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Title: Biologically Inspired Ligand Design for Asymmetric Diastereodivergent 1,3-Dipolar Cycloaddition

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A Highly Enantioselective Copper/Phosphoramidite-Thioether-Catalyzed Diastereodivergent 1,3-Dipolar Cycloaddition of Azomethine Ylides and Nitroalkenes

Bin Feng,[a] Jia-Rong Chen,[a] Yun-Fang Yang,[b] Bin Lu,[a] and Wen-Jing Xiao*[a,c]

Abstract: In contrast to the plethora of catalytic systems that enable access to any enantiomers of the chiral products by simply choosing between a pair of enantiomeric or pseudoenantiomeric chiral catalysts, few analogously effective protocols exist for the synthesis of compounds bearing multiple stereogenic centers with full control of the absolute and relative stereochemical configurations. Here, we report the application of our previously developed modular phosphoramidite-thioether ligands for the copper-catalyzed diastereodivergent asymmetric 1,3-dipolar cycloaddition of azomethine ylides and nitroalkenes. Our catalytic system enables wide substrate scope, great stereochemical control, and high reaction efficiency.

Drug chirality is now a prominent theme in the drug discovery and library design, as such fundamental property is of immense significance to biological recognition in many pharmacologically relevant events.[1] In particular, both the absolute and relative configurations usually have distinct effects on the physiological or pharmacological activities of a given chiral bioactive compound.[2] Over the past several decades, asymmetric catalysis has proven to be a powerful and attractive tool to produce enantioenriched molecules for its maximum efficiency.[3] A variety of broadly useful reactions for the synthesis of chiral compounds have been invented by ligand-controlled transition metal catalysis and covalent or noncovalent activation-based organocatalysis. Despite extensive efforts, however, developing efficient catalytic systems that allow at will to access any diastereomer of a chiral molecule with multiple stereogenic centers remains a challenge. This is largely due to the fact that the formation of certain diastereomers is usually inherently favored when using conformationally rigid ligands or catalysts.[4]

In recent years, diastereodivergent asymmetric catalysis has established its unwavering position in the synthesis of full complement of diastereomers from the same set of starting materials.[5] Representative methods include the ad hoc adjustment of the reaction parameters (e.g., solvents, additives, and temperature),[6] adapting organocatalysts,[7] metals,[8] or ligands,[9] and two chiral catalysts-based dual catalysis.[10,11] From the viewpoint of atom-economy and operational simplicity, a single type of metal or ligand-based catalytic strategy represents an ideal approach for diastereodivergent synthesis,[8,9] which eliminates the compatibility issue that always needs to be considered in dual catalysis.[10] In biological system, minor structural change of functional proteins and enzymes by noncovalent interaction or covalent modification can result in a distinct three-dimensional architecture, leading to modulation of the timely intra- or extracellular events to proceed with precise synergy (Figure 1a).[12] Inspired by this intriguing biological process, we hypothesized that exploration of conformationally flexible chiral ligands would allow to dictate the diastereodivergency in asymmetric catalysis even when using a single metal. Shibasaki and Kumagai in 2009 disclosed that complexation of L-valine-derived amide with $Sc(O^iPr)_3$ or $Er(O^iPr)_3$ resulted in two conformational distinct chiral catalysts with different chiroptical properties, enabling diastereodivergent direct asymmetric catalytic Mannich-type reactions of *α*-cyanoketones and *N*-Boc imines.[8a,b] On the basis of this pioneering work and our long standing interest in asymmetric catalysis,[13] we conceived that our previously developed chiral P,S-type ligands might enable diastereodivergent asymmetric catalysis (Figure 1b). This ligand architecture exhibit a number of features: (1) the coordination of P and S atoms with metal might provide highly enantioselective chiral environment, and (2) in analogy to the functional proteins and enzymes, modification of the N substitution would result in a distinct conformation of the catalyst.

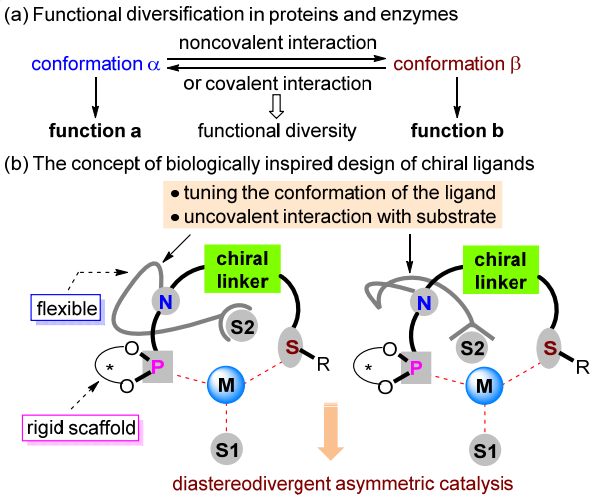

Figure 1. (a) Functional diversification in functional proteins and enzymes and (b) biologically inspired ligand design for the diastereodivergent asymmetric catalysis.

Catalytic asymmetric 1,3-dipolar cycloaddition reaction of azomethine ylides with activated alkenes is an important type of transformation for assembly of structurally diverse pyrrolidines from conveniently prepared starting materials.[14] Despite the significant advances in this field, however, the catalytic asymmetric diastereodivergent variants are still rare. Recently,

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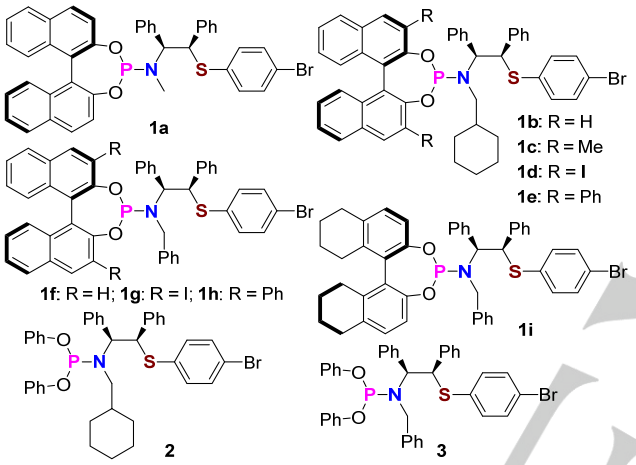
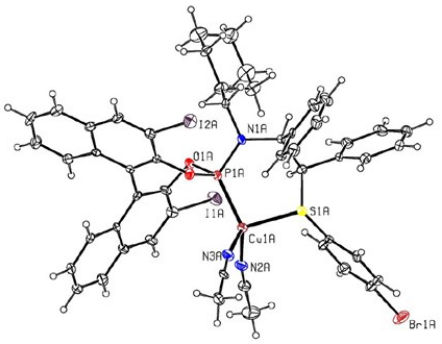
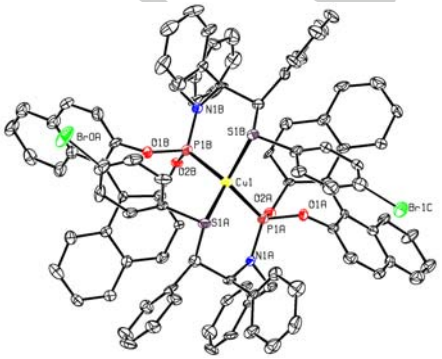
Hou disclosed an elegant and creative strategy for the switch of diastereoselectivity in the asymmetric Cu(I)/P,N-ferrocene-catalyzed 1,3-dipolar cycloaddition by simply adjusting the electronic properties of aryl substituent in the ligands.[9a] The development of novel ligands showing highly efficient control of diastereodivergency remains a great challenge. Herein, we describe the application of our previously developed chiral P,S-ligands bearing privileged (*R*)-BINOL-derived phosphoramidite scaffold (Scheme 1),[15] to copper-catalyzed asymmetric diastereodivergent 1,3-dipolar cycloaddition of azomethine ylides and nitroalkenes. Notably, the modular structure of such type of ligands facilitates their rapid synthesis, readily tuning, and screening of a small library ligands.[16] Figure 2 shows the X-ray crystal structures derived from $[Cu(CH_3CN)_2]BF_4$/**1d** and $[Cu(CH_3CN)_2]BF_4$/**1f** with 1:1 or 1:2 ratios.[17] As expected, the P and S atoms coordinate with Cu to form a chiral environment that is essential for the enantioselective induction; and both cyclohexyl and benzyl groups lie away from the copper atom, which might serve as a potentially flexible handle.



Scheme 1. Modularly designed phosphoramidite-thioether ligands.



X-ray structure of [Cu]/**1d**

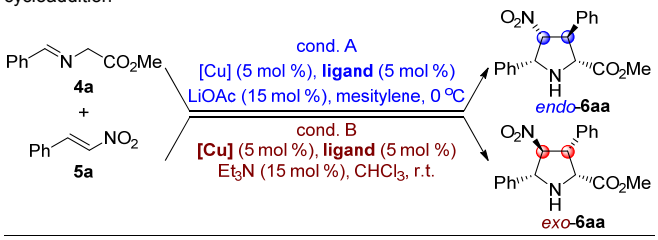


X-ray structure of [Cu]/**1f**

Figure 2. X-Ray crystal structures derived from the $[Cu(CH_3CN)_2]BF_4$/**1d** and $[Cu(CH_3CN)_2]BF_4$/**1f** complexes. Counter sanion has been omitted for clarity.

With the phosphoramidite-thioether ligands **1a-i** (Scheme 1), we initially explored the ligand effect on the Lewis acid copper-catalyzed 1,3-dipolar cycloaddition of azomethine ylide **4a** and nitroalkene **5a**.[14] Representative results of the optimization study are highlighted in Table 1, demonstrating that these ligands showed high catalytic activity but with variable stereoselectivity.[18] For example, the catalyst system consisting of ligand **1a** with $Cu(CH_3CN)_4OTf$ in toluene at 0 °C could efficiently catalyze the reaction in the presence of LiOAc as the base; and the corresponding *endo*-**6aa** was formed as the major product in excellent yield though with only 16% ee (entry 1). To improve the enantioselectivity, we proceeded to modify the substituents on the N atom and binaphthyl scaffold according to our design plan. When introducing a cyclohexyl methyl group on the N atom, incorporating the more sterically encumbered R group resulted in higher enantioselectivity (entries 2-5). Finally, ligand **1e** was identified to be the best choice, and afforded *endo*-**6aa** in 85% isolated yield with >19:1 dr and 94% ee, when the reaction temperature was lowered to -5 °C (entry 6). To our delight, replacement of the cyclohexyl methyl group on N atom with a benzyl group resulted in a complete diastereochemical switch. For instance, the use of ligand **1f** and $(CuOTf)_2$•Tol as the catalyst and catalytic amount of Et_3N as the base in $CHCl_3$ gave the *exo*-**6aa** as the major product with 88% ee (entry 7). Though variation in the steric properties of the substituents on the binaphthyl moiety did not result in any further improvement of stereoselectivity (entries 8-9), H8-BINOL derived ligand **1i** gave rise to a significant increase of enantioselectivity (entry 10). Further optimization study revealed that the *exo*-**6aa** could be formed exclusively with 93% ee, when the reaction was performed in a 5:1 mixture of $CHCl_3$/toluene at 0 °C (entry 11). To prove the concept of our ligand design, we performed the control experiments with ligands **2** and **3** without the binaphthyl scaffold (entries 12-13). The moderate stereoselectivity suggested that this privileged scaffold is critical to the chiral induction.

Table 1: Optimization of asymmetric diastereodivergent 1,3-dipolar cycloaddition[a]



Entry	L	Cond.	*t* [h]	Yield [%][b]	Endo/exo[c]	*ee* [%][d]
1	**1a**	A	3	77	10:1	16
2	**1b**	A	3	96	8:1	24
3	**1c**	A	3	99	>19:1	82
4	**1d**	A	3	93	>19:1	82
5	**1e**	A	6	84	>19:1	86
6[e]	**1e**	**A**	**14**	**95(85)**[f]	**>19:1**	**94**
7	**1f**	A	3	92	1:10	88
9	**1g**	B	3	90	1:1	37
9	**1h**	B	3	85	1:1	51
10	**1i**	B	3	81	1:10	92
11[g]	**1i**	**B**	**3**	**94(90)**[f]	**<1:19**	**93**
12	**2**	A	3	92	>19:1	20

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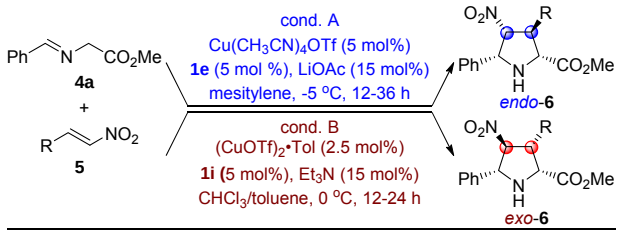
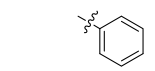
13	**3**	B	3	95	1:1	17

[a] Condition A: **4a** (0.3 mmol), **5a** (0.2 mmol), $Cu(CH_3CN)_4OTf$ (5 mmol %) and **ligand** (5 mmol %) in mesitylene (2.0 mL) at 0 °C. Condition B: **4a** (0.4 mmol), **5a** (0.2 mmol), $(CuOTf)_2$·Tol (2.5 mmol %) and **ligand** (5 mmol %) in $CHCl_3$ (2.0 mL) at r.t.. [b] Determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by ^1H NMR analysis of the crude reaction mixtures. [d] The ee values of the major diastereomers were determined by chiral HPLC analysis. [e] Performed at -5 °C. [f] Isolated yield in parentheses. [g] Performed in $CHCl_3$/toluene (5:1, 2.0 mL) at 0 °C.

Table 2: Scope of the nitroalkenes.[a, b]



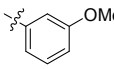


cond. A: *endo*-**6aa**
85%, >19:1dr, 94% ee
cond. B: *exo*-**6aa**
90%, >19:1 dr, 93% ee

cond. A: *endo*-**6ab**
97%, >19:1dr, 91% ee
cond. B: *exo*-**6ab**
93%, >19:1 dr, 91% ee

cond. A: *endo*-**6ac**
94%, >19:1dr, 90% ee
cond. B: *exo*-**6ac**
92%, >19:1 dr, 94% ee

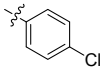
cond. A: *endo*-**6ad**
85%, >19:1dr, 90% ee
cond. B: *exo*-**6ad**
85%, >19:1 dr, 92% ee



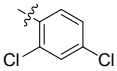
cond. A: *endo*-**6ae**
91%, >19:1dr, 90% ee
cond. B: *exo*-**6ae**
95%, >19:1 dr, 97% ee

cond. A: *endo*-**6af**
92%, >19:1dr, 90% ee
cond. B: *exo*-**6af**
81%, >19:1 dr, 90% ee

cond. A: *endo*-**6ag**
88%, >19:1dr, 88% ee
cond. B: *exo*-**6ag**
92%, >19:1 dr, 98% ee



cond. A: *endo*-**6ah**
85%, >19:1dr, 94% ee
cond. B: *exo*-**6ah**
93%, >19:1 dr, 93% ee

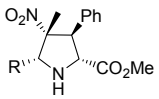


cond. A: *endo*-**6ai**
90%, >19:1dr, 94% ee
cond. B: *exo*-**6ai**
94%, >19:1 dr, 93% ee

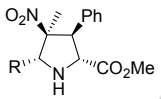
cond. A: *endo*-**6aj**
83%, >19:1dr, 94% ee
cond. B: *exo*-**6aj**
94%, >19:1 dr, 94% ee

cond. A: *endo*-**6ak**
71%, >19:1 dr, 91% ee
cond. B: *exo*-**6ak**
74%, >19:1 dr, 93% ee

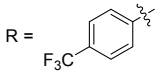
cond. A: *endo*-**6al**
79%, >19:1 dr, 91% ee
cond. B: *exo*-**6al**
74%, 6:1 dr, 95% ee



cond. A: *endo*-**6fm**[c]
90%, >19:1 dr, 84% ee



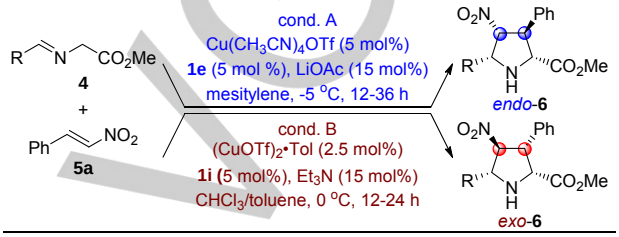
cond. B: *exo*-**6fm**
98%, >19:1 dr, 95% ee



[a] Reaction conditions A are the same as in entry 6 of Table 1. Reaction conditions B are the same as in entry 11 of Table 1. [b] Isolated yields. The dr values were determined by ^1H NMR analysis of the crude reaction mixtures. The ee values were determined by chiral HPLC analysis. [c] CsOAc (15 mol%) was used as the base instead of LiOAc.

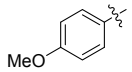
With the two sets of optimal conditions established, we first explored the substrate scope of nitroolefins by reacting with imino ester **4a** (Table 2). In addition to **5a**, a range of differently substituted nitroolefins **5b-h** bearing an electron-donating (e.g., Me, OMe) and electron-withdrawing (e.g., Cl, Br) substituent at the *ortho*-, *meta*- and *para*-positions were all well tolerated. The corresponding products *endo*-**6ab-ah** and *exo*-**6ab-ah** were obtained exclusively in generally high yields with excellent diastereoselectivity (>19:1) and enantioselectivity (88-98% ee). Moreover, as demonstrated in the synthesis of **6ai**, the steric property or substitution pattern of the phenyl ring has no obvious effect on the reaction efficiency or stereoselectivity. The reaction of heteroaryl-substituted (e.g., 2-furyl and 2-thiophenyl) nitroolefins **5j** and **5k** also proceeded smoothly, leading to the diastereodivergent synthesis of **6aj** and **6ak** in good yields with 91-94% ee values. In the case of *β*-alkyl-substituted nitroolefins, such as **5l**, condition **A** still enabled excellent *endo*-selectivity and enantioselectivity in cycloadduct product **6al**, while moderate diastereoselectivity was observed in the formation of the *exo*-**6al**. These results indicate that the heteroaromatic and aromatic rings of the nitroolefins might be beneficial for the control of diastereoselectivity switch. Remarkably, our diastereodivergent asymmetric catalyst systems also proved to be suitable for the sterically hindered trisubsituted nitroalkenes, such as **5m** with a methyl group at the α-position, affording products *endo*- and *exo*-**6fm** bearing a chiral quaternary carbon center at 4-position with high enantioselectivity. To the best of our knowledge, there is no precedent about the diastereoselective synthesis of these challenging pyrrolidines.

Table 3: Scope of the azomethine ylides.[a, b]

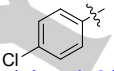


cond. A: *endo*-**6aa**
80%, >19:1dr, 93% ee
cond. B: *exo*-**6aa**
90%, >19:1 dr, 93% ee

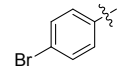
cond. A: *endo*-**6ba**
70%, >19:1dr, 90% ee
cond. B: *exo*-**6ba**
91%, >19:1 dr, 94% ee



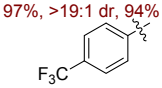
cond. A: *endo*-**6ca**
77%, >19:1 dr, 85% ee[c]
cond. B: *exo*-**6ca**
97%, >19:1 dr, 94% ee



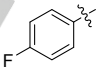
cond. A: *endo*-**6da**
84%, >19:1dr, 93% ee
cond. B: *exo*-**6da**
85%, >19:1 dr, 94% ee



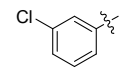
cond. A: *endo*-**6ea**
84%, >19:1dr, 92% ee
(1.58 g, 97%, >19:1 dr, 90% ee)
cond. B: *exo*-**6ea**
94%, >19:1 dr, 94% ee
(1.52 g, 95%, >19:1 dr, 94% ee)



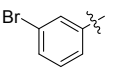
cond. A: *endo*-**6fa**
90%, >19:1dr, 91% ee
cond. B: *exo*-**6fa**
98%, >19:1 dr, 95% ee



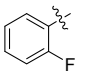
cond. A: *endo*-**6ga**
89%, >19:1 dr, 92% ee
cond. B: *exo*-**6ga**
93%, >19:1 dr, 95% ee



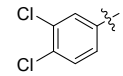
cond. A: *endo*-**6ha**
98%, >19:1 dr, 93% ee
cond. B: *exo*-**6ha**
94%, >19:1 dr, 98% ee



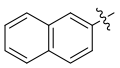
cond. A: *endo*-**6ia**
99%, >19:1 dr, 92% ee
cond. B: *exo*-**6ia**
94%, >19:1 dr, 98% ee



cond. A: *endo*-**6ja**
90%, >19:1 dr, 90% ee
cond. B: *exo*-**6ja**
86%, 4:1 dr, 91% ee



cond. A: *endo*-**6ka**
92%, >19:1 dr, 90% ee
cond. B: *exo*-**6ka**
97%, >19:1 dr, 97% ee



cond. A: *endo*-**6la**
96%, 12:1 dr, 88% ee
cond. B: *exo*-**6la**
97%, >19:1 dr, 94% ee

cond. A: *endo*-**6ma**
75%, >19:1 dr, 56% ee[c]
cond. B: *exo*-**6ma**
68%, >19:1 dr, 98% ee

cond. A: *endo*-**6na**[d]
83%, >19:1dr, 94% ee
cond. B: *exo*-**6na**
NR

[a] Reaction conditions A are the same as in entry 6 of Table 1. Reaction conditions B are the same as in entry 11 of Table 1. [b] Isolated yields. The dr values were determined by ^1H NMR analysis of the crude reaction mixtures. The ee values were determined by chiral HPLC analysis. [c] Performed with KOAc (15 mol%) as the base. [d] CsOAc (15 mol%) was used as the base instead of LiOAc. NR = No Reaction.

Then, we proceeded to examine the substrate generality of the diastereodivergent 1,3-dipolar cycloaddition regarding the azomethine ylides (Table 3). As expected, either the substitution patterns or the electronic characteristics of the phenyl ring within azomethine ylides show no apparent effect on the reaction efficiency and stereoselectivity. For instance, a range of mono-

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substituted azomethine ylides **4b-g** with electron-donating (e.g., Me, MeO) and electron-withdrawing (e.g., Cl, Br, CF_3, F) groups at the *para*-position of the benzene ring all reacted with nitroolefin **5a** nicely, furnishing the cycloaddition adducts *endo*- and *exo*-**6ba-ga** in consistently high yields with excellent enantioselectivities (85-95% ee). Notably, synthetically useful halogen groups such as Cl, Br and F, could also be incorporated into the *meta*- and *ortho*-positions of the phenyl ring. The corresponding products *endo*-**6ha-ja** and *exo*-**6ha-ia** can be obtained in satisfactory yields and high dr and ee values. In the case of *exo*-**6ja**, the moderate *exo*-selectivity was probably due to the steric hindrance in their transition states. Again, the reactions with imino ester **4k** bearing multiple chlorides on the phenyl ring proceeded smoothly to give both of the *endo*- and exo-**6ka** with excellent yields and stereoselectivity. Moreover, the fused aromatic group substituted substrate **4l** also reacted well with **5a** to produce both of the *endo*- and *exo*-**6la** in good yield with 88% and 94% ee, respectively. However, 2-thiophene-substituted imino ester **4m** proved to be only suitable as 1,3-dipole for the *exo*-selective reaction. And the aliphatic imino ester **4n** only readily participated in the *endo*-selective reaction to give *endo*-**6na** with excellent ee values. To demonstrate the synthetic applicability of our catalytic systems, we performed a gram-scale reaction between imino ester **4e** and **5a** under the standard conditions. Pleasingly, the reactions still proceeded smoothly with almost no influence on the yields and stereoselectivity (90-94% ee), indicating that this catalytic system should be potential for large-scale chemical production of densely tetrasubstituted pyrrolidines.[18]

The absolute configurations of enantiomerically pure *endo*-**6ea** and *exo*-**6ea** were clearly determined to be (2*R*, 3*S*, 4*R*, 5*R*) and (2*R*, 3*R*, 4*S*, 5*R*), respectively, by X-ray crystallography (Figure 3).[17] Stereochemistry of the other cycloaddition products was assigned based on analogy to these compounds. Notably, the same absolute configuration (2*R*, 5*R*) at the C-2 and C-5 positions of **6ea** suggests that a preferred attack from the same face of Cu(I)-bound imino ester to the nitroalkene occurs in both cases of the ligands **1e** and **1i**. It means that both of the chiral ligands shield the same prochiral faces of the azomethine ylide-derived copper complexes. Thus, the diastereoselectivity switch might originate from the different interactions between the catalyst and nitroalkene.

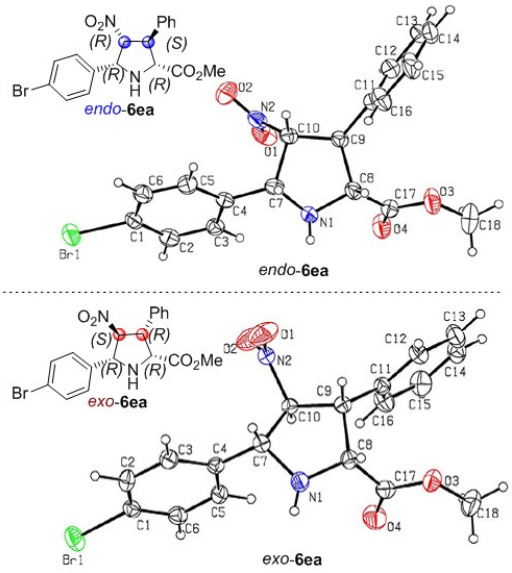
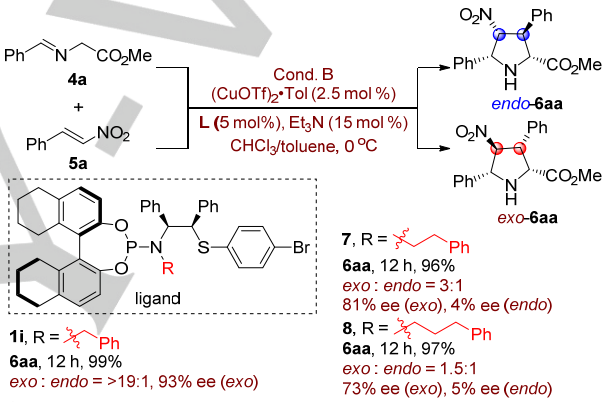


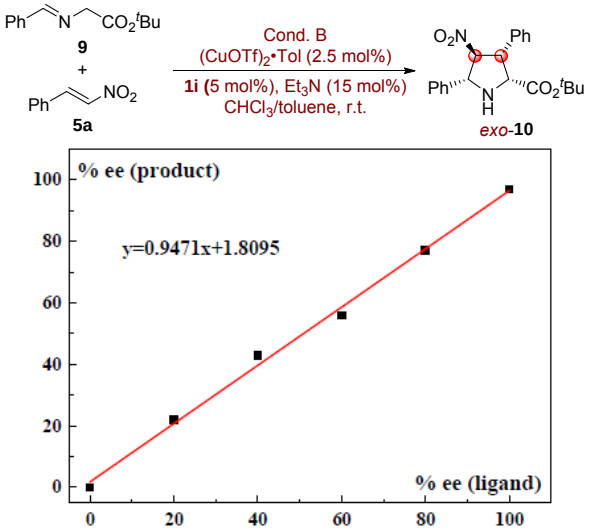
Figure 3. X-Ray crystal structures of *endo*-**6ea** and *exo*-**6ea**.

With this hypothesis in mind, we also synthesized ligands **7** and **8** bearing 3-phenemyl and 3-hydrocinnamyl at the N-atom respectively to confirm the importance of the N-benzyl unit within ligand **1i**. With **1i** as the reference ligand, we examined the catalytic ability of these structurally analogous ligands **7** and **8** in the model reaction (Scheme 2). In contrast to **1i**, while still moderate to good enantioselectivities were obtained in the reactions using ligands **7** and **8**, the *exo*-selectivity decreased significantly from >19:1 (*exo*-/*endo*-) to 3:1 and 1.5:1, respectively under the identical conditions. These results clearly demonstrate that the presence of a phenyl ring and its appropriate position is critical to the complete switch of the diastereoselectivity, namely from the *endo*- to *exo*-selectivity, as well as enantioselective induction. Specifically, there might be a π-π interaction of the N-benzyl with the aromatic ring of azomethine ylide. Moreover, the formation of *exo*-products should proceed through a stepwise pathway based on the fact that we could also successfully isolate the conjugate addition intermediate of exo-**6ag** in good yields with excellent stereoselectivity when performing the reaction at -30 °C.[18]



Scheme 2. Control experiments.

Then, we carried out the study of nonlinear effect to gain more insight into the mode of catalyst activation. We prepared ligand **1i** in six different levels of enantiopurity and evaluated their catalytic activity in the reaction of azomethine ylide **9** and nitroalkene **5a** (Scheme 3). It was found that the enantiopurity of the exclusively formed product *exo*-**10** displays a linear relationship with that of the chiral ligand **1i**, suggesting that the active catalyst species for the reaction was consistent with a 1:1 ratio of the Cu(I) catalyst and ligand.[18]



Scheme 3. Study of the nonlinear relationship between the optical activity of ligand **1i** and products.

In summary, we have described the application of our previously developed modular phosphoramidite-thioether ligands for highly enantioselective Cu(I)-catalyzed diastereodivergent 1,3-dipolar cycloaddition of azomethine ylides and nitroalkenes. Both of the densely functionalized *endo*- and *exo*-pyrrolidines can be obtained at will in good yields with excellent diastereo- and enantioselectivity. Mechanistic investigation suggests that the key to successful modulating the enforced sense of diastereoselectivity was presumably due to the tuning of the conformation and chiral environment of the catalyst by minor ligand modification. Ongoing efforts are directed toward the substrate scope of asymmetric diastereoselective 1,3-dipolar cycloaddition induced by these P,S-ligands, and elucidating the basis of the subtle ligand structural properties that control the diastereoswitching.

Acknowledgements

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Keywords: diastereodivergent catalysis • phosphoramidite-thioether ligand • 1,3-dipolar cycloaddition • enantioselectivity

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[17] CCDC 1558965 ([$Cu(CH_3CN)_2$]BF_4/**1d**), 1584930 ([$Cu(CH_3CN)_2$]BF_4/**1f**), 1558993 (*endo*-**6ea**) and 1558982 (*exo*-**6ea**) contain the supplementary crystallographic data.

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

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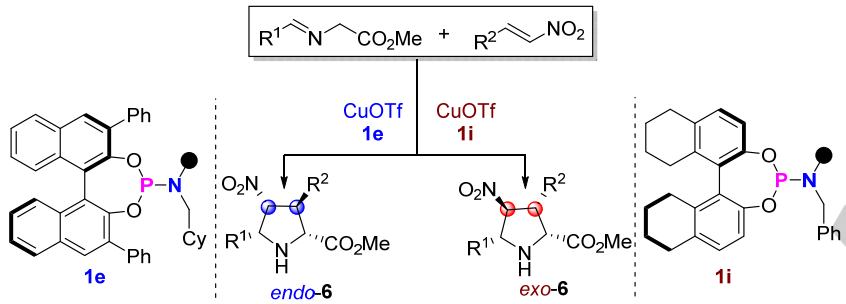

*Bin Feng, Jia-Rong Chen, Yun-Fang Yang, Bin Lu, and Wen-Jing Xiao**

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A Highly Enantioselective Copper/Phosphoramidite-Thioether-Catalyzed Diastereodivergent 1,3-Dipolar Cycloaddition of Azomethine Ylides and Nitroalkenes

In contrast to the plethora of catalytic systems that enable access to any enantiomers of the chiral products by simply choosing between a pair of enantiomeric or pseudoenantiomeric chiral catalysts, few analogously effective protocols exist for the synthesis of compounds bearing multiple stereogenic centers with full control of the absolute and relative stereochemical configurations. Here, we report the application of our previously developed modular phosphoramidite-thioether ligands for the copper-catalyzed diastereodivergent asymmetric 1,3-dipolar cycloaddition of azomethine ylides and nitroalkenes. Our catalytic system enables wide substrate scope, great stereochemical control, and high reaction efficiency.