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Organo-catalyzed highly diastereo- and enantio-selective direct aldol reactions in water

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Abstract

The asymmetric direct aldol reactions of a wide scope of aromatic aldehydes, with unmodified ketones in the presence of 1 mol % of organocatalyst prepared from (2*R*,3*R*)-diethyl 2-amino-3-hydroxysuccinate and *trans*-4-hydroxy-L-proline, were performed in water, affording aldol products in high yields with excellent diastereoselectivities of up to >99:1 and enantioselectivities of up to 98%.

Keywords: Water; Organocatalysis; Direct aldol; Diastereo- and enantio-selective

The use of water as a solvent not only makes the reaction environmentally amenable, but much safer to handle since aqueous conditions principally avoid flammable organic solvents and strict anhydrous conditions. The development of efficient water-compatible reactions is of great importance and has received increasing interests.[1] Recently, organo-catalyzed reactions in water[2] have received much attention since Hayashi,[3] Barbas III and Tanaka,[4] independently discovered organo-catalyzed highly enantio-selective direct aldol reactions in pure water. Among them, the organo-catalyzed direct aldol reaction in water is the most studied.[5] However, most of the organo-catalyzed aldol reactions are suffering from the high catalyst loading and large excess of donor that somehow surpasses their commercial application. Herein, we report that as little as 1 mol % of an L-proline amide derivative catalyzes the direct asymmetric aldol reactions between ketones and aromatic aldehydes in water with up to >99:1 dr and 98% ee (see Fig. 1).

Previously, we found that L-proline amides derived from chiral amino alcohols acted as efficient catalysts for the asymmetric direct aldol reaction in aqueous environment[6] as well as in organic solvent.[7] To further investigate the L-proline amide derivatives catalyzed aldol reaction, pure water was used as the solvent. Interestingly, all of these

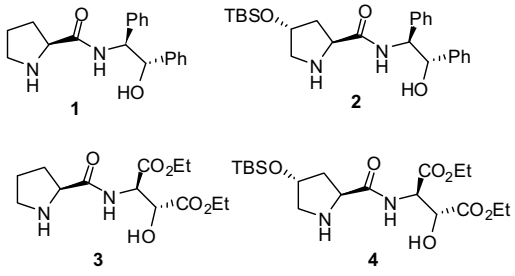

Fig. 1. Organocatalysts evaluated in this study.

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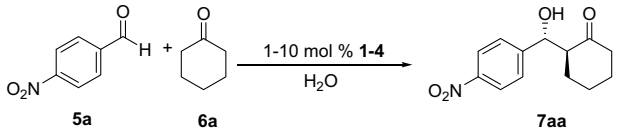
Table 1
Direct aldol reaction of cyclohexanone with 4-nitrobenzaldehyde catalyzed by L-proline amide derivatives **1–4** in water[a]



5a **6a** **7aa**

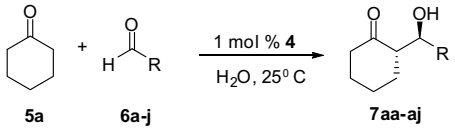
Entry	Catalyst (mol %)	Temperature (°C)	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	**1** (10)	0	24	89	99:1	96
2	**2** (10)	0	24	68	>99:1	93
3	**3** (10)	0	24	41	2:1	94
4	**4** (10)	0	4	95	>99:1	97
5	**4** (10)	25	0.25	99	>99:1	93
6	**4** (2)	25	3	99	>99:1	92
7[e]	**4** (1)	25	5	99	>99:1	94
8	**4** (1)	0	24	93	98:2	95
9[f]	**4** (2)	0	72	75	96:4	95
10[g]	**4** (1)	−5	24	95	84:16	94
11[g]	**4** (1)	−10	30	60	89:11	95

[a] Conditions: **5a** (0.5 mmol) and **6a** (1.0 mmol, 2 equiv) in water (0.5 mL).
[b] Isolated yield.
[c] Determined by ^{1}H NMR of the crude product.
[d] Determined by chiral-phase HPLC analysis.
[e] See Ref. 8.
[f] Donor **6a** (0.5 mmol, 1 equiv) was used.
[g] The reaction was carried out in brine.

L-proline amides are indeed efficient in catalyzing direct aldol reaction in pure water. The direct aldol reactions of cyclohexanone with 4-nitrobenzaldehyde catalyzed by 10 mol % of **1–4** took place smoothly in water with excellent diastereoselectivity and enantioselectivity (Table 1, entries 1–4). Significantly, quantitative yield, excellent diastereoselectivity (>99:1), and enantioselectivity (93%) were obtained by performing the reaction at room temperature for 15 min (Table 1, entry 5). In terms of the reaction rate, diastereoselectivity and enantioselectivity, the prolinamide derivative **4** can be considered the best catalyst. To our delight, by using pure water as the solvent, only 1 mol % of **4** was efficient enough to mediate the aldol reaction in a quantitive yield with an excellent diastereomeric ratio of >99:1 in favor of *anti*-diastereomer as well as a high enantioselectivity of 94% ee (Table 1, entry 7). In contrast to the known reaction using a large excess of donor, only 1 or 2 equiv of donor to the aldehyde was used in this case (Table 1, entry 9). Using brine as the solvent and performing the aldol reaction at low temperature did not improve the enantioselectivity but the yield and diastereoselectivity were sacrificed and a prolonged reaction time was required to ensure a complete conversion (Table 1, entries 10 and 11).

Direct aldol reactions of various substituted benzaldehydes with cyclohexanone were carried out in the presence of 1 mol % **4** under the optimal conditions to examine the scope and limitation. The results are summarized in Table 2. The aldol reactions of both electron-deficient and electron-rich benzaldehydes with cyclohexanone proceeded

Table 2
trans-4-Hydroxy-prolinamide **4** catalyzed direct aldol reactions of **5a** with various aldehydes in water[a]



5a **6a-j** **7aa-aj**

Entry	R	7	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	4-$NO_2C_6H_4$	**7aa**	5	99	>99:1	94
2	3-$NO_2C_6H_4$	**7ab**	8	95	98:2	92
3	2-$NO_2C_6H_4$	**7ac**	10	85	>99:1	95
4	Ph	**7ad**	24	75	>99:1	92
5	4-CN C_6H_4	**7ae**	24	90	96:4	92
6	4-$CF_3C_6H_4$	**7af**	10	93	>99:1	95
7	2,6-$Cl_2C_6H_4$	**7ag**	5	95	>99:1	98
8	4-ClC_6H_4	**7ah**	24	80	>99:1	93
9	4-BrC_6H_4	**7ai**	24	94	>99:1	93
10	4-MeC_6H_4	**7aj**	24	50	>99:1	92

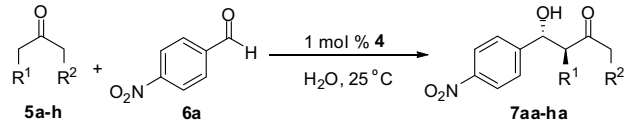
[a] See Ref. 8.
[b] Isolated yield.
[c] Determined by ^{1}H NMR of the crude product.
[d] Determined by chiral-phase HPLC analysis for *anti*-product.

smoothly to give the aldol adducts with excellent diastereoselectivities (up to >99:1) and enantioselectivities (up to 98% ee). Notably, in most cases, the diastereoselectivities reach >99:1, much higher than those reported previously.[4,5] Furthermore, not only the aromatic aldehydes bearing electron-withdrawing groups lead to the formation of **7aa–7aj** with very high diastereoselectivities ranging from 96:4 to >99:1 and enantioselectivities ranging from 92% to 98% ee (entries 1–9), but also the ones bearing an electron-donating group gave extremely high diastereoselectivity of >99:1 and enantioselectivity of 92% ee (entry 10).

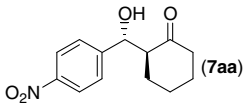
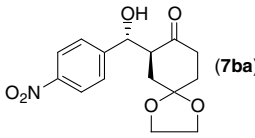
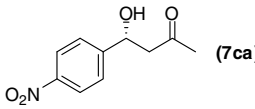
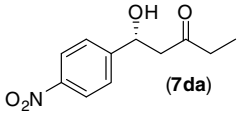
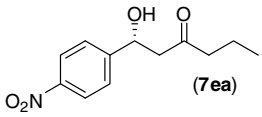
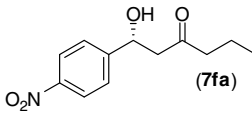
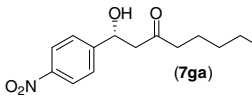
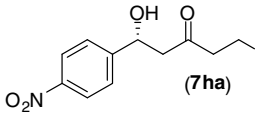
To examine the generality of the current process, the aldol reactions between 4-nitrobenzaldehyde (**6a**) and different ketones, including cyclic and acyclic ketones (**5b–k)** were tested (Table 3). As can be seen from the results summarized in Table 3, the diastereo and enantioselectivities are significantly influenced by the structure of ketones. Surprisingly, although both **5b** and **6a** are solid and suspending in water, the reaction occurred smoothly to furnish the desired product (**7ba**) in a good yield of 75% with a diastereoselectivity of 90:10 and enantioselectivity of 95% ee (Table 3, entry 2). For acyclic ketones, the enantioselectivities obtained range from 71% to 89% (Table 3, entries 3–8). Importantly, the present protocol shows high regioselectivity for the aldolization of unbranched ketones, except 2-butanone, which reacted with 4-nitrobenzaldehyde to give a small amount of the regiomer of **7da**. The other unbranched ketones evaluated here preferentially reacted at the methyl group, exclusively giving the corresponding aldol adduct as a single product without detecting its regiomer (Table 3, entries 3–8).

Based on the proposed transition state model (Fig. 2),[7a,b] the stereochemistry of the aldol products was

Table 3
trans-4-Hydroxy-prolinamide **4** catalyzed direct aldol reactions of **6a** with various ketones in water[a]



5a-h **6a** **7aa-ha**

Entry	Product	Time (h)	Yield[b] (%)	dr[c] (*anti*:*syn*)	ee[d] (%)
1	 (**7aa**)	5	99	>99:1	94
2	 (**7ba**)	70	75	90:10	95
3	 (**7ca**)	14	85	—	71
4[e]	 (**7da**)	12	30	—	78
5[f]	 (**7ea**)	35	75	—	85
6[f]	 (**7fa**)	24	62	—	84
7[f]	 (**7ga**)	24	80	—	85
8[f]	 (**7ha**)	70	88	—	89

[a] See Ref. 8.
[b] Isolated yield.
[c] Determined by ^{1}H NMR of the crude product.
[d] Determined by chiral-phase HPLC analysis.
[e] Other isomer amount is of 25%.
[f] Only one of the regio-selective isomers was observed.

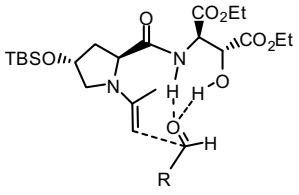


Fig. 2. Proposed transition state model.

easy to be explained. Similar to the reported results,[3,4,5o] this reaction takes place under biphasic basic conditions and the catalytic efficiency is somewhat dependent on the balance between hydrophilicity and hydrophobicity of the catalyst as well as the substrate. As shown in Table 1, catalyst **1** and **4** are better than **2** and **3**, respectively. This may be due to **2** being too hydrophobic while **3** being too hydrophilic. Proline amide **3**, the best catalyst used in previous studies,[6b,7b,c] bears two electron-withdrawing ester group which strengthen the double hydrogen bonds but, unfortunately, increase the hydrophilicity of the catalyst too much. In catalyst **4**, the over increased hydrophilicity was compensated by the introduction of the hydrophobic siloxy group. The relationship between hydrophobicity and catalyst efficiency was also observed in the direct aldol reactions of acyclic ketones. The enantioselectivity increases as the length of alkyl chain becomes longer (Table 3, entries 3–8). The highest enantioselectivity of 89% ee was observed for 4-phenyl-butan-2-one. This might be attributed to the stronger hydrophobicity of the longer alkyl chain.

In summary, we have discovered highly efficient organocatalyzed direct aldol reactions of acyclic and cyclic ketones with a wide range of aromatic aldehydes in water, which afforded high yields with excellent diastereo and enantioselectivities. The catalyst **4** is highly efficient and as little as 1 mol % of **4** is significant to efficiently catalyze the direct aldol reaction in water. Apparently, the current water-compatible aldol reaction tolerates a wide scope of donors, which will enhance its utility in organic synthesis. What is more, highly efficient asymmetric direct stoichiometric aldol reactions can be realized in water, which makes this protocol atom-economical and 'green'.

Acknowledgement

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References and notes

1. (a) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095; (b) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751; (c) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209. See also references cited therein.
2. (a) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3093; (b) Palomo, C.; Vera, S.; Mielgo, A.; Gomez Bengoa, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 5984; (c) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 4966; (d) Mosse, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559; (e) Mosse, S.; Alexakis, A. *Org. Lett.* **2006**, *8*, 3577; (f) Reyes, E.; Vicario, J. L.; Badia, D.; Carrillo, L. *Org. Lett.* **2006**, *8*, 6135; (g) McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599; (h) Barros, M. T.; Phillips, A. M. F. *Eur. J. Org. Chem.* **2007**, 178; (i) Sulzer-MossM, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123.
3. Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958.
4. Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 734.

5. (a) Chimni, S. S.; Mahajan, D. *Tetrahedron: Asymmetry* **2006**, *17*, 2108; (b) Hayashi, Y.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5527; (c) Jiang, Z.; Liang, Z.; Wu, X.; Lu, Y. *Chem. Commun.* **2006**, 2801; (d) Dziedzic, P.; Zou, W.; Hffren, J.; Cordova, A. *Org. Biomol. Chem.* **2006**, *4*, 38; (e) Luo, S.; Mi, X.; Liu, S.; Xu, H.; Cheng, J.- P. *Chem. Commun.* **2006**, 3687; (f) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417; (g) Guillena, G.; Hita, M. D. C.; Tjera, C. N. *Tetrahedron: Asymmetry* **2006**, *17*, 1493; (h) Pihko, P. M.; Laurikainen, K. M.; Usano, A.; Nyberg, A. I.; Kaavi, J. A. *Tetrahedron* **2006**, *62*, 317; (i) Font, D.; Jimeno, C.; Pericas, M. A. *Org. Lett.* **2006**, *8*, 4653; (j) Guizzetti, S.; Benaglia, M.; Raimondi, L.; Celentano, G. *Org. Lett.* **2007**, *9*, 1247; (k) Hayashi, Y.; Aratake, S.; Itoh, T.; Okano, T.; Sumiya, T.; Shoji, M. *Chem. Commun.* **2007**, 957; (l) Wu, X.; Jiang, Z.; Shen, M.; Lu, Y. *Adv. Synth. Catal.* **2007**, *349*, 812; (m) Rodnguez, B.; Bruckmann, A.; Bolm, C. *Chem. Eur. J.* **2007**, *13*, 4710; (n) Huang, J. M.; Zhang, X. T.; Amstrong, D. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 9073; (o) Maya, V.; Raj, M.; Singh, V. K. *Org. Lett.* **2007**, *9*, 2593.

6. (a) Tang, Z.; Yang, Z. H.; Cun, L. F.; Gong, L. Z.; Mi, Q. A.; Jiang, Y. Z. *Org. Lett.* **2004**, *6*, 2285; (b) Chen, X. H.; Tang, Z.; Luo, S. W.; Cun, L. F.; Mi, A. Q.; Jiang, Y. Z.; Gong, L. Z. *Chem. Eur. J.* **2007**, *13*, 689.

7. (a) Tang, Z.; Jiang, F.; Yu, L. T.; Cui, X.; Gong, L. Z.; Mi, A. Q.; Jiang, Y. Z.; Wu, Y. D. *J. Am. Chem. Soc.* **2003**, *125*, 5262; (b) Tang, Z.; Jiang, F.; Cui, F.; Gong, L. Z.; Mi, A. Q.; Jiang, Y. Z.; Wu, Y. D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5755; (c) Tang, Z.; Yang, Z. H.; Chen, X. H.; Cun, L. F.; Mi, A. Q.; Jiang, Y. Z.; Gong, L. Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285; (d) Tang, Z.; Cun, L. F.; Gong, L. Z.; Mi, A. Q.; Jiang, Y. Z. *Org. Lett.* **2006**, *8*, 1263; (e) Jiang, J.; He, L.; Luo, S. W.; Cun, L. F.; Gong, L. Z. *Chem. Commun.* **2007**, 736; (f) He, L.; Jiang, J.; Tang, Z.; Cui, X.; Mi, A. Q.; Jiang, Y. Z.; Gong, L. Z. *Tetrahedron: Asymmetry* **2007**, *18*, 265; (g) Xu, X. Y.; Wang, Z. Y.; Gong, L. Z. *Org. Lett.* **2007**, *9*, 4247.

8. *General procedure for prolinamide* **4***-catalyzed aldol reaction in water*: To a mixture of prolinamide **4** (0.005 mmol) in water (0.5 mL), ketone (1.0 mmol) and aldehyde (0.5 mmol) were added at 25 °C under air. The reaction mixture was vigorously stirred for the indicated time. Then 10 mL saturated ammonium chloride was added. The reaction mixture was extracted with ethyl acetate, dried over anhydrous $MgSO_4$. After the removal of the solvent, the residue was purified through flash column chromatography on a silica gel to give the corresponding aldol products.