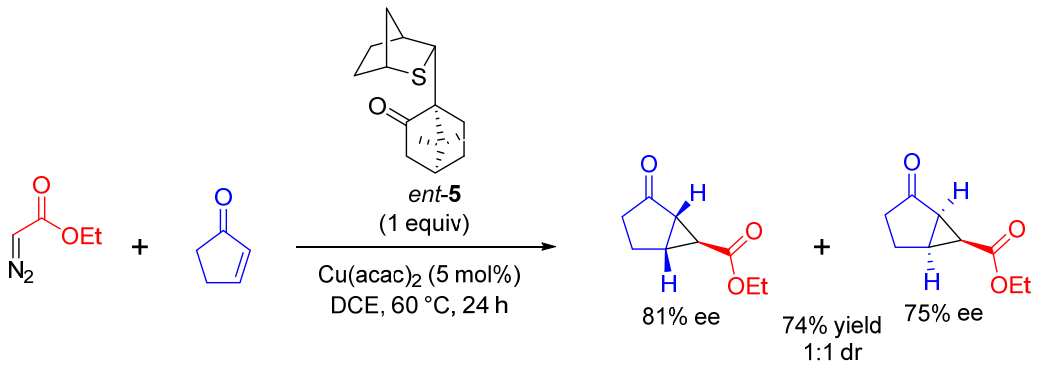


Scheme 36. Aggarwal's sulfide-promoted diastereoselective cyclopropanation.

Table 12. Scope of Aggarwal's sulfide-promoted diastereoselective cyclopropanation (Scheme 36).

Entry	R^1	R^2	R^3	n	Yield (%)	dr
1	Ph	H	Ph	2	72	4:2:1
2	Me	H	H	2	64	>95:5
3	OEt	H	COOEt	2	68	>95:5
4	Me	Me	Me	2	5	>95:5
5		$-(CH_2)_2-$	H	1	81	1:1

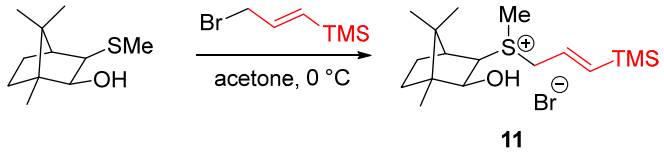
Aggarwal and co-workers also studied carbene-based stabilized ylides generated from an enantiomer of chiral sulfide **5** (*ent*-**5**) in the cyclopropanation of cyclic α,β-unsaturated ketones. Fused bicyclic cyclopropanes were formed with high enantioselectivity, but without any observed diastereoselectivity (Scheme 37) [93]. However, the equivalent reaction using the stoichiometric sulfonium salt deprotonation method of generating the ylide was shown to provide high diastereoselectivity but low enantioselectivity for one of the products. The difference between the $Cu(acac)_2$-catalyzed reaction and the preformed ylide reaction was explained by the authors as being because of one of the diastereomeric betaines ring-closing slowly due to non-bonded steric interactions in the transition state and, thus, undergoing competitive base- and/or ylide-mediated equilibration under these conditions. This base/ylide-mediated proton transfer did not occur in the $Cu(acac)_2$-catalyzed reaction (Scheme 37) because of the neutral conditions and the low concentration of ylide intermediates in these reactions.



Scheme 37. Aggarwal's sulfide-promoted enantioselective cyclopropanation.

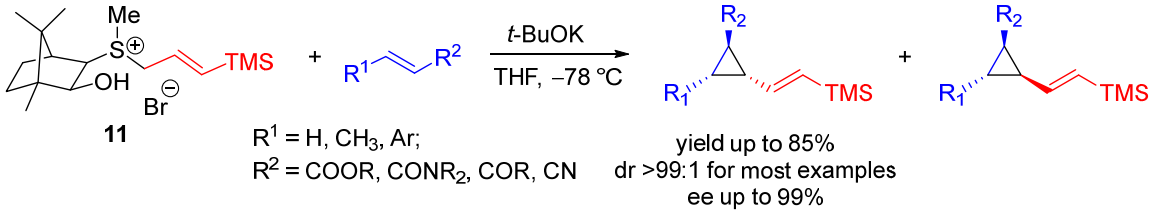
4.3.2. Allyl Sulfonium Ylide-Promoted Cyclopropanation

Many research groups have been attracted to working with vinylcyclopropanes, which are popular subunits in natural products and useful synthetic intermediates [94,95]. Asymmetric synthesis of 1,2,3-trisubstituted vinylcyclopropanes is a challenging task because of the difficulties associated with the control of regioselectivity, diastereoselectivity, and enantioselectivity. Tang's group developed a one-step cyclopropanation reaction to construct highly enantioenriched 1,3-disubstituted-2-silylvinylcyclopropanes in good yields through the use of chiral sulfonium allyl ylides [96]. The precursor **11** for the chiral sulfonium ylide was readily available from the corresponding sulfide derivatized from D-camphor according to a published procedure (Scheme 38) [97].



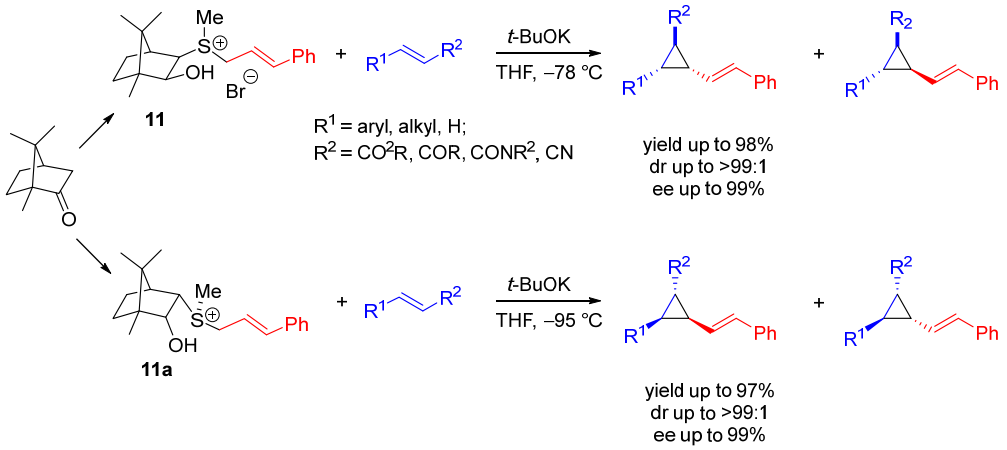
Scheme 38. Preparation of the precursor **11** for the chiral sulfonium ylide.

The chiral allyl sulfonium ylide, generated from the corresponding salt in situ by treatment with *t*-BuOK (3 equiv), could react with *α*,*β*-unsaturated esters, amides, ketones, and nitriles to form cyclopropane rings with excellent diastereoselectivity and enantioselectivity (Scheme 39) [96]. Tang initially proposed that the stereoselectivity for this reaction was controlled by the formation of a rigid six-membered ring transition state. The ylide was most likely stabilized through a bonding interaction between the sulfur and the oxygen atom to limit [2,3]-*σ* rearrangement. Less-reactive methyl crotonate and methyl *cis*-cinnamate could only produce poor or trace amounts of the cyclopropanes. The silylvinylcyclopropane derivatives were oxidized into synthetically useful aldehydes or epoxide intermediates without loss of enantiomeric excess [96].



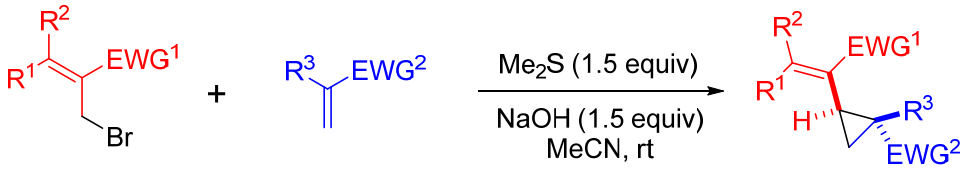
Scheme 39. Asymmetric ylide cyclopropanation of allyl sulfonium salts with Michael acceptors.

Tang and co-workers were able to expand the substrate scope for their camphor-derived chiral sulfonium-promoted asymmetric cyclopropanation by changing the TMS silyl group to a phenyl group a few years later [43]. The electron-withdrawing phenyl group helped to increase the acidity of the allylic hydrogen of the sulfonium salts through stabilization of the ylide. This modification was effective for reaction with *β*-aryl and *β*-alkyl-*α*,*β*-unsaturated esters, ketones, amides, and nitriles (Scheme 40). Additionally, only 20 mol% of the preformed sulfonium salt was required, in the presence of 1.5 equiv of cinnamyl bromide, for successful conversion to the desired vinylcyclopropane. High yields and diastereoselectivities (dr up to 87:13) were achieved using this catalytic cycle, with moderate-to-high enantioselectivities (ee up to 88%) also observed. Both enantiomers of the phenylvinylcyclopropanes could be obtained by using either *exo*- or *endo*-sulfonium salts (**11** and **11a**). Density functional theory calculations supported the proposal that hydrogen bonding between the sidearm hydroxyl group of **11**/**11a** and the Michael acceptor substrate played an important role in controlling the diastereoselectivity and enantioselectivity of the reaction [43]. Methylation of this oxygen was shown to prevent formation of the desired product. Therefore, it was inferred that the hydroxy sidearm helps to organize the transition state, leading to excellent face-selectivity.



Scheme 40. Enantioselective synthesis of both enantiomers of phenylvinylcyclopropane.

Kim and co-workers reported achiral dimethyl sulfide-catalyzed cyclopropanation of cyclic enones with allylic bromides derived from Baylis–Hillman adducts (Scheme 41) (Table 13) [98]. In these cases, although the sulfide was regenerated during the reaction, the use of 1.5 equiv of sulfide was necessary to provide the cyclopropanation product, in moderate yield but with excellent *trans*-selectivity. This methodology was only suitable for acyclic enones, and reactions with cyclic enones, acrylates, and acrylonitrile were unsuccessful. A range of substituted allylic bromides were compatible with the system.



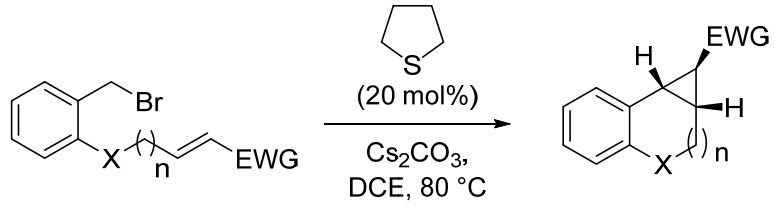
Scheme 41. Kim's diastereoselective cyclopropane synthesis.

Table 13. Scope of Kim's diastereoselective cyclopropane synthesis (Scheme 41).

Entry	R^1	R^2	EWG^1	R^3	EWG^2	Time (h)	Yield (%)
1	Ph	H	COOMe	H	COMe	12	45
2	*p*-MeC_6H_4	H	COOMe	H	COMe	12	47
3	*p*-ClC_6H_4	H	COOMe	H	COMe	13	49
4	*p*-MeC_6H_4	H	COOMe	Cl	CN	20	57
5	H	Ph	CN	H	COMe	12	48

4.3.3. Catalytic Cyclopropanation

Later, Tang and co-workers extended their work on cyclopropanations to include a catalytic intramolecular cyclopropanation reaction providing several fused benzotricyclic derivatives [99]. The use of 20 mol% of tetrahydrothiophene as catalyst in these reactions, in the presence of Cs_2CO_3 as base, in 1,2-dichloroethane solvent at 80 °C, afforded the desired fused tricyclic compounds as single diastereomers in moderate-to-good yields (Scheme 42) (Table 14). The reaction could be applied to tethered *α*,*β*-unsaturated esters, ketones, and aldehydes, and both *E*- and *Z*-alkenes were found to give the same major diastereomer of the product.



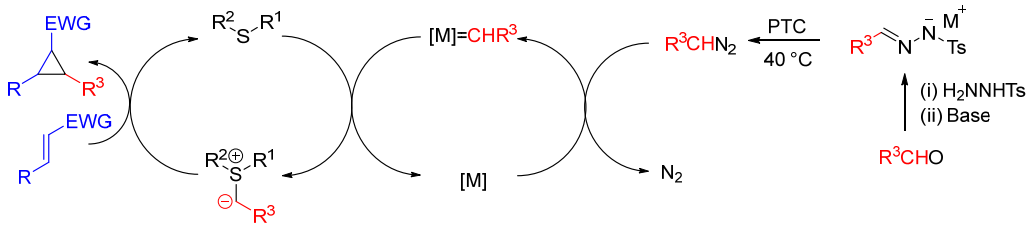
Scheme 42. Tang's catalytic intramolecular cyclopropanation reaction.

Table 14. Scope of Tang's catalytic intramolecular cyclopropanation reaction (Scheme 42).

Entry	X	n	EWG	Yield (%)
1	O	1	COOMe	76
2	CH_2	0	COOMe	53 [a]
3	CH_2	1	COOEt	63
4	CH_2	1	CHO	64
5	CH_2	1	COPh	64 [a]

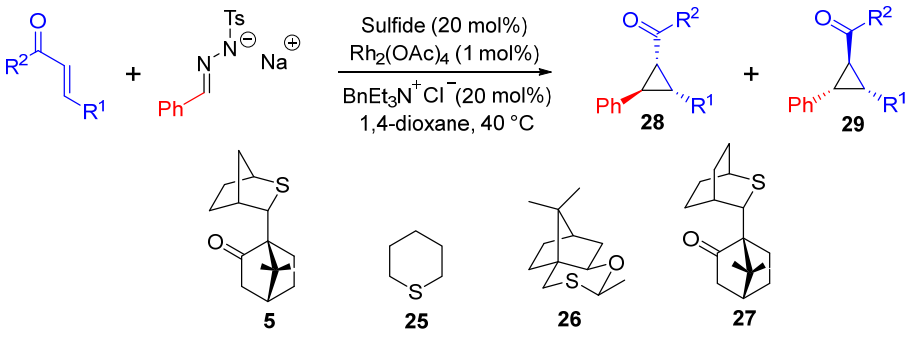
[a] At 45 °C.

In analogy to their approach in developing successful epoxidation and aziridination reactions, Aggarwal and co-workers developed a chiral sulfide-catalyzed stereoselective cyclopropanation, where ylides were generated from a metallocarbene under neutral conditions (Scheme 43).



Scheme 43. Catalytic cycle for Aggarwal's cyclopropanation.

Semistabilized ylides were generated in situ from the reaction of phenyl diazomethane metal salt with $Rh_2(OAc)_4$ in the presence of various six-membered-ring sulfides, and effected cyclopropanation in reaction with several α,β-unsaturated ketones and esters, with high yields and moderate diastereoselectivities (Scheme 44) (Table 15) [92,93]. Six-membered-ring sulfides such as tetrahydrothiopyran (**25**), chiral sulfide **5** and **26** gave better yields than five-membered ring sulfides (Table 15, entry 2, Scheme 44). The cyclopropanation reactions are slower than the corresponding epoxidation and aziridination reactions. As a result, ylide equilibration can become competitive and it has been noted that products resulting from Sommelet–Hauser rearrangements have been obtained in reactions employing tetrahydrothiophene as the ylide precursor [100].



Scheme 44. Aggarwal's catalytic cyclopropanation.

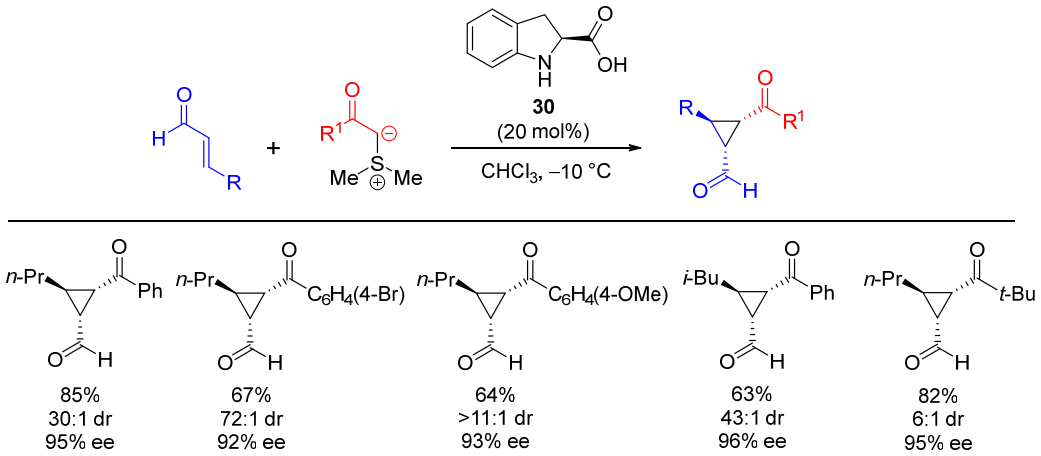
Table 15. Scope of Aggarwal's catalytic cyclopropanation (Scheme 44).

Entry	R^1	R^2	Sulfide	Yield (%)	28:29	28 ee (%)
1	Ph	Ph	**25**	92	4:1	–
2	Ph	Ph	THT	40	1:1	–
3	Ph	Ph	**26**	38	4:1	97
4	Ph	Ph	**5**	30 [a]	5:1	89
5	Ph	Ph	**27**	73	4:1	91
6	Ph	Me	**27**	5	–	–
7	Me	Ph	**27**	50	4:1	90
8	H	OEt	**27**	10	7:1	–

[a] 50% Starting material recovered.

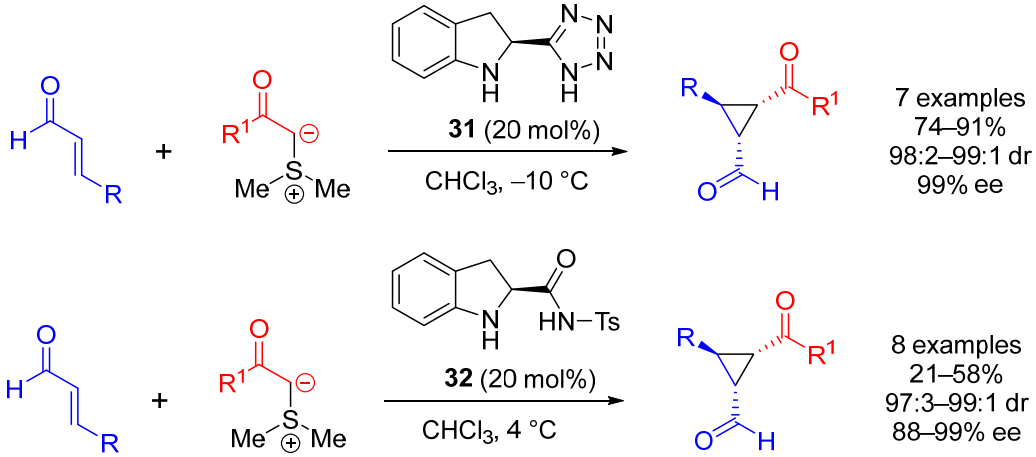
Over the past 10–15 years, catalytic cyclization reactions of sulfonium ylides have been explored beyond conventional sulfide-centric catalysis by several groups. Catalytic technologies using asymmetric organocatalysis, such as chiral aminocatalysis, nucleophilic catalysis, H-bonding catalysis, organometallic catalysis, including Lewis acid catalysis and transition metal catalysis, and photocatalysis have been successfully applied in this research area [101].

Kunz and MacMillan, in 2005, introduced for the first time an enantioselective cyclopropanation reaction of α,β-unsaturated aldehydes with stabilized sulfonium ylides, in the presence of a chiral amino acid **30** as the catalyst [102]. The formation of iminium ion intermediates from chiral amine catalysts and α,β-unsaturated aldehydes enabled the activation of the substrates through lowering of their LUMO energies whilst simultaneously facilitating enantiocontrol at the newly formed stereocenters. This reaction provided a series of structurally diverse chiral cyclopropanes in good yields with high enantio- and diastereoselectivity (Scheme 45).



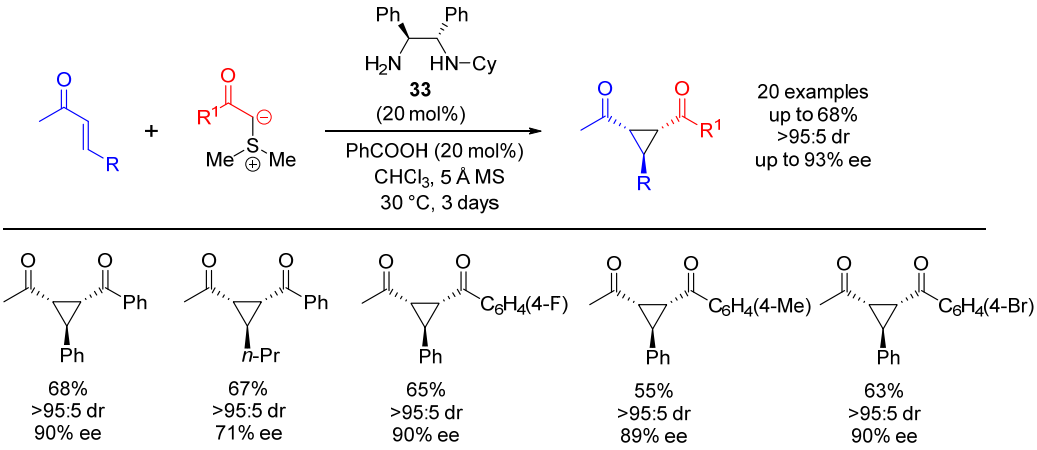
Scheme 45. Substrate scope of MacMillan's enantioselective cyclopropanation.

Arvidsson and co-workers later further modified this chiral amine-catalyzed cyclopropanation and developed two new amine catalysts by replacing the carboxylic acid component of the amino acid catalyst with tetrazole **31** or an aryl sulfonamide **32** [103,104]. When these two organocatalysts were applied to the enantioselective cyclopropanation of α,β-unsaturated aldehydes with stabilized sulfonium ylides, somewhat improved diastereo- and enantioselectivities were obtained (Scheme 46). The authors explained that the improved enantioselectivities and diastereoselectivites were due to the increased steric bulk of the tetrazole/aryl sulfonamide component while retaining the structural requirements of the directed electrostatic activation needed to provide an improved enantiofacial discrimination for the incoming sulfonium ylide reagent during the first C–C bond formation step.



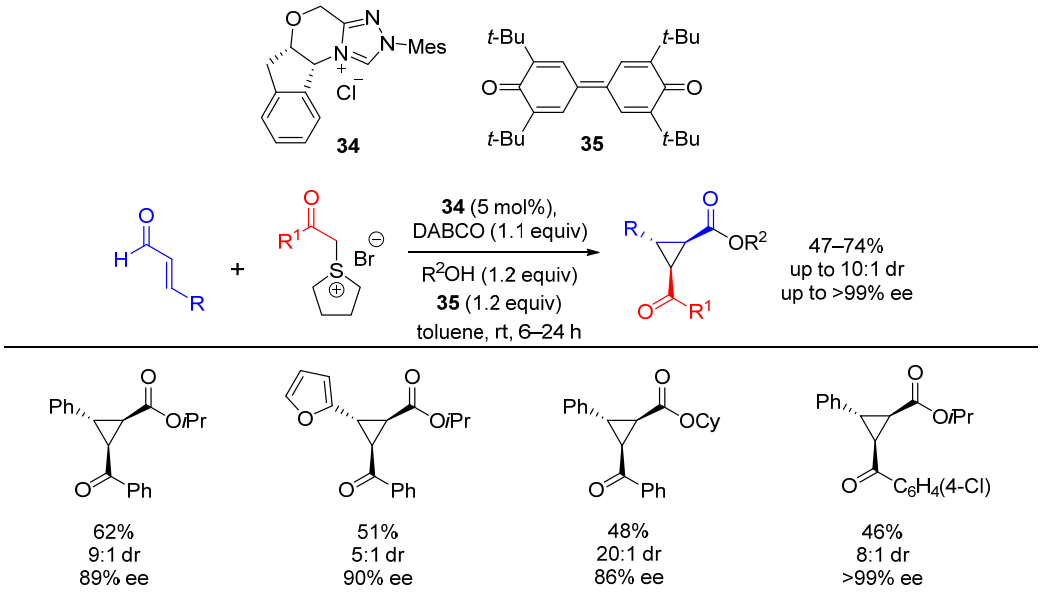
Scheme 46. Scope of Arvidsson's catalytic enantioselective cyclopropanation.

Feng and colleagues further explored this methodology of chiral amine-catalyzed cyclopropanation and introduced a chiral diamine-catalyzed enantio- and diastereoselective cyclopropanation of α,β-unsaturated ketones with stabilized sulfonium ylides under mild conditions, albeit with long reaction times (Scheme 47) [105]. In the presence of 20 mol% of both chiral diamine catalyst **33** and benzoic acid, this methodology provided cyclopropane derivatives in moderate yields but with good enantioselectivities and diastereoselectivities. However, a mixture of cyclopropane and cyclopentanone products was afforded in some cases. The authors proposed that the formation of different cycloadducts, cyclopropanes, and cyclopentanones was due to different intramolecular S_N2 substitution processes terminating the catalytic cycle.



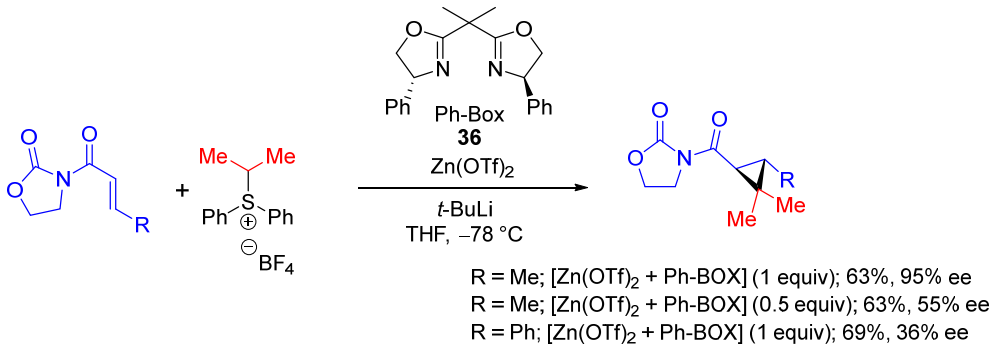
Scheme 47. Feng's catalytic enantioselective cyclopropanation.

Studer and co-workers introduced an elegant chiral NHC-catalyzed enantio- and diastereoselective oxidative cyclopropanation of α,β-unsaturated aldehydes with stabilized sulfonium ylides (Scheme 48) [106]. In the presence of NHC catalyst precursor **34**, organic base DABCO, and benzoquinone **35** as oxidant, cyclopropanation of α,β-unsaturated aldehydes with stabilized sulfonium ylides furnished fully substituted cyclopropane derivatives in moderate yields with good enantio- and diastereoselectivities.



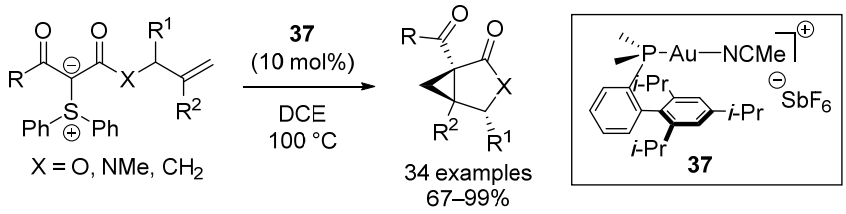
Scheme 48. Substrate scope of Studer's chiral NHC-catalyzed enantio- and diastereoselective oxidative cyclopropanation.

Madalengoitia and co-workers developed a Lewis acid-catalyzed asymmetric cyclopropanation of α,β-unsaturated amides with an unstabilized sulfonium ylide (Scheme 49) [107]. In the presence of a chiral zinc catalyst, generated from $Zn(OTf)_2$ and the chiral Ph-BOX ligand **36**, the best results were obtained. However, the enantiopurity of the highly substituted cyclopropane product was completely dependent upon the loading of chiral Lewis acid catalyst employed. Reduced enantioselectivity at lower chiral Lewis acid loadings (0.5 equiv) is possibly due to the result of an uncatalyzed background reaction or $LiBF_4$-catalyzed background reaction. A stoichiometric amount of $LiBF_4$ is formed during the in situ generation of the sulfonium ylides from diphenylisopropyl sulfonium tetrafluoroborate and *t*-BuLi, and $LiBF_4$ could function as a Lewis acid to compete with the expected chiral $Zn(OTf)_2$/**36**-catalyzed enantioselective reaction.



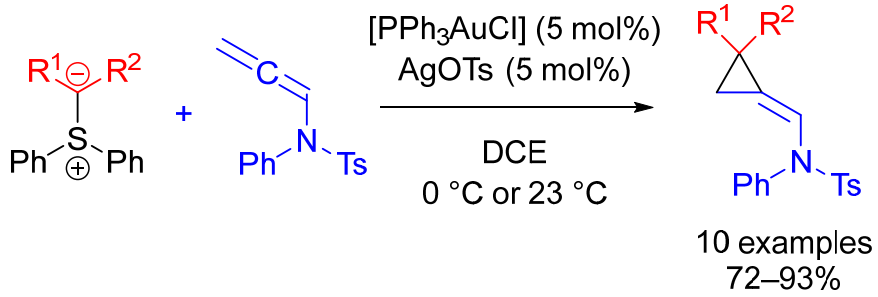
Scheme 49. Madalengoitia's enantioselective synthesis of cyclopropanes from α,β-unsaturated amides.

Maulide and co-workers developed a novel stereoselective Au(I)-catalyzed method for the intramolecular cyclopropanation of electron-neutral and electron-rich olefins by sulfonium ylides (Scheme 50) [108]. This protocol provided easy and direct access to functionalized fused bicyclic products from the easily handled sulfonium ylides, with high regio- and stereoselectivities. The authors also performed DFT analysis to investigate the possible mechanism involving catalysis by **37** [109]. Their study revealed that the Au(I)-catalyzed cyclopropanation reaction proceeded through an unusual alkene activation pathway and that two consecutive intramolecular C–C bond formations gave the cyclopropane products.



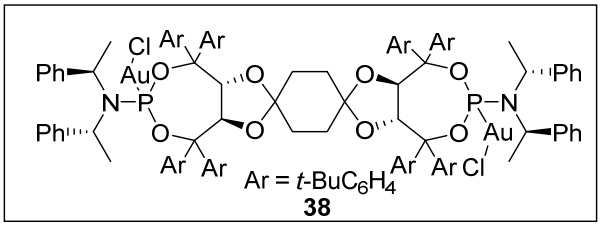
Scheme 50. Maulide's Au(I)-catalyzed diastereoselective intramolecular cyclopropanation.

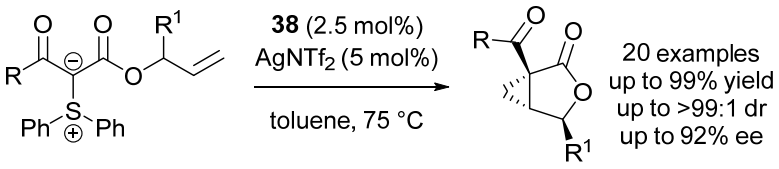
Maulide's group also introduced a stereoselective Au(I)-catalysed intermolecular cyclopropanation of allenamides and allenamines with stabilized sulfonium ylides (Scheme 51) [110]. This methodology enabled the efficient and direct synthesis of diacceptor-substituted alkylidenecyclopropanes, and proceeded under very mild conditions through allene activation by the gold catalyst. The sulfonium ylide acted as a nucleophile in attacking the activated allene. The possibility of generation of a gold carbenoid from the gold catalyst and sulfonium ylides was ruled out.



Scheme 51. Maulide's Au(I)-catalyzed intermolecular cyclopropanation of allenamides and allenamines.

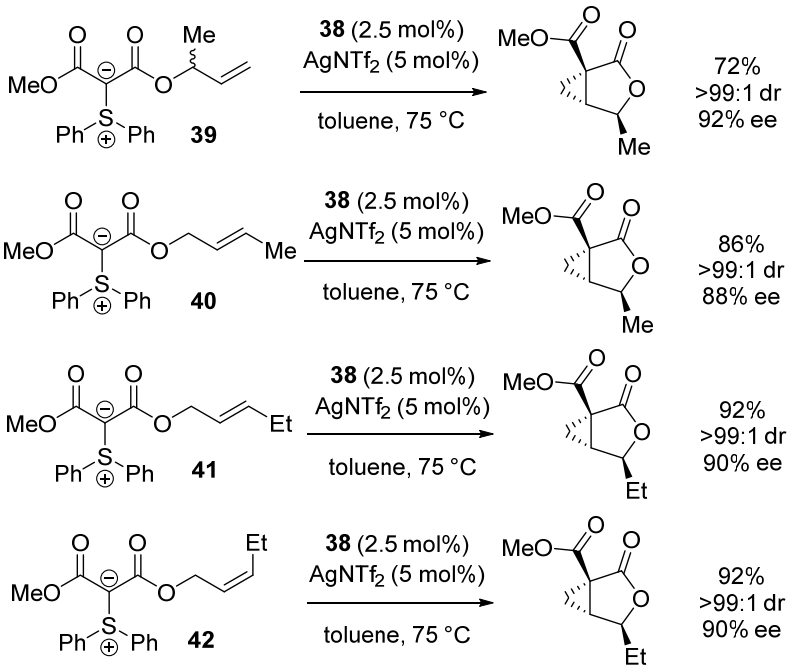
Maulide and colleagues in 2015 reported the first example of a Au(I)-catalyzed asymmetric intramolecular cyclopropanation of electron-neutral olefins with sulfonium ylides in the presence of a bimetallic catalyst with a novel dimeric TADDOL-phosphoramidite ligand **38** (Scheme 52) [111]. In this methodology, which only required a low loading (2.5 mol%) of the chiral Au(I)-ligand catalyst, a rare gold-catalyzed dynamic deracemization of chiral racemic substrates was facilitated. The products, which were formed with high yields and good enantiocontrol, are useful building blocks in synthesis and enable expeditious access to naturally occurring molecules, such as butenolide natural products.





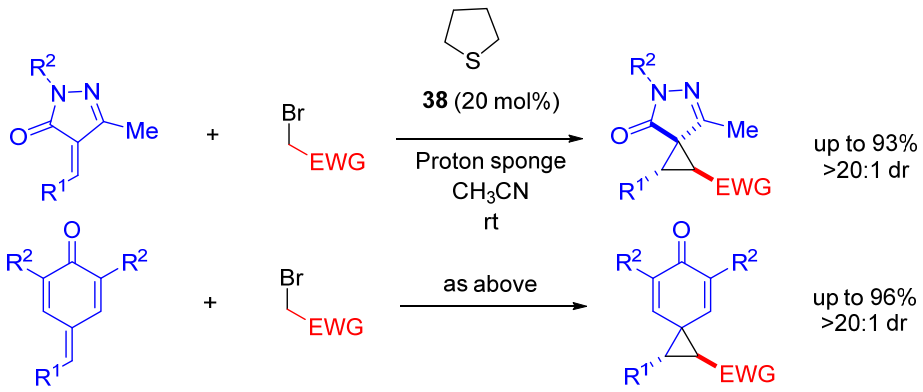
Scheme 52. Maulide's Au(I)-catalyzed asymmetric intramolecular cyclopropanation of electron-neutral olefins.

Interestingly, the authors also found that the use of the racemic branched substrate **39** and the linear substrate **40**, as well as both variants of double-bond geometry, in **41** and **42**, gave the same products with nearly the same yields and enantioselectivity (Scheme 53).



Scheme 53. Examples of Maulide's Au(I)-catalyzed asymmetric intramolecular cyclopropanation of electron-neutral olefins.

Two recent examples of sulfide-catalyzed spirocyclopropanations were reported by Hu's group (Scheme 54) [112,113]. An achiral sulfide-catalyzed [2 + 1]-cycloaddition of arylidenepyrazolones with mainly α-bromoketones to afford spiro-cyclopropanyl-pyrazolones (up to 93% yield) in highly diastereoselective fashion (dr > 20:1) was achieved [112]. The method was also tolerant of various other arylidene derivatives and enones, efficiently converting them to spirocyclopropanation products. A similar approach was found to be very effective with *para*-quinone methides as the substrate. The sulfide-catalyzed [2 + 1]-cycloaddition of *para*-quinone methides with α-bromoketones and α-bromoesters provided spirocyclopropanyl-cyclohexadienones in good-to-excellent yields (up to 96%) and with excellent diastereoselectivity (dr > 20:1) [113].

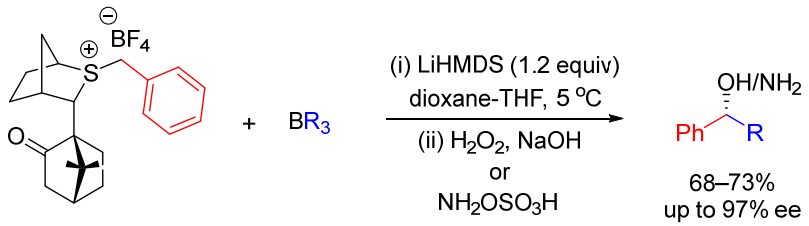


Scheme 54. Examples of Hu's sulfide-catalyzed spirocyclopropanations.

4.4. Miscellaneous Stereoselective Reactions of Sulfonium Ylides

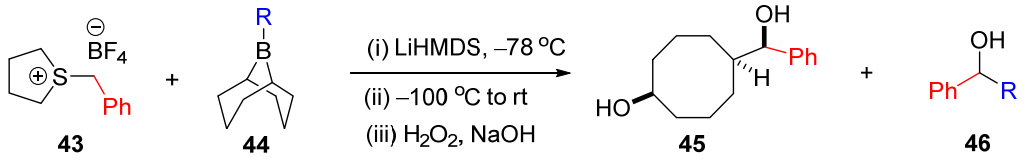
4.4.1. Borane Homologation Reactions

The synthetic use of organoboranes has been growing very fast, as useful synthetic intermediates are produced which can then be converted into a broad range of functional groups stereospecifically [114–116]. These transformations mainly involve nucleophilic addition of an ylide to the electrophilic boron atom, followed by a 1,2-migration. The ylide is a suitable nucleophile for this purpose as it possesses a leaving group attached directly to the carbanion. Among the known ylides, sulfonium ylides were found to be ideal for reaction with boranes as they exhibit the best balance of stability, reactivity, and leaving group ability [20]. Furthermore, chiral sulfonium ylides are capable of inducing enantioselectivity in such reactions. Aggarwal and co-workers reported the reaction of a chiral aryl-stabilized sulfonium ylide, generated in situ from its precursor sulfonium salt, with triaryl or trialkyl boranes [27–29,117]. This reaction furnished homologated boranes, which after subsequent oxidation produced the corresponding alcohols or amines in high yields and with excellent enantiomeric excesses (Scheme 55). This methodology was applied directly during the synthesis of anti-inflammatory agents, neobenodine and cetirizine [27–29].



Scheme 55. Aggarwal's enantioselective borane homologation reaction.

However, homologation reactions with 9-BBN derivatives **44** gave complex results (Scheme 56) (Table 16) [118]. Aryl, alkenyl, and secondary alkyl borane derivatives gave the major product from selective migration of the desired boron substituent, whereas hexynyl and cyclopropyl borane derivatives resulted in exclusive migration of the boracycle. In the case of primary alkyl borane derivatives, a complex mixture of substituent and boracycle migrated products was obtained.

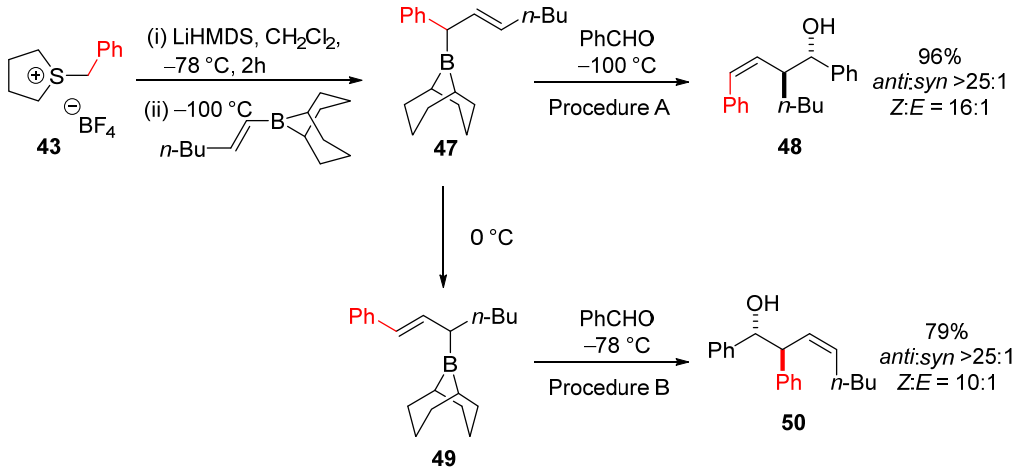


Scheme 56. Homologation reactions of 9-BBN derivatives.

Table 16. Scope of homologation reactions involving 9-BBN derivatives (Scheme 56).

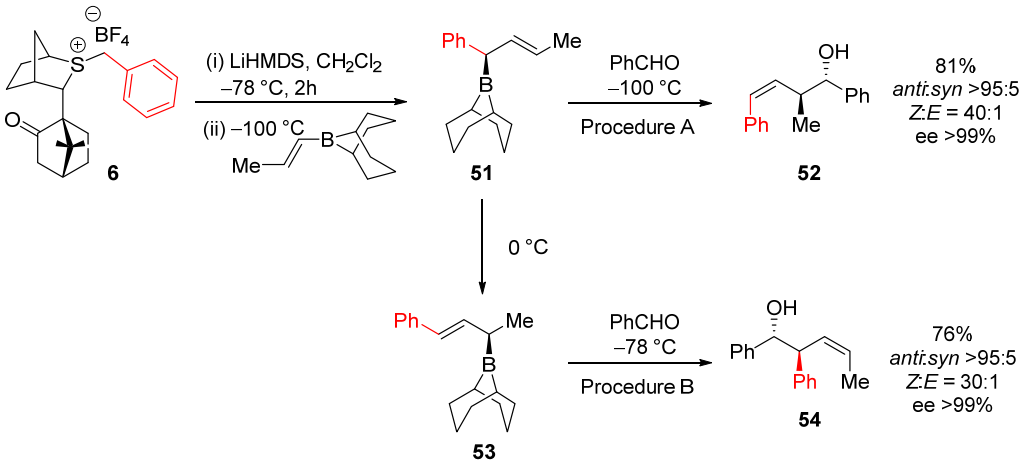
Entry	R	Yield (%) 45	Yield (%) 46
1	Hexyl	56	41
2	Allyl	51	39
3	Benzyl	51	35
4	*i*-Pr	Trace	77
5	Cyclopropyl	89	Trace
6	Ph	Trace	94
7	1-Hexenyl	Trace	21
8	1-Hexynyl	92	Trace

Aggarwal and colleagues reported the synthesis of highly labile α,γ-disubstituted allylic boranes through the reactions of alkenyl 9-BBN derivatives with sulfonium ylides [119]. Reaction of the ylide generated in situ from sulfonium salt **43** with vinylboranes at −100 °C, followed by the addition of benzaldehyde at the same temperature, and subsequent warming to room temperature, furnished the homoallylic alcohol **48** in 96% yield as the *anti*-diastereoisomer with high *Z*-selectivity (Procedure A, Scheme 57). Under the latter reaction conditions, the aldehyde trapped the highly labile α,γ-disubstituted allylic borane intermediate **47** as it was formed, thus not allowing sufficient time for isomerization to occur. The high lability of allylic boranes was also exploited by allowing the α,γ-disubstituted allylic borane intermediate **47** to warm up to 0 °C to isomerize into thermodynamically more stable allylic borane **49**. **49** was trapped with benzaldehyde at −78 °C to give the isomeric homoallylic alcohol **50** in high yield and with similarly high *anti*-diastereoselectivity (Procedure B, Scheme 57).



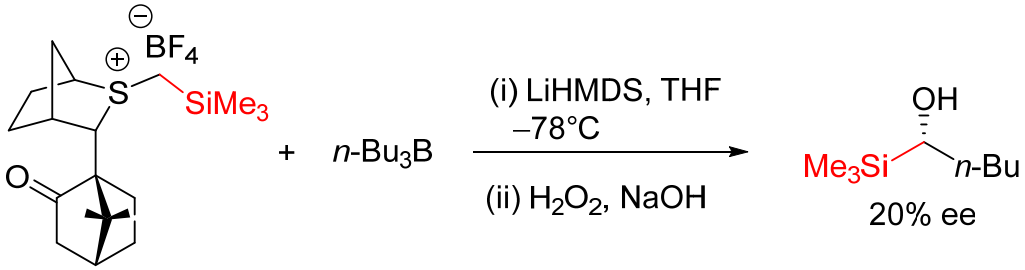
Scheme 57. Diastereoselective synthesis of homoallylic alcohols through borane homologation.

The same methodology was extended to the enantioselective synthesis of homoallylic alcohols [119]. Starting from enantiopure sulfonium salt **6** using procedure A, the desired homoallylic alcohol **52** was isolated with excellent enantioselectivity, good *anti*-diastereoselectivity, and with very high *Z*-selectivity (Scheme 58) [119]. The chiral sulfide was also routinely recovered in greater than 90% yield. Applying procedure B to the same vinyl borane and chiral sulfonium salt **6**, the desired homoallylic alcohol **54** was isolated with excellent enantio- and *anti*-diastereoselectivity, and with high *Z*-olefin selectivity (Scheme 58).



Scheme 58. Enantioselective synthesis of homoallylic alcohols through borane homologation.

Aggarwal and co-workers also examined the substrate scope of the chiral sulfonium ylide and found that reactions of sulfonium ylides with boranes afforded the best results when there is aryl substitution on the sulfonium salt; alkyl- and silyl-substituted ylides provided low enantioselectivity [120]. In the case of alkyl- and silyl-substituted sulfonium ylides, the intermediate ate-complex formation is reversible and the migration step becomes selectivity-determining (Scheme 59).

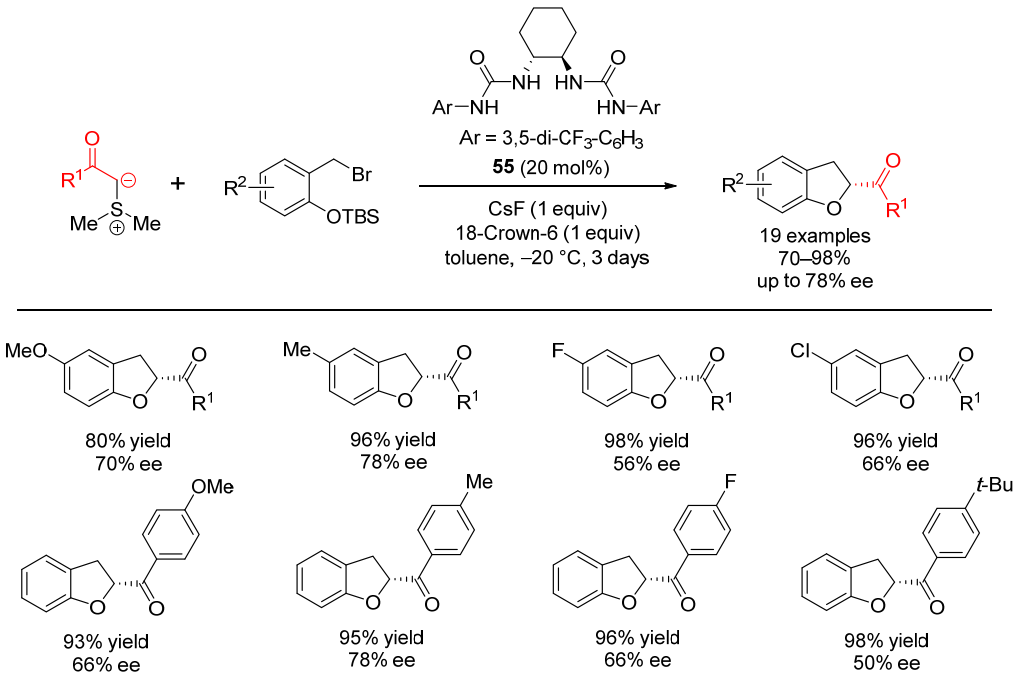


Scheme 59. Borane homologation with silyl-substituted sulfonium salt.

4.4.2. [4 + 1] Cycloadditions

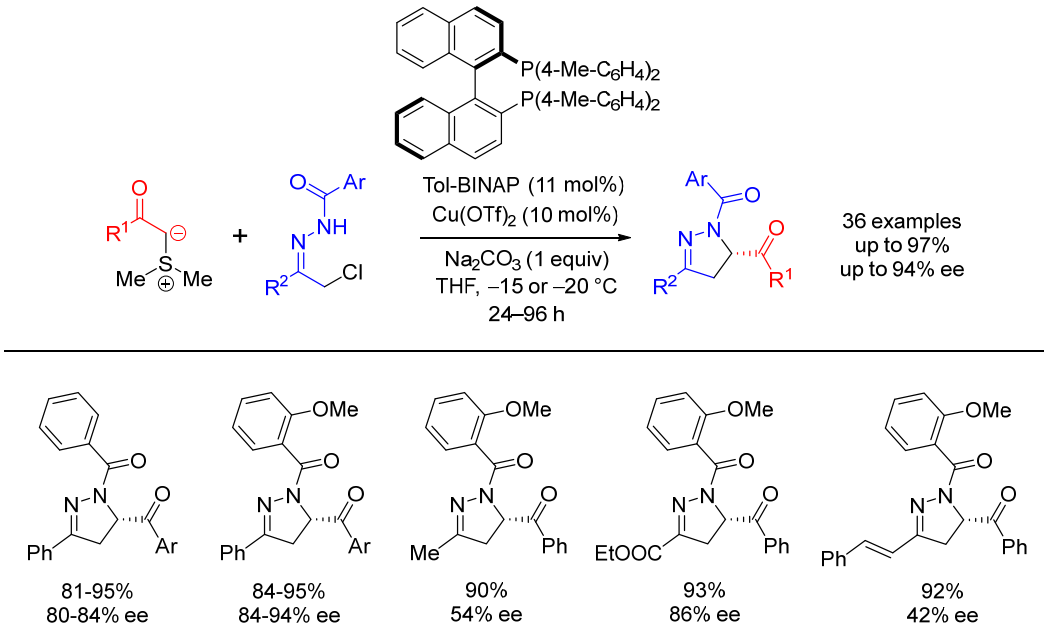
Asymmetric H-bonding catalysis is an important mode of organocatalysis, which uses hydrogen bonding interactions (lowering the LUMO of electrophiles) to accelerate organic reactions through general or specific acid catalysis, while simultaneously inducing enantioselectivity through non-bonded steric interactions in the transition state.

Recently, Xiao and co-workers reported the first example of a catalytic asymmetric formal [4 + 1] annulation reaction between stabilized sulfonium ylides and in situ generated *ortho*-quinone methides (*o*-QMs) in the presence of a H-bonding chiral C_2-symmetric urea catalyst **55** [121]. This represented a new and straightforward route to chiral 2-acyl-2,3-dihydrobenzofurans, providing the products in high yields and with moderate enantioselectivities (Scheme 60).



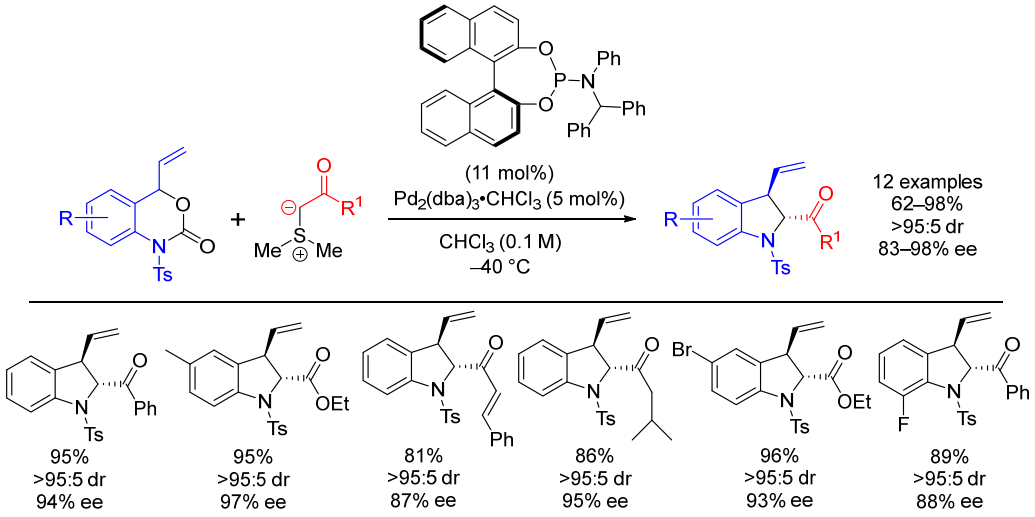
Scheme 60. Catalytic enantioselective formal [4 + 1] annulation reaction of stabilized sulfonium ylides and in situ generated *ortho*-quinone methides.

In 2012, Bolm and colleagues reported the first example of Cu(II)-catalyzed asymmetric formal [4 + 1] cycloaddition reactions of stabilized sulfonium ylides with in situ-generated azoalkenes from α-halo hydrazones and a base (Scheme 61) [122]. The chiral Cu(II)/Tol-BINAP complex provided catalysis in this unprecedented strategy and facilitated access to substituted dihydropyrazoles with high yields and moderate-to-good enantioselectivities.



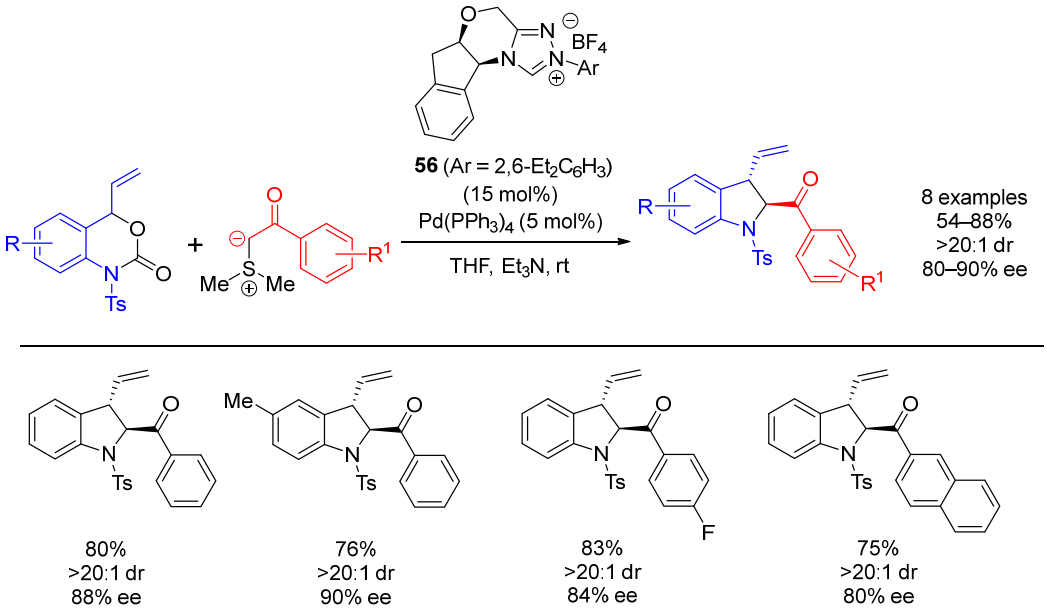
Scheme 61. Bolm's catalytic enantioselective [4 + 1] of sulfonium ylides and azoalkenes.

Xiao and colleagues developed an asymmetric decarboxylative formal [4 + 1] cycloaddition reaction of vinyl cyclic carbamates with stabilized sulfonium ylides, through the enantioselective trapping of a chiral Pd(II)-π-allyl intermediate by the ylide (Scheme 62) [123]. This methodology provided access to a wide range of chiral 3-vinyl-2-acylindolines in good yields and with high stereoselectivities. The authors also demonstrated that the electrostatic interaction between the NTs anion and the sulfonium cation was responsible for the complete regioselectivity in the key allylation step.



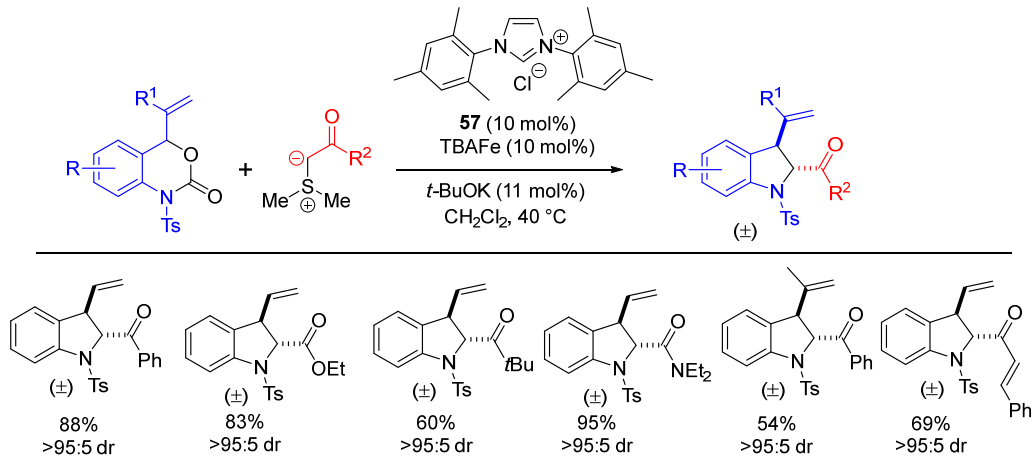
Scheme 62. Xiao's asymmetric decarboxylative formal [4 + 1] cycloaddition of vinyl cyclic carbamates with stabilized sulfonium ylides.

Very recently, Guo and Glorius achieved the same asymmetric transformation with the use of achiral palladium catalyst $Pd(PPh_3)_4$ and a chiral NHC ligand **56**, affording indoline products in moderate-to-good yields, with excellent diastereoselectivities and high enantioselectivities (Scheme 63) [124].



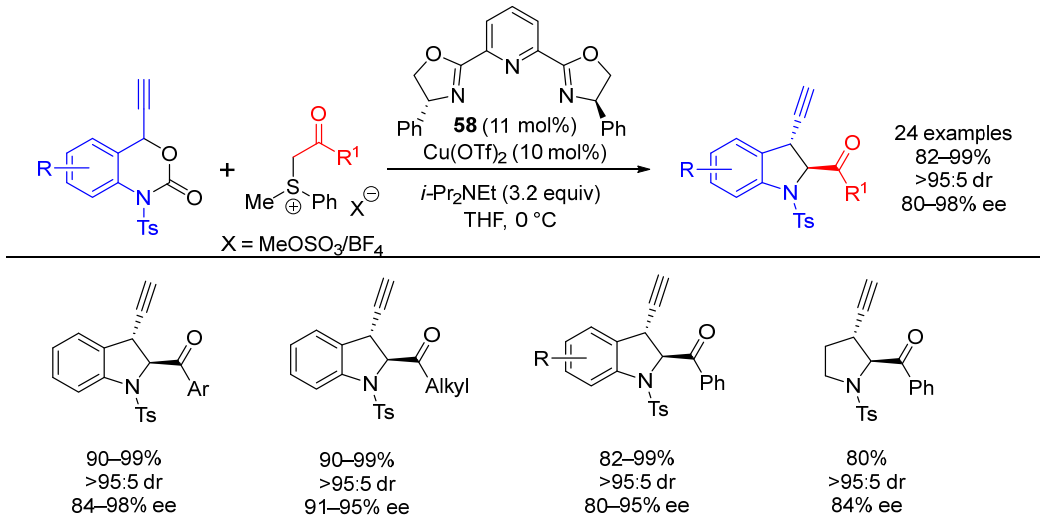
Scheme 63. Pd(0)/chiral NHC-catalyzed decarboxylative formal [4 + 1] cycloaddition of vinyl cyclic carbamates with stabilized sulfonium ylides.

Xiao and colleagues introduced the first example of an iron-catalyzed decarboxylative formal [4 + 1] cycloaddition reaction using a combination of TBAFe $\{Bu_4N^+[Fe(CO)NO]^-\}$ and the NHC carbene ligand **57** (Scheme 64) [125]. Notably, this methodology exhibited better substrate compatibility than the corresponding Pd(0)-catalyzed transformations, providing several racemic 3-vinyl indoline products with more structural diversity and with high yields and diastereoselectivities. The authors performed control experiments with the π-allyl–iron complex and a chiral vinyl carbamate, as well as DFT calculations, and the results showed a different reaction pathway from palladium catalysis. The proposed iron catalysis mechanism consists of two S_N2' nucleophilic substitutions and one S_N2 nucleophilic substitution. It appears that formation of a π-allylic iron complex is not a necessary intermediate for this transformation, unlike in the analogous palladium-catalyzed pathway.



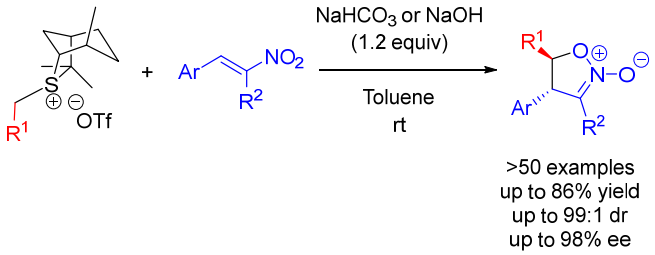
Scheme 64. TBAFe/ NHC-catalyzed decarboxylative formal [4 + 1] cycloaddition of vinyl cyclic carbamates with stabilized sulfonium ylides.

Xiao and co-workers also developed the first Cu(II)/PYBOX-catalyzed asymmetric decarboxylative [4 + 1] cycloaddition of propargylic carbamates and stabilized sulfonium ylides in the presence of *i*-Pr_2NEt (Scheme 65) [126]. This strategy led to a series of chiral indolines with synthetically flexible alkyne groups in good yields and with high enantio- and diastereoselectivities. The authors proposed a mechanism involving dinuclear copper complex—chiral ligand-promoted catalysis with key amide-containing copper—allenylidene intermediates. This proposal was supported by X-ray crystallographic analysis of the copper catalyst and the observed non-linear relationship between ee of the chiral ligand and ee of the product.



Scheme 65. Scope of Cu(II)-PYBOX-catalyzed [4 + 1] cycloaddition of propargylic carbamates and stabilized sulfonium ylides.

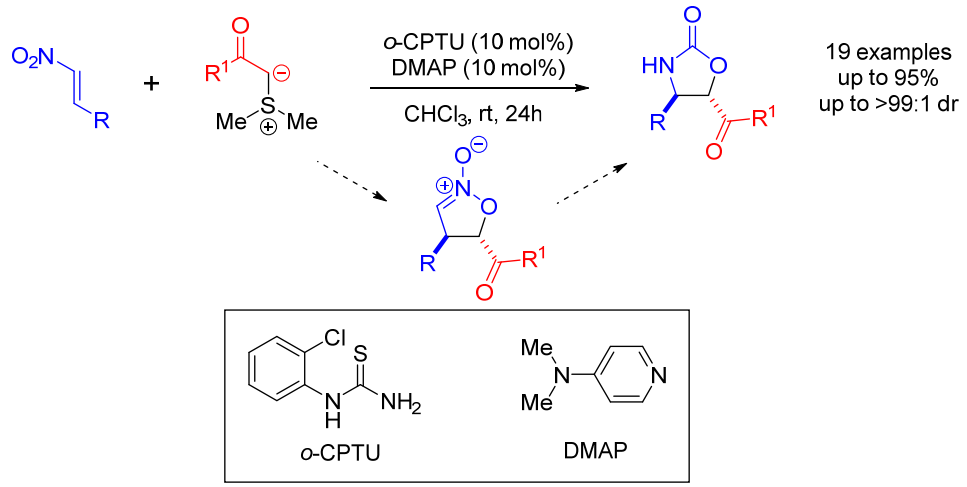
In 2022, Xie's group reported a diastereoselective and enantioselective entry to isoxazoline-N-oxides through the reaction of isothiocineole-derived chiral sulfonium ylides with nitroolefins (Scheme 66) [127]. Both stabilized and semi-stabilized sulfonium ylides were found to perform effectively.



Scheme 66. [4 + 1] cycloaddition of nitroolefins with stabilized chiral sulfonium ylides.

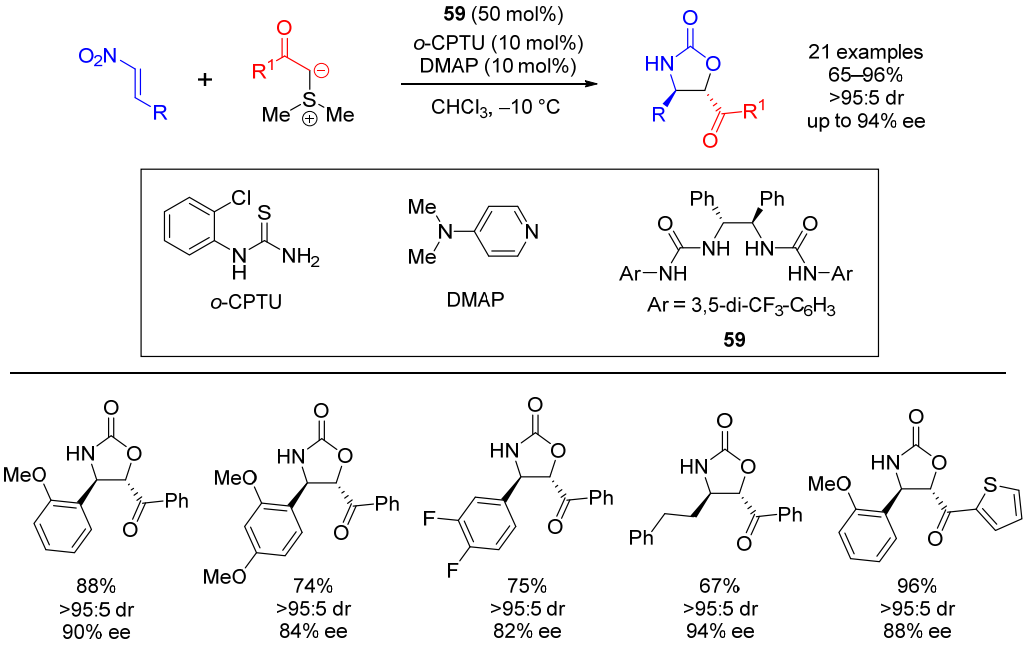
4.4.3. [4 + 1]-Cycloaddition Cascade Reactions

In 2008, Xiao's group developed a novel cascade cyclization reaction of stabilized sulfonium ylides and nitroolefins to access diverse and structurally complex oxazolidin-2-ones. The reaction sequence (cascade) consisted of an *o*-CPTU catalyzed formal [4 + 1] cycloaddition and a DMAP-catalyzed rearrangement reaction (Scheme 67) [128].



Scheme 67. Xiao's diastereoselective synthesis of oxazolidin-2-ones from nitroolefins and stabilized sulfonium ylides.

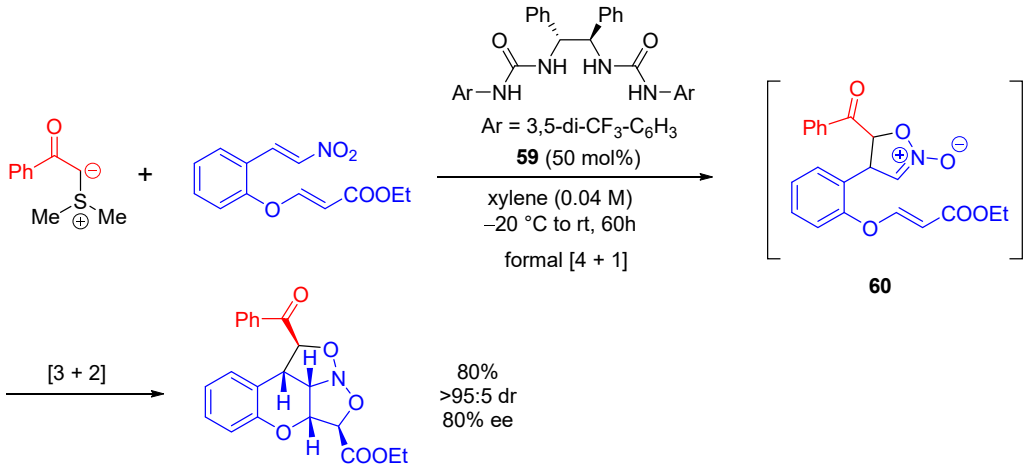
The same group in 2012 reported an enantioselective variant by employing a H-bonding catalyst **59** to promote an asymmetric [4 + 1] annulation/rearrangement cascade of stabilized sulfonium ylides with nitroolefins [129]. This methodology provides a facile route to enantioenriched 4,5-substituted oxazolidinones in moderate-to-excellent isolated yields with excellent stereocontrol (Scheme 68). In this asymmetric transformation, the catalyst *o*-CPTU was still necessary along with the chiral C_2-symmetric urea catalyst **59** to ensure high yields of chiral oxazolidinone products. The authors also performed gram-scale reactions to illustrate the synthetic utility of the methodology.



Scheme 68. Xiao's enantioselective synthesis of oxazolidin-2-ones from nitroolefins and stabilized sulfonium ylides.

The concept of asymmetric H-bonding catalysis was successfully extended to many other catalytic asymmetric cyclization reactions of sulfonium ylides. Xiao and co-workers developed a formal [4 + 1]/[3 + 2] cycloaddition cascade of stabilized sulfonium ylides with designed ethyl acrylate-linked nitrostyrenes to afford fused-tetracyclic heterocyclic compounds with high efficiency and selectivity via the nitronate intermediate **60** [130]. A

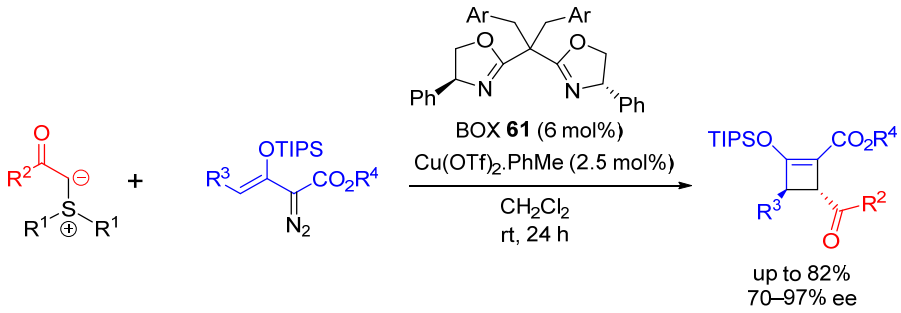
catalytic asymmetric variant of this reaction was disclosed, where the H-bonding chiral C_2-symmetric urea catalyst **59** was employed, resulting in the product being formed with good yields and good enantioselectivity (Scheme 69).



Scheme 69. Xiao's enantioselective [4 + 1]/[3 + 2] cycloaddition cascade.

4.4.4. [3 + 1]-Cycloadditions

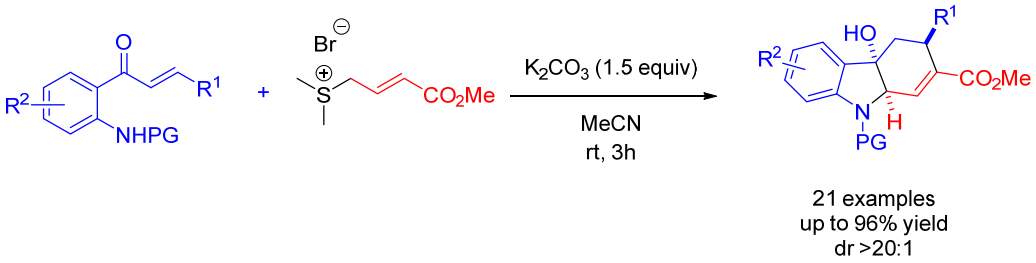
Doyle's group reported the asymmetric synthesis of cyclobutenes through a copper(II)-chiral bisoxazoline-catalyzed formal [3 + 1]-cycloaddition of sulfonium ylides and enoldiazo carbonyl derivatives in 2017 (Scheme 70) [131]. A key part of the reaction mechanism is the formation of a copper carbenoid through decomposition of the enoldiazo precursor by the copper catalyst. Nucleophilic attack of the sulfonium ylide on the copper carbenoid, followed by cyclization and elimination of the copper catalyst, resulted in the formation of the cyclobutene product. The sterically bulky bisoxazoline ligand **61** controlled enantioselectivity, with good-to-excellent levels (70–97% ee) being obtained.



Scheme 70. Doyle's enantioselective synthesis of cyclobutenes via a formal [3 + 1]-cycloaddition.

4.4.5. [3 + 3]/[1 + 4] Tandem Cycloaddition

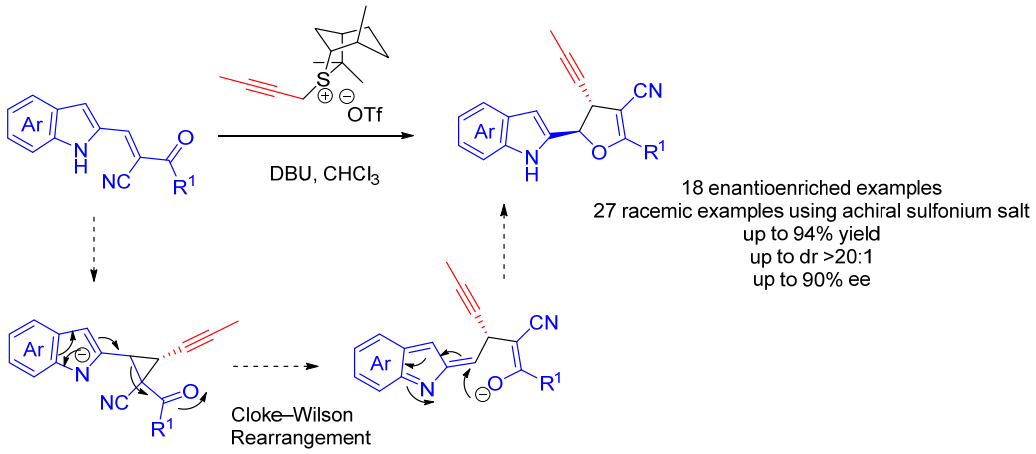
In 2020, Hui and co-workers reported the base-mediated [3 + 3]/[1 + 4] tandem reaction of N-tosyl-protected *ortho*-amino *α*,*β*-unsaturated ketones with an allyl sulfonium ylide to access functionalized hydrocarbazoles (Scheme 71) [132]. The tricyclic products were formed in high yields and with high diastereoselectivity (dr > 20:1) under mild conditions. The hydrocarbazole products were readily transformed into functionalized carbazoles.



Scheme 71. Hui's base-mediated [3 + 3]/[1 + 4] tandem cycloaddition reaction.

4.4.6. Corey–Chaykovsky Cyclopropanation/Cloke−Wilson Rearrangement

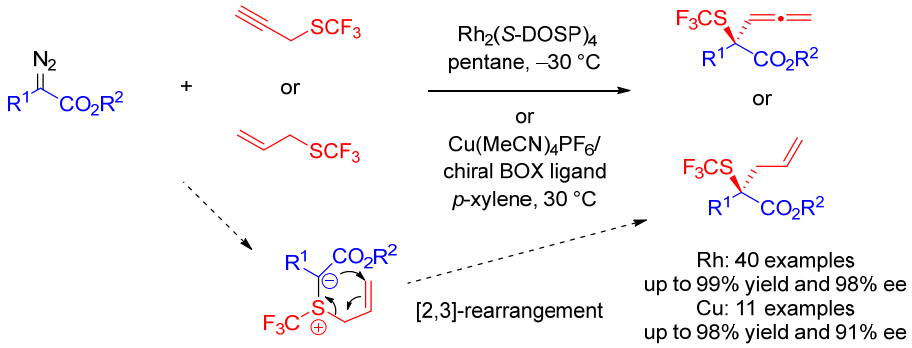
In 2021, Huang's group introduced a method for the diastereoselective and enantioselective synthesis of 2,3-dihydrofurans which involved a Corey–Chaykovsky cyclopropanation/Cloke–Wilson rearrangement sequence (Scheme 72) [133]. The sequential reaction between propargyl sulfonium salts and acrylonitrile derivatives provided the desired tetra-substituted 2,3-dihydrofurans in moderate-to-excellent yields (57–98%), and good-to-excellent diastereoselectivities (dr 7:1 to >20:1). The use of a chiral propargyl sulfonium salt derived from isothiocineole facilitated the formation of 2,3-dihydrofurans with good-to-excellent enantioselectivity (66–90% ee).



Scheme 72. Huang's stereoselective synthesis of 2,3-dihydrofurans.

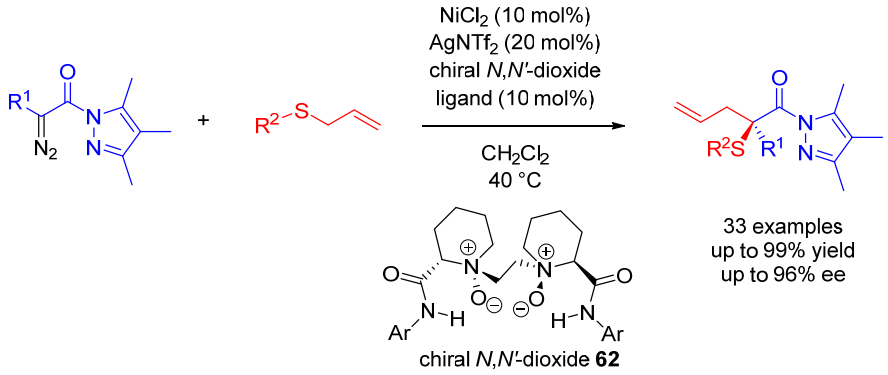
4.4.7. [2,3]-Sigmatropic Rearrangements

In 2017, the Wang group reported the first highly enantioselective Doyle–Kirmse reaction without the need for a chiral auxiliary (Scheme 73) [134]. The use of a chiral Rh or chiral Cu complex provided the desired allyl- or allenyl-substituted products in moderate-to-excellent yields (up to 99%) and with good-to-excellent enantioselectivity (70–98% ee), from electron-poor trifluoromethyl sulfides and a broad range of alkenyl-, aryl-, and heteroarylsubstituted diazoacetate derivatives.



Scheme 73. Wang's enantioselective Doyle–Kirmse reaction.

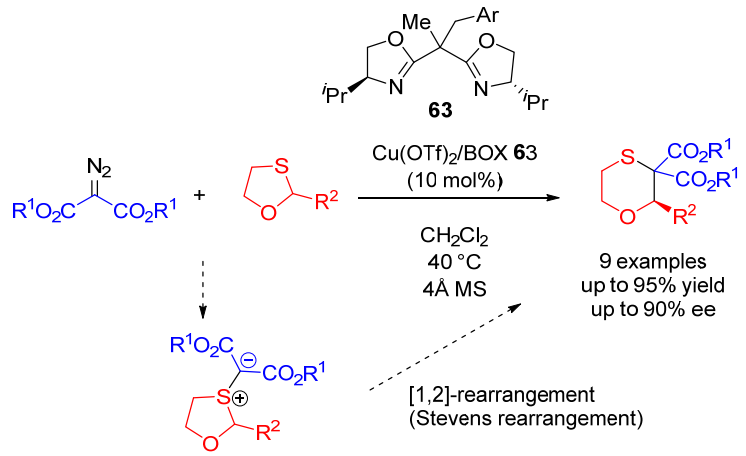
Shortly after, Feng and co-workers also reported on the Doyle–Kirmse reaction and demonstrated that a chiral Ni(II)-*N*,*N*′-dioxide complex could catalyze the reaction of allyl sulfides with diazopyrazoloamides to afford the desired enantioenriched allyl sulfides (Scheme 74) [135]. The pyrazole in the diazo substrate facilitates the strong interaction of the chiral catalyst with the sulfonium ylide intermediate, thus enabling high enantiocontrol; the absence of the pyrazole motif in the diazo substrate leads to virtually racemic product.



Scheme 74. Feng's enantioselective Doyle–Kirmse reaction.

4.4.8. [1,2]-Rearrangements

Tang's group reported a catalytic enantioselective Stevens rearrangement in the copper-chiral bisoxazoline-catalyzed reaction of diazomalonates with 1,3-oxathiolanes. The methodology afforded six-membered 1,4-oxathianes in good-to-excellent yields (66–95%) and good enantioselectivity (up to 90% ee) (Scheme 75) [136].



Scheme 75. Tang's catalytic enantioselective Stevens rearrangement.

5. Conclusions

Sulfonium ylides constitute an immensely important class of zwitterionic species, familiar to many organic chemists through the textbook examples provided for the synthesis of cyclic products. Continued work in this area since the 1960s has revealed many more opportunities for the synthesis of an array of useful cyclic products, including both monocyclic and polycyclic. The unique ability of sulfur ylides, especially sulfonium ylides, to provide both a reactive nucleophile and a good leaving group has enabled many cyclization strategies to be implemented. This dual role has proven essential in enabling the streamlined synthesis of many three-to-five-membered monocyclic and bicyclic fused heterocycles. Many successful enantioselective variants of these formal cycloadditions/sequential/cascade reactions have been developed by employing a chiral sulfide, in stoichiometric or catalytic quantities, or a chiral organocatalyst/chiral transition metal complex to control enantiofacial selection. Continued work in the area of catalytic asymmetric synthesis methodologies will lead to further practical applications, such as the synthesis of pharmaceutical, agrochemical, and other pharmacologically active compounds. The development of cooperative catalytic reactions involving a chiral sulfide catalyst working in tandem with a chiral transition metal complex or additional chiral organocatalyst would appear to be an area ripe for exploration. In addition, the study of more cascade/sequential/one-pot reactions powered by the reactivity of sulfonium ylides (as exemplified by Xiao's enantioselective [4 + 1]/[3 + 2] cycloaddition cascade) would likely lead to many fruitful applications with desirably efficient atom economy. Moreover, the development of catalytic enantioselective reactions exploiting sulfonium ylides under photocatalytic conditions remains under-exploited territory.

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