DOI: 10.1002/ejoc.200600307

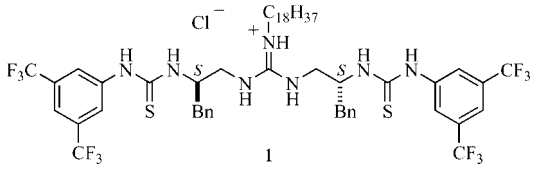
Diastereoselective and Enantioselective Henry (Nitroaldol) Reaction Utilizing a Guanidine-Thiourea Bifunctional Organocatalyst

Yoshihiro Sohtome,[a] Yuichi Hashimoto,[a] and Kazuo Nagasawa*[b]

Keywords: Organocatalysis / Bifunctional catalyst / Guanidine / Thiourea / Henry reaction

A highly enantio- and diastereoselective Henry reaction of various aldehydes with nitroethane was developed using the guanidine-thiourea bifunctional catalyst **1** (*syn* selectivity of 86:14 to 99:1 with 84–99 % *ee*). A variety of nitroalkanes was treated with unbranched and branched aldehydes and gave nitro alcohols with high *syn* diastereoselectivities (90:10 to 99:1) and high enantioselectivities (85–95 % *ee*). This reaction was successfully utilized in a straightforward synthesis of (4*S*,5*R*)-*epi*-cytoxazone.

The Henry (nitroaldol) reaction is an important carbon–carbon bond-forming reaction which affords valuable synthetic intermediates.[1] Much effort has been made to develop an asymmetric version of this reaction,[2] using prochiral aldehydes and nitromethane in the presence of a chiral metal catalyst[3] or organocatalyst.[4] Nevertheless, only one report has appeared on highly diastereo- and enantioselective catalytic Henry reactions of nitroalkanes and prochiral aldehydes by Shibasaki et al., utilizing LLB (La-lithium-BINOL) catalyst.[5] As part of our program to develop guanidine-containing organocatalysts,[6] we recently reported on the guanidine-thiourea bifunctional organocatalyst **1** that efficiently catalyzes the Henry reaction with high enantioselectivity.[6d] Here, we describe the first example of the organocatalyst **1** catalyzing the Henry reaction with high diastereo- and enantioselectivity. (Figure 1).



1

Figure 1. Structure of guanidine-thiourea bifunctional catalyst **1**.

In the Henry reaction of nitromethane (**3a**) (R^2 = H, Figure 2) and prochiral aldehydes in the presence of the guanidine-thiourea bifunctional catalyst **1**, nitromethane and the aldehyde coordinate to the guanidine and thiourea groups[7] in **1**, respectively, and the Henry reaction proceeds via the *anti*-conformational transition state **I** rather than the *gauche* conformation **II** (Figure 2). Therefore, nitro alcohol adducts with (*R*) configuration were obtained as the major isomer when (*S*,*S*)-**1** was used. In the case of the Henry reaction with prochiral nitroalkanes (R^2 = alkyl groups etc., Figure 2), the *anti* conformation of the R^2 group with respect to the carbonyl group of the aldehyde is also considered to be more favorable (conformation **I**) than the *gauche* conformation **III**, and the diastereo- and enantioselectivities of the nitro alcohol adducts are expected to be well controlled, if the reaction proceeds via a transition state similar to that in the reaction with nitromethane (**3a**). On the basis of these speculations, the diastereo- and enantioselective Henry reaction with the bifunctional organocatalyst **1** was further explored.

First, the Henry reaction was examined with 3-phenylpropionaldehyde (**2a**) and nitroethane (**3b**) in the presence of (*S*,*S*)-**1**. After optimization of the reaction conditions,[8] the *syn*-nitro alcohol product (*R*,*R*)-**4a**[9] was obtained with high diastereo- and enantioselectivity (*syn*/*anti* = 90:10, 83 % *ee*) in 76 % yield, by using toluene/aqueous potassium hydroxide (10 mol-%)[10] in the presence of 10 mol-% of catalyst (*S*,*S*)-**1** at 0 °C for 48 h (Scheme 1).

The newly generated stereochemistry of the nitro alcohol **4a**, i.e. (*R*,*R*) configuration, is consistent with the proposed reaction transition state (Figure 2, conformation **I**). Since the *ee* value of **4a** is much higher than in the case of the Henry reaction with nitromethane (**3a**) and **2a** (55 % *ee*),[6d] the transition state of the reaction with nitroethane (**3b**) is considered to be strictly controlled by the methyl group (corresponding to the R^2 group in Figure 2).

Using the optimized conditions in Scheme 1, the reactions with various aldehydes and nitroethane (**3b**) were examined (Table 1). Unbranched aliphatic butyraldehyde (**2b**)

[a] Institute of Molecular and Cellular Biosciences, The University of Tokyo,
Bunkyo-ku, Tokyo 113-0032, Japan
[b] Department of Biotechnology and Life Science, Faculty of Technology, Tokyo University of Agriculture and Technology,
Koganei, Tokyo 184-8588, Japan
Fax: +81-042-388-7295
E-mail: knaga@cc.tuat.ac.jp

Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

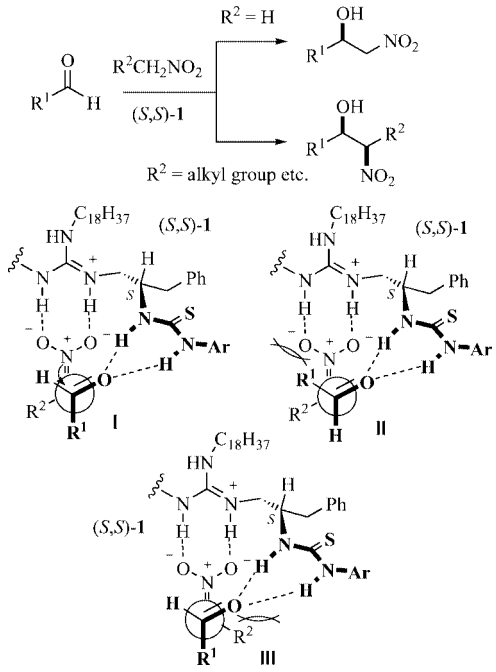
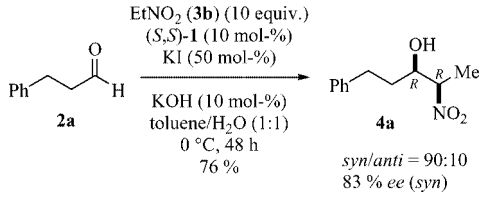


Figure 2. Transition state of the Henry reaction catalyzed by (*S*,*S*)-**1**. Conformation **I**: *anti* conformation (nitro group and R^1 are in an *anti* relationship, carbonyl group and R^2 are *anti*); conformation **II**: *gauche* conformation; conformation **III**: *gauche* conformation (R^2 and carbonyl group, and R^2 and R^1 are in *gauche* relationships).



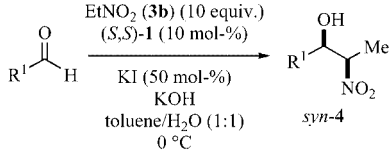
Scheme 1. Henry reaction of **2a** with nitroethane (**3b**) catalyzed by (*S*,*S*)-**1**.

gave **4b** with similar enantio- and *syn* selectivity to **2a** (Entry 1). In the case of the aliphatic α-branched-chain and cyclic aldehydes, the corresponding Henry adducts (*R*,*R*)-**4c**–**e** were obtained with high *syn* selectivity and high enantiomeric excess (Entries 2–4, 97:3 to 99:1, 90–93% *ee*). β-Substituted aliphatic aldehydes **2f** and α- and β-heteroatom-substituted aldehydes **2g** and **2h** also served as substrates and gave the nitro alcohols **4f**–**h** with high selectivity (Entries 5–7, 86:14 to 93:7, 92–99% *ee*).[11]

Other nitroalkanes **3c**–**3f** were treated with unbranched and cyclic-aliphatic aldehydes **2b** and **2e** (Table 2). In most instances, high *syn* selectivity and enantioselectivity were observed, with ratios of 90:10 to 99:1 (*syn*/*anti*) and 85–95% *ee*.

The success of the *syn*-selective enantioselective nitroaldol reaction led to a practical synthesis of (4*S*,5*R*)-*epi*-cytoxazone (**5**), a type-2 cytokine selective inhibitor[12] (Scheme 2). Nitroaldol reaction of **2g** with **3g**[13] (3 equiv.) in the presence of (*R*,*R*)-**1** gave the nitro alcohol (4*S*,5*R*)-**4q** with high *syn* selectivity (90:10) and 95% *ee* in 76% yield.

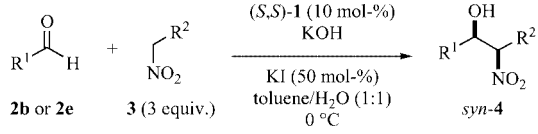
Table 1. Enantio- and *syn*-selective Henry reaction of aldehydes **2b**–**h** with nitroethane (**3b**) in the presence of **1**.



Entry	R^1		KOH (mol-%)	Time (h)	Product yield (%)	*syn*/*anti*[a]	% *ee*[b,c] (*syn*)
1	$CH_3CH_2CH_2$	**2b**	20	24	**4b** (91)	87:13	84
2	$(CH_3)_2CH$	**2c**	8	24	**4c** (50)	97: 3	90
3	Et_2CH	**2d**	20	24	**4d** (52)	99: 1	91
4	*c*-C_6H_{11}	**2e**	8	24	**4e** (77)	99: 1	93
5	$(CH_3)_2CHCH_2$	**2f**	5	24	**4f** (58)	93: 7	99
6	$TBSOCH_2$	**2g**	6	48	**4g** (63)	86:14	98
7	$TBSOCH_2CH_2$	**2h**	8	24	**4h** (50)	90:10	92

[a] Diastereoselectivities were determined by ^1H NMR spectroscopy. The relative stereochemistry was determined from the ^1H NMR chemical shifts. [b] The enantiomeric excess was determined by HPLC using a chiral column. [c] In all cases, the enantiomeric excess of *anti* adducts was low (10–30% *ee*).

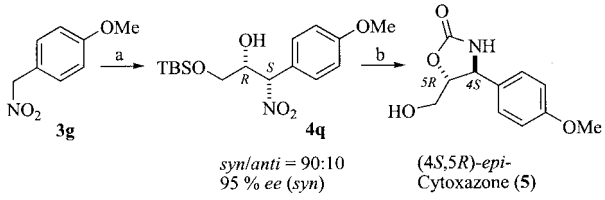
Table 2. Enantio- and *syn*-selective Henry reaction of **2b** or **2e** with nitroalkanes **3c**–**3f** in the presence of **1**.



Entry	**2**	Nitroalkane		KOH (mol-%)	Time (h)	Product Yield (%)	*syn*/*anti*[a]	% *ee*[b,c] (*syn*)
1[d]	**2b**	$CH_3CH_2CH_2NO_2$	**3c**	5	48	**4i** (63)	90: 10	85
2	**2b**	$TBSOCH_2CH_2NO_2$	**3d**	3	48	**4j** (51)	93: 7	87
3	**2b**	$TIPSOCH_2CH_2NO_2$	**3e**	3	24	**4k** (58)	92: 8	87
4	**2b**	$PhCH_2NO_2$	**3f**	10	24	**4l** (70)	91: 9	87
5[d]	**2e**	**3c**		5	40	**4m** (61)	99: 1	95
6	**2e**	**3d**		7	48	**4n** (63)	99: 1	90
7	**2e**	**3e**		6	48	**4o** (60)	99: 1	90
8	**2e**	**3f**		7	48	**4p** (67)	99: 1	95

[a] Diastereoselectivities were determined by ^1H NMR spectroscopy. The relative stereochemistry was determined from the ^1H NMR chemical shifts. [b] The enantiomeric excess was determined by HPLC using a chiral column. [c] In all cases, the enantiomeric excess of *anti* adducts was low. [d] 10 equiv. of **3c** was used.

Reduction of **4q** with $NiCl_2/NaBH_4$,[14] followed by cyclization with *N*,*N*′-carbonyldiimidazole (CDI), and subsequent deprotection of the TBS group with HF gave **5** in 43% yield (3 steps).



Scheme 2. Synthesis of (4*S*,5*R*)-*epi*-cytoxazone (**5**): a) **2g**, (*R*,*R*)-**1**, KOH, KI, toluene/H_2O, 0 °C, 76%; b) (1) $NiCl_2$, $NaBH_4$, MeOH, 0 °C, (2) CDI, CH_3CN, 80 °C, (3) HF, CH_3CN, 0 °C, 43% (3 steps).

In conclusion, highly enantio- and *syn*-selective Henry reactions have been achieved by using the guanidine-thiourea bifunctional organocatalyst **1** under mild biphasic reaction conditions. This reaction is applicable to a variety of aldehydes and nitroalkanes, and was successfully utilized in a straightforward synthesis of (4*S*,5*R*)-*epi*-cytoxazone (**5**).

Experimental Section

Typical Procedure for Enantioselective and *syn*-Selective Henry Reaction of 2e with 3b: To a mixture of (*S*,*S*)-**1e** (12.9 mg, 0.0112 mmol), KI (9.3 mg, 0.0558 mmol) and nitroethane (**3b**) (80.1 μL, 1.12 mmol) in toluene (1.12 mL)/8 mM KOH(aq) (1.12 mL) was added cyclohexanecarboxaldehyde (**2e**) (13.4 μL, 0.112 mmol) at 0 °C. The resulting mixture was stirred vigorously at 0 °C for 24 h. Then saturated NH_4Cl(aq) was added, and the organic layer was extracted with ethyl acetate. The extracts were dried with $MgSO_4$, filtered, and concentrated in vacuo, and the residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 20:1, 10:1, and chloroform/methanol, 9:1) to give **4e** (16.0 mg, 77%); **1e** was recovered (12.8 mg, 99%). Relative stereochemistry and diastereoselectivity (*syn*/*anti* = 99:1) of **4e** were determined based upon the reported ^{1}H NMR data.[15] $[\alpha]_D^{26}$ = –6.7 (*c* = 0.52, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2925, 2852, 1552, 1450, 1391 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.72 (dq, *J* = 6.8, 6.8 Hz, 1 H), 3.65 (dd, *J* = 6.8, 4.9 Hz, 1 H), 2.13 (br. s, 1 H), 1.78–1.65 (m, 4 H), 1.53 (d, *J* = 6.7 Hz, 3 H), 1.48–0.94 (m, 7 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 85.5, 77.2, 39.9, 30.0, 26.3, 26.2, 26.1, 25.9, 16.6 ppm. The enantiomeric excess of **4e** (93% *ee*) was determined by means of chiral HPLC analysis [CHIRALPAC AD-H; 0.46 cm (diameter) × 25 cm (length); *n*-hexane/2-propanol, 97:3; 1.0 mL/min; minor: 16.8 min, major: 25.3 min].

Supporting Information (see footnote on the first page of this article): Spectroscopic data for **4a**–**d** and **4f**–**4p**, and synthesis of **5**.

Acknowledgments

This research was supported by the Nagase Science and Technology Foundation. Y. S. is grateful for a JSPS Research Fellowship for Young Scientists. We thank Dr. Sakamoto (RIKEN) for kindly providing the spectra of synthetic (4*S*,5*R*)-*epi*-cytoxazone (**5**).

[1] L. Henry, *C. R. Hebd. Seances Acad. Sci.* **1895**, *120*, 1265.
[2] For recent reviews, see: a) C. Palomo, M. Oiarbide, A. Mielgo, *Angew. Chem. Int. Ed.* **2004**, *43*, 5442; b) F. A. Luzio, *Tetrahedron* **2001**, *57*, 915; c) N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, **2001**; d) M. Shibasaki, H. Gröger, in *Comprehensive Asymmetric Catalysis*, vol. III (Eds.: E. N. Jacobsen, A. Pfaltz, H, Yamamoto), Springer, Berlin, **1999**, pp. 1075–1090; e) M. Shibasaki, H. Gröger, M. Kanai, in *Comprehensive Asymmetric Catalysis*, suppl. 1 (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **2004**, pp. 131–133..
[3] a) H. Sasai, T. Suzuki, S. Arai, T. Arai, M. Shibasaki, *J. Am. Chem. Soc.* **1992**, *114*, 4418; b) B. M. Trost, V. S. C. Yeh, *Angew. Chem. Int. Ed.* **2002**, *41*, 861; c) D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw, C. W. Downey, *J. Am. Chem. Soc.* **2003**, *125*, 12692; d) C. Christensen, K. Juhl, R. G. Hazell, K. A. Jorgensen, *J. Org. Chem.* **2002**, *67*, 4875; e) C. Palomo, M. Oiarbide, A. Laso, *Angew. Chem. Int. Ed.* **2005**, *44*, 3811.
[4] Enantioselective Henry reaction, see: a) R. Chinchilla, C. Najera, P. Sanchez-Agullo, *Tetrahedron: Asymmetry* **1994**, *5*, 1393; b) M. T. Allingham, A. Howard-Jones, P. J. Murphy, D. A. Thomas, P. W. R. Caulkett, *Tetrahedron Lett.* **2003**, *44*, 8677; c) T. Ooi, K. Doda, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 2054; d) H. Li, B. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 732; e) T. Marcelli, R. N. S. van der Haas, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem. Int. Ed.* **2006**, *45*, 929; diastereoselective Henry reaction with chiral aldehydes, see; f) D. Ma, Q. Pan, F. Han, *Tetrahedron Lett.* **2002**, *43*, 9401; g) E. J. Corey, F.-Y. Zhang, *Angew. Chem. Int. Ed.* **1999**, *38*, 1931; Aza-Henry reaction, see: h) B. M. Nugent, R. A. Yoder, J. N. Johnston, *J. Am. Chem. Soc.* **2004**, *126*, 3418; i) T. Okino, S. Nakamura, T. Furukawa, Y. Takemoto, *Org. Lett.* **2004**, *6*, 625; j) X. Xu, T. Furukawa, T. Okino, H. Miyabe, Y. Takemoto, *Chem. Eur. J.* **2006**, *12*, 466; k) T. P. Yoon, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2005**, *44*, 466; l) F. Fini, V. Sgarzani, D. Pettersen, R. P. Herrera, L. Bernardi, A. Ricci, *Angew. Chem. Int. Ed.* **2005**, *44*, 7975; m) C. Palomo, M. Oiarbide, A. Laso, R. Lopez, *J. Am. Chem. Soc.* **2005**, *127*, 17622; n) L. Bernardi, F. Fini, R. P. Herrera, A. Ricci, V. Sgarzani, *Tetrahedron* **2006**, *62*, 375.
[5] H. Sasai, T. Tokunaga, S. Watanabe, T. Suzuki, N. Itoh, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 7388.
[6] a) K. Nagasawa, A. Georgieva, H. Takahashi, T. Nakata, *Tetrahedron* **2000**, *56*, 187; b) K. Nagasawa, A. Georgieva, H. Takahashi, T. Nakata, *Tetrahedron* **2001**, *57*, 8959; c) T. Kita, A. Georgieva, Y. Hashimoto, T. Nakata, K. Nagasawa, *Angew. Chem. Int. Ed.* **2002**, *41*, 2832; d) Y. Sohtome, Y. Hasimoto, K. Nagasawa, *Adv. Synth. Catal.* **2005**, *347*, 1643; diastereoselective Henry reaction using **1**, see: e) Y. Sohtome, N. Takemura, T. Iguchi, Y. Hashimoto, K. Nagasawa, *Synlett* **2006**, 144.
[7] Reviews, see: a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289; b) P. M. Pihko, *Angew. Chem. Int. Ed.* **2004**, *43*, 2062; asymmetric reaction using Jacobsen's catalyst, see: c) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299; d) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; e) D. E. Fuerst, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 8964, and references cited therein; Takemoto's bifunctional catalyst, see: f) Y. Hoashi, T. Okino, Y. Takemoto, *Angew. Chem. Int. Ed.* **2005**, *44*, 4032, and references cited therein; bis-thiourea-type catalyst, see: g) Y. Sohtome, A. Tanatani, Y. Hashimoto, K. Nagasawa, *Tetrahedron Lett.* **2004**, *45*, 5589; other catalysts, see: h) Y. Sohtome, A. Tanatani, Y. Hashimoto, K. Nagasawa, *Chem. Pharm. Bull.* **2004**, *52*, 477; i) B. Vakulya, S. Varga, A. Csampai, T. Soos, *Org. Lett.* **2005**, *7*, 1967; j) R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, *Angew. Chem. Int. Ed.* **2005**, *44*, 6576.
[8] As in the Henry reaction of nitromethane (**3b**);[6d] potassium iodide was effective to improve the enantiomeric excess of the nitro alcohol adduct **4a**.
[9] Relative stereochemistry and absolute stereochemistry of **4a** were determined based upon the reported ^{1}H NMR chemical shift and $[\alpha]_D$ value.[5]
[10] The concentration of potassium hydroxide strongly influences the enantioselectivities of the nitro alcohols **4**.
[11] In the case of benzaldehyde, diastereo- and enantioselectivity were low (*dr* = 63:37, 16% and 0% *ee*, respectively). Application of alternative catalysts to aromatic aldehydes is under investigation.
[12] Isolation and structure determination of (4*R*,5*R*)-cytoxazone, see: a) H. Kakeya, M. Morishita, K. Kobinata, M. Osono, M. Ishizuka, H. Osada, *J. Antibiot.* **1998**, *51*, 1126; b) H. Kakeya, M. Morishita, H. Koshino, T. Morita, K. Kobayashi, H. Osada, *J. Org. Chem.* **1999**, *64*, 1052; first synthesis and recent synthesis of (4*R*,5*R*)-cytoxazone and/or **5**, see: c) Y. Sakamoto, A. Shiraishi, J. Seonhee, T. Nakata, *Tetrahedron Lett.* **1999**, *40*, 4203; d) Z. Tokic-Vujosevic, G. Petrovic, B. Rakic, R. Matovic, R. N. Saicic, *Synth. Commun.* **2005**, *35*, 435; e) S. Tosaki, R. Tsuji, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 2147; f) N. R. Swamy, P. Krishnaiah, N. S. Reddy, Y. Venkateswarlu, *J. Carbohydr. Chem.* **2004**, *23*, 217; g) S. Milicevic, R.

Matovic, R. N. Saicic, *Tetrahedron Lett.* **2004**, *45*, 955; h) P. H. Carter, J. R. LaPorte, P. A. Scherle, C. P. Decicco, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1237; other synthetic studies of (4*R*,5*R*)-cytoxazone are cited in ref.[12g]
[13] R. Ballini, L. Barboni, G. Giarlo, *J. Org. Chem.* **2004**, *69*, 6907.
[14] A. Nose, T. Kudo, *Chem. Pharm. Bull.* **1981**, *29*, 1159.
[15] S. E. Denmark, B. S. Kesler, Y.-C. Moon, *J. Org. Chem.* **1992**, *57*, 4912.

Received: April 8, 2006
Published Online: May 8, 2006

