J|A|C|S
COMMUNICATIONS

The Catalytic Asymmetric Mannich-Type Reactions in Aqueous Media

Shū Kobayashi,* Tomoaki Hamada, and Kei Manabe

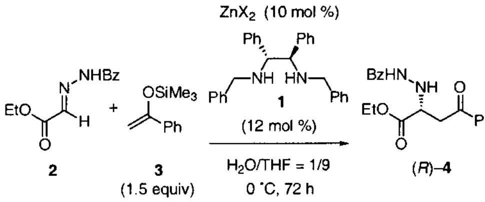
Graduate School of Pharmaceutical Sciences, The University of Tokyo, CREST, Japan Science and Technology Corporation (JST), Hongo, Bunkyo-ku, Tokyo 113-0033 Japan

Received March 5, 2002

Recently, Lewis acid catalysts have been developed for enantioselective addition reactions to imines,[1] including processes such as Mannich-type,[2] Strecker,[3] allylation,[4] and aza-Diels−Alder[5] reactions. Among them, asymmetric Mannich-type reactions provide useful routes for the synthesis of optically active *β*-amino ketones or esters, which are versatile chiral building blocks for the preparation of many nitrogen-containing, biologically important compounds.

In recent years, organic reactions in aqueous media have attracted a great deal of attention, not only because these reactions eliminate the necessity of vigorous drying of solvents and substrates, but also because unique reactivity and selectivity are often observed in aqueous reactions.[6] In the course of our investigations to develop efficient organic reactions in water, we have exploited several carbon−carbon bond-forming reactions catalyzed by water-compatible Lewis acids such as rare earth metal triflates in aqueous media.[7] Quite recently, we and others have also developed catalytic asymmetric versions of Lewis acid-mediated reactions such as aldol,[8] Diels−Alder,[9] and allylation[10] reactions in water-containing solvents. However, as far as we know, catalytic asymmetric Mannich-type reactions in aqueous media have not been reported. Here we report the first example of this type of reaction using a combination of ZnF_2 and a chiral diamine.

Table 1. Effect of Counterions



entry	ZnX_2	yield (%)	ee (%)
1	$Zn(OTf)_2$	21	24
2	$Zn(ClO_4)_2 \cdot 6H_2O$	25	26
3	$ZnBr_2$	trace	−
4	$ZnCl_2$	N.R.[a]	−
5	ZnF_2	7	86

[a] N.R.= no reaction.

The most important feature in designing a chiral ligand for Lewis acid-mediated reactions in aqueous media is its binding property to metal cations. We noted the strong binding ability of ethylenediamine to Zn^{2+} cation,[11] and decided to test various chiral analogues of ethylenediamine for Mannich-type reactions in aqueous media. As for substrates, we focused on acylhydrazones,[12] which are imine surrogates stable even in aqueous media.[13] After many trials, we found that the use of diamine ligand **1**[14] and $Zn(OTf)_2$ gave low but significant ee (24% ee) in the reaction of hydrazono ester **2** with silyl enol ether **3** in H_2O/THF (1/9). The effect of counteranions of Zn^{2+} was then examined (Table 1), and it was found that the same level of enantioselectivity was obtained when $Zn(ClO_4)_2$ was used. While no desired product was obtained when $ZnBr_2$ or $ZnCl_2$ was employed, it was remarkable to find that high enantioselectivity was obtained with the use of ZnF_2. Although the yield was low, this high ee prompted us to investigate the ZnF_2-mediated reaction further.

The reaction conditions were examined to improve the yield (Table 2), and first, the amount of ZnF_2 was increased to 100 mol %. Interestingly, although the yield was low, high enantioselectivity was still maintained despite using a large excess of ZnF_2 (entry 1). Next, we examined the effect of additives. It was exciting to find that a catalytic amount of trifluoromethanesulfonic acid (TfOH) dramatically increased the yield (entries 1 and 2), and that the best ee was obtained when 1 mol % of TfOH was used. The same level

---

* Corresponding author. E-mail: skobayas@mol.f.u-tokyo.ac.jp.

(1) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

(2) For representative examples of Lewis acid-promoted enantioselective Mannich-type reactions, see: (a) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520. (b) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153. (c) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180. (d) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474. (e) Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J., III; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67. (f) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 2995.

(3) For representative examples of Lewis acid-catalyzed enantioselective Strecker reactions, see: (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315. (b) Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3186. (c) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762. (d) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284. (e) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1650.

(4) (a) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242. (b) Gastner, T.; Ishitani, H.; Akiyama, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1896.

(5) (a) Hattori, K.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 3264. (b) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357. (c) Kobayashi, S.; Komiyama, S.; Ishitani, H. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 979. (d) Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 2435. (e) Bromidge, S.; Wilson, P. C.; Whiting, A. *Tetrahedron Lett.* **1998**, *39*, 8905.

(6) (a) Li, C.-J.; Chan, T.-H. *Organic Reactions on Aqueous Media*; John Wiley & Sons: New York, 1997. (b) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blacky Academic and Professional: London, England, 1998.

(7) Kobayashi, S. In *Lanthanides*: *Chemistry and Use in Organic Synthesis*; Kobayashi, S., Ed.; Springer: Berlin, 1999; p 63.

(8) (a) Kobayashi, S.; Nagayama, S.; Busujima, T. *Tetrahedron* **1999**, *55*, 8739. (b) Nagayama, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 11531. (c) Kobayashi, S.; Hamada, T.; Nagayama, S.; Manabe, K. *Org. Lett.* **2001**, *3*, 165.

(9) Otto, S.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1999**, *121*, 6798.

(10) Loh, T.-P.; Zhou, J.-R. *Tetrahedron Lett.* **2000**, *41*, 5261.

(11) The binding constant of Zn^{2+} and ethylenediamine in water is $10^{5.7}$ M^{-1}: Martell, A. E.; Smith, R. M. *Critical Stability Constants*; Plenum Press: New York, 1974, 1975, 1977; Vol. 1−3.

(12) (a) Oyamada, H.; Kobayashi, S. *Synlett* **1998**, 249. (b) Hirabayashi, R.; Ogawa, C.; Sugiura, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 9493.

(13) Kobayashi, S.; Hamada, T.; Manabe, K. *Synlett* **2001**, 1140.

(14) Mimoun, H.; Laumer, J. Y. S.; Giannini, L.; Scopelliti, R.; Floriani, C. *J. Am. Chem. Soc.* **1999**, *121*, 6158.

10.1021/ja026094p CCC: $22.00

Table 2. Several Reaction Conditions

$$\mathbf{2} + \underset{(3.0\ \text{equiv})}{\mathbf{3}} \xrightarrow[\substack{H_2O/THF = 1/9 \\ 0\ ^\circ C,\ 72\ h}]{ZnF_2,\ \text{Ligand}\ \mathbf{1},\ TfOH} (R)\text{-}\mathbf{4}$$

entry	ZnF_2 (mol %)	TfOH (mol %)	**1** (mol %)	yield (%)	ee (%)
1	100	–	10	19	90
2	100	1	10	93	92
3	100	2	10	90	88
4[a]	100	1	20	95	94
5	50	1	10	89	92
6	30	1	10	34	89
7[b]	10	1	1	17	85
8	100	1	–	34	–

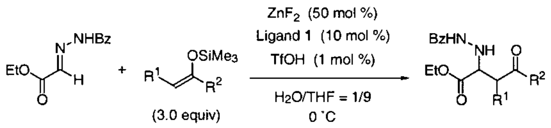
[a] 27 h. [b] 143 h.

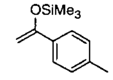
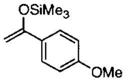
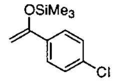
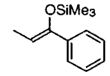
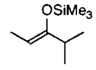
of enantioselectivity was obtained when the amount of ZnF_2 was lowered to 50 mol % (entry 5), although the yield was decreased when the amount of ZnF_2 was lowered further (entries 6 and 7). It should be noted that the presence of **1** significantly improved the yield (entry 2 vs 8), and that this ligand effect is a key to the success in the present catalytic system.[15] In addition, it was also revealed that the use of aqueous solvents was another key to obtain high yield and selectivity. For example, the reaction of **2** with **3** did not proceed at all in THF without water in the presence of ZnF_2 (100 mol %), TfOH (1 mol %), and **1** (10 mol %) at 0 °C for 50 h. In H_2O/THF (1/1), the same reaction proceeded at 5 °C for 45 h to afford (*R*)-**4** in 64% yield with 83% ee.

Currently, we speculate that this reaction proceeds with double activation where Zn^{2+} acts as a Lewis acid to activate **2** and the fluoride anion acts as a Lewis base to attack the silicon atom of **3**.[16,17] It is unlikely that the reaction involves a zinc enolate as an intermediate, because when ethylzinc enolate prepared by the known method[18] was added to an aqueous solution of **1** and **2**, only a trace amount of the desired product was produced.

Several examples of the Mannich-type reactions are shown in Table 3. Silyl enol ethers derived from aromatic and aliphatic ketones gave the desired products in mostly high yields with high enantioselectivity. Furthermore, the desired *syn* products were obtained in high yields with high diastereo- and enantioselectivities (entries 4 and 5).[19] It is noted that the product from **2** and **5** was highly crystalline, and that one recrystallization from 2-propanol/hexane afforded the diastereomerically and enantiomerically pure material (>99.5% ee).

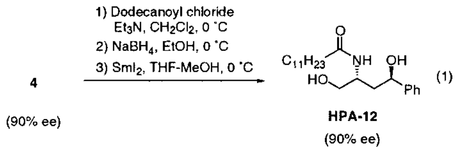
Table 3. Catalytic Asymmetric Mannich-Type Reactions



Entry	Silyl Enol Ether	Time (h)	Yield (%)	*syn*/*anti*	Ee (%)
1		120	82	–	91
2		72	63	–	91
3[a]		96	88	–	89
4[a]	 **5**	72	91	96/4 (100/0	88 >99.5[b])
5[a]		420	30	90/10	91

[a] 100 mol % of ZnF_2 and 20 mol % of ligand **1** were used. [b] After one recrystallization.

This asymmetric Mannich-type reaction was successfully applied to the synthesis of (1*R*,3*R*)-*N*-(3-hydroxy-1-hydroxymethyl-3-phenylpropyl)dodecanamide (HPA-12),[20] which is the first compound of a specific inhibitor for sphingomyelin synthesis in mammalian cells and is expected as a drug that inhibits intracellular trafficking of sphingolipids. Mannich adduct **4** was *N*-acylated in 90% yield, and the ketone and ester groups were reduced by $NaBH_4$ in 79% yield. Finally, the N–N bond of the hydrazine was cleaved by SmI_2[21] to afford HPA-12 in 64% yield without decreasing the enantiomeric purity (eq 1). A single recrystallization gave an enantiomerically pure compound.



In summary, the catalytic, diastereo- and enantioselective Mannich-type reaction of a hydrazono ester with silyl enol ethers in aqueous media has been achieved with zinc fluoride and a chiral diamine ligand. The use of water and a small amount of TfOH is essential for the reactions to proceed in high yield. Enantioselective synthesis of HPA-12 has been attained in four steps by using this asymmetric reaction. This reaction system will provide a novel efficient method to synthesize various nitrogen-containing molecules including amino acid derivatives. Further studies to clarify the precise mechanism including the roles of water and TfOH are now in progress.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from Japan Society of the Promotion of Science.

Supporting Information Available: Experimental section including determination of stereochemistry (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA026094P

---

(15) For effects of achiral ligands on allylantion in aqueous media, see: Kobayashi, S.; Aoyama, N.; Manabe, K. *Synlett* **2002**, 483.

(16) For a similar type of double activation, see: (a) Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247. (b) Gauthier, D. R., Jr.; Carreira, E. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2363. (c) Yanagisawa, A.; Nakatsuka, Y.; Asakawa, K.; Kageyama, H.; Yamamoto, H. *Synlett* **2001**, 69. (d) Friestad, G. K.; Ding, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4491. See also ref 3e.

(17) For Lewis base activation of silyl enolates in Mannich-type reactions: (a) Miura, K.; Tamaki, K.; Nakagawa, T.; Hosomi, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1958. (b) Miura, K.; Nakagawa, T.; Hosomi, A. *J. Am. Chem. Soc.* **2002**, *124*, 536.

(18) Aoki, Y.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1995**, 463.

(19) The *syn*-selectivity is unprecedented.[2e] Cf. Supporting Information.

(20) (a) Yasuda, S.; Kitagawa, H.; Ueno, M.; Ishitani, H.; Fukasawa, M.; Nishijima, M.; Kobayashi, S.; Hanada, K. *J. Biol. Chem.* **2001**, *276*, 43994. (b) Ueno, M.; Kitagawa, H.; Ishitani, H.; Yasuda, S.; Nishijima, K.; Hanada, K.; Kobayashi, S. *Tetrahedron Lett.* **2001**, *42*, 7863. (c) Kobayashi, S.; Matsubara, R.; Kitagawa, H. *Org. Lett.* **2002**, *4*, 143.

(21) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266.