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Highly Enantioselective Organocatalytic Direct Aldol Reaction in an Aqueous Medium†

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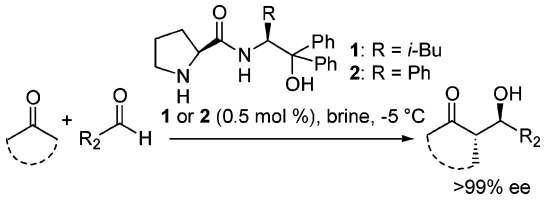
ABSTRACT



We have demonstrated that small organic molecules 1 and 2 catalyzed the direct aldol reaction of both acyclic and cyclic ketones with different aldehydes in an excess of water/brine. Excellent enantioselectivities up to >99% and diastereoselectivities up to 99% with very good yields were obtained by using much lower catalyst loadings (0.5 mol %).

The enantioselective aldol reaction catalyzed by small organic molecules is an important C−C bond formation reaction for which excellent enantioselectivities have been achieved.[1] The reaction is presumed to proceed via an enamine intermediate, mimicking nature, where the type I aldolase enzyme[2] catalyzes the aldol reaction in water. It would be a win−win situation from a green chemistry perspective if high enantiocontrol is achieved using small organic molecules in water.[3,4] Early studies with small organic molecules in an aqueous medium had limited success until recently when Barbas[5] and Hayashi[6] independently reported efficient proline-derived chiral catalysts which catalyzed the aldol reaction with high enantiocontrol in the presence of a large excess of water.[7] Most of the studies have been done with 10 mol % catalyst loading except in one example where Hayashi has shown that the catalyst loading can be reduced to 1 mol %, but at the cost of a longer reaction time (2 days). Therefore, there is a great need for efficient chiral organocatalysts, which can work at a lower

† This paper is Dedicated to Prof. (Dr.) Lutz F. Tietze, Institut für Organische und Biomolekulare Chemie Universität Göttingen, Germany, on his 65th birthday.

(1) For selected reviews on aldol and other related reactions using asymmetric organocatalysis, see: (a) List, B. *Chem. Commun*. **2006**, 819. (b) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed. Engl*. **2004**, *43*, 5138. (d) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580. (e) List, B. *Acc. Chem. Res.* **2004**, *37*, 548. (f) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y.; Houk, K. N. *Acc.Chem. Res.* **2004**, *37*, 558.

(2) Heine, A.; Desantis, G.; LuZ, J. G.; Mitchell, M.; Wong, C.-H.; Wilson, I. A. *Science* **2001**, *294*, 369.

(3) For a very interesting discussion on whether this kind of reaction should be called "in water", "on water", "in the presence of water", or "concentrated organic phases", see: (a) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 8100. (b) Hayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8103. (c) Blackmond, D. G.; Armstrong, A.; Coombe, V.; Wells, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 2.

(4) The above phrases in using water for the reaction are a matter of semantics. However, we prefer to use "in an aqueous medium" for our reactions.

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(6) (a) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958. (b) Hayashi, Y.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5527.

(7) For some recent selected references on aldol reaction in water via asymmetric organocatalysis, see: (a) Guizzetti, S.; Benaglia, M.; Raimondi, L.; Celentano, G. *Org. Lett.* **2007**, *9*, 1247. (b) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett*. **2006**, *8*, 4417. (c) Jiang, Z.; Liang, Z.; Wu, X.; Lu, Y. *Chem. Commun*. **2006**, 2801. (d) Dziedzic, P.; Zou, W.; Hafren, J.; Cardova, A. *Org. Biomol. Chem.* **2006**, *4*, 38. (e) Chimni, S. S.; Mahajan, D. *Tetrahedron: Asymmetry* **2006**, *17*, 2108. (f) Guillena, G.; Hita, M. D. C.; Najera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1493. (g) Fu, Y.-Q.; Li, Z.-C.; Ding, L.-N.; Tao, J.-C.; Zhang, S.-H.; Tang, M.-S. *Tetrahedron: Asymmetry* **2006**, *17*, 3351. (h) Pihko, P. M.; Laurikainen, K. M.; Usano, A.; Nyberg, A. I.; Kaavi, J. A. *Tetrahedron* **2006**, *62*, 317.

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loading without affecting the enantioselectivity and the reaction time. The catalysts should also have a wide substrate scope, with respect to both ketones and aldehydes. Herein, we wish to disclose such small organic molecules which are very efficient for enantioselective aldol reaction in water/brine.

We have recently reported that L-proline-derived organocatalysts **1** and **2** (Figure 1) are very effective in an organic

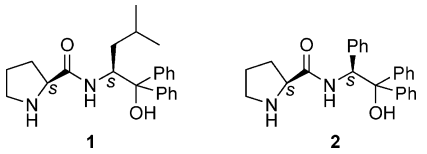
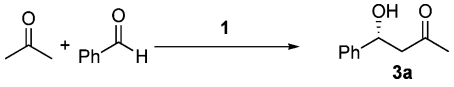


Figure 1. Organocatalysts evaluated in the direct aldol reaction.

medium for enantioselective direct aldol reaction between acetone and aldehydes (under neat conditions).[8] Due to environmental concern, water should be an ideal medium for any organic reaction.[9] While working in an area for development of new water-compatible chiral organocatalysts, we discovered that catalysts **1** and **2** gave extraordinary results for the direct aldol reaction in an aqueous medium.

At the outset, aldol reaction of acetone (2 mmol) and benzaldehyde (0.5 mmol) was studied by using different loading of the catalyst **1** (10−0.5 mol %) in 0.5 mL of water/brine (Table 1). It was observed that yields and ee's were

Table 1. Optimization of Reaction Conditions



entry	catalyst mol %	solvent	temp (°C)	time (h)	% yield[a]	% ee[b]
1	10	water	rt	1.5	75	80
2	10	brine	rt	2	81	86
3	2	water	rt	3	76	77
4	2	brine	rt	2	80	94
5	0.5	water	rt	8	75	95
6	0.5	brine	rt	5	78	97
7	0.5	brine	10	7	75	>99
8	0.5	brine	−5	10	72	>99
9	0.5	brine	−10	12	70	>99
10[c]	0.5	brine	10	5	80	67
11[c]	0.5	brine	−5	10	78	86
12[c]	0.5	brine	−10	12	70	87

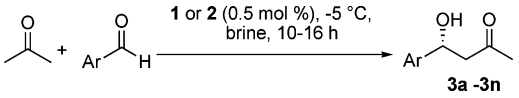
[a] Isolated yields. [b]The ee's were determined by HPLC using Chiralpak AD-H columns. [c]4-NO_2-benzaldehyde was used as substrate.

superior in brine to those in water. With 2 mol % of the catalyst in brine at room temperature, the reaction was complete in 2 h and the product was obtained in 80% yield and 94% ee (Table 1, entry 4). Reducing the catalyst loading to 0.5 mol %, the reaction took a little longer time (5 h), but the ee increased to 97% (entry 6).

It was further observed that the enantioselectivity was >99% on lowering the temperature to 10 °C (entry 7). Reaction of acetone was studied with a more reactive aldehyde such as 4-nitro-benzaldehyde (entries 10−12). In this particular case, we could obtain only up to 87% ee. To show the practicality of the method, the reaction was tested at a large scale. Acetone (2.77 mL, 37.7 mmol) was allowed to react with benzaldehyde (0.955 mL, 9.4 mmol) by using the catalyst **1** (17 mg, 0.5 mol %) in brine (9.5 mL) at −5 °C. The reaction was complete in 24 h, and the aldol product was obtained in 68% yield and 98.5% ee.

Having optimized the reaction conditions for enantioselective aldol reaction in brine, it was extended to other substrates using both the catalysts, **1** and **2**. A variety of aromatic aldehydes were tested for the reaction using acetone as a donor (Table 2). In most of the cases, excellent enantioselectivity (>99% ee) was obtained.

Table 2. Screening of Different Aromatic Aldehydes with Acetone



			% yield[a]		% ee[b]	
entry	Ar	product	**1**	**2**	**1**	**2**
1	Ph	**3a**	72	83	>99	>99
2	2-Cl-Ph	**3b**	78	80	98	>99
3	3-F-Ph	**3c**	80	85	>99	>99
4	2,5-Di-F-C_6H_4	**3d**	75	80	99	>99
5	3-Cl-Ph	**3e**	73	85	98	99
6	2-Cl-6-F-C_6H_4	**3f**	79	84	>99	>99
7	4-F-Ph	**3g**	75	80	>99	>99
8	3-OMe-Ph	**3h**	72	85	>99	>99
9	4-NO_2-Ph	**3i**	78	80	86	85
10	4-CF_3-Ph	**3j**	79	84	99	91
11	3-Br-Ph	**3k**	70	75	99	>99
12	4-OMe-Ph	**3l**	72	75	97	>99
13	3-Me-Ph	**3m**	71	72	>99	>99
14	2-naphthyl	**3n**	73	70	92	84

[a] Isolated yields. [b]The ee's were determined by HPLC using Chiral columns.

Using cyclohexanone as a donor, high diastereoselectivities and excellent enantioselectivities (96−99% ee) were obtained with different aromatic aldehydes (Table 3). Enantioselective aldol reaction was also extended to other ketones as donors and aldehydes as acceptors (Table 4). Along with aromatic aldehydes, aliphatic aldehydes such as isobutyraldehyde and cyclohexancarboxaldehyde also proved to be better acceptors

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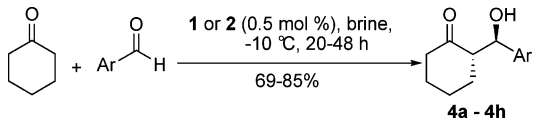
Table 3. Screening of Different Aromatic Aldehydes with Cyclohexanone



			anti/syn[a]		% ee[b] (anti)	
entry	Ar	product	**1**	**2**	**1**	**2**
1	Ph	**4a**	94:6	95:5	>99	>99
2	4-NO_2-Ph	**4b**	86:14	87:13	86	91
3	4-OMe-Ph	**4c**	98:2	96:4	99	91
4	4-CN-Ph	**4d**	97:3	94:6	83	85
5	4-CF_3-Ph	**4e**	96:4	98:2	>99	93
6	4-Cl-Ph	**4f**	99:1	98:2	99	94
7	2-furyl	**4g**	95:5	97:3	95	96
8	2-naphthyl	**4h**	92:8	99:1	95	98

[a] Diastereoselectivities were determined by ^{1}H NMR analysis of the products. [b]The ee's were determined by HPLC using Chiral columns.

(entries 1 and 2). It is gratifying to see that excellent enantioselectivities (99−>99% ee) were obtained in all the cases.

The stereochemical outcome in the above direct aldol reaction catalyzed by **1** and **2** can be explained by a transition state (Figure 2), which is based on a previous model supported by DFT calculations.[8,10] The aldehyde is activated by hydrogen bonding with the NH and OH of the catalyst in a manner such that C−C bond formation takes place from its *re* face. The alternative *si* face is unfavored due to nonbonding interaction between the R_2 group and the hydroxyl group. The presence of *gem*-diphenyl groups at the β-carbon restricts the conformation and makes the hydroxyl group a better hydrogen-bond donor. The model requires formation of an enamine for which there is enough evidence in the literature.[11,12] It has been pointed out that general base catalysis must be minimized to promote enantioselectivity by an enamine mechanism in water.[3a] However, in our case, it appears that reaction takes place under biphasic basic conditions. This can be explained by using a hydrophobic effect where the organocatalyst and substrates assemble in water and sequester the transition state from water.[5] Aggregation of organic molecules excludes water from the organic phase and drives the equilibrium toward enamine

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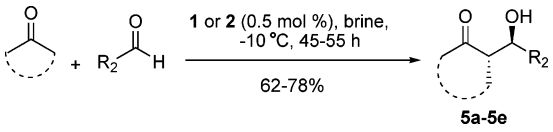
Table 4. Screening of Some Other Ketones and Aldehydes



				anti/syn[a]		% ee[b] (anti)	
entry	ketone	R_2	product	**1**	**2**	**1**	**2**
1	acetone	^{i}pr	**5a**	–	–	>99	>99
2	acetone	cyclohexyl	**5b**	–	–	99	>99
3	-$CH_2CH_2CH_2$-	cyclohexyl	**5c**	94:6	99:1	99	99
4	-CH_2OCH_2-	Ph	**5d**	97:3	95:5	>99	99
5	-CH_2SCH_2-	Ph	**5e**	99:1	94:6	>99	99

[a] Diastereoselectivities were determined by ^{1}H NMR analysis of the products. [b]The ee's were determined by HPLC using Chiral columns.

formation. This is further facilitated by brine (salting-out effect).[13] This helps the reaction to proceed faster because of the concentrated organic phase.

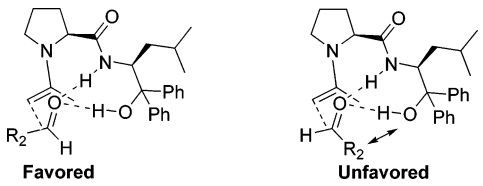


Figure 2. Transition State Models.

In summary, we have successfully reported highly efficient organocatalysts for an asymmetric direct aldol reaction using both cyclic and acyclic ketones and various aldehydes in an aqueous medium. In most of the cases, we have achieved >99% ee by using 0.5 mol % of the catalyst in brine. The added advantage of the catalyst is that it does not require any acid additive to achieve high enantioselectivity.

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Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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