ORGANIC LETTERS

2010
Vol. 12, No. 10
2214−2217

N,N′-Dioxide−Cu(OTf)$_2$ Complex Catalyzed Highly Enantioselective Amination Reaction of *N*-Acetyl Enamide

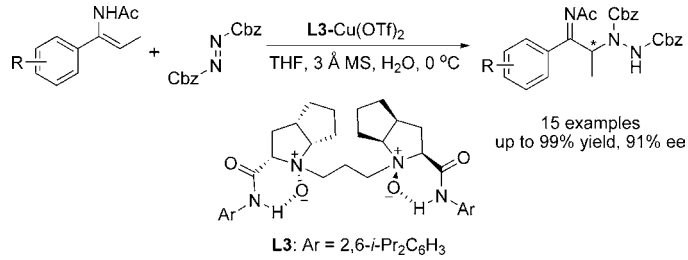
Lu Chang, Yulong Kuang, Bo Qin, Xin Zhou, Xiaohua Liu, Lili Lin, and Xiaoming Feng*

Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, People's Republic of China

xmfeng@scu.edu.cn

Received March 4, 2010

ABSTRACT



The *N,N′*-dioxide−Cu(OTf)$_2$ complexes were applied in the asymmetric amination reaction of *N*-acetyl enamides with dialkyl azodicarboxylate, giving the corresponding products in good yields with high enantioselectivities (up to 91% ee). Precursors of vicinal diamine were readily obtained with excellent diastereoselectivities (>95:5) by $NaBH_4$ reduction.

The vicinal diamine backbone, as one of the most valuable functionalities, is a frequently recurring motif in natural products and biologically active compounds.[1] For example, many antibiotics such as edeines A1 and B1 possess 2,3-diaminopropanoic acid in their chemical structure.[2] The 2,3-diaminopropanamide functionality is also found in bleomycins, which are a family of chemotherapeutic agents used for clinical treatment of malignancies.[3] Meanwhile, 1,2-diamines are employed in many catalytic asymmetric reactions.[4] Over the past years, several approaches toward such useful structures have been successfully developed, for instance, ring-opening of aziridines with nitrogen nucleophiles, reductive coupling of imines, and Mannich-type reactions.[1c]

In 2006, Kobayashi et al. reported the first asymmetric amination[5] of enecarbamate,[6] which was established as an attractive methodology for the synthesis of vicinal diamines. However, the synthesis of enecarbamate usually involves the addition of organometallic reagents to the aromatic nitriles or the rearrangement of α,*β*-unsaturated carboxylic acids.[7] The synthetic features of both methods potentially limit the practical application of enecarbamate. In contrast, the enamides which could be prepared directly from the corresponding ketones[8] provide a good way to compensate for this limitation. Moreover, the *Z* and *E* isomers are generally stable crystals, which facilitate its purification and separation. Nevertheless, the amination of enamide was scarcely investigated in detail.[9]

Chiral *N,N′*-dioxide compounds, as well as their metal complexes,[10] have emerged as efficient catalysts in asym-

(1) For reviews of vicinal diamines, see: (a) Kotti, S. R. S. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101. (b) Viso, A.; Fernández de la Pradilla, R.; García, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167. (c) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed* **1998**, *37*, 2580, and references cited therein.

(2) Roncari, G.; Kurylo-Borowska, Z.; Craig, L. C. *Biochemistry* **1966**, *5*, 2153.

(3) (a) Stubbe, J.; Kozarich, J. W. *Chem. Rev.* **1987**, *87*, 1107. (b) Otsuka, M.; Masuda, T.; Haupt, A.; Ohno, M.; Shiraki, T.; Sugiura, Y.; Maeda, K. *J. Am. Chem. Soc.* **1990**, *112*, 838.

(4) (a) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161. (b) Anaya de Parrodi, C.; Juaristi, E. *Synlett* **2006**, 2699. (c) Hems, W. P.; Groarke, M.; Zanotti-Gerosa, A.; Grasa, G. A. *Acc. Chem. Res.* **2007**, *40*, 1340.

10.1021/ol100540p
Published on Web 04/19/2010

metric catalysis. As part of our ongoing research using *N*,*N*′-dioxide compound as a structurally modified ligand,[11] we herein describe an enantioselective amination reaction of *N*-acetyl enamides with azodicarboxylate catalyzed by chiral $Cu(OTf)_2$/*N*,*N*′-dioxide complex, giving the corresponding adducts in excellent yields with high enantioselectivities.

A preliminary investigation[12] revealed that $Cu(OTf)_2$−*N*,*N*′-dioxide **L1** (Figure 1) could efficiently catalyze the amination

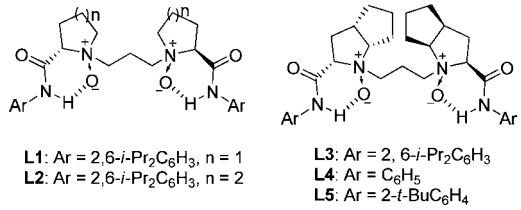
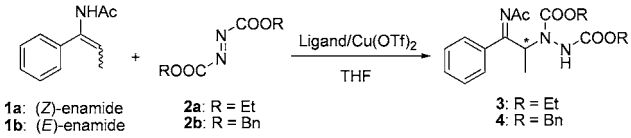


Figure 1. *N*,*N*′-Dioxide ligands evaluated for this reaction.

of enamide, giving the corresponding product in 64% yield with 56% ee (Table 1, entry 1). Subsequent intensive screening of the chiral ligands disclosed the significant impact of the amino acid backbone on the enantioselectivity (Table 1, entries 1−3). L-Ramipril acid-derived *N*,*N*′-dioxide **L3** was superior to **L1** (derived from L-proline) and **L2** (derived from L-pipecolic acid) (Table 1, entry 3 vs entries 1 and 2). The

Table 1. Selected Results for the Optimization of Reaction Conditions[a]



1a: (*Z*)-enamide
1b: (*E*)-enamide
2a: R = Et
2b: R = Bn
3: R = Et
4: R = Bn

entry	ligand	R	additive	yield (%)[b]	ee (%)[c]
1	**L1**	Et		64	56 (*S*)[d]
2	**L2**	Et		61	20 (*R*)
3	**L3**	Et		51	61 (*S*)
4	**L4**	Et		22	6 (*S*)
5	**L5**	Et		78	30 (*S*)
6[e]	**L3**	Et		99	65 (*S*)
7[e,f]	**L3**	Et		66	79 (*S*)
8[e,f]	**L3**	Bn		48	90 (*S*)[d]
9[e,f,g]	**L3**	Bn	H_2O	88	89 (*S*)
10[e,f,h]	**L3**	Bn	H_2O/3 Å MS	88	91 (*S*)
11[e,f,i]	**L3**	Bn	3 Å MS	38	61 (*S*)
12[e,f,h,j]	**L3**	Bn	H_2O/3 Å MS	95	75 (*R*)

[a] Unless otherwise noted, reactions were carried out with ligand (10 mol %), $Cu(OTf)_2$ (10 mol %), **1a** (0.1 mmol), and **2** (0.15 mmol) in THF (0.4 mL) at rt for 24 h. [b] Isolated yield of the hydrolysis product. [c] Determined by HPLC, using chiral AD-H column after hydrolysis. [d] Absolute configuration was determined by comparison with the literature data (refs 6 and 15a). [e] Ligand: $Cu(OTf)_2$ = 1:1.25. [f] Performed at 0 °C. [g] H_2O (3 μL) was added. [h] 3 Å MS (30 mg) and H_2O (5 μL) were added. [i] 3 Å MS (30 mg) was added. [j] **1b** (0.1 mmol) was used as substrate.

opposite configuration of the product obtained from **L2** proved the decisive role of amino acid scaffold in determining the absolute stereochemical outcome of the reaction (Table 1, entry 2). In addition, the amide moiety of the *N*,*N*′-dioxide played an important role on the reactivity. Increasing the steric hindrance on the ortho position of the aromatic ring was favorable to achieve high yield (Table 1, entries 3 and 5 vs entry 4). It was considered that the introduction of the bulky group at the ortho position led to a twisted delocalization of the large conjugated system including the aromatic ring, nitrogen, and the carbonyl group, which affected the Lewis acidity of the central metal indirectly.

When a little excess of metal was used, the yield was increased to 99% with a gentle increase of the enantioselectivity (Table 1, entry 6). Decreasing the reaction temperature to 0 °C improved the enantiomeric excess of the product to 79% (Table 1, entry 7). When dibenzyl azodicarboxylate was used as the electrophile, the enantioselectivity was further increased to 90% ee (Table 1, entry 8).

(5) For reviews of α-amination, see: (a) Erdik, E. *Tetrahedron* **2004**, *60*, 8747. (b) Greck, C.; Drouillat, B.; Thomassigny, C. *Eur. J. Org. Chem.* **2004**, 1377. (c) Janey, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4292. (d) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584, and references cited therein. For selected examples of amination of 1,3-dicarbonyl compounds with dialkyl azodicarboxylate as nitrogen source, see: (e) Marigo, M.; Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1367. (f) Pihko, P. M.; Pohjakallio, A. *Synlett* **2004**, 2115. (g) Bernardi, L.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5772. (h) Foltz, C.; Stecker, B.; Marconi, G.; Bellemin-Laponnaz, S.; Wadepohl, H.; Gade, L. H. *Chem. Commun.* **2005**, 5115. (i) Xu, X.; Yabuta, T.; Yuan, P.; Takemoto, Y. *Synlett* **2006**, 137. (j) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044. (k) Kang, Y. K.; Kim, D. Y. *Tetrahedron Lett.* **2006**, *47*, 4565. (l) Comelles, J.; Pericas, À.; Moreno-Mañas, M.; Vallribera, A.; Drudis-Solé, G.; Lledos, A.; Parella, T.; Roglans, A.; García-Granda, S.; Roces-Fernández, L. *J. Org. Chem.* **2007**, *72*, 2077. For selected examples of amination of 2-oxindoles with dialkyl azodicarboxylate as nitrogen source, see: (m) Cheng, L.; Liu, L.; Wang, D.; Chen, Y. J. *Org. Lett.* **2009**, *11*, 3874. (n) Qian, Z. Q.; Zhou, F.; Du, T. P.; Wang, B. L.; Ding, M.; Zhao, X. L.; Zhou, J. *Chem. Commun.* **2009**, 6753. (o) Bui, T.; Borregan, M.; Barbas, C. F., III *J. Org. Chem.* **2009**, *74*, 8935. (p) Mouri, S.; Chen, Z.; Mitsunuma, H.; Furutachi, M.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 1255. For selected examples of other substrates, see: (q) Juhl, K.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 2420. (r) Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F., III *Org. Lett.* **2003**, *5*, 1685. (s) Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120. (t) Ma, S.; Jiao, N.; Zheng, Z.; Ma, Z.; Lu, Z.; Ye, L.; Deng, Y.; Chen, G. *Org. Lett.* **2004**, *6*, 2193. (u) Liu, X.; Li, H.; Deng, L. *Org. Lett.* **2005**, *7*, 167. (v) Poulsen, T. B.; Alemparte, C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 11614. (w) Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973. (x) Mashiko, T.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 2725. (y) Mashiko, T.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 14990.

(6) Matsubara, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 7993.

(7) For review, see: (a) Matsubara, R.; Kobayashi, S. *Acc. Chem. Res.* **2008**, *41*, 292. For other synthetic methods of enecarbamate, see: (b) Fürstner, A.; Brehm, C.; Cancho-Grande, Y. *Org. Lett.* **2001**, *3*, 3955. (c) Wallace, D. J.; Klauber, D. J.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749. (d) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667.

(8) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084.

(9) Matsubara, R.; Doko, T.; Uetake, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 3047.

(10) For reviews on chiral *N*-oxides in asymmetric catalysis, see: (a) Chelucci, G.; Murineddu, G.; Pinna, G. A. *Tetrahedron: Asymmetry* **2004**, *15*, 1373. (b) Malkov, A. V.; Kočovský, P. *Eur. J. Org. Chem.* **2007**, 29.

(11) For examples of our recent work, see: (a) Yang, X.; Zhou, X.; Lin, L. L.; Chang, L.; Liu, X. H.; Feng, X. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7079. (b) Tan, C.; Liu, X. H.; Wang, L. W.; Wang, J.; Feng, X. M. *Org. Lett.* **2008**, *10*, 5305. (c) Zhou, X.; Shang, D. J.; Zhang, Q.; Lin, L. L.; Liu, X. H.; Feng, X. M. *Org. Lett.* **2009**, *11*, 1401. (d) Shang, D. J.; Liu, Y. L.; Zhou, X.; Liu, X. H.; Feng, X. M. *Chem.—Eur. J.* **2009**, *15*, 3678. (e) Liu, Y. L.; Shang, D. J.; Zhou, X.; Zhu, Y.; Lin, L. L.; Liu, X. H.; Feng, X. M. *Org. Lett.* **2010**, *12*, 180.

(12) Preliminary investigation of Lewis acid mainly focused on Cu(I) and Cu(II), see the Supporting Information.

It was exciting that water showed a positive effect on the reactivity. Full conversion could be observed within 40 h with H_2O (3 μL) as additive. It should be noted that one of the most challenging problems for this reaction is to obtain the relatively unstable α-aminated imine products, which were versatile intermediates for different transformations. However, only a mixture of imine and the corresponding ketone was obtained during the screening. Further investigation indicated that the addition of 3 Å molecular sieves could suppress the hydrolysis efficiently without any influence on the yield and enantioselectivity (Table 1, entry 10). The effect of water on the amination reaction was further confirmed by an independent experiment (Table 1, entry 11). Both the yield and enantioselectivity were decreased if the moisture was completely removed by 3 Å molecular sieves.

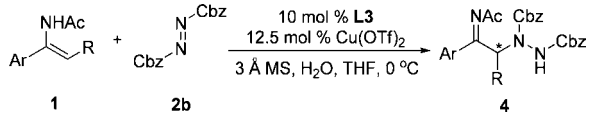
Although the *E* isomer exhibited higher reactivity than the *Z* counterpart and was converted to the corresponding adduct with the opposite configuration, the enantioselectivity was low (Table 1, entry 12).

With the optimized conditions (Table 1, entry 10) in hand, the substrate scope of the catalytic asymmetric amination of enamides was then tested. As summarized in Table 2, a wide range of *N*-acetyl enamides were found to be suitable substrates for this reaction. The enantioselectivity was significantly affected by the branch of the enamide (Table 2, entries 1−3). Prolongation of the alkyl chain of the enamide to propyl (compound **1d**) also gave smoothly the desired product, but the ee value was decreased to 60% (Table 2, entry 3). Regardless of the electronic or steric nature of the substituents on the aromatic ring, the amination reactions proceeded smoothly and delivered the corresponding α-amino imines in excellent yields (86−99%). Moreover, the enamides with electron-withdrawing groups exhibited somewhat better performance in terms of enantioselectivity than those with electron-donating groups. It was noteworthy that the scope of this reaction could also be extended to α-2-naphthyl enamide **1o** and α-thiophenyl enamide **1p** (Table 2, entries 14 and 15), which have never been reported.[6,9]

This reaction provided an efficient approach to the synthesis of 1,2-diamine precursors. Reduction of the product **4** with $NaBH_4$ at low temperature (−78 to −45 °C) proceeded smoothly in a highly diastereoselective manner (dr >95:5) (Figure 2). The corresponding products[13] **5** were obtained in good yields without any loss of enantioselectivity. The resulting imine could also be hydrolyzed into α-aminated ketone **4′** by simple treatment with 1 N $KHSO_4$ solution,[14] which is also an important synthetic intermediate, especially for the construction of optically active amino alcohol.[15]

To explain the stereochemical outcome of this reaction, two possible transition states were postulated based on the absolute configuration of the product. The sterically bulky

Table 2. Substrate Scope for the Direct Catalytic Asymmetric Amination Reaction[a]



1 2b 4

entry	1	Ar	R	yield (%)[b]	ee (%)[c]
1	**1a**	Ph	Me	99	91 (*S*)
2	**1c**	Ph	Et	99	85
3	**1d**	Ph	*n*-Pr	88	60
4	**1e**	3-MeC_6H_4	Me	99	86
5	**1f**	3-MeOC_6H_4	Me	88	89
6	**1g**	3-ClC_6H_4	Me	94	90
7	**1h**	3-BrC_6H_4	Me	95	91
8	**1i**	3-$CF_3C_6H_4$	Me	86	90
9	**1j**	4-MeC_6H_4	Me	99	86
10	**1k**	4-BrC_6H_4	Me	96	91
11	**1l**	4-ClC_6H_4	Me	90	90
12	**1m**	4-FC_6H_4	Me	93	84
13	**1n**	3, 4-$Cl_2C_6H_3$	Me	85	91
14	**1o**		Me	98	82
15	**1p**		Me	96	86

[a] Unless otherwise noted, reactions were carried out with **1** (0.1 mmol), **2b** (0.15 mmol), **L3** (0.01 mmol), and $Cu(OTf)_2$ (0.0125 mmol) in THF (0.4 mL) at 0 °C. 3 Å MS (30 mg) and H_2O (5 μL) were added. [b] Isolated yield. [c] Determined by HPLC, using commercial chiral columns after hydrolysis.

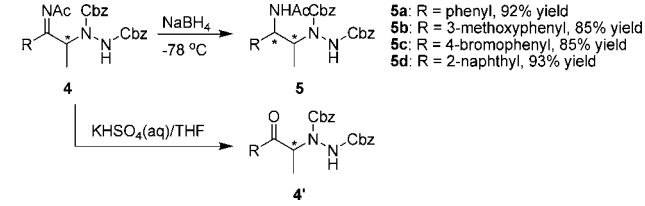


Figure 2. Application of the current amination reaction of enamides.

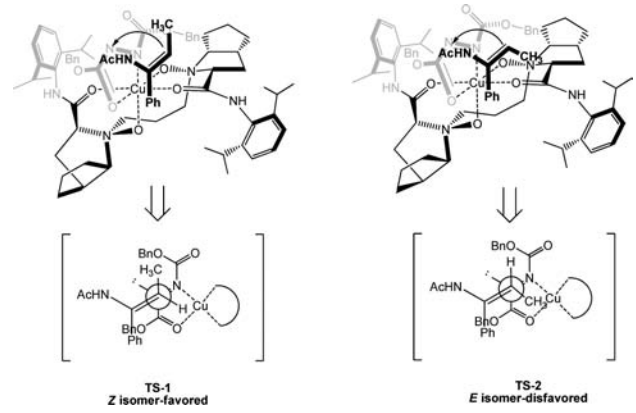


Figure 3. Proposed transition states for the amination reaction.

(13) For further deprotection and N−N bond cleavage with H_2-Pd/C followed by treatment of H_2-Raney Ni or Zn-acetone in acetic acid see refs 5e, 5g, 5p−5r.

(14) The hydrolysis cannot be conducted with HBr/THF.

(15) (a) Yamashita, Y.; Ishitani, H.; Kobayashi, S. *Can. J. Chem.* **2000**, *78*, 666. (b) Liu, T. Y.; Cui, H. L.; Zhang, Y.; Jiang, K.; Du, W.; He, Z. Q.; Chen, Y. C. *Org. Lett.* **2007**, *9*, 3671.

phenyl group efficiently hindered the *Si* face of the azodicarboxylate, and the *N*-acetyl enamide could only attack the *Re* face of the azodicarboxylate, which led to the desired product with *S* configuration. In contrast, the steric effect between the methyl group of the *E* configured enamide and the complex made the attack disfavored in TS-2 (Figure 3).

In summary, we have developed a highly enantioselective amination reaction of *N*-acetyl enamides catalyzed by *N*,*N*′-dioxide/$Cu(OTf)_2$ complexes. The reaction performed well over a range of substituted α-aromatic *N*-acetyl enamides, giving the desired products in excellent yields (up to 99%) with high enantioselectivities (up to 91% ee). The methodology provided a very convenient path to the optically active vicinal diamines. Other features of this approach included the easy accessibility of the starting material from the ketone. Further studies of the details of the reaction mechanism are ongoing.

Acknowledgment. We thank the National Natural Science Foundation of China (Nos. 20732003 and 20702033), PCSIRT (No. IRT0846), and National Basic Research Program of China (973 Program) (No. 2010CB833300) for financial support. We also thank Sichuan University Analytical & Testing Center for NMR analysis.

Supporting Information Available: Experimental procedures and spectral and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100540P