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Highly efficient prolinamide-based organocatalysts for the direct asymmetric aldol reaction in brine

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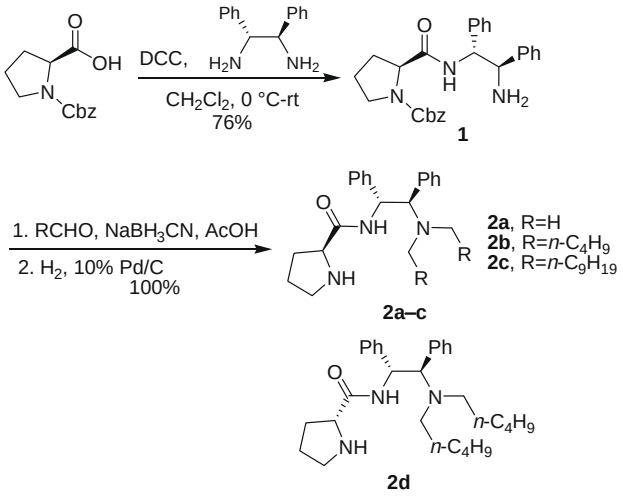
ABSTRACT

Four prolinamide-based organocatalysts were readily synthesized and applied to the direct asymmetric aldol reactions of ketones and aromatic aldehydes in brine. When 2,4-dinitrophenol (DNP) was used as an acidic additive, 1 mol % low loading of **2b** afforded aldol products with excellent diastereoselectivity of up to 98/2 dr and high enantioselectivity of up to 97% ee.

Asymmetric aldol reaction is one sort of the most important carbon–carbon formation reactions, which can generate many valuable biologically optically active β-hydroxy carbonyl compounds and it has tremendous utility in organic synthesis.[1] Up to now, three direct procedures can be performed to achieve chiral aldol products. They are biocatalysis methods,[2] procedures catalyzed by chiral metal especially zinc-involved complexes,[3] and the asymmetric organocatalytic protocols.[4] Among these methods, the third one is currently the most important and interesting procedure. Many highly efficient small molecular organocatalysts have been developed[5] and the asymmetric organocatalytic aldol reactions have rapidly grown to their adolescence from infancy[6] since List et al. successfully demonstrated that L-proline can highly catalyze the simple aldol reaction of acetone and aldehydes.[7] Although the water in which the aldol reaction is performed is more fascinating and challenging today, most of these disclosed results used organic solvents as reaction media to date.[8] Use of water as reaction medium is quite important and urgent for the sustainable development and protection of the environment in today's society because it is cheap, safe, easy to operate, and environmentally beneficial.[9] Moreover, only few reports[10] described the use of less than 5 mol % catalyst loading to perform the aldol reactions in aqueous media although groups of Singh,[10c] Gong,[10a] and Hayashi[10d] successfully disclosed a 0.5% and 1% loading catalyst in the aldol reaction with high enantioselective outcome in aqueous medium, respectively. Therefore, development of chiral organocatalysts that not only can be used in the aqueous medium but also can achieve high enantioselectivity and yield with their low loading is still extensively interesting and urgently desired. Herein we report our results on this topic that a prolinamide-based secondary–tertiary diamine could effectively catalyze the highly enantioselective aldol reaction in brine with only 1 mol % of catalyst.



Scheme 1. Synthesis of chiral organocatalysts **2a–d**.

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Four organocatalysts were readily prepared according to the routine methods (Scheme 1). The Cbz-protected L-proline was condensed with (R,*R*)-diphenylethyl diamine by DCC method to yield compound **1**. The routine N-alkylation of **1** with aliphatic aldehydes and $NaBH_3CN$ quantitatively furnished the tertiary amines.[11] Then direct deprotection of Cbz group by hydrogenation with Pd/C quantitatively gave the catalysts **2a–c**.[12a–c] Catalyst **2d**[12d] was prepared according to the same procedure as **2b** starting with D-proline.

Initially, 10 mol % of **2a** was tested in the model reaction of 4-nitrobenzaldehyde with acetone in the presence of water at room temperature. To our disappointment, it gave very poor enantioselectivity (Table 1, entry 1). Considering the effects of acid additives on increasing the enantioselectivity and yield,[13] a series of acidic additives with a gradient pK_a were tested in succession. Indeed, the acidic additives increased the enantioselectivity and yield (Table 1, entry 2). When water was replaced with the saturated brine, the enantioselectivity was sharply increased to 80% ee from 53% ee (Table 1, entries 2 and 3). However, strong acidic additives such as trifluoroacetic acid (TFA) and 2,4,6-trinitrophenol (TNP) nearly did not allow the reaction to proceed and only trace product was observed even after 36 h (Table 1, entries 6 and 7). Using phenol as an additive provided very low enantioselectivity (Table 1, entry 8). Acetic acid gave low yield in spite of higher enantioselectivity (Table 1, entry 10). The stearic acid with a hydrophobic long alkyl chain contributed a lot to yield with only moderate ee (Table 1, entry 9). But with 2,4-dinitrophenol (DNP) as an additive,[14] both the high yield (96%) and enantioselectivity (80%) were obtained. Therefore, DNP was identified as the optimal additive.

Next, the catalysts **2a–d** and influence of the loading on the reaction were investigated (Table 2). Interestingly, reducing the amount of catalyst **2a** from 10 mol % to 5 mol % led to higher ee without sacrifice of the yield (Table 1, entry 3 vs Table 2, entry 1). When the loading was reduced to only 1 mol %, the enantioselectivity was greatly increased to 92% ee at the cost that the reaction time was largely prolonged (Table 2, entries 1 and 3). The same trend was found when **2b** was used (Table 2, entries 4 and 5). Although 5 mol % **2b** exhibited the same enantioselectivity (83% ee) as 5 mol % **2a**, 1 mol % **2b** provided the highly increased ee of 94%. Further lowering the loading to 0.5 mol % **2b** resulted in slightly decreased ee with sharply decreased yield. Low temperature did not contribute to high enantioselectivity but made the reaction quite sluggish (Table 2, entries 2 and 6). For **2c**, longer reaction time than that needed for **2b** was needed though it achieved high yield and enantioslectivity as well (Table 2, entry 8). The catalyst **2d** gave a greatly decreased ee with the inversed configuration (Table 2, entry 9). So the configuration of the aldol product was controlled by the chiral pyrrolidine moiety.[15,16] In summary, among catalysts **2a–d**, 1 mol % **2b** afforded the adduct not only with good yield but also with the highest enantioselectivity in the shortest reaction time.

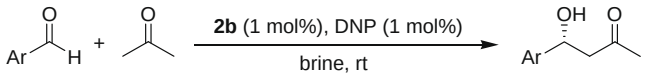
A set of arylaldehydes were examined under the optimized conditions: 1 mol % **2b** and 1 mol % DNP in brine at room temperature (Table 3). The results showed that the aldehydes with strong electron-withdrawing substituent participated in a fast reaction and afforded high enantioselectivities. When the substituents of the phenyl ring reduced their strength of withdrawing the electrons such as halogen, the reaction was very sluggish and gave sharply decreased yields and slightly decreased enantioselectivities. While

Table 2
Direct asymmetric aldol reaction of acetone with 4-nitrobenzaldehyde catalyzed by **2** in brine[a]

Entry	Catalyst (mol %)	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**2a** (5)	rt	18	99	82
2	**2a** (5)	0	23	97	83
3	**2a** (1)	rt	68	85	92
4	**2b** (5)	rt	4	98	83
5	**2b** (1)	rt	20	96	94
6	**2b** (1)	0	40	30	90
7	**2b** (0.5)	rt	43	47	90
8	**2c** (1)	rt	29	94	93
9	**2d** (1)	rt	21	84	−72[d]

[a] Conditions: 4-nitrobenzaldehyde (0.2 mmol), acetone (2 mmol), **2**, and DNP in brine (1.2 mL). An equimolar amount of DNP was used as to the catalyst **2**.
[b] Isolated yield.
[c] Determined by HPLC.
[d] (*S*)-Isomer was the major product.

Table 3
Direct asymmetric aldol reaction in brine



Entry	Ar	Time (h)	Yield[a] (%)	ee[b] (%)
1	4-NO_2-Ph	20	96	94
2	3-NO_2-Ph	12	97	91
3	2-NO_2-Ph	12	85	89
4	4-Br-Ph	120	64	90
5	4-Cl-Ph	120	26	77
6	4-F-Ph	120	17	89
7[c]	4-NO_2-Ph	20	93	92
8[d]	4-NO_2-Ph	20	85	82

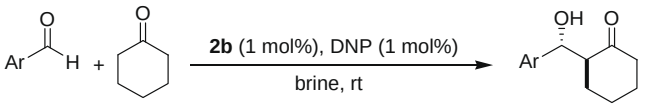
[a] Isolated yield.
[b] Determined by HPLC.
[c] The first recycled catalyst **2b** was employed.
[d] The second recycled catalyst **2b** was employed.

Table 1
Direct asymmetric aldol reaction of acetone with 4-nitrobenzaldehyde catalyzed by **2a** at room temperature[a]

Entry	Catalyst (mol %)	Solvent	Additive	Time (h)	Yield[b] (%)	ee[c] (%)
1	**2a** (10)	Water	None	16.5	82	11
2	**2a** (10)	Water	DNP	36	92	53
3	**2a** (10)	Brine	DNP	14	96	80
4	**2a** (10)	Water	PhCOOH	24	87	46
5	**2a** (10)	Brine	PhCOOH	17	89	49
6	**2a** (10)	Brine	TFA	36	Trace	—
7	**2a** (10)	Brine	TNP	36	Trace	—
8	**2a** (10)	Brine	Phenol	14.5	45	19
9	**2a** (10)	Brine	Stearic acid	28	90	41
10	**2a** (10)	Brine	AcOH	24	25	79

[a] Conditions: 4-nitrobenzaldehyde (0.2 mmol), acetone (2 mmol), **2a** (0.02 mmol), and additive (0.02 mmol) in water/brine (1.2 mL).
[b] Isolated yield.
[c] Determined by HPLC.

Table 4
Direct asymmetric aldol reaction of cyclohexanone in brine



Entry	Ar	Time (h)	Yield[a] (%)	dr[b]	ee[b] (%)
1	4-NO_2-Ph	22	84	79:21	93
2	3-NO_2-Ph	13	95	67:33	95
3	2-NO_2-Ph	12	99	92:8	95
4	4-Br-Ph	60	73	85:15	93
5	4-Cl-Ph	60	76	89:11	88
6	3-Cl-Ph	60	75	74:26	91
7	2-Cl-Ph	60	84	94:6	93
8	2,4-Di-Cl-C_6H_4	19	90	81:19	89
9	4-CF_3-Ph	20	92	58:42	94
10	**2-CF_3-Ph**	**68**	**69**	**98:2**	**97**
11	4-CH_3-Ph	125	38	89:11	82
12	4-OCH_3-Ph	125	10	92:8	79
13[c]	4-NO_2-Ph	11	97	63:37	77

[a] Isolated yield for aldol product (*anti* + *syn*).
[b] Determined by HPLC. The value of dr is *anti*/*syn*.
[c] Cyclopentanone was used instead of cyclohexanone.

aliphatic aldehydes were used as electrophiles of acetone, no aldol adducts could be achieved. Notably, the catalyst could be recycled once without reducing its catalytic activity.[17]

Hydrophobic cyclohexanone was further observed as a nucleophilic ketone. The same optimized reaction conditions were applied and the results are summarized in Table 4.[17] The electron-deficient arylaldehydes gave faster reaction rates, higher yields, and higher enantioselectivities than the electron-rich ones. When aliphatic aldehydes such as phenylpropionaldehyde and isobutyraldehyde were used to replace the aromatic aldehydes, the reaction failed to give aldols even with the increased loading of **2b**. Clearly, the predominant products were anti-isomers. It could be easily found that the substituted position of the phenyl ring largely effected the diastereoselectivity (dr) and the order was *ortho* > *para* > *meta*, such as that of the three nitro-substituted benzaldehydes: 2-nitrobenzaldehyde gave the highest 92/8 dr, 4-nitrobenzaldehyde afforded 79/21 dr whereas 3-nitrobenzaldehyde gave only 67/33 dr. Similar results could be found among the three chloro-substituted benzaldehydes. The highest enantioselectivity (97% ee) and diastereoselectivity (98/2 dr) were achieved when 2-trifluoromethylbenzaldehyde was used as a substrate. But when cyclopentanone was employed as the nucleophilic reagent, lower diastereoselectivity and enantioselectivity than those achieved using cyclohexanone were afforded (Table 4, entry 13).

Based on that the configuration of the aldol product was determined by the chiral pyrroline moiety and the previously reported speculations on the stereochemical outcome,[10c,13g,15] the transition state shown in Figure 1 was proposed, in which the two hydroxyl bonds from the aldehyde with the tertiary ammonium salt and the amide group of the diamine framework should be favored to activate the aldehyde. The enamine formed from the pyrrolidine and acetone would chiefly attack the aldehyde from its Re-face. Thus, the predominant *R* secondary alcohols were generated.

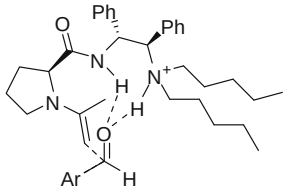


Figure 1. Proposed transition state model.

In conclusion, four prolinamide-based organocatalysts were readily developed and employed to the highly asymmetric aldol reactions of ketones and aromatic aldehydes in brine. The low amount of 1 mol % **2b**/DNP catalyst system showed excellent catalytic activity, diastereoselectivity and enantioselectivity at room temperature in brine.

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12. (a) *Compound* **2a**: White solid; mp 146–148 °C; $[\alpha]_D^{20}$ +31 (*c* 2.13, $CHCl_3$); ^1H NMR (400 MHz $CDCl_3$) δ 8.50 (br, 1H), 7.19–7.25 (m, 3H), 7.04–7.12 (m, 7H), 5.22–5.27 (dd, 1H, *J* = 10.8 Hz, *J* = 5.6 Hz), 3.75–3.78 (dd, 1H, *J* = 8.8 Hz, *J* = 4.8 Hz), 3.72–3.75 (d, 1H, *J* = 10.4 Hz), 2.98–3.06 (m, 2H), 2.41 (br, 1H), 2.17 (s, 6H), 2.01–2.13 (m, 2H), 1.72–1.79 (m, 2H); ^{13}C NMR (100 MHz $CDCl_3$) δ 174.5, 140.9, 133.6, 129.6, 127.9, 127.6, 127.4, 126.7, 73.6, 60.9, 53.7, 47.2, 41.1, 30.7, 26.0; HRMS exact mass calcd for $C_{21}H_{27}N_3O$ ($[M+H]^+$) 338.2227, found 338.2222; IR (KBr) 3323, 3030, 2920, 2852, 2780, 1637, 1500, 1453, 1105, 1014, 870, 749, 700, 615 cm^{-1}. (b) *Compound* **2b**: White solid; mp 51–52 °C; $[\alpha]_D^{20}$ +13 (*c* 2.00, $CHCl_3$); ^1H NMR (400 MHz $CDCl_3$) δ 8.82 (br, 1H), 7.17–7.23 (m, 3H), 7.01–7.09 (m, 7H), 5.09–5.12 (d, 1H, *J* = 10 Hz), 3.81–3.84 (d, 1H, *J* = 10.8 Hz), 3.74–3.78 (dd, 1H, *J* = 9.2 Hz, *J* = 4.8 Hz), 3.01–3.09 (m, 2H), 2.53–2.60 (m, 2H), 2.03–2.11 (m, 4H), 1.70–1.85 (m, 3H), 1.24–1.53 (m, 12H), 0.93 (t, 6H, *J* = 7.4 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 174.5, 141.7, 134.8, 129.6, 127.8, 127.6, 127.3, 127.2, 126.6, 126.5, 69.1, 60.9, 54.1, 49.7, 47.3, 30.5, 29.7, 28.3, 26.3, 22.7, 14.1; HRMS exact mass calcd for $C_{29}H_{43}N_3O$ ($[M+H]^+$) 450.3479, found 450.3482; IR (KBr) 3342, 3062, 3083, 3027, 2956, 2928, 2860, 2818, 1661, 1490, 1457, 1378, 1296, 1158, 1103, 1074, 756, 701, 612 cm^{-1}. (c) *Compound* **2c**: White ceraceous solid; mp 42–45 °C; $[\alpha]_D^{20}$ +10 (*c* 1.81, $CHCl_3$); ^1H NMR (400 MHz $CDCl_3$) δ 8.63–8.64 (d, 1H, *J* = 4.4 Hz), 7.15–7.25 (m, 3H), 7.00–7.08 (m, 7H), 5.11–5.15 (dd, 1H, *J* = 10.8 Hz, *J* = 4.8 Hz), 3.86–3.89 (d, 1H, *J* = 11.2 Hz), 3.68–3.72 (dd, 1H, *J* = 8.8 Hz, *J* = 6.0 Hz), 2.99–3.04 (m, 2H), 2.52–2.59 (m, 2H), 2.04–2.16 (m, 3H), 1.93–1.99 (m, 2H), 1.73–1.79 (m, 2H), 1.19–1.49 (m, 32H), 0.89 (t, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 141.7, 134.8, 129.6, 127.8, 127.6, 127.3, 127.2, 126.5, 69.0, 60.9, 54.1, 49.7, 47.4, 31.9, 30.5, 29.8, 29.7, 29.6, 29.3, 28.7, 27.5, 26.3, 22.7, 14.1; HRMS exact mass calcd for $C_{39}H_{63}N_3O$ ($[M+H]^+$) 590.5044, found 590.5048; IR (KBr) 3332, 3062, 3027, 2924, 2854, 1660, 1488, 1378, 1300, 1186, 1148, 1106, 1073, 1026, 909, 880, 757, 700, 614 cm^{-1}. (d) *Compound* **2d**: Colorless colloid solid; $[\alpha]_D^{20}$ +87 (*c* 2.06, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.82 (br, 1H), 7.16–7.22 (m, 3H), 6.99–7.08 (m, 7H), 5.09–5.13 (dd, 1H, *J* = 11 Hz, *J* = 3 Hz), 3.81–3.84 (d, 1H, *J* = 11.2 Hz), 3.74–3.77 (dd, 1H, *J* = 8.8 Hz, *J* = 5.2 Hz), 3.01–3.08 (m, 2H), 2.53–2.60 (m, 2H), 2.02–2.11 (m, 4H), 1.68–1.85 (m, 3H), 1.24–1.53 (m, 12H), 0.93 (t, 6H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 142.0, 134.9, 129.6, 127.8, 127.6, 127.2, 127.1, 126.5, 69.2, 61.0, 54.1, 49.4, 47.4, 30.9, 29.6, 28.1, 26.2, 22.7, 14.1; HRMS exact mass calcd for $C_{29}H_{43}N_3O$ ($[M+H]^+$) 450.3479, found 450.3469; IR (KBr) 3326, 3084, 3062, 3030, 2955, 2928, 2861, 1670, 1496, 1456, 1379, 1299, 1247, 1157, 1098, 757, 700, 625 cm^{-1}.
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16. Similar to **2b**, we also synthesized another catalyst **2e** starting from L-proline and racemic diphenylethyl diamine. However, the diastereoselectivity of **2e** was not 1:1 but 2:1 with the ratio of (*S*,*R*,*R*)- to (*S*,*S*,*S*)-isomer, which was determined by ^1H NMR, because of the stereoselectivity of the chiral building blocks in synthetic course. With 1% **2e** in brine at room temperature, the reaction of acetone with 4-nitrobenzaldehyde afforded aldol with 92% yield and slightly lowered enantioselectivity (85%) within 20 h. It could be concluded in combination of the asymmetric outcome of **2d** that the catalyst from L-Pro and (*R*,*R*)-diphenylethyl diamine should be superior to that from L-Pro and (*S*,*S*)-diphenylethyl diamine in consideration of the enantioselectivity of the reaction. *Compound* **2e**: (*S*,*R*,*R*): ^1H NMR (400 MHz $CDCl_3$) δ 8.86 (br, 1H), 6.99–7.77 (m, 10H), 5.10–5.18 (m, 1H), 3.81–3.84 (m, 1H), 3.73–3.75 (m, 1H), 2.92–3.07 (m, 2H), 2.51–2.60 (m, 2H), 2.04–2.18 (m, 4H), 1.61–1.86 (m, 3H), 1.17–1.50 (m, 12H), 0.92 (t, 6H, *J* = 7.0 Hz); (*S*,*S*,*S*): ^1H NMR (400 MHz $CDCl_3$) δ 8.67 (br, 1H), 6.99–7.77 (m, 10H), 5.26–5.33 (m, 1H), 3.87–3.93 (m, 1H), 3.65–3.69 (m, 1H), 3.11–3.19 (m, 2H), 2.73–2.76 (m, 2H), 2.22–2.27 (m, 4H), 1.91–2.05 (m, 3H), 1.17–1.50 (m, 12H), 0.92 (t, 6H, *J* = 7.0 Hz).
17. *General procedure for* **2b**-*catalyzed aldol reaction in brine.* A mixture of ketone (2.0 mmol), DNP (0.37 mg), and the catalyst **2b** (0.9 mg) in brine (1.2 mL) was introduced with aldehyde (0.2 mmol). Then the reaction mixture was stirred at room temperature until the reaction was complete (determined by TLC). After addition of saturated aqueous NH_4Cl (5 mL), the mixture was extracted with ethyl acetate thrice. Then the combined organic layers were dried over anhydrous Na_2SO_4, concentrated to dryness in vacuo, and purified by preparative TLC to achieve the aldol products and the recycled catalyst **2b**.