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Highly Diastereo- and Enantioselective Direct Aldol Reactions in Water***Yujiro Hayashi,* Tatsunobu Sumiya, Junichi Takahashi, Hiroaki Gotoh, Tatsuya Urushima, and Mitsuru Shoji*

Reactions in which water is used as the solvent have attracted a great deal of attention because water is an environmentally friendly, safe medium, which avoids the problems of pollution that are inherent with organic solvents.^[1] The synthesis of enantiopure molecules is another important issue, and the development of enantioselective reactions in water is an extensively investigated topic,^[2] although it was long thought to be mainly confined to the realm of enzymes. Successful catalytic versions of enantioselective reactions have mostly employed transition-metal complexes,^[3] and may require toxic, rare, and expensive metals, and suffer from possible contamination of the products by metal. Organocatalysts,^[4] however, are free from these problems, and moreover are inexpensive and stable to moisture and air. Thus, the development of small organic molecules that catalyze enantioselective reactions in water is currently a highly sought-after goal in chemistry.

The aldol condensation is a key carbon–carbon bond-forming reaction, which creates the β -hydroxy carbonyl structural unit found in many natural products and drugs.^[5] In nature, type I and II aldolases catalyze this reaction in water with perfect enantiocontrol through an enamine mechanism and by using a zinc cofactor, respectively.^[6] The Mukaiyama aldol reaction proceeds in aqueous organic solvent, but this is an indirect method that requires preformation of a silyl enol ether as a nucleophile.^[7] A Zn-proline-catalyzed aldol reaction occurs in aqueous media with moderate enantiomeric excess.^[8] However, proline can catalyze direct aldol reactions in polar organic solvents with high enantioselectivity,^[4,9] but it affords the racemate in water.^[10] Although several chiral organocatalysts have been developed for the aldol reaction,^[4,11] and some of them provide aldols enantioselectively in aqueous organic solvents,^[12] they still require the use of an organic solvent.^[13] As far as we are aware, only enzymes and antibodies of very high molecular

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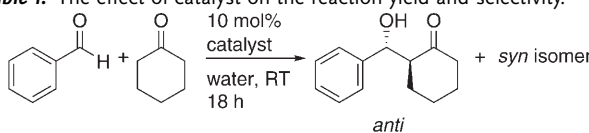


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weight have been able to catalyze the direct aldol reaction in water with high enantioselectivity.^[5,6] Moreover, a rather large catalyst loading is usually required for the aldol reactions mediated by organocatalysts. Herein we describe a synthetic small organic molecule that promotes highly diastereo- and enantioselective aldol reactions in the presence of water.

We have previously reported that 4-*tert*-butyldimethylsiloxyproline (**1a**), which is easily prepared from commercially available *trans*-4-hydroxyproline, is a highly active proline surrogate in the α -aminoxylation of carbonyl compounds and the Mannich reaction.^[14] Application of this siloxyproline as a catalyst to the aldol reaction of cyclohexanone and benzaldehyde led to an unexpected result, namely, the asymmetric aldol reaction proceeded efficiently in the presence of water and the *anti*-aldol product was obtained with excellent diastereoselectivity in a nearly optically pure form (Table 1,

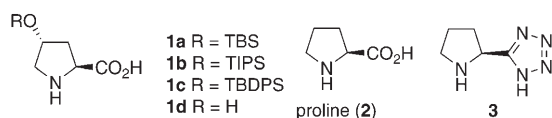
Table 1: The effect of catalyst on the reaction yield and selectivity.^[a]



Entry	Catalyst	Yield [%] ^[b]	<i>anti:syn</i> ^[c]	<i>ee</i> [%] ^[d]
1	1a	61	19:1	> 99
2 ^[e]	1a	66	20:1	> 99
3 ^[f]	1a	69	20:1	> 99
4 ^[g]	1a	61	1.8:1	89
5 ^[h]	1a	65	1:1	80
6	1b	71	14:1	> 99
7	1c	78	13:1	> 99
8	1d	< 5	—	—
9	2	< 5	—	—
10	3	< 5	—	—

[a] Unless otherwise shown, the reaction was performed with benzaldehyde (0.4 mmol), cyclohexanone (207 μ L, 2.0 mmol), catalyst (0.04 mmol), and H₂O (0.13 mL) at room temperature for 18 h. [b] Yield refers to the combined yield of isolated diastereomers. [c] Diastereoselectivity was determined by ¹H NMR analysis of the reaction mixture. [d] Optical yield refers to that of the *anti* isomer and was determined by HPLC analysis on a chiral phase (chiralcel OD-H). [e] H₂O (72 μ L) was employed. [f] H₂O (36 μ L) was employed. [g] The reaction was performed neat. [h] The reaction was performed in DMSO (0.4 mL).

entry 1).^[15] This is the first highly diastereoselective and enantioselective aldol reaction carried out in the presence of water without using an organic solvent. Screening the reaction (Table 1) demonstrated that not only TBS-protected proline **1a** (Scheme 1) but also TIPS- and TBDPS-protected prolines **1b** and **1c**^[16] were excellent catalysts, and in all cases the *anti*



Scheme 1. Organocatalysts examined in this study. TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl, TBDPS = *tert*-butyldiphenylsilyl.

isomer was obtained in good yield with excellent diastereoselectivity in a nearly optically pure form (entries 1, 6, and 7). Although the amount of water had little effect on the yield and selectivities, with the reaction proceeding in a two-phase system, the reactions without a solvent or in an organic solvent (DMSO)^[17] resulted in lower enantioselectivity, with formation of nearly equal amounts of *anti* and *syn* isomers (entries 1–5). These results indicate that water is indispensable for the high diastereo- and enantioselectivities.^[18] The reaction scarcely proceeded with the tetrazole catalyst **3** in the presence of water; this catalyst, however, promoted the aldol reaction of chloral in the presence of water (entry 10).^[12a] As proline (**2**) and hydroxyproline (**1d**) did not promote the reaction in the presence of water, the siloxy group of catalyst **1** is clearly essential for the success of this reaction (entries 8, 9).

The generality of the reaction was examined in detail using catalyst **1c**, and the results are summarized in Table 2. The reaction has broad applicability with respect to the aldehyde: Both excellent enantioselectivity (over 95 % *ee*) and *anti* selectivity were obtained when cyclohexanone and cyclopentanone were employed. Not only reactive, electron-deficient aldehydes, but neutral aldehydes are also excellent electrophilic partners in this reaction. Excellent *ee* values were obtained in the case of electron-rich aldehydes, although the yield was only moderate (entry 4). Both aromatic and aliphatic aldehydes could be employed. Heteroaromatic aldehydes such as furfural and *para*-pyridinecarbaldehyde were also excellent substrates (entries 6 and 7). 2,2-Dimethyl-1,3-dioxan-5-one can be employed successfully as the nucleophilic ketone, and affords a polyoxy compound with excellent selectivity (entry 11).^[12f,19] A water-soluble aldehyde such as formaldehyde can also be employed successfully (entry 12).^[12a,d] The method has its limitations, however: Although the aldol reaction of acetone and hydroxyacetone proceeded in water, the enantioselectivity was moderate.

The effectiveness of the siloxyproline catalysts compared to proline and hydroxyproline can be attributed to the solubility of the catalysts. Although proline and hydroxyproline dissolve in water, siloxyproline is only partially soluble in water and forms an organic phase with the aldehyde and ketone in which the aldol reaction proceeds efficiently.

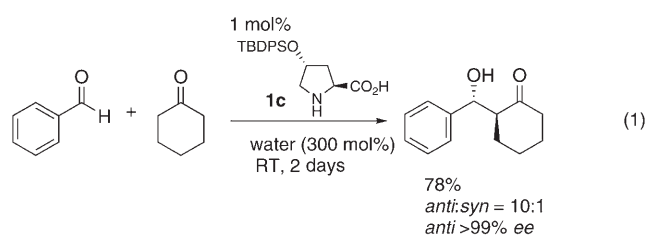
A preliminary study showed that the catalyst loading can be reduced to as low as 1 mol% without compromising the enantioselectivity, and 300 mol% of water is enough for the reaction to be effected in a diastereo- and enantioselective manner, although a longer reaction time is needed (2 days). These reaction conditions are suitable for a preparative-scale synthesis. After the reaction, filtration of the reaction mixture through a short pad of silica gel removed the water and the organocatalyst **1c**, and only a small amount of extra solvent was needed. The direct distillation of the filtrate afforded the product in 78 % yield with excellent enantioselectivity on a 6-mmol scale [Eq. (1)].^[20] It should be noted that this is the first organocatalyst-mediated aldol reaction, in which only 1 mol% of organocatalyst can promote the reaction with high diastereoselectivity and excellent enantioselectivity.

Our results show that the synthetic compounds **1** are the first asymmetric organocatalysts that promote the aldol

Table 2: The catalytic asymmetric aldol reaction in water catalyzed by siloxyproline **1c**.^[a]

$ \begin{array}{c} \text{10 mol\%} \\ \text{TBDSO}_2\text{C(CH}_3)_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H} \\ \text{1c} \\ \text{R}^1\text{CHO} + \text{R}^2\text{C(=O)R}^3 \xrightarrow[\text{water, RT}]{\text{1c}} \text{R}^1\text{CH(OH)CH(R}^2\text{)C(=O)R}^3 + \text{syn isomer} \\ \text{anti} \end{array} $											
Entry	Product	<i>t</i> [h]	Yield [%] ^[b]	<i>anti:syn</i> ^[c]	<i>ee</i> [%] ^[d]	Entry	Product	<i>t</i> [h]	Yield [%] ^[b]	<i>anti:syn</i> ^[c]	<i>ee</i> [%] ^[d]
1		18	78	13:1	> 99	8		20	54	> 20:1	> 99
2		5	86	20:1	> 99	9		24	76	> 20:1	> 99
3		28	80	20:1	97	10 ^[e]		18	74	9:1	> 99
4		50	21	5:1	96	11		18	48	25:1	95
5		40	89	19:1	97	12 ^[f]		90	37	—	96
6 ^[e]		28	79	4.7:1	97	13 ^[g]		18	63	—	67
7		2.5	92	12:1	95	14		72	61	1:1	64, 61 ^[h]

[a] The reaction was performed with aldehyde (0.4 mmol), ketone (2.0 mmol), **1c** (0.04 mmol), and H₂O (0.13 mL) at room temperature. [b] Combined yield of isolated diastereomers. [c] Diastereoselectivity was determined by ¹H NMR analysis of the reaction mixture. [d] Optical yield refers to that of the *anti* isomer and was determined by HPLC analysis on a chiral phase. [e] Catalyst **1a** was used instead of **1c**. [f] Aqueous formalin (35 %, 35 μL, 0.4 mmol) and NaCl (47 mg) were employed. [g] Acetone (10.8 mmol) was employed. [h] Optical yield of the *syn* isomer.



reaction in the presence of water without organic solvent, a process that has hitherto belonged to the realm of enzyme chemistry. The reaction catalyzed by these siloxy catalysts has the following notably features: 1) It proceeds in the presence of water without organic solvent; 2) very high enantioselectivity is attained in most cases; 3) both diastereo- and enantioselectivities are higher than for the reaction performed in an organic solvent; 4) the catalysts themselves can be easily prepared in large quantities from *trans*-hydroxyproline, both enantiomers of which are commercially available; 5) a low catalyst loading (1 mol %) can be utilized. As the synthetic catalysts can be easily modified, their selectivity and reactivity may be tunable, and hence the findings reported

herein may open up a new avenue for the design of catalysts that possess even better properties and are effective in water.

Experimental Section

Experimental procedure of Equation (1): Catalyst **1c** (22.2 mg, 0.06 mmol) was added to a suspension of benzaldehyde (0.60 mL, 6.0 mmol), cyclohexanone (3.1 mL, 30 mmol), and water (0.32 mL, 18 mmol) at room temperature. The reaction mixture was stirred for 48 h, and silica gel (220 mg) was added to the reaction mixture. The mixture was filtered through silica gel using ethyl acetate (10 mL), and the crude organic materials were purified by distillation to afford 2-(hydroxyphenylmethyl)cyclohexanone (954.3 mg, 78 %) as a colorless oil: *anti:syn* = 10:1 (by ¹H NMR spectroscopy of the crude mixture), > 99 % *ee* (by HPLC on a chiralcel OD-H column, λ = 213 nm, *i*PrOH/hexane 1:100, 1.0 mL min⁻¹; *t*_R = 19.4 min (major), 25.9 min (minor)).

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