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A Highly *syn*-Selective Nitroaldol Reaction Catalyzed by Cu^{II}–Bisimidazoline

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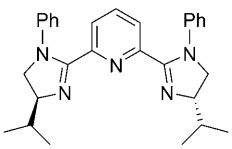
The nitroaldol (Henry) reaction is a valuable and atom-economic C–C bond-formation reaction between a nitroalkane and a carbonyl compound to furnish a 1,2-nitro alcohol that is over 100 years old.[1] Since Shibasaki et al. first used this reaction in a catalytic enantioselective manner,[2] much effort has been devoted to this area because facile reduction of the enantioenriched 1,2-nitro alcohols readily provides chiral 1,2-amino alcohols, which are ubiquitous segments in natural products, pharmaceuticals, synthetic intermediates, and chiral ligands.[3] A highly enantioselective nitroaldol reaction using nitromethane as a nucleophile has been achieved by metal catalysis,[4] organocatalysis,[5] and biocatalysis.[6] However, highly diastereo- and enantioselective nitroaldol reactions that use nitroethane and other nitroalkanes to simultaneously form two stereocenters still remain challenging and less explored. In 1995, the Shibasaki group reported the first *syn* selective[7,8] and enantioselective nitroaldol reaction,[9] catalyzed by their modified heterobimetallic catalyst[2] with 6,6′-disubstituted 1,1′-binaphthol (BINOL) in place of BINOL. Nitroethane added to hydrocinnamaldehyde at −20 °C for 75 h to afford 4-nitro-1-phenylpentan-3-ol in 70% yield with a *syn*/*anti* diastereoselectivity of 89:11 and 93% enantiomeric excess (*ee*) of the *syn* product. Very few substrates have been used to date. Only sporadic and tentative examples were reported until recently.[10] Nagasawa et al. disclosed that their guanidinium–thiourea molecule is a highly *syn*-selective organocatalyst for the nitroaldol reaction of nitroalkanes with aliphatic aldehydes.[11] Arai et al. obtained improved *syn* selectivity for the reaction of α-branched-aliphatic aldehydes by modifying their Cu^{II}–diamine catalyst[4m] to a Cu^{I}–sulfonyldiamine–pyridine system.[12] Problems still remain in these limited examples: low reaction temperatures, long reaction times, a narrow range of aldehydes, and in particular, low *syn* selectivity for aromatic aldehydes.[13,14] Therefore, a more efficient catalyst for highly *syn*-selective nitroaldol reaction is of great significance. We herein report a highly *syn*-selective nitroaldol reaction of nitroethane with both aromatic and aliphatic aldehydes catalyzed by a Cu^{II}–bisimidazoline system.



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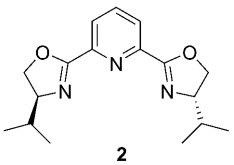

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We previously reported a highly enantioselective nitroaldol reaction between various aldehydes and nitromethane, catalyzed by our rationally designed chiral bisimidazoline catalyst **1**.[4j] To probe deeper into the potential of this catalyst, we decided to further investigate the nitroaldol reaction by using nitroethane as a nucleophile. Under the optimal conditions we used for the reaction of nitromethane (10 mol% ligand **1**, $Cu(OTf)_2$ (Tf = trifluoromethanesulfonyl),[15] and Et_3N in ethanol), the reaction of nitroethane with benzaldehyde proceeded smoothly. After 24 h at room temperature, the desired nitroaldol adduct was obtained in 80% yield with a *syn*/*anti* diastereoselectivity of 1.5:1, and the *ee* value of the *syn* product was 78% (Table 1, entry 1). After preliminary screening of the reaction solvent, dioxane gave a promising *syn*/*anti* selectivity of 2.6:1, and the *ee* value was 86% (Table 1, entry 6). Different bases were then tested. Both the more bulky secondary amine, diisopropylamine, and tertiary amine, diisopropylethylamine, showed much improved reactivity, but the stereoselectivity only increased slightly with the bulkiness of the base (Table 1, entries 6–8). The inorganic base potassium carbonate gave very low enantioselectivity, while a moderate diastereoselectivity was observed (Table 1, entry 9). Azacycloalkanes exhibited very

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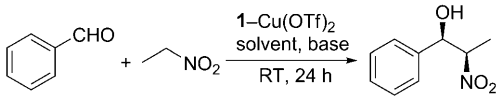
Table 1. Condition screening for the diastereoselective nitroaldol reaction of nitroethane with benzaldehyde catalyzed by **1**–$Cu(OTf)_2$.[a]



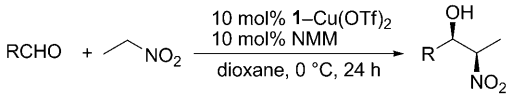
	Base	Solvent	Yield [%][b]	d.r. (*syn*/*anti*)[c]	*ee* [%] (*syn*)[c]
1	Et_3N	EtOH	80	1.5:1	78
2	Et_3N	toluene	80	1.6:1	59
3	Et_3N	CH_2Cl_2	72	1.7:1	56
4	Et_3N	THF	87	1.7:1	72
5	Et_3N	$EtNO_2$	82	1.9:1	74
6	Et_3N	dioxane	72	2.6:1	86
7	iPr_2NH	dioxane	92	2.8:1	88
8	iPr_2NEt	dioxane	90	3.5:1	92
9	K_2CO_3	dioxane	93	2.1:1	9
10	pyrrolidine	dioxane	48	4.3:1	87
11	piperidine	dioxane	93	3.5:1	91
12	morpholine	dioxane	87	4.9:1	94
13	NMP	dioxane	95	3.0:1	92
14	NMM	dioxane	92	6.1:1	95
15[d]	NMM	dioxane	92	8.1:1	97

[a] Reaction conditions: benzaldehyde (0.25 mmol), nitroethane (10 *equiv*), solvent (0.2 mL), **1**–$Cu(OTf)_2$ (10 mol%), base (10 mol%); the local RT was (10±2)°C when the experiment was conducted. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The reaction was carried out at 0°C.

interesting results (Table 1, entries 10–12): When pyrrolidine was employed, the diastereoselectivity was improved to 4.3:1, but the yield was only 48%. Piperidine exhibited good reactivity and enantioselectivity of the *syn* product, but the diastereoselectivity was only 3.5:1. Morpholine, which has an oxygen atom in place of 4-methylene of the piperidine ring gave a nice yield of 87% and a good diastereoselectivity of 4.9:1 with the *syn* product dominating with 94% *ee*. *N*-Methylmorpholine (NMM)[16] further improved the yield to 92% and the diastereoselectivity to 6.1:1 while methylated piperidine (NMP) almost did not affect the result (Table 1, entries 13 and 14).[17] Lowering the reaction temperature to 0°C had no effect on the reactivity, but slightly increased the diastereoselectivity to 8.1:1 and the enantioselectivity to 97% (Table 1, entry 15). The absolute configuration of the main diastereomer was determined to be *R*,*R* by comparing with HPLC data in the literature (see the Supporting Information). For comparison, the bisoxazoline analogue **2** was tested under the optimal conditions. It exhibited almost no diastereoselectivity and low enantioselectivity (40% yield, 1.1:1 of *syn*/*anti*, and 39% *ee syn*). This comparison clearly suggested that the subtle structural change significantly affects the selectivity of the catalyst.

With the optimal conditions in hand (Table 1, entry 15), the scope of substrates was investigated by performing the nitroaldol reaction of nitroethane (10 equiv) with aldehydes in the presence of **1**–$Cu(OTf)_2$ (10 mol%) as the catalyst and NMM (10 mol%) as the base in dioxane at 0°C. The results are summarized in Table 2. For a variety of aromatic, heteroaromatic, α,β-unsaturated, and aliphatic aldehydes, the reaction proceeded cleanly within 24 h to afford the desired nitroaldol adduct as the single product in good yield

Table 2. Nitroaldol reaction of nitroethane with different aldehydes catalyzed by **1**–$Cu(OTf)_2$.[a]



	R	Yield [%][b]	d.r. (*syn*/*anti*)[c]	*ee* [%] (*syn*)[d]
1	Ph	92	8.3:1	97
2	2-MeO-Ph	87	2.9:1	97
3	2-NO_2-Ph	95	2.7:1	91
4	3-Me-Ph	72	7.7:1	98
5	3-MeO-Ph	90	9.1:1	96
6	3-F-Ph	93	7.2:1	94
7	3-Cl-Ph	75	6.7:1	96
8	3-NO_2-Ph	90	4.4:1	91
9	4-Me-Ph	64	7.7:1	98
10	4-MeO-Ph	58	7.2:1	96
11	4-F-Ph	73	8.4:1	94
12	4-Cl-Ph	80	5.6:1	93
13	4-Br-Ph	82	6.3:1	95
14	4-NO_2-Ph	90	4.3:1	91
15	4-CN-Ph	82	5.0:1	91
16	1-naphthyl	86	2.5:1	96
17	2-naphthyl	87	7.7:1	97
18	2-furyl	90	8.3:1	90
19	2-thiophenyl	75	9.1:1	92
20	(*E*)-PhCH=CH	75	16.7:1	96
21	$PhCH_2CH_2$	91	50:1	93
22	$CH_3(CH_2)_2$	77	12.5:1	96
23	$CH_3(CH_2)_3$	80	25:1	95
24	$CH_3(CH_2)_7$	65	50:1	96
25	$(CH_3)_2CH$	92	50:1	98
26	$(CH_3)_2CHCH_2$	88	14.3:1	92
27	cyclopropyl	60	17:1	97
28	cyclopentyl	98	33.3:1	98
29	cyclohexyl	90	50:1	99
30[e]	$(CH_3)_2CH$	70	50:1	99
31[f]	Ph	92	8.3:1	97
32[f]	$PhCH_2CH_2$	90	50:1	92

[a] Reaction conditions: aldehyde (0.25 mmol), nitroethane (10 equiv), dioxane (0.2 mL), **1**–$Cu(OTf)_2$ (10 mol%), NMM (10 mol%). [b] Isolated yield. [c] Determined by ^1H NMR spectroscopy analysis of the crude reaction mixture. [d] Determined by chiral HPLC analysis. [e] Catalyst loading: 2.5 mol%; reaction time: 48 h. [f] The reaction was performed under an air atmosphere.

with predominately the *syn* diastereomer and an excellent *ee* value. For aromatic aldehydes, the electronic nature of the substituent on the phenyl ring has limited effect on the diastereoselectivity, regardless of whether it is electron-withdrawing or -donating. However, the location of the substituent has a significant effect on the diastereoselectivity: *ortho*-Substituted benzaldehydes exhibited much lower diastereoselectivity than *meta*- and *para*-substituted ones. For instance, while the reaction with 2-methoxybenzaldehyde afforded the adduct with a *syn*/*anti* diastereoselectivity of 2.9:1, the reactions with 3-methoxybenzaldehyde and 4-methoxybenzaldehyde gave 9.1:1 and 7.2:1, respectively (Table 2, entries 2, 5, and 10). More interestingly, the reaction of 2-methylbenzaldehyde did not proceed at all. The significant lower diastereoselectivity for 1-naphthylaldehyde relative to 2-naphthylaldehyde could also be attributed to this *ortho*-position effect (Table 2, entries 16 and 17). It was

delightful that heteroaromatic aldehydes also showed good reactivity and stereoselectivity (Table 2, entries 18 and 19).

The addition to aliphatic aldehydes worked much better than to aromatic aldehydes in terms of diastereoselectivity. The reaction of hydrocinnamaldehyde afforded the desired product in 91% yield with a *syn*/*anti* diastereoselectivity of 50:1 and 93% *ee* of the *syn* product. A compromised diastereoselectivity of 16.7:1 was obtained for *trans*-cinnamaldehyde, which could probably be attributed to the conjugation of the aldehyde group with the aromatic phenyl group (Table 2, entries 20 and 21). For linear aliphatic aldehydes, the diastereoselectivity increased significantly when the alkyl carbon chain lengthened (Table 2, entries 22–24). α-Branched aliphatic aldehydes exhibited much improved diastereoselectivity than linear aldehydes, whereas β-branched aldehydes showed no impact at all (Table 2, entries 25 and 26). For cycloalkyl aldehydes, the diastereoselectivity largely increased when the cycloalkyl group became bigger, in accordance with the trend of linear aldehydes (Table 2, entries 27–29). It was noteworthy that although the diastereoselectivity obtained for aromatic aldehydes was lower than aliphatic aldehydes, the enantioselectivity was excellent in all cases.[18] For certain aldehydes, such as isobutyraldehyde, both the diastereo- and enantioselectivity remained unaltered even with 2.5 mol% of catalyst loading, although the reaction was much slower (Table 2, entry 30). Moreover, our catalytic system was inert to air. The reaction carried out under an air atmosphere gave the same results as that carried out under the controlled conditions (Table 2, entries 31 and 32).

A single crystal of the complex **1**–$Cu(OTf)_2$ was serendipitously obtained from a solvent mixture of dichloromethane and toluene in the presence of pyridine (1 equiv) (Figure 1).[19] X-ray crystallographic analysis clearly revealed that the complex **1**–$Cu(OTf)_2$ adopts an octahedral geometry around the copper center. The four nitrogen atoms from the imidazoline moieties, the pyridinyl spacer, and pyridine occupy the four equatorial positions of the octahedron, and two oxygen atoms from OTf anions occupy the two zeniths. The two isopropyl groups stand out of the imidazoline plane up and down, respectively, which forms a chiral environment around the copper center for chiral induction. Note that the two methyl groups of the isopropyl moiety both point away from the copper center, indicating a proper and tight space around the copper center.[20]

Based on the single-crystal structure, we propose two possible transition states to interpret the stereoselectivity of the nitroaldol reaction catalyzed by **1**–$Cu(OTf)_2$ (Scheme 1). In the nitroaldol reaction, the aldehyde takes the position of pyridine in the crystal structure. Nitroethane can only approach to the copper center from one side and one oxygen atom of the nitro group replaces one OTf anion to coordinate with copper. Because of the repulsion between the methyl group of nitroethane and the isopropyl group of the catalyst in transition-state II (TS-II), which will lead to the *anti* product, transition-state I (TS-I) is most favored and results in *syn* product.

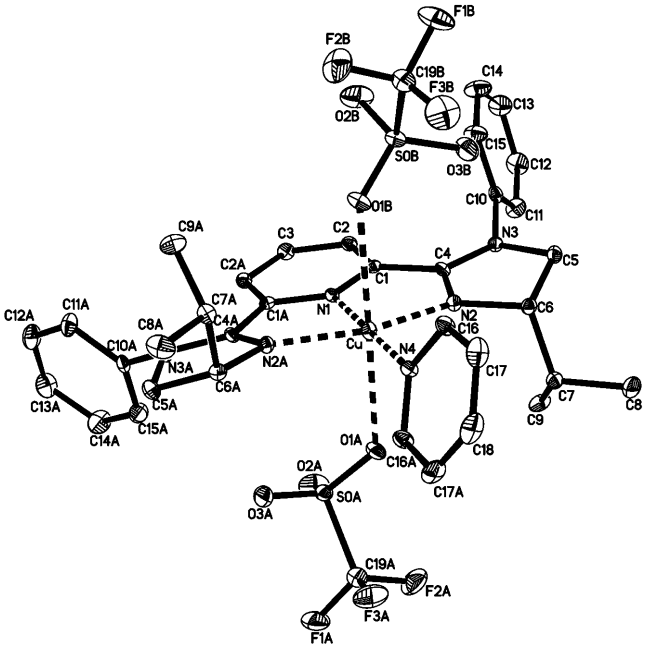
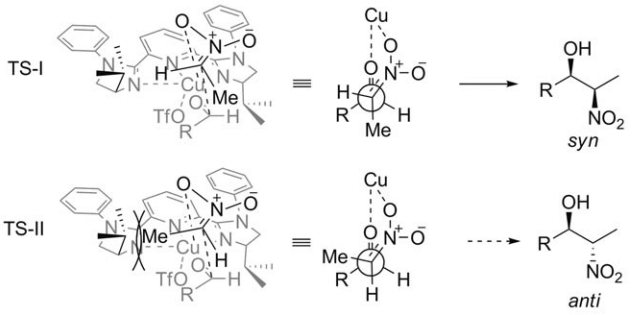


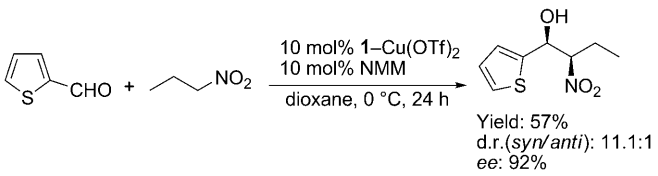
Figure 1. The X-ray crystallographic structure of **1**–$Cu(OTf)_2$–pyridine. Thermal ellipsoids are shown at the 30% probability level.



Scheme 1. The proposed transition states of the nitroaldol reaction catalyzed by **1**–$Cu(OTf)_2$.

The nice diastereoselectivity for heteroaromatic aldehydes was further demonstrated by the reaction of thiophene-2-carbaldehyde with nitropropane (Scheme 2). Under the optimal conditions, the targeted 2-nitro-1-(thiophen-2-yl)butan-1-ol was obtained in 57% yield with 92% *ee* of the *syn* diastereomer dominating (*syn*/*anti* = 11.1:1).

In summary, we have demonstrated that the chiral bisimidazoline ligand **1**, together with $Cu(OTf)_2$ in the presence of *N*-methylmorpholine, is a highly *syn*-selective nitroaldol reaction catalytic system. X-ray analysis of a single crystal of **1**–$Cu(OTf)_2$–pyridine clearly showed the chiral environment around the copper center, which helped us to understand the *syn* selectivity of the nitroaldol reaction catalyzed by **1**–$Cu(OTf)_2$. The ease of making ligand **1** from the readily available natural amino acid,[4j] the simpleness of the reaction procedure and the generally high *syn* selectivity and excellent enantioselectivity for a broad range of aldehydes, including aromatic, heteroaromatic, α,β-unsaturated, and ali-



Scheme 2. Nitroaldol reaction of nitropropane with thiophene-2-carbaldehyde catalyzed by **1**–$Cu(OTf)_2$.

phatic aldehydes, make our catalytic system very applicable. Although the results for aromatic aldehydes are not as good as those obtained for aliphatic aldehydes, to the best of our knowledge, they are the best ever achieved. Efforts are still underway to improve the diastereoselectivity for the nitroaldol reaction of aromatic aldehydes.

Experimental Section

General procedure for the catalytic asymmetric nitroaldol reaction: $Cu(OTf)_2$ (9.05 mg, 0.025 mmol), ligand (11.9 mg, 0.026 mmol), and dioxane (0.2 mL) were added to a Schlenk tube fitted with a magnetic stirring bar under nitrogen. The mixture was allowed to stir for 2 h and then cooled to 0 °C. An aldehyde (0.25 mmol) was added, followed by the addition of a freshly distilled nitroethane (2.5 mmol) and *N*-methylmorpholine (2.74 μL, 0.025 mmol). The reaction mixture was stirred for 24 h at 0 °C. After removal of volatile compounds in vacuo and the catalyst by filtering through a plug of silica gel, the filtrate was concentrated and the residue was analyzed by ^{1}H NMR spectroscopy to determine the diastereomeric ratio. Then the residue was purified by column chromatography on silica gel to afford the corresponding 1,2-nitro alcohol. The enantiomeric excess was finally determined by HPLC analysis on a chiral AD-H or AS-H column.

Acknowledgements

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Keywords: aldehydes · asymmetric catalysis · bisimidazoline · copper · nitroaldol reaction

[1] L. Henry, C. R. Hebd, *Séances Acad. Sci.* **1895**, *120*, 1265–1267.
[2] H. Sasai, T. Suzuki, S. Arai, T. Arai, M. Shibasaki, *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420.
[3] For reviews on the catalytic asymmetric Henry reaction, see: a) M. Shibasaki, H. Gröger in *Comprehensive Asymmetric Catalysis, Vol. III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 1075–1090; b) M. Shibasaki, H. Gröger, M. Kanai in *Comprehensive Asymmetric Catalysis, Supplement 1* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **2004**, pp. 131–133; c) C. Palomo, M. Oiarbide, A. Mielgo, *Angew. Chem.* **2004**, *116*, 5558–5560; *Angew. Chem. Int. Ed.* **2004**, *43*, 5442–5444; d) J. Boruwa, N. Gogoi, P. P. Saikia, N. C. Barua, *Tetrahedron: Asymmetry* **2006**, *17*, 3315–3326; e) C. Palomo, M. Oiarbide, A. Laso, *Eur. J. Org. Chem.* **2007**, 2561–2574.
[4] Rare-earth metals, see reference [2] and the following: a) J. M. Saá, F. Tur, J. González, M. Vega, *Tetrahedron: Asymmetry* **2006**, *17*, 99–106; b) reaction of trifluoromethyl ketones: F. Tur, J. M. Saá, *Org. Lett.* **2007**, *9*, 5079–5082; zinc: c) B. M. Trost, V. S. C. Yeh, *Angew. Chem.* **2002**, *114*, 889–891; *Angew. Chem. Int. Ed.* **2002**, *41*, 861–863; d) C. Palomo, M. Oiarbide, A. Laso, *Angew. Chem.* **2005**, *117*, 3949–3952; *Angew. Chem. Int. Ed.* **2005**, *44*, 3881–3884; e) S. Liu, C. Wolf, *Org. Lett.* **2008**, *10*, 1831–1834; f) A. Bulut, A. Aslan, Ö. Dogan, *J. Org. Chem.* **2008**, *73*, 7373–7375; copper(II): g) reaction of α-ketoesters: C. Christensen, K. Juhl, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 4875–4881; h) D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw, C. W. Downey, *J. Am. Chem. Soc.* **2003**, *125*, 12692–12693; i) S. K. Ginotra, V. K. Singh, *Org. Biomol. Chem.* **2007**, *5*, 3932–3937; j) K. Ma, J. You, *Chem. Eur. J.* **2007**, *13*, 1863–1871; k) H. Maheswaran, K. L. Prasanth, G. G. Krishna, K. Ravikumar, B. Sridhar, M. L. Kantam, *Chem. Commun.* **2006**, 4066–4068; l) T. Arai, M. Watanabe, A. Fujiwara, N. Yokoyama, A. Yanagisawa, *Angew. Chem.* **2006**, *118*, 6124–6127; *Angew. Chem. Int. Ed.* **2006**, *45*, 5978–5981; m) T. Arai, M. Watanabe, A. Yanagisawa, *Org. Lett.* **2007**, *9*, 3595–3597; n) M. Bandini, F. Piccinelli, S. Tommasi, A. Umani-Ronchi, C. Ventrici, *Chem. Commun.* **2007**, 616–618; copper(I): o) Y. Xiong, F. Wang, X. Huang, Y. Wen, X. Feng, *Chem. Eur. J.* **2007**, *13*, 829–833; p) B. Qin, X. Xiao, X. Liu, J. Huang, Y. Wen, X. Feng, *J. Org. Chem.* **2007**, *72*, 9323–9328; cobalt(II): q) Y. Kogami, T. Nakajima, T. Ashizawa, S. Kezuka, T. Ikeno, T. Yamada, *Chem. Lett.* **2004**, *33*, 614–615; r) Y. Kogami, T. Nakajima, T. Ikeno, T. Yamada, *Synthesis* **2004**, 1947–1950; magnesium: s) B. M. Choudary, K. V. S. Ranganath, U. Pal, M. L. Kantam, B. Sreedhar, *J. Am. Chem. Soc.* **2005**, *127*, 13167–13171; chromium (III): t) R. Kowalczyk, P. Kwiatkowski, J. Skarżewski, J. Jurczak, *J. Org. Chem.* **2009**, *74*, 753–756.
[5] For selected examples, see: a) Y. Sohtome, Y. Hashimoto, K. Nagasawa, *Adv. Synth. Catal.* **2005**, *347*, 1643–1648; b) T. Marcelli, R. N. S. Van der Haas, J. H. Van Maarseveen, H. Hiemstra, *Angew. Chem.* **2006**, *118*, 943–945; *Angew. Chem. Int. Ed.* **2006**, *45*, 929–931; c) reaction of α-ketoesters: H. Li, B. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 732–733; d) reaction of α-ketophosphonates: T. Mandal, S. Samanta, C. Zhao, *Org. Lett.* **2007**, *9*, 943–945.
[6] The first biocatalytic asymmetric Henry reaction was reported, but it is highly substrate dependent, see: a) T. Purkarthofer, K. Gruber, M. Gruber-Khadjawi, K. Waich, W. Skranc, D. Mink, H. Griengl, *Angew. Chem.* **2006**, *118*, 3532–3535; *Angew. Chem. Int. Ed.* **2006**, *45*, 3454–3456; b) M. Gruber-Khadjawi, T. Purkarthofer, W. Skranc, H. Griengl, *Adv. Synth. Catal.* **2007**, *349*, 1445–1450. The addition of nitroethane to benzaldehyde gave 9:1 *anti*-selectivity.
[7] The *anti*-selective Henry reaction was first achieved by using silyl nitronates as the donors, see: a) T. Ooi, K. Doda, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 2054–2055; b) T. Risgaard, K. V. Gothelf, K. A. Jørgensen, *Org. Biomol. Chem.* **2003**, *1*, 153–156.
[8] The direct *anti*-selective Henry reaction was reported recently, see: a) D. Uraguchi, S. Sakaki, T. Ooi, *J. Am. Chem. Soc.* **2007**, *129*, 12392–12393; b) S. Handa, K. Nagawa, Y. Sohtome, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2008**, *120*, 3274–3277; *Angew. Chem. Int. Ed.* **2008**, *47*, 3230–3233; c) T. Nitabaru, A. Nojiri, M. Kobayashi, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 13860–13869; d) T. Nitabaru, N. Kumagai, M. Shibasaki, *Tetrahedron Lett.* **2008**, *49*, 272–276; e) G. Blay, L. R. Domingo, V. Hernández-Olmos, J. R. Pedro, *Chem. Eur. J.* **2008**, *14*, 4725–4730; f) S. Selvakumar, D. Sivasankaran, V. K. Singh, *Org. Biomol. Chem.* **2009**, *7*, 3156–3162; and also see reference [6].
[9] a) H. Sasai, T. Tokunaga, S. Watanabe, T. Suzuki, N. Itoh, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 7388–7389; b) T. Arai, Y. M. A. Yamada, N. Yamamoto, H. Sasai, M. Shibasaki, *Chem. Eur. J.* **1996**, *2*, 1368–1372.
[10] a) A. V. Davis, M. Driffield, D. K. Smith, *Org. Lett.* **2001**, *3*, 3075–3078; b) A. Toussaint, A. Pfaltz, *Eur. J. Org. Chem.* **2008**, 4591–4597; c) H. Y. Kim, K. Oh, *Org. Lett.* **2009**, *11*, 5682–5685; and also see reference [4e] and [4m].

[11] a) Y. Sohtome, Y. Hashimoto, K. Nagasawa, *Eur. J. Org. Chem.* **2006**, 2894–2897; b) Y. Sohtome, N. Takemura, K. Takada, R. Takagi, T. Iguchi, K. Nagasawa, *Chem. Asian J.* **2007**, *2*, 1150–1160.
[12] T. Arai, R. Takashita, Y. Endo, M. Watanabe, A. Yanagisawa, *J. Org. Chem.* **2008**, *73*, 4903–4906.
[13] For *syn*-selective nitroaldol reaction for aromatic aldehydes, see references [4e], [10b], and [10c].
[14] High *anti*-selectivity for aliphatic aldehydes is still a challenge.
[15] Other Lewis acids, such as $[Cu(acac)_2]$, $[Cu(OAc)_2]\cdot H_2O$, $Zn(OTf)_2$, $Mg(OTf)_2$, and $Sc(OTf)_3$, gave low stereoselectivity, except $[Cu(ClO_4)_2]\cdot 6H_2O$, which showed comparable reactivity and stereoselectivity with $Cu(OTf)_2$.
[16] NMM was previously reported to show less reactivity and enantioselectivity than Et_3N in the nitroaldol reaction of pyruvate with nitromethane, see reference [4g]. It was also inferior to Et_3N in the reaction of benzaldehyde with nitromethane in our catalytic system: 63% yield and 89% *ee* in EtOH; 77% yield and 90% *ee* in dioxane.
[17] NMM and NMP are known bases to avoid racemization in the mix anhydride method of peptide synthesis, see: a) G. W. Anderson, J. E. Zimmerman, F. M. Callahan, *J. Am. Chem. Soc.* **1967**, *89*, 5012–5017; b) F. M. F. Chen, R. Steinauer, N. L. Benoiton, *J. Org. Chem.* **1983**, *48*, 2939–2941.
[18] In our case, the enantiomeric excesses of the minor *anti*-adducts were low (7–81% *ee*). These results indicate that the eventual epimerization of the *syn* adduct to the *anti* adduct remains at a lower level.
[19] CCDC-764747 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.
[20] When the more bulkyl *tert*-butyl group took the place of the isopropyl group in the catalyst, the diastereo- and enantioselectivity dropped dramatically.

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