Cycloadditions

International Edition: DOI: 10.1002/anie.201602542
German Edition: DOI: 10.1002/ange.201602542

Diastereo- and Enantioselective Copper(I)-Catalyzed Intermolecular [3+2] Cycloaddition of Azomethine Ylides with β-Trifluoromethyl β,β-Disubstituted Enones

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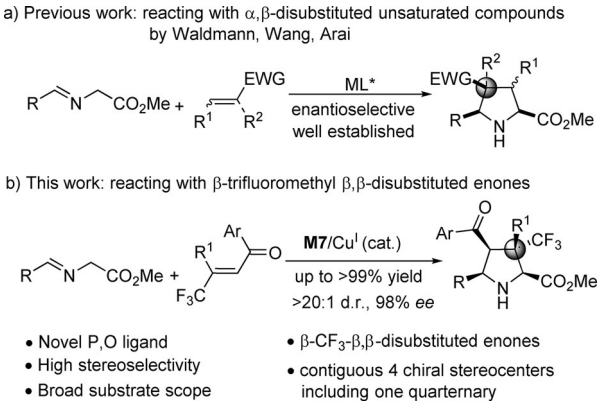
Abstract: *Reported herein is an asymmetric [3+2] cycloaddition reaction of azomethine ylides with β-trifluoromethyl β,β-disubstituted enones, a reaction which is enabled by a Ming-Phos-derived copper(I) catalyst (Ming-Phos = chiral sulfinamide monophosphines, Figure 2). This method provides scalable and efficient access to the highly substituted pyrrolidines with a trifluoromethylated, all-carbon quaternary stereocenter in good yields with up to greater than 20:1 d.r. and 98 % ee. The reaction has a broad substrate scope and tolerates a wide range of functional groups.*

Five-membered nitrogen heterocycles, especially highly substituted pyrrolidines, are frequently found in pharmaceuticals, natural alkaloids, and as fascinating building blocks in organic synthesis, as well as outstanding catalysts in asymmetric catalysis.[1] The transition metal catalyzed asymmetric 1,3-dipolar [3+2] cycloaddition of azomethine ylides with electron-deficient alkenes is one of the most powerful and widely used methods for the construction of these compounds.[2] Despite great progress in this field,[3] the synthesis of chiral pyrrolidines with four contiguous stereocenters, including at least one all-carbon quaternary stereocenter[4] at either the 3- or 4-position, still poses a considerable challenge because of the requisite use of sterically encumbered and less reactive β,β- or α,β-disubstituted unsaturated compounds. Recently, the latter cycloaddition was successfully achieved by the groups of Waldmann, Wang, and Arai,[5] and provides facile access to chiral pyrrolidines with one all-carbon quaternary stereocenter at the 4-position (Scheme 1 a). However, to the best of our knowledge, a metal-catalyzed diastereo- and enantioselective intermolecular [3+2] cycloaddition reaction of azomethine ylides with β,β-disubstituted unsaturated compounds, such as enones, has not been reported thus far. Therefore, the development of novel transition-metal catalysts to enable this asymmetric [3+2] cycloaddition is highly desirable.



Scheme 1. [3+2] cycloaddition of azomethine ylides with disubstituted α,β-unsaturated compounds. EWG = electron-withdrawing group.

Meanwhile, it is well established that the strategic introduction a trifluoromethyl (CF_3) group into heterocycles can substantially modify their metabolic stability, lipophilicity, and bioavailability.[6] Consequently, the development of reliable synthetic approaches to CF_3-bearing heterocycles has attracted much attention from synthetic chemists in recent years.[7] However, the enantioselective construction of a trifluoromethylated all-carbon quaternary stereocenter has been less-often reported and remains extremely challenging, especially for construction of an all-carbon quaternary stereocenter bearing both CF_3 and CH_3.[8] With the importance of pyrrolidines with one trifluoromethylated all-carbon quaternary stereocenter in mind (Figure 1),[9] we decided to develop an efficient method to construct this skeleton. Recently, we developed a new chiral sulfinamide phosphine ligand, Ming-Phos, which can be easily made from inexpensive commercially available starting materials (i.e., *tert*-butanesulfinamide 2200 CNY kg^{-1}). This Ming-Phos showed good performance in the asymmetric gold-catalyzed dipolar

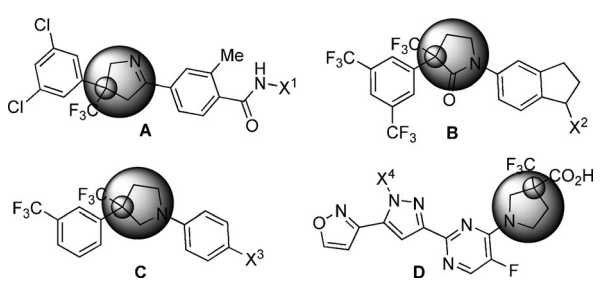


Figure 1. Pharmaceuticals and agrochemicals featuring ring-fused CF_3-bearing pyrrolidine.

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Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201602542.

[3+3] cycloaddition reaction of 2-(1-alkynyl)-alk-2-en-1-ones with nitrones.[10] To extend the utility of this ligand to other dipolar cycloaddition reactions, we examined the asymmetric intermolecular [3+2] cycloaddition reaction of azomethine ylides with β-trifluoromethyl β,β-disubstituted enones. Herein, we present a highly diastereo- and enantioselective copper(I)/Ming-Phos-catalyzed intermolecular [3+2] cycloaddition reaction of azomethine ylides with β-trifluoromethyl β,β-disubstituted enones (Scheme 1b), a reaction, which to the best of our knowledge, is the first of its kind.

With a series of Ming-Phos ligands (**M1**–**M5**; Figure 2) in hand and inspired by the high catalytic activity of copper in [3+2] asymmetric cycloaddition reactions of azomethine ylides, we started to examine the performance of copper/Ming-Phos in the asymmetric [3+2] cycloaddition of the enone **1a** and azomethine ylide **2a** (for structures see Table 1;

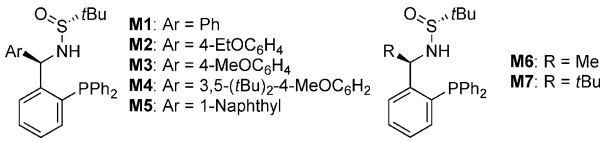
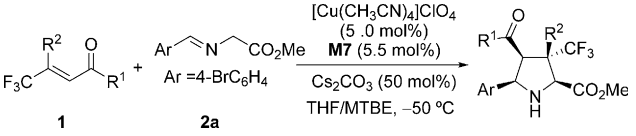


Figure 2. Screened ligands.

for results see Table S1 in the Supporting Information). Gratifyingly, the reaction proceeded to give **3aa** in 95% yield as a single diastereomer (d.r. > 20:1) in 63% *ee*, when the Ming-Phos **M1**, having a phenyl ring, was used as the chiral ligand. The modified ligands **M2**–**M5**, having different aryl rings, failed to improve the enantioselectivity (Table S1, entries 2–5). We then studied the performance of **M6**, bearing an alkyl group (R = Me), but the enantioselectivity was still moderate (Table S1, entry 6). Gratifyingly, **M7**, with a bulky *tert*-butyl group, led to a much higher *ee* value (Table S1, entry 7). Inspired by this result, other copper(I) salts such as $[Cu(CH_3CN)_4]ClO_4$ and $[Cu(CH_3CN)_4]NTf_2$ were then examined as precatalysts for the reaction under identical reaction conditions (Table S2, entries 8 and 9), and $[Cu(CH_3CN)_4]ClO_4$ exhibited better enantioselectivity (Table S1, entry 9; 95% yield, > 20:1 d.r., 89% *ee*). Meanwhile, a series of commercially available chiral ligands such as (*S*)-TF-BiphamPhos, (*S*)-BINAP, (*R*)-SEGPHOS, (*R*)-DM-SEGPHOS, (*R*,*S*)-*O*-PINAP, (*R*)-MOP, Binol-derived phosphoramidite, P,N ligands, and chiral bis(oxazoline)s were screened (see Table S2). Among them, the ferrocenyl P,N ligand (*R*)-1-[(*S*)-2-diphenylphosphino]ferrocenylethylamine was the most promising, and delivered **3aa** in 83% yield with 88% *ee* and 6:1 diastereoselectivity. Then, we studied the solvent effect with the use of **M7** as the chiral ligand. By changing the solvent to either xylene or MTBE (methyl tertiary butyl ether) increased the *ee* value to 90% (Table S1, entries 10 and 11). When the temperature was lowered to −50 °C in THF, the *ee* value of the desired product **3aa** was increased from 89 to 91% (Table S1, entries 8 and 12), whereas, only trace amounts of product were detected at −50 °C in MTBE (Table S1, entry 13). Finally, the optimal reaction conditions were found to be: a mixed solvent system (THF and MTBE) at −50 °C with the use of $[Cu(CH_3CN)_4]ClO_4$ as the precatalyst and **M7** as the ligand (Table S1, entry 14; 98% yield, > 20:1 d.r., 95% *ee*).

With the optimal reaction conditions in hand, we turned to examine the reaction scope by variation of the enone component **1** (Table 1). Both electron-donating and electron-withdrawing substituents on the aryl ring (R^1) were tolerated (entries 1–8) and the reaction afforded the desired products

Table 1: Exploration of enone scope.[a]



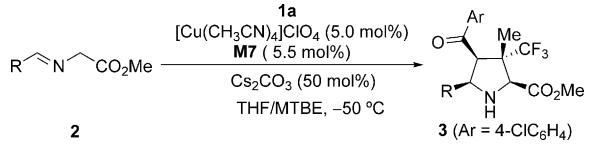
Entry	R^1/R^2	(−)-**3**	Yield [%][b]	*ee* [%]
1	4-ClC_6H_4/Me (**1a**)	(−)-**3aa**	98	95
2	4-FC_6H_4/Me (**1b**)	(−)-**3ba**	98	90
3	4-BrC_6H_4/Me (**1c**)	(−)-**3ca**	92	94
4	4-CNC_6H_4/Me (**1d**)	(−)-**3da**	94	95
5	4-$NO_2C_6H_4$/Me (**1e**)	(−)-**3ea**	88	90
6	4-$CF_3C_6H_4$/Me (**1f**)	(−)-**3fa**	99	95
7	4-$CH_3C_6H_4$/Me (**1g**)	(−)-**3ga**	> 99	93
8	4-$CH_3OC_6H_4$/Me (**1h**)	(−)-**3ha**	94	90
9[c]	3,4-$Cl_2C_6H_3$/Me (**1i**)	(−)-**3ia**	96	84
10[c]	Ph/Me (**1j**)	(−)-**3ja**	98	96
11	4-ClC_6H_4/Et (**1k**)	(−)-**3ka**	97	94
12	4-ClC_6H_4/Ph (**1l**)	(−)-**3la**	> 99	98
13	4-ClC_6H_4/2-naphthyl (**1m**)	(−)-**3ma**	94	96
14	4-ClC_6H_4/3,5-$(CH_3)_2C_6H_3$ (**1n**)	(−)-**3na**	94	90
15	Me/Ph (**1o**)	**3oj**	0	0
16[d]	**1j**	(−)-**3jj**	93	94

[a] Unless otherwise noted, all reactions were carried out with 0.2 mmol of **1**, 0.4 mmol of **2a**, 5 mol% of catalyst ([Cu]/**M7** = 1:1.1) in 4.0 mL MTBE/THF (V_{MTBE}/V_{THF} = 3:1) at −50 °C for 2–12 h and the diastereomeric ratios are > 20:1. [b] Yield of the isolated product. [c] −70 °C. [d] **2j** was used.

3aa–**ha** in yields ranging from 88 to greater than 99% with *ee* values of 90–95%. For the 3,4-dichlorophenyl-substituted enone **1i** and phenyl-substituted enone **1j**, the reactions required a lower temperature (−70 °C) to achieve high enantioselectivities of **3ia** and **3ja**, respectively, as single diastereomers in 96–98% yields (entries 9 and 10). Meanwhile, the β-trifluoromethyl β-ethyl enone **1k** delivered the corresponding product **3ka** in 97% yield and 94% *ee*. Gratifyingly, the reaction could be also successfully extended to β-trifluoromethyl β-aryl enones and excellent enantioselectives of **3la**–**na** were generally obtained (entries 12–14). Unfortunately, the less reactive methyl enone **1o** could not be used in the present dipolar [3+2] cycloaddition and even the racemic reaction did not occur (entry 15). It is noteworthy that the phenyl-substituted product **3jj** was obtained with excellent diastereo- and enantioselectivity (> 20:1 d.r., 94% *ee*) with a lower reaction temperature of −70 °C (entry 16).

Next, we examined the scope with respect to the azomethine ylide component **2** by reaction with **1a** (Table 2). Both the electron-rich and electron-deficient aryl-aldehyde-derived **2b**–**m** delivered the corresponding products **3ab**–**am** in high yields with excellent diastereo- and enantioselectivities (92–> 99% yields, > 20:1 d.r., 91–97% *ee*;

Table 2: Exploration of azomethine ylide scope.[a]



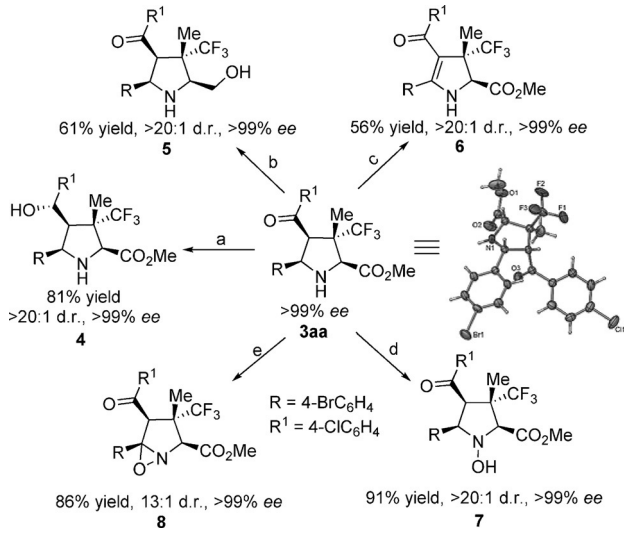
Entry	R	(−)-3	Yield [%][b]	*ee* [%]
1	3-BrC_6H_4 (**2b**)	(−)-**3ab**	99	92
2	2-BrC_6H_4 (**2c**)	(−)-**3ac**	98	93
3	4-ClC_6H_4 (**2d**)	(−)-**3ad**	92	95
4	3-ClC_6H_4 (**2e**)	(−)-**3ae**	98	91
5	4-FC_6H_4 (**2f**)	(−)-**3af**	95	95
6	4-$CF_3C_6H_4$ (**2g**)	(−)-**3ag**	98	94
7	4-CNC_6H_4 (**2h**)	(−)-**3ah**	>99	92
8	Ph (**2i**)	(−)-**3ai**	>99	91
9	4-PhC_6H_4 (**2j**)	(−)-**3aj**	>99	97
10	4-$CH_3C_6H_4$ (**2k**)	(−)-**3ak**	>99	95
11	4-$CH_3OC_6H_4$ (**2l**)	(−)-**3al**	>99	93
12	3-$CH_3C_6H_4$ (**2m**)	(−)-**3am**	99	91
13	2-naphthyl (**2n**)	(−)-**3an**	98	95
14[c]	2-thienyl (**2o**)	(−)-**3ao**	97	85
15[d]	styryl (**2p**)	(−)-**3ap**	70	80
16[e]	cyclohexyl (**2q**)	(−)-**3aq**	94	86

[a] Unless otherwise noted, all reactions were carried out with 0.2 mmol of **1**, 0.4 mmol of **2a**, 5 mol% of catalyst ([Cu]/**M7** = 1:1.1) in 4.0 mL MTBE/THF (V_{MTBE}/V_{THF} = 3:1) at −50 °C for 2–12 h and the diastereomeric ratios are >20:1. [b] Yield of the isolated product. [c] −70 °C. [d] d.r. = 4:1. [e] 10 mol% of catalyst was used.

entries 1–12). The 2-naphthyl-substituted **2n** afforded **3an** in 98% yield with 95% *ee* (entry 13). Additionally, the thiophene-2-carbaldehyde-derived imino ester **2o** worked well, thus leading to 97% yield of **3ao** with 85% *ee* (entry 14). The styryl-substituted **2p** delivered the corresponding compound **3ap** in 70% yield with 4:1 d.r. and 80% *ee* (entry 15). Notably, the less reactive **2q**, derived from an aliphatic aldehyde, is also applicable to this reaction, thereby giving the corresponding product **3aq** in 94% yield with high diastereo- and enantioselectivity (entry 16). Unfortunately, the reaction of an α-methyl iminoester with **1a** is messy, thus indicating that the construction of pyrrolidine with two contiguous quaternary stereocenters still pose a considerable challenge.

The absolute configuration of **3aa** was determined by single-crystal X-ray diffraction analysis (Scheme 2).[11] Fortunately, the single-crystal of [(**M7**)Cu(CH_3CN)]ClO_4 was also obtained (Figure 3a).[11] X-ray diffraction analysis revealed that the copper binds to both the phosphine and oxygen atom, thus indicating that **M7** serves as a P,O ligand here, and is different to the case of the gold complex (only binding to the phosphine).[10] With the assistance of the X-ray structure of the copper(I) complex, a possible model for asymmetric induction is also proposed (Figure 3b).

A gram-scale reaction delivered 1.43 grams of **3aa** in 94% yield with excellent diastereo- and enantioselectivity (>20:1 d.r., 94% *ee*), thus indicating the present asymmetric cycloaddition is easy to scale-up. Gratifyingly, the enantiopure **3aa** (>99% *ee*) can be easily obtained by simple recrystallization of the crude reaction mixture from *n*-hexanes. To demonstrate the synthetic utility, several transformations of **3aa** were carried out. Firstly, the ketone and ester group of **3aa** could be



Scheme 2. The synthetic transformations of **3aa**.[a] [a] Reaction conditions: a) $NaBH_4$ (2.0 equiv), MeOH, RT, 30 min. b) DIBAL-H (5.0 equiv), THF, −78 to −30 °C, 4 h. c) DDQ (1.2 equiv), toluene, 40 °C, 36 h. d) MCPBA (1.1 equiv), DCM, RT, 5 h. e) MCPBA (2.1 equiv), DCM, RT, 12 h. DCM = dichloromethane, DDQ = 2,3-dichloro-5,6-dicyano1,4-benzoquinone, DIBAL-H = diisobutylaluminum hydride, MCPBA = *m*-chloroperbenzoic acid, THF = tetrahydrofuran.

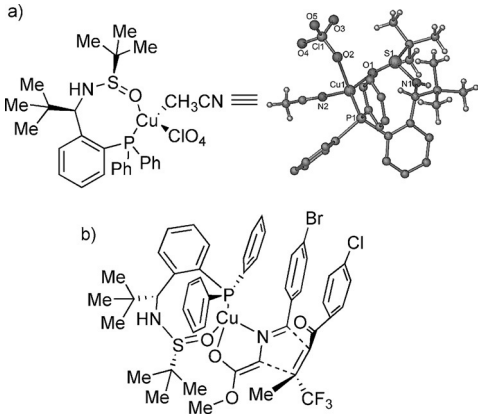


Figure 3. a) X-ray crystal structure of [(**M7**)Cu(CH_3CN)]ClO_4. b) Proposed model for asymmetric induction.

selectively reduced by different reducing reagents, thus leading to the corresponding alcohols **4** and **5** in 81 and 61% yields, respectively (Scheme 2). The absolute configuration of **4** was established by single-crystal X-ray diffraction analysis.[11] Treatment of **3aa** with DDQ delivered the highly substituted 2-pyrroline **6** in 56% yield. It is very interesting to find that the oxidation of **3aa** with different equivalents of *m*-CPBA could produce the *N*-hydroxyl pyrrolidine **7** and bicyclic compound **8**, respectively, in high yields.

In summary, we developed the first highly enantioselective copper-catalyzed [3+2] cycloaddition reaction of azomethine ylides with β-trifluoromethyl β,β-disubstituted enones by the employing a cheap copper catalyst and a readily available chiral ligand, in which the Ming-Phos serves as a P,O ligand. This method provides a reliable strategy for the excellent enantioselective construction of highly substituted

pyrrolidines with a trifluoromethylated all-carbon quaternary stereocenter. The salient features of this cycloaddition include high efficiency, high diastereo- and enantioselectivity, a novel ligand, an inexpensive copper catalyst, outstanding functional-group tolerance, and diverse transformations. Further studies, including synthetic application and the employment of the chiral catalyst to other reactions, are currently underway and will be reported in due course.

Acknowledgments

We gratefully acknowledge the funding support of NSFC (21425205), 973 Program (2015CB856600), and the Program of Eastern Scholar at Shanghai Institutions of Higher Learning.

Keywords: azomethine ylides · cycloaddition · copper · heterocycles · P,O ligand

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 6324–6328
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Received: March 25, 2016
Published online: April 13, 2016

