Asymmetric Copper(I)-Catalyzed Henry Reaction with an Aminoindanol-Derived Bisoxazolidine Ligand

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ABSTRACT



Bisoxazolidine 1 is an effective ligand in the Me_2Zn -promoted and the Cu(l)-catalyzed Henry reaction. While a wide range of nitroaldol products are obtained in high yields and ee's in both cases, the replacement of dimethylzinc with copper(l) acetate results in a complete reversal of the sense of asymmetric induction. The Cu(l)-catalyzed enantioselective addition of nitromethane to methyl 4-oxobutanoate followed by hydrogenation and spontaneous lactamization gives (*S*)-5-hydroxypiperidin-2-one in 72% overall yield and 98% ee which compares favorably with previously reported methods.

The asymmetric Henry reaction has emerged as a powerful synthetic tool for the stereoselective formation of carbon–carbon bonds.¹ The resultant β -hydroxy nitroalkanes are important pharmaceutical precursors² and can be readily transformed to β -amino alcohols and α -hydroxy carboxylic acids.³ Many asymmetric nitroaldol reaction procedures reported to date require the use of an excess of dimethyl zinc or activated silyl nitronates and tetrabutylammonium triphenylsilyldifluorosilicate (TBAT)⁴ and provide excellent results with aromatic aldehydes, but yields and ee's often decrease when aliphatic substrates are used.^{1,5} Although aliphatic aldehydes carrying a second functional group are commercially available and provide important excess to a range of important biologically active

compounds, the compatibility of multifunctional substrates and thus the full scope of the asymmetric Henry reaction remain almost unexplored. The usefulness of this reaction for the asymmetric synthesis of key building blocks exhibiting more than the typical hydroxyl and the nitro groups attached to the aliphatic scaffold has barely been demonstrated to date.⁶ Asymmetric Henry reaction protocols generally involve the use of a chiral catalyst derived from Co(II),⁷ Mg(II),⁸ Zn(II),^{2,9} Cu(II),¹⁰ or rare earth metals.¹¹ A few interesting Cu(I)-catalyzed variants have also been reported.¹² In particular, Xiong's and Arai's groups have

⁽¹⁾ For a recent review on the asymmetric Henry reaction: Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561–2574.

^{(2) (}a) Trost, B. M.; Yeh, V. S. C.; Ito, H.; Bremeyer, N. Org. Lett. **2002**, *4*, 2621–2623. (b) Bandini, M.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A.; Ventrici, C. Chem. Commun. **2007**, 616–618.

⁽³⁾ Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York; 2001.

^{(4) (}a) Risgaard, K. V.; Gothelf, K. A.; Jorgensen, K. A. Org. Biomol. Chem. **2003**, *1*, 153–156. (b) Ooi, T.; Doda, K.; Maruoka, K. J. Am. Chem. Soc. **2003**, *125*, 2054–2055.

^{(5) (}a) Palomo, C.; Oiarbide, M.; Mielgo, A. Angew. Chem., Int. Ed. **2004**, 43, 5442–5444. (b) Gan, C.; Lai, G.; Zhang, Z.; Wang, Z.; Zhou, M.-M. Tetrahedron: Asymmetry **2006**, 17, 725–728. (c) Sedlak, M.; Drabina, P.; Keder, R.; Hanusek, J.; Cisarova, I.; Ruzicka, A. J. Organomet. Chem. **2006**, 691, 2623–2630. (d) Boruwa, J.; Gogoi, N.; Saikia, P. P.; Barua, N. C. Tetrahedron: Asymmetry **2006**, 17, 3315–3326. (e) Mansawat, W.; Saengswang, I.; U-prasitwong, P.; Bhanthumnavin, W.; Vilaivan, T. Tetrahedron Lett. **2007**, 48, 4235–4238. (f) Colak, M.; Demirel, N. Tetrahedron: Asymmetry **2008**, 19, 635–639. (g) Arai, T.; Yokoyama, N.; Yanagisawa, A. Chem.–Eur. J. **2008**, 2052–2059.

⁽⁶⁾ Sohtome, Y.; Kato, Y.; Handa, S.; Aoyama, N.; Nagawa, K.; Matsunaga, S.; Shibasaki, M. Org. Lett. **2008**, *10*, 2231–2234.

shown that a tetrahydrosalen-derived and a sulfonyldiamino Cu(I) complex, respectively, catalyze the nitroaldol reaction of a variety of aromatic substrates with good to high yields and ee's. The latter catalyst also generates aliphatic nitroaldol products with high asymmetric induction but at the cost of long reaction times (up to 120 h) unless a large excess of pyridine is employed.

We recently reported the synthesis of the first diketonederived C_2 -symmetric bisoxazolidine (not to be confused with structurally quite different bisoxazolines) and showed several applications of this new class of chiral ligands in asymmetric catalysis. The aminoindanol-derived bisoxazolidine 1 (Figure 1) has been proven to be broadly useful for a variety of



Figure 1. Structure of bisoxazolidine 1.

dialkylzinc promoted reactions.¹³ We found that this ligand catalyzes the enantioselective alkynylation of aromatic and aliphatic aldehydes, generating chiral propargylic alcohols in high yield and ee.14 We also obtained excellent results when this catalyst was applied in the alkylation of aldehydes with Me₂Zn and Et₂Zn.¹⁵ We have most recently developed a synthetic protocol for the asymmetric nitroaldol reaction utilizing bisoxazolidine 1, nitromethane, and dimethylzinc to generate the reactive zinc nitronate in situ.¹⁶ Although the Henry reaction products were obtained in high yields and ee's, a remaining drawback of this procedure is that 3 equiv of expensive, pyrophoric dimethylzinc is required. We therefore decided to explore the possibility of a dimethylzincfree bisoxazolidine-catalyzed nitroaldol reaction.

(7) (a) Kogami, Y.; Nakajima, T.; Ashizawa, T.; Kezuka, S.; Ikeno, T.; Yamada, T. Chem. Lett. 2004, 614-615. (b) Kogami, Y.; Nakajima, T.; Ikeno, T.; Yamada, T. Synthesis 2004, 1947-1950.

(8) Choudary, B. M.; Ranganath, K. V. S.; Pal, U.; Kantam, M. L.;

 Sreedhar, B. J. Am. Chem. Soc. 2005, 127, 13167–13171.
 (9) (a) Trost, B. M.; Yeh, V. S. C. Angew. Chem., Int. Ed. 2002, 41, 861-863. (b) Palomo, C.; Oiarbide, M.; Laso, A. Angew. Chem., Int. Ed. 2005, 44, 3881-3884. (c) Colak, M.; Aral, T.; Hogoren, H.; Demirel, N. Tetrahedron: Asymmetry 2007, 18, 1129-1133. (d) Bulut, A.; Aslant, A.; Dogan, O. J. Org. Chem. 2008, 73, 7373-7375.

(10) (a) Christensen, C.; Juhl, K.; Jørgensen, K. A. Chem. Commun. 2001, 2222-2223. (b) Christensen, C.; Juhl, K.; Hazell, R. G.; Jørgensen, K. A. J. Org. Chem. 2002, 67, 4875-4881. (c) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. J. Am. Chem. Soc. 2003, 125, 12692-12693. (d) Foltz, C.; Stecker, B.; Marconi, G.; Bellemin-Laponnaz, S.; Wadepohl, H.; Gade, L. H. Chem. Commun. 2005, 5115-5117. (e) Maheswaran, H.; Prasant, K. L.; Krishna, G. G.; Ravikumar, B.; Sridhar, B.; Kantam, M. L. Chem. Commun. 2006, 4066-4068. (f) Bandini, M.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A.; Ventrici, C. Chem. Commun. 2007, 616-618. (g) Blay, G.; Climent, E.; Fernandez, I.; Hernandez-Olmos, V.; Pedro, J. R. Tetrahedron: Asymmetry 2006, 17, 2046-2049. (h) Ma, K.; You, J. Chem.-Eur. J. 2007, 13, 1863-1871. (i) Bandini, M.; Benaglia, M.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. Org. Lett. 2007, 9, 2151-2153. (j) Ginotra, S. K.; Singh, V. K. Org. Biomol. Chem. 2007, 5, 3932–3937. (k) Arai, T.; Watanabe, M.; Yanagisawa, A. Org. Lett. 2007, 9, 3595-3597. (1) Gan, C. Can. J. Chem. 2008, 86, 261-263. (m) Blay, G.; Domingo, L. R.; Hernandez-Olmos, V.; Pedro, J. R. Chem.-Eur. J. 2008, 4725–4730. (n) Tanaka, K.; Hachiken, S. Tetrahedron Lett. 2008, 49. 2533-2536.

Initial screening of several metal salts using ethanol as solvent revealed that copper acetate complexes afford the most promising results. We found that the use of 10 mol % of 1 and Cu(I) acetate at room temperature allows smooth reaction between nitromethane and benzaldehyde toward 2-nitro-1-phenylethanol in 96% yield and 68% ee within 1.5 h. The replacement of Cu(I) by Cu(II) acetate gave the Henry reaction product in similar ee's but at only 50% conversion after 24 h. Further optimization of catalyst loading, solvents, additives such as pyridine, temperature, and substrate concentration showed that the best results can be obtained with 10 mol % of 1 and 9 mol % of CuOAc in ethanol at -15 °C. Under these conditions, we obtained 2-nitro-1-phenylethanol from benzaldehyde in 93% yield and 89% ee after 16 h (Scheme 1).



We then decided to explore other aromatic substrates (Table 1). In general, the bisoxazolidine-CuOAc-catalyzed

OH





^a All reactions were performed on a 1 mmol scale using 10 mol % of 1, 9 mol % of CuOAc, and 10 equiv of nitromethane in 2.4 mL of EtOH. ^b Isolated yields. ^c The ee's and absolute configurations were determined by chiral HPLC analysis using Chiralcel OD and Chiralpak AD as described in the literature.

Henry reaction furnishes a wide range of β -hydroxy nitroalkanes in up to 95% yield and 89% ee within 24 h. For example, the formation of 2-nitro-1-(4-bromophenyl)ethanol was accomplished within 16 h with 93% yield and 86% ee (Table 1, entry 5). However, less reactive aldehydes such as 4-methoxybenzaldehyde require longer reaction times and give diminished yields.

Since several nitroaldol reaction protocols providing high yields and ee's with aromatic aldehydes have appeared in the literature, we were more interested in testing the substrate scope of our procedure with aliphatic substrates (Table 2).

Table 2. Enantioselective Henry Reaction of Aliphatic Aldehydes

	1 (10 mol %)	OH		
R H	CuOAc (9 mol %)			

entry	substrate	product	temp (°C)	<i>t</i> (h)	yield ^b	ee ^c
1	СНО		-10	24	87%	93% (S)
2	₩сно		-10	24	85%	91% (S)
3	\)_4		-10	48	91%	93% (S) ^d
4	Y)7		-10	48	92%	93% (S)
5	\downarrow		-10	48	91%	93% (S)
6	χ^{g}		0	48	85%	92% (S)
7			0	48	97%	97% (S)
8	ССНО	OH NO ₂	-15	24	90%	88% (S)

^a All reactions were performed on a 1 mmol scale using 10 mol % of 1, 9 mol % of CuOAc, and 10 equiv of nitromethane in 2.4 mL of EtOH. Isolated yields. ^c The ee's and absolute configurations were determined by chiral HPLC analysis using Chiralcel OD and Chiralpak AD as described in the literature.^{10c,17,18} ^d The absolute configuration was assigned by analogy to nonanal (entry 4).

We were pleased to discover that the bisoxazolidine-Cu(I)catalyzed nitroaldol reaction gives the corresponding β -hydroxy nitroalkanes in up to 97% yield and 97% ee. Importantly, sterically hindered aldehydes are well tolerated, and we were able to obtain (S)-3,3-dimethyl-1-nitrobutan-2-ol in 85% yield and 92% ee (Table 2, entry 6). The reaction procedure was also compatible with α,β -unsaturated aldehydes, and (S)-1-nitro-4-phenyl-but-3-en-2-ol was produced in 90% yield and 88% ee (Table 2, entry 8).

In recent years, the concept of reversing the enantioselectivity of a catalytic reaction while maintaining a single chiral induction source has received increasing attention.¹⁹ In particular, when the chiral catalyst is derived from a natural product that is only readily available as a single enantiomer, it is advantageous if one can simply modify reaction conditions (solvent, additives, temperature, etc.) to obtain the opposite product configuration. In a few cases, this has been achieved by changing the metal center of a chiral catalyst. For example, Du et al. have shown that replacement of Cu(OTf)₂ with Et₂Zn in the presence of the same tridentate bisoxazoline ligand can switch the enantioselective outcome of the addition of nitromethane to α -ketoesters.²⁰ We have now observed a highly efficient reversal of enantioselectivity for the Henry addition of aldehydes. As reported previously, employing Me₂Zn in the bisoxazolidine-catalyzed nitrolaldol reaction of various aldehydes generally favors formation of the corresponding (R)- β -hydroxy nitroalkanes.¹⁶ By contrast, we predominantly obtain the (S)-enantiomer when catalytic amounts of CuOAc are used (Scheme 2). We assume that this can be attributed

Scheme 2. Control of the Stereoselective Outcome of the Bisoxazolidine-Catalyzed Henry Reaction



to a different coordination sphere of the catalytically active zinc(II) and copper(I) species. The use of 1 and dimethylzinc in the Henry reaction is likely to generate a pentacoordinate methylzinc-derived transition state that carries the bidentate bisoxazolidine ligand, the activated nitronate anion, and the

(13) This ligand is commercially available at Strem (catalogue no. 07-0488), US 20070265255A1 patent pending.

(14) Wolf, C.; Liu, S. J. Am. Chem. Soc. 2006, 128, 10996–10997.

(15) Liu, S.; Wolf, C. Org. Lett. 2007, 9, 2965–2968.
(16) Liu, S.; Wolf, C. Org. Lett. 2008, 10, 1831–1834.

(17) (a) Saá, J. M.; Tur, F.; González, J.; Vega, M. Tetrahedron: Asymmetry 2006, 17, 99-106. (b) Blay, G.; Climent, E.; Fernández, I.; Hernández-Olmos, V.; Pedro, J. Tetrahedron: Asymmetry 2007, 18, 1603-1612. (c) Bulut, A.; Aslan, A.; Dogan, O. J. Org. Chem. 2008, 73, 7373-7375.

^{(11) (}a) Sasai, J.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. J. Am. Chem. Soc. 1992, 114, 4418-4420. (b) Sasai, J.; Suzuki, T.; Itoh, N.; Shibasaki, M. Tetrahedron Lett. 1993, 34, 851-854. (c) Sasai, H.; Zuzuki, N.; Itoh, K.; Tanaka, T.; Date, K.; Okamura, K.; Shibasaki, M. J. Am. Chem. Soc. 1993, 115, 10372-10373.

^{(12) (}a) Arai, T.; Watanabe, M.; Fujiwara, A.; Yokoyama, N.; Yanagisawa, A. Angew. Chem., Int. Ed. 2006, 45, 5978-5981. (b) Qin, B.; Xiao, X.; Liu, X.; Huang, J.; Wen, Y.; Feng, X. J. Org. Chem. 2007, 72, 9323-9328. (c) Xiong, Y.; Wang, F.; Huang, X.; Wen, Y.; Feng, X. Chem.-Eur. J. 2007, 13, 829-833. (d) Jiang, J.-J.; Shi, M. Tetrahedron: Asymmetry 2007, 18, 1376–1382. (e) Arai, T.; Takashita, R.; Endo, Y.; Watanabe, M.; Yanagisawa, A. J. Org. Chem. 2008, 73, 4903-4906.

aldehyde substrate.¹⁶ In the case of CuOAc, proton transfer from nitromethane to the acetate group which is subsequently replaced with the substrate is expected to generate a tetracoordinate Cu(I) transition state favoring Re-face attack of the nitronate anion on the aldehyde as shown in Figure 2.



Figure 2. Cu(I)-catalyzed Henry reaction using ligand 1.

Following the enantioselective C-C bond formation, the aldol product is released upon protonation by the intermediate acetic acid which completes the catalytic cycle and regenerates the unloaded tetrahedral bisoxazolidine-derived CuOAc complex.

Finally, we decided to evaluate the general usefulness of our asymmetric nitroaldol reaction procedure with bifunctional aldehyde **2**. An enantioselective synthesis of **3**, which provides access to heterocycles **4** and **5**, has not been described. We envisioned that the bisoxazolidine-catalyzed Henry reaction between **2** and nitromethane followed by sequential reduction and lactamization should give the important alkaloid precursors 5-hydroxypiperidin-2-one, **4**, and 5-(aminomethyl)dihydrofuran-2(3*H*)-one, **5**, in high yields and ee's (Scheme 3).²¹ To date, the most efficient





syntheses of (*S*)-**4** and (*S*)-**5** start from (*S*)-glutamic acid and require five steps with 24% overall yield and six steps with 19% yield, respectively.²² We were able to prepare **3** in 85% chemical yield and 89% ee. Hydrogenation followed by spontaneous cyclization then gave (*S*)-**4** in 85% yield and 98% ee after one recrystallization. Notably, this lactam can be converted to lactone (*S*)-**5** with 78% yield.²³ We have thus introduced a much more efficient synthetic approach toward these important building blocks.

In summary, we have shown that bisoxazolidine **1** is an effective ligand in the Cu(I)-catalyzed Henry reaction. High yields and ee's were achieved with a wide range of substrates. In particular, the results obtained with aliphatic aldehydes are remarkable. The replacement of dimethylzinc with copper(I) acetate results in a complete change in the sense of asymmetric induction without compromising yields and ee's. The general usefulness and potential of this nitroaldol reaction procedure was also demonstrated. Employing methyl 4-oxobutanoate, we were able to prepare (S)-5-hydroxypiperidin-2-one in 72% overall yield and 98% ee within two steps which compares favorably with previously reported methods.

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Supporting Information Available: Synthetic procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽¹⁸⁾ Blay, G.; Domingo, L. R.; Hernández-Olmos, V.; Pedro, J. R. Chem. Eur. J. 2008, 14, 4725–4730.

⁽¹⁹⁾ Wolf, C., Ed. *Dynamic Stereochemistry of Chiral Compounds*; RSC Publishing: Cambridge, 2008. For a recent review on reversing enantioselectivity: Tanaka, T.; Hayashi, M. *Synthesis.* **2008**, 3361–3376.

⁽²⁰⁾ Du, D.-M.; Lu, S.-F.; Fang, T.; Xu, J. J. Org. Chem. 2005, 70, 3712–3715.

^{(21) (}a) Gagnon, A.; Danishefsky, S. J. Angew. Chem., Int. Ed. 2002, 41, 1581–1584. (b) Fenster, M. D. B.; Dake, G. R. Org. Lett. 2003, 5, 4313–4316. (c) Fan, G.-J.; Wang, Z.; Wee, A. G. H. Chem. Commun. 2006, 3732–3734. (d) Morgan, I. R.; Yazici, A.; Pyne, S. G. Tetrahedron 2008, 64, 1409–1419.

^{(22) (}a) Fabiano, E.; Golding, B. T.; Sadeghi, M. M. Synthesis **1987**, 190–192. (b) Olsen, R. K.; Bhat, K. L.; Wardle, R. B. J. Org. Chem. **1985**, 50, 896–899. (c) Humphries, M. E.; Murphy, J.; Phillips, A. J.; Abell, A. D. J. Org. Chem. **2003**, 68, 2432–6243. (d) Andres, J. M.; Pedrosa, R.; Perez-Encabo, A. Tetrahedron Lett. **2006**, 47, 5317–5320. (e) Feng, C.-G.; Chen, J.; Ye, J.-L.; Ruan, Y.-P.; Zheng, X.; Huang, P.-Q. Tetrahedron **2006**, 62, 7459–7465.

⁽²³⁾ Herdeis, C. Synthesis 1986, 232-233.