

# Enantioselective Aza-Henry Reaction Catalyzed by a Bifunctional Organocatalyst

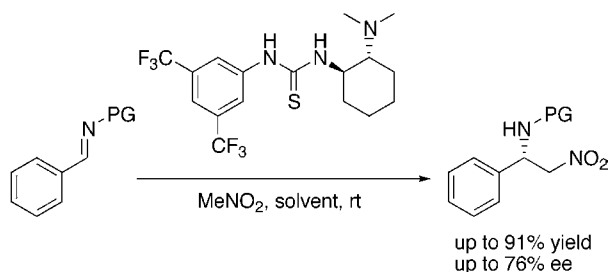
Tomotaka Okino, Satoru Nakamura, Tomihiro Furukawa, and Yoshiji Takemoto\*

Graduate School of Pharmaceutical Sciences, Kyoto University,  
Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

takemoto@pharm.kyoto-u.ac.jp

Received December 17, 2003

## ABSTRACT



The aza-Henry reaction of imines with nitroalkanes was promoted by chiral thiourea with an *N,N*-dimethylamino group to give  $\beta$ -nitroamines with good enantioselectivity. Various *N*-protected imines were examined as substrates. *N*-Phosphinoylimine gave the best result in terms of chemical yield and enantioselectivity (up to 91% yield, up to 76% ee).

The aza-Henry reaction, the nucleophilic addition of nitroalkanes to imines to give  $\beta$ -nitroamine derivatives, is a useful carbon-carbon bond-forming process in organic chemistry. The diversity of the transformations of the  $\beta$ -nitroamines, such as reduction to 1,2-diamines<sup>1</sup> and Nef reaction to  $\alpha$ -amino acids,<sup>2</sup> provides numerous applications of this process.<sup>3–6</sup> The enantioselective version of this reaction was not known until quite recently.<sup>7–10</sup> To the best of our knowledge, there were only two groups that had reported

on catalytic asymmetric aza-Henry reaction and all of the reactions reported were metal-catalyzed. Shibasaki et al. reported that heterobimetallic complexes with lanthanide BINOL systems promoted the aza-Henry reaction to give  $\beta$ -nitroamines with high enantioselectivity.<sup>9</sup> Jørgensen et al. also developed a catalytic asymmetric version of this reaction with bisoxazoline copper(II) complexes.<sup>10</sup>

Although urea derivatives are known to act as acid catalysts in several reactions,<sup>11</sup> enantioselective reactions were rare (Figure 1).<sup>12</sup> We have recently reported novel

(1) (a) Beck, A. K.; Seebach, D. *Chem. Ber.* **1991**, *124*, 2897–2911. (b) Poupart, M. A.; Fazal, G.; Goulet, S.; Mar, L. T. *J. Org. Chem.* **1999**, *64*, 1356–1361. (c) Barrett, A. G. M.; Spilling, C. D. *Tetrahedron Lett.* **1988**, *29*, 5733–5734. (d) Lloyd, D. H.; Nichols, D. E. *J. Org. Chem.* **1986**, *51*, 4294–4295.

(2) Pinnick, H. W. *Org. React.* **1990**, *38*, 655–792.

(3) Calderari, G.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1592–1604.

(4) Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423–434.

(5) (a) Meyer, V.; Wurster, C. *Ber. Dtsch. Chem. Ges.* **1873**, *6*, 1168–1172. (b) Kamlet, M. J.; Kaplan, L. A.; Dacons, J. C. *J. Org. Chem.* **1961**, *26*, 4371–4375.

(6) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339–5342.

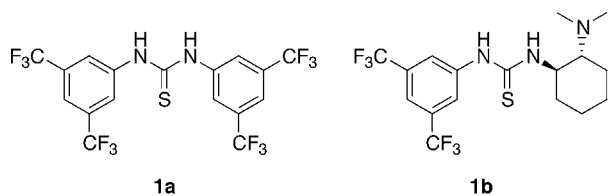
(7) Westermann, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 151–153.

(8) Adams, H.; Anderson, J. C.; Peace, S.; Pennell, A. M. K. *J. Org. Chem.* **1998**, *63*, 9932–9934.

(9) (a) Yamada, K.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3504–3506. (b) Yamada, K.; Moll, G.; Shibasaki, M. *Synlett* **2001**, 980–982. (c) Tsuritani, N.; Yamada, K.; Yoshikawa, N.; Shibasaki, M. *Chem. Lett.* **2002**, 276–277.

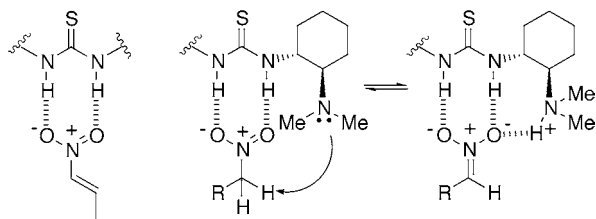
(10) (a) Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843–5844. (b) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2992–2995.

(11) (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *Tetrahedron Lett.* **2003**, *44*, 2817–2821. (b) Curran, D. P.; Kuo, L. H. *J. Org. Chem.* **1994**, *59*, 3259–3261. (c) Curran, D. P.; Kuo, L. H. *Tetrahedron Lett.* **1995**, *36*, 6647–6650. (d) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217–220. (e) Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407–414. (f) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289–296.



**Figure 1.** Structure of thiourea derivatives.

thiourea derivatives with several tertiary amino groups, which act as bifunctional organocatalysts on enantioselective Michael reaction of malonates to nitroolefins.<sup>13</sup> In this reaction, the thiourea seems to interact with a nitro group of the nitroolefins and enhance electrophilicity of nitroolefins (Figure 2).<sup>14</sup>



**Figure 2.** Working hypothesis.

Hence, we expected that the corresponding nitronate could be produced from nitroalkane with the bifunctional thiourea via the hydrogen-bonding activation with the thiourea moiety and subsequent deprotonation by the neighboring tertiary amino group. If so, the catalyst would promote the asymmetric aza-Henry reaction (eq 1). Herein we report the first enantioselective aza-Henry reaction catalyzed by a bifunctional organocatalyst.

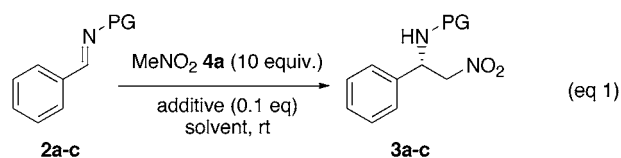
We first investigated the racemic reaction of imines **2a–c** bearing various protecting groups (PG) with nitromethane **4a** in the presence of Et<sub>3</sub>N (TEA) and thiourea **1a** (Table 1). The reaction of *N*-phenylimine **2a** with 0.1 equiv of TEA afforded no desired  $\beta$ -nitroamine **3a** due to the low reactivity of **2a** (entry 1). On the other hand, subjection of *N*-tosylimine **2b** under the same reaction conditions gave  $\beta$ -nitroamines **3b**<sup>15</sup> in good yield (entry 2, 74%). In the case of *N*-phosphinoylimine **2c**,<sup>16</sup> the desired adduct **3c** was obtained in 57% yield in the presence of 0.1 equiv of TEA, while

**Table 1.** Effect of Thiourea Catalysts<sup>a</sup>

entry	PG	additive	adduct	yield <sup>b</sup> (%)
1	Ph ( <b>2a</b> )	TEA	<b>3a</b>	0
2	Ts ( <b>2b</b> )	TEA	<b>3b</b>	74
3	P(O)Ph <sub>2</sub> ( <b>2c</b> )	TEA	<b>3c</b>	57
4	P(O)Ph <sub>2</sub> ( <b>2c</b> )	<b>1a</b>	<b>3c</b>	0
5	P(O)Ph <sub>2</sub> ( <b>2c</b> )	TEA + <b>1a</b>	<b>3c</b>	49

<sup>a</sup> Reaction was conducted with additive (0.1 equiv), **4a** (10 equiv), and CH<sub>2</sub>Cl<sub>2</sub> at room temperature for 24 h. <sup>b</sup> Isolated yield.

treatment of **2c** with thiourea **1a** did not give **3c** at all. Then, with the expectation that coexistence of TEA and **1a** would promote the generation of the nitronate anion from **4a**, the reaction of **2c** was carried out in the presence of TEA and **1a**, but **3c** was only obtained in moderate yield (49%, entry 5).



This result indicates that the thiourea and amine seem to mutually weaken their reactivities. However, the bifunctional thiourea **1b**, whose amino group and thiourea moiety are located in appropriate positions, can be used for this purpose (Figure 2). Hence, we investigated the reaction of imines **2a–c** with nitromethane **4a** in the presence of bifunctional organocatalyst **1b**<sup>13</sup> (Table 2, entries 1–3). In practice,

**Table 2.** Optimization of Reaction Conditions<sup>a</sup>

entry	PG	solvent	adduct	time (h)	yield <sup>b</sup> (%)	% ee <sup>c</sup> (config <sup>d</sup> )
1	Ph ( <b>2a</b> )	CH <sub>2</sub> Cl <sub>2</sub>	<b>3a</b>	24	e	e
2	Ts ( <b>2b</b> )	CH <sub>2</sub> Cl <sub>2</sub>	<b>3b</b>	4.5	99	4 (–) <sup>e</sup>
3	P(O)Ph <sub>2</sub> ( <b>2c</b> )	CH <sub>2</sub> Cl <sub>2</sub>	<b>3c</b>	24	87	67 (S)
4	P(O)Ph <sub>2</sub> ( <b>2c</b> )	MeCN	<b>3c</b>	48	e	e
5	P(O)Ph <sub>2</sub> ( <b>2c</b> )	MeOH	<b>3c</b>	48	44	33 (S)
6	P(O)Ph <sub>2</sub> ( <b>2c</b> )	toluene	<b>3c</b>	140	47	62 (S)
7	P(O)Ph <sub>2</sub> ( <b>2c</b> )	THF	<b>3c</b>	48	43	75 (S)
8	P(O)Ph <sub>2</sub> ( <b>2c</b> )	dioxane	<b>3c</b>	75	73	76 (S)

<sup>a</sup> Reaction was conducted with **1b** (0.1 equiv), **4a** (10 equiv), and several solvents at room temperature. <sup>b</sup> Isolated yield. <sup>c</sup> Enantiomeric excess was determined by HPLC analysis of **3b** and **3c** using a chiral column. <sup>d</sup> Absolute configuration was determined by comparison of the HPLC retention time with that of literature data.<sup>9a</sup> <sup>e</sup> Not determined.

whereas the reaction of **2a** in CH<sub>2</sub>Cl<sub>2</sub> afforded no desired  $\beta$ -nitroamines **3a**, **2b** and **2c** reacted with nitromethane efficiently to give the desired adducts **3b** and **3c** in good yield (entries 1–3). In the case of **2c**, the enantioselectivity of the adduct **3c** was 67% ee, while **2b** gave an almost

(12) (a) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867–870. (b) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014. (c) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965.

(13) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

(14) (a) Bordwell, F. G.; Ji, G. *J. Am. Chem. Soc.* **1991**, *113*, 8398–8401. (b) Etter, M. C.; Urbańczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415–8426. (c) Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072–7080.

(15) Qian, C.; Gao, F.; Chen, R. *Tetrahedron Lett.* **2001**, *42*, 4673–4675.

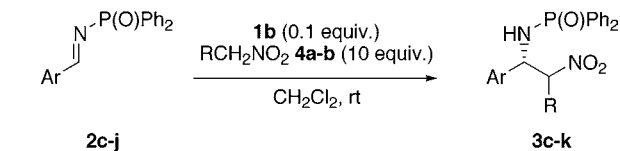
(16) Jennings, W. B.; Lovely, C. J. *Tetrahedron* **1991**, *47*, 5561–5568.

racemic adduct **3b**. The enantiomeric excess was determined by HPLC analysis of **3c** using a chiral column, and the absolute configuration of **3c** was determined by comparison of the HPLC retention time with that of literature data. We selected **2c** as a substrate and optimized the reaction solvent. The adduct **3c** was negligibly obtained or obtained with low enantioselectivity in a polar solvent (MeCN, MeOH), since these solvents probably inhibit hydrogen-bonding interaction between nitromethane **4a** and the thiourea moiety of **1b** (Table 1, entries 4 and 5). In contrast, nonpolar solvents such as toluene provided **3c** with good enantioselectivities (62% ee, entry 6), while the reaction rate decreased dramatically. On the other hand, when the reaction was carried out in ether solvents (THF or 1,4-dioxane), the adduct **3c** was obtained with up to 76% ee after a slightly prolonged reaction time (75 h, entries 7 and 8).

We examined the reaction of various phosphinoylimines **2c–j** with nitroalkanes **4a** and **4b** in CH<sub>2</sub>Cl<sub>2</sub> due to the reasonable reaction rate. Table 3 summarizes the results of the reactions. In all cases, the corresponding  $\beta$ -nitroamines **3c–j** were obtained in good yields with moderate to good enantioselectivities. Introduction of electron-donating or electron-withdrawing groups on the aromatic ring of imines did not affect the enantioselectivities (entries 1–3). When sterically hindered imine **2f** was used as a substrate, the enantioselectivity of the adduct **3f** slightly increased (70% ee, entry 4). Similarly, imines **2g–i** possessing a heteroaromatic ring provided  $\beta$ -nitroamines with good enantioselectivities (64–76% ee, entries 5–7). The same reaction of imine **2j**, prepared from cinnamylaldehyde, proceeded regioselectively to give the 1,2-addition adduct **3j** as the single product with moderate stereoselectivity (entry 8). Finally, we examined enantio- and diastereoselective aza-Henry reaction of **2c** with nitroethane **4b** in the presence of **1b** (entry 9). When nitroethane **4b** was reacted with imine **2c** under the same reaction conditions, the corresponding desired products **3k** were obtained as a diastereomixture (the ratio of 3:1), while the enantioselectivity of the major diastereomer was kept to a good level (67% ee).

In summary, thiourea **1b** worked well as a chiral organocatalyst in the aza-Henry reaction of various phosphinoylimines with nitroalkanes, and gave the  $\beta$ -nitroamines

**Table 3.** Aza-Henry Reaction of *N*-Phosphinoylimines Catalyzed by Bifunctional Organocatalyst<sup>a</sup>



entry	Ar	<b>4</b> (R)	adduct	yield <sup>b</sup> (%)	% ee <sup>c</sup> (dr <sup>d</sup> )
1	Ph ( <b>2c</b> )	H	<b>3c</b>	87	67
2	4-MeC <sub>6</sub> H <sub>4</sub> ( <b>2d</b> )	H	<b>3d</b>	72	63
3	4-ClC <sub>6</sub> H <sub>4</sub> ( <b>2e</b> )	H	<b>3e</b>	76	67
4	2-naph ( <b>2f</b> )	H	<b>3f</b>	78	70
5	2-furyl ( <b>2g</b> )	H	<b>3g</b>	85	76
6	2-pyridyl ( <b>2h</b> )	H	<b>3h</b>	91	68
7	2-thienyl ( <b>2i</b> )	H	<b>3i</b>	57	64
8	cinnamyl ( <b>2j</b> )	H	<b>3j</b>	68	65
9	Ph ( <b>2c</b> )	Me	<b>3k</b>	83	67 <sup>e</sup> (73/27)

<sup>a</sup> Reaction was carried out with **1b** (0.1 equiv), **4a** or **4b** (10 equiv), and CH<sub>2</sub>Cl<sub>2</sub> at room temperature. <sup>b</sup> Isolated yield. <sup>c</sup> Enantiomeric excess was determined by HPLC analysis of **3c–k** using a chiral column. <sup>d</sup> Diastereomeric ratio was determined by <sup>1</sup>H NMR. <sup>e</sup> Major diastereomer.

with moderate to good enantioselectivity. This is the first example of enantioselective aza-Henry reaction with an organocatalyst. Further investigations to improve the enantioselectivity with other thiourea catalysts are under way in these laboratories.

**Acknowledgment.** This work was partially supported by grants from 21st Century COE Program “Knowledge Infrastructure for Genome Science”, the NOVARTIS Foundation (Japan) for the promotion of Science, the Japan Health Sciences, and a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

**Supporting Information Available:** Experimental procedures and spectroscopic data for products **3c–k**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL0364531