Asymmetric Synthesis

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Highly Efficient Asymmetric Direct Stoichiometric Aldol Reactions on/in Water**

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Many enzymes catalyze reactions in water under mild conditions with high efficiency and excellent stereoselectivity. This highly effective and environmentally benign synthetic methodology is often regarded as a goal in modern organic chemistry.[1] Although enzymes have synthetic utility, they are usually limited by their lack of large-scale compatibility.[2] It is highly desirable to develop a chemical system that can mimic the action of enzymes and effect organic reactions in water with excellent efficiency and stereoselectivity. Water can be a safe, inexpensive, and environmentally friendly solvent, which makes its use favorable both in academic laboratories and in industry. The pioneering studies of Diels–Alder reactions in water by Breslow[3] in the early 1980s triggered a more widespread interest in the use of water as a medium for organic synthesis, not only because these reactions eliminate the necessity of vigorously drying solvents and substrates, but also because of the unique reactivity and selectivity often observed in aqueous reactions. In the past two decades considerable effort has been made in developing water-based synthetic organic reactions.[4] Thus far, only a relatively limited number of enantioselective organic reactions can be carried out effectively in this solvent and the associated mechanisms can be unclear.[5] Indeed, it appears that asymmetric synthesis in water is still not a routine or preferred procedure.

Enantioselective metal catalysis has revolutionized asymmetric synthesis over the past 20 years and was recognized by the 2001 Nobel Prize in Chemistry.[6] Subsequently, the seminal work by List, Lerner, and Barbas on the intermolecular adaptation of the proline-catalyzed direct asymmetric aldol reaction[7] has focused attention on the catalytic asymmetric reaction by metal-free small organic molecules (organocatalysts). This synthetic approach has received much attention in light of its green chemistry advantages.[8] Proline is regarded as an effective and versatile small-molecule "enzyme"[9] that catalyzes a wide range of organic transformations. However, unlike enzymatic reactions in nature that occur in water, enantioselective organocatalytic processes have typically been carried out in organic solvents. For example, proline-catalyzed aldol reactions[10] can only afford high enantioselectivity in solvents such as dimethylsulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF). The presence of a large amount of water has typically resulted in the formation of products with low or no enantioselectivity.[11] DMSO or DMF as solvents make the proline-catalyzed reaction workup and catalyst recycling difficult. In nature, aldolase enzymes catalyze the direct aldol reaction in water with excellent stereocontrol the reaction proceeds in a hydrophobic pocket to diminish contacts between bulk water and the reaction transition state.[8f] We therefore wanted to expand the concept of a hydrophobic pocket in water for the asymmetric assembly of direct aldol reactions under environmentally benign conditions.

The field of enantioselective organocatalysis in water afforded further unsatisfactory results[11–14] until recently when breakthrough contributions were made by the groups of Barbas[15b,c] Takabe,[15b,c] and Hayashi.[15d,e] They used proline-derived catalysts in the presence of water to demonstrate the direct asymmetric aldol reaction and the Michael reaction with high yields and with excellent diastereoselectivities and enantioselectivities. Thereafter, many organocatalysts have been designed for the direct aldol reaction and other reactions in aqueous conditions on the basis of the so-called "enamine catalysis", a process that mimics type I aldolases.[15,16] It should be noted that with all of the organocatalysts and reaction conditions, a large excess of ketone is employed. When an expensive ketone is used in large excess, it is not reassuring for the direct aldol reaction with atom-economical "green" credentials. In particular, the use of less-volatile ketones in large excess, for example, cyclohexanone (b.p. 155 °C), complicates the reaction workup and product purification.[13f] A highly efficient, stereoselective, and atom-economical reaction in water is currently a sought-after goal in chemistry.[17] Herein, we describe a *tert*-butylphenoxyproline (**4**)/cyclodextrin system (Figure 1) for highly efficient asymmetric synthesis in water. We envision that cyclodextrins mimic enzymes to form a hydrophobic pocket in water,[17f] which can concentrate the organocatalyst and reactants, assemble substrates, diminish contacts between bulk water

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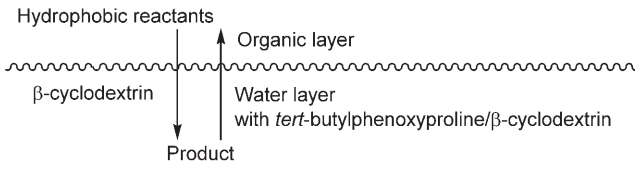
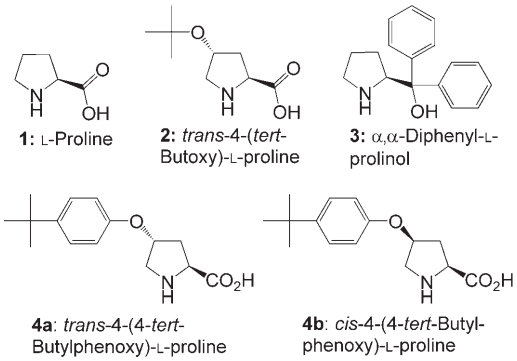


Figure 1. The asymmetric catalytic system in water mediated by water-soluble β-cyclodextrins.

and the reaction transition states, and thus alter the reaction mechanism and stereochemistry. Initial focus is on the atom-economical aldol reaction using stoichiometric amounts of cyclohexanone and various aryl aldehydes.

The catalytic activities of **1**–**4** for the asymmetric direct aldol reaction were investigated by performing a model



reaction using stoichiometric amounts of benzaldehyde and cyclohexanone, and the results are summarized in Table 1. List and co-workers reported that the reaction of benzaldehyde in DMSO/cyclohexanone (4:1 v/v) catalyzed by proline

Table 1: Screening of organocatalysts for the direct aldol reaction of cyclohexanone with benzaldehyde on water.[a]

Entry	Catalyst	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][c]
1	**1**	0		
2[d]	**1**	67	70:30	68
3	**2**	8	87:13	98
4	**3**	0		
5	**4b**	70	93:7	87
6[d]	**4b**	59	74:26	81
7	**4a**	78	90:10	92
8[d]	**4a**	48	78:22	59
9[e]	**4a**	46	67:33	64
10[f]	**4a**	82	84:16	91
11[g]	**4a**	82	83:17	92
12[h]	**4a**	82	87:13	98

[a] Reaction conditions: benzaldehyde (5.0 mmol), cyclohexanone (5.0 mmol), catalyst (2 mol%, 0.1 mmol), and water (2.0 mL), at room temperature for 48 h. [b] Combined yield of isolated diastereomers. [c] Determined by ^{1}H NMR spectroscopy and HPLC on a chiral stationary phase. [d] 2.0 mL of $[BMIM]^+[NTf_2]^-$ used as solvent. [e] 2.0 mL of cyclohexanone used as solvent. [f] 2.0 mL of saturated brine used as solvent. [g] 2.0 mL of aqueous lithium chloride solution (200 mol% LiCl) used as solvent. [h] 2.0 mL of aqueous guanidine hydrochloride solution (200 mol% $NH_2C(NH)NH_2{\cdot}HCl$) used as solvent.

(30 mol%) at room temperature for 4 days afforded the aldol product in 85% yield with no diastereoselectivity and moderate enantioselectivity (85% *ee* for the *anti* isomers and 76% *ee* for the *syn* isomers).[18] When water was used to replace the organic solvent (DMSO), no reaction progress was detected after 2 days for the stoichiometric reaction (Table 1, entry 1), probably because proline is dissolved in the water phase and thereby separated from the hydrophobic reactants of cyclohexanone and benzaldehyde. Under the same conditions, catalyst **2** with a hydrophobic *tert*-butyl group was not effective, and a low conversion (8% yield) was observed (Table 1, entry 3). However, encouraged by the excellent enantioselectivity achieved with catalyst **2** (98% *ee* for the *anti* isomer), we investigated catalyst **4**, which has an even more hydrophobic *tert*-butylphenyl moiety, and it exhibited greatly improved catalysis "on water"[19] (Table 1, entries 5 and 7). The organocatalyst **4** is not soluble in water, because of the highly hydrophobic *tert*-butylphenyl moiety. The role of water is to bring the hydrophobic catalyst and reactants closer together, and to form tiny "oil" droplets floating on water during the vigorous stirring of the reaction mixture. We reasoned that the association of **4** with hydrophobic reactants in the tiny "oil" droplets was required to carry out the reaction on water, so that bulk water was largely excluded from the reaction transition states. This reaction afforded the aldol products in good yield and with high stereoselectivity. When the same volume of cyclohexanone was used to replace water as the solvent to produce a homogeneous phase (Table 1, entries 7 and 9), the reaction slowed down remarkably, and a significant drop in both diastereoselectivity and enantioselectivity was observed. In the solvent-free stoichiometric reaction, a comparable yield was achieved for the aldol product but with significantly decreased enantioselectivity and diastereoselectivity relative to the same reaction on water (compare Table 2, entry 1 and Table 1, entry 7). It seemed that the concentration of organocatalyst determined the reaction rate and that a large excess of ketone was not advisable for the direct aldol reaction as it decreased the yield. When the reaction was conducted on water, both the enantio- and diastereoselectivities increased greatly, thus indicating that water participated in the reaction transition states through hydrogen bonding and enhanced the stereoselectivity of the reaction.[19c] The stoichiometric aldol reaction was significantly improved after only 50 mol% water was introduced; the corresponding product was obtained in a good yield with both high diastereoselectivity and enantioselectivity (Table 2, entries 1 and 2). Further addition of water (up to 300 mol% or in a large volume of water, Table 2, entries 2–5 and Table 1, entry 7) did not decrease the yield or stereoselectivity. The carboxylic acid function seemed to be important for the asymmetric catalysis, as the hydrophobic

Table 2: Effect of water on the solvent-free reaction of cyclohexanone with benzaldehyde catalyzed by **4a**.[a]

Entry	H_2O [mol%]	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][c]
1	0	85	69:31	61
2	50	84	89:11	94
3	100	84	90:10	91
4	200	84	90:10	94
5	300	83	89:11	93

[a] Reaction conditions: benzaldehyde (5.0 mmol), cyclohexanone (5.0 mmol), **4a** (2 mol%, 0.1 mmol), and various amounts of added water, at room temperature for 48 h. [b] Combined yield of isolated diastereomers. [c] Determined by ^{1}H NMR spectroscopy and HPLC on a chiral stationary phase.

catalyst **3** did not afford any products on water (Table 1, entry 4). Switching to the ionic liquid $[BMIM]^+[NTf_2]^-$ as solvent (Table 1, entries 2, 6, and 8) made the reaction a homogeneous phase, but did not lead to either good yield or stereoselectivity (BMIM = 1-butyl-3-methyimidazolium, NTf_2 = bis(trifluoromethylsulfonyl)imide). Salt effects on the reaction were investigated (Table 1, entries 10–12), and a remarkably high *ee* value was achieved in the aqueous guanidine hydrochloride solution (98% *ee* for the *anti* isomer).

Encouraged by the excellent enantioselectivity achieved with the "salt-in" effect of guanidine hydrochloride (Table 1, entry 12), we used surfactants to generate micelles to associate the hydrophobic organocatalyst and reactants in water. Excellent diastereoselectivity and enantioselectivity were achieved in water mediated by different types of surfactants (Table 3, entries 1–3). However, the applicability of the method is limited by the problematic workup of the emulsified reactions, as separation of the aqueous and organic phases is difficult.[20]

Table 3: The direct aldol reaction of cyclohexanone with benzaldehyde in water mediated by surfactants and cyclodextrin.[a]

Entry	Catalyst	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][c]
1[d]	**4a**	17	92:8	99
2[e]	**4a**	67	91:9	98
3[f]	**4a**	72	93:7	98
4[g]	**4b**	70	93:7	94
5[g]	**1**	0		
6[g]	**4a**	78	90:10	96
7[h]	**4a**	15	90:10	98

[a] Reaction conditions: benzaldehyde (5.0 mmol), cyclohexanone (5.0 mmol), catalyst (2 mol%, 0.1 mmol), surfactant (20 mol%) or sulfated β-cyclodextrin (10 mol%), and water (2.0 mL), at room temperature for 48 h. [b] Combined yield of isolated diastereomers. [c] Determined by ^{1}H NMR spectroscopy and HPLC on a chiral stationary phase. [d] Mediated by the anion-type surfactant sodium dodecyl sulfate. [e] Mediated by the cation-type surfactant hexadecyltrimethyl ammonium bromide. [f] Mediated by the zwitterion-type surfactant *N*-dodecyl-*N*,*N*-dimethyl-3-ammonio-1-propanesulfonate. [g] Mediated by sodium sulfated β-cyclodextrin. [h] Homogeneous reaction: cyclohexanone (0.5 mmol), benzaldehyde (0.5 mmol), **4a** (20 mol%, 0.1 mmol), sulfated β-cyclodextrin (300 mol%), and water (5.0 mL), at room temperature for 48 h.

It is well-documented that cyclodextrin (CD) can act as an inverse phase-transfer catalyst to allow water-insoluble molecules to react in an aqueous medium.[21] Although the hydrophobic reactants benzaldehyde and cyclohexanone could be transferred into the water phase by sulfated β-CD, no product was detected from the aldol reaction using L-proline as the catalyst (Table 3, entry 5), because the reactants were kept in the hydrophobic cavities of the CDs and were separated from the L-proline catalyst, which resided in water. To our delight, stoichiometric amounts of cyclohexanone and benzaldehyde were catalyzed by **4** using sulfated β-CD as an inverse phase-transfer reagent in water and afforded the aldol product in good yields and with both high enantioselectivity and diastereoselectivity (Table 3, entries 4 and 6). β-CD binds 4-*tert*-butylphenol in water with an association constant of $3.6 \times 10^4\ M^{-1}$.[22] The strong inclusion complex is hydrophobic and results from the association of the *tert*-butylphenyl moiety with the hydrophobic cavity of β-CD. Therefore, **4** may strongly bind sulfated β-CD in water and generate the enamine intermediate and transition states in situ from reactants in the hydrophobic pocket formed by the CD. In the above reactions, only 10 mol% of sulfated β-CD was applied as an inverse phase-transfer reagent, and the reaction system was not homogeneous, but rather formed two phases. The question arises: Does the aldol reaction occur in the tiny "oil" phase on water, in the cavities formed by the CDs in water, or both? To address this question, the exact location of catalyst **4** must be determined. We examined the water solubility of **4** by adding 13.2 mg of **4a** (0.05 mmol) to 2 mL of D_2O, which produced a suspension. After 0.10 mmol of sodium sulfated β-CD was added to the mixture, it formed a clear homogeneous solution. The partitioning of **4a** between organic solvents and water was examined by extraction of the above solution with 2 mL of $CDCl_3$. ^{1}H NMR spectroscopic analysis of both $CDCl_3$ and D_2O phases demonstrated that there was no detectable **4a** in the $CDCl_3$ organic phase. It is concluded that the aldol reaction occurred in the water phase where organocatalyst **4** resided with sulfated β-CD. Furthermore, a homogeneous reaction was achieved using 300 mol% of sulfated β-CD to transfer all of the organocatalyst and reactants in a large amount of water. This reaction exhibited excellent enantioselectivity and high diastereoselectivity but a low yield (Table 3, entry 7). The yield obtained in this homogeneous aldol reaction was low because the catalyst and reactants were sequestered in separate CDs and were diluted in water.

A series of aldehydes was evaluated to examine the scope of aldol reactions using this asymmetric catalytic system in water (Table 4). The sulfated β-CD acted only as an inverse phase-transfer reagent. It could not catalyze the aldol reaction (Table 4, entry 3) without binding with **4a**, which generated the enamine intermediate with the ketone and attacked the

Table 4: The asymmetric aldol reactions of cyclohexanone with various aryl aldehydes in water mediated by cyclodextrin.[a]

Entry	Aryl aldehyde	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][c]
1	benzaldehyde	78	90:10	96
2	2-nitrobenzaldehyde	97	>99:1	>99
3[d]	2-nitrobenzaldehyde	0		
4	3-nitrobenzaldehyde	97	96:4	>99
5	4-nitrobenzaldehyde	100	96:4	>99
6	4-chlorobenzaldehyde	80	95:5	99
7	4-bromobenzaldehyde	92	93:7	99
8	4-trifluoromethylbenzaldehyde	100	94:6	>99
9	4-methylbenzaldehyde	65	88:12	98
10	2-methylbenzaldehyde	62	92:8	96
11	2-furaldehyde	71	84:16	98

[a] Reaction conditions: aryl aldehyde (5.0 mmol), cyclohexanone (5.0 mmol), **4a** (2 mol%, 0.1 mmol), sulfated β-cyclodextrin (10 mol%), and water (2.0 mL), at room temperature for 48 h. [b] Combined yield of isolated diastereomers. [c] Determined by ^{1}H NMR spectroscopy and HPLC on a chiral stationary phase. [d] Without catalyst **4a**.

aldehyde with high stereoselectivity. In general, regardless of the electronic nature of the aromatic aldehydes, excellent stereoselectivities were obtained. After the reaction was complete, the products were obtained by simple filtration or phase separation. No trace of organocatalyst **4a** could be detected in the products by ^{1}H NMR spectroscopy, thus indicating that *tert*-butylphenoxyproline **4** was trapped by sulfated β-CD in the water phase. Notably, the extremely high stereoselectivity (> 99 % enantioselectivity and > 99 % diastereoselectivity) and almost quantitative yield were achieved in stoichiometric aldol reactions of cyclohexanone and strong electron-withdrawing aromatic aldehydes with a small amount of catalyst **4a** (2 mol %).

In conclusion, we have developed an asymmetric catalytic system in water mediated by sulfated β-CD which can bind an organocatalyst of *tert*-butylphenoxyproline and associated hydrophobic reactants. This system demonstrates up to > 99 % enantioselectivity and > 99 % diastereoselectivity and near quantitative yields for stoichiometric direct aldol reactions of cyclohexanone and aryl aldehydes. When the strong electron-withdrawing substituted aryl aldehydes were subjected to the asymmetric catalytic system, simple filtration or phase separation afforded the highly enantiopure aldol products in near quantitative yields. Additional studies to elucidate the full scope of this asymmetric catalytic system in water and the related reaction mechanisms are currently under investigation and will be reported in due course.

Experimental Section

The general procedure for the aldol reaction in water mediated by sulfated β-cyclodextrin: Cyclohexanone (0.52 mL, 5 mmol) and aryl aldehyde (5 mmol) were added to a solution of organocatalyst (2 mol %, 0.1 mmol) and sulfated β-cyclodextrin (10 mol %) in water (2.0 mL), and the reaction mixture was stirred at room temperature for 48 h. Filtration or liquid phase separation afforded the crude product, which was either pure or further purified by silica gel flash chromatography (hexanes/EtOAc). The *anti*/*syn* ratio (diastereoselectivity) and *ee* values (enantioselectivity) were determined by ^{1}H NMR spectroscopy and HPLC on a chiral stationary phase. HPLC conditions: Chiralpak IB (15 cm × 4.6 mm, Chiral Technologies, Inc.), 1 % v/v *i*PrOH in heptane as mobile phase, 1 mL min^{-1} flow rate, 213 nm UV detector.

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