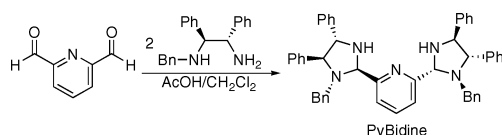


Chiral Bis(imidazolidine)pyridine–Cu(OTf)₂: Catalytic Asymmetric Endo-Selective [3 + 2] Cycloaddition of Imino Esters with NitroalkenesTakayoshi Arai,^{*,†} Asami Mishiro,[†] Naota Yokoyama,[†] Kuniko Suzuki,[†] and Hiroyasu Sato[‡]*Department of Chemistry, Graduate School of Science, Chiba University, Inage, Chiba 263-8522, Japan, and Application Laboratory, Rigaku Corporation, Akishima, Tokyo 196-8666, Japan*

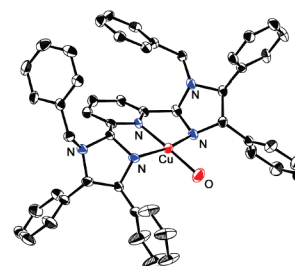
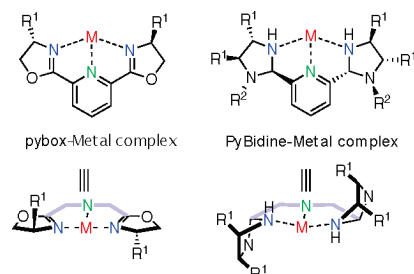
Received January 17, 2010; E-mail: tarai@faculty.chiba-u.jp

Pyrrolidines, which are five-membered N-heterocycles, are widely observed in biologically significant compounds and thus have become a core skeleton of many drug candidates. Catalytic asymmetric 1,3-dipolar cyclization¹ using chiral metal catalysts (containing metals such as Co,² Zn,³ Ag,⁴ Cu,⁵ Ca,⁶ and Ni⁷) and organocatalysts⁸ for the stereoselective construction of the pyrrolidine ring has been successfully developed. In particular, the reaction of the azomethine ylide generated from an imino ester and a nitroalkene is a fascinating reaction system in which an additional nitro functionality can be introduced onto the pyrrolidine ring.^{9–12} For this particular reaction, Carretero and co-workers^{10a} reported one example of exo-selective asymmetric pyrrolidine ring construction in 2005. Although Hou and co-workers¹¹ succeeded in switching the endo/exo selectivity by tuning the electron density of the chiral ligand, endo-selective cyclization remains rather limited.¹² Herein, we report the highly efficient catalytic asymmetric endo-selective [3 + 2] cycloaddition of imino esters with nitroalkenes using a newly developed bis(imidazolidine)pyridine–Cu(OTf)₂ complex.¹³

The novel C₂-symmetric bis(imidazolidine)pyridine (PyBidine) ligand¹⁴ was easily synthesized in a single condensation of 2,6-pyridyl aldehyde and optically active (S,S)-diphenylethylenediamine (Scheme 1). The all-trans stereochemical outcome on the imidazolidine ring was designed on the basis of the steric repulsion relayed from the substituents of the chiral diamine.^{13d}

Scheme 1. Synthesis of the Bis(imidazolidine)pyridine (PyBidine) Ligand

The newly developed PyBidine ligand readily provided a metal complex with Cu(OTf)₂. The structure was determined by X-ray crystallographic analysis of a single crystal as an aqua complex (Figure 1). The two triflate anions occupy the apical positions, and the imidazolidines of PyBidine coordinate to the Cu with retention of the protons on the nitrogen atoms (see the Supporting Information). Figure 2 shows a comparison of the tridentate coordination feature of PyBidine and the structure of the famous C₂-symmetric bis(oxazolinyl)pyridine (pybox) ligand.¹⁵ In the pybox–metal complex, the pyridine and oxazoline rings lie sprawled in the equatorial plane in coordination with the metal center, and the two alkyl groups at the stereogenic centers of the oxazolines are arranged as “chiral fences.” In the current PyBidine–Cu(OTf)₂ complex, the two imidazolidine rings stand perpendicular (~93°) to the equatorial tridentate coordination plane. Thus, the imidazolidine rings

**Figure 1.** X-ray structure of the PyBidine–Cu(OTf)₂–H₂O complex. Counteranions and protons have been omitted for clarity.**Figure 2.** Structural comparison of the PyBidine–metal and pybox–metal complexes.

themselves act as the chiral fences in the C₂-symmetric PyBidine–Cu(OTf)₂ complex to shield the first and third quadrants.

The catalytic activity was demonstrated in the [3 + 2] cycloaddition of imino esters with nitroalkenes. The PyBidine–Cu(OTf)₂ complex smoothly catalyzed the reaction of *trans*-nitrostyrene (NA1) and an imino ester (IE1) with the assistance of a basic additive. Under the optimized reaction conditions using Cs₂CO₃ in dioxane (Table 1, entry 8), the 1,3-dipolar cycloaddition was smoothly catalyzed by PyBidine–Cu(OTf)₂ to give the endo pyrrolidine product in 96% yield (endo/exo = 99:1). The enantioselectivity of the endo adduct was as high as 99% ee.

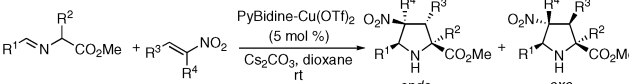
Table 1. Optimization of the Reaction Conditions for PyBidine–Cu(OTf)₂-Catalyzed [3 + 2] Cycloaddition

entry	base	solvent	time (h)	yield (%)	endo/exo	ee of endo (%)
1	none	dioxane	23	18	83:17	51
2	Et ₃ N	dioxane	21	84	96:4	74
3	Et ₃ N	CH ₃ CN	21	58	78:2	35
4	Et ₃ N	CH ₂ Cl ₂	21	>99	90:10	70
5	Et ₃ N	toluene	21	65	89:11	72
6	Et ₃ N	THF	21	<66 ^a	n.d. ^a	n.d. ^a
7	K ₂ CO ₃	dioxane	24	89	96:4	95
8	Cs ₂ CO ₃	dioxane	22	96	99:1	99

^a Inseparable byproducts were included.[†] Chiba University.
[‡] Rigaku Corporation.

The generality of the PyBidine–Cu(OTf)₂-catalyzed pyrrolidine synthesis is summarized in Table 2. Electron-deficient and electron-rich substituents were compatible for both R¹ and R³, maintaining high endo selectivity and excellent enantiomeric excesses. Aliphatic nitroalkenes were also successfully employed in the reaction (entries 14–16). Furthermore, using trisubstituted nitroalkenes afforded products having chiral quaternary carbon centers in 99% ee (entries 17 and 18). The reaction using the alanine-derived imino ester (**IE9**) constructed the chiral quaternary carbon center at the 2-position of the pyrrolidine ring. The PyBidine–Cu(OTf)₂ catalyst was tolerant of the hydroxy functionality of **NA5**.

Table 2. PyBidine–Cu(OTf)₂-Catalyzed Pyrrolidine Synthesis



IE1: R¹=Ph, R²=H-
IE2: R¹=4-MeOC₆H₄, R²=H-
IE3: R¹=4-MeOC₆H₄, R²=H-
IE4: R¹=3-MeOC₆H₄, R²=H-
IE5: R¹=2-MeOC₆H₄, R²=H-
IE6: R¹=4-ClC₆H₄, R²=H-
IE7: R¹=1-naphthyl, R²=H-
IE8: R¹=2-naphthyl, R²=H-
IE9: R¹=Ph, R²=Me-
NA1: R³=Ph, R⁴=H-
NA2: R³=4-MeOC₆H₄, R⁴=H-
NA3: R³=4-ClC₆H₄, R⁴=H-
NA4: R³=3,4-(OCH₂)₂-C₆H₃, R⁴=H-
NA5: R³=4-HOCH₂CH₂O-C₆H₄, R⁴=H-
NA6: R³=i-Pr, R⁴=H-
NA7: R³=CH₃(CH₂)₄, R⁴=H-
NA8: R³=Ph(CH₂)₂, R⁴=H-
NA9: R³=Ph, R⁴=Me-
NA10: R³=Ph, R⁴=Et-

entry	imino ester	nitroalkene	time (h)	yield (%)	endo/exo	ee of endo (%)
1	IE1	NA1	22	96	99:1	99
2	IE2	NA1	25	>99	97:3	99
3	IE3	NA1	21	87	95:5	98
4	IE4	NA1	22	78	97:3	99
5	IE5	NA1	26	75	96:4	94
6 ^a	IE6	NA1	24	63	95:5	93
7	IE7	NA1	22	78	97:3	94
8	IE8	NA1	22	60	97:3	87
9 ^{b,c}	IE9	NA1	115	64	>99:1	94
10	IE1	NA2	21	82	97:3	94
11 ^{a,b}	IE1	NA3	22	84	>99:1	94
12	IE1	NA4	22	70	>99:1	95
13	IE1	NA5	20	72	99:1	96
14	IE1	NA6	21	80	95:5	98
15	IE1	NA7	22	60	>99:1	97
16	IE1	NA8	23	80	98:2	98
17	IE1	NA9	21	68	98:2	99
18 ^b	IE1	NA10	48	69	>99:1	99

^a The catalyst was prepared using Cs₂CO₃, and Et₃N was used in the catalysis. ^b Using 10 mol % catalyst. ^c Using Et₃N as the base.

Notably, the pybox–Cu(OTf)₂ complex¹⁵ and the pybim–Cu(OTf)₂ complex¹⁶ gave trace amounts of the adduct under conditions similar to those of Table 2, entry 1. The results summarized in Table 2 illustrate the most efficient and useful metal-catalyzed endo-selective construction of pyrrolidine rings to date.

On the basis of the selective formation of the (2*S*,3*R*,4*S*,5*S*)-pyrrolidine using (S,S,S,S)-PyBidine–Cu(OTf)₂ catalyst, the enantioface selection in the [3 + 2] cycloaddition is explained as follows. The Cu catalyst would form the Cu-bound imino ester (or Cu azomethine ylide). When the imino ester coordinates to the Cu using the equatorial and upper apical sites, the nitroalkene approaches from the second quadrant (Figure 2). In this reaction sphere, to give the (2*S*,3*R*,4*S*,5*S*)-pyrrolidine, the nitrogen atom of the imino ester should stand at the upper apical site of Cu to react with nitroalkene using the *Re* face of the imine. Subsequent access of the nitroalkene to the activated imino ester while avoiding the steric interaction is appropriate to give the product in an endo-selective manner (see the model of the transition state in the Supporting Information).

In conclusion, we have succeeded in the development of a new bis(imidazolidine)pyridine–Cu complex for the highly endo-selective [3 + 2] cycloaddition of imino esters to nitroalkenes. The unique reaction sphere produced by PyBidine has the potential to furnish highly efficient asymmetric catalyses.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supporting Information Available: Detailed descriptions of experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (b) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235.
- (2) Allway, P.; Grigg, R. *Tetrahedron Lett.* **1991**, *32*, 5817.
- (3) (a) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236. (b) Dogan, Ö.; Koyuncu, H.; Garner, P.; Bulut, A.; Youngs, W. J.; Panzner, M. *Org. Lett.* **2006**, *8*, 4687.
- (4) (a) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400. (b) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174. (c) Knöpfel, T. F.; Aschewanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971. (d) Stohler, R.; Wahl, F.; Pfaltz, A. *Synthesis* **2005**, 1431. (e) Alemparte, C.; Blay, G.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 4569. (f) Zeng, W.; Zhou, Y.-G. *Org. Lett.* **2005**, *7*, 5055. (g) Zeng, W.; Chen, G.-Y.; Zhou, Y.-G.; Li, Y.-X. *J. Am. Chem. Soc.* **2007**, *129*, 750. (h) Nájera, C.; Retamosa, M. d. G.; Sansano, J. M. *Org. Lett.* **2007**, *9*, 4025. (i) Zheng, W.; Zhou, Y.-G. *Tetrahedron Lett.* **2007**, *48*, 4619. (j) Nájera, C.; Retamosa, M. d. G.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6055. (k) Wang, C.-J.; Xue, Z.-Y.; Liang, G.; Lu, Z. *Chem. Commun.* **2009**, 2905. (l) Iglesias-Sigüenza, J.; Ros, A.; Díez, E.; Magríz, A.; Vázquez, A.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *Dalton Trans.* **2009**, 8485.
- (5) (a) Oderaotshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett.* **2003**, *5*, 5043. (b) Gao, W.; Zhang, X.; Raghunath, M. *Org. Lett.* **2005**, *7*, 4241. (c) Llamas, T.; Arrayás, R. G.; Carretero, J. C. *Org. Lett.* **2006**, *8*, 1795. (d) Fukuzawa, S.; Oki, H. *Org. Lett.* **2008**, *10*, 1747. (e) López-Pérez, A.; Adrio, J.; Carretero, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 10084. (f) Wang, C.-J.; Liang, G.; Xue, Z.-Y.; Gao, F. *J. Am. Chem. Soc.* **2008**, *130*, 17250. (g) López-Pérez, A.; Adrio, J.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 340. (h) Hernández-Toribio, J.; Arrayás, R. G.; Martín-Matute, B.; Carretero, J. C. *Org. Lett.* **2009**, *11*, 393. Also see refs 10 and 11.
- (6) (a) Saito, S.; Tsubogo, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2007**, *129*, 5364. (b) Tsubogo, T.; Saito, S.; Seki, K.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 13321.
- (7) Shi, J.-W.; Zhao, M.-X.; Lei, Z.-Y.; Shi, M. *J. Org. Chem.* **2008**, *73*, 305.
- (8) (a) Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5168. (b) Ibrahim, I.; Rios, R.; Vesely, J.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 6252. (c) Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652. (d) Chen, X.-H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819. Also see ref 12.
- (9) For mechanistic studies of the [3 + 2] cycloaddition of imino esters and nitroalkenes, see: (a) Ayerbe, M.; Arrieta, A.; Cossío, F. P. *J. Org. Chem.* **1998**, *63*, 1795. (b) Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossío, F. P. *J. Am. Chem. Soc.* **2000**, *122*, 6078.
- (10) (a) Cabrera, S.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394. (b) Cabrera, S.; Arrayás, R. G.; Martín-Matute, B.; Cossío, F. P.; Carretero, J. C. *Tetrahedron* **2007**, *63*, 6587.
- (11) Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1979.
- (12) (a) Xie, J.; Yoshida, K.; Takasu, K.; Takemoto, Y. *Tetrahedron Lett.* **2008**, *49*, 6910. (b) Guo, C.; Xue, M.-X.; Zhu, M.-K.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 3414. Chen and co-workers have explained the organocatalytic reaction using the model of an endo-selective transition state. See: (c) Liu, Y.-K.; Liu, H.; Du, W.; Yue, L.; Chen, Y.-C. *Chem.—Eur. J.* **2008**, *14*, 9873.
- (13) For recent progress on chiral ligands containing the imidazolidine motif, see: (a) Braga, A. L.; Vargas, F.; Silveira, C. C.; de Andrade, L. H. *Tetrahedron Lett.* **2002**, *43*, 2335. (b) Lee, E.-K.; Kim, S.-H.; Jung, B.-H.; Ahn, W.-S.; Kim, G.-J. *Tetrahedron Lett.* **2003**, *44*, 1971. (c) Jin, M.-J.; Takale, V. B.; Sarkar, M. S.; Kim, Y.-M. *Chem. Commun.* **2006**, 663. (d) Arai, T.; Suzuki, K. *Synlett* **2009**, 3167. For a review of chiral imidazolidines as N-heterocyclic carbene ligands, see: (e) Douthwaite, R. E. *Coord. Chem. Rev.* **2007**, *251*, 702.
- (14) Bidine is the abbreviation of bis(imidazolidine).
- (15) Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horiata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846.
- (16) For the bis(imidazoline)pyridine (pybim) ligand, see: Bhor, S.; Anilkumar, G.; Tse, M. K.; Klawonn, M.; Döbler, C.; Bitterlich, B.; Grotevandt, A.; Beller, M. *Org. Lett.* **2005**, *7*, 3393.

JA100265J