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A Highly Enantio- and Diastereoselective Cu-Catalyzed 1,3-Dipolar Cycloaddition of Azomethine Ylides with Nitroalkenes**

Xiao-Xia Yan, Qian Peng, Yan Zhang, Kai Zhang, Wei Hong, Xue-Long Hou, and Yun-Dong Wu*

Dedicated to Professor Wei-Yuan Huang
on the occasion of his 85th birthday

The 1,3-dipolar cycloaddition of azomethine ylides to electron-deficient alkenes is one of the most powerful methods for the construction of highly substituted pyrrolidine rings.[1] Following early research on the preparation of optically active pyrrolidines in the presence of either a stoichiometric amount of a chiral metal complex[2] or a chiral auxiliary,[3] an asymmetric catalytic version of this reaction has been developed recently.[4–8] The groups of Jørgensen,[4a] Zhang,[5a] Schreiber,[6] Zhou,[8a] and Carretero[8b] have reported that the reaction of glycine derivatives with electron-deficient alkenes is highly enantio- and *endo*-selective in the presence of chiral Zn^{II}–bisoxazolines, Ag^{I}–phosphanes, Ag^{I}–quinap, Ag–P,N ligands, and Cu–fesulphos, while the groups of Komatsu and Zhang have reported *exo* selectivity with a Cu–diphosphane complex and P,N ligands as catalyst.[5b,7] Each of these reactions involves derivatives of unsaturated carboxylates as the dipolarophiles and the diastereoselectivity is not switchable.[9a] Herein, we report a Cu^{I}–P,N-ferrocene-catalyzed 1,3-dipolar cycloaddition of nitroalkenes to an imino ester derived from glycine and our observation of a dramatic switch in *exo*/*endo* selectivity due to

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[*] Dr. X.-X. Yan, Y. Zhang, Prof. Dr. X.-L. Hou
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
354 Fenglin Road, Shanghai 200032 (China)
Fax: (+86) 21-5492-5100
E-mail: xlhou@mail.sioc.ac.cn

Q. Peng, K. Zhang, W. Hong, Prof. Dr. X.-L. Hou, Prof. Dr. Y.-D. Wu
Shanghai–Hong Kong Joint Laboratory in Chemical Synthesis
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences,
354 Fenglin Road, Shanghai 200032 (China)

Prof. Dr. Y.-D. Wu
Department of Chemistry
Hong Kong University of Science and Technology
Hong Kong (China)

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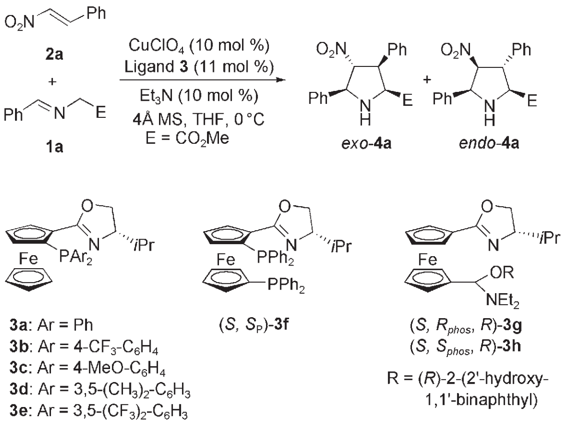
the electronic properties of the chiral ligand. A qualitative model is also proposed to rationalize the observed stereochemistry.

Initially, the reaction of imino ester **1a** with nitroalkene **2a** was examined in the presence of $CuClO_4$ and ligands **3a**[9b] and **3f–h** [Eq. (1)].[10d,11] The results are compiled in Table 1.



(1)

Table 1: Reaction of **1a** with **2a** in the presence of different ligands.[a]

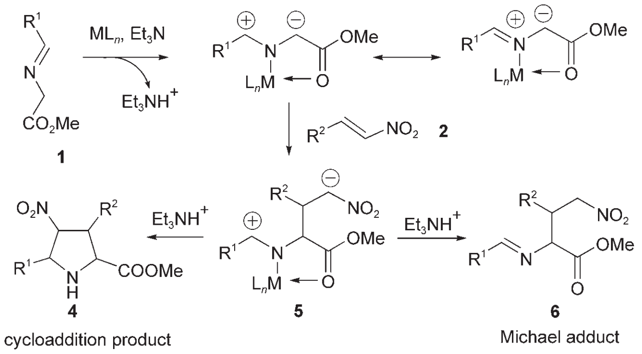
Entry	Ligand	Yield [%][b]	*exo*/*endo*[c]	*ee* [%] (*exo*/*endo*)[d]
1	**3a**	58	only *exo*	97 (n.d.)
2	**3b**	67	73:27	95 (84)
3	**3c**	65	only *exo*	98 (n.d.)
4	**3d**	49	only *exo*	98 (n.d.)
5	**3e**	62	18:82	88 (97)
6	**3f**	37	49:51	92 (15)
7	**3g**	75	only *endo*	n.d. (17)
8	**3h**	60	18:82	n.d. (3)

[a] Molar ratio of **1a** to **2a** = 1.2:1. [b] Yield of isolated product. [c] Determined by ^1H NMR spectroscopy. [d] Determined by chiral HPLC. n.d. = not determined.

The reaction with ligand **3a** yielded *exo*-**4a**[12] as the sole product in 58% yield with 97% *ee* (Table 1, entry 1), while the *endo* isomer was obtained with 17% *ee* with ligand **3g** (Table 1, entry 7). A sharp decrease in diastereo- and/or enantioselectivities was observed with ligands **3f** and **3h** (Table 1, entries 6 and 8, respectively).

Encouraged by the result with ligand **3a**, we synthesized a series of P,N-ferrocenyl ligands **3b–e** bearing different aryl groups on the P atom[11,13] and used them in the reaction. As shown in Table 1, a dramatic variation in diastereoselectivity was observed. Ligands **3c** and **3d**, which have electron-donating substituents on the phenyl rings, gave exclusively the *exo* product with excellent enantioselectivity (entries 3 and 4, Table 1), whereas ligand **3b**, which has one electron-withdrawing CF_3 group on each phenyl ring, gave a mixture of *exo* and *endo* isomers in a ratio of 73:27 with 95% and 84% *ee*, respectively. Ligand **3e** with two CF_3 substituents on each phenyl ring, gave the *endo* isomer as the major product with 97% *ee* (entry 5, Table 1). THF proved to be a better solvent than CH_2Cl_2, toluene, Et_2O, or CH_3CN in terms of yields and diastereoselectivities. When AgOAc and ligand **3a** were used in THF for the reaction, an 87:13 ratio of *exo* and *endo* isomers (91% and 62% *ee*, respectively) was obtained in an overall yield of 67%.

Although the reaction provides the pyrrolidine derivatives with high *ee*, the yields are only moderate because Michael addition occurs as a side reaction.[12] This supports the stepwise mechanism proposed by Cossío and co-workers.[12,14] As shown in Scheme 1, a zwitterionic species **5** should be formed as an intermediate, from which the cycloaddition product **4** is formed. However, **5** can also be protonated by Et_3NH^+, the conjugate acid of Et_3N, to form the Michael adduct. In this case the yield of pyrrolidine **4** could be improved by using a stronger base (weaker conjugate acid) to slow down the protonation. Indeed, when *t*BuOK was used as the base in the reaction of **1a** and **2a** with **3a** as ligand, the yield of *exo*-**4a** increased from 58% to 87%, albeit with a slight decrease in *ee* (from 97% to 95%).

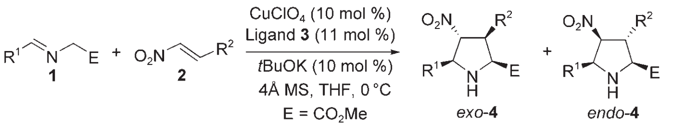


Scheme 1. Proposed mechanism of the reaction of **1** with **2**.

The 1,3-cycloaddition of different imino esters **1** and nitroalkenes **2** in the presence of ligands **3a** and **3e** was studied under these optimized conditions (Table 2).[15] All reactions in the presence of **3a** provided *exo*-**4** either exclusively (Table 2, entries 1–7) or as the major isomer in a ratio between 88:12 and 92:8 (Table 2, entries 8–11). The yields were always high and the *ee* values for *exo*-**4** ranged from 92% to 98%, except for product **4k** (Table 2, entry 11). An aliphatic nitroalkene was also found to be a suitable dipolarophile; it gave *exo*-**4g** as the sole diastereomer with 98% *ee* (Table 2, entry 7). When ligand **3e** was used, the *endo*-**4** diastereomers were obtained in high yields. The ratio of *endo*-**4** to *exo*-**4** ranged from 70:30 to 94:6 (Table 2, entries 12–19), with *ee* values between 92% and 98% (Table 2, entries 12–16 and 18), with the exception of products **4i** and **4k**, for which the *ee* values were 84 and 88%, respectively (Table 2, entries 17 and 19). After one recrystallization from dichloromethane/petroleum ether, *exo*-**4k** and *endo*-**4k** were obtained with over 99% and 96% *ee*, respectively.

The absolute configurations of *exo*-**4k** and *endo*-**4k** were assigned as (2*S*,3*S*,4*R*,5*R*) and (2*S*,3*R*,4*S*,5*R*), respectively, by X-ray diffraction analysis (Figure 1). The same (2*S*,5*R*) configuration for the two products indicates that the addition

Table 2: Enantioselective Cu^{I}-catalyzed 1,3-dipolar cycloaddition of azomethine ylides **1** to nitroalkenes **2**.



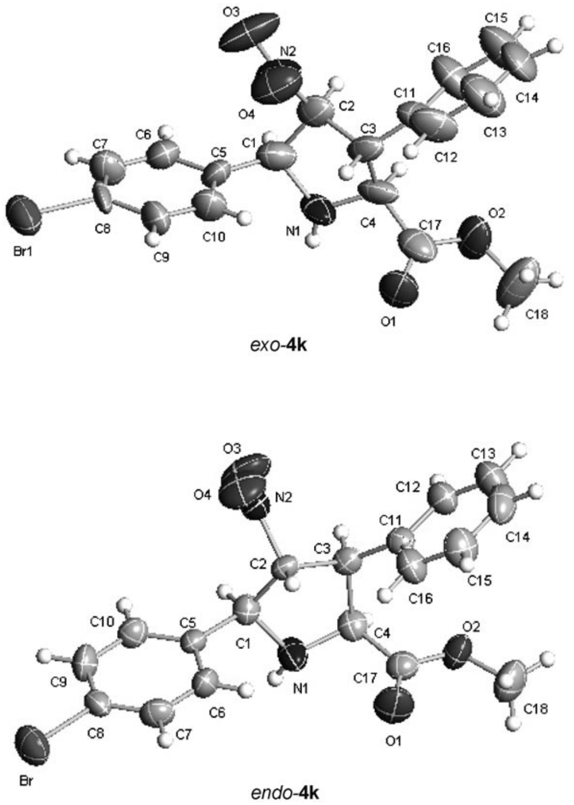
Entry	R^1	R^2	Ligand	*exo/endo*[a]	Product	Yield [%][b]	*ee* [%][c]
1	Ph	Ph	**3a**	only *exo*	**4a**	87	95
2	Ph	p-NO_2-C_6H_4	**3a**	only *exo*	**4b**	70	96
3	Ph	p-MeO-C_6H_4	**3a**	only *exo*	**4c**	77	96
4	Ph	p-Me-C_6H_4	**3a**	only *exo*	**4d**	73	96
5	Ph	p-Cl-C_6H_4	**3a**	only *exo*	**4e**	64	92
6	Ph	m-Cl-C_6H_4	**3a**	only *exo*	**4f**	74	95
7	Ph	iPr	**3a**	only *exo*	**4g**	75	98
8	p-MeO-C_6H_4	Ph	**3a**	89:11	**4h**	96	97
9	m-Cl-C_6H_4	Ph	**3a**	88:12	**4i**	97	92
10	2-naphthyl	Ph	**3a**	92:8	**4j**	92	92
11	p-Br-C_6H_4	Ph	**3a**	86:14	**4k**	77	83 (99)[d]
12	Ph	Ph	**3e**	14:86	**4a**	85	98
13	Ph	p-MeO-C_6H_4	**3e**	30:70	**4c**	79	95
14	Ph	m-Cl-C_6H_4	**3e**	11:89	**4f**	82	92
15	Ph	iPr	**3e**	6:94	**4g**	88[e]	97
16	p-MeO-C_6H_4	Ph	**3e**	18:82	**4h**	79	96
17	m-Cl-C_6H_4	Ph	**3e**	17:83	**4i**	98	84
18	2-naphthyl	Ph	**3e**	19:81	**4j**	98	97
19	p-Br-C_6H_4	Ph	**3e**	18:82	**4k**	71	88 (96)[d]

[a] Determined by ^1H NMR spectroscopy. [b] Yield of isolated product. [c] Major product determined by HPLC. [d] The *ee* value obtained after one recrystallization is given in parentheses. [e] Yield of isolated *endo* products.

of the nitroalkene occurs at the *Si* face of the Cu-bound imino ester anion with both **3a** and **3e**.

Varying the electronic properties of ligands to fine-tune the stereoselectivity in asymmetric catalysis has been conceptually attractive.[16] Pioneered by Jacobsen[16a] and others, there have since been many reports of improved stereoselectivity by utilizing this electronic effect.[11,16] However, there has been only limited success in switching the stereoselectivity.[16d,h,j–l] Our current finding of a dramatic switch in diastereoselectivity while still keeping high enantioselectivity represents an exceptional example. Our results also indicate that the effect is not due to a π–π interaction (see entries 7 and 15 in Table 2).

A computational study of the complex formed by Cu–**3a** and the anion of the imino ester **1a** was also performed. The two structures were fully optimized with the density functional theory method at the B3LYP/6-31G*(lanldz) level.[17] When these structures assume a distorted tetrahedral geometry with a more or less coplanar Cu-P-N-N array (Figure 2), structure **A** is calculated to be about 4.3 kcal mol^{-1} more stable than **B**.[18] The latter is significantly destabilized by the steric interactions between the phenyl group of the imino ester and one of the phenyl groups of the ligand and the ferrocene. Therefore, the stereoselectivity can be discussed on the basis of the addition of nitroalkene to structure **A**.[19]



exo-**4k**

endo-**4k**

Figure 1. ORTEP diagrams of the X-ray crystal structures of *exo*-**4k** and *endo*-**4k**.

The *Re* face of structure **A** is apparently shielded by the isopropyl group, as indicated by the short C1−H1 distance (3.14 Å). On the other hand, the two phenyl groups on the P atom are oriented in such a way that they do not shield the *Si* face. Therefore, it is reasonable to assume that the attack of nitroalkene occurs at the *Si* face of the Cu-bound imino ester anion, in agreement with the experimental observations (Figure 1). As shown by the Newman projections, there are three transition structures with staggered conformations for the *exo* and *endo* diastereomers. Upon nucleophilic addition at C2 of the nitroalkene there should be an accumulation of negative charge at C3. Therefore, we argue that **7c** and **8b** are more favorable transition structures for the *exo* and *endo* products, respectively, because the developing negative charge at C3 can be stabilized by electrostatic interaction with the Cu center. In structure **7c**, the nitro group, which carries partial negative charge, lies away from the valley formed by the two aryl groups of the P ligand, whereas the nitro group in **8b** lies in the valley. Therefore, when the aryl groups are electron-rich, structure **7c** is expected to be more stable than **8b**, which leads to the favorable formation of the

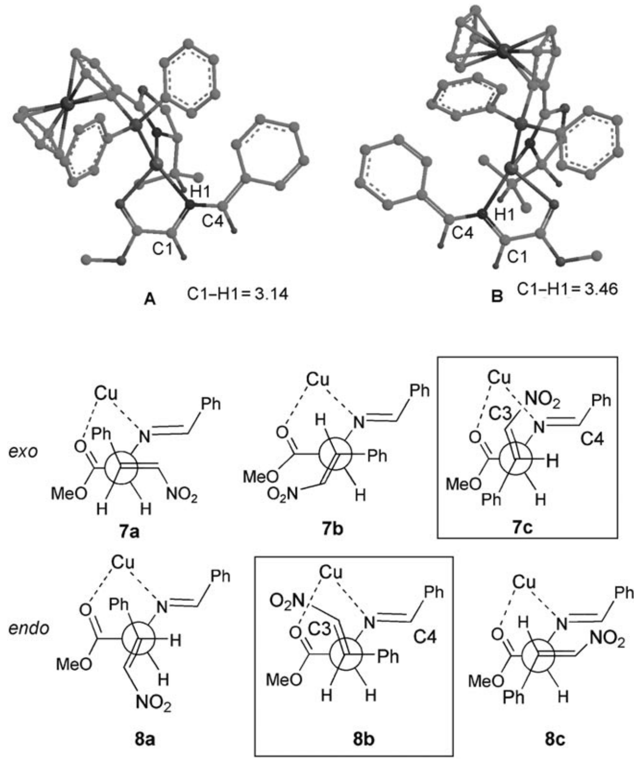


Figure 2. Calculated structures (**A** and **B**) of complexation modes of Cu^{I}–**3a** with the anion of imino ester **1a** and staggered transition-structure models of nitrostyrene on the *Si* face of the Cu-bound imino ester anion. Fe brown, Cu black, C green, O red, N blue, H violet.

exo product. When the aryl groups are electron-deficient, however, structure **8b** is stabilized by electrostatic interaction, which leads to formation of the *endo* product.

The present report reveals for the first time the Cu^{I}-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides to nitroalkenes.[20] A high yield of either *exo* or *endo* adducts can be achieved, with excellent enantioselectivity, by using electron-rich or electron-deficient aryl groups on the P atom of chiral P,N-ferrocene ligands, respectively. A qualitative model has been proposed to rationalize the observed stereoselectivity. These results point to a new possibility to switch the stereoselectivity of the reaction by varying the electronic properties of the ligands. Furthermore, useful hints for ligand design are revealed. The application of this reaction and the use of other electron-deficient alkenes as dipolarophiles is currently being studied further.

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[20] Whilst this paper was under review, Carretero and co-workers published a paper that includes one example of the use of a nitroalkene in Cu-catalyzed asymmetric dipolar cycloaddition. See ref. [8b].