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Umpolung of Imines Enables Catalytic Asymmetric Regio-Reversed [3+2] Cycloadditions of Iminoesters with Nitroolefins

Bin Feng,[#] Liang-Qiu Lu,[#] Jia-Rong Chen, Guoqiang Feng, Bin-Qing He, Bin Lu, and Wen-Jing Xiao*

Dedicated to Prof. Xiyan Lu on the occasion of his 90th birthday.

Abstract: *A copper-catalyzed regio-reversed asymmetric [3+2] cycloaddition of iminoesters with nitroolefins was disclosed for the first time. This protocol allows the facile synthesis of polysubstituted chiral pyrrolidines bearing at least one chiral quaternary center in high yields with excellent regio-, diastereo- and enantioselectivities. The application of chiral P,S-ligands and the unique effect of α-aryl groups on the iminoesters were the keys to the success of this method. The practicality and versatility of the reaction methodology were also demonstrated.*

Imines are a family of privileged compounds in organic chemistry that are involved in more than 50 named reactions and are widely used in the synthesis of nitrogen-containing molecules.[1] One reason for their versatility is the inherent and tunable electrophilicity of imines (Figure 1a, with Nu^-). Recently, reversing this inherent reactivity (the umpolung of imines) has opened a new pathway for the further development of imine chemistry (Figure 1a, with E^+).[2] To date, many elegant transformations have been reported that use this umpolung strategy, including arylation reactions,[3] allylic additions,[4] nucleophilic additions,[5] and transaminations of imines.[6] However, most of these works have focused on reactions that produce a single chemical bond. Further exploitation of this concept in cycloaddition reactions, especially catalytic asymmetric processes, will provide additional opportunities for the construction of important aza-heterocycles.

In recent years, azomethine ylides have been shown to be important dipolar intermediates that can participate in a series of [3+2] cycloadditions with various dipolarophiles.[7] Given the unique imine structure of iminoesters, precursors of azomethine ylides, the development of regio-reversed catalytic asymmetric [3+2] cycloadditions of iminoesters using an umpolung strategy involving imines would enable the efficient synthesis of new pyrrolidine compounds.[8,9] However, to our knowledge, very few studies have been reported in this field. In 2009, Gong and co-workers disclosed the first example of catalytic asymmetric umpolung/[3+2] cycloaddition reactions of iminoesters and methyleneindolinone with chiral phosphoric acid as an efficient catalyst.[9a,b] Two other impressive umpolung/cycloaddition reactions of ketimines, which were derived from isatins or CF_3-substituted ketones, were subsequently developed using chiral squaramide catalysts.[9c,d] Analogously to organocatalysis, asymmetric Lewis acid catalysis is another efficient strategy for asymmetric catalysis; however, to our surprise, this strategy remains underexploited for catalytic asymmetric umpolung/[3+2] cycloaddition reactions of iminoesters.[10,11] In this work, with our ongoing interest in the applications of chiral P,S ligands in asymmetric synthesis,[12] we describe a highly enantioselective and regio-reversed [3+2] cycloaddition of iminoesters through asymmetric Lewis acid catalysis (Figure 1b; Lewis acid = Cu). This novel protocol provides direct access to important and structurally diverse chiral pyrrolidines[13] that bear chiral quaternary stereocenters with high efficiency and excellent regio-, diastereo- and enantioselectivities.

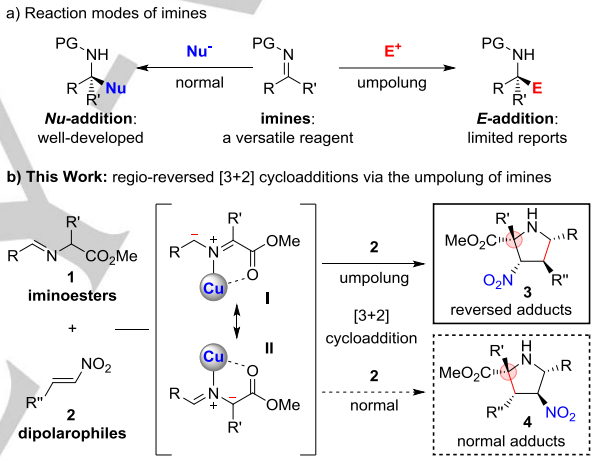

Figure 1. Reaction design: Cu-catalyzed regio-reversed asymmetric [3+2] cycloadditions. PG: protecting group; Nu^-/E^+: nucleophile/electrophile.

We began this project with the regio-reversed [3+2] cycloaddition of 2,4-diphenyl iminoester **1a** and nitrostyrene **2a** as a model reaction using 5 mol% chiral Cu complex as the catalyst and 30 mol% CsOAc as the base. As highlighted in Table 1, the Cu catalyst with our chiral P,S-ligand (**L1a**) indeed promoted this reaction with a high yield albeit with modest enantioselectivity (Table 1, entry 1, 80% yield, >19:1 dr and -20% ee). Encouraged by this result, other structurally related P,S-ligands were evaluated (Table 1, entries 2-4). Ligands **L1c** and **L1d**, which have bulky substituents (i.e., an iodine atom or a phenyl group) at the 3,3'-positions of the binaphthyl scaffold, were determined to be super choices as they provided the desired products in 99% yields with high levels of enantiocontrol (Table 1, entries 3 and 4). P,S-ligand **L2**, which bears an achiral phosphoramidite unit and is known to be successful in Pd-catalyzed asymmetric decarboxylative [4+2] cycloadditions, was also evaluated here, but it failed to give high enantioselectivity. Other commercial chiral P-ligands, N-ligands and P,N-ligands were also examined for this cycloaddition, but none of these ligands provided superior yields and enantioselectivities to chiral P,S-ligands **L1c** and

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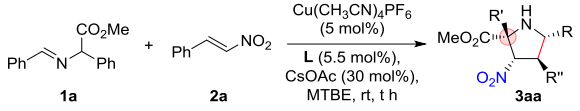
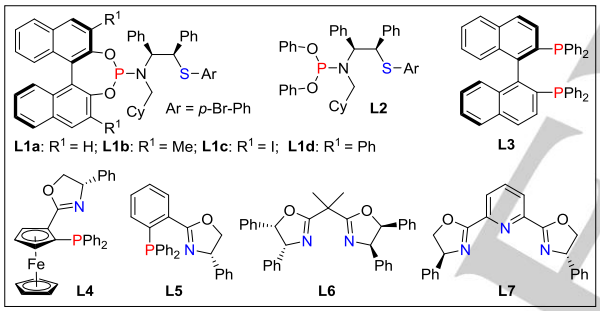
L1d (Table 1, entries 6-10 vs 3 and 4). To our delight, performing the reaction at -40 °C with an extended reason time can greatly improve the results (Table 1, entry 10, 94% yield, >19:1 dr and 97% ee).[14]

Table 1: **O**ptimization of the reaction conditions[a]



Entry	L	Time [h]	Yield [%][b]	ee [%][c]
1	**L1a**	1	80	-20
2	**L1b**	1	99	60
3	**L1c**	1	99	87
4	**L1d**	1	99	88
5	**L2**	1	99	30
6	**L3**	1	94	3
7	**L4**	1	96	22
8	**L5**	3	91	35
9	**L6**	1	70	0
10	**L7**	10	43	44
11[d]	**L1d**	8	94 (83)[e]	97

[a] Reaction conditions: **2a** (0.3 mmol), **3a** (0.2 mmol), $Cu(CH_3CN)_4PF_6$ (5.0 mol%), ligand (5.5 mol%), CsOAc (30 mol%) in MTBE (2.0 mL) at rt. [b] Determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard; dr >19:1. [c] Determined by chiral HPLC. [d] Performed at -40 °C. [e] Isolated yield in parentheses. MTBE: methyl *tert*-butyl ether.



After establishing the optimal conditions, we probed the generality of this cycloaddition.[15] As summarized in Table 2, we were glad to find that a wide range of iminoesters with varied electronic properties and substitution patterns were well-tolerated and were converted to the corresponding pyrrolidine products in high yields and excellent enantioselectivities (Table 2, entries 1-12, **3aa**-**3la**: 83-99% yields and 92-99% ee). Moreover, substrates with fused aromatic rings, such as 1-napthyl and 2-napthyl derivatives, and heteroaryls, such as 2-furyl and 2-thiophenyl, were smoothly converted by this reaction to products **3ma**-**3pa** with high levels of enantiocontrol (Table 2, entries 13-16: 80-96% yields and 88-97% ee). This catalytic system has been successfully applied to iminoesters derived from aliphatic aldehydes. For example, a cyclohexyl-substituted iminoester was well tolerated in the Cu-catalyzed regio-reversed [3+2] cycloaddition and provided 5-cyclohexyl-substuted product **3qa** in 96% yield and 95% ee (Table 2, entry 17). Furthermore, iminoesters with different aryl groups at the α-position were examined for this transformation. Gratifyingly, all were found to be efficient substrates. This included electron-deficient and electron-rich aryls as well as heteroaryls; the desired products were provided in 84-92% yields and 90-97% ee (Table 2, entries 18-21, **3ra**-**3ua**).

Next, we examined the scope of nitroolefin components. As shown in Table 3, nitroolefins containing a series of electron-donating and electron-withdrawing substituents on the *β*-aryl ring reacted with iminoester **2a** very well. Enantioenriched pyrrolidines with different aryl groups at the 4-positon were

Table 2: Scope of azomethine ylides.[a]

Entry	R	R'	Product	Yield (%)[b]	ee (%)[c]
1	C_6H_5	C_6H_5	**3aa**	83	97
2	*p*-MeO-C_6H_4	C_6H_5	**3ba**	87	92
3	*p*-Me-C_6H_4	C_6H_5	**3ca**	84	95
4	*p*-Br-C_6H_4	C_6H_5	**3da**	99	94
5[d]	*p*-NO_2-C_6H_4	C_6H_5	**3ea**	96	93
6	*p*-CN-C_6H_4	C_6H_5	**3fa**	99	96
7	*p*-CF_3-C_6H_4	C_6H_5	**3ga**	92	97
8	*o*-Me-C_6H_4	C_6H_5	**3ha**	85	96
9	*o*-Br-C_6H_4	C_6H_5	**3ia**	99	99
10	*m*-Me-C_6H_4	C_6H_5	**3ja**	94	94
11[d]	*m*-NO_2-C_6H_4	C_6H_5	**3ka**	95	94
12[d]	*m,p*-$(MeO)_2$-C_6H_3	C_6H_5	**3la**	85	96
13	1-naphthyl	C_6H_5	**3ma**	96	96
14[d]	2-naphthyl	C_6H_5	**3na**	94	97
15	2-furyl	C_6H_5	**3oa**	87	94
16	2-thiophenyl	C_6H_5	**3pa**	80	88
17[e]	cyclohexyl	C_6H_5	**3qa**	96	95
18	C_6H_5	*p*-Me-C_6H_4	**3ra**	84	91
19	C_6H_5	*p*-Cl-C_6H_4	**3sa**	92	95
20	C_6H_5	*o*-Cl-C_6H_4	**3ta**	90	90
21	C_6H_5	2-thiophenyl	**3ua**	86	97

[a] Unless otherwise noted, reactions were carried out as indicated in entry 12, Table 1, dr > 19:1. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Using chiral ligand **L1c** at 0 °C. [e] rt.

produced in high yields and good enantioselectivities (Table 3, entries 1-8, **3ab-3ai**: 86-96% yields and 88-97% ee). Fused aryl- and heteroaryl-substituted nitroolefins were compatible with this

Table 3: Scope of nitroolefins.[a]

Entry	R	R'	Product	Yield (%)[b]	ee (%)[c]
1	*p*-MeO-C_6H_4	H	**3ab**	96	96
2	*p*-Me-C_6H_4	H	**3ac**	93	97
3	*p*-Cl-C_6H_4	H	**3ad**	86	90
4	*o*-Me-C_6H_4	H	**3ae**	90	95
5	*o*-Br-C_6H_4	H	**3af**	86	93
6	*o*-Cl-C_6H_4	H	**3ag**	94	88
7	*m*-Me-C_6H_4	H	**3ah**	99	91
8	2,4-Cl_2-C_6H_4	H	**3ai**	90	91
9	2-naphthyl	H	**3aj**	99	97
10	2-furyl	H	**3ak**	94	97
11	2-thiophenyl	H	**3al**	94	97
12	isopropyl	H	**3am**	81	98

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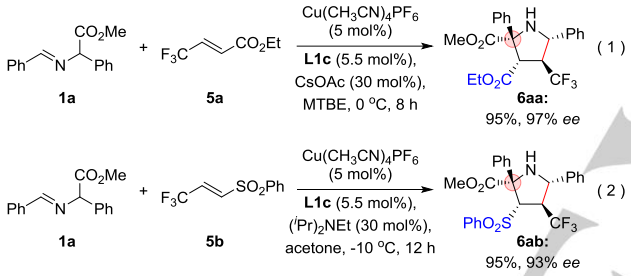
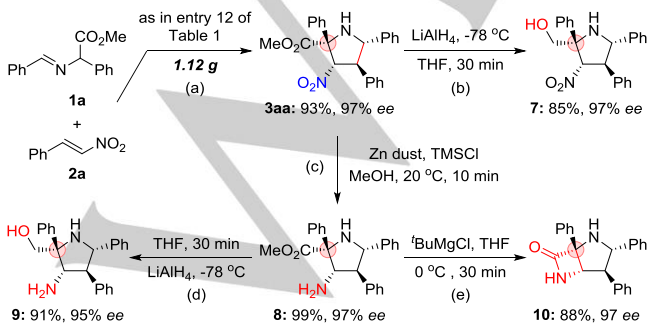
13[d]	cyclohexyl	H	**3an**	82	92
14[d]	C_6H_5	Me	**3ao**	81	93

[a] Unless otherwise noted, reactions were carried out as indicated in entry 12, Table 1, dr > 19:1. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Using chiral ligand **L1c** at 0 °C.

reaction system, and the corresponding products were delivered in excellent yields and enantioselectivities (Table 3, entries 9-11, **3aj-3ak**: up to 99% yield and 97% *ee*). Moreover, alkyl-substituted nitroolefins, such as the isopropyl- and cyclohexyl-substituted substrates, were efficient substrates for this reaction (Table 3, entry 12, **3am**: 81% yield and 98% ee; entry 13, **3an**: 82% yield and 92% ee). To our delight, the umpolung/cycloaddition reaction of *α*-methyl nitrostyrene proceeded well; product **3ao**, bearing two vicinal quaternary stereocenters, was afforded in 81% yield and 93% ee (Table 3, entry 14). Notably, the success of this Cu-catalyzed regio-reversed [3+2] cycloaddition could be extended to *β*-CF_3-substituted alkenes, which can be utilized to prepare trifluoromethylated pyrrolidines.[16] For example, when *β*-CF_3-substituted enoate **5a** and vinyl sulfone **5b** were subjected to the optimal reaction conditions, products **6aa** and **6ab** were generated with high reaction efficiency and excellent regio- and enantioselectivities (Eqs. 1 and 2).



As presented in Scheme 2a, to demonstrate the practicality of reaction methodology, we performed a gram-scale experiment of the model reaction under the optimal conditions. As a result, 1.12 g of chiral pyrroline product **3aa** was prepared with high reaction efficiency and excellent enantioselectivity. Then, several synthetic transformations were carried out to highlight the potential uses of this product. For example, the selective reduction of the ester by $LiAlH_4$ or the nitro group by Zn dust afforded the corresponding chiral alcohol **7** or amine **8** in high yields without erosion of the enantiomeric excess (Scheme 2b and 2c). Furthermore, chiral amine **8** was converted to amino alcohol **9** in good yield by treatment with $LiAlH_4$ (Scheme 2d). Remarkably, treatment of **8** with ^{t}BuMgCl in THF provided *β*-lactam **10** in 88% yield and 97% ee (Scheme 2e).



Scheme 2. A gram-scale reaction and demonstration of synthetic utility of the product.

Regarding the origin of reversed regio-selectivity of this Cu-catalyzed asymmetric [3+2] dipolar cycloaddition, we envisioned that the α-aryl group of the iminoester helps stabilize the 2-azaallyl anion of the azomethine ylide intermediate, thus promoting the umpolung of iminoester **1**. To verify this hypothesis, control experiments with α-Bn-, α-Me- and α-H-substituted iminoesters were performed under the standard conditions. As expected, cycloaddition products with normal regio-selectivity were observed (Figure 2). In addition, based on the X-ray structure of the Cu-complex with the chiral P,S-ligands,[12f] a possible stereoinduction mode was proposed to account for the observed stereochemistry of the products. As depicted in Figure 2, a six-membered copper chelate consisting of the P,S-ligand, Cu core and azomethine ylide might first take on a distorted tetrahedral geometry. Then, the *N*-metalated azomethine ylide can approach the *Si*-face of the nitroolefin.[17] The steric hindrance between the imine group and the phenyl group of the nitroolefin forces the two phenyl group at C4 and C5 in an *anti*-conformation thus providing chiral *exo*-**3aa**.

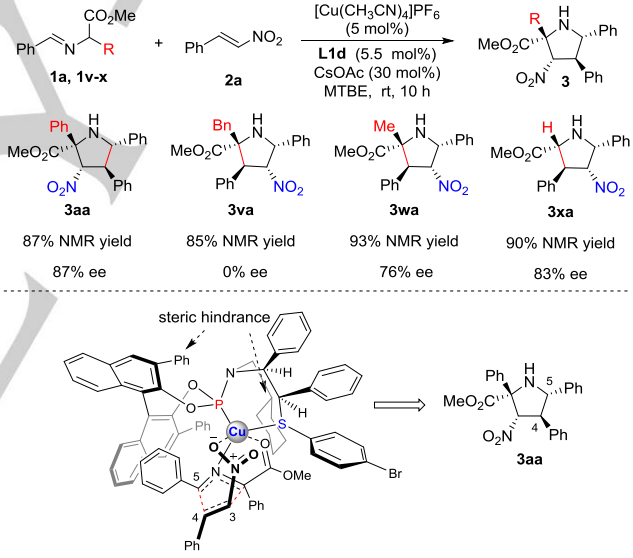


Figure 2. Control experiments of the iminoesters with varied α-substituted groups and a proposed stereoinduction mode.

In summary, we have successfully developed a copper-catalyzed asymmetric regio-reversed [3+2] cycloaddition of iminoesters with nitroolefins and CF_3-containing alkenes. A wide range of polysubstituted chiral pyrrolidines bearing at least one chiral quaternary center were generated in high yields and with excellent regio-, diastereo- and enantioselectivities. The success of this reaction in achieving the umpolung of imines can be attributed to the use of our chiral P,S-ligand and the unique effect of the α-aryl group of the iminoesters.

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Keywords: umpolung of imines • dipolar cycloaddition • chiral P,S ligand • azomethine ylide • nitroolefin

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[14] Please see the Supporting Information for more details.

[15] The absolute and related configurations of chiral pyrrolidine products **3aa** and **6ab** was established through the X-ray diffraction analysis of single crystals. CCDC 1586125 (**3aa**) and CCDC 1586127 (**6ab**) contain the supplementary crystallographic data. The configurations of other products were presumed according to these two compounds.

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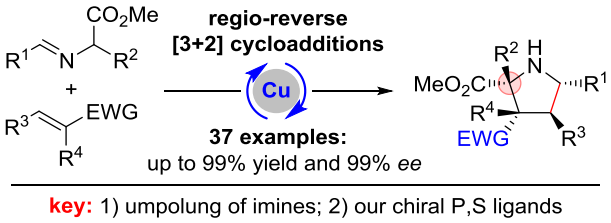
Heterocycles



key: 1) umpolung of imines; 2) our chiral P,S ligands

A copper-catalyzed regio-reversed asymmetric [3+2] cycloaddition of iminoesters with nitroolefins was disclosed for the first time. This protocol allows the facile synthesis of polysubstituted chiral pyrrolidines bearing at least one chiral quaternary center in high yields with excellent regio-, diastereo- and enantioselectivities. The application of chiral P,S-ligands and the unique effect of α-aryl groups on the iminoesters were the keys to the success of this method. The practicality and versatility of the reaction methodology were also demonstrated.

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Page No. – Page No.

Umpolung of Imines Enables Catalytic Asymmetric Regio-Reversed [3+2] Cycloadditions of Iminoesters with Nitroolefins