Solvent-free Organocatalytic Asymmetric Conjugate Addition of Thiols to α,β-Unsaturated Aldehydes

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A highly enantioselective asymmetric conjugate addition of thiols to α,β-unsaturated aldehydes has been achieved catalyzed by newly designed organocatalyst without solvent.

Most organic reactions are performed under the influence of catalysts in organic solvents and proceed smoothly under homogeneous conditions. On the other hand, organic reactions in water[1] or in the presence of water[2] are extensively investigated in recent years. Because water is inexpensive, nonflammable, and environment-friendly. Furthermore, water has very unique characters because of its high polarity. For example, Kobayashi and co-workers reported the scandium triflate-catalyzed Mukaiyama aldol reaction in the presence of water.[3]

More recently, organocatalytic reactions which are performed in the presence of water have been reported by a few groups. Hayashi and co-workers reported siloxy proline catalyzes direct asymmetric aldol reaction in the presence of water.[4] Barbas and co-workers reported hydrophobic chiral 1,2-diamine, which is derived from (*S*)-proline, catalyzes direct asymmetric aldol reaction[5] and the Michael reaction[6] in the presence of water or brine. These reactions can be catalyzed by a chiral secondary amine which has a hydrophobic-functional group. These catalysts also act as a surfactant in the presence of water. However, the organocatalytic asymmetric Michael reaction in brine proceeds without the formation of emulsion.[7] Thus, we hypothesized that oraganocatalytic reactions in water proceed smoothly by the catalyst having hydrophobic functional groups.

To demonstrate our hypothesis, we designed a hydrophobic organocatalyst which has highly hydrophobic functional groups (Figure 1). For the purpose of increasing the number of hydrophobic functional groups in the proline-derived catalyst, we applied *trans*-4-hydroxy-(*S*)-proline to the starting material. Furthermore, to increase the hydrophobic nature, we introduced a trifluoromethyl group which is the hydrophobic functional group in organic compounds and a silyloxy group into the catalyst molecule. So, the designed catalyst **1** was readily prepared from *trans*-4-hydroxy-(*S*)-proline in 6 steps.[8] First, we examined the conjugate addition of thiol to enal under the influence of known oraganocatalysts in brine (Figure 2 and Table 1). Organocatalytic asymmetric conjugate addition of 2-methyl-2-propanethiol to cinnamaldehyde was performed in brine at −20 °C.[9,10] Jørgensen and co-workers reported that racemization of the conjugate adducts occurred immediately at 20 °C.[11] Therefore, we isolated the corresponding primary alcohol after the reduction with $NaBH_4$. The hydrophobic diamine catalyst **2** which was efficiently utilized in aldol reaction and the Michael reaction in the presence of water was not effective for this reaction (Entry 1). Prolinol silyl ethers[12] afforded the corresponding products in moderate yields with moderate enantiomeric excess (Entries 2–5). Jørgensen's catalyst **7**[13,14] catalyzed conjugate addition (Entry 6) in good enantioselectivity. However, the

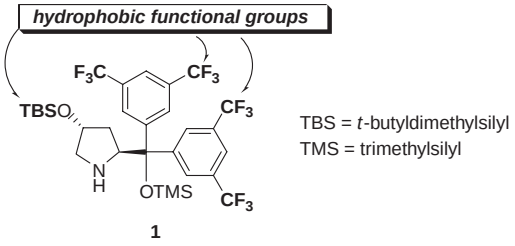

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Figure 1. Our newly designed organocatalyst.

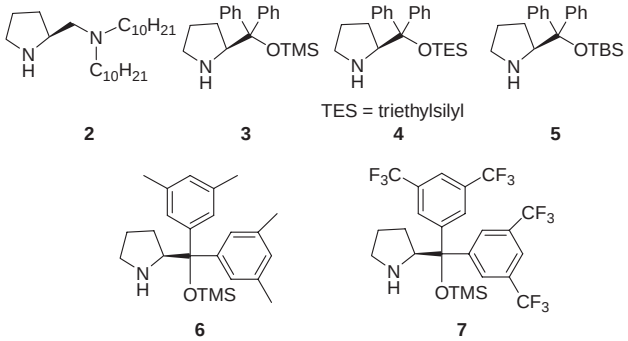
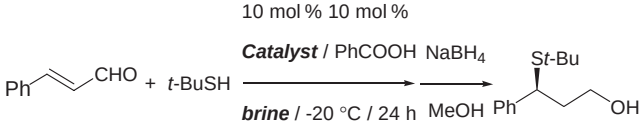


Figure 2. Organocatalyst examined in this study.

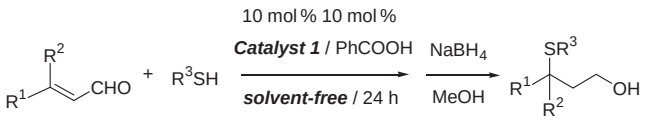
Table 1. Catalyst screening for asymmetric conjugate addition of thiol to enal[a]



Entry	Catalyst	Yield/%	ee/%[e]
1	**2**	41	26
2	**3**	54	62
3	**4**	32	50
4	**5**	37	50
5	**6**	58	59
6	**7**	33	87
7[b]	**7**	21	88
8	**1**	48	89
9[c]	**1**	54	91
10[d]	**1**	73	92
11[b]	**1**	72	95

[a]Unless otherwise specified, the reactions were performed using cinnamaldehyde (0.3 mmol), 2-methyl-2-propanethiol (0.2 mmol), catalyst (0.02 mmol), and benzoic acid (0.02 mmol) in brine (0.5 mL) at −20 °C. [b]Solvent-free conditions. [c]Brine (0.2 mL) was used. [d]Brine (0.05 mL) was used. [e]Ee was determined by HPLC analysis with a chiral column.

Table 2. Asymmetric conjugate addition of thiols to various enals[a]



Entry	R^1	R^2	R^3	Temp/°C	Yield/%	ee/%
1	Me	H	*t*-Bu	−30	67	98[c]
2	Et	H	*t*-Bu	−20	76	92[c]
3	*n*-Pr	H	*t*-Bu	−20	79	95[c]
4	*i*-Pr	H	*t*-Bu	−20	53	99[c]
5	*n*-Hexyl	H	*t*-Bu	−20	90	96[c]
6[b]	4-$MeOC_6H_4$	H	*t*-Bu	−20	24	>99[c]
7	Et	H	Bn	−30	52	85[d]
8	*n*-Pr	H	Bn	−30	66	87[d]
9	*i*-Pr	H	Bn	−20	59	86[d]
10	*n*-Hexyl	H	Bn	−20	71	88[d]
11	Me	Me	Bn	−20	67	—
12	citral		Bn	−10	53	56[d]

[a]Unless otherwise specified, the reactions were performed using α,β-unsaturated aldehyde (0.3 mmol), thiol (0.2 mmol), catalyst **1** (0.02 mmol), and benzoic acid (0.02 mmol) under solvent-free conditions. [b]Toluene (0.05 mL) was added. [c]Ee was determined by HPLC analysis with a chiral column after conversion to the corresponding benzoate. [d]Ee was determined by HPLC analysis with a chiral column.

product was obtained in low yield. On the other hand, our designed organocatalyst **1** catalyzed this reaction in modest yield with high enantioselectivity (Entry 8). By decreasing the amount of brine, chemical yields and enantioselectivities were improved (Entries 9 and 10). Surprisingly, when highly hydrophobic organocatalyst **1** was used under solvent-free conditions, the corresponding conjugate adduct was obtained in 72% yield with 95% ee (Entry 11). On the contrary, Jørgensen's catalyst was not effective under solvent-free conditions (Entry 7). Solvent-free conditions[15] are more ideal reaction conditions from the green chemical point of view, so that we decided that these reaction conditions were optimal for the asymmetric conjugate addition of thiol to enal.

Next, we tested various α,β-unsaturated aldehydes and thiols (Table 2).[16] When organocatalytic asymmetric conjugate additions of 2-methyl-2-propanethiol to crotonaldehyde or 4-methyl-2-pentenal were performed by using catalyst **1**, the desired products were obtained with excellent enantioselectivities (Entries 1 and 4). Pentenal, hexenal, and nonenal were used as an enal substrate, and the reactions proceeded smoothly; good yields and high enantioselectivities were observed (Entries 2, 3, and 5). Unfortunately, in the case of 4-methoxycinnamaldehyde, the reaction mixture was heterogeneous so that no reaction occurred. However, when a small amount of toluene (0.05 mL) was added, the corresponding sulfide was obtained in enantiomerically pure form (Entry 6, >99% ee). Furthermore, we examined the reaction of various α,β-unsaturated aldehyde with phenylmethanethiol. α,β-Unsaturated aldehydes were consistently converted to conjugate adducts with good enantioselectivities (Entries 7–10). Regardless of its bulkiness, β,β-disubstituted α,β-unsaturated aldehyde reacted with phenylmethanethiol (Entry 11, 67% yield). Moreover, the reaction of bulky β,β-disubstituted α,β-unsaturated aldehyde such as citral, interestingly, afforded the product in moderate yield with moderate enantioselectivity (Entry 12). We succeeded in the first conjugate addition of thiol to β,β-disubstituted α,β-unsaturated aldehyde such as citral.

In conclusion, we have developed solvent-free organocatalytic asymmetric conjugate addition of thiols to α,β-unsaturated aldehydes. In the presence of well-designed organocatalyst **1**, the reaction proceeds without any organic solvents, giving the corresponding chiral sulfides in almost enantiomerically pure form (up to 99% ee). Moreover, β,β-disubstituted α,β-unsaturated aldehydes also reacted with phenylmethanethiol. This method is environment-friendly, economical, and convenient. Solvent-free reactions are very interesting from the point of the reaction mechanism. Further studies of solvent-free organocatalytic reactions are under way in our laboratory.

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References and Notes

1 For reviews, see: a) U. M. Lindstrom, *Chem. Rev.* **2002**, *102*, 2751. b) C.-J. Li, *Chem. Rev.* **2005**, *105*, 3095.
2 Y. Hayashi suggested the term "in the presence of water": Y. Hayashi, *Angew. Chem., Int. Ed.* **2006**, *45*, 8103.
3 S. Kobayashi, T. Wakabayashi, S. Nagayama, H. Oyamada, *Tetrahedron Lett.* **1997**, *38*, 4559.
4 a) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem., Int. Ed.* **2006**, *45*, 958. b) Y. Hayashi, S. Aratake, T. Okano, J. Takahashi, T. Sumiya, M. Shoji, *Angew. Chem., Int. Ed.* **2006**, *45*, 5527.
5 N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas, III, *J. Am. Chem. Soc.* **2006**, *128*, 734.
6 N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas, III, *J. Am. Chem. Soc.* **2006**, *128*, 4966.
7 When hydrophobic diamine catalyst **2** was used in brine, we did not observe the formation of emulsion.
8 Hydrophobic organocatalyst **1** was prepared starting from hydroxyproline by the following 6 steps: 1) $SOCl_2$, MeOH, 2) ZCl, Et_3N, MeOH, 3) TBSCl, imidazole, DMF, 4) ArMgBr, THP, 5) H_2, cat. Pd–C, MeOH, 6) TMSCl, imidazole, DMF.
9 Saturated aqueous NaCl solution was used.
10 A general experimental procedure: Thiol (0.2 mmol) was added to a mixture of catalyst **1** (0.02 mmol, 14.5 mg), benzoic acid (0.02 mmol, 2.4 mg), and α,β-unsaturated aldehyde (0.3 mmol) at −20 °C. After being stirred for 24 h, the reaction mixture was diluted with methanol (2 mL), and sodium borohydride (30 mg, 0.8 mmol) was added to the reaction mixture at 0 °C. After being vigorously stirred for 30 min, reaction was quenched with 1 M HCl (7 mL). The reaction mixture was extracted with ethyl acetate (7 mL × 3). The combined organic layer was washed with brine and dried over Na_2SO_4. The solvents were removed in vacuo, the product was purified by silica-gel thin-layer chromatography.
11 M. Marigo, T. Schulte, J. Franzen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 15710.
12 Prolinol silyl ether catalyzed reactions, see: a) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. b) H. Gotoh, R. Masui, H. Ogino, M. Shoji, Y. Hayashi, *Angew. Chem., Int. Ed.* **2006**, *45*, 6853. c) H. Sunden, I. Ibrahem, A. Cordova, *Tetrahedron Lett.* **2006**, *47*, 99.
13 a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem., Int. Ed.* **2005**, *44*, 794. b) J. Franzen, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjaersgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296.
14 Very recently, K. A. Jørgensen et al. reported Michael-aldol domino reaction catalyzed by **7**, see: S. Brandau, E. Maerten, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 14986.
15 Organocatalytic solvent-free reactions, see: a) B. Rodríguez, T. Rantanen, C. Bolm, *Angew. Chem., Int. Ed.* **2006**, *45*, 6924. b) A. Carlone, M. Marigo, C. North, A. Landa, K. A. Jørgensen, *Chem. Commun.* **2006**, 4928.
16 Other organocatalytic conjugate additions of thiols, see: a) H. Hiemstra, H. Wynberg, *J. Am. Chem. Soc.* **1981**, *103*, 417. b) P. McDaid, Y.-G. Chen, L. Deng, *Angew. Chem., Int. Ed.* **2002**, *41*, 338. c) T. C. Wabnitz, J. B. Spencer, *Org. Lett.* **2003**, *5*, 2141. d) W. Wang, H. Li, J. Wang, L. Zu, *J. Am. Chem. Soc.* **2006**, *128*, 10354. e) R. Rios, H. Sunden, I. Ibrahem, G.-L. Zhao, L. Eriksson, A. Cordova, *Tetrahedron Lett.* **2006**, *47*, 8547.

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