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Highly Efficient Threonine-Derived Organocatalysts for Direct Asymmetric Aldol Reactions in Water

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Abstract: The introduction of siloxy groups at the hydroxy function of natural threonine resulted in efficient hydrophobic organocatalysts, which could efficiently catalyze the direct aldol reactions of both cyclic and acyclic ketones with aromatic aldehydes in water with excellent enantiomeric excess.

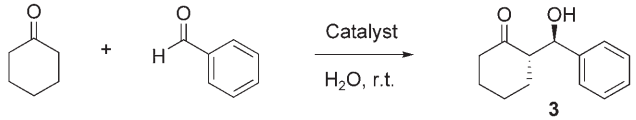
Keywords: aldol reaction; asymmetric catalysis; hydrophobic effect; organic catalysis; water

The asymmetric aldol reaction[1] is one of the most powerful methods for constructing carbon-carbon bonds in organic synthesis. Asymmetric organocatalysis has progressed at an astonishing pace in recent years.[2] A wide range of small organic molecules, including proline[3] and various other chiral pyrrolidine derivatives,[4] have been shown to be efficient catalysts for asymmetric aldol reactions. Proline and its analogues are believed to catalyze the direct aldol reaction *via* the enamine mechanism, which mimics the action of natural class I aldolase. However, the vast majority of organocatalytic reactions would yield racemic products if the reactions took place in water.[5] Water is an ideal solvent for chemical reactions due to its low cost, safety and environmentally benign nature. Since the seminal contribution from Breslow on the unusual rate acceleration of the Diels–Alder reaction in water,[6] aqueous organic chemistry has gained more and more recognition.[7] Recently, it was shown by the groups of Takabe, Barbas and Hayashi that the direct asymmetric aldol reaction and the Michael reaction could be catalyzed by the proline-derived hydrophobic catalysts in water.[8] Cordova et al. demonstrated that acyclic amino acids or small peptides could effect direct aldol reactions in an aqueous system.[9] We recently reported the tryptophan-promoted direct aldol reactions between cyclic ketones and aromatic aldehydes in water.[10] In this communication, we disclose our findings that simple natural threonine derivatives are excellent organocatalysts for the direct aldol reactions *in aqua*.

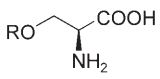
For the design of novel catalysts, we are particularly interested in the organocatalysts that can be easily derived from the chiral pool. We hypothesized that incorporation of a hydrophobic group into a natural amino acid could generate a hydrophobic organocatalyst, which may interact favorably with organic substrates in aqueous media due to its hydrophobic nature.[11] With the properly designed catalysts, water can be sequestered from the transition state and high stereocontrol may be expected. This approach is particularly attractive in view of the ready availability of natural amino acids and of the various chiral structural scaffolds that they can offer.

Serine and threonine seem to be good chiral structural scaffolds, as the hydroxy group allows for the easy attachment of various hydrophobic groups. We prepared bulky siloxy derivatives of serine and threonine, and screened these catalysts in the direct aldol reactions between cyclohexanone and benzaldehyde in water (Table 1). Natural serine or threonine, as well as other hydrophobic amino acids such as valine, leucine and isoleucine were not efficient organocatalysts (entries 1 to 5). The incorporation of hydrophobic siloxy groups into serine and threonine resulted in effective organocatalysts capable of catalyzing the direct aldol reaction in water (entries 6 to 11). Among the three siloxy derivatives, the catalysts containing the *tert*-butyldimethylsilyl (TBS) group gave the best yield and enantioselectivity. The threonine derivative **2c** turned out to be the most efficient catalyst. With 2 mol% catalyst loading, the desired aldol product was obtained in about 60% yield and with 96% *ee* in less than two days (entry 12). When the reaction was carried out neat, both yield and diastereoselectivity decreased (entry 13).

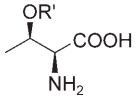
Table 1. Screening of organocatalysts.[a]



Catalysts studied:



1a (R = TIPS)
1b (R = TBDPS)
1c (R = TBS)



2a (R' = TIPS)
2b (R' = TBDPS)
2c (R' = TBS)

Entry	Catalyst	Catalyst Loading [%]	Time [h]	Yield[b] [%]	*anti:syn*[c]	*ee*[d] [%]
1	L-Ser	10	48	<5[e]	-	-
2	L-Thr	10	48	<5[e]	-	-
3	L-Val	10	48	<5[e]	-	-
4	L-Leu	10	48	<10[e]	-	-
5	L-Ile	10	48	<10[e]	-	-
6	**1a**	10	48	49	4:1	42
7	**1b**	10	24	23	2:1	13
8	**1c**	10	24	65	7:1	89
9	**2a**	10	36	41	3:1	13
10	**2b**	10	36	34	2:1	10
11	**2c**	10	18	66	8:1	96
12[f]	**2c**	***2***	***45***	***58***	***8:1***	***96***
13[g]	**2c**	2	45	40	5:1	96

[a] The reactions were performed with benzaldehyde (0.5 mmol), cyclohexanone (2.5 mmol) and catalyst (0.05 mmol) in water (5 mmol) at room temperature.
[b] Isolated yield.
[c] The *anti* to *syn* ratio was determined by ^{1}H NMR analysis of the crude product.
[d] The *ee* value of the *anti*-isomer was determined by chiral HPLC analysis.
[e] Estimated by ^{1}H NMR analysis of the crude mixture.
[f] Aldehyde/cyclohexanone/water/catalyst ratio was 1/2/1/0.02.
[g] The reaction was performed neat.

The hydrophobic catalyst **2c** proved to be remarkably effective (Table 2). In the presence of only 2 mol% of catalyst **2c**, most reactions between cyclohexanone and various aromatic aldehydes afforded the aldol products in excellent yield and nearly perfect *ee in aqua*. For the substrates with electron-donating groups, a slightly higher catalyst loading (5%) was needed to promote the reaction rate (entries 9 and 10).

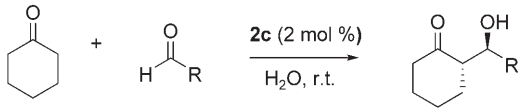
We next attempted to broaden the substrate scope to include acyclic and functionalized ketones (Table 3). Hydroxyacetone is a useful donor substrate as its aldol reactions provide an easy access to diols.[12] The direct aldol reaction between hydroxyacetone and *para*-nitrobenzaldehyde in water was ineffective (entry 1), this is not surprising since hydroxyacetone is rather hydrophilic. Protection of the free hydroxy function with the TBS group furnished a hydrophobic substrate, which then efficiently reacted with the aldehyde *in aqua*. All three threonine-derived hydrophobic catalysts were effective, affording the aldol products in excellent enantiomeric excess (entries 2 to 4). The reactions are also applicable to other aromatic aldehydes (entries 6 to 8). Currently, acceptors in our method are limited to aryl aldehydes, since we were unable to obtain satisfactory results with aliphatic aldehydes.

The catalytic efficiency of our catalysts is noteworthy. Such catalysts may be very suitable for large-scale preparations.[14] Moreover, the hydrophobic catalysts reported herein may be recycled and reused (Table 4).[15] For instance, the recycled **2c** was able to catalyze the aldol reactions in up to three runs without any decrease in yield and stereoselectivity.

Although the reaction mechanism is unclear at the moment, the transition states of the reactions described in this account may be similar to the one depicted in our previous report.[10] The hydrophobic siloxy groups were expected to stack closely to the aromatic ring of the substrates due to the hydrophobic interactions. The carboxylic acid group of the catalyst facilitates the formation of a defined transition state by forming hydrogen bonds with the substrate.[16]

In summary, we have developed a series of highly efficient hydrophobic catalysts for direct aldol reactions in water by the simple derivatization of natural threonine. The reactions described in this report are highly enantioselective, environmentally benign and

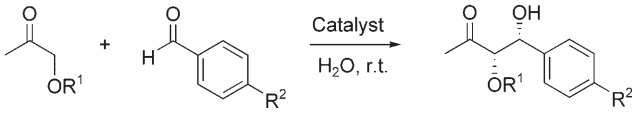
Table 2. Organocatalyst **2c**-catalyzed direct aldol reactions in water.[a]



Entry	Product	Time [h]	Yield[b] [%]	*anti*:*syn*[c]	*ee*[d] [%]
1	**4** (R = *p*-NO_2-C_6H_4)	20	99	10:1	96
2[e]	**4** (R = *p*-NO_2-C_6H_4)	24	99	4:1	96
3	**5** (R = *o*-NO_2-C_6H_4)	24	97	19:1	99
4	**6** (R = *m*-NO_2-C_6H_4)	24	95	11:1	99
5	**7** (R = *p*-CN-C_6H_4)	48	97	5:1	96
6	**8** (R = *p*-Br-C_6H_4)	48	98	5:1	95
7	**9** (R = 2-naphthyl)	48	82	9:1	96
8	**10** (R = 1-naphthyl)	48	56	4:1	97
9[f]	**11** (R = *p*-OMe-C_6H_4)	48	54	5:1	93
10[f]	**12** (R = *m*-OMe-C_6H_4)	48	71	5:1	91

[a] The reactions were performed with aldehyde (1 mmol), cyclohexanone (2 mmol) and **2c** (0.02 mmol) in water (1 mmol) at room temperature.
[b] Isolated yield.
[c] The *anti* to *syn* ratio was determined by ^{1}H NMR analysis of the crude product.
[d] The *ee* value of the *anti*-isomer was determined by chiral HPLC analysis.
[e] The reaction was carried out neat.
[f] 5 mol% catalyst was used.

Table 3. The direct aldol reactions of hydroxyacetone with various aromatic aldehydes in water.[a]



Entry	Product	Catalyst/Loading [%]	Time [h]	Yield[b] [%]	*anti*:*syn*[c]	*ee*[d] [%]
1	**13** (R^1 = H, R^2 = NO_2)	**2c**/10	96	< 5	-	-
2	**14** (R^1 = TBS, R^2 = NO_2)	**2c**/10	18	91	1:7	97
3	**14**	**2b**/10	6	92	1:8	98
4	**14**	**2a**/10	4	95	1:7	97
5	**14**	**2b**/2	6	92	1:6	95
6	**15** (R^1 = TBS, R^2 = CN)	**2b**/2	23	91	1:7	96
7	**16** (R^1 = TBS, R^2 = H)	**2b**/5	20	76	1:3	91
8	**17** (R^1 = TBS, R^2 = Cl)	**2b**/2	30	80	1:4	92

[a] The reactions were performed with aldehyde (0.25 mmol), hydroxyacetone (0.5 mmol) in water (3.75 mmol) at room temperature.
[b] Isolated yield.
[c] The *anti* to *syn* ratio was determined by ^{1}H NMR analysis of the crude product.
[d] The *ee* value of the *syn*-isomer was determined by chiral HPLC analysis, the absolute configuration was determined by chiral HPLC analysis of desilylated **16**, comparing with the literature data.[13]

operationally simple. Our findings represent a novel application of primary amino acids as asymmetric organocatalysts in aqueous organic reactions. Mechanistic studies, the development of catalytic systems applicable to a broader range of substrates and the extension of our catalysts to other organic transformations are currently being investigated in our laboratory, and will be reported in due course.

Experimental Section

Representative Procedure

To a mixture of catalyst **2c** (4.6 mg, 0.02 mmol) and cyclohexanone (0.2 mL, 2 mmol) were added benzaldehyde (102 μL, 1 mmol) and water (18 μL, 1 mmol). The resulting mixture was stirred at room temperature under an atmosphere of argon for 45 h. The reaction mixture was diluted with ethyl acetate and filtered through silica gel (1 g) to

Table 4. The recycling of catalyst **2c**.[a]

Run	Time [h]	Yield[b] [%]	*anti*:*syn*[c]	*ee*[d] [%]
1	20	60	8:1	96
2	24	61	7:1	97
3	36	63	7:1	95
4	48	33	5:1	96

[a] The reactions were performed with benzaldehyde (4 mmol), cyclohexanone (16 mmol) and **2c** (0.2 mmol) in water (4 mmol) at room temperature.
[b] Isolated yield.
[c] The *anti* to *syn* ratio was determined by ^{1}H NMR analysis of the crude product.
[d] The *ee* value of the *anti*-isomer was determined by chiral HPLC analysis.

remove the catalyst. The solvent was removed under vacuum to afford the crude product as a pale yellow oil, which was purified by column chromatography (ethyl acetate:hexane = 1:10 to 1:5) to afford **3** as a colorless oil; yield: 117 mg (58%); *anti*:*syn* = 8:1. The *ee* of the *anti* isomer was 96% [by chiral HPLC analysis using a chiralcel AS-H column, λ = 210 nm, *i*-PrOH:hexane = 5:95, 0.5 mL min^{-1}, t_R = 33.45 min (major), t_R = 35.58 min (minor)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25–1.30 (m, 1H), 1.59–1.90 (m, 4H), 2.05–2.20 (m, 1H), 2.35–2.75 (m, 3H), 4.80–4.85 (d, J = 8.4 Hz, 1H), 7.30–7.45 (m, *5*H).

Supporting Information

General methods, procedures for the preparation of the substrates and the ^{1}H NMR of all the final products are available as Supporting Information.

Acknowledgements

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[14] In an illustrative example, in the presence of 40 mg of **2c**, 2 g of compound **4** with 96% *ee* was obtained after a single recrystallization.
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