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Highly efficient primary amine organocatalysts for the direct asymmetric aldol reaction in brine

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ABSTRACT

Organocatalytic systems made up of six primary amine organocatalysts, derived from natural primary amino acids, in combination with 2,4-dinitrophenol (DNP) have proven to be efficient in the presence of brine without further addition of organic solvents. The system formed by **1f** and DNP was the most efficient one; it can catalyze the direct aldol reaction with a broad range of ketones and aromatic aldehydes, giving the corresponding aldol products in high yields with up to nearly perfect diastereo- and enantioselectivities (up to 99/1 *syn*/*anti*, >99% ee).

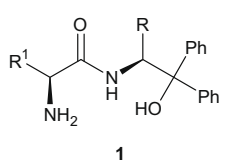
1. Introduction

The asymmetric aldol reaction, which is one of the most important C–C bond forming reactions, has witnessed an explosive growth in the recent years.[1] Stereoselective reactions in water is another important research area,[2] mainly due to the low cost, safety and environmentally benign nature of water, which avoids the problems of pollution of organic solvents. Water often inhibits the activity of catalyst or alters enantioselectivity by interfering in the transition states of the reactions. Previous studies on the aldol reactions using small organic molecules in aqueous medium have gained limited success.[3] It would be a win–win situation from a green chemistry perspective if excellent enantioselectivity could be obtained using small organic catalysts in water.

Recently, Hayashi,[4] Barbas,[5] Pericas,[6] Gong[7] and our group[8] reported direct asymmetric aldol reactions catalyzed by proline-derived chiral catalysts with high diastereoselectivities and enantioselectivities in the presence of water. Meanwhile, other successful examples of chiral catalysts in aqueous solvent were also described, including tryptophan, small peptides and other pyrrolidine-based catalysts.[9]

However, only a few reports have employed simple primary amino acids as catalysts to perform the aldol reactions,[10] which demonstrated low efficiency (30 mol % loading). Most of the presently successful enamine organocatalysts utilize secondary amines instead. Compared with the well-explored pyrrolidine-based organocatalysts in enamine catalysis, the development of efficient primary amine organocatalysts remains an elusive goal until recently.[11] Luo et al.[11c,d,l] have reported a highly efficient primary amine catalyst derived from cyclohexanediamine with a broad range of linear aliphatic ketones in organic solvent. Barbas et al.[11e] have reported that reactions of protected dihydroxyacetone proceeded in aqueous media without the addition of organic solvents.

Very recently, we[12] and Gong[13] have designed a family of new primary amine organocatalysts (Fig. 1) obtained from inexpensive, commercially available and natural acyclic amino acids. With these organocatalysts in hand, we reported that **1f** and the co-catalyst DNP composed a high efficient chiral catalytic system, providing highly diastereo- and enantioselectivities for aldol reactions of aldehydes with various ketones in organic solvents. Nevertheless, their drawbacks have been realized. One of the major limitations is the high catalyst loading, along with low conversion and long reaction time.



1

1a: R^1 = Me, R = Ph
1b: R^1 = Me, R = Bn
1c: R^1 = Me, R = *i*-Bu
1d: R^1 = *i*-Pr, R = *i*-Bu
1e: R^1 = *i*-Bu, R = Ph
1 f: R^1 = *i*-Bu, R = *i*-Bu

Figure 1.

In addition, it is difficult to find an organocatalytic system that works both in organic solvents and in water. Due to environmental concerns, the development of primary amine organocatalysts which were able to catalyze stereoselective reactions with low loading in pure water is a real challenge. Herein, we report our results on this topic and wish to disclose such primary amine

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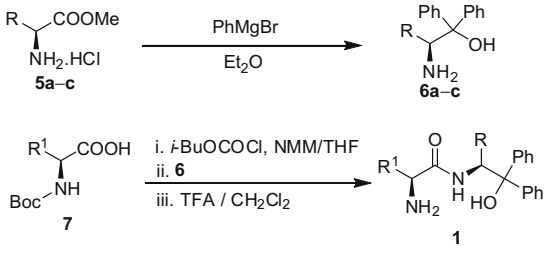
organocatalysts which are very efficient for enantioselective aldol reaction in water/brine.

2. Result and discussion

The six organocatalysts **1a–f** were readily prepared by using the routine mixed anhydride method to combine the Boc-protected amino acids **7** with the diphenyl amino alcohols **6a–c**, and then removing the Boc group with TFA (Scheme 1).[12]

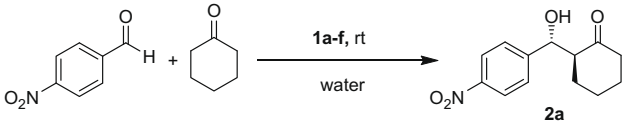


Scheme 1. Synthesis of the catalysts **1a**–**f**.

In an initial experiment, a model aldol reaction of cyclohexanone and 4-nitrobenzaldehyde was studied by using different catalysts **1a–f** in water at room temperature (Table 1). Neither the catalyst nor the solid aldehyde could be dissolved in water. Hence the catalyst and aldehyde should be pre-resolved in excessive ketone. After the introduction of water, the reaction mixture gradually turned emulsive in the stirring course. By working in dissolved this emulsive mixture, the reactions promoted by **1a–f** were quite slow, affording undesirable ee (25%) and poor dr (Table 1, entry 1). Considering the effects of acidic additives on increasing the enantioselectivity and yield, 2,4-dinitrophenol (DNP) was used to improve the activities and enantioselectivities in a previously reported study.[12] As expected, DNP increased the enantioselectivity and yield drastically, accompanied with a decrease in the reaction time (Table 1, entries 7–12). With the exception of **1b** (87% ee), desirable enantioselectivities (>90% ee) were obtained in all cases. The results indicated that **1f** turned out to be the most efficient catalyst and gave the best result with 97% ee in 4 h (Table 1, entry 12).

When the water was replaced with the saturated brine, the enantio- and diastereoselectivity (*anti*/*syn*) were not affected, but the reaction was effectively abbreviated to 2 h (Table 1, entry 13). Brine (salting-out effect) helps the reaction to proceed faster because of the concentrated organic phase.[14] The transformation in brine takes place in the more concentrated organic phase environment in comparison with water and thus proceeds more quickly. After the reaction, the mixture automatically separates into two phases with the upper organic layer just as in water. Further introduction of water into the saturated brine did not deteriorate the enantioselectivity but led to a slightly longer reaction time and decreased diastereoselectivity (Table 1, entries 16–18). Similar results were observed with lesser amounts of the ketone; the enantioselectivity remained the same but at the cost of decreased yield and diastereoselectivity and longer reaction times (entries 14 and 15). Interestingly, with 5 mol % catalyst loading, the desired aldol product was obtained in about 95% yield and with 97% ee (Table 1, entry 18). Replacing the organic solvent cyclohexanone with brine improved the activity of the primary amine organocatalytic system and reduced the loading of the catalyst from 20 mol % to only 5 mol % to achieve high yields and enantioselectivities. Therefore, this is a successful case of using a very low loading of primary amine organic catalyst to achieve high

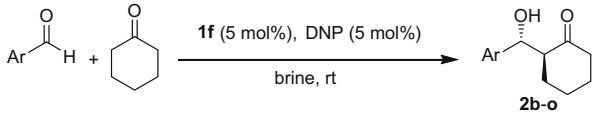
Table 1
Direct aldol reaction of cyclohexanone with 4-nitrobenzaldehyde catalyzed by **1a–f**[a]



Entry	Catalyst[b] (%)	Additive[b] (%)	Time (h)	Yield[c] (%)	*anti*/*syn*[d]	ee[d,e] (%)
1	**1a** (10)	—	100	56	3:2	25
2	**1b** (10)	—	100	52	3:2	19
3	**1c** (10)	—	100	64	3:2	22
4	**1d** (10)	—	100	40	3:2	3
5	**1e** (10)	—	100	49	3:1	20
6	**1f** (10)	—	100	46	2:3	4
7	**1a** (10)	DNP (10)	4	80	5:2	95
8	**1b** (10)	DNP (10)	4	88	5:2	87
9	**1c** (10)	DNP (10)	4	93	7:3	94
10	**1d** (10)	DNP (10)	4	84	3:1	96
11	**1e** (10)	DNP (10)	4	93	5:2	91
12	**1f** (10)	DNP (10)	4	90	5:2	97
13[f]	**1f** (10)	DNP (10)	2	92	4:1	97
14[g]	**1f** (5)	DNP (5)	5	90	4:1	96
15[h]	**1f** (5)	DNP (5)	7	80	7:1	97
16[i]	**1f** (5)	DNP (5)	4	89	3:1	96
17[j]	**1f** (5)	DNP (5)	4	92	5:1	97
18[f]	**1f** (5)	DNP (5)	3.5	95	11:1	97

[a] General reaction conditions: 4-nitrobenzaldehyde (0.2 mmol), cyclohexanone (2 mmol), **1a**–**f** (0.02 mmol) and DNP (0.02 mmol) in water/brine (1 mL) at room temperature.
[b] Data in the parentheses are the amount of the catalyst/additive.
[c] Isolated yield.
[d] Determined by chiral HPLC.
[e] For the *anti*-isomer.
[f] The reaction was performed in brine.
[g] Cyclohexanone (1.0 mmol) was employed in brine.
[h] Cyclohexanone (0.4 mmol) was employed in brine.
[i] The solvent was a mixture of brine/water in 3:7.
[j] The solvent was a mixture of brine/water in 7:3.

Table 2
Asymmetric aldol reaction of cyclohexanone and aldehydes in brine[a]



2b-o

Entry	Ar	Time (h)	Yield[b] (%)	dr[c]	ee[c,e] (%)
1	3-NO_2–Ph	3.5	94	13:1	>99
2[f]	2-NO_2–Ph	0.5	68	62:1	>99
3	2-NO_2–Ph	4	92	5:1	>99
4[f]	2-Cl–Ph	120	26	11:1	91
5	2-Cl–Ph	22.5	78	24:1	98
6	4-Cl–Ph	23	88	3:1[d]	95
7	3-Cl–Ph	23	89	3:1[d]	96
8	4-CF_3–Ph	10	70	5:2[d]	96
9	4-Br–Ph	24	89	4:1[d]	98
10	4-F–Ph	24	68	4:1[d]	97
11	3-OCH_3–Ph	76	50	25:1[d]	96
12[h]	Ph	19	50	12:1	93 (66[g])
13[h]	4-CH_3–Ph	19	50	10:1	92
14[h]	Cy	10	n.d	—	—

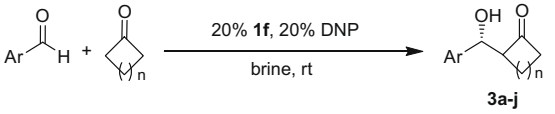
[a] The reaction was performed with aldehyde (0.2 mmol), cyclohexanone (2.0 mmol), **1f** (0.01 mmol), DNP (0.01 mmol) and brine (1.0 mL) at room temperature.
[b] Isolated yield.
[c] Determined by chiral HPLC. Dr is *anti*/*syn* here.
[d] Determined by ^{1}H NMR.
[e] For the *anti*-isomer.
[f] Reaction conditions: 4-nitrobenzaldehyde (0.2 mmol), **1f** (0.04 mmol) and DNP (0.04 mmol) in neat cyclohexanone (0.8 mL) at room temperature.
[g] The reaction was performed with 5 mol % catalyst **1f** and 5 mol % DNP.
[h] The reaction was performed with 20 mol % catalyst **1f** and 20 mol % DNP.

enantioselectivity and yield in this model asymmetric reaction under mild reaction conditions.

Subsequent studies were focused on other substrates such as various substituted benzaldehydes using cyclohexanone as a donor. As shown in Table 2, high diastereoselectivities and excellent enantioselectivities (95% to >99% ee) were obtained with different aromatic aldehydes, which possess either electron-donating (Table 2, entry 11) or electron-withdrawing (Table 2, entries 1–10) groups. However, the benzaldehyde with 5 mol % catalyst afforded an undesirable *anti*-product in only 66% ee. With 20 mol % catalyst loading, good results were observed with an enhanced enantioselectivity (93% ee) and shorter reaction time (Table 2, entry 12). It should be noted that the aldol products were attainable with nearly perfect enantioselectivities in these reactions, exceeding those obtained with other primary amine organocatalysts in aqueous media without the addition of organic solvents.[15] For the sake of comparison with the reaction in cyclohexanone (Table 2, entries 2 and 4),[12] when the reaction was performed in brine, it became faster and employed the largely reduced loading of the catalyst without an apparent loss in enantioselectivities; in many cases, the enantioselectivities were increased. The reaction of 4-nitrobenzaldehyde and cyclohexanecarboxaldehyde in brine was next investigated (Table 2, entry 14). No reaction progress was detected under the aqueous condition.

To examine the generality of the current procedure, aldol reactions between electron-deficient benzaldehydes and different cyclic ketones were tested (Table 3). When using cyclopentanone as a donor, enantioselectivities ranged from 87% to >99%. With 10 mol % catalyst loading, cyclopentanone achieved excellent enantioselectivity (>99% ee) with the predominant *syn*-products in water under primary amine organocatalysts (Table 3, entry 2). When the reaction was carried out in neat, the enantioselectivity decreased (93% ee, entry 3). The results show that aldehydes with strong electron-withdrawing groups react fast and afford high enantioselectivities. When the substituents on the phenyl ring such as halogen reduced their

Table 3
Asymmetric aldol reaction of cyclic ketones and aldehydes in brine[a]



3a-j

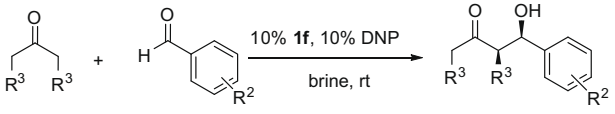
Entry	*n*	Ar	Time (h)	Yield[b] (%)	*anti*/*syn*[c]	ee[c]
1	1	4-NO_2–Ph	24	71	2:5[d]	80[e]
2[g]	2	4-NO_2–Ph	5.5	76	1:2	>99[f]
3[h]	2	4-NO_2–Ph	0.5	93	1:2	93[f]
4[g]	2	3-NO_2–Ph	4.5	80	1:2	96[f]
5[g]	2	2-NO_2–Ph	5	75	1:1	95[f]
6	2	4-Cl–Ph	1.5	50	1:1	87[f]
7	2	4-F–Ph	4	55	2:3	87[f]
8	2	4-CF_3–Ph	4	70	1:4	87[f]
9	4	4-NO_2–Ph	16	65	12:1	72[e]
10	5	4-NO_2–Ph	23	82	2:5[d]	19[e]

[a] The reaction was performed with aldehyde (0.2 mmol), ketone (2.0 mmol), **1f** (0.04 mmol), DNP (0.04 mmol) and brine (1.0 mL) at room temperature.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Determined by ^{1}H NMR.
[e] For the *anti*-isomer.
[f] For the *syn*-isomer.
[g] The reaction was performed with 10 mol % catalyst **1f** and 10 mol % DNP.
[h] Reaction conditions: 4-nitrobenzaldehyde (0.2 mmol), **1f** (0.04 mmol) and DNP (0.04 mmol) in neat cyclopentanone (0.8 mL) at room temperature.

strength by withdrawing the electrons, the reactions give decreased yields and enantioselectivities. The aldol reactions of other cyclic ketones such as cyclobutanone and cycloheptanone, have not been reported with primary organic catalysts in aqueous medium. Herein, we tested the aldol reactions with these cyclic ketones in brine under primary amine organocatalysts.[10,11,15] In contrast with cyclohexanone and cyclopentanone, the aldol reaction between other cyclic ketones and 4-nitrobenzaldehyde were very slow and gave lower enantioselectivities (Table 3, entries 1, 9 and 10); the expanded cyclo ketone sharply decreased the enantioselectivity.

Acetone and 3-pentanone were finally explored as aldol donors. The results are listed in Table 4. When acetone was examined as a

Table 4
Asymmetric aldol reaction of symmetrical ketones and aldehydes in brine[a]



4a-l

Entry	R_3	R_2	Time (h)	Yield[b] (%)	*syn*/*anti*[c]	ee[d] (%)
1	H	2-NO_2	12	66	—	94
2	H	3-NO_2	12	60	—	94
3	H	4-NO_2	12	70	—	90
4	H	2-Cl	27	35	—	>99
5	H	4-Cl	24	30	—	84
6	H	2-Br	28	45	—	>99
7	H	4-Br	27	30	—	91
8	H	3-MeO	28	20	—	93
9	H	2-Naphth	36	30	—	95
10[f]	Me	4-NO_2	40	92	6:1	98[e]
11[f]	Me	3-NO_2	40	90	6:1	>99[e]
12[f]	Me	2-Cl	96	84	99:1	>99[e]

[a] The reaction was performed with aldehyde (0.2 mmol), ketone (2.0 mmol), **1f** (0.02 mmol), DNP (0.02 mmol) and brine (1.0 mL) at room temperature.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC.
[e] For the *syn*-isomer.
[f] The reaction was performed with 20 mol % **1f** and 20 mol % DNP.

substrate in brine, the catalytic system showed high enantioselectivities ranging from 90% to >99% (Table 4, entries 1–9). Only in the case of 4-chlorobenzaldehyde which gave 84% ee. Excellent enantioselectivities (up to >99% ee) were obtained, but with low yields. We are the first to successfully demonstrate the highest enantioselectivity of the reaction of acetone in aqueous media promoted by primary amine organocatalysts to date.

When 3-pentanone was taken as another aldol donor, all the aldol products (Table 4, entries 10–12) were attainable with excellent diastereo- and enantioselectivities (98% ee to >99% ee) in brine, exceeding the results obtained by Luo[11d] and Gong.[13b] 2-Chlorobenzaldehyde afforded an unprecedented diastereo- and enantioselectivity (99/1 *syn*/*anti*, up to >99% ee) under primary amine organocatalysts in brine.[12,13] This is the highest enantioselectivity of the reaction of 3-pentone and aldehydes in water up to now.

3. Conclusion

In conclusion, we have successfully demonstrated that asymmetric direct aldol reactions could be highly catalyzed by primary amine catalysts in aqueous media with addition of the efficient cocatalyst DNP but without addition of any organic solvent. In comparison with the disclosed corresponding organic solvents, using brine as a reaction medium could effectively enhance the activity of the catalytic systems made up of the primary amine organocatalyts **1a**–**f** and the cocatalyst DNP, as well as reducing the reaction time, and reducing the reported catalyst loading without a loss in enantioselectivity or yield. The highest efficient catalytic system with primary amine catalyst **1f** and DNP could be used in the asymmetric Aldol reactions with cyclo or linear ketones as substrates and gave very high enantioselectivities and yields. With the substrates of cyclohexanone, cyclopentanone, acetone and 3-pentanone, the reactions all gave the highest over 99% enantioselectivities. To the best of our knowledge, this result represents the highest ee value in the asymmetric aldol reactions of cyclohexanone, cyclopentanone, acetone and 3-pentanone with arylaldehydes catalyzed by primary amine organocatalysts in aqueous reaction medium to date.

4. Experimental

4.1. General information

All reagents were commercial products. The reactions were monitored by TLC (thin layer chromatography). The column and preparative TLC purification were carried out using silica gel. Melting points were measured on X-4 melting point apparatus without correction. Optical rotations were recorded on a polarimeter. ^{1}H NMR spectra were recorded on 200 MHz and 400 MHz spectrometers. The chemical shifts were reported in ppm with TMS as an internal standard. Data were reported as follows: chemical shift, multiplicity (s = single, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz). ^{13}C NMR spectra were recorded on 400 MHz. HRMS were measured with ESI mass spectrometer. IR spectra were obtained by FT-IR. The ee value determination was carried out using chiral HPLC with OD-H, AS-H, OJ-H or AD-H column.

4.2. General procedure for the preparation of diphenyl aminoalcohols 6a–c[16]

The freshly prepared Grignard reagent PhMgBr 60 mL (2.5 M, 150 mmol) in ether was cooled to 0 °C under an argon atmosphere, 15 mmol hydrochloride of methyl ester of amino acid **5** was added in 10 portions (addition of too much methyl ester hydrochloride in one portion would make the reaction too violent on account of the rapid reaction of HCl with PhMgBr). The reaction was then naturally warmed to room temperature and allowed to stir overnight. When the reaction was completely checked by TLC, the mixture was slowly poured into 60 mL stirring ice water, then 0.25 mmol concentrated HCl was added. The mixture was stirred for an hour, filtered and washed thrice with water to afford a yellow solid. The yellow solid was introduced with NaOH (55 mL, 0.25 mmol), stirred for another 30 min, and then extracted thrice with ether. The ether layers were combined and concentrated in vacuo, and the resulting solid was recrystallized from ethyl acetate or ethanol to yield the amino alcohols **6a**–**c**.

4.2.1. (*S*)-Diphenyl phenylglycinol 6a[16a]

Yield 55%; mp 121–123 °C; $[\alpha]_D^{20} = -242$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.76 (d, 2H, *J* = 7.6 Hz), 7.38–7.42 (t, 2H, *J* = 7.2 Hz, *J* = 8.4 Hz), 7.26 –7.30 (t, 1H, *J* = 8.0 Hz, *J* = 6.8 Hz), 7.00 –7.25 (m, 10 H), 5.01 (s, 1H), 1.61 (br, 1H).

4.2.2. (*S*)-Diphenyl phenylalaninol 6b[16c]

Yield 53%; mp 145–146 °C; $[\alpha]_D^{20} = -73$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.66 (dd, 4H, *J* = 8.4 Hz, *J* = 8.0 Hz), 7.28–7.35 (m, 6H), 7.17–7.25 (m, 5H), 4.16–4.20 (dd, 1H, *J* = 2.6 Hz, *J* = 10.6 Hz), 2.62–2.66 (dd, 1H, *J* = 2.0 Hz, *J* = 14.0 Hz), 2.41–2.47 (dd, 1H, *J* = 10.8 Hz, *J* = 13.6 Hz).

4.2.3. (*S*)-Diphenyl leucinol 6c[16c]

Yield 51%; mp 121–123 °C; $[\alpha]_D^{20} = -96$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.62 (d, 2H, *J* = 7.6 Hz), 7.47–7.48 (d, 2H, *J* =7.2 Hz), 7.14–7.33 (m, 6H), 3.97–3.99 (dd, 1H, *J* = 2.0 Hz, *J* = 10.0 Hz), 1.55–1.62 (m, 1H), 1.21–1.30 (m, 2H), 0.89–0.90 (d, 3H, *J* = 6.4 Hz), 0.86–0.87 (d, 3H, *J* = 6.8 Hz).

4.3. General procedure for the preparation of catalysts 1a–f[12]

At first ClCOOiBu 0.67 mL (5.1 mmol) was slowly introduced dropwise into a solution of 5.1 mmol Boc-protected amino acid **7** (Boc-Leu) and 0.56 mL NMM (5.1 mmol) in 25 mL dry THF under an argon atmosphere at −15 °C. Five minutes later, amino alcohol **6** was added dropwise into the mixture. After stirring for 30 min, the reaction was continued at room temperature until it was completely checked by TLC. Then THF was evaporated in vacuo, and the residue was re-dissolved with CH_2Cl_2, washed successively with dilute HCl, water, 10% $NaHCO_3$, water and a little brine, dried with anhydrous Na_2SO_4, and then condensed in vacuo. It was recrystallized from ethyl acetate and petroleum ether to give a crystal or solid. The solid was re-dissolved with CH_2Cl_2 and cooled to 0 °C, then TFA in CH_2Cl_2 (TFA/CH_2Cl_2 = 1:1) was added dropwise. The mixture was stirred for 1–2 h until the reaction was completely checked by TLC, and then condensed to dryness in vacuo. The residue was re-dissolved with CH_2Cl_2 and $NH_3{\cdot}H_2O$ was added to adjust the solution pH to 10.0 or so. The organic layer was separated, and the aqueous layer was re-extracted thrice with CH_2Cl_2. Then the combined organic layers were washed with a little brine, dried with anhydrous Na_2SO_4, condensed to dryness in vacuo. The residue was recrystallized from ethyl acetate and petroleum ether to give the catalyst **1**.

4.3.1. (*S*,*S*)-2-Amino-*N*-(2-hydroxy-1,2,2-triphenylethyl)propanamide 1a

Yield 50%; mp 236–237 °C; $[\alpha]_D^{20} = -190$ (*c* 1.0, DMSO); FT-IR 3430, 3389, 3299, 1643, 1515,1495, 1448, 1156, 1061, 752, 735, 700 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (d, 1H, *J* = 9.6 Hz), 7.50 (d, 2H, *J* = 7.6 Hz), 7.27 (t, 2H, *J* = 7.6 Hz), 6.97–7.22 (m, 11H), 6.08 (s, 1H), 5.79 (d, 1H, *J* = 8.8 Hz), 3.10–3.15 (m, 1H), 0.79 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.6,

146.4, 145.2, 139.7 129.2, 127.7 127.3, 126.8, 126.5 126.2, 126.1 126.0 80.1 58.5, 50.1, 21.5; HRMS calcd for $(C_{23}H_{24}N_2O_2+H)^+$ 361.1911, found 361.1904. Anal. Calcd for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 76.68; H, 6.80; N, 7.71.

4.3.2. (*S*,*S*)-2-Amino-*N*-(1-hydroxy-1,1,3-triphenylpropan-2-yl)propanamide1b

Yield 53%; mp 203–204 °C; $[\alpha]_D^{20} = -18$ (*c* 1.0, DMSO); FT-IR 3405, 3290, 1711, 1645, 1524, 1447, 1154, 1061, 752, 699 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.77 (d, 1H, *J* = 9.6 Hz), 7.62 (d, 2H, *J* = 7.2 Hz), 7.53 (d, 2H, *J* = 7.6 Hz), 7.35 (t, 2H, *J* = 7.4 Hz),7.07–7.21 (m, 9H), 6.23 (s, 1H), 5.08 (t, 1H, *J* = 9.0 Hz), 2.86–2.91 (dd, 1H, *J* = 6.8 Hz, *J* = 13.2 Hz), 2.58–2.71 (m, 2H), 1.46 (s, 2H), 0.62 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.8, 146.5, 146.3, 139.2, 129.2, 128.2, 127.8, 127.4, 126.3, 126.1, 125.8, 125.7, 125.5, 80.1, 56.1, 50.0, 36.0, 21.2; HRMS calcd for $(C_{24}H_{26}N_2O_2+H)^+$ 375.2067, found 375.2061. Anal. Calcd for $C_{24}H_{26}N_2O_2$: C, 76.98; H, 7.00; N, 7.48. Found: C, 77.05; H, 7.21; N, 7.54.

4.3.3. (*S*,*S*)-2-Amino-*N*-(1-hydroxy-4-methyl-1,1-diphenylpentan-2-yl)propanamide 1c

Yield 46%; mp 172–173 °C; $[\alpha]_D^{20} = -54$ (*c* 1.0, DMSO); FT-IR 3428, 3307, 2956, 2930, 1645, 1525, 1449, 1140, 1061, 750, 702 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.55 (d, 1H, *J* = 9.6 Hz), 7.45–7.47 (m, 4H), 7.25 (t, 2H, *J* = 7.4 Hz), 7.03–7.17 (m, 4H), 5.88 (d, 1H, *J* = 3.6 Hz), 4.91 (t, 1H, *J* = 9.6 Hz), 2.94–2.96 (m, 1H), 1.55 (s, 2H), 1.43–1.49 (m, 2H), 0.89–0.94 (m, 1H), 0.81 (d, 3H, *J* = 5.6 Hz), 0.73 (d, 3H, *J* = 6.4 Hz), 0.72 (d, 3H, *J* = 5.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.5, 146.9, 146.3, 128.0, 127.4, 126.2, 126.0, 125.6, 125.3, 80.2, 52.4, 50.1, 24.1, 21.6; HRMS calcd for $(C_{21}H_{28}N_2O_2+H)^+$ 341.2224, found 341.2218. Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 73.94; H, 8.61; N, 8.17.

4.3.4. (*S*,*S*)-2-Amino-*N*-(1-hydroxy-4-methyl-1,1-diphenylpentan-2-yl)-3-methylbutanamide 1d

Yield 51%; mp 177–178 °C; $[\alpha]_D^{20} = -49$ (*c* 1.0, DMSO); FT-IR 3428, 3383, 3325, 2956, 2928, 2871, 1645, 1511, 1447, 1165, 1063, 747, 700 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.68 (d, 1H, *J* = 9.2 Hz), 7.49–7.53 (m, 4H), 7.28 (t, 2H, *J* = 7.4 Hz), 7.05–7.20 (m, 4H), 5.96 (s, 1H), 4.94–4.99 (t, 1H, *J* = 10.0 Hz), 2.71 (s, 1H), 1.67–1.70 (m, 1H), 1.48–1.54 (m, 2H), 1.43 (s, 2H), 0.92–0.98 (m, 1H), 0.85 (d, 3H, *J* = 6.0 Hz), 0.75 (d, 3H, *J* = 6.4 Hz), 0.65 (d, 3H, *J* = 6.8 Hz), 0.50 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.1, 146.9, 146.4, 128.0, 127.5, 126.1, 126.0, 125.6, 125.3, 80.1, 59.7, 52.7, 39.2, 30.6, 24.2, 24.1, 21.5, 19.5, 16.1; HRMS calcd for $(C_{23}H_{32}N_2O_2+H)^+$ 369.2537, found 369.2529. Anal. Calcd for $C_{23}H_{32}N_2O_2$: C, 74.96; H, 8.75; N, 7.60. Found: C, 75.07; H, 8.92; N, 7.48.

4.3.5. (*S*,*S*)-2-Amino-*N*-(2-hydroxy-1,2,2-triphenylethyl)-4-methylpentanamide 1e

Yield 56%; mp 204–205 °C; $[\alpha]_D^{20} = -155$ (*c* 1.0, DMSO); FT-IR 3400, 3330, 3298, 2953, 2926, 1643, 1516, 1448, 1161, 1061, 748, 734, 699 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, 1H, *J* = 9.6 Hz), 7.52 (d, 2H, *J* = 8.0 Hz), 7.25–7.28 (t, 2H, *J* = 7.2 Hz, *J* = 8.0 Hz), 7.17–7.20 (t, 3H, *J* = 7.2 Hz, *J* = 6.0 Hz), 6.98–7.08 (m, 8H), 6.08 (s, 1H), 5.80 (d, 1H, *J* = 8.8 Hz), 2.96–3.00 (dd, 1H, *J* = 5.2 Hz, *J* = 8.8 Hz), 1.53 (br, 1H), 1.39–1.46 (m, 1H), 1.01–1.08 (m, 1H), 0.92–0.93 (m, 1H), 0.68 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.4, 145.2, 139.7, 129.2, 127.7, 127.3, 126.7, 126.4, 126.2, 126.0, 80.1, 63.4, 58.6, 44.0, 40.1, 23.8, 23.0, 21.7; HRMS calcd for $(C_{26}H_{30}N_2O_2+H)^+$ 403.2380, found 403.2378. Anal. Calcd for $C_{26}H_{30}N_2O_2$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.82; H, 7.69; N, 7.06.

4.3.6. (*S*,*S*)-2-Amino-*N*-(1-hydroxy-4-methyl-1,1-diphenylpentan-2-yl)-4-methylpentanamide 1f

Yield 54%; mp 180–182 °C; $[\alpha]_D^{20} = -44$ (*c* 1.0, DMSO); FT-IR 3389, 3347, 2953, 2297, 2868, 1643, 1518, 1447, 1167, 1135, 1062, 745, 699 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.63 (d, 1H, *J* = 9.6 Hz), 7.50 (d, 4H, *J* = 7.6 Hz), 7.29 (t, 2H, *J* = 7.6 Hz), 7.12–7.20 (m, 3H), 7.06–7.09 (t, 1H, *J* = 7.2 Hz), 5.91 (s, 1H), 4.93–4.98 (m, 1H), 2.86–2.89 (dd, 1H, *J* = 5.6 Hz, *J* = 8.8 Hz), 1.49–1.54 (m, 4H), 1.33–1.39 (m, 1H), 0.98–1.04 (m, 2H), 0.89–0.97 (m, 1H), 0.87 (d, 3H, *J* = 6.8 Hz), 0.76 (d, 3H, *J* = 6.4 Hz), 0.68 (d, 6H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.4, 146.9, 146.4, 128.0, 127.4, 126.1, 125.9, 125.6, 125.3, 80.1, 53.0, 52.5, 44.1, 39.2, 24.1, 23.8, 23.1, 21.7, 21.6; HRMS calcd for $(C_{24}H_{34}N_2O_2+H)^+$ 383.2693, found 383.2696. Anal. Calcd for $C_{24}H_{34}N_2O_2$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.49; H, 9.11; N, 7.24.

4.4. General procedure for the aldol reaction

The following procedure for the reaction of cyclohexanone with 4-nitrobenzaldehyde in brine is representative.

In a typical experiment, a mixture of 4-nitrobenzaldehyde (0.2 mmol), **1f** (usually 5 mol %), cyclohexanone (2.0 mmol) and DNP (usually 5 mol %) were stirred in brine (1.0 mL) at room temperature until the reaction was completed as judged by TLC. This solution was quenched in aqueous NH_4Cl (4 mL) and extracted thrice with AcOEt (4 mL). Then the organic layers were combined, dried with anhydrous Na_2SO_4, concentrated to dryness under reduced pressure, purified by preparative TLC or column to achieve the aldol product. The absolute configuration was analyzed with HPLC and ^1H NMR.

All the known aldol adducts matched the reported characteristics.[9,11,12,14,17] Characterization data for selected examples are given below.

4.4.1. (2*S*,1*R*)-2-[Hydroxy-(4-nitrophenyl)-methyl]-cyclohexan-1-one 2a

Yield 95%; $[\alpha]_D^{20} = +37$ (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 8.19–8.24 (m, 2H), 7.46–7.52 (m, 2H), 4.89–4.93 (d, 1H, *J* = 8.4 Hz), 4.1 (s, 1H), 2.29–2.47 (m, 3H), 2.08–2.18 (m, 1H), 1.48–1.86 (m, 5H). *anti*/*syn* = 11/1, determined by chiral HPLC. Ee = 97%. The enantiomeric excess was determined by HPLC with an AD-H column (hexane/*i*-PrOH = 80/20), 0.5 mL/min; t_R = 24.71 (minor), t_R = 31.52 (major).

4.4.2. (*R*)-4-Hydroxy-4-(4-nitrophenyl)butan-2-one 4a

Yield 70%; $[\alpha]_D^{20} = +45$ (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 8.16–8.23 (m, 2H), 7.52–7.58 (m, 2H), 5.24–5.30 (m, 1H), 3.62 (br, 1H), 2.84–2.88 (m, 2H), 2.23 (s, 3H). Ee = 90%, determined by chiral HPLC with AS-H column (hexane/*i*-PrOH = 70/30), 1.0 mL/min, t_R = 14.4 (major), t_R = 19.9 (minor).

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References

1. (a) Machajewski, T. D.; Wong, C. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352; (b) Mukaiyama, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 5590; (c) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III *J. Am. Chem. Soc.* **2001**, *123*, 5260; (d) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929.
2. (a)*Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic & Professional: London, 1998; (b) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751; (c) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095.
3. (a) Dickerson, T. J.; Janda, K. D. *J. Am. Chem. Soc.* **2000**, *122*, 7386; (b) Córdova, A.; Notz, W.; Barbas, C. F., III *Chem. Commun.* **2002**, 3024; (c) Chimni, S. S.;

Mahajan, D. *Tetrahedron: Asymmetry* **2006**, *17*, 2108; (d) Peng, Y.-Y.; Ding, Q.-P.; Li, Z.; Wang, P. G.; Cheng, J.-P. *Tetrahedron Lett.* **2003**, *44*, 3871.
4. (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.
5. Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 734.
6. Font, D.; Jimeno, C.; Pericas, M. A. *Org. Lett.* **2006**, *8*, 4653.
7. Chen, X. H.; Luo, S.-W.; Tang, Z.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Chem. Eur. J.* **2007**, *13*, 689.
8. Jia, Y.-N.; Wu, F.-C.; Ma, X.; Zhu, G.-J.; Da, C.-S. *Tetrahedron Lett.* **2009**, *50*, 3059.
9. (a) Dziedzic, P.; Zou, W.; Hafren, J.; Córdova, A. *Org. Biol. Chem.* **2006**, *4*, 38; (b) Luo, S.; Mi, X.; Liu, S.; Xu, H.; Cheng, J.-P. *Chem. Commun.* **2006**, 3687; (c) Raj, M.; Singh, V. K. *Org. Lett.* **2007**, *9*, 2593; (d) Gryko, D.; Saletra, W. J. *Org. Biomol. Chem.* **2007**, *5*, 2148; (e) Chimni, S. S.; Singh, S.; Mahajan, D. *Tetrahedron: Asymmetry* **2008**, *19*, 2276; (f) Guizzeeti, S.; Benaglia, M.; Raimondi, M.; Celentano, G. *Org. Lett.* **2007**, *9*, 1247; (g) Wu, X.; Jiang, Z.; Shen, H.; Lu, Y. *Adv. Synth. Catal.* **2007**, *349*, 812; (h) Ramasastry, S. S. V.; Albertshofer, K.; Utsumi, N., ; Barbas, C. F., III *Org. Lett.* **2006**, *10*, 1621; (i) Zu, L.; Xie, H.; Li, H.; Wang, J.; Wang, W. *Org. Lett.* **2006**, *10*, 1211; (j) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417;; (k) Tzeng, Z.-H.; Chen, H.-Y.; Huang, C.-T.; Chen, K. *Tetrahedron Lett.* **2008**, *49*, 4134; (l) Lei, M.; Shi, L.; Li, G.; Chen, S.; Fang, W.; Ge, Z.; Cheng, T.; Li, R. *Tetrahedron* **2007**, *63*, 7892; (m) Teo, Y.-C. *Tetrahedron: Asymmetry* **2007**, *18*, 1155; (n) Wu, F.-C.; Da, C.-S.; Du, Z.-X.; Guo, Q.-P.; Li, W.-P.; Yi, L.; Jia, Y.-N.; Ma, X. *J. Org. Chem.* **2009**, *74*, ASAP article (doi: 10.1021/jo9005766).
10. (a) Córdova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W.-W. *Chem. Commun.* **2005**, 3586; (b) Córdova, A.; Zou, W.; Dziedzic, P.; Ibrahem, I.; Reyes, E.; Xu, Y. *Chem. Eur. J.* **2006**, *12*, 5383; (c) Tanaka, F.; Thayumanavan, R.; Mase, N., ; Barbas, C. F., III *Tetrahedron Lett.* **2004**, *45*, 325; (d) Amedjkouh, M. *Tetrahedron: Asymmetry* **2005**, *16*, 1411; (e) Amedjkouh, M. *Tetrahedron: Asymmetry* **2007**, *18*, 390; (f) Pizzarello, S.; Weber, A. L. *Science* **2004**, *303*, 1151; (g) Bassan, A.; Zou, W.; Reyes, E.; Himo, F.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7028.
11. For recent references on primary amine organocatalysts, see: (a) Peng, F.; Shao, Z. *J. Mol. Catal.: A* **2008**, *285*, 1; (b) Zheng, B.-L.; Liu, Q.-Z.; Guo, C.-S.; Wang, X.-L.; He, L. *Org. Biomol. Chem.* **2007**, *5*, 2913; (c) Luo, S.; Xu, H.; Zhang, L.; Li, J.; Cheng, J.-P. *Org. Lett.* **2008**, *10*, 653; (d) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J.-P. *J. Am. Chem. Soc.* **2007**, *129*, 3074; (e) Ramasastry, S. S. V.; Albertshofer, K.; Utsumi, N.; Barbas, C. F., III *Org. Lett.* **2008**, *10*, 1621; (f) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2007**, *129*, 288; (g) Ramasastry, S. S. V.; Utsumi, N.; Tanaka, F.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2007**, *46*, 5572; (h) Utsumi, N.; Imai, M.; Tanaka, F.; Ramasastry, S. S. V.; Barbas, C. F., III *Org. Lett.* **2007**, *9*, 3445; (i) Xu, L.-W.; Ju, Y.-D.; Li, L.; Qiu, H.-Y.; Jiang, J.-X; Lai, G.-Q. *Tetrahedron Lett.* **2008**, *49*, 7037; (j) Luo, S.; Xu, H.; Chen, L.; Cheng, J.-P. *Org. Lett.* **2008**, *10*, 1775; (k) Liu, J.; Yang, Z.; Wang, Z.; Wang, F.; Chen, X.; Liu, X.; Feng, X.; Su, Z.; Hu, C. *J. Am. Chem. Soc.* **2008**, *130*, 5654; (l) Tsogoeva, S. B.; Wei, S. *Tetrahedron: Asymmetry* **2005**, *16*, 1947; (m) Zou, W.; Ibrahem, I.; Dziedzic, P.; Sunden, H.; Córdova, A. *Chem. Commun.* **2005**, 4946; (n) Wu, X.; Jiang, Z.; Shen, H.-M.; Lu, Y. *Adv. Synth. Catal.* **2007**, *349*, 812; (o) Zhou, J.; Wakchaure, V.; Kraft, P.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 7656; (p) Xu, L.-W.; L, J.; Lu, Y. *Chem. Commun.* **2009**, 1807.
12. Da, C.-S.; Che, L.-P.; Guo, Q.-P.; Wu, F.-C.; Ma, X.; Jia, Y.-N. *J. Org. Chem.* **2009**, *74*, 2541.
13. (a) Xu, X.-Y.; Wang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2007**, *9*, 4247; (b) Zhu, M.-K.; Xu, X.-Y.; Gong, L.-Z. *Adv. Syn. Catal.* **2008**, *350*, 1390.
14. (a) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 4966; (b) Maya, V.; Singh, V. K. *Org. Lett.* **2007**, *9*, 1117.
15. (a) Jiang, Z.; Liang, Z.; Wu, X.; Lu, Y. *Chem. Commun.* **2006**, 2801; (b) Peng, F.-Z.; Shao, Z.-H.; Pu, X.-W.; Zhang, H.-B. *Adv. Synth. Catal.* **2008**, *350*, 2199; (c) Miura, T.; Yasaku, Y.; Koyata, N.; Murakami, Y.; Imai, N. *Tetrahedron Lett.* **2009**, *50*, 2632.
16. (a) Dragoli, D. R.; Burdett, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 10127; (b) Ashby, E. C.; DePriest, R. N.; Goel, A. B.; Wenderoth, B.; Pham, T. N. *J. Org. Chem.* **1984**, *49*, 3545; (c) O'Hagan, D.; Tavasli, M. *Tetrahedron: Asymmetry* **1999**, *10*, 1189.
17. (a) Rodriguez, B.; Bruckmann, A.; Bolm, C. *Chem. Eur. J.* **2007**, *13*, 4710; (b) 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; (c) Puleo, G. L.; Iuliano, A. *Tetrahedron: Asymmetry* **2007**, *18*, 2894; (d) Giacalone, F.; Gruttadauria, M.; Meo, P. L.; Riela, S.; Noto, R. *Adv. Synth. Catal.* **2008**, *350*, 2747; (e) Inoue, H.; Kikuchi, M.; Ito, J.; Nishiyama, H. *Tetrahedron* **2008**, *64*, 493; (f) Cobb, J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84; (g) Wang, W.; Mei, Y.; Li, H.; Wang, J. *Org. Lett.* **2005**, *7*, 601.