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# Metal catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides: structural diversity at the dipole partner

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The 1,3-dipolar cycloaddition of azomethine ylides represents a versatile approach for synthesizing pyrrolidines, valuable structural motifs in synthetic and medicinal chemistry. However, most studies to date have relied predominantly on  $\alpha$ -iminoesters as ylide precursors, thereby limiting the broader synthetic applications of this strategy. This feature article highlights alternative azomethine ylide precursors, beyond conventional  $\alpha$ -iminoesters, which have facilitated the preparation of pyrrolidines with new substitution patterns.

## 1 Introduction

Cycloaddition reactions are fundamental in organic chemistry, providing a primary method for the preparation of complex cyclic molecules with multiple stereocenters.<sup>1</sup> In particular, 1,3-dipolar cycloadditions offer efficient stereocontrolled approaches for synthesizing different heterocyclic compounds.<sup>2</sup> For instance, the use of azomethine ylides as dipole partners enables the effective synthesis of chiral polysubstituted pyrrolidines.<sup>3</sup> Pyrrolidine is a privileged heterocycle in organic and medicinal chemistry, as many of its derivatives exhibit a wide range of bioactivities, including antibiotic, antibacterial, anticancer, and antihypertensive properties. Consequently, pyrrolidine derivatives provide an excellent opportunity for the potential discovery of new pharmaceutical agents.<sup>4</sup> In addition, chiral pyrrolidines can be used as optimal scaffolds for ligand design in both transition metal-mediated and organocatalytic processes.<sup>5</sup>

In recent decades, metal-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides has emerged as one of the most widely employed methodologies for the enantioselective synthesis of pyrrolidines.<sup>6</sup> A common procedure involves the *in situ* generation of the azomethine ylide from the corresponding  $\alpha$ -iminoester in combination with a transition metal salt and a base. The high efficacy of this approach arises from the N,O-coordination of the  $\alpha$ -iminoester to the metal forming a five-membered chelate ring. This coordination significantly enhances the acidity of the proton at the  $\alpha$  position of the ester

group and also fixes the W-conformation of the 1,3-dipole, which determines the usual 2,5-*cis* configuration of the final pyrrolidine. Furthermore, if a chiral ligand is used, the formation of a rigid five-membered chelate ring facilitates asymmetric induction, allowing for the preparation of enantioenriched pyrrolidines (Scheme 1).

The first example of this kind of process was reported by Grigg and co-workers<sup>7</sup> in 1991, using stoichiometric amounts of a cobalt salt and a chiral ligand derived from ephedrine, and the reaction proceeded with high yield and enantioselectivity. Inspired by this work, the first catalytic examples of this cycloaddition were reported by the groups of Zhang<sup>8</sup> and Jorgensen<sup>9</sup> in 2002, employing Zn- and Ag-based catalytic systems, respectively.

Since these early papers, the effort of many research groups has been focussed on the development of new catalyst systems. As a result, many Lewis acids have been described based on the combination of different metals (such as Ag,<sup>10</sup> Cu,<sup>11</sup> Zn,<sup>12</sup> Ni,<sup>13</sup> Au<sup>14</sup> and Ca<sup>15</sup>) and a wide variety of ligands with central, axial or planar chirality (Fig. 1). In addition, efficient organocatalysts have also been developed.<sup>16</sup>

The use of these catalyst systems has facilitated the preparation of proline derivatives with high reactivity and impressive levels of diastereo- and enantioselectivity. Two diastereomers can form depending on the *endo* or *exo* approach of the



**Scheme 1**  $\alpha$ -Iminoesters as dipole precursors in catalytic asymmetric 1,3-dipolar cycloaddition reactions.

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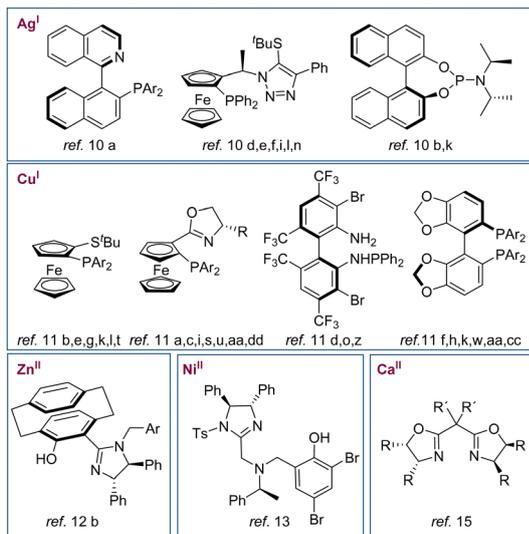


Fig. 1 Selected examples of efficient catalytic systems.

1,3-dipole to the dipolarophile. Similar to the Diels–Alder reaction, the *endo* approach is typically favored by secondary orbital interactions. However, these stabilizing interactions are generally much weaker in 1,3-dipolar cycloadditions, making diastereoselectivity challenging to predict in most cases. As a general trend, silver-catalyzed 1,3-dipolar cycloadditions tend to exhibit greater *endo* selectivity compared to copper-catalyzed reactions.

Azomethine ylides generated from iminoesters, due to their electron-rich nature, preferentially react with electron-deficient dipolarophiles. The excellent regioselectivity observed in these reactions is attributed to the dominant FMO interaction between the HOMO of the dipole and the LUMO of the dipolarophile.<sup>17</sup> Recently, the structural scope of this asymmetric cycloaddition has been expanded through the incorporation of novel types of dipolarophiles, beyond the standard acrylates and related  $\alpha,\beta$ -unsaturated esters.<sup>6</sup> In contrast, the structural scope of the cycloaddition has been more limited with regard to the azomethine ylide precursor since most of the reported examples used  $\alpha$ -iminoesters of non-enolizable aldehydes (mainly aryliminoesters) as ylide precursors. Accordingly, the variety of pyrrolidines that can be obtained using this strategy is limited to derivatives that have an ester group at C-2 and usually an aryl substitution at C-5 (Scheme 2).<sup>18</sup>

This structural pattern is not present in most of the pyrrolidine scaffolds contained in natural or biologically active products. Therefore, to enhance the synthetic applicability of the process, it is crucial to broaden the scope of the cycloaddition to include the use of other types of dipole precursors.



Scheme 2 Structural pattern of pyrrolidines formed through 1,3-dipolar cycloadditions using  $\alpha$ -iminoesters as azomethine ylide precursors.

Our research group has been deeply involved in the study of azomethine ylide dipolar cycloadditions since 2005, focusing on developing new reaction partners. This Feature Article reviews literature examples that explored the use of azomethine ylide precursors beyond the classic  $\alpha$ -iminoesters. Emphasis is placed on methodologies developed by our research group. Additionally, selected works by other groups, chosen for their relevance, will also be discussed.

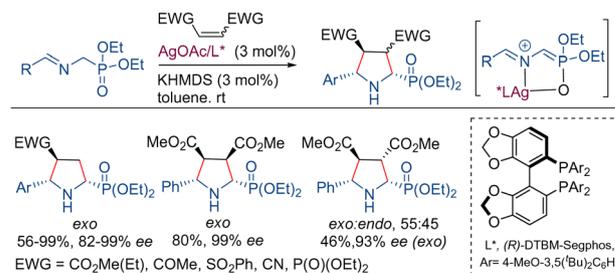
## 2. Azomethine ylide precursors beyond $\alpha$ -iminoesters

### 2.1. $\alpha$ -Iminophosphonates

$\alpha$ -Aminophosphonic acids and their phosphonate esters are regarded as bioisosteres of  $\alpha$ -amino acids and represent a significant class of compounds with diverse applications in medicinal chemistry.<sup>19</sup> The use of Schiff bases of  $\alpha$ -aminophosphonates as azomethine ylide precursors in 1,3-dipolar cycloadditions for the preparation of proline phosphonate derivatives has been hampered probably due to the lower acidity of their  $\alpha$ -protons.<sup>20</sup> In 2010, Kobayashi and co-workers described the first example of the use of iminophosphonates in catalytic asymmetric 1,3-dipolar cycloadditions. This process is based on the use of a chiral silver amide complex, prepared from AgOTf, KHMDS, and the ligand DTBM-Segphos.<sup>21</sup> Under these conditions, the reaction proceeds with excellent yields and high levels of *exo*-diastereo- and enantioselectivities for a wide variety of dipolarophiles ( $\alpha,\beta$ -unsaturated alkenes such as esters, amides, ketones, sulfones, and phosphonates, Scheme 3).

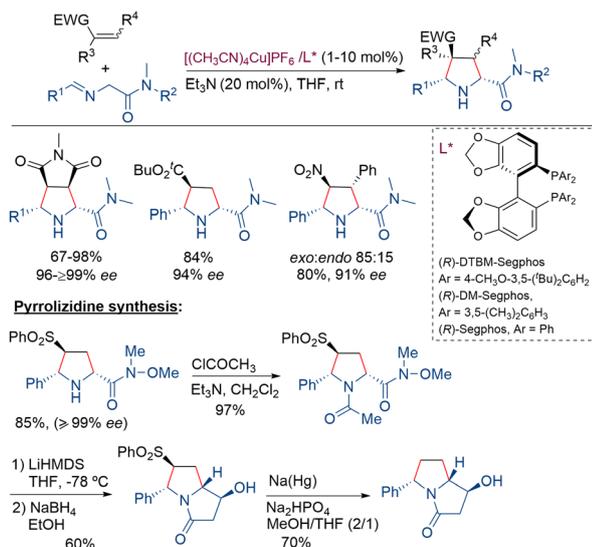
### 2.2. $\alpha$ -Iminoamides

Despite their inherent interest, there are few examples in the literature where  $\alpha$ -iminoamides have been used as azomethine ylide precursors.<sup>22</sup> In 2012, our research group reported the first methodology enabling the use of  $\alpha$ -iminoamides in the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides.<sup>23</sup> The catalytic systems formed by Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub> as a metal and several ligands from the Segphos family showed outstanding efficiency, giving rise to the corresponding 2-amidopyrrolidines with high yields and excellent levels of diastereo- and enantioselectivities (Scheme 4). The methodology exhibited an unusual broad structural scope, being compatible with  $\alpha$ -iminoamides of different electronic nature, as well



Scheme 3 Catalytic asymmetric 1,3-dipolar cycloaddition with  $\alpha$ -iminophosphonates.



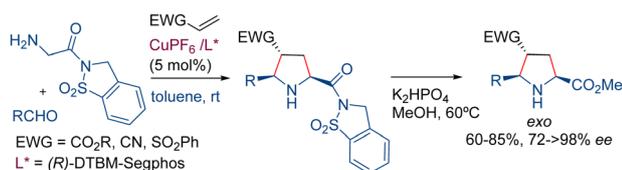


**Scheme 4** Cu-catalyzed asymmetric (3+2) cycloaddition of  $\alpha$ -iminoamides.

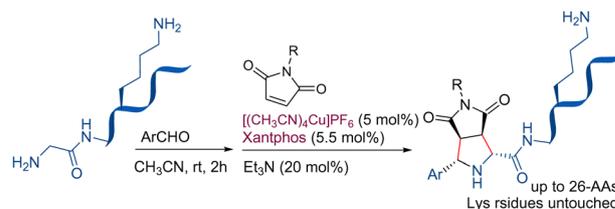
as with both deactivated (fumarates and maleates) and monoactivated (such as acrylates, vinylsulfones, nitrostyrenes, and chalcones) dipolarophiles. Remarkably, most of the reactions take place using only 1 mol% of catalyst loading. The synthetic utility of the method was demonstrated through the synthesis of enantioenriched pyrrolidines. The 1,3-dipolar cycloaddition between Weinreb derived iminoamide and phenyl vinyl sulfone afforded the corresponding pyrrolidine with high yield and excellent enantiomeric excess. Subsequent acylation, cyclization, and desulfonation steps yielded the target pyrrolizidine (39% overall yield, Scheme 4).

More recently, Garner and co-workers published a procedure based on the use of glycol sultams as precursors of azomethine ylides.<sup>24</sup> In this multicomponent reaction, the sultam group activates the  $\alpha$  position of the Schiff base, making feasible the generation of azomethine ylides *in situ* from the corresponding aldehydes (Scheme 5). Using a  $[(\text{CH}_3\text{CN})_4\text{Cu}]\text{PF}_6/\text{DTBM-Segphos}$  complex as a catalytic system, in the absence of an external base, pyrrolidines are obtained with high yields and enantioselectivities. Interestingly, this method is compatible with the use of labile enolizable aldehydes (such as acetaldehyde and propionaldehyde).

These studies have paved the way for using (3+2) cycloadditions of azomethine ylides in late-stage peptide modification, a crucial advancement for developing new applications of this important class of molecules. In 2024, Kanemoto and co-workers<sup>25</sup> developed a diastereoselective methodology for the



**Scheme 5** Catalytic asymmetric cycloaddition using glycol sultams as azomethine ylide precursors.

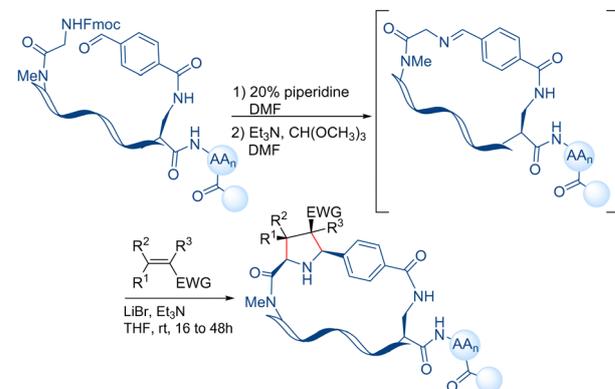


**Scheme 6** Modification of peptides *via* 1,3-dipolar cycloaddition.

N-terminal-specific modification of peptides *via* 1,3-dipolar cycloaddition between glycine amide derived azomethine ylides and maleimides. The cycloaddition under copper catalysis afforded the *exo* adduct with excellent yield and diastereoselectivity. Oligopeptides containing up to 26 amino acids, including several lysine moieties, are suitable substrates affording exclusively the N-termini adducts (Scheme 6).

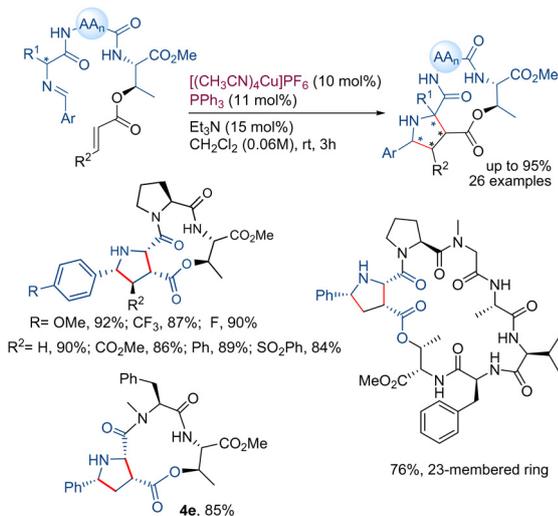
Cyclic peptides are highly valuable molecules due to their unique biological properties. Guéret Waldmann and co-workers<sup>26</sup> described the incorporation of pyrrolidines as structural elements that define and constrain the conformation of macrocyclic hot loop-derived peptides. The cyclic peptides were synthesized on a solid support through macrocyclization *via* imine formation. The subsequent 1,3-dipolar cycloaddition in the presence of lithium bromide and Et<sub>3</sub>N efficiently afforded the corresponding adducts. The configuration of the pyrrolidine fragment determines the conformation of the peptide residue responsible for binding with the target protein (Scheme 7).

Recently, our research group has developed an efficient strategy for synthesizing unnatural cyclic peptides through Cu-catalyzed 1,3-dipolar cycloaddition of azomethylene ylides.<sup>27</sup> This method enables the incorporation of pyrrolidine units with up to four new stereocenters into the cyclic peptide structure. Exceptional stereocontrol over the newly formed stereogenic centers within the pyrrolidine ring was achieved taking advantage of the stereocenters already present in the peptide chain. This cycloaddition approach is compatible with a broad range of natural amino acids in the peptide chain, accessing various macrocyclic ring sizes, and being compatible with different dipolarophiles (Scheme 8). Mechanistic studies suggest that copper coordination



**Scheme 7** Incorporation of pyrrolidines to cyclic peptides *via* 1,3-dipolar cycloaddition.





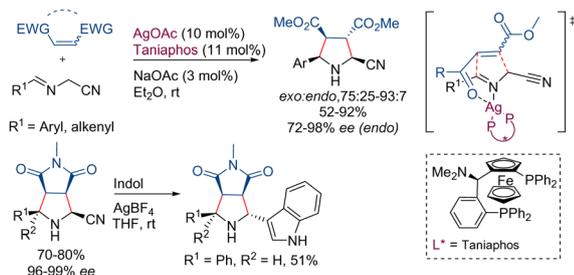
**Scheme 8** Synthesis of cyclic peptides through Cu-catalyzed 1,3-dipolar cycloaddition.

with both the dipole and dipolarophile is essential for establishing the preorganization necessary for the 1,3-dipolar reaction to proceed efficiently.

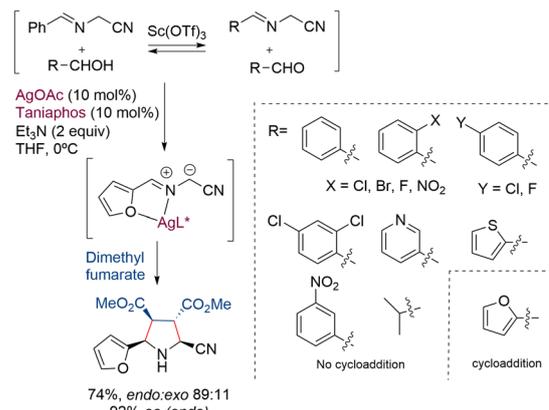
### 2.3. $\alpha$ -Iminonitriles

Considering that  $\alpha$ -iminoacetone nitriles have an  $\alpha$ -hydrogen with an acidity comparable to that of  $\alpha$ -iminoesters, they are expected to readily form azomethine ylides stabilized by the cyano group. The 1,3-dipolar cycloaddition of these ylides leads to 2-cyanopyrrolidines, structural motifs known for their significant biological activity. Additionally, 2-cyanopyrrolidines may serve as valuable synthetic intermediates, as the cyano group could act as a leaving group in further transformations, facilitating the synthesis of a diverse range of C-2 substituted pyrrolidines. Despite this potential, before 2010, only a few non-asymmetric examples of the use of  $\alpha$ -imino nitriles in 1,3-dipolar cycloaddition reactions had been reported.<sup>28</sup>

In 2010, our research group described a protocol for the catalytic asymmetric cycloaddition between  $\alpha$ -imino nitriles and activated alkenes.<sup>29</sup> In the presence of an AgOAc/Taniaphos complex, the reaction with methyl fumarate and *N*-methylmaleimide afforded the corresponding 2-cyanopyrrolidines with good *endo* diastereoselectivities and enantioselectivities (Scheme 9). X-ray diffraction studies and DFT theoretical calculations suggest that coordination



**Scheme 9** (3+2) Cycloaddition of  $\alpha$ -imino nitriles.



**Scheme 10** Dynamic systemic resolution of  $\alpha$ -imino nitriles via catalytic asymmetric 1,3-dipolar cycloaddition.

between the metal complex and the  $\alpha$ -imino nitrile occurs solely through the imine nitrogen, resulting in a 1,3-metalodipole with *syn* configuration. The approach of the dipolarophile takes place through the less hindered face, which explains the good diastereo- and enantioselectivity of the process. This methodology enabled the synthesis of pyrrolidines diversely substituted at the C-2 position by nucleophilic substitution of the cyano group.

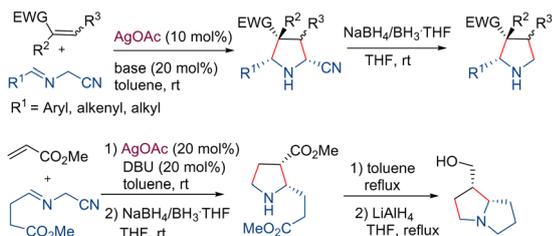
Using the same catalytic system, Ramström and co-workers<sup>30</sup> developed a dynamic systemic resolution protocol of  $\alpha$ -imino nitriles using a transamination/catalytic asymmetric 1,3-dipolar cycloaddition sequence, in which the silver complex worked as both a catalyst and an external selector. The dynamic imine system was generated from the  $\alpha$ -iminophenylacetone nitrile mixed with 12 different aldehydes in the presence of Sc(OtF)<sub>3</sub>. This system was subsequently subjected to 1,3-dipolar cycloaddition conditions (AgOAc/Taniaphos complex, Et<sub>3</sub>N, in CH<sub>2</sub>Cl<sub>2</sub>) affording exclusively the 5-furyl-pyrrolidine products with good yield and diastereo- and enantioselectivity (Scheme 10). The formation of a bidentate metallacycle enhances the interaction with the catalyst and favours the dipolar cycloaddition. The authors argue that the less effective overlap between silver and sulfur accounts for the lower reactivity of the thiophenyl derivative.

Later, Zhang and coworkers developed a new strategy for the preparation of racemic 5-unsubstituted pyrrolidines using a silver-catalyzed diastereoselective 1,3-dipolar cycloaddition of  $\alpha$ -imino nitriles and a subsequent NaBH<sub>4</sub>-induced reductive decyanation reaction.<sup>31</sup> The methodology was applied to the total synthesis of the pyrrolidine natural product isoretronecanol (Scheme 11).

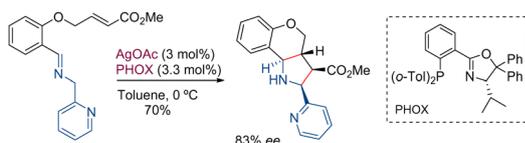
### 2.4. $\alpha$ -N-(Heteroaryl-methyl)imine derivatives

The first work in which imines with heteroaryl groups, instead of an ester group at position C-2, were used as precursors of azomethine ylides was reported by Grigg in 1983.<sup>32</sup> Specifically, this involved the reaction between  $\alpha$ -imino heterocycles and *N*-phenylmaleimide carried out in the absence of a catalyst at elevated temperatures which gave rise to racemic pyrrolidines with yields ranging from 60% to 82%, although the diastereoselectivity





**Scheme 11** Diastereoselective synthesis of 5-unsubstituted pyrrolidines by 1,3-dipolar cycloaddition of  $\alpha$ -iminonitriles.



**Scheme 12** Intramolecular cycloaddition using *N*-(2-pyridylmethyl)imines.

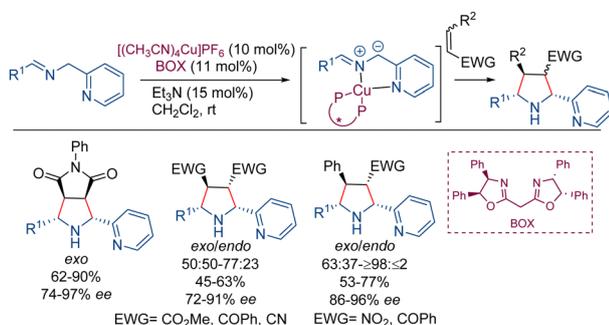
was low. Seven years later, the same research group described the intramolecular version of this reaction.<sup>33</sup>

In 2005, Pfaltz and co-workers<sup>34</sup> described a catalytic asymmetric version of the intramolecular process. When AgOAc and the PHOX ligand were used as the catalytic system, the final tricyclic system was obtained with a good yield and an enantiomeric excess of 83% (Scheme 12).

In 2010, our research group studied the intermolecular cycloaddition reaction between  $\alpha$ -iminopyridines and activated olefins.<sup>35</sup> The coordination of the metal to both the imine and pyridine nitrogens facilitated the formation of a highly reactive metallodipole, which was crucial to achieve good stereochemical discrimination in the cycloaddition with the dipolarophile. Using Cu<sup>I</sup>/BOX as the catalytic system, the reaction with *N*-phenylmaleimide exhibited almost complete *exo*-selectivity and excellent enantioselectivity (Scheme 13). Although the reaction with dipolarophiles with a *trans* configuration was less diastereoselective, it still maintained high enantioselectivity (72–96% ee).

## 2.5. $\alpha$ -Silylimines

$\alpha$ -Silylimines represent a different and less commonly used type of azomethine ylide precursor, leading to 5-unsubstituted



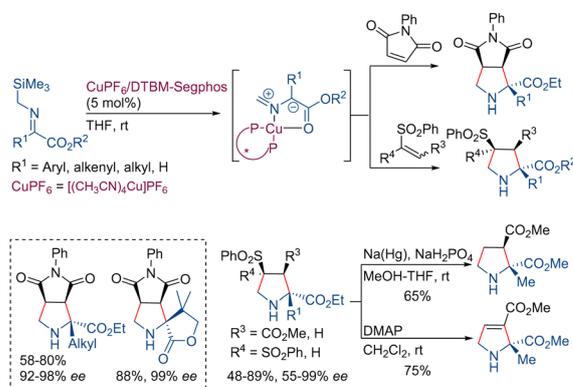
**Scheme 13** Intermolecular (3+2) cycloaddition between *N*-(2-pyridylmethyl)imines and different dipolarophiles.

pyrrolidines, a substitution pattern that cannot be directly achieved through the typical process involving Schiff bases of amino acid esters.<sup>36</sup> Despite the synthetic interest in these dipoles, the asymmetric catalytic version of this reaction has been barely studied.

In 2012, our research group developed the first catalytic asymmetric cycloaddition using  $\alpha$ -silyliminoesters as azomethine ylide precursors.<sup>37</sup> The use of the Cu<sup>I</sup>/(*R*)-DTBM-Segphos complex as a catalytic system enabled the formation of a wide variety of enantioenriched pyrrolidines with a quaternary centre at position C-2. Employing maleimide as a dipolarophile the corresponding adducts were obtained with good yields and enantioselectivities (81–98% ee). Interestingly, the reaction worked well from alkyl substituted  $\alpha$ -silylimines. Excellent results were also obtained using sulfonated dipolarophiles, which after desulfonation facilitated the preparation of proline derivatives with a quaternary centre. The presence of a coordinating group (carboxylate) in the silylimine, which allows the formation of a five-membered metallodipole, is essential for the reaction to occur with good selectivity (Scheme 14).

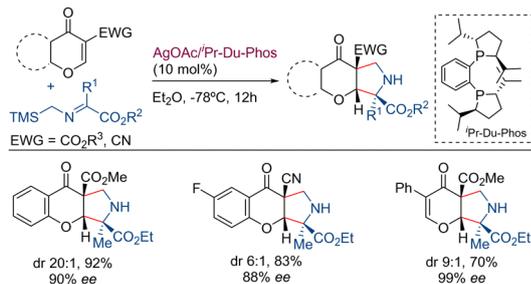
In 2016, Kumar and co-workers<sup>38</sup> explored the application of this methodology for the preparation of complex quaternary-carbon rich scaffolds. To this end, they chose pyrones and benzopyrones with trisubstituted olefin moieties as dipolarophiles. The use of AgOAc/<sup>t</sup>Pr-DuPhos as a catalyst system allowed accessing the expected bicyclic and tricyclic adducts with excellent yield and diastereo- and enantioselectivity. The resulting adducts served as starting materials for the synthesis of tetracyclic structures with three quaternary chiral centres. The authors again proposed a transition state in which the coordination of the Ag<sup>I</sup>/DuPhos complex with the oxygen of the carbonyl and the nitrogen of the azomethine ylide provided the necessary chiral environment for achieving high asymmetric inductions (Scheme 15).

Considering the good results obtained by our research group using  $\alpha$ -iminopyridines as azomethine ylide precursors,<sup>35</sup> we envisaged that a pyridylsilylimine could form the 5-membered metallodipole necessary for achieving high reactivity and asymmetric induction. The reaction in the presence



**Scheme 14** Catalytic asymmetric cycloaddition using  $\alpha$ -silyliminoesters as azomethine ylide precursors.





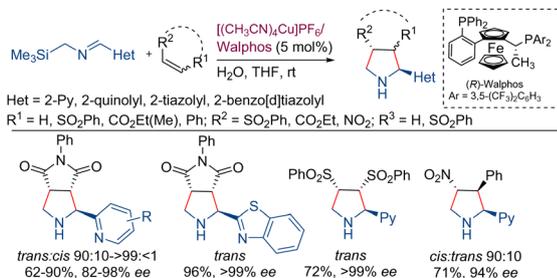
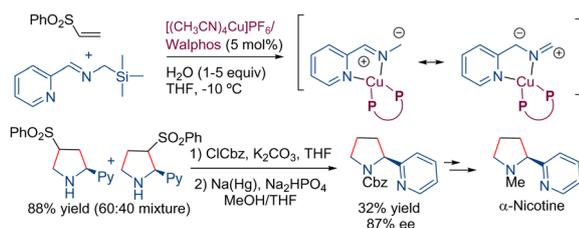
Scheme 15 Extension to the use of pyrones as dipolarophiles.

of Cu<sup>I</sup>/*(R)*-Walphos provided the expected pyrrolidines with high yields and high levels of enantioselectivity (up to ≥99% ee) and diastereoselectivity (major formation of C-2/C-4 *trans*-substituted pyrrolidines).<sup>39</sup> The use of water as an additive significantly improved the reactivity of the process, probably by accelerating the desilylation step in the formation of the metallodipole. It is worth noting that the method is compatible with different heteroaryl groups such as 2-quinoly, 2-benzothiazolyl and 2-thiazolyl (Scheme 16).

The effectiveness of this methodology was demonstrated through the formal total synthesis of  $\alpha$ -nicotine. The (3+2) cycloaddition between pyridylsilylimine and vinyl sulfone produced the corresponding adduct as a mixture of regioisomers, likely due to the participation of the two resonance structures of the dipole (Scheme 17). Subsequent protection of the nitrogen as Cbz and reductive sulfonyl elimination by treatment with Na(Hg) provided the  $\alpha$ -nicotine precursor (87% ee).

## 2.6. $\alpha$ -Fluoromethylimines

Fluorinated pyrrolidines are of significant interest in medicinal chemistry as it is well known that substituting hydrogen atoms

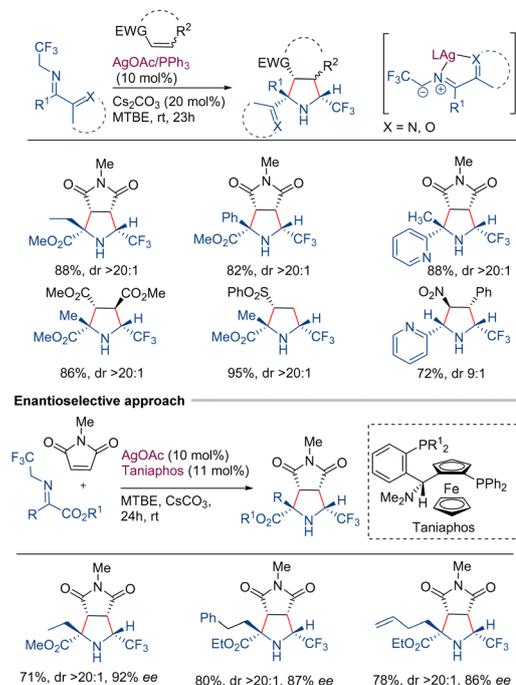
Scheme 16  $\alpha$ -Heteroarylsilylimines as dipole partners.Scheme 17 Formal total synthesis of  $\alpha$ -nicotine.

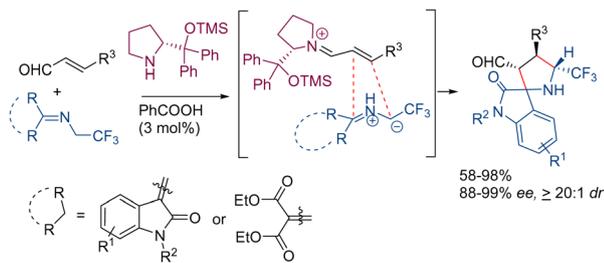
with fluorine in organic compounds can enhance their biological properties.<sup>40</sup> The catalytic asymmetric 1,3-dipolar cycloaddition between azomethine ylides and activated fluorinated alkenes has emerged as one of the most convenient methodologies for preparing enantioenriched pyrrolidines with fluorine atoms in positions 3 or 4.<sup>41</sup> However, the use of fluorinated azomethine ylide precursors in 1,3-dipolar cycloadditions has been rarely explored, and only some non-enantioselective examples have been reported.<sup>42</sup>

In 2016, our research group reported a new trifluoromethylated azomethine ylide precursor with a coordinating group (either ester or pyridine) that promotes the formation of a bidentate metallodipole, providing the required activation of the imine for the reaction to proceed.<sup>43</sup> A variety of 2-fluorinated pyrrolidines were obtained with good yields and high diastereoselectivities using simply AgOAc/PPh<sub>3</sub> as a catalyst system. The highest enantioselectivities (86–92% ee) were achieved using the AgOAc/*(R)*-taniaphos catalytic system.

NBO analysis revealed that the charge is mainly localized at the  $\alpha$ -position to the CF<sub>3</sub> group, which is consistent with the regioselectivity experimentally observed (Scheme 18).

Simultaneously with the development of this work, Wang and co-workers reported the first example of organocatalytic 1,3-dipolar cycloaddition of *N*-(2,2,2-trifluoroethyl)-ketimines (obtained by the condensation of trifluoroethylamine and isatins) with enals.<sup>44</sup> Using the Hayashi-Jorgensen catalyst and benzoic acid as the additive, the 1,3-dipolar cycloaddition gave the corresponding products bearing four contiguous stereogenic centres in excellent yields and diastereo- and enantioselectivities (Scheme 19). The chiral

Scheme 18 Catalytic asymmetric 1,3-dipolar cycloaddition of  $\alpha$ -fluorinated imines.



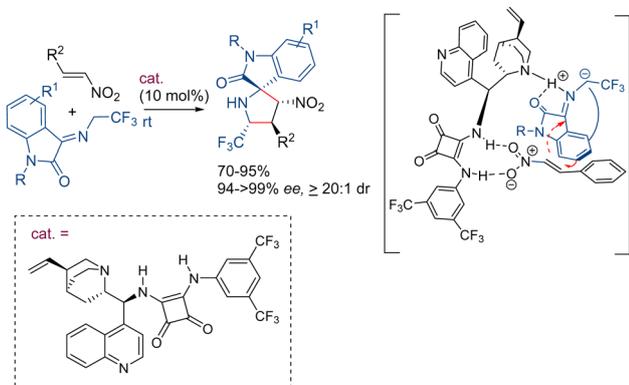
**Scheme 19** Organocatalytic 1,3-dipolar cycloaddition of *N*-(2,2,2-trifluoroethyl)-ketimines.

iminium intermediate, formed by the reaction of diphenylprolinol silyl ether with the 2-enals, induces *Si*-facial cycloaddition on the oxindole-derived azomethine ylide by shielding the *Re*-face with bulky aryl groups. Later, this methodology was extended to the use of diethyl 2-oxomalonate derived trifluoromethyl imines as azomethine ylide precursors.<sup>45</sup>

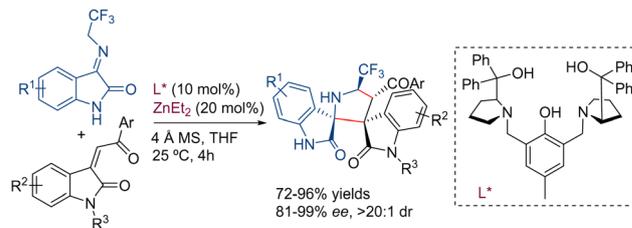
In 2015, the same research group reported the catalytic asymmetric cycloaddition of trifluoromethyl-containing azomethine ylides with  $\beta$ -nitroalkenes.<sup>46</sup> Various spiro[pyrrolidin-3,2'-oxindoles] were synthesized with excellent yields and high diastereo- and enantioselectivities using a cinchona alkaloid-derived squaramide-catalyst. The bifunctional catalyst activated both substrates, the squaramide moiety coordinates *via* the nitro styrene while the tertiary nitrogen of the cinchona coordinates *via* the azomethine ylide, then the cycloaddition by the *Re*-face would take place (Scheme 20).

Since the publication of these works, numerous examples of the use of isatin derived imines in organocatalytic cycloadditions with different dipolarophiles<sup>47</sup> such as arylfuran-2(3*H*)-ones,<sup>48</sup>  $\beta$ -trifluoromethyl electron-deficient alkenes,<sup>49</sup> aurones,<sup>50</sup> 2,3-dioxopyrrolidines,<sup>51</sup>  $\beta$ -unsaturated pyrazolones,<sup>52</sup> ethylene sulfonyl fluoride,<sup>53</sup>  $\beta$ - $\gamma$ -unsaturated  $\alpha$ -keto esters,<sup>54</sup> 2-nitrobenzothiophene,<sup>55</sup> isatylidene isoxazoles,<sup>56</sup> methyleneindolinones,<sup>57</sup> 5-alkenyl thiazolones,<sup>58</sup> and rhodamine derivatives<sup>59</sup> and benzylidenemalononitriles,<sup>60</sup> have been described.

In comparison with the organocatalytic procedures, the transition metal-catalyzed asymmetric 1,3-dipolar cycloaddition of *N*-2,2,2-trifluoroethylisatinketimines has been much less studied. Wang and co-workers have reported the use of chiral dinuclear Zn



**Scheme 20** Cycloaddition of isatin derived-trifluoroethylketimines with  $\beta$ -nitroalkenes.

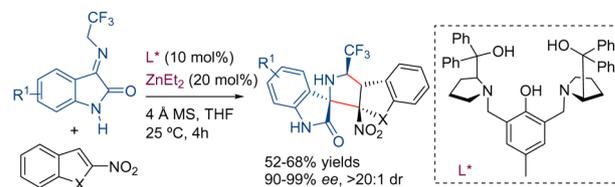


**Scheme 21** Zn-catalyzed asymmetric (3+2) cycloaddition of trifluoromethylated azomethine ylides and methyleneindolinones.

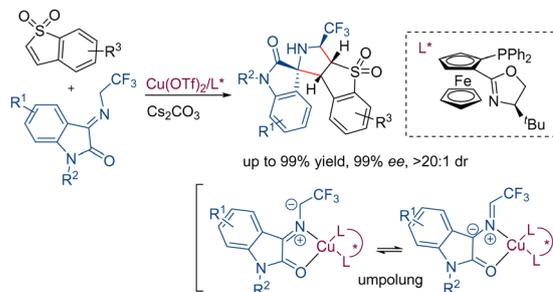
complexes as catalysts. First, they demonstrated that the cycloaddition between  $\text{CF}_3$ -containing isatin derived azomethine ylides and methyleneindolinones afforded the corresponding spirocyclic adducts with two adjacent spiro quaternary stereocenters in high yield and enantio- and *exo'*-diastereoselectivity (3,4-*trans*-configuration). This stereochemical outcome indicates that the reaction takes place by a stepwise mechanism *via* an *anti*-selective Michael/Mannich sequence (Scheme 21).<sup>61</sup> Later, they reported that under similar conditions aurones are also suitable dipolarophiles for this transformation.<sup>62</sup>

The same catalytic system was also effective in the dearomative cycloaddition of  $\text{CF}_3$ -containing *N*-unprotected isatin-derived azomethine ylides with 2-nitrobenzofurans and 2-nitrobenzothiophenes. Pyrrolidinyl-spirooxindoles containing a 2,3-fused-dihydrobenzofuran (or dihydrobenzothiophene) moiety were obtained with excellent diastereoselectivity and moderate to high enantiomeric excess (Scheme 22).<sup>63</sup>

In 2022, Yuan, Zhao, Zhang and co-workers<sup>64</sup> described the use of benzo[*b*]thiophene sulfones as dipolarophiles. Using a  $\text{Cu}(\text{OTf})_2/\text{Phosferrox}$  complex as a ligand, and  $\text{Cs}_2\text{CO}_3$  as a base, different substituted pentacyclic spirooxindoles were obtained with excellent diastereo- and enantioselectivities. The umpolung

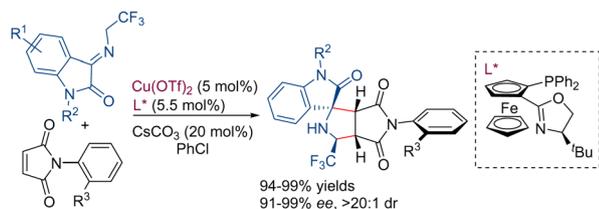


**Scheme 22** Cycloaddition of  $\text{CF}_3$ -isatin-derived azomethine ylides with 2-nitrobenzofurans.



**Scheme 23** Benzo[*b*]thiophene sulfones as dipolarophiles.





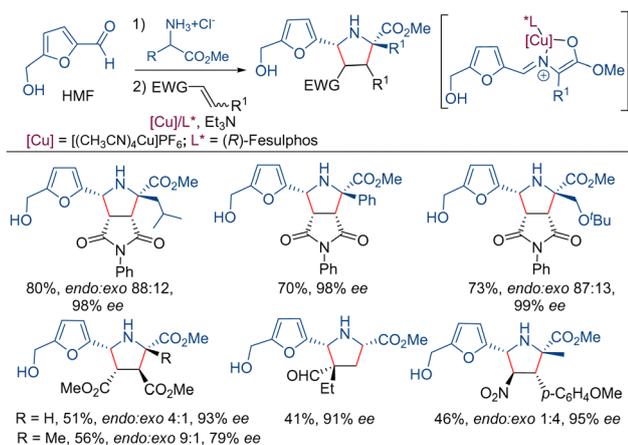
**Scheme 24** Desymmetrization of *N*-arylmaleimides by 1,3-dipolar cycloaddition with trifluoroethylstatin ketimines.

of *N*-2,2,2-trifluoroethylstatin ketimines led to an unexpected regioisomer of the spirooxindole compounds (Scheme 23).

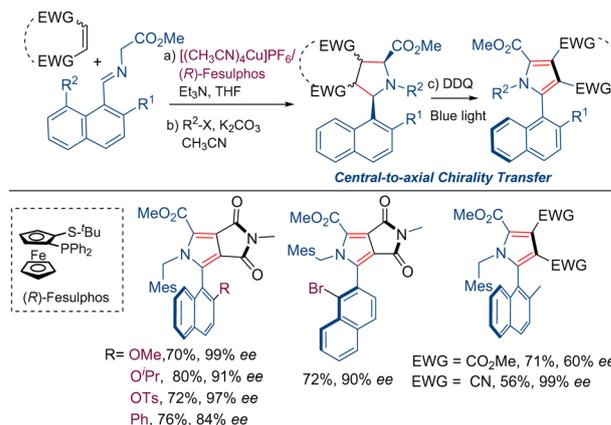
Shortly later,<sup>65</sup> the same research group described the desymmetrization of *N*-arylmaleimides by copper catalyzed 1,3-dipolar cycloaddition with trifluoroethylstatin ketimines. Using a  $\text{Cu}(\text{OTf})_2$ /chiral ferrocenyl P,N-ligand complex as a catalyst, a series of octahydropyrrolo[3,4-*c*]pyrroles, with a chiral C–N axis, were obtained with excellent yields and high diastereo- and enantioselectivity (Scheme 24).

### 2.7. HMF derived azomethine ylides

The use of renewable raw materials derived from biomass instead of those arising from petrochemicals for the preparation of fine chemicals is a key goal of modern organic synthesis. A remarkable example of these platform molecules is 5-hydroxymethylfurfural (HMF), which is obtained by the dehydration of 6-carbon sugars and offers great synthetic potential.<sup>66</sup> However, the use of HMF as a starting material for the preparation of enantioenriched products by asymmetric catalysis has been scarcely studied.<sup>67</sup> Recently, our research group has demonstrated that catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides is an efficient tool for the preparation of enantioenriched highly functionalized pyrrolidines from HMF.<sup>68</sup> The cycloaddition between the HMF-iminoester (obtained by condensation with methyl glycinate) and *N*-methylmaleimide using a  $\text{Cu}^{\text{I}}$ /Fesulphos catalyst system exclusively afforded *endo*-pyrrolidine with excellent enantiocontrol (75% yield, 95% ee, Scheme 25).



**Scheme 25** Cycloaddition between HMF derived-iminoesters and activated olefins.



**Scheme 26** Synthesis of axially chiral arylpyrroles via a cycloaddition/oxidation sequence.

### 2.8. Synthesis of axially chiral arylpyrroles

Axial chiral molecules are important structural motifs present in natural products and biologically active substances.<sup>69</sup> Moreover, a great number of chiral ligands and organocatalysts are based on skeletons with axial chirality. In 2024, our research group has developed a new method for the synthesis of axially chiral arylpyrroles using the 1,3-dipolar cycloaddition reaction of azomethine ylides as the key step.<sup>70</sup> The  $\text{Cu}^{\text{I}}$ /Fesulphos catalyzed (3+2)-cyclization using naphthyl derived iminoesters as azomethine ylide precursors takes place with good yield and high levels of diastereo- and enantioselectivity. The subsequent nitrogen alkylation and aromatization gives rise to the corresponding axial chiral pyrroles. The mild conditions used in the DDQ/blue light mediated aromatization process provide an effective central-to-axial chirality transfer affording the corresponding pyrroles with high atroposelectivity (Scheme 26).

## 3. Conclusions

The catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides has witnessed significant progress over the past few decades, providing a reliable procedure for the enantioselective synthesis of polysubstituted pyrrolidines. During this time, numerous research groups have greatly expanded the range of both dipoles and dipolarophiles compatible with this reaction. This feature article highlights examples that use azomethine ylide precursors beyond the standard  $\alpha$ -iminoesters, including  $\alpha$ -iminophosphonates,  $\alpha$ -iminoamides,  $\alpha$ -iminonitriles,  $\alpha$ -iminopyridines,  $\alpha$ -silylimines and  $\alpha$ -fluoromethylimines. These advancements have expanded the scope of pyrrolidine derivatives that can be synthesized through this methodology, opening up new avenues for the preparation of complex pyrrolidines. Despite these notable achievements, challenges remain, for example, while non-stabilized azomethine ylides have been extensively employed in natural product synthesis, their use in asymmetric catalysis remains underexplored. In this regard, a key aspect is the generation of active monodentate chiral chelates through coordination of a metal complex to the imine nitrogen. Addressing this gap



could significantly enhance the synthetic applicability of this methodology.

## Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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