JOC*Note*

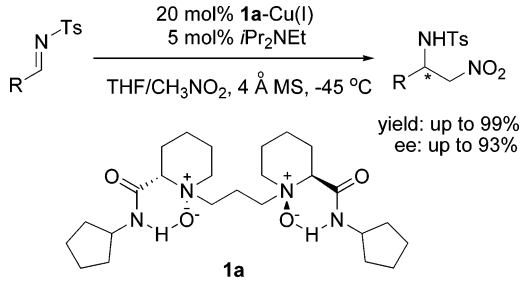
Highly Enantioselective Aza-Henry Reaction of *N*-Tosyl Imines Catalyzed by *N*,*N*′-Dioxide−Cu(I) Complexes

Hui Zhou,[†] Dan Peng,[†] Bo Qin,[†] Zongrui Hou,[†] Xiaohua Liu,[†] and Xiaoming Feng*[,†,‡]

Key Laboratory of Green Chemistry & Technology (Sichuan University), Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China, and State Key Laboratory of Oral Diseases, Sichuan University, Chengdu 610041, China

xmfeng@scu.edu.cn

Received October 10, 2007



The *N*,*N*′-dioxide−Cu(I) complexes have been developed to catalyze the addition of nitromethane to *N*-tosyl aldimines. The aza-Henry reaction proceeds smoothly affording the corresponding nitro amines in good yields with high enantioselectivities. A catalytic cycle is proposed to explain the origin of reactivity.

The aza-Henry (nitro-Mannich) reaction provides a powerful and efficient method for the synthesis of β-nitro amines which can be readily converted into 1,2-diamines[1] and α-amino acids.[2] Tremendous efforts have been directed toward the development of catalytic enantioselective variants.[3] Since the pioneering work of Shibasaki using heterobimetalic metal−BINOLate complexes,[4b] various catalysts including metal complexes[4] and organocatalysts[5] have been developed for the asymmetric aza-Henry reaction. However, there were few reports on the highly enantioselective aza-Henry reaction of *N*-sulfonyl protected imines which are usually bench-stable solids[6] and could be easily prepared.

In light of our success in developing enantioselective cyanosilylation,[7] cyanoformylation,[8] and allylation[9] reactions catalyzed by *N*-oxide-metal complexes,[10] we tried to extend them to the enantioselective aza-Henry reaction. In this paper, we wish to report the utility of an *N*,*N*′-dioxide−Cu(I) catalyst for the highly enantioselective aza-Henry reaction of *N*-Ts (Ts = *p*-tosyl) imines.

The initial optimization studies with *N*-Ts imines **5a** and nitromethane were summarized in Table 1. After the screening of central metals,[11] Cu(I) was found to be the most suitable for this reaction when *N*,*N*′-dioxides were used as ligands. Therefore, a series of *N*,*N*′-dioxides (Figure 1) were examined in the presence of CuOTf as metal salt (Table 1). The *N*,*N*′-dioxide derived from L-pipecolinic acid was superior to those derived from L-proline and L-ramiprol acid in both yield and ee (Table 1, entry 1 vs 5 and 8). The R substituent of the amide moiety of *N*,*N*′-dioxides affected the yield as well as the enantioselectivity (Table 1, entries 1−4), and the best result was obtained with the cyclopentylamine-base *N*,*N*′-dioxide **1a** (Table 1, entry 1, 52% yield, 68% ee). As the flexibility of the *N*,*N*′-dioxides could influence the chiral pocket built by the coordination between the ligand and the metal, the linker length of the *N*,*N*′-dioxide was examined. The results showed either elongation of

[†] College of Chemistry, Sichuan University.
[‡] State Key Laboratory of Oral Diseases, Sichuan University.

(1) For a review, see: Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580.

(2) For reviews, see: (a) Pinnick, H. W. *Org. React.* **1990**, *38*, 655. (b) Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017. For the application of this approach to the synthesis of optically active α-amino acids, see: (c) Foresti, E.; Palmieri, G.; Petrini, M.; Profeta, R. *Org. Biomol. Chem.* **2003**, *1*, 4275.

(3) A review of catalytic asymmetric aza-Henry reactions: Westermann, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 151.

(4) With nitroalkanes: (a) Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 4900. (b) Yamada, K.-I.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3504. (c) Yamada, K.-I.; Moll, G.; Shibasaki, M. *Synlett* **2001**, 980. (d) Trost, B. M.; Lupton, D. W. *Org. Lett.* **2007**, *9*, 2023. (e) Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A.; López, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 117. (f) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2992. For a related asymmetric aza-Henry reaction of *N*-tosyl imines with nitromethane, see: (g) Gao, F.; Zhu, J.; Tang, Y.; Deng, M.; Qian, C. *Chirality* **2006**, *18*, 741. With preformed silyl nitronates: (h) Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843. (i) Anderson, J. C.; Howell, G. P.; Lawrence, R. M.; Wilson, C. S. *J. Org. Chem.* **2005**, *70*, 5665. For a related example with *tert*-butyl 2-nitropropanoate as a nucleophile, see: (j) Knudsen, K. R.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362.

(5) With thioureas: (a) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466. (b) Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem. Eur. J.* **2006**, *12*, 466. (c) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625. (d) Chang, Y.; Yang, J.; Dang, J.; Xue, Y. *Synlett*, **2007**, 2283. With a chiral proton catalyst: (e) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418. With cinchona alkaloids: (f) Palomo, C.; Oiarbide, M.; Laso, A.; López, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622. (g) Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7975. (h) Bernardi, L.; Fini, F.; Herrera, R. P.; Ricci, A.; Sgarzani, V. *Tetrahedron* **2006**, *62*, 375. With heterogeneous catalysts: (i) Lee, A.; Kim, W.; Lee, J.; Hyeon, T.; Kim, B. M. *Tetrahedron*: *Asymmetry* **2004**, *15*, 2595. For a related example of asymmetric aza-Henry reactions of *N*-*p*-tolylsulfinylimines, see: (j) Luis, J.; Ruano, G.; Topp, M.; López-Cantarero, J.; Aleman, J.; Remuiñán, M. T.; Belén Cid, M. *Org. Lett.* **2005**, *7*, 4407.

(6) At −20 °C, most purified *N*-Ts imines kept their purity for at least 3 months.

(7) (a) Zeng, B. Q.; Zhou, X.; Liu, X. H.; Feng, X. M. *Tetrahedron* **2007**, *63*, 5129. (b) Li, Q. H; Liu, X. H.; Wang, J.; Shen, K.; Feng, X. M. *Tetrahedron Lett.* **2006**, *47*, 4011. (c) Shen, Y. C.; Feng, X. M.; Li, Y.; Zhang, G. L.; Jiang, Y. Z. *Eur. J. Org. Chem.* **2004**, 129. (d) Shen, Y. C.; Feng, X. M.; Zhang, G. L.; Jiang, Y. Z. *Synlett* **2002**, 1353.

(8) Li, Q. H.; Chang, L.; Liu, X. H.; Feng, X. M. *Synlett* **2006**, 1675.

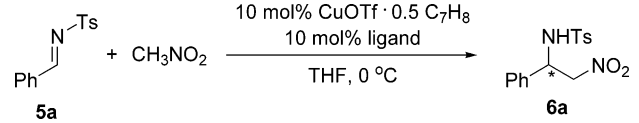
(9) (a) Zhang, X.; Chen, D. H.; Liu, X. H.; Feng, X. M. *J. Org. Chem.* **2007**, *72*, 5227. (b) Zheng, K.; Qin, B.; Liu, X. H.; Feng, X. M. *J. Org. Chem.* **2007**, *72*, 8478.

(10) For reviews of chiral *N*-oxides in asymmetric catalysis, see: (a) Malkov, A. V.; Kočovský, P. *Eur. J. Org. Chem.* **2007**, *29*. (b) Malkov, A. V.; Kočovský, P. *Curr. Org. Chem.* **2003**, *7*, 1737. (c) Nakajima, M. *J. Synth. Org. Chem. Jpn.* **2003**, *61*, 1081. (d) Chelucci, G.; Marineddn, G.; Pinna, G. A. *Tetrahedron*: *Asymmetry* **2004**, *15*, 1373.

(11) For more details, see the Supporting Information.

10.1021/jo702200u CCC: $37.00
Published on Web 11/29/2007

TABLE 1. The Screening of Ligands for the Aza-Henry Reaction[a]



5a 6a

entry	ligand	yield[b] (%)	ee[c] (%)
1	**1a**	52	68
2	**1b**	48	22
3	**1c**	32	37
4	**1d**	16	16
5	**1e**	28	36
6	**1f**	70	27[d]
7	**1g**	30	25
8	**2**	32	40
9	**3**	43	6[d]
10	**4**	31	0
11[e]	**1a**	N.D.[g]	
12[f]	**1a**	63	31

[a] Reaction was conducted with **5a** (0.1 mmol) and CH_3NO_2 (10 equiv) in THF (1.0 mL) with 10 mol % CuOTf·0.5C_7H_8 and 10 mol % ligand at 0 °C for 40 h, unless otherwise indicated. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel OD-H column. [d] The absolute configuration of the major product was inverse compared with the others by the analysis of HPLC on a Chiralcel OD-H column. [e] 5 mol % **1a** and 10 mol % CuOTf·0.5C_7H_8 were used. [f] 20 mol % **1a** and 10 mol % CuOTf·0.5C_7H_8 were used. [g] N.D. = not detected.

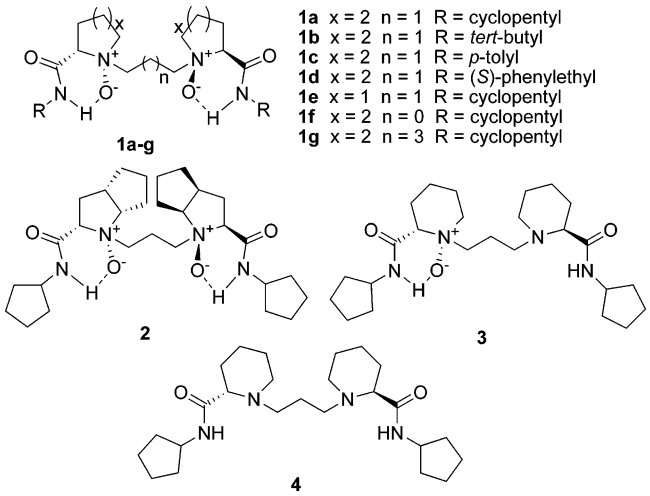


FIGURE 1. Chiral ligands evaluated for the asymmetric aza-Henry reaction.

the carbon chain of **1a** to **1g** or shortening to **1f** led to lower enantioselectivities (Table 1, entry 1 vs 6 and 7). To determine the function of bis-*N*-oxide moiety, the single-side *N*-oxide **3** and diamide **4** (Figure 1) were also explored in the reaction. While **3** or **4** was used as the ligand, poor results were obtained (Table 1, entry 1 vs 9 and 10), which indicated that the bis-*N*-oxide was essential for good yield and enantioselectivity. The combination of **1a** to CuOTf in a ratio of 1:1 afforded the best catalyst for the present reaction while increasing or decreasing the ratio led to disappointing results (Table 1, entry 1 vs 11 and 12).

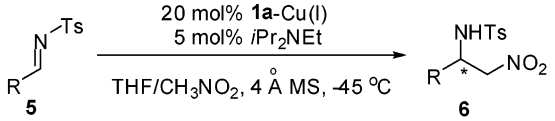
To further improve the enantioselectivity, other conditions were investigated.[11] The screening of solvents showed that CH_3NO_2 exhibited the best performance at 0 °C (Table 2, entry 1). The catalyst loading has an effect on the reactivity and enantioselectivity of the reaction. The reactivity and enantioselectivity were improved gradually by increasing the catalyst loading from 5 to 20 mol % (Table 2, entries 1−3). Fortunately, lowering the temperature to −20 °C further increased the enantioselectivity (Table 2, entry 4). However, further lowering the temperature to −45 °C almost stopped the reaction (the reaction mixture frozen for the relatively high melting point of nitromethane). Therefore a mixture of THF and CH_3NO_2 was used as the solvent; however, the reactivity did not reach the accepted level. The additives which were able to increase catalyst turnover and enantioselectivity in previous work were investigated. Fortunately, 4 Å MS (molecular sieve) and achiral *tert*-amine both showed positive effects (Table 2, entries 5 and 6). Under the optimized condition (at −45 °C, in the presence of 20 mol % **1a**−CuOTf, 5 mol % *i*Pr_2NEt, and 100 mg/mmol 4 Å MS in the mixture of THF and CH_3NO_2), **6a** was obtained in 90% yield with 91% ee (Table 2, entry 6).

TABLE 2. Selected Further Optimization of the Reaction Conditions[a]

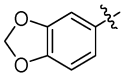
entry	catalyst loading (mol %)	solvent	*T* (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	5	CH_3NO_2	0	16	30	69
2	10	CH_3NO_2	0	17	76	71
3	20	CH_3NO_2	0	16	99	74
4	20	CH_3NO_2	−20	21	75	81
5[d]	20	CH_3NO_2	−20	16	76	81
6[d,e]	20	THF/CH_3NO_2[f]	−45	57	90	91

[a] Reaction was conducted with **5a** (0.1 mmol) in a certain solvent (1.0 mL) with *x* mol % **1a**−CuOTf complex; the molar ratio of **1a** to CuOTf was 1:1. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel OD-H column. [d] 10 mg 4 Å MS was added. [e] 5 mol % *i*Pr_2NEt was added. [f] THF: CH_3NO_2 = 2:1 (v/v).

TABLE 3. Enantioselective Aza-Henry Reaction with Various *N*-Ts Imines 5[a]



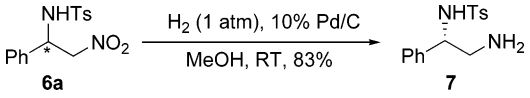
5 6

entry	imine (R)	time (h)	yield[b] (%)	Ee (%)
1	C_6H_5 (**5a**)	57	90	91[c]
2	1-Naphthyl (**5b**)	22	88	86[c]
3	2-Naphthyl (**5c**)	57	80	93[d]
4	4-MeC_6H_4 (**5d**)	70	81	93[c]
5[f]	3-MeC_6H_4 (**5e**)	64	96	92[c]
6[f]	2-MeC_6H_4 (**5f**)	87	79	89[d]
7[f]	4-$MeOC_6H_4$ (**5g**)	70	64	90[c]
8[f]	 (**5h**)	87	63	89[e]
9	2-Furyl (**5i**)	31	89	84[c]
10	4-ClC_6H_4 (**5j**)	64	99	84[c]
11[g]	C_6H_5 (**5a**)	40	87	91[c]

[a] Reaction was conducted with **5** (0.05 mmol) in the mixture of THF and CH_3NO_2 (0.5 mL, THF:CH_3NO_2 = 2:1, v/v) with 20 mol % **1a**−CuOTf complex, the molar ratio of **1a** to CuOTf was 1:1, 5 mg 4 Å MS and 5 mol % *i*Pr_2NEt were added, unless otherwise indicated. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel OD-H column. [d] Determined by HPLC on a Chiralpak AD-H column. [e] Determined by HPLC on a Chiralpak IA column. [f] The concentration of imine was 0.2 M. [g] The reaction was carried out on 1 mmol scale in 10 mL of solvent.

The current catalytic system was applied to various *N*-Ts imines (Table 3). Aryl imines with either an electron-donating substituent or an electron-withdrawing substituent, as well as heteroaryl imines, afforded the corresponding products in good yields with high enantioselectivities (Table 3, entries 4−10).[12] The imines derived from the bulker aldehydes such as 1-naph-

SCHEME 1. Synthesis of 1,2-Diamine



thaldehyde and 2-naphthaldehyde also gave high yields and enantioselectivities (Table 3, entries 2 and 3). Aryl imines bearing the electron-rich substituent or ortho-substituted aryl imines showed relatively lower reactive rates than others (Table 3, entries 6−8). Moreover, the reaction could be carried out on 1 mmol scale without any decrease in the enantioselectivity and reactivity (Table 3, entry 11). The absolute configuration of **6a** was determined as *S* by reduction to 1,2-diamine **7**, which was assigned to be *S* by comparison with the sign of the reported optical rotation value (Scheme 1).[13]

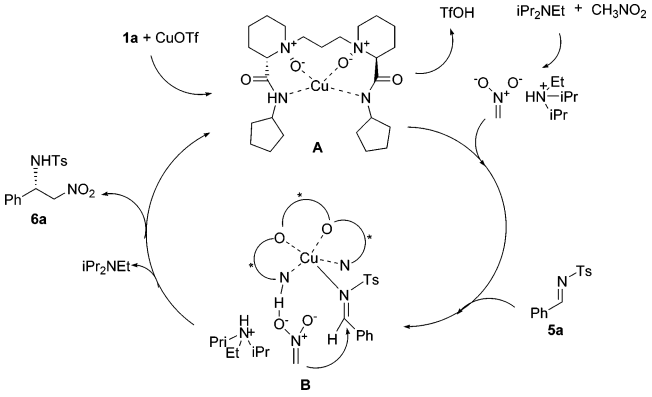


FIGURE 2. The proposed catalytic cycle.

In the present reaction, the bis-*N*-oxide, the linker of a three carbon chain of the ligand as well as the 1:1 ratio of Cu(I) to ligand were essential to good enantioselectivity. According to these experimental results and previous studies,[7−9,14] we assumed that complex **A** (Figure 2) would be the active species,[15] and a possible catalytic cycle that would explain the origin of the reactivity was proposed. The complex **A** was generated in situ by the mixture of **1a** and CuOTf. The *i*Pr_2NEt deprotonated the α-proton of nitromethane to generate an ammonium nitronate. The imine and the nitronate would interact with the Cu complex thus generating the complex **B**:[5b−d] the chiral catalyst positioned the nitronate on the *Re* face of the imine, which accords with steric and electronic considerations. Addition of the nitronate to the imine followed by protonation afforded the product and regenerated the catalyst.

In summary, we have successfully applied the *N*-oxide−metal complexes to the enantioselective aza-Henry reaction of *N*-tosyl imines and the corresponding nitro amines were obtained in good yields (up to 90%) and high enantioselectivities (up to 93% ee). This method benefited from the easily modified *N*,*N*′-dioxide and the stable and easily available *N*-tosyl imines. Moreover, the reaction could be carried out on 1 mmol scale without any decrease in the enantioselectivity and reactivity. Further investigations are underway in our laboratory for the detailed mechanism and the application of *N*-oxide−metal complexes to other versions of asymmetric catalysis.

Experimental Section

Typical Experimental Procedure for the Aza-Henry Reaction. The mixture of ligand **1a** (92.9 mg, 0.2 mmol), CuOTf·0.5C_7H_8 (51.7 mg, 0.2 mmol), and 4 Å MS (100 mg) was stirred in the mixture of THF/CH_3NO_2 (THF:CH_3NO_2 = 2:1, v/v, 6.0 mL) at room temperature under air atmosphere for 10 min to generate the catalyst. The reaction mixture was cooled to −45 °C followed by the addition of imine **5a** (1.0 mmol) and the mixture of THF/CH_3NO_2 (THF:CH_3NO_2 = 2:1, v/v, 4.0 mL), then *i*Pr_2NEt (0.05 mmol, 5 mol %) was added to the mixture. The stirring was continued for 40 h at −45 °C. The reaction mixture was quenched with 0.1 M HCl (10 mL), and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by silica gel flash column chromatography (AcOEt:petroleum ether, 1:4) afforded the corresponding product **6a** as a white solid, 91% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.4 Hz, 2H), 7.24−7.27 (m, 5H), 7.10−7.08 (m, 2H), 4.98 (t, J = 6.6 Hz, 1H), 4.84 (q, 1H), 4.69 (q, 1H), 2.40 (s, 3H); $[\alpha]^{29}_D$ 73.5 (*c* 0.10, CH_2Cl_2); HPLC (Chiralcel OD-H column, hexane/2-propanol = 80/20, flow 1.0 mL/min, detection at 215 nm) t_r = 16.6 min (major) and t_r = 19.8 min (minor).

Acknowledgment. We appreciate the financial support from the National Natural Science Foundation of China (No. 20732003). We also thank Sichuan University Analytical & Testing Center for NMR analysis and the State Key Laboratory of Biotherapy for HRMS analysis.

Supporting Information Available: Experimental procedures and characterization of products for catalysts and racemates, ^{1}H NMR and ^{13}C NMR spectra, HRMS and HPLC conditions, etc. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702200U

(12) Alkyl and α,β-unsaturated *N*-Ts-protected imines are less suitable substrates for the reaction. For instance, the aza-Henry adduct from the cinnamaldehyde-derived Ts-imine was obtained in 40% yield with 65% ee at −45 °C, while the adduct from the cyclohexyl aldehyde derived Ts-imine was obtained in 64% yield with 9% ee at −20 °C.

(13) Hayes, A.; Clarkson, G.; Wills, M. *Tetrahedron*: *Asymmetry* **2004**, *15*, 2079. For more details of the determination of the absolute configuration of **6a**, see the Supporting Information.

(14) (a) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533. (b) Balahura, R. J.; Jordan, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 1533. (c) Fairlie, D. P.; Angus, P. M.; Fenn, M. D.; Jackson, W. G. *Inorg. Chem.* **1991**, *30*, 1564. (d) Antolovich, M.; Phillips, D. J.; Rae, A. D. *Inorg. Chim. Acta* **1989**, *156*, 189.

(15) According to the experimental results and the studies with ESI-HRMS and ^{1}H NMR of **1a**-Cu(I), we speculated that complex **A** should be the active species. For more details of discussion and the proposed transition state model, see the Supporting Information.