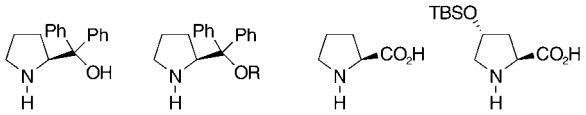
Organocatalysis

Diphenylprolinol Silyl Ethers as Efficient Organocatalysts for the Asymmetric Michael Reaction of Aldehydes and Nitroalkenes**

Yujiro Hayashi, Hiroaki Gotoh, Takaaki Hayashi, and Mitsuru Shoji*

A subtle change in catalyst structure can sometimes improve catalytic activity dramatically, as we found in our recent study on α-aminoxylation, tandem O-nitroso aldol/Michael reactions, and Mannich reactions catalyzed by the siloxyproline **4**, a highly active proline surrogate (Scheme 1).[1] The simple



1 **2a** R = TMS **2b** R = TES **2c** R = TBS **3** **4**

Scheme 1. Organocatalysts examined in this study. TMS = trimethylsilyl, TES = triethylsilyl, TBS = *tert*-butyldimethylsilyl.

introduction of a siloxy group into the proline structure leads to an increase in the catalytic activity, thus allowing a decrease in catalyst loading and shorter reaction times, without compromising the enantioselectivity, and is accompanied by broadening of the substrate scope. This higher activity can be attributed to the increased solubility of **4** in organic solvents. The fact that the substitution of a hydroxy group for a siloxy group can dramatically affect catalytic activity prompted us to investigate other catalytic systems, and these investigations led us to the diphenylprolinol silyl ether **2**. The parent diphenyl-2-pyrrolidinemethanol (**1**, diphenylprolinol), a commercially available amino alcohol developed by Corey and co-workers, has proved to be a very useful ligand for asymmetric synthesis: *B*-alkylated oxazaborodine is a useful catalyst for the CBS reduction,[2] while an effective, asymmetric Lewis acid catalyst prepared from *B*-aryl oxazaborodine and a Brønsted acid promotes the Diels–Alder reaction of a broad range of substrates with excellent enantioselectiv-

[*] Prof. Dr. Y. Hayashi, H. Gotoh, T. Hayashi, Dr. M. Shoji
Department of Industrial Chemistry
Faculty of Engineering, Tokyo University of Science
Kagurazaka, Shinjuku-ku, Tokyo 162-8601 (Japan)
Fax: (+81) 3-5261-4631
E-mail: hayashi@ci.kagu.tus.ac.jp

[**] We thank Prof. K. Saigo and Dr. Y. Ishida (The University of Tokyo) for the use of a high-pressure mercury lamp. This work was partially supported by a Grand-in-Aid for Scientific Research on Priority Area (A): "Creation of Biologically Functional Molecules", from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

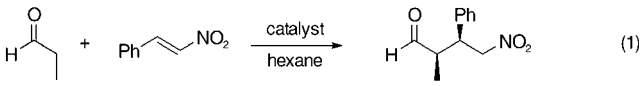
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  DOI: 10.1002/anie.200500599

ity[3] and also catalyzes asymmetric cyanosilylation.[4] Herein we disclose another synthetically useful feature of diphenylprolinol (**1**), the silyl ethers **2** of which were found to be exceptionally effective in the asymmetric catalysis of the Michael reaction of aldehydes and nitroalkenes.[5]

The Michael reaction of a carbon nucleophile with a nitroalkene[6] is one useful synthetic method for the preparation of nitroalkanes, which are versatile synthetic intermediates owing to the various possible transformations of the nitro group into other useful functional groups. The need for environmentally friendly and metal-free reactions has led recently to great progress in the organocatalyst-mediated Michael addition to nitroalkenes: Asymmetric Michael reactions of malonates and β-ketoesters as nucleophiles are promoted by a cinchona-alkaloid derivative[7] and a bifunctional thiourea catalyst.[8] The reactions of ketones and aldehydes as nucleophiles are catalyzed by proline,[9] pyrrolidinyltetrazole,[10] aminomethylpyrrolidine,[11] and 2,2′-bipyrrolidine.[12] Kotsuki and co-workers have developed an excellent Michael reaction of ketones with a pyrrolidine catalyst that includes pyridine as the conjugate base.[13] Recently, Wang et al. reported a highly enantio- and diastereoselective Michael reaction of aldehydes, although the catalyst loading was high (20 mol%) and an alkyl-substituted nitroalkene was a poor Michael acceptor (22% *ee*).[14] The development of more-effective asymmetric catalysts in terms of both enantioselectivity and substrate scope is desirable.

The Michael reaction of propanal and nitrostyrene was selected as a model [Eq. (1), Table 1]. The first catalyst



(1)

Table 1: The effect of the catalyst in the Michael reaction of propanal and nitrostyrene.

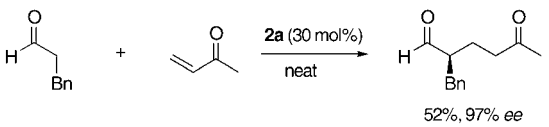
Entry	Catalyst (mol%)	*T* [°C]	*t* [h]	Yield [%][a]	*syn*/*anti*[b]	*ee* [%][c]
1	**3** (20)	0	24	44	97:3	28
2	**4** (20)	0	24	25	92:8	75
3	**1** (20)	23	24	29	86:14	95
4	**2a** (10)	23	1	82	85:15	99
5	**2a** (10)	0	5	85	94:6	99
6	**2a** (5)	23	38	85	96:4	99
7	**2b** (10)	0	22	72	93:7	99
8	**2c** (10)	0	27	80	95:5	99

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy (400 MHz). [c] The *ee* values were determined by HPLC analysis on a chiral phase (chiralcel OD-H).

examined, proline (**3**), led to a low yield and low enantioselectivity (Table 1, entry 1). Higher enantioselectivity (75% *ee*) was observed with the siloxyproline **4**, but the yield was poor (Table 1, entry 2). Although excellent enantioselectivity (95% *ee*) was observed when diphenylprolinol (**1**) was employed, the progress of the reaction was slow, and the yield was unsatisfactory (29%) even after 24 h (Table 1, entry 3). The reactivity of the catalyst was increased dramatically, along with the enantioselectivity, when the hydroxy group in **1** was exchanged for a siloxy group. That is, the reaction was complete within 1 h at room temperature in the presence of the diphenyl siloxy proline **2a**, and the adduct was afforded in good yield (82%) and with increased enantioselectivity (99% *ee*; Table 1, entry 4). When the reaction was performed at a lower temperature (0°C), the adduct was obtained in nearly optically pure form (99% *ee*), in good yield, and also with high diastereoselectivity (*syn*/*anti* 94:6; Table 1, entry 5). The catalyst loading can be reduced to 5 mol% without compromising the enantioselectivity, but the reaction must then be carried out at room temperature, and a longer reaction time is needed. Not only the TMS-substituted compound **2a**, but also the TES and TBS derivatives **2b** and **2c** are excellent catalysts; however, the reaction becomes slower as the silyl substituent becomes bulkier. As excellent results had been obtained with the model system, the generality of the reaction was examined in detail, with the results summarized in Table 2.

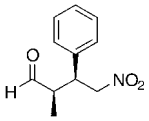
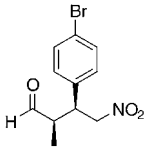
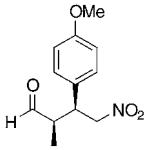
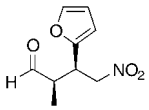
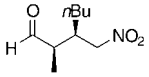
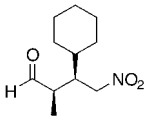
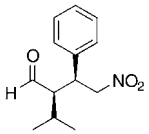
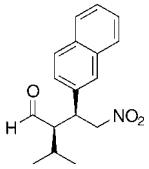
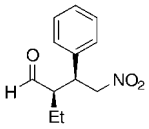
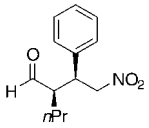
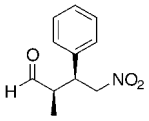
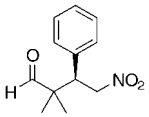
The reaction has broad applicability with respect to both the Michael acceptor and the donor; the adducts were obtained in nearly optically pure form (99% *ee*) and with excellent *syn* diastereoselectivity in most of the cases examined. Both aryl- and alkyl-substituted nitroalkenes are excellent Michael acceptors: Not only phenyl, but also electron-rich and electron-deficient aryl groups and heteroaromatic substituents can be present on the nitroalkene. Alkyl-substituted nitroalkenes, such as 1-nitro-1-hexene and 2-cyclohexyl-1-nitroethene, are also excellent Michael acceptors (Table 2, entries 5 and 6). Not only propanal, but also other linear aldehydes, such as *n*-butanal and *n*-pentanal (Table 2, entries 9 and 10), and branched aldehydes, such as isovaleraldehyde (Table 2, entries 7 and 8), can be employed successfully as the Michael donor, again to afford the adducts in nearly optically pure form. In the reaction of (*Z*)-nitrostyrene[15] with propanal, the same high levels of diastereo- and enantioselectivity were observed as those found in the reaction of the *E* isomer (Table 2, entries 1 and 11). In this reaction, the rapid isomerization of (*Z*)-nitrostyrene to the corresponding *E* isomer was observed by TLC. This method also has its limitations, however: Isobutyraldehyde was found to be a poor nucleophile; in its reaction with nitrostyrene the product was afforded with only moderate enantioselectivity (68% *ee*; Table 2, entry 12). The β,β′-disubstituted nitroolefin (*E*)-2-methyl-2-phenyl-1-nitroethene was found to be a poor Michael acceptor, with the desired adduct formed in low yield.

A preliminary study showed that not only nitroalkenes, but also α,β-unsaturated ketones can be employed as the Michael acceptor: 3-Phenylpropanal reacted with methyl vinyl ketone in the presence of **2a** to afford the Michael adduct[16] in 52% yield and with 97% *ee* [Eq. (2); Bn = benzyl].



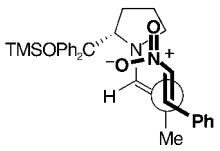
(2)

Table 2: Catalytic asymmetric Michael reaction of aldehydes and nitroalkenes.

Entry	Catalyst loading [mol%]	Product	*T* [°C]	*t* [h]	Yield [%][a]	*syn*/*anti*[b]	*ee* [%][c]
1	10		0	5	85	94:6	99
2	10		0	1	72	95:5	99
3	10		0	5	80	95:5	99
4	10		0	5	81	94:6	99
5	10		0	25	52	84:16	99
6	20		23	48	56	96:4	99
7	20		23	46	72	93:7	99
8	20		23	24	77	94:6	99
9	10		0	48	66	93:7	99
10	10		0	48	74	95:5	99
11[d]	10		0	5	84	96:4	99
12	20		23	96	85	–	68

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy (400 MHz). [c] The *ee* values were determined by HPLC analysis on a chiral phase (chiralpak AS-H, IA, AD-H, and chiralcel OD-H). [d] (*Z*)-Nitrostyrene was used as the Michael acceptor.

The higher reactivity of **2** relative to that of the parent compound **1** can be attributed to effective formation of the corresponding enamine without generation of the aminal, which would be formed in the case of diphenylprolinol (**1**).[5] The high diastereoselectivities and excellent enantioselectivities can be explained as follows: The *anti* enamine, with its double bond oriented away from the diphenylsiloxymethyl group, would be formed selectively and would react with nitrostyrene via an acyclic synclinal transition state proposed by Seebach and Golinski,[17] as shown in Scheme 2. In this model, an electrostatic interaction between nitro group and the nitrogen atom of the enamine would be operating.[12c] The bulky diphenylsiloxymethyl group on the pyrrolidine ring would play two important roles towards the excellent enantioselectivity: promotion of the selective formation of the *anti* enamine and selective shielding of the *Re* face of the enamine double bond.



Scheme 2. Transition-state model.

In summary, with the development of a highly enantioselective Michael reaction of aldehydes and nitroalkenes we have shown that silylation of the prolinol **1** can dramatically improve its catalytic activity. This reaction has several noteworthy features: 1) The catalyst **2** is easily prepared from commercially available diphenylprolinol in a single step, 2) a broad range of Michael acceptors (nitroalkenes) and Michael donors (aldehydes) can be used, and 3) the adducts were obtained in nearly optically pure form in almost all cases examined.

Experimental Section

Typical experimental procedure: Propanal (0.75 mL, 10 mmol) was added to a solution of nitrostyrene (154 mg, 1.0 mmol) and **2a** (34 mg, 0.1 mmol) in hexane (1.0 mL) at 0 °C. After the reaction mixture had been stirred for 5 h at that temperature, the reaction was quenched by the addition of aqueous 1N HCl. Organic materials were extracted three times with AcOEt, and the combined organic phases were dried (Na_2SO_4), concentrated, and purified by preparatory TLC (chloroform) to afford the Michael adduct (183 mg, 85%) as a clear oil: *syn*/*anti* 94:6 (by ^{1}H NMR spectroscopy of the crude mixture), 99% *ee* (by HPLC on a chiral phase: chiralcel OD-H column, $\lambda = 254$ nm, *i*PrOH/hexane 1:10, 1.0 mL min^{-1}; $t_R = 14.5$ min (minor), 19.7 min (major)).[11a]

Received: February 17, 2005
Revised: April 19, 2005
Published online: June 1, 2005

Keywords: asymmetric catalysis · diphenylprolinol · Michael addition · nitroalkenes · organocatalysis

[1] Y. Hayashi, J. Yamaguchi, K. Hibino, T. Sumiya, T. Urushima, M. Shoji, D. Hashizume, H. Koshino, *Adv. Synth. Catal.* **2004**, *346*, 1435.

[2] a) E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551; b) E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, V. K. Singh, *J. Am. Chem. Soc.* **1987**, *109*, 7925; c) C. J. Hetal,

P. A. Magriotis, E. J. Corey, *J. Am. Chem. Soc.* **1996**, *118*, 10938. CBS is an abbreviation of Corey–Bakshi–Shibata.
[3] a) Q.-Y. Hu, G. Zhou, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 13708, and references therein; b) for a Review, see: E. J. Corey, *Angew. Chem.* **2002**, *114*, 1724; *Angew. Chem. Int. Ed.* **2002**, *41*, 1650.
[4] D. H. Ryu, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 8106.
[5] During the preparation of this manuscript, **2** was reported to be an excellent catalyst for the α sulfenylation of aldehydes: M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804; *Angew. Chem. Int. Ed.* **2005**, *44*, 794.
[6] For an excellent review, see: O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877.
[7] H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906.
[8] a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672; b) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119.
[9] a) B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423; b) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260; c) D. Enders, A. Seki, *Synlett* **2002**, 26.
[10] a) A. J. A. Cobb, D. A. Longbottom, D. M. Shaw, S. V. Ley, *Chem. Commun.* **2004**, 1808; b) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 84.
[11] a) J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737; b) N. Mase, R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 2527; c) J. M. Betancort, K. Sakthivel, R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Synthesis* **2004**, 1509; d) for a review, see: W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580.
[12] a) A. Alexakis, O. Andrey, *Org. Lett.* **2002**, *4*, 3611; b) O. Andrey, A. Alexakis, G. Bernardinelli, *Org. Lett.* **2003**, *5*, 2559; c) O. Andrey, A. Alexakis, A. Tomassini, G. Bernardinelli, *Adv. Synth. Catal.* **2004**, *346*, 1147.
[13] T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, *J. Am. Chem. Soc.* **2004**, *126*, 9558.
[14] W. Wang, J. Wang, H. Li, *Angew. Chem.* **2005**, *117*, 1393; *Angew. Chem. Int. Ed.* **2005**, *44*, 1369.
[15] T. Ohwada, T. Ohta, K. Shudo, *J. Am. Chem. Soc.* **1986**, *108*, 3029.
[16] P. Melchiorre, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 4151.
[17] D. Seebach, J. Golinski, *Helv. Chim. Acta* **1981**, *64*, 1413.

