

## Enantio- and Diastereoselective, Stereospecific Mannich-Type Reactions in Water

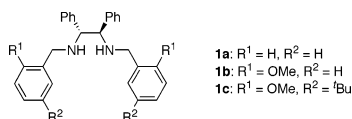
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In recent years, use of water as a reaction solvent has received much attention in synthetic organic chemistry,<sup>1</sup> because water is safe, cheap, and environmentally friendly. In addition, dehydrative drying of substrates and solvents is not required, and unique reactivity and selectivity are often observed when water is used as a solvent. Whereas catalytic asymmetric carbon–carbon bond-forming reactions in organic solvents have reached a fairly high level of sophistication, comparable progress has not yet been achieved for the reactions in aqueous solvents. In particular, these reactions in water without using organic cosolvents are difficult to achieve. Recently, some catalytic asymmetric reactions in water have been developed.<sup>2</sup> However, to the best of our knowledge, catalytic asymmetric Mannich-type reactions in water have not been reported despite the synthetic utility of the Mannich adducts ( $\beta$ -amino ketones or esters), which are versatile chiral building blocks for the preparation of many nitrogen-containing, biologically important compounds.<sup>3</sup> Previously, we reported catalytic asymmetric Mannich-type reactions in aqueous THF.<sup>4,5</sup> However, direct application of this catalytic system to reactions in water without THF gave unsatisfactory results. In this paper, we report that further exploration has led to a new system that enables enantio- and diastereoselective, stereospecific Mannich-type reactions in water without any organic cosolvents.

Initial examination focused on the reaction of acylhydrazone ester **2** with the silyl enol ether derived from acetophenone (Table 1).



**Table 1.** Improvement of Asymmetric Mannich-Type Reaction

entry	diamine	time (h)	yield (%)	ee (%)
1 <sup>a</sup>	<b>1a</b>	72	93	92
2	<b>1a</b>	72	55	95
3	<b>1b</b>	20	86	93
4	<b>1c</b>	20	95	96
5 <sup>b</sup>	<b>1c</b>	20	91	95

<sup>a</sup> H<sub>2</sub>O/THF = 1/9 was used as a solvent instead of H<sub>2</sub>O. <sup>b</sup> Without TfOH.

Acylhydrazones are imine surrogates that are more stable than imines even in aqueous media.<sup>6,7</sup> Moreover, hydrazines such as the products in the Mannich-type reactions are interesting compounds, not only because hydrazines themselves can be used as unique building blocks<sup>8</sup> but also because the N–N bond can be easily cleaved to afford amines. When a combination of ZnF<sub>2</sub> (100 mol %), **1a** (10 mol %), and TfOH (1 mol %) was used,<sup>4</sup> the reaction in pure water proved to give a much lower yield than that in H<sub>2</sub>O/

**Table 2.** Asymmetric Mannich-Type Reactions in Water

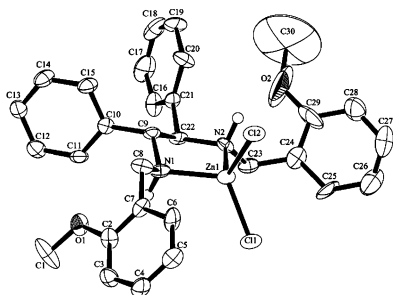
entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	additive (mol %)	yield (%)	syn/anti	ee (%)
1 <sup>a</sup>	H	H	4-Me-C <sub>6</sub> H <sub>4</sub>		91		95
2 <sup>a</sup>	H	H	4-MeO-C <sub>6</sub> H <sub>4</sub>		93		91 (98) <sup>b</sup>
3 <sup>a,c</sup>	H	H	4-Cl-C <sub>6</sub> H <sub>4</sub>		94		95
4 <sup>d</sup>	Me	H	Ph		6	91/9	94 <sup>e</sup>
5 <sup>d</sup>	Me	H	Ph	TfOH (1)	5	91/9	90 <sup>e</sup>
6 <sup>d</sup>	Me	H	Ph	SDS (5)	9	91/9	78 <sup>e</sup>
7 <sup>d</sup>	Me	H	Ph	Triton X-405(5)	10	91/9	93 <sup>e</sup>
8 <sup>d</sup>	Me	H	Ph	CTAB (5)	94	94/6	97 <sup>e</sup>
9 <sup>d</sup>	Me	H	Ph	CTAB (2)	93	94/6	96 <sup>e</sup>
10 <sup>d,f</sup>	Me	H	Ph	CTAB (2)	84	93/7	97 <sup>e</sup>
11	Et	H	Ph	CTAB (2)	76	96/4	96 <sup>e</sup>
12 <sup>g,h</sup>	Me	H	Et	CTAB (2)	57	98.5/1.5 <sup>b</sup>	>99.5 <sup>e</sup> <sup>b</sup>
						86/14	97 <sup>i</sup>
						98.5/1.5 <sup>b</sup>	>99.5 <sup>e</sup> <sup>b</sup>
13 <sup>h,j</sup>	H	Me	Et	CTAB (2)	94	12/88	94 <sup>i</sup>
14 <sup>k</sup>	Me	H	S <sup>t</sup> Bu	CTAB (2)	39	8/92	94 <sup>i</sup>
15 <sup>l</sup>	H	Me	S <sup>t</sup> Bu	CTAB (2)	51	93/7	67 <sup>i</sup>
16 <sup>l,m</sup>	H	Me	S <sup>t</sup> Bu	CPB (2)	69	92/8	62 <sup>i</sup>

<sup>a</sup> **1c** was used instead of **1b**. <sup>b</sup> After one recrystallization. <sup>c</sup> Time = 36 h. <sup>d</sup> E/Z = <1/>99. <sup>e</sup> Ee of syn adduct. <sup>f</sup> Performed with 5 mol % **1b**. <sup>g</sup> E/Z = 2/98. <sup>h</sup> Time = 72 h. <sup>i</sup> Ee of major diastereomer. <sup>j</sup> E/Z = 76/24. <sup>k</sup> E/Z = 98/2. <sup>l</sup> E/Z = 3/97. <sup>m</sup> Time = 48 h.

THF (entry 1 vs 2). To our delight, however, the enantioselectivity obtained was higher in water. We then decided to examine several conditions to speed up the reaction in water. After many trials, we finally found that use of **1b**<sup>7d</sup> led to remarkable acceleration of the reaction in water (entry 3). Furthermore, when **1c** was used, a 95% yield was obtained after 20 h, and a high level of selectivity was also attained (entry 4). Finally, it was surprising to find that the reaction proceeded smoothly with excellent enantioselectivity in the absence of TfOH (entry 5).<sup>9</sup>

Since the new catalyst system using **1c** has been established, we then employed this system in reactions with other silyl enol ethers in water. In the cases of 4'-substituted acetophenone-derived silyl enol ethers, the corresponding adducts were obtained in high yields with excellent ees (Table 2, entries 1–3).

We next turned our attention to the enantio- and diastereoselective reactions using the silyl enol ethers derived from  $\alpha$ -monosubstituted carbonyl compounds such as propiophenone. Unexpectedly, this type of reaction was found to proceed sluggishly regardless of the existence of TfOH (entries 4, 5).<sup>10</sup> To accelerate the reaction, addition of surfactants was then investigated.<sup>11</sup> While sodium dodecyl sulfate (SDS) or Triton X-405 was not effective (entries 6, 7), it was remarkable that cetyltrimethylammonium bromide (CTAB) gave an excellent yield and that it also improved the ee slightly (entry 8). It is noteworthy that a cationic surfactant is effective in this reaction,<sup>12</sup> while an anionic surfactant has been



**Figure 1.** Ortep drawing of  $[\text{ZnCl}_2\text{-1b}]$  moiety in the X-ray crystal structure of  $[\text{ZnCl}_2\text{-1b}\cdot\text{CH}_2\text{Cl}_2]$ . Hydrogen atoms except NH are omitted for clarity.

reported to work well in Lewis acid-catalyzed aldol reactions.<sup>13</sup> The reaction under neat conditions gave a much lower yield (4% yield, syn/anti = 91/9, 94% ee (syn) for 5 h) than that in water (68% yield, syn/anti = 94/6, 97% ee (syn) for 5 h), suggesting the importance of water. Moreover, it was found that 2 mol % CTAB was sufficient for giving high yield and ee (entry 9). Under these optimized conditions, it was possible to reduce the amount of **1b** to 5 mol % (entry 10). Butyrophene-derived silyl enol ether also afforded the adduct in good yield with high stereoselectivity (entry 11).

The reaction of **2** with the (*Z*)-silyl enol ether derived from 3-pentanone (**3Z**) using **1b** and CTAB afforded the adduct with good syn selectivity and high ee (entry 12). To our surprise, the anti adduct was obtained with good diastereoselectivity by the reaction with the (*E*)-silyl enol ether (**3E**) under the same conditions (entry 13). We next took an interest in the stereospecificity in the reactions using the (*E*)- and (*Z*)-ketene silyl acetal derived from *S*-*tert*-butyl thiopropionate (**4E** and **4Z**), which gave synthetically useful  $\beta$ -hydrazino thioesters. When **4E** was employed, the anti adduct was obtained selectively with high diastereo- and enantioselectivity (entry 14). In contrast, **4Z** proved to afford high syn selectivity (entry 15). It was found that use of cetylpyridinium bromide (CPB) instead of CTAB suppressed the hydrolysis of **4Z** to some degree to improve the yield (entry 16).<sup>14</sup> In effect, good to high stereospecificities were observed in the reactions with both **3** and **4**.<sup>15</sup> It is noted that these stereospecificities are rare examples in the catalytic asymmetric Mannich-type reactions<sup>16</sup> and that both syn and anti adducts can be prepared by simply changing the geometry of the silicon enolates. Furthermore, in many cases, the adducts were highly crystalline, and one recrystallization from ethanol/hexane afforded the diastereomerically and enantiomerically almost pure materials (entries 2, 8,<sup>4</sup> 11, and 12).

To clarify the origin of the unique stereoselectivities, we finally investigated the structure of the chiral catalyst. Although the single crystal of  $\text{ZnF}_2\text{-1b}$  complex was difficult to prepare due to the low solubility of  $\text{ZnF}_2$ , a complex suitable for X-ray analysis was obtained from  $\text{ZnCl}_2$  and **1b** (Figure 1). In this X-ray structure, the asymmetric environment of the two Ph groups on the asymmetric carbons was transferred to the two benzyl moieties on the nitrogen atoms, as expected, which would play a key role for the high stereoselectivity. In addition, interactions between the MeO groups of **1b** and  $\text{Zn}^{2+}$  were not observed. On the basis of this observation and the similar ees given by **1a** and **1b** (Table 1), it is implied that the MeO groups of **1b** do not coordinate to  $\text{Zn}^{2+}$  even in the transition states in the asymmetric reactions.

In conclusion, we have developed efficient enantio- and diastereoselective Mannich-type reactions of a hydrazono ester with silicon enolates. Characteristic points of these reactions are as follows: (1) The new catalyst system remarkably accelerated the reactions in water without using any organic cosolvents. (2) TfOH

was not necessary in the system, and a cationic surfactant was effective in some cases. (3) In contrast with most asymmetric Mannich-type reactions, either syn or anti adducts were stereospecifically obtained from (*E*)- or (*Z*)-silicon enolate. (4) Some pertinent information on the chiral catalysts, the Zn–chiral diamine complexes, was obtained. We anticipate that this work will provide a useful guide for the development of asymmetric carbon–carbon bond-forming reactions in water.

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

## References

- (1) (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.; Blackie Academic and Professional: London, 1998.
- (2) (a) Sinou, D. *Adv. Synth. Catal.* **2002**, *344*, 221. (b) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751. (c) Manabe, K.; Kobayashi, S. *Chem. Eur. J.* **2002**, *8*, 4094.
- (3) (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (b) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10.
- (4) Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 5640.
- (5) For the other recent reports on the asymmetric reactions of imines with silicon enolates in water-containing solvents, see: (a) Notz, W.; Tanaka, F.; Watanabe, S.-I.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F., III. *J. Org. Chem.* **2003**, *68*, 9624. (b) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018.
- (6) (a) Kobayashi, S.; Hamada, T.; Manabe, K. *Synlett* **2001**, 1140. (b) Oyamada, H.; Kobayashi, S. *Synlett* **1998**, 249. (c) Manabe, K.; Oyamada, H.; Sugita, K.; Kobayashi, S. *J. Org. Chem.* **1999**, *64*, 8054.
- (7) For reports on the catalytic asymmetric carbon–carbon bond-forming reactions using acylhydrazones, see: (a) Kobayashi, S.; Hasegawa, Y.; Ishitani, H. *Chem. Lett.* **1998**, 1131. (b) Kobayashi, S.; Shimizu, H.; Yamashita, Y.; Ishitani, H.; Kobayashi, J. *J. Am. Chem. Soc.* **2002**, *124*, 13678. (c) Kobayashi, S.; Ogawa, C.; Konishi, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 6610. (d) Hamada, T.; Manabe, K.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3927. (e) Friestad, G. K.; Shen, Y.; Ruggles, E. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5061. (f) Keith, J. M.; Jacobsen, E. N. *Org. Lett.* **2004**, *6*, 153. See also ref 4.
- (8) Schiessl, H. W. In *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th ed.; Kroschwitz, J. I., Howe-Grant, M., Eds.; Wiley: New York, 1995; Vol. 13, pp 560–606.
- (9) In a  $\text{H}_2\text{O}/\text{THF}$  (1:9) solvent, the reaction using **1a** proceeded sluggishly without TfOH.<sup>4</sup>
- (10) In the reactions using the silyl enol ethers derived from  $\alpha$ -monosubstituted carbonyl compounds, **1b** was used instead of **1c**, because **1b** gave higher selectivities (Table 2, entry 9) in the reactions using propiophenone-derived silyl enol ether than **1c** (86%, syn/anti = 94/6, 92% ee).
- (11) (a) Fendler, J. H.; Fendler, E. J. *Catalysis in Micellar and Macromolecular Systems*; Academic Press: London, 1975. (b) *Mixed Surfactant Systems*; Holland, P. M., Rubingh, D. N., Eds.; American Chemical Society: Washington, DC, 1992. (c) *Structure and Reactivity in Aqueous Solution*; Cramer, C. J., Truhlar, D. G., Eds.; American Chemical Society: Washington, DC, 1994. (d) *Surfactant-Enhanced Subsurface Remediation*; Sabatini, D. A., Knox, R. C., Harwell, J. H., Eds.; American Chemical Society: Washington, DC, 1994. (e) *Reactions and Synthesis in Surfactant Systems*; Texter, J., Ed.; Marcel Dekker: New York, 2001.
- (12) When CTAB (5 mol %) was used in the reaction in Table 1, entry 5, remarkable acceleration of the reaction was not observed, and the ee was decreased (56% yield, 92% ee for 5 h).
- (13) (a) Manabe, K.; Mori, Y.; Wakabayashi, T.; Nagayama, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 5640. (b) Kobayashi, S.; Mori, Y.; Nagayama, S.; Manabe, K. *Green Chem.* **1999**, 175. (c) Kobayashi, S.; Wakabayashi, T.; Nagayama, S.; Oyamada, H. *Tetrahedron Lett.* **1997**, *26*, 4559.
- (14) Use of CPB in the reactions shown in Table 2, entries 12 and 14, gave almost the same results ( $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{H}$ ,  $\text{R}^3 = \text{Et}$ , CPB (2 mol %) 58% yield, syn/anti = 87/13, 97% ee (syn);  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{H}$ ,  $\text{R}^3 = \text{S}^t\text{Bu}$ , CPB (2 mol %) 38% yield, syn/anti = 10/90, 94% ee (anti)).
- (15) With regard to the relationship between the configurations of the enolates and the relative configurations of the products, **3** and **4** afforded opposite results, possibly due to the steric difference between the Ph and  $\text{S}^t\text{Bu}$  groups.
- (16) Although diastereoselectivities were not as high as the present reactions, stereospecificities were also observed in the asymmetric Mannich-type reactions. See: Kobayashi, S.; Matsubara, R.; Nakamura, Y.; Kitagawa, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 2507.

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