

Review

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# Application of sulfonium and sulfoxonium ylides in organocatalyzed asymmetric reaction

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## Abstract

Sulfur-based ylides are very important and valuable reagents in organic synthesis and have been widely applied in the preparation of cyclic compounds and the formation of C-X (X = C, N, O, S, B, P) bond. Since the early 2000s, asymmetric organocatalysis has become a powerful strategy in organic synthesis (even highlighted by the 2021 Nobel Prize in Chemistry) and has attracted widespread research interest among synthetic organic chemists. In this area, a large number of outstanding achievements have been registered in the novel chiral catalysts design, new compounds synthesis, various reagents application, and versatile reaction discovery. Given the extensive application of sulfonium and sulfoxonium ylides in organic synthesis, in this review, we mainly summarize the organocatalyzed asymmetric reactions involving these ylide reagents as one of the reactants. Detailed reaction mechanisms, transition states and some synthetic applications are highlighted. The challenges and opportunities of this field are also discussed in the outlook.

**Keywords:** Asymmetric catalysis, organocatalysis, sulfonium ylides, sulfoxonium ylides, cyclization reaction



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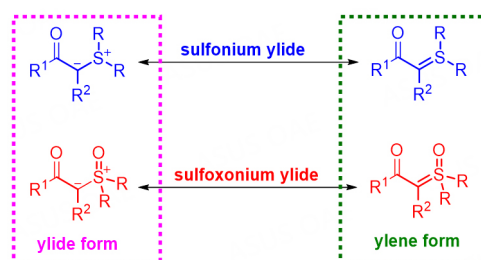


## INTRODUCTION

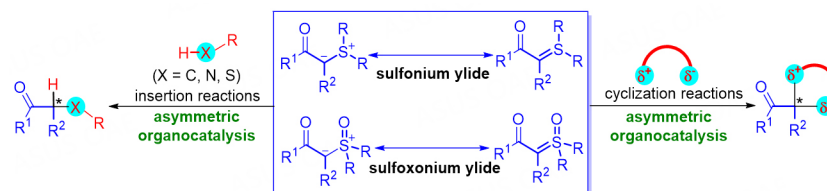
Sulfur-containing compounds are very important in organic chemistry, not only because of their prevalence in a number of fascinating natural products, clinical drugs, and pharmaceutical candidates<sup>[1-3]</sup>, but also due to their applicability as chiral auxiliary, chiral ligands, or chiral organocatalysts for various asymmetric transformations<sup>[4-6]</sup>. Actually, a large number of organosulfur reagents have been identified and confirmed as versatile reactants for many different kinds of reactions<sup>[7,8]</sup>. However, among the diverse prominent organosulfur reagents, sulfur-based ylides should belong to the most important and widely-used sulfur-containing reactants in the realm of organic synthetic chemistry. Through literature survey and search, it was found that since the pioneering work of Ingold and Jessop<sup>[9]</sup> and the groundbreaking work of Johnson and Lacount<sup>[10]</sup>, Corey and Chaykovsky in the 1960s<sup>[11-14]</sup>, the study on sulfur-based ylides chemistry has achieved an impressive development during the past nearly 60 years<sup>[15-19]</sup>. In this area, especially, stabilized sulfonium and sulfoxonium ylides bearing a carbonyl group at the  $\alpha$ -carbon atom [Figure 1] have occupied a dominant position, probably due to some of their inherent characteristics including thermal stability, easy preparation and use, and low toxicity, as well as owing to their powerful functions as nucleophilic 1,1'-dipolar species for realizing numerous chemical transformations. Moreover, with the rapid development of catalytic asymmetric synthesis, several stereocontrolled strategies, including asymmetric organometallic catalysis and organocatalysis, have been implemented in the reactions involving sulfonium and sulfoxonium ylides for the construction of chiral compounds.

With the increase of reports on various reactions involving sulfonium and sulfoxonium ylides, several reviews concerning the application of sulfonium and sulfoxonium ylides in organic synthetic chemistry have been published in recent years. In 2017, Lu *et al.* summarized the catalytic cyclization reactions of sulfur ylides<sup>[20]</sup>. In 2018, Neuhaus *et al.* reported the developments in the transition metal-catalyzed reactions involving sulfonium and sulfoxonium ylides<sup>[21]</sup>. One year later, a review on the bond-forming and -breaking reactions from organic sulfur(IV) molecules including sulfonium salts and sulfur ylides was also published from the same group<sup>[22]</sup>. Subsequently, the versatile applications of sulfoxonium ylides in organic synthesis were also reviewed by Bernardi's and Burtoloso's groups, respectively<sup>[23,24]</sup>. In addition, Fan *et al.* also published an overview of sulfonium salt and sulfur ylide chemistry<sup>[25]</sup>. Although these reviews have been published, a critical survey of the literature reveals that there are a lot of elegant works on the catalytic asymmetric reactions of sulfonium and sulfoxonium ylides by organocatalysis has been reported, but no special review summarizes these works. In this context, based on a serious consideration involving the rapid development of asymmetric organocatalysis and the wide application of sulfur-based ylides in organic synthesis, a comprehensive review on this aspect is needed.

It is an indisputable fact that asymmetric organocatalysis has emerged as a powerful strategy in organic synthesis for the construction of chiral molecule scaffolds since the early 2000s<sup>[26-29]</sup>. In this research area, a large number of outstanding achievements have been made from various aspects. Many useful reagents have been successfully applied to diverse organocatalyzed asymmetric reactions, and the sulfonium and sulfoxonium ylides are not an exception. In this review, we will comprehensively present the application of sulfonium ylides and sulfoxonium ylides in asymmetric chemical transformations with organocatalysis tactics. In addition, the substrate scope, possible mechanism, transition states, and synthetic applications are also introduced. For better understanding, this review is classified into two main sections according to the type of sulfur-based ylides: (1) organocatalytic asymmetric reactions of sulfonium ylides; (2) organocatalytic asymmetric reactions of sulfoxonium ylides. In each section, the reaction types include both asymmetric X-H (X = C, N, S) bond insertion reactions and asymmetric cyclization reactions [Figure 2]. In addition, it should be declared here that this review only focuses on the organocatalytic asymmetric reactions where involving *performed* sulfonium ylides and sulfoxonium ylides as reactants, but the reactions where the sulfur



**Figure 1.** Representative structures of sulfonium and sulfoxonium ylides.



**Figure 2.** Application of sulfonium and sulfoxonium ylides in the asymmetric reactions by organocatalysis.

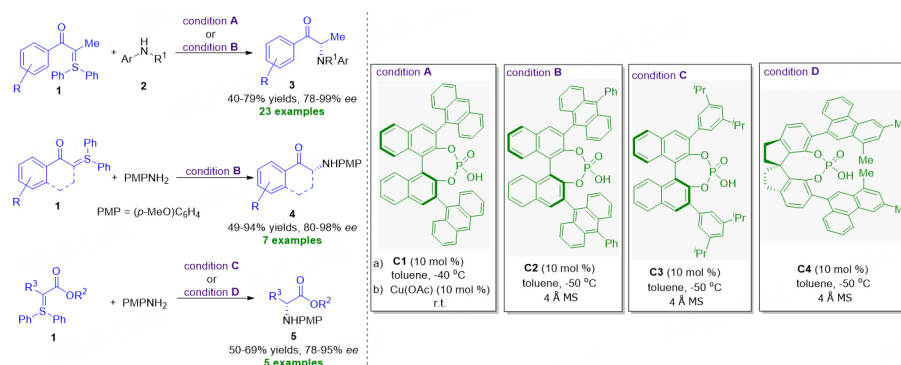
ylides participated in the transformations are *generated in-situ* from the corresponding salt precursors under basic conditions are not discussed<sup>[30-33]</sup>. Nevertheless, the related asymmetric reactions with chiral sulfide-centric catalysts involving chiral sulfur ylide intermediates<sup>[34-39]</sup> and those with chiral auxiliary-derived sulfonium salts as reactants are also not discussed here. This arrangement is mainly based on the consideration that those reactions were well described in previous elegant reviews<sup>[15,16,40,41]</sup>.

## ORGANOCATALYTIC ASYMMETRIC REACTION OF SULFONIUM YLIDES

Sulfonium ylides can be represented by ylide form which contains a carbanion connecting a positively charged sulfur (IV) atom, or by ylene form which contains a C = S(IV) double bond [Figure 1]. The stability of sulfonium ylides depends largely on the degree of electron delocalization on the carbanion center. Therefore, stabilized sulfonium ylides generally bear an electron-withdrawing functional group connected to the carbanion center; thus, these ylides are readily prepared and usually used in various reactions. The stabilized  $\alpha$ -carbonyl sulfonium ylides can be applied as one-carbon synthons to construct C-X (X = C, N, S) bonds<sup>[17,40,42]</sup>. Moreover, they are more commonly used in cyclization reactions with electron-poor  $\pi$ -systems for the synthesis of various ring compounds<sup>[20,22]</sup>. In the area of organocatalysis, stabilized sulfonium ylides have been used in N-H bond insertion reactions, cyclopropanation reactions, and [4 + 1] cyclization reactions under the promotion from various organocatalyst *via* different activation patterns.

### Asymmetric N-H bond insertion reaction

Chiral organocatalysts promoted asymmetric heteroatom-H bond insertion reaction with the sulfonium ylides remained highly challenging in the past two decades, and successful research was virtually nonexistent. Until 2020, Guo *et al.* disclosed the asymmetric N-H bond insertion reactions by  $\alpha$ -carbonyl sulfonium ylides using chiral phosphoric acids as catalysts, affording a series of chiral  $\alpha$ -amino ketone compounds with excellent efficiency and enantioselectivity [Figure 3]<sup>[43]</sup>. Under conditions A or B, the transformation with  $\alpha$ -methyl sulfonium ylides **1** as substrates proceeded smoothly to form  $\alpha$ -tertiary amino ketones **3** in 40%-79% yields with 78%-99% *ee*. As for the  $\alpha$ -non-methyl sulfonium ylide or cyclic sulfonium ylide substrates, the reaction with condition B could give the corresponding  $\alpha$ -amino ketones **4** bearing various alkyl chains or Cyclic  $\alpha$ -amino ketones in 49%-94% yields with 80%-98% *ee*. In addition,  $\alpha$ -alkyl esters derived sulfonium ylides **1** could also act as available starting materials to participate in the N-H bond



**Figure 3.** Asymmetric N-H bond insertion reaction by  $\alpha$ -carbonyl sulfonium ylides. This figure is used with permission from the American Chemical Society<sup>[43]</sup>.

insertion reaction with condition C or D, generating the desired  $\alpha$ -amino esters 5 in excellent results (50%-69% yields, 78%-95% *ee*).

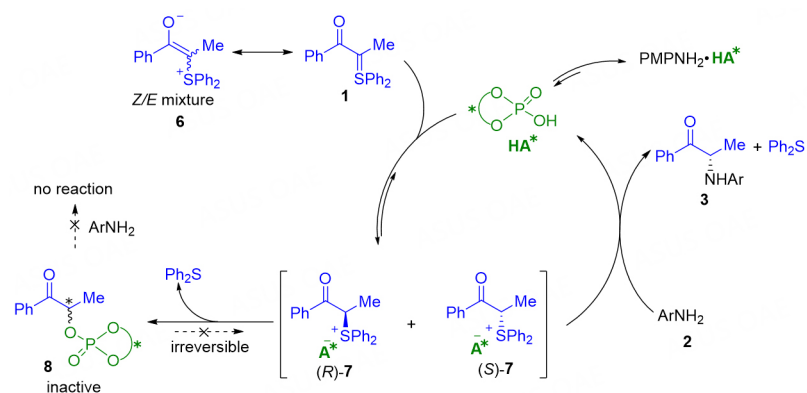
Moreover, the authors also investigated the possible mechanism. The mechanistic studies revealed that the reaction undergoes a protonation-amination sequence and the enantioselectivity is controlled by dynamic kinetic resolution in the amination step, rather than the initial protonation<sup>[43]</sup>. In the proposed mechanism [Figure 4], the chiral phosphoric acid enables the protonation of sulfonium ylide 1 that is in resonance with the enolate mixture of *Z/E*-isomers 6, to give an intermediate mixture of (*S*)-7 and (*R*)-7 that pair with chiral phosphate anion. Subsequent amine substitution by 2 delivers the desired chiral  $\alpha$ -amino product 3 and simultaneously releases the chiral phosphoric acid catalyst. Indeed, intermediate 7 is in the catalyst resting state and permits sufficient epimerization of the labile tertiary stereocenter in (*S*)-7 and (*R*)-7. Thus, the enantioselectivity is controlled during amination by pseudo dynamic kinetic resolution of the intermediate mixture of (*S*)-7 and (*R*)-7. In addition, phosphate ester 8 as a by-product could be found in the catalytic mixture but is unable to react with amine 2 due to its inactiveness.

### Asymmetric cyclization reaction of sulfonium ylides

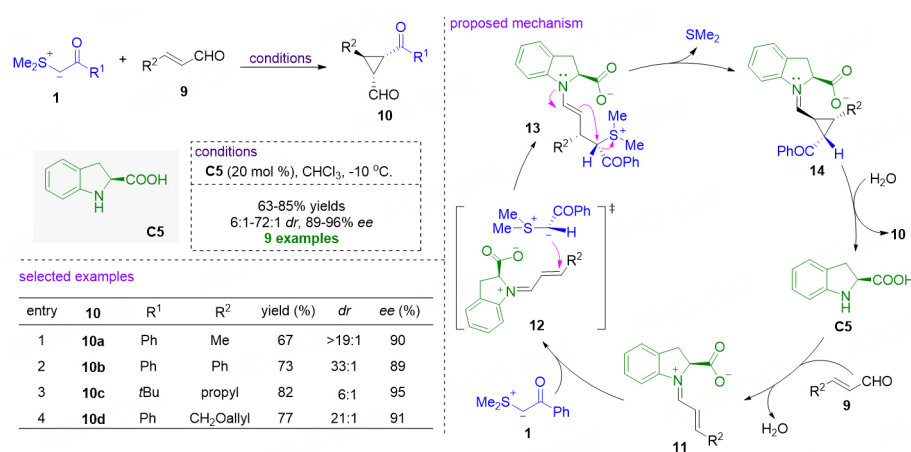
Intermolecular cycloaddition is one of the most essential and powerful tools for the construction of cyclic skeletons. Indeed, since the significant breakthrough of asymmetric organocatalysis in the early 2000s<sup>[26-29]</sup>, organocatalyzed enantioselective cycloaddition reactions involving sulfonium ylides have been widely explored for the synthesis of diverse cyclic compounds. In this section, we divide the organocatalyzed asymmetric transformations of sulfonium ylides into two categories: cyclopropanation and [4 + 1] cyclization reaction for simplicity.

#### Organocatalyzed asymmetric cyclopropanation

Since cyclopropanation of sulfonium ylides with electron-deficient olefins was developed by Corey and Chaykovsky in 1965<sup>[13]</sup>, the research on the corresponding asymmetric version has been devoted continuous attention from chemists, and many great achievements have been made in this aspect<sup>[20]</sup>. The first enantioselective organocatalytic cyclopropanation was achieved by means of iminium activation in 2005 [Figure 5]<sup>[44]</sup>. In this work, MacMillan and coworker chose chiral 2-carboxylic acid dihydroindole C5 as the catalyst to activate  $\alpha,\beta$ -unsaturated aldehydes 9 for generating iminium ion intermediates 11. Due to the existence of the attractive electrostatic interactions of sulfonium cation and carboxylate anion, the *Si* face of the sulfonium ylide approaches the *Re* face of the iminium ion through the transition state 12 to give the intermediate 13. And then, an intramolecular cyclization gives chiral cyclopropane products 10 in good yields (63%-85%) with high diastereo- and enantioselectivities (6:1-72:1 *dr* and 89%-96% *ee*) [Figure 5]. In



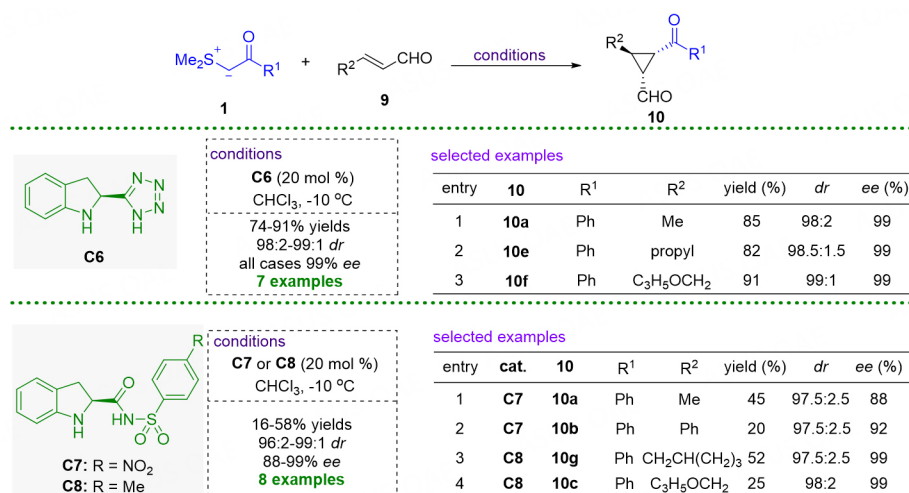
**Figure 4.** Proposed mechanism for chiral phosphoric acid catalyzed asymmetric N-H bond insertion reaction by  $\alpha$ -carbonyl sulfonium ylides. This figure is used with permission from the American Chemical Society<sup>[43]</sup>.



**Figure 5.** Chiral 2-carboxylic acid dihydroindole catalyzed enantioselective cyclopropanations of  $\alpha,\beta$ -unsaturated aldehydes. This figure is used with permission from the American Chemical Society<sup>[44]</sup>.

this report, the authors proposed a directed electrostatic activation (DEA) mechanism, in which the negative carboxylate group interacts with the positive thionium moiety, thus reducing the activation energy and increasing the reaction rate. However, Mayr disapproved of some MacMillan's conclusions, but accepted the DEA mechanism as a justification for the experimental high reaction rates<sup>[45]</sup>. On the base of former research on this aspect, Santos and coworkers demonstrated that the cyclopropanation reaction occurs through a two-step mechanism and that the overall enantioselectivity relies on the relative energies of the two steps by taking advantage of computational study<sup>[46]</sup>.

In 2007, Hartikka *et al.* also described the enantioselective cyclopropanation of  $\alpha,\beta$ -unsaturated aldehydes with sulfonium ylides by using newly developed chiral amine catalysts [Figure 6]<sup>[47,48]</sup>. With the tetrazolic acid functionalized dihydroindol **C6** as the catalyst, chiral cyclopropanes **10** could be obtained in 99% ee for the seven examples<sup>[29]</sup>. In the presence of **C7** or **C8**, the reactions gave the products with moderate yields with good to excellent diastereo- and enantioselectivities<sup>[30]</sup>. In their work, it was demonstrated that the larger steric bulk catalysts could increase enantioselective induction, thus leading to better enantioselectivities compared with the results obtained in Kunz and MacMillan's work<sup>[44]</sup>.



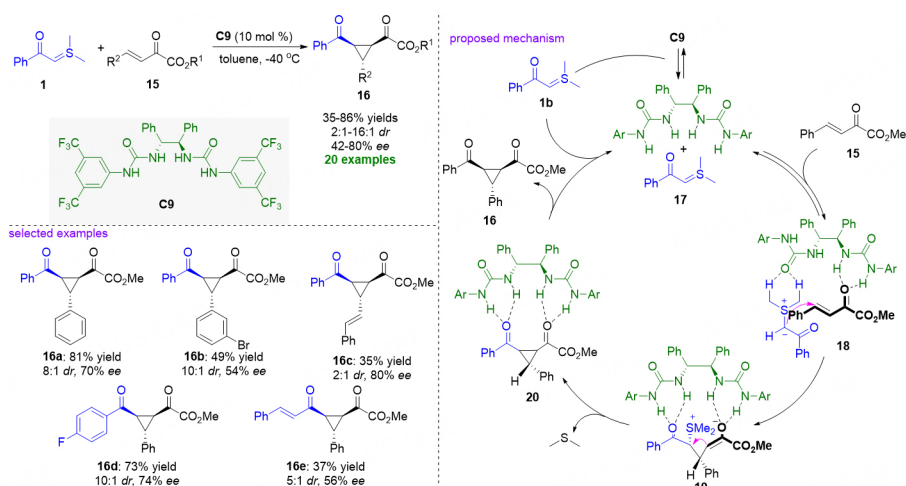
**Figure 6.** Chiral dihydroindole derived amines catalyzed enantioselective cyclopropanation of  $\alpha,\beta$ -unsaturated aldehydes. This figure is used with permission from the American Chemical Society<sup>[47]</sup> and Elsevier Ltd<sup>[48]</sup>.

In the area of asymmetric organocatalysis, asymmetric hydrogen-bonding catalysis, which takes advantage of the hydrogen bonding interactions between the chiral catalysts and reactants to promote organic transformation and concurrently induce the stereoselectivity through lowering the LUMO of electrophiles, occupies a very important position<sup>[49-51]</sup>. In 2011, Cheng *et al.* employed C<sub>2</sub>-symmetric urea as a hydrogen-bond catalyst for the asymmetric cyclopropanation of  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters **15** with stabilized sulfonium ylides **1**, providing a series of optically pure 1,2,3-trisubstituted cyclopropane derivatives **16** in moderate to good yields, diastereoselectivities, and enantioselectivities [Figure 7]<sup>[52]</sup>. <sup>1</sup>H NMR spectroscopic studies were conducted to demonstrate that the existence of H-bond interaction between C<sub>2</sub>-symmetric urea **C9** and sulfonium ylide **1** could form complex **17**. In the proposed pathway, complex **17** incorporates with  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoester **15** to form transition state **18**. Then sulfonium ylide attacks the  $\gamma$ -position of ketoester to generate intermediate **19**. Finally, intermediate **19** undergoes an intramolecular nucleophilic substitution reaction to give intermediate **20** that delivers corresponding chiral cyclopropane derivatives **16** and releases the hydrogen-bond urea catalyst for the next catalytic cycle.

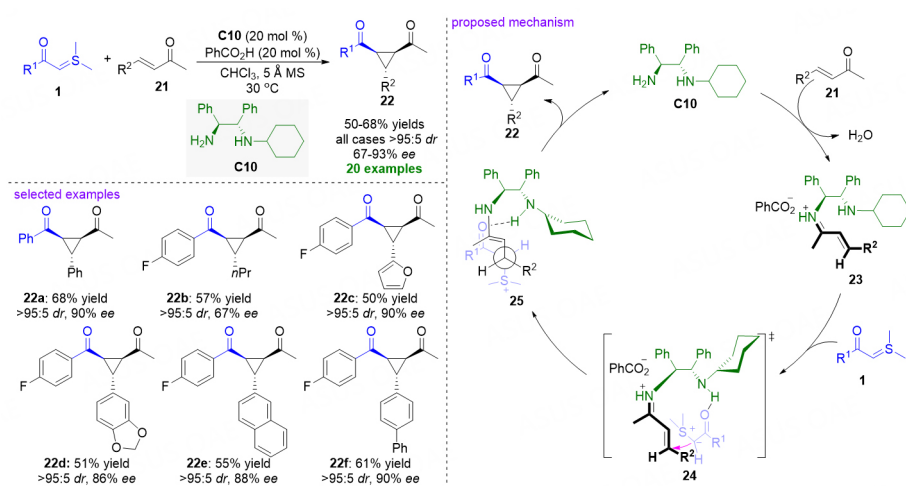
Until 2013, organocatalyzed asymmetric cyclopropanation of  $\alpha,\beta$ -unsaturated ketone substrates with stabilized sulfonium ylides was reported by Wang *et al.* [Figure 8]<sup>[53]</sup>. In the developed method, the primary amine part of chiral diamine catalyst **C10** combines with  $\alpha,\beta$ -unsaturated ketones **21** to form the iminium ion intermediates **23**. Simultaneously, the secondary amine moiety of **C10** incorporates with sulfonium ylides **1** through H-bond interaction. Then a Michael addition reaction is then performed from sulfonium ylides **1** to the *Si* face of iminium ion moiety, leading to the formation of intermediates **25**. Subsequently, an intramolecular cyclization generates the desired cyclopropanation adducts **22** and releases the catalyst into the next cycle.

#### Organocatalyzed asymmetric [4 + 1] cyclization reactions

There have been many reports on catalytic asymmetric [4 + 1] cyclization of sulfonium ylides for the construction of diverse five-membered cycles by using sulfide-centric catalysis, transition-metal catalysis, and organocatalysis. In particular, the organocatalysis strategy in this research area has gained increasing interest from the synthetic community due to its sustainable and green features.



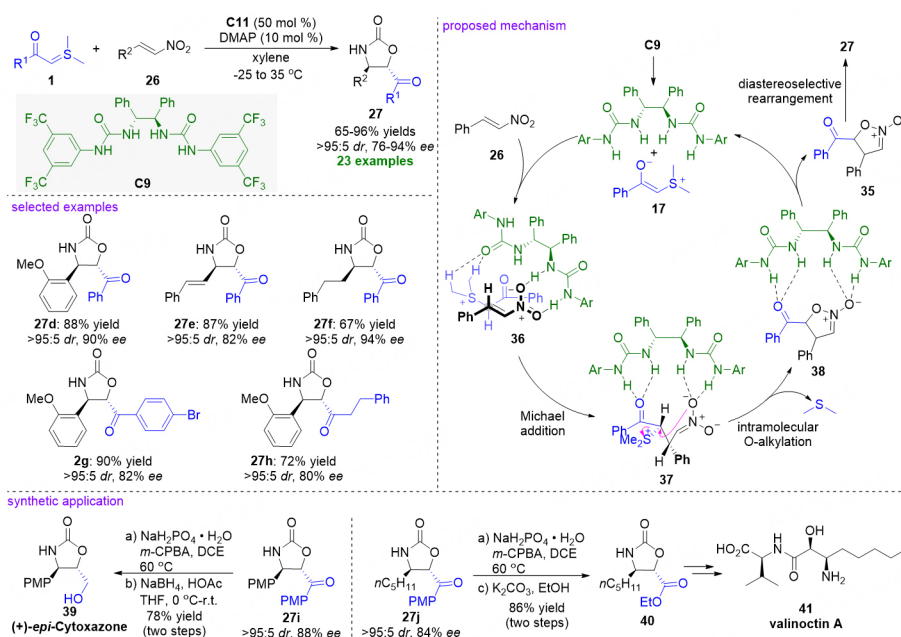
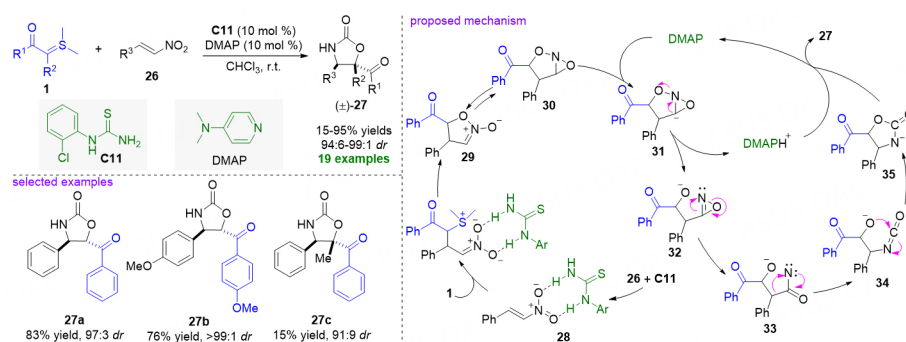
**Figure 7.** Chiral  $C_2$ -symmetric urea-catalyzed cyclopropanation of  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters. This figure is used with permission from the American Chemical Society<sup>[52]</sup>.



**Figure 8.** Chiral diamine-catalyzed asymmetric cyclopropanation of  $\alpha,\beta$ -unsaturated ketones. This figure is used with permission from the American Chemical Society<sup>[53]</sup>.

In 2008, Lu *et al.* reported an organocatalytic [4 + 1] cyclization reaction of nitroolefins **26** and sulfonium ylides **1** under *ortho*-chlorophenyl thiourea **C11** and *N,N*-dimethylaminopyridine (DMAP) cooperative catalysis, allowing efficient and rapid access to diverse and structurally complex oxazolidin-2-ones ( $\pm$ )-**27** [Figure 9]<sup>[54]</sup>. In their proposed plausible mechanism, the thiourea catalyst enables formal (4 + 1) cycloaddition to furnish isoxazoline *N*-oxide **29**, which undergoes an intramolecular cyclization to form intermediate **30**. In the presence of DMAP, deprotonation from **30** releases intermediate **31**, which could convert into nitrene **33** *via* intermediate **32**. Followed by Hofmann rearrangement and intramolecular cyclization, the resulting intermediate **35** reacts with DMAP- $\text{H}^+$  to deliver oxazolidin-2-one **27**.

Impressively, the catalytic asymmetric version of the above [4 + 1] cyclization reaction between nitroolefins **26** and sulfonium ylides **1** was realized by the same group in 2012 [Figure 10]<sup>[55]</sup>. The chiral  $C_2$ -symmetric multiple hydrogen-bonding urea catalyst **C9** shows the best positive effect on enantioselectivity and the method displays a broad substrate scope to give optically active oxazolidin-2-ones **27** in good to excellent

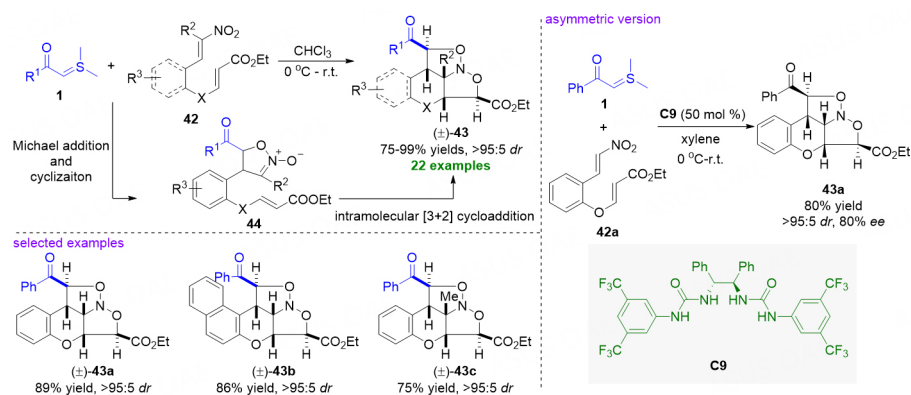


**Figure 10.** Catalytic asymmetric [4 + 1] cyclization reaction of nitroolefins and stabilized sulfonium ylides. This figure is used with permission from the Wiley-VCH Verlag<sup>[55]</sup>.

yields and stereoselectivities (65%–96% yields, > 95:5 *dr*, and 76%–94% *ee*). The authors think the formation of chiral oxazolidin-2-ones depends largely on asymmetric [4 + 1] cyclization reaction, including a cascade Michael addition/intramolecular O-alkylation/rearrangement process. In addition, stepwise operation at temperature could ensure the high enantioselectivity of the reaction. Moreover, synthetic applications were also conducted. (+)-*epi*-cytozaxone 39<sup>[56]</sup> and key intermediate 40 for synthesis of the valinocin A 41<sup>[57]</sup> were respectively provided after two steps.

Based on their successful implementation of thiourea/DMAP cooperative-catalysis strategy for the diastereoselective [4 + 1] cyclization reaction of nitroolefins and sulfonium ylides<sup>[54]</sup>, Xiao and coworkers became interested in the application of the vital isoxazoline *N*-oxides 29 [Figure 9] intermediate as a type of 1,3-dipole species for the possible further reactions. In 2009, Lu *et al.* reported a catalyst-free sequential intermolecular [4 + 1] and intramolecular [3 + 2] cycloaddition reaction between sulfonium ylides 1 and alkene-tethered nitroolefins 42 [Figure 11]<sup>[58]</sup>. The protocol exhibits a wide substrate scope and excellent





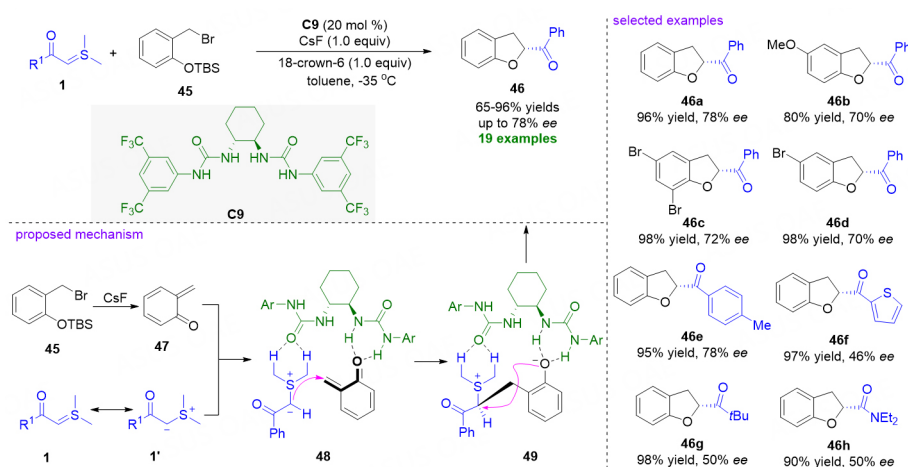
**Figure 11.** Formal [4 + 1]/[3 + 2] cycloaddition cascade of sulfonium ylides and alkene-tethered nitroolefins. This figure is used with permission from the Wiley-VCH Verlag<sup>[58]</sup>.

diastereocontrol, but also smoothly delivers a range of important *N*-containing polycyclic compounds ( $\pm$ )-**43** bearing five consecutive stereogenic centers in good to high yields (75%–99%) with excellent diastereoselectivities (all cases > 95:5 *dr*). In the cascade process, sulfonium ylides **1** and alkene-tethered nitroolefins **42** firstly undergo a Michael addition and cyclization to form an important intermediate **44**, which quickly converts to products **43** through an intramolecular [3 + 2] cycloaddition. In addition, asymmetric synthesis of the polycyclic product was also investigated. Selecting chiral  $C_2$ -symmetric urea **C9** as multiple hydrogen bond catalyst, the reaction proceeded smoothly and afforded chiral product **43a** in 80% yield with > 95:5 *dr* and 80% *ee*.

Chiral 2,3-dihydrobenzofurans are ubiquitous and important ring structures embedded in some natural products and synthetic drugs with diverse bioactivities. Consequently, the synthesis of structurally diverse 2,3-dihydrobenzofuran compounds *via* a catalytic asymmetric manner has attracted tremendous attention from synthetic chemists<sup>[59,60]</sup>. In 2015, Lei *et al.* reported a facile synthesis of racemic 2,3-dihydrobenzofurans *via* formal [4 + 1] cyclization of sulfonium ylides and *in situ* generated *ortho*-quinone methides (*o*-QMs) from *O*-silylated phenols<sup>[61]</sup>. Two years later, Yang and Xiao developed a catalytic asymmetric version of the same reaction as reported by Sun and Xu, using the chiral  $C_2$ -symmetric multiple hydrogen-bonding urea catalyst **C9** [Figure 12]<sup>[62]</sup>. The developed asymmetric catalytic protocol exhibits a broad substrate scope and high functional group tolerance. A wide range of chiral 2,3-dihydrobenzofurans could be obtained in good to excellent yields with moderate stereoselectivities. In the proposed reaction mechanism, the organocatalyst **C9** simultaneously interacts with sulfonium ylide **1** and the *in situ* generated *ortho*-quinone methide **47** by H-bonding interactions to form complex **48**. Subsequently, asymmetric Michael addition leads to the formation of complex **49**, which then undergoes an intramolecular  $S_N2$  displacement to deliver chiral 2,3-dihydrobenzofuran products **46**.

## ORGANOCATALYTIC ASYMMETRIC REACTION OF SULFOXONIUM YLIDES

Compared to sulfonium ylides, sulfoxonium ylides contain a positively charged sulfur(VI) atom in the ylide form or a C = S(VI) double bond in the ylene form due to the binding of one oxygen atom to the sulfur atom. Therefore, the sulfur oxidation state would result in some differences in the property and the reactivity for the ylides. The sulfoxonium ylides are relatively more stable and have lower nucleophilicity. In addition, the electronegative oxygen atom readily coordinates with a chiral Lewis acid catalyst or combines with the hydrogen bond of organocatalysts, thereby enhancing the stereoselectivity control in asymmetric catalysis. Consequently, in the past three decades, many elegant implementations of sulfoxonium ylides in organic synthesis have been reported by many research communities and those in the industry<sup>[17,23,24]</sup>.



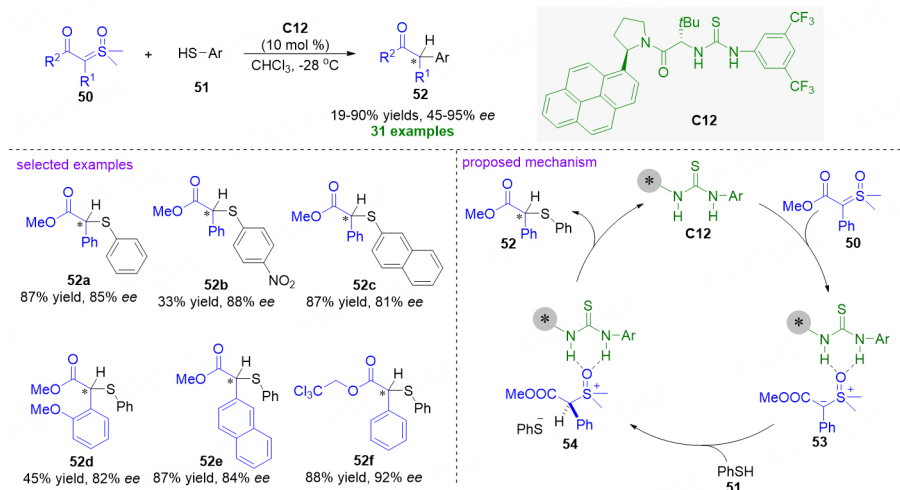
**Figure 12.** Catalytic asymmetric [4 + 1] cyclization reaction of sulfonium ylides with the in situ generated *ortho*-quinone methides. This figure is used with permission from the Wiley-VCH Verlag<sup>[62]</sup>.

However, probably due to the relatively less reactive and low nucleophilicity of carbanion by comparing with their sulfonium ylide counterparts, significant progress on sulfoxonium ylides-involved asymmetric reaction by organocatalysis is far lagging behind, although transition-metal catalytic asymmetric transformations were reported from 2007<sup>[63-67]</sup>. Likewise, in this section, the organocatalytic asymmetric reaction of sulfoxonium ylides will also be discussed in two parts, including the X-H (X = S, N, C) bond insertion reaction and cyclization reaction.

### Asymmetric X-H (X = S, N, C) bond insertion reaction

In 2016, Burtoloso and coworkers reported a catalyst-free S-H bond insertion reaction of sulfoxonium ylides into aryl thiols, which exhibits a broad substrate scope and high yields for the direct synthesis of  $\beta$ -keto thioethers under mild reaction conditions<sup>[68]</sup>. By the year 2020, Burtoloso, Mattson and co-workers realized an enantioselective S-H bond insertion reaction of  $\alpha$ -carbonyl sulfoxonium ylides to a diverse array of aryl thiols by taking advantage of a known thiourea catalyst **C12** to control the enantioselectivity [Figure 13]<sup>[69]</sup>. Under the influence of **C12**, the asymmetric reaction also shows a relatively broad substrate scope, furnishing 2-thioacetate derivatives **52** in excellent levels of enantiocontrol (up to 95% *ee*) and yields (up to 97%). Additional investigations on the mechanism indicate that the bonding interactions between the thiourea moiety of **C12** and the S = O functional group of sulfoxonium ylides **50** play a key role in determining the enantioselectivity. In addition, a plausible reaction pathway was proposed, that is, the chiral thiourea catalyst **C12** incorporates sulfoxonium ylide **50** by hydrogen bond to form complex **53**. Deprotonation of thiophenol **51** with complex **53** forms ion pair **54**. And then, the thiolate undergoes a substitution reaction to give rise to the corresponding product **52** and release chiral thiourea **C12** concurrently.

$\alpha$ -Amino esters as versatile building blocks have significant applications in organic synthesis as well as widespread distribution in complex natural products, biomolecules and clinically used drugs<sup>[70]</sup>. Thereby remarkable achievements have been made in the development of various asymmetric methods for the construction of optically pure  $\alpha$ -imino esters<sup>[71]</sup>. Indeed, the asymmetric N-H insertion reactions of  $\alpha$ -carbonyl sulfoxonium ylides to amines are able to provide direct access to chiral  $\alpha$ -amino esters. In 2021, Furniel *et al.* reported the first asymmetric reaction of  $\alpha$ -carbonyl sulfoxonium ylides and anilines by using a copper-bifunctional squaramide cooperative catalysis strategy, which undergoes an asymmetric N-H insertion process to afford a series of chiral  $\alpha$ -aryl glycine esters **5** in good to excellent yields and

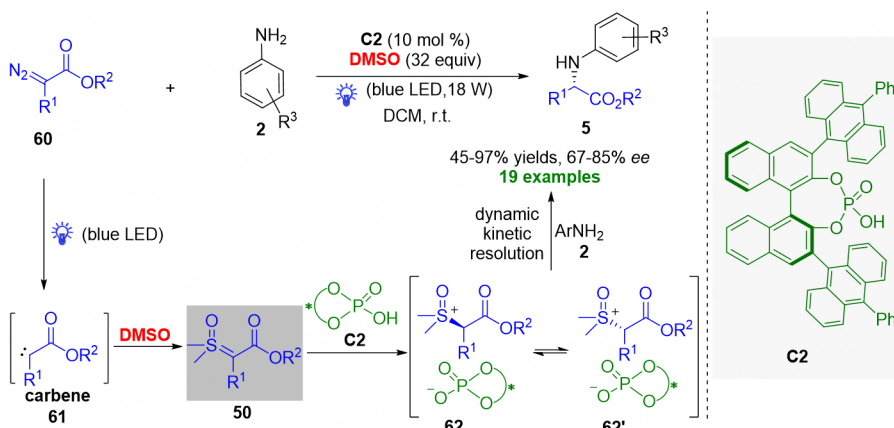
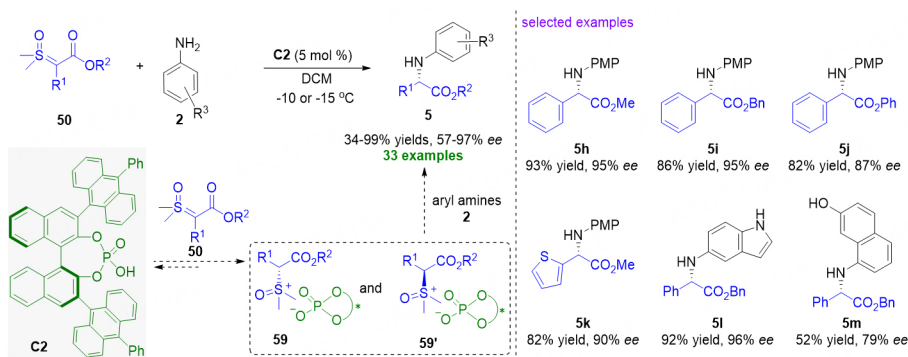
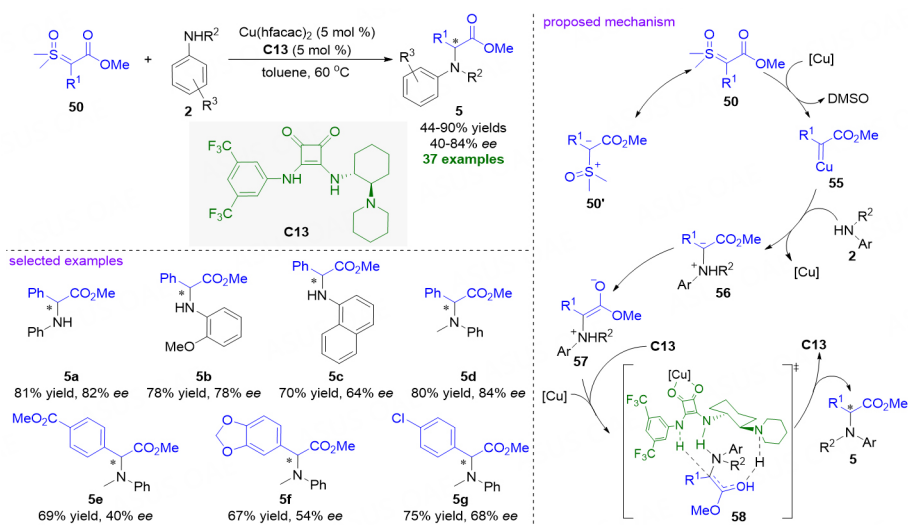


**Figure 13.** Chiral thiourea catalyzed enantioselective S-H insertion reactions of  $\alpha$ -carbonyl sulfoxonium ylides to aryl thiols. This figure is used with permission from the Wiley-VCH Verlag.<sup>[69]</sup>

enantioselectivities ranging between 40%-84% *ee* [Figure 14]<sup>[72]</sup>. A mechanism proposal was also proposed. At first, the nucleophilic attack of sulfoxonium ylide **50** to copper complex generates copper carbene intermediate **55**, which could transform into ammonium ylide intermediate **56** by the attack of aniline **2**. And then, the intermediate **56** tautomerizes to the enol intermediate **57**, which readily interacts with copper-chiral squaramide complex through hydrogen bond to form transition state **58**. Finally, under asymmetric induction, protonation of the enol intermediate **57** leads to the formation of enantioenriched N-H insertion products  $\alpha$ -aryl glycine esters **5**.

Almost at the same time, Guo *et al.* also reported a chiral phosphoric acid-catalyzed asymmetric N-H insertion reaction of aryl amines **2** with  $\alpha$ -carbonyl sulfoxonium ylides **50** [Figure 15]<sup>[73]</sup>. With bulky chiral phosphoric acid **C2** as the catalyst, a wide range of  $\alpha$ -aryl glycines were obtained in generally excellent yields and enantiomeric excesses (34%-99% yield and 57%-97% *ee*). In the proposed mechanism, the weak basicity of sulfoxonium ylides could cause the interaction with chiral phosphoric acid **C2** to form the ion pair intermediates **59** and **59'**, which undergo nucleophilic attack by the aryl amines **2**, thus leading to the formation of  $\alpha$ -aryl glycine esters **5**. After detailed mechanistic studies, the authors think that the protonation of **50** favors the formation of intermediates **59** and **59'**. Due to reversibility of this step, the chiral phosphate anion can control the stereochemistry in the C-N bond formation *via* dynamic kinetic resolution. The C-N bond formation is also rate-determining step.

Although that catalytic asymmetric insertion reaction of metal carbenes into N-H bond with the enantioselective control *via* metal-chiral metal interaction has been well-established<sup>[74,75]</sup>, the asymmetric insertion reaction of free carbenes into N-H bond faces a challenge due to strong background reactions and lack of any anchor for a catalyst interaction. Recently, Guo *et al.* made progress in the catalytic enantioselective insertion reaction of free carbenes into N-H bond using an indirect approach<sup>[76]</sup>. In their developed protocol [Figure 16], with visible light as a promoter, the  $\alpha$ -diazoesters **60** could be converted to free carbene intermediate **61**, which was captured rapidly by DMSO to *in situ* form sulfoxonium ylide **50**. And then, chiral phosphoric acid catalyst **C2** protonated ylide **50** to generate diastereomeric intermediates **62** and **62'**. Ultimately, under the control of a chiral catalyst, the amine reactants **2** reacted preferentially with one of the intermediates **62** and **62'** to deliver a range of optically pure  $\alpha$ -aminoesters with high efficiency (45%-97% yield) and good enantioselectivity (67%-85% *ee*) through a dynamic kinetic resolution



process. Moreover, the authors declared that the key to the success of the method lay in the formation of sulfoxonium ylide by the additive DMSO capturing the free carbene intermediate.

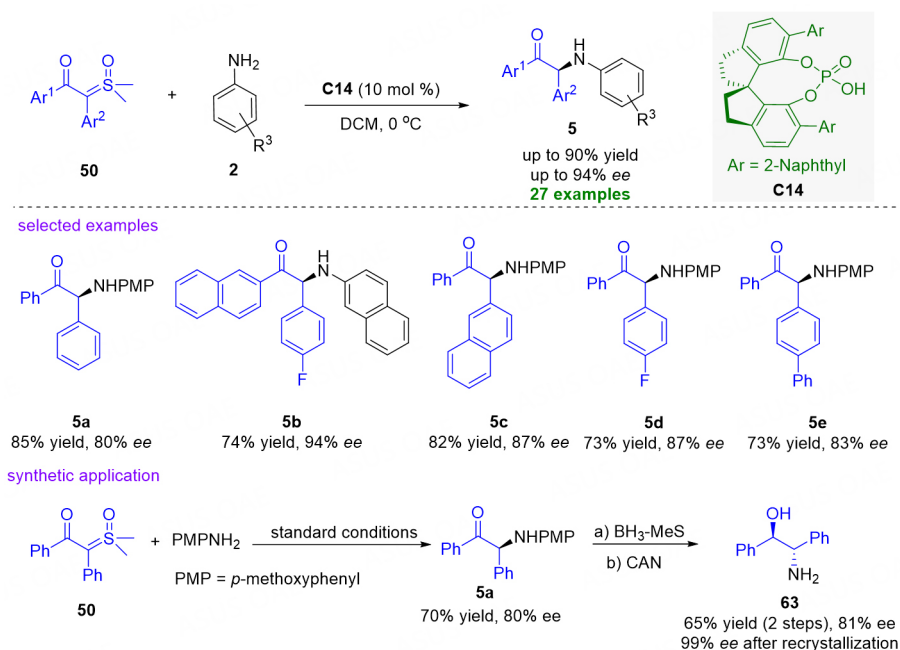
Almost immediately, the same group also discovered an efficient organocatalytic formal N-H insertion reaction of  $\alpha$ -keto sulfoxonium ylides **50** bearing two aryl groups and arylamines **2** using chiral phosphoric acid **C14** as catalyst [Figure 17]<sup>[77]</sup>. With the developed protocol, a broad range of  $\alpha$ -tertiary aminoketones **5** could be smoothly obtained in good to excellent yields (up to 90%) and *ee* values (up to 94%). Their mechanistic study supported that the C-N bond formation *via* dynamic kinetic resolution is not only the rate-determining step but also the enantio-determining step. In addition, the synthetic utility of the method was also demonstrated by the preparation of 2-amino-1,2-diphenylethanol **63** in 65% yield with 81% *ee* through a two-step transformation from **5a**. More delightfully, enantiopure **63** could be readily obtained by single recrystallization in 60% yield.

Very recently, Guo *et al.* discovered an organocatalytic asymmetric azidation of  $\alpha$ -carbonyl sulfoxonium ylides through a H-N<sub>3</sub> insertion process [Figure 18]<sup>[78]</sup>. In the developed method, with the *in situ* formed H N<sub>3</sub> as nitrogen source and a superb chiral squaramide **C15** as the catalyst, a series of  $\alpha$ -carbonyl sulfoxonium ylides **50** could be smoothly converted into optically active  $\alpha$ -azido ketones **65** in 46%-96% yield with 67%-96% *ee*. In the proposed mechanism, the catalyst **C15** with the double N-H motifs activates sulfoxonium ylides **50**, giving intermediate **66**. And then, the *in situ* generated HN<sub>3</sub> promotes the protonation of intermediate **66** to form ion pair intermediate **67** as diastereomeric mixture, in which the azide anion also interacts with the squaramide catalyst through hydrogen bond. Notably, the reversible protonation process in the **66** to **67** step allows (*R*)-**67** and (*S*)-**67** to rapidly equilibrate with each other, resulting in the epimerization of the stereogenic center. Finally, the enantioenriched (*S*)-**65** could be preferentially generated by the azide substitution *via* dynamic kinetic resolution process under the stereoselective control of chiral squaramide catalyst **C15**.

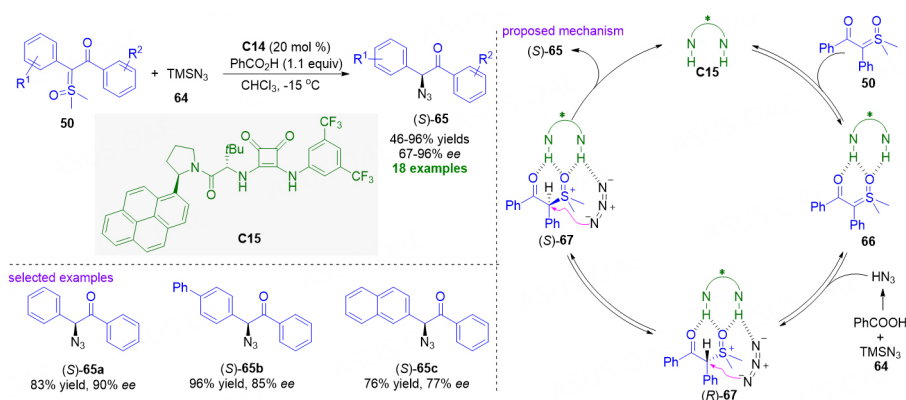
After the catalytic asymmetric S-H, N-H insertion reaction of sulfoxonium ylides, Leveille *et al.* recently reported the first organocatalytic enantioselective C-H insertion reaction of sulfoxonium ylides to indoles with chiral phosphoric acid as the catalyst **2021** [Figure 19]<sup>[79]</sup>. The authors investigated 29 examples using  $\alpha$ -carbonyl sulfoxonium ylides insertion into C-H bond of free indoles, obtaining moderate yields (ranging from 12% to 50%) with 20%-93% *ee* values. A proposed pathway for the C-H insertion reaction was also introduced. Initially, chiral phosphoric acid **C16** protonates the  $\alpha$ -carbonyl sulfoxonium ylides **50** to form an ion pair intermediate **70**. And then, the indole partners attack the intermediate **70** *via* a substitution reaction under the enantioselective induction of chiral phosphoric acid catalyst to give rise to the chiral product **69**, simultaneously reprotonation of catalyst ion to release **C15** into the next cycle. Notably, the N-H moiety of indole **68** is crucial to enantioselectivity in this transformation. The reaction involving *N*-Me indole proceeded smoothly to furnish product **69d** in 35% yield, but essentially no enantiomeric excess was observed.

### Asymmetric cyclization reaction of sulfoxonium ylides

Similarly to sulfonium ylides, in addition to the participation in the above-mentioned catalytic asymmetric X-H (X = S, N, C) bond insertion reactions, sulfoxonium ylides can also be employed as nucleophilic 1C synthons for the cyclization reaction to access cyclic compounds. However, the asymmetric cyclization reaction involving sulfoxonium ylides by means of an organocatalysis tactic is rarely studied. Until recently, Bernardi, Fochi, and coworkers reported the first organocatalytic tandem cyclopropanation/hemiaminalization reaction between 2'-hydroxycinnamaldehydes **72** and stabilized  $\alpha$ -carbonyl sulfoxonium ylides **50** by using Jørgensen-Hayashi catalyst **C17**, providing cyclopropane-fused chromane derivatives **74**



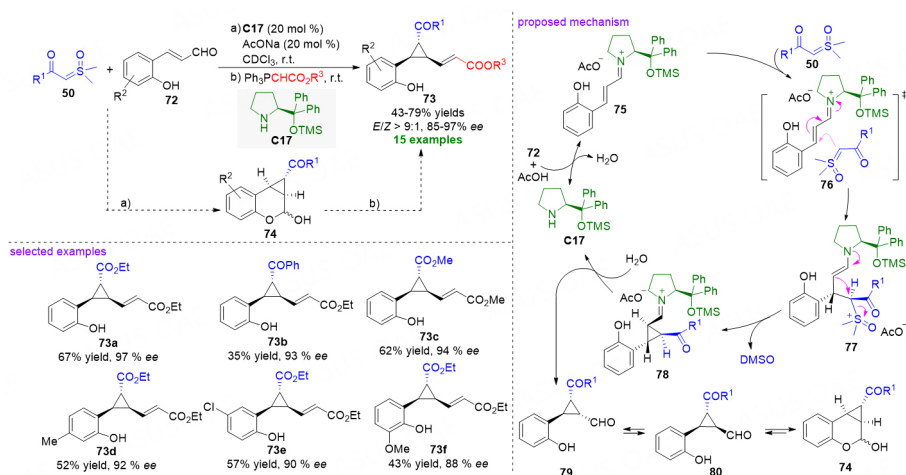
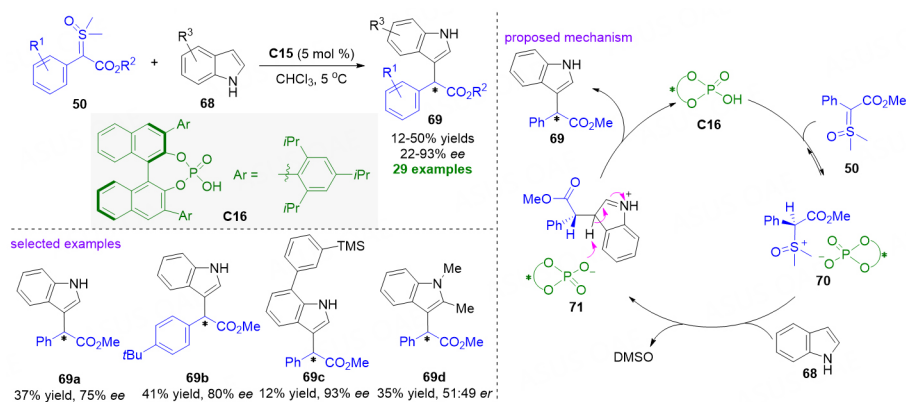
**Figure 17.** Organocatalytic formal N-H insertion reaction of arylamines with  $\alpha$ -keto sulfoxonium ylides bearing two aryl groups. This figure is used with permission from the Royal Society of Chemistry<sup>[77]</sup>.



**Figure 18.** Chiral squaramide-catalyzed enantioselective H-N<sub>3</sub> insertion of  $\alpha$ -carbonyl sulfoxonium ylides. This figure is used with permission from the Royal Society of Chemistry<sup>[78]</sup>.

in moderate-to-good yields with very good stereocontrol. Moreover, after a Wittig olefination to the chromanol moiety of **70**, the tricyclic ring-fused compounds **74** could be further transformed into a series of cyclopropanation products **73** [Figure 20]<sup>[80]</sup>.

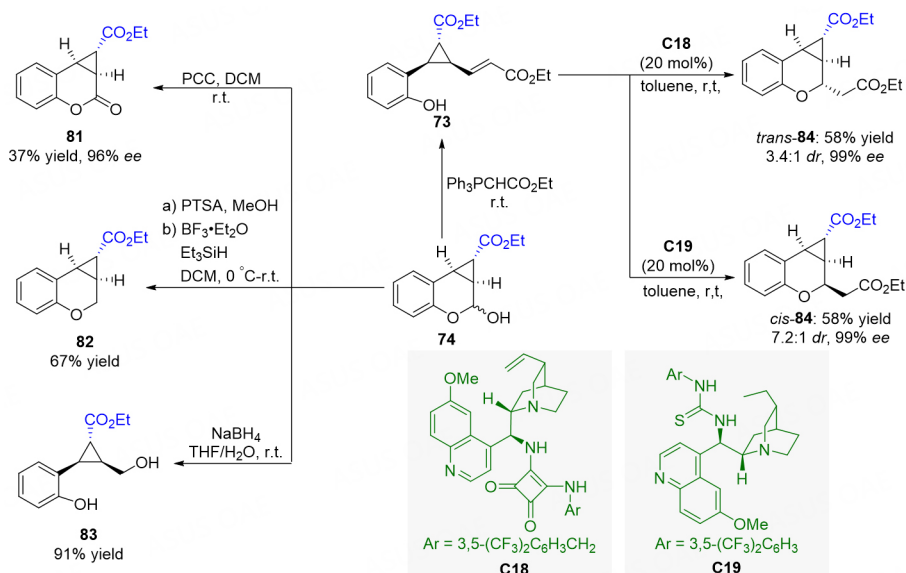
In the proposed reaction pathway [Figure 20], acid mediated condensation of 2'-hydroxycinnamaldehydes **72** and chiral catalyst **C17** forms reactive iminium ion intermediate **75**, which is attacked by the sulfoxonium ylides **50** via transition state **76** to furnish intermediate **77**. And then, an intramolecular nucleophilic substitution reaction of **77** leads to the formation of iminium ion **78**, which would undergo hydrolysis to release the catalyst **C17** and to deliver 2,3-*trans* cyclopropane **79**. Subsequent epimerization of the  $\alpha$ -position of the aldehyde function would give rise to the generation of 2,3-*cis*-isomers **80**, which undergo hemiacetalization to give cyclopropane-fused chromane products **74**.



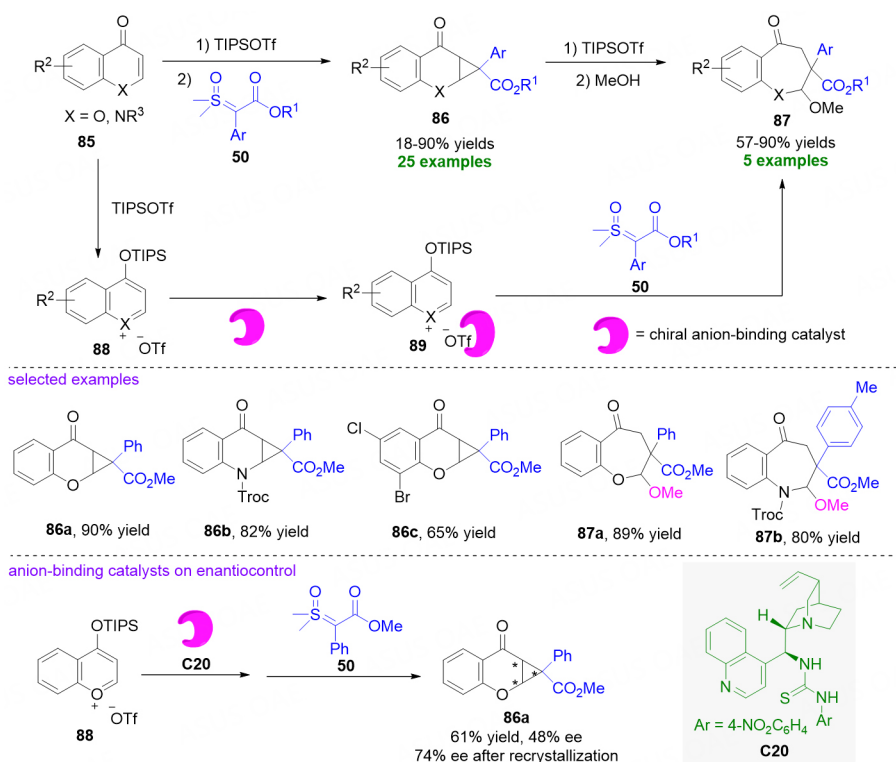
**Figure 20.** Organocatalytic asymmetric tandem cyclopropanation/hemiaminalization reaction of 2'-hydroxycinnamaldehydes and stabilized  $\alpha$ -carbonyl sulfoxonium ylides. This figure is used with permission from the American Chemical Society<sup>[80]</sup>.

In addition, the synthetic applications of the protocol were also demonstrated by the versatile derivatizations of the cyclopropane-fused chromane **74** and the cyclopropanation product **73**. As shown in [Figure 21](#), the hemiacetal functionality of **74** can be leveraged as a synthetic handle enabling access to some other compounds. A treatment of **74** with PCC gives rise to the oxidation of the hemiacetal group to form compound **81** in moderate yield. **4** could be smoothly reduced to **82** in 67% yield by using triethylsilane in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$ , and could also be converted to **83** in 91% yield with  $\text{NaBH}_4$ . Moreover, cyclopropanation product **73** could undergo intramolecular asymmetric oxa-Michael reaction. With *Cinchona* alkaloid-derived bifunctional catalysts **C18** and **C19** for the Michael addition, the tricyclic ring-fused products *trans*-**84** and *cis*-**84** could be obtained in moderate yield with high diastereoselectivity and excellent enantioselectivity, respectively.

In 2022, Leveille *et al.* discovered that the benzopyrylium triflates **88** *in situ* generated from chromenones/quinolones **85** and triisopropylsilyl triflate (TIPSOTf) could react with sulfoxonium ylides **50** *via* a cyclopropylation process to access a range of cyclopropanated products **86** in 18%-90% yield<sup>[81]</sup>. Furthermore, the authors also converted several products **86** into benzo[*b*]oxepines **87** with 57%-90% yield *via* acid-mediated ring-expansion in the presence of a nucleophile [[Figure 22](#)]<sup>[81]</sup>. In addition, the authors



**Figure 21.** Various derivatizations of cyclopropane-fused chromane **70** and the cyclopropanation product **69**. This figure is used with permission from the American Chemical Society<sup>[80]</sup>.



**Figure 22.** Dearomatization of in situ generated benzopyrylium triflates with sulfoxonium ylides. This figure is used with permission from the Royal Society of Chemistry<sup>[81]</sup>.

also conceived that the possibility of controlling the enantioselectivity of the cyclopropanation would be offered by a suitable chiral anion-binding catalyst through the non-covalent interaction with benzopyrylium triflates **88** for the formation of intermediate **89**. Therefore, with a cinchonidine-derived thiourea **C20** as the



catalyst, the reaction of benzopyrylium triflate **88** and sulfoxonium ylide **50** gave rise to product **86a** in 61% yield with 48% *ee*, which could be improved to 74% *ee* after simple recrystallization.

## CONCLUSION AND OUTLOOK

Sulfur-based ylides have been identified and confirmed as versatile reactants for a wide range of chemical transformations. In this review, organocatalyzed asymmetric reactions involving sulfonium and sulfoxonium ylides are summarized and reviewed. Due to the eminent characteristics of stabilized sulfonium and sulfoxonium ylides, such as thermal stability, easy preparation, storage, and use, and low toxicity, these compounds have drawn great attention from many research groups and are widely used in various catalytic asymmetric reactions over the past twenty years with the rapid development of organocatalysis. As to the research on sulfonium ylides, the organocatalyzed enantioselective transformations mainly focus on the cyclopropanation and [4 + 1] cyclization reaction, and only one report concerning the N-H bond insertion reaction has been published so far. However, with respect to the sulfoxonium ylides, synthetic chemists put relatively more research emphasis on the catalytic asymmetric X-H (X = S, N, C) bond insertion reaction for the C-C and C-X (X = N, S) bond construction, and only one example about asymmetric cyclization reaction has been reported with organocatalysis at present.

Although a number of reports are available on the application of sulfonium and sulfoxonium ylides in various asymmetric reactions, there is still a vast space for research on the fast-developing asymmetric organocatalysis. First of all, since the stabilized sulfur ylides are still limited, more and more newly stabilized sulfonium or sulfoxonium ylides with more fascinating skeletons should be explored. Second, searching for a new catalytic system for the application of unstabilized sulfur ylides in the possible asymmetric reaction should also be investigated. Third, expanding the scopes and sources of reaction partners with sulfur ylides to develop novel asymmetric reactions for the construction of pharmaceutically valuable molecules with innovative structures is very necessary. Finally, applying the developed asymmetric organocatalysis methodology involving sulfonium or sulfoxonium ylides for the efficient synthesis of natural products or pharmaceutical molecules is also worth pursuing. The main purpose of this review is to disclose the current situation of organocatalyzed asymmetric reaction of sulfonium and sulfoxonium ylides, but we would rather it will provoke further exciting, groundbreaking discoveries soon. In a word, the authors hope this review in this phase benefits the development of sulfur ylides research area. Moreover, the authors would like to apologize in advance for any omissions in the literature survey.

## DECLARATIONS

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### Authors' contributions

Wrote the draft manuscript: Wang ZH

Revised the manuscript: Sun TJ, Zhang YP, You Y, Zhao JQ, Yin JQ

Guided this work, revised and rewrote some parts of the manuscript: Yuan WC

### Availability of data and materials

Not applicable.

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### Conflicts of interest

All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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