ORGANIC LETTERS

2008
Vol. 10, No. 1
21−24

Organic Solvent-Free, Enantio- and Diastereoselective, Direct Mannich Reaction in the Presence of Water

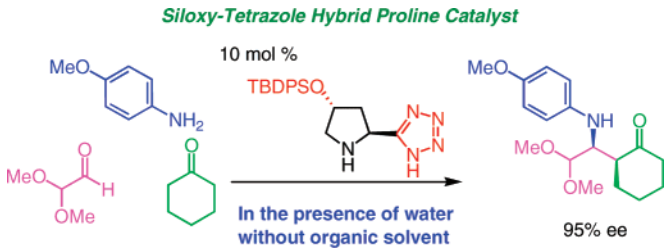
Yujiro Hayashi,* Tatsuya Urushima, Seiji Aratake, Tsubasa Okano, and Kazuki Obi

Department of Industrial Chemistry, Faculty of Engineering, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

hayashi@ci.kagu.tus.ac.jp

Received October 11, 2007

ABSTRACT



An organocatalyst-mediated, asymmetric Mannich reaction in the presence of water without using organic solvents has been developed. A highly reactive siloxytetrazole hybrid catalyst has been developed for the reaction of dimethoxyacetaldehyde, while the sodium salt of siloxyproline is an effective catalyst of α-imino glyoxylate. Excellent enantioselectivity can be realized, and the usage of organic solvents can be reduced compared to the conventional reactions in organic solvents.

The development of reactions in the presence of water[1] without using organic solvents is one of the important topics in current chemistry.[2] The catalytic, asymmetric Mannich reaction is one of the most powerful methods for the construction of chiral nitrogen-containing molecules.[3] Thus, there is an endeavor to realize the enantioselective Mannich reaction in the presence of water. Although there are several aqueous non-enantioselective Mannich reactions of silyl enol ether,[4] there is only one asymmetric catalytic reaction in the presence of water catalyzed by an organometallic reagent so far as we are aware: Kobayashi and co-workers reported the asymmetric Mannich-type reaction of acylhydrazone and silyl enol ether in aqueous organic solvent using a diamine−ZnF_2−surfactant system.[5]

Organocatalysis-mediated, direct, enantioselective Mannich reactions[6−9] have been developed over the past few years that proceed in polar organic solvents such as DMSO and NMP. Although there is a proline-mediated Mannich reaction in aqueous media,[8e,f] the reaction in the presence of water without using an organic solvent had not been reported until recently.

(1) (a) Hayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8103. (b) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 8100.

(2) (a) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie A & P: London, 1998. (b) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751. (c) Blackmond, D. G.; Armstrong, A.; Coombe, V.; Wells, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3798. (d) *Organic Reactions in Water*; Lindstrom, U. M, Ed.; Blackwell Publishing: Oxford, 2007.

(3) (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (b) Denmark, S. E.; Nicaise, O. J.-C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Ed.; Springer: Berlin, 1999; p 923. (c) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (d) *Enantioselective Synthesis of α-Amino Acids*; Juaristi, E., Ed.; VCH: Weinheim, Germany, 1997. (e) Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Chapter 2.3, Vol. 2, p 893. (f) Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 348.

(4) For aqueous Mannich reaction of silyl enol ether, see: (a) Loh, T. P.; Wei, L. L. *Tetrahedron Lett.* **1998**, *39*, 323. (b) Manabe, K.; Kobayashi, S. *Org. Lett.* **1999**, *1*, 1965. (c) Akiyama, T.; Takaya, J.; Kagoshima, H. *Synlett* **1999**, 1426. (d) Manabe, K.; Mori, Y.; Kobayashi, S. *Tetrahedron* **2001**, *57*, 2537. (e) Akiyama, T.; Itoh, J.; Fuchibe, K. *Synlett* **2002**, 1269.

(5) (a) Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 7768. (b) Hamada, T.; Manabe, K.; Kobayashi, S. *Chem.—Eur. J.* **2006**, *12*, 1205.

10.1021/ol702489k CCC: $40.75
Published on Web 12/04/2007

As for the aldol reaction, Barbas' group[10] and ours[11−13] independently developed asymmetric aldol reactions catalyzed by organocatalysts in the presence of water. While Barbas and co-workers used a diamine with a long alkyl chain in the presence of acid, we employed siloxyproline[11] and a combined proline−surfactant organocatalyst.[12] Following these reports, several organocatalysts have been developed for the enantioselective aldol reaction in the presence of water,[14] and recently, a threonine-derived organocatalyst was applied to the Mannich reaction in the presence of water, in which only alkoxyacetone was investigated.[15] During the application of siloxyproline to the asymmetric Mannich reaction in the presence of water, we found effective Mannich catalysts, affording adducts with excellent enantioselectivity, which will be disclosed in this communication.

First, the three-component Mannich reaction of dimethoxyacetaldehyde, *p*-anisidine, and cyclohexanone was selected as a model. Dimethoxyacetaldehyde is commercially available as aqueous solution; therefore, this reaction must be performed in the presence of water. Moreover, the Mannich product obtained is a synthetically useful polyfunctionalized compound. The reaction was performed as follows: Mixing anisidine, an aqueous solution of aldehyde (60 wt % solution), and water (total volume of water is 18 equiv) for 0.5 h in the presence of the catalyst generated an oily material that separated from the water. To this mixture we added 2 equiv of ketone, and the reaction proceeded in a biphase system. Organocatalysts (Figure 1) were screened, with the

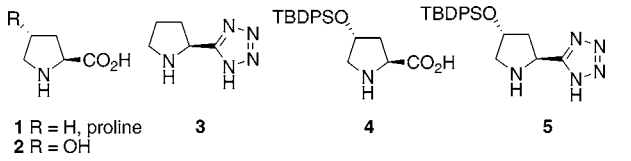


Figure 1. The organocatalysts examined in this study.

results summarized in Table 1. Low yield and enantioselectivity were obtained in the reactions with proline (**1**) and 4-hydroxyproline (**2**). Tetrazole catalyst **3**[16] gave 50% ee, and a moderate ee (72%) was observed with siloxyproline **4**.[11,17] Among other catalysts, siloxytetrazole hybrid catalyst **5** afforded the adduct not only in excellent yield but also with very high enantioselectivity. By lowering the reaction temperature, higher diastereoselectivity and enantioselectivity were realized. As for the diastereoselectivity, although proline (**1**) and siloxyproline **4** gave *anti*-isomer predominantly, *syn*-isomer was obtained selectively when tetrazolesiloxy hybrid catalyst **5** was employed. It should be noted that tetrazole catalyst **3** and siloxyproline **4**, both of which are active catalysts in several transformations, are not suitable, but the combination of a siloxy and tetrazole moiety in a pyrrolidine scaffold created a highly efficient Mannich catalyst **5**. The reaction also proceeds in good yield with excellent enantioselectivity in the presence of a large excess (100 equiv) of water (entry 7). Practically, the amount of water should be reduced, and the reaction was found to proceed efficiently without the additional amount of water.

The generality of the reaction was examined, with the results summarized in Table 2. Both cyclohexanone and

(6) For our contributions in the Mannich reaction, see: (a) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *J. Am. Chem. Soc.* **2003**, *125*, 11208. (b) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed*. **2003**, *42*, 3677. (c) Hayashi, Y.; Urushima, T.; Shoji, M.; Uchimaru, T.; Shiina, I. *Adv. Synth. Catal*. **2005**, *347*, 1595. (d) Hayashi, Y.; Urushima, T.; Shin, M.; Shoji, M. *Tetrahedron* **2005**, *61*, 11393. (e) Hayashi, Y.; Urushima, T.; Tsuboi, W.; Shoji, M. *Nat. Protocols* **2007**, *2*, 113.

(7) For recent selected papers of direct enantioselective Mannich reactions, see: (a) Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc*. **2006**, *128*, 2778. (b) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc*. **2006**, *128*, 6048. (c) Shibasaki, M.; Matsunaga, S. *J. Organomet. Chem*. **2006**, *691*, 2089. (d) Cordova, A. *Acc. Chem. Res*. **2004**, *37*, 102.

(8) For representative papers of Mannich reactions catalyzed by organocatalysis, see: (a) List, B. *J. Am. Chem. Soc*. **2000**, *122*, 9336. (b) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc*. **2002**, *124*, 827. (c) Cordova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc*. **2002**, *124*, 1842. (d) Cordova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc*. **2002**, *124*, 1866. (e) Cordova, A.; Barbas, C. F., III. *Tetrahedron Lett*. **2003**, *44*, 1923. (f) Notz, W.; Tanaka, F.; Watanabe, S.; Chawdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F., III. *J. Org. Chem*. **2003**, *68*, 9624. (g) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed*. **2004**, *43*, 1566. (h) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc*. **2004**, *126*, 5356. (i) Westermann, B.; Neuhaus, C. *Angew. Chem., Int. Ed*. **2005**, *44*, 4077. (j) Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem., Int. Ed*. **2005**, *44*, 4079. (k) Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc*. **2005**, *127*, 16408. (l) Paulsen, T. B.; Alemparte, C.; Saaby, S.; Bella, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2005**, *44*, 2896. (m) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc*. **2005**, *127*, 11256. (n) Mitsumori, S.; Zhang, H.; Cheong, P. H.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc*. **2006**, *128*, 1040. (o) Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc*. **2006**, *128*, 9630. (p) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc*. **2007**, *129*, 288. (q) Liu, T.-Y.; Cui, H.-L.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *J. Am. Chem. Soc*. **2007**, *129*, 1878. (r) Yang, J. W.; Stadler, M.; List, B. *Angew. Chem., Int. Ed*. **2007**, *46*, 609. (s) Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054 and the references cited therein.

(9) For reviews of organocatalysis, see: (a) Berkssel, A.; Groger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, Germany, 2005. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (c) Hayashi, Y. *J. Synth. Org. Chem. Jpn*. **2005**, *63*, 464. (d) List, B. *Chem. Commun*. **2006**, 819. (e) Marigo, M.; Jørgensen, K. A. *Chem. Commun*. **2006**, 2001. (f) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79. (g) Gaunt, M. J.; Johnsson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8. (h) *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, Germany, 2007.

(10) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc*. **2006**, *128*, 734.

(11) (a) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed*. **2006**, *45*, 958. (b) Aratake, S.; Itoh, T.; Okano, T.; Nagae, N.; Sumiya, T.; Shoji, M.; Hayashi, Y. *Chem.—Eur. J*. **2007**, DOI: 10.1002/chem.200700363.

(12) Hayashi, Y.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed*. **2006**, *45*, 5527.

(13) (a) Hayashi, Y.; Aratake, S.; Itoh, T.; Okano, T.; Sumiya, T.; Shoji, M. *Chem. Commun*. **2007**, 957. (b) Aratake, S.; Itoh, T.; Okano, T.; Usui, T.; Shoji, M.; Hayashi, Y. *Chem. Commun*. **2007**, 2524.

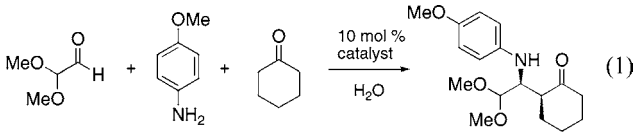
(14) (a) Jiang, Z.; Liang, Z.; Wu, X.; Lu, Y. *Chem. Commun*. **2006**, 2801. (b) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett*. **2006**, *8*, 4417. (c) Font, D.; Jimeno, C.; Pericas, M. A. *Org. Lett*. **2006**, *8*, 4653. (d) Guillena, G.; Hita, M. C.; Najera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1493. (e) Wu, X.; Jiang, Z.; Shen, H.-M.; Lu, Y. *Adv. Synth. Catal*. **2007**, *349*, 812. (f) Maya, V.; Raj, M.; Singh, V. K. *Org. Lett*. **2007**, *9*, 2593.

(15) (a) Cheng, L.; Wu, X.; Lu, Y. *Org. Biomol. Chem*. **2007**, *5*, 1018. (b) Cheng, L.; Han, X.; Huang, H.; Wong, M. W.; Lu, Y. *Chem. Commun*. **2007**, 4143.

(16) (a) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983. (b) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem*. **2005**, *3*, 84. (c) Hartikka, A.; Arvidsson, P. I. *Eur. J. Org. Chem*. **2005**, 4287.

(17) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Shoji, M.; Hashizume, D.; Koshino, K. *Adv. Synth. Catal*. **2004**, *346*, 1435.

Table 1. Effect of Catalyst on the Mannich Reaction in the Presence of Water[a]



(1)

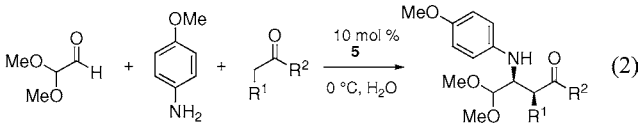
entry	catalyst	time [h]	yield [%][b]	*syn*:*anti*[c]	ee [%][d]
1	**1**	48	36	1:2.3	16
2	**2**	48	34	1:2.2	1
3	**3**	48	48	1:1.1	50
4	**4**	16	95	1:1.4	72
5	**5**	16	95	4.4:1	93
6[e]	**5**	48	61	6.1:1	96
7[e,f]	**5**	70	95	4.2:1	93
8[e,g]	**5**	48	93	4.6:1	95

[a] Unless otherwise shown, the reaction was conducted with 0.04 mmol of catalyst, 60 μL of dimethoxyacetaldehyde solution (60 wt %, 0.4 mmol), 0.44 mmol of *p*-anisidine, 0.8 mmol of cyclohexanone, and water (102 μL) at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Enantiomeric excess of *syn*-isomer. Determined by chiral HPLC (see Supporting Information). [e] The reaction temperature is 0 °C. [f] The reaction was performed in the presence of 100 equiv of water (0.72 mL). [g] The reaction was performed without the additional water.

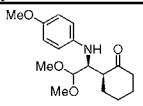
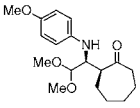
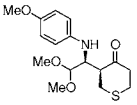
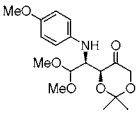
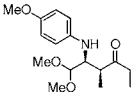
cycloheptanone are suitable nucleophiles to afford the Mannich adduct with high diastereoselectivity and enantioselectivity. 2,2-Dimethyl-1,3-dioxa-5-one can be employed successfully as the nucleophilic ketone, affording a polyoxyamine derivative with high enantioselectivity, which is an important synthetic intermediate of aminosugars.[8i,j] Acyclic ketones such as 3-pentanone are also suitable nucleophiles.

Next, the catalyst was applied to the Mannich reaction of α-imino ethyl glyoxylate. This reaction is synthetically important for the formation of the α-amino acid. Its original reaction in organic solvent catalyzed by proline was developed by Barbas and co-workers.[8c,d] While proline (**1**) and tetrazole catalyst **3** were poor catalysts in the presence of water, both siloxyproline **4** and siloxytetrazole hybrid catalyst **5** gave a complex mixture in the presence of water without an organic solvent. This is contrary to the reaction of dimethoxyacetaldehyde (eq 1, Table 1). The decomposition of imine was observed, probably because of the instability of imine in the presence of the acidity of the catalyst. After several experiments, it was found that good yield and excellent enantioselectivity were obtained when the reaction was carried out in aqueous $NaHCO_3$ solution instead of water in the presence of siloxyproline **4** (Table 3). The same excellent results were obtained when the isolated sodium salt of **4** was used as the catalyst.[18] Moreover, the lithium and potassium salts of **4** also gave the same excellent diastereoselectivity and enantioselectivity. It should be noted that the excellent diastereoselectivity is in marked contrast to the low selectivity (*syn*/*anti* = 3:1) reported when the reaction was performed in dioxane and catalyzed by proline.[8d] Propanal, *n*-butanal, and *n*-pentanal are suitable nucleophiles, affording the adducts in good yield with excellent selectivities. Aldehydes and ketones such as cyclohexanone react with

Table 2. Asymmetric Mannich Reaction of Dimethoxyacetaldehyde under Wet Conditions[a]

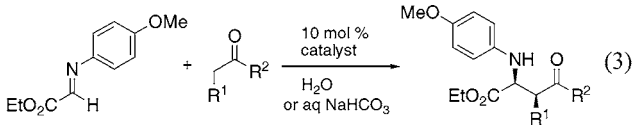


(2)

entry	product	time [h]	yield [%][b]	*syn*:*anti*[c]	ee [%][d]
1		48	93	4.6:1	95
2		254	78	10:1	95
3		136	85	2.9:1	97
4		135	63	>20:1	83
5[e]		280	58	>20:1	95

[a] The reaction was conducted with 0.04 mmol of **5**, 60 μL of dimethoxyacetaldehyde solution (60 wt %), 0.44 mmol of *p*-anisidine, and 0.8 mmol of ketone at 0 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Enantiomeric excess of *syn*-isomer, which was determined by chiral HPLC analysis. [e] Ketone (5 equiv) and water (18 equiv) were used.

Table 3. Mannich Reaction of α-Imino Ethyl Glyoxylate in the Presence of Water[a]



(3)

entry	R^1, R^2	catalyst	solvent	time [h]	yield [%][b]	*syn*:*anti*[c]	ee [%][d]
1	Me, H	**1**	H_2O	1	<5	nd	nd
2	Me, H	**3**	H_2O	1	<5	nd	nd
3	Me, H	**4**	H_2O	1	cm	nd	nd
4	Me, H	**5**	H_2O	1	cm	nd	nd
5	Me, H	**4**	aq $NaHCO_3$	1	81	>95:5	97
6	Me, H	Na salt **4**	H_2O	1	88	>95:5	95
7	Me, H	Li salt **4**	H_2O	1	70	>95:5	95
8	Me, H	**4**	aq $KHCO_3$	1	69	>95:5	97
9	Et, H	**4**	aq $NaHCO_3$	2	78	>95:5	98
10	*n*-Pr, H	**4**	aq $NaHCO_3$	3	66	>95:5	97
11	$-(CH_2)_4-$	**5**	H_2O	9	40	>95:5	95

[a] The reaction was conducted with 0.03 mmol of catalyst, 0.3 mmol of imine, and 0.6 mmol of carbonyl compound and water (49 μL, 9 equiv) at room temperature; cm = complex mixture; nd = not determined. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC (see Supporting Information).

imine in the presence of siloxytetrazole hybrid **5** to afford the product in moderate yield with excellent enantioselectivity.

The same enantiomer was obtained selectively in the reaction catalyzed by the sodium salt of **4** in the presence of

water as that in the reaction using proline in organic solvent. These results would indicate that sodium has the same role in the transition state as the proton of the carboxylic acid of proline does.[8a,19]

In summary, we have developed an organocatalyst-mediated, asymmetric Mannich reaction in the presence of water without using organic solvents. Reactive siloxytetrazole hybrid catalyst **5** has been developed for the reaction of dimethoxyacetaldehyde, while the Na salt of siloxyproline **4** is an effective catalyst of α-imino glyoxylate. One of the advantages of the organic solvent-free reaction is the decreased amount of organic solvent compared with the reaction in organic solvent. As the reaction mixture was directly charged on silica gel for column chromatography, organic solvents are not necessary for either the reaction or the extraction. They are only required for column chromatography.

Acknowledgment. This work was partially supported by Toray Science Foundation and a Grand-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Detailed experimental procedures, full characterization, copies of ^{1}H, ^{13}C NMR, and IR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702489K

(18) Yamaguchi and co-workers reported an excellent Michael reaction using Pro-Rb; see: Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem., Int. Ed. Engl*. **1993**, *32*, 1176.

(19) Bahmanyar, S.; Houk, K. N. *Org. Lett.* **2003**, *5*, 1249.