Organocatalytic Asymmetric 1,3-Dipolar Cycloaddition of Nitrones to Nitroolefins

Wei Du, Yan-Kai Liu, Lei Yue, Ying-Chun Chen*

Key Laboratory of Drug-Targeting and Drug Deliver System of Education Ministry, West China School of Pharmacy, Sichuan University, Chengdu 610041, P. R. of China
Fax +86(28)85502609; E-mail: ycchenhuaxi@yahoo.com.cn; E-mail: ycchen@scu.edu.cn
Received 1 August 2008

Abstract: The asymmetric 1,3-dipolar cycloaddition of nitrones to nitroolefins was investigated by employing novel thiourea-containing organocatalysts. This transformation exhibited excellent diastereoselectivities (generally >99:1 dr) and moderate to high enantioselectivities (up to 88% ee). A 2,3-diaminopropanol derivative with three contiguous chiral centers was efficiently prepared from one cycloaddition adduct.

Key words: dipolar cycloaddition, nitrones, nitroolefins, thiourea, orgaoncatalysis

The asymmetric 1,3-dipolar cycloaddition reaction is one of the most important pericyclic reactions to generate optically pure heterocycles in a very straightforward manner.[1] A number of 1,3-dipoles, such as azomethine ylides,[2] azomethine imines,[3] nitrile oxides,[4] and others[5] have been widely applied in the cycloaddition with various alkenes and alkynes. In particular, nitrones[6] as 1,3-dipoles have received special interest, because not only they are easily handled compounds and readily available, but also because the resulting isoxazolidines can be smoothly converted to 1,3-amino alcohols. These amino alcohols find wide applications in the synthesis of natural products and pharmaceutical compounds. An array of dipolarophiles, including vinyl ether[7] and various α,β-unsaturated carbonyl compounds,[8] have been well represented in the asymmetric 1,3-dipolar cycloaddition of nitrones. Nevertheless, the reaction of nitrones and nitroolefins has been rarely explored,[9] although nitroolefins have been identified as one of the most versatile electrophiles in organic synthesis.[10] To the best of our knowledge, its catalytic asymmetric variant has not been provided to date. Here we would like to report the first organocatalytic 1,3-dipolar cycloaddition of nitrones to nitroolefins promoted by thiourea-containing compounds. This reaction can be conducted enantioselectively in the presence of new chiral thiourea-pyrrole catalysts.

Recently, chiral thioureas have performed as powerful Brønsted acid catalysts for a large number of asymmetric reactions through hydrogen-bonding interaction.[11] Nitroolefins have proved to be a suitable type of substrates with thiourea catalysis since the pioneering work of Takemoto in 2003.[12] In our continuing catalytic studies based on thiourea compounds,[13] we expected that the stereoselectivity of 1,3-dipolar cycloaddition between nitrones and nitroolefins could be controlled by the use of chiral thioureas.

A number of diversely structured thiourea catalysts (Figure 1) were screened in the asymmetric 1,3-dipolar cycloaddition of *C*,*N*-diphenyl nitrone (**2a**) and alkyl nitroolefin **3a** (10 mol% catalyst, toluene, r.t., 4 Å MS).[9,14]

As outlined in Table 1, almost no reaction occurred without the thiourea catalyst (entry 1). To our gratification, thiourea **1a**[12a] smoothly promoted this transformation. The desired cycloaddition product **4a** was obtained in moderate yield with excellent diastereoselectivity after 3 days (dr >99:1). However, the ee value was very disappointing (entry 2). Poor results were attained when different functionalized thioureas **1b**,[12e] **1c**,[13e] and **1d**[13e] were utilized (entries 3–5). Racemic **4a** was obtained in the presence of Jacobsen's thiourea-pyrrole catalyst **1e** (entry 6).[15] While newly designed thiourea-pyrrole **1f** from chiral 1,2-diphenylethylenediamine still delivered an unacceptable ee value (entry 7),[16] we were pleased to find that the enantioselectivity could be dramatically improved with thiourea-pyrrole **1g** derived from (*R*,*R*)-1,2-diaminohexane (entry 8). Consequently, more modifications were made on the pyrrole moiety. While the same ee was

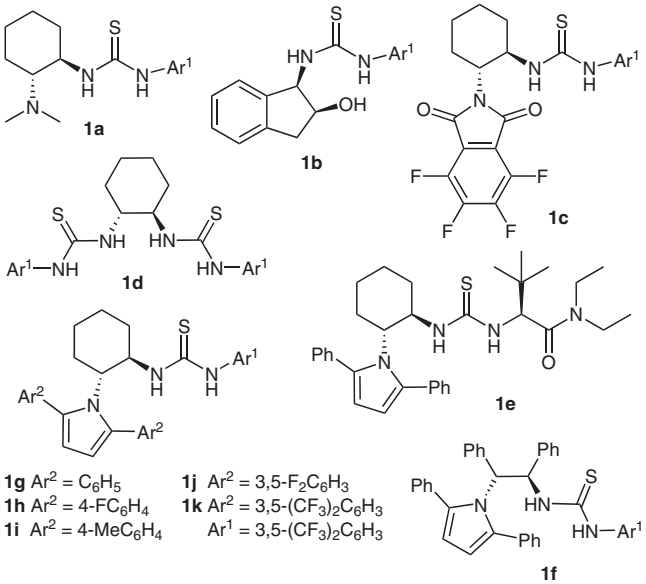
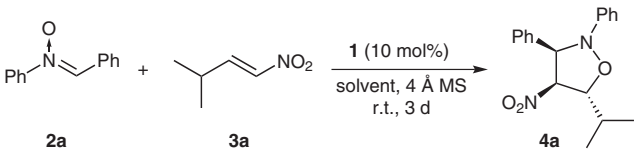


Figure 1 Structures of various thiourea catalysts

SYNLETT 2008, No. 19, pp 2997–3000
Advanced online publication: 23.10.2008
DOI: 10.1055/s-0028-1087300; Art ID: W12008ST

Table 1 Screening Studies of Organocatalytic 1,3-Dipolar Cycloaddition of Nitrone **2a** and Nitroolefin **3a**[a]



2a **3a** **4a**

Entry	Catalyst **1**	Solvent	Yield (%)[b]	ee (%)[c]
1	–	Toluene	–	–
2	**1a**	Toluene	56	9
3	**1b**	Toluene	69	8
4	**1c**	Toluene	39	24
5	**1d**	Toluene	79	23
6	**1e**	Toluene	45	0
7	**1f**	Toluene	67	11
8	**1g**	Toluene	71	60
9	**1h**	Toluene	84	60
10	**1i**	Toluene	42	37
11	**1j**	Toluene	77	66
12	**1k**	Toluene	78	64
13[d]	**1j**	Toluene	76	74
14[d]	**1k**	Toluene	73	70
15[d,e]	**1j**	Toluene	67	73
16[d,f]	**1j**	Toluene	74	72
17[d]	**1j**	CH_2Cl_2	23	32
18[d]	**1j**	FPh	71	63
19[d]	**1j**	CF_3Ph	52	67
20[d]	**1j**	*m*-Xylene	69	72
21[d]	**1j**	*m*-Mesitylene	76	80
22[d]	**1j**	MTBE	79 (58)	82 (99)

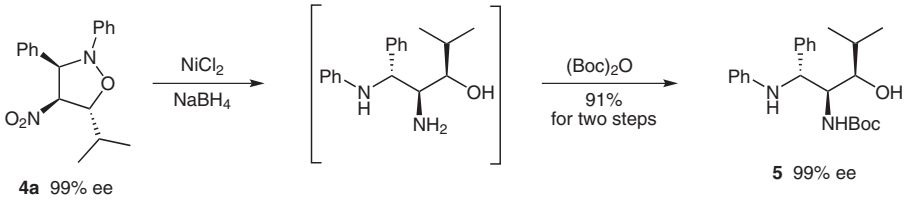
[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **2a**, 0.12 mmol of **3a**, 10 mol% of **1**, 50 mg 4 Å MS in 0.5 mL of solvent at r.t. for 3 d.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis, dr >99:1 in all cases. The absolute configuration of **4a** was determined by X-ray analysis after some derivation (see Figure 2).
[d] At 0 °C for 6 d.
[e] With 5 mol% of **1j**.
[f] With 15 mol% of **1j**.

gained for catalyst **1h** with a *p*-fluorophenyl substitution (entry 9), the enantioselectivity was significantly decreased for **1i** bearing an electron-donating group (entry 10). As a result, thiourea **1j** and **1k** possessing stronger electron-withdrawing groups were prepared, which gave rise to slightly better enantioselectivities as expected (entries 11 and 12). The results could be further improved when the reaction was conducted at 0 °C, but the time had to be extended to obtain good yields (entries 13 and 14). A decreased yield was isolated in the presence of 5 mol% of **1j** (entry 15). Unfortunately, the results could not be improved by increasing the catalytic loading to 15 mol% (entry 16). Subsequently, several solvents were investigated with the superior catalyst **1j** at 0 °C. While reduced enantioselectivities were observed in some solvents (entries 17–20), satisfactory data were afforded in less common solvents such as *m*-mesitylene and methyl *tert*-butyl ether (MTBE) (entries 21 and 22). A simple recrystallization from 2-PrOH–*n*-hexane provided isoxazolidine **4a** in an enantiopure form (entry 22, 99% ee).

We then examined a spectrum of nitrones and nitroolefins to explore the reaction generality.[17] The reactions were conducted with 10 mol% of catalyst **1j** in MTBE at 0 °C for 6 days. In general, excellent diastereoselectivities (dr >99:1) were observed in the tested reactions. As summarized in Table 2, for *C*,*N*-diphenyl nitrone (**2a**), good enantioselectivities and isolated yields were obtained for various aliphatic nitroolefins bearing a branched, linear, or functionalized side chain (entries 1–7). On the other hand, the reaction of diversely substituted nitrones with β-ethyl nitroethene was investigated. Nitrones bearing electron-donating substitutions afforded good results (entries 8–10). Nitrones possessing electron-withdrawing groups exhibited slightly poorer solubility in MTBE. Modest yields were attained in the specific time, while the enantioselectivities remained high (entries 11–14). A good ee with modest yield was attained for a nitrone possessing a 2-furyl group (entry 15). In addition, a nitrone with an *N*-*o*-anisyl substitution, which could be easily removed through mild oxidative conditions, afforded a satisfactory yield (entry 16). Moreover, good results were also gained for the nitrone bearing an *N*-*p*-fluorophenyl group (entry 17). The nitrone in situ formed from PhNHOH and propionaldehyde showed high reactivity in the 1,3-dipolar cycloaddition, but only moderate enantioselectivity could be achieved (entry 18).

As illustrated in Scheme 1, enantiomerically pure isoxazolidine **4a** (99% ee, after recrystallization) could be directly converted to its 2,3-diaminopropanol derivative, which was easily isolated as *N*-Boc-protected compound **5**, without any racemization.[18] Moreover, single crystals suitable for X-ray crystallographic analysis were obtained from an *N*-methanesulfonyl derivative **6** (Figure 2).[19] In this way, the absolute stereochemistry of cycloadduct **4a** was determined and the regioselectivity of the cycloaddition confirmed.

In conclusion, we have presented the first stereoselective 1,3-dipolar cycloaddition reaction of nitrones to β-alkyl nitroolefins promoted by newly designed thiourea-pyrrole catalysts. In general excellent diastereo- (dr >99:1) and moderate to high enantioselectivities (up to 88% ee) could be obtained for an array of substrates. Enantiopure 2,3-diaminopropanol derivatives with three contiguous chiral centers could be efficiently prepared from the cycloaddition adducts obtained. Current studies are under way to in-

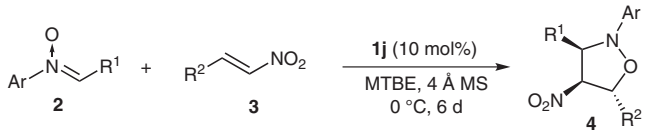


4a 99% ee

5 99% ee

Scheme 1 Conversion of cycloadduct **4a** to its corresponding 2,3-diaminopropanol derivative **5**

Table 2 Asymmetric 1,3-Dipolar Cycloaddition of Nitrone **2** and Nitroolefin **3**



Entry	Ar	R^1	R^2	Yield (%)[a]	ee (%)[b]
1	Ph	Ph	*i*-Pr	**4a** 79	82
2	Ph	Ph	Cyclohexyl	**4b** 85	83
3	Ph	Ph	Et	**4c** 84	87
4	Ph	Ph	*n*-Pr	**4d** 93	84
5	Ph	Ph	*i*-Bu	**4e** 89	80
6	Ph	Ph	*n*-Hexyl	**4f** 72	84
7	Ph	Ph	2-BnOEt	**4g** 92	82
8	Ph	4-$MeOC_6H_4$	Et	**4h** 78	88
9	Ph	4-MeC_6H_4	Et	**4i** 71	86
10	Ph	3-MeC_6H_4	Et	**4j** 93	80
11	Ph	4-FC_6H_4	Et	**4k** 58	82
12	Ph	4-ClC_6H_4	Et	**4l** 54	87
13	Ph	4-BrC_6H_4	Et	**4m** 54	84
14	Ph	2-ClC_6H_4	Et	**4n** 78	84
15	Ph	2-Furyl	Et	**4o** 43	83
16	2-$MeOC_6H_4$	Ph	Et	**4p** 91	81
17	4-FC_6H_4	Ph	Et	**4q** 65	84
18[c]	Ph	Et	Et	**4r** 84	40

[a] Isolated yields.
[b] Determined by chiral HPLC analysis. Absolute stereochemistry of **4b**–**r** assigned by analogy with **4a**.
[c] With in situ formed nitrone; dr >90:10 by ^1H NMR analysis.

vestigate the catalytic mechanism and expand the synthetic utility of this catalytic system.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

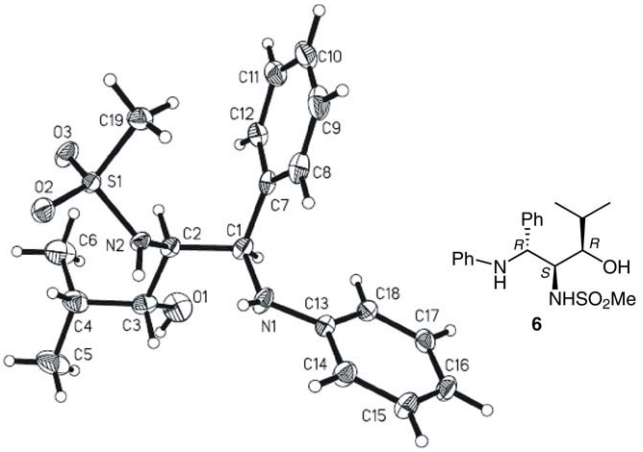


Figure 2 X-ray crystallographic structure of enantiopure **6**

Acknowledgment

We are grateful for the financial support from Natural Science Foundation of China (20502018 and 20772084) and Chinesisch-Deutsches Zentrum für Wissenschaftsförderung [GZ422 (362/6)].

References and Notes

(1) (a) For a comprehensive review of 1,3-dipolar cycloadditions, see: *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A.; Pearson, W. H., Eds.; John Wiley and Sons: Hoboken NJ, **2003**. For recent reviews of asymmetric 1,3-dipolar cycloadditions, see: (b) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235. (c) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.

(2) For reviews, see: (a) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765. (b) Nájera, C.; Sansano, J. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6272. (c) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484.

(3) For selected examples, see: (a) Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778. (b) Suárez, A.; Downey, C. W.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11244. (c) Suga, H.; Funyu, A.; Kakehi, A. *Org. Lett.* **2007**, *9*, 97. (d) Chen, W.; Yuan, X.-H.; Li, R.; Du, W.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Adv. Synth. Catal.* **2006**, *348*, 1818. (e) Chen, W.; Du, W.; Duan, Y.-Z.; Wu, Y.; Yang, S.-Y.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2007**, *46*, 7667. (f) Sibi, M. P.; Rane, D.; Stanley, L. M.; Soeta, T. *Org. Lett.* **2008**, *10*, 2971.

(4) For selected examples, see: (a) Luft, J. A. R.; Meleson, K.; Houk, K. N. *Org. Lett.* **2007**, *9*, 555. (b) Shing, T. K. M.; Wong, W. F.; Cheng, H. M.; Kwok, W. S.; So, K. H. *Org. Lett.* **2007**, *9*, 753. (c) Sibi, M. P.; Ma, Z.; Itoh, K.; Prabagaran, N.; Jasperse, C. P. *Org. Lett.* **2005**, *7*, 2349. (d) Sibi, M. P.; Itoh, K.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 5366.

(5) For selected examples, see: (a) Sibi, M. P.; Stanley, L. M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 8276. (b) Sibi, M. P.; Stanley, L. M.; Soeta, T. *Org. Lett.* **2007**, *9*, 1553. (c) Kanemasa, S.; Kanai, T. *J. Am. Chem. Soc.* **2000**, *122*, 10710. (d) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2174.

(6) For reviews, see: (a) Frederikson, M. *Tetrahedron* **1997**, *53*, 403. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun.* **2000**, 1449.

(7) (a) Jiao, P.; Nakashima, D.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 2411. (b) Simonsen, K. B.; Bayon, P.; Hazell, R. G.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 3845.

(8) For selected examples, see: (a) Viton, F.; Bernardinelli, G.; Kundig, E. P. *J. Am. Chem. Soc.* **2002**, *124*, 4968. (b) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718. (c) Palomo, C.; Oiarbide, M.; Arceo, E.; García, J. M.; López, R.; González, A.; Linden, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 6187. (d) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 11926. (e) Huang, Z.-Z.; Kang, Y.-B.; Zhou, J.; Ye, M.-C.; Tang, Y. *Org. Lett.* **2004**, *6*, 1677. (f) Suga, H.; Nakajima, T.; Itoh, K.; Kakehi, A. *Org. Lett.* **2005**, *7*, 1431. (g) Evans, D. A.; Song, H.-J.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 3351. (h) Lim, K.-C.; Hong, Y.-T.; Kim, S. *Adv. Synth. Catal.* **2008**, *350*, 380. (i) Wang, Y.; Wolf, J.; Zavalij, P.; Doyle, M. P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1439. For limited examples by organocatalysis, see: (j) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874. (k) Karlsson, S.; Högberg, H.-E. *Eur. J. Org. Chem.* **2003**, 2782.

(9) (a) Yakura, T.; Nakazawa, M.; Takino, T.; Ikeda, M. *Chem. Pharm. Bull.* **1992**, *40*, 2014. (b) Karthikeyan, K.; Perumal, P. T.; Etti, S.; Shanmugam, G. *Tetrahedron* **2007**, *63*, 10581.

(10) For reviews, see: (a) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877. (b) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2002**, 1701.

(11) For reviews on thiourea catalysis, see: (a) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (b) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418. (c) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (d) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516. (e) Connon, S. J. *Chem. Commun.* **2008**, 2499.

(12) (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (c) McCooey, S. H.; Connon, S. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 6367. (d) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481. (e) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 6576. (f) Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713. (g) Liu, T.-Y.; Cui, H.-L.; Chai, Q.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Chem. Commun.* **2007**, 2228. (h) Hynes, P. S.; Stranges, D.; Stupple, P. A.; Guarna, A.; Dixon, D. J. *Org. Lett.* **2007**, *9*, 2107. (i) Hynes, P. S.; Stupple, P. A.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 1389. (j) Wang, J.; Xie, H.; Li, H.; Zu, L.; Wang, W. *Angew. Chem. Int. Ed.* **2008**, *47*, 4177. (k) Lu, L.-Q.; Cao, Y.-J.; Liu, X.-P.; An, J.; Yao, C.-J.; Ming, Z.-H.; Xiao, W.-J. *J. Am. Chem. Soc.* **2008**, *130*, 6946.

(13) (a) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, 603. (b) Liu, T.-Y.; Long, J.; Li, B.-J.; Jiang, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Org. Biomol. Chem.* **2006**, *4*, 2097. (c) Liu, T.-Y.; Li, R.; Chai, Q.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Chem. Eur. J.* **2007**, *13*, 319. (d) Liu, T.-Y.; Cui, H.-L.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *J. Am. Chem. Soc.* **2007**, *129*, 1878. (e) Zhang, Y.; Liu, Y.-K.; Kang, T.-R.; Hu, Z.-K.; Chen, Y.-C. *J. Am. Chem. Soc.* **2008**, *130*, 2456. (f) Tian, X.; Jiang, K.; Peng, J.; Du, W.; Chen, Y.-C. *Org. Lett.* **2008**, *10*, 3583. (g) Han, B.; Liu, Q.-P.; Li, R.; Tian, X.; Xiong, X.-F.; Deng, J.-G.; Chen, Y.-C. *Chem. Eur. J.* **2008**, *14*, 8094.

(14) β-Nitrostyrene exhibited very sluggish reactivity in the catalytic 1,3-dipolar cycloaddition even at much higher temperature (>50 °C).

(15) (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558. (b) Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 6700. (c) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404.

(16) Thiourea-pyrrole catalysts **1f–k** were prepared in a similar procedure as **1e**, see ref. 14.

(17) **General Procedure for the Asymmetric 1,3-Dipolar Cycloaddition Reaction**
Catalyst **1j** (6.6 mg, 0.01 mmol, 10 mol%), nitrone **2a** (20.0 mg, 0.1 mmol) and 4 Å MS (50 mg) were stirred in redistilled MTBE (0.4 mL) at 0 °C. Then nitroolefin **3a** (14.0 mg, 0.12 mmol) in MTBE (0.1 mL) was added. After 6 d, product **4a** was isolated by FC on SiO_2 eluted with EtOAc–PE as an oil; 24.5 mg, 79% yield; R_f = 0.5 (PE–EtOAc, 15:1); $[\alpha]_D^{20}$ –101.3 (*c* 1.00 in CH_2Cl_2); 82% ee, determined by HPLC analysis [Daicel chiralcel OD, *n*-hexane–*i*-PrOH (95:5), 1.0 mL/min, l = 254 nm, t_R(major) = 7.70 min, t_R(minor) = 11.16 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.41 (m, 2 H), 7.35–7.33 (m, 3 H), 7.21–7.17 (m, 2 H), 7.04–6.98 (m, 3 H), 5.29 (dd, *J* = 9.2, 7.2 Hz, 1 H), 4.80 (t, *J* = 7.2 Hz, 1 H), 4.74 (d, *J* = 9.2 Hz, 1 H), 2.08–2.03 (m, 1 H), 1.14 (d, *J* = 6.8 Hz, 3 H), 1.02 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 148.1, 133.3, 129.2, 128.8, 128.7, 128.2, 124.1, 116.4, 94.5, 84.7, 73.0, 30.7, 19.0, 17.9 ppm. ESI-HRMS: *m/z* calcd for $C_{18}H_{20}N_2O_3$ + Na: 335.1372; found: 335.1320.

(18) **General Procedure for the Synthesis of 2,3-Diaminopropanol 5**
Compound **4a** (31 mg, 0.1 mmol, 99% ee) and $NiCl_2 \cdot 6H_2O$ (100 mg, 0.4 mmol) were stirred in MeOH (1 mL) and THF (0.5 mL) at r.t. for 10 min. Then $NaBH_4$ (33 mg, 0.9 mmol) was added in portions at 0 °C. After stirring for 5 min, EtOAc (5 mL) and H_2O (5 mL) were added. After filtration, the filtrate was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue and $(Boc)_2O$ (26 mg, 0.12 mmol) were dissolved in CH_2Cl_2 and stirred for 2 h. The solvent was then removed in vacuo, and the residue was purified by flash chromatography on SiO_2 (EtOAc–PE) to give *N*-Boc-diaminopropanol **5** as an oil; 35 mg, 91% yield for two steps; R_f = 0.4 (PE–EtOAc, 5:1); $[\alpha]_D^{20}$ +18.6 (*c* 0.70 in CH_2Cl_2); 99% ee, determined by HPLC analysis [Daicel chiralcel AD, *n*-hexane–*i*-PrOH (90:10), 1.0 mL/min, l = 254 nm, t_R(minor) = 5.48 min, t_R(major) = 9.32 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.28 (m, 4 H), 7.23–7.21 (m, 1 H), 7.11–7.07 (m, 2 H), 6.70–6.67 (m, 1 H), 6.59–6.57 (m, 2 H), 5.46 (s, 1 H), 5.12 (d, *J* = 8.4 Hz, 1 H), 4.84–4.77 (m, 1 H), 4.03 (s, 1 H), 3.54 (s, 1 H), 1.86–1.84 (m, 1 H), 1.30 (s, 9 H), 1.06 (d, *J* = 6.8 Hz, 3 H), 1.02 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 155.4, 147.0, 140.6, 129.1, 128.5, 127.1, 126.9, 118.3, 114.8, 79.6, 78.8, 58.6, 56.1, 29.9, 28.2, 19.4, 18.2 ppm. ESI-HRMS: *m/z* calcd for $C_{23}H_{32}N_2O_3$ + H: 385.2491; found: 385.2453.

(19) CCDC-700901 (**6**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.