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Highly Diastereo- and Enantioselective Direct Aldol Reaction Catalyzed by Simple Amphiphilic Proline Derivatives

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Abstract Two novel amphiphilic L-proline derivatives bearing long alkyl chain on the 4-position via ether bonds, **1a** and **1b**, have been synthesized and evaluated for the asymmetric direct aldol reaction in organic solvents as well as in water. The catalytic activities with 5 mol% of **1a** are better than that of 30 mol% of proline itself being used. Especially, high yields (up to 99%), excellent enantioselectivities (up to 99% ee) and *anti*-diastereoselectivities (up to 99:1) are achieved in the reactions of aromatic aldehydes and cyclic ketones at room temperature with 5 mol% of **1a** in water.

Keywords Asymmetric synthesis · Direct aldol reaction · Organocatalysis · Proline derivatives · Amphiphilic · Water

1 Introduction

The last few years have witnessed spectacular advancement in new catalytic methods based on metal-free organic molecules [1–3]. One of the preparative advantages of the organocatalysis is that the reaction usually can be performed under an aerobic atmosphere with wet solvents, even in water/aqueous media, similar as an enzymatic process in nature. On the other hand, stereoselective reactions in water have received a great deal of interest also in recent years mainly due to the low cost, safety, and environmentally benign nature of water [4, 5].

Proline is arguably the most efficient and versatile small organic "enzyme" that catalyze direct aldol reaction and other related organic transformations [6, 7]. However, the rather poor solubility of L-proline in organic solvents limits its application as a catalyst. For example, excess loading of catalyst and strong polar solvent such as DMSO are required to achieve high activity and good enantioselectivity in aldol reaction. To overcome these limitations of proline as organocatalyst, several new compounds derived from L-proline have been found to be more soluble in common organic solvents than proline and promote the direct aldol reactions with high enantioselectivity in the past few years, e.g. 4-substituted-L-proline [8–11], *N*-sulfonylcarboxamides [12], tetrazole [13], diamine-protonic acid [14], small peptides [15], and prolinamides [16–21].

Although proline is soluble in water, the enantioselectivity for the aldol reaction in water are demonstrated poor [22, 23], unless other co-catalysts were involved [24]. Some proline-derived compounds, such as siloxyproline analogues [25], diamine/acid [26], proline-derived small peptides [27], tetrazole [28], primary amines [29], prolinamide phenols [30], etc., have been demonstrated to increase the reactivity and stereoselectivity in aldol reactions in water or in wet solvents. Recently, Hayashi et al. [31] reported successful cross-aldol reactions catalyzed by a combined proline/surfactant organocatalyst in water. Li et al. [32] further investigated the role of water on this class of catalysts. The long hydrophobic chain in proline makes it does just like a chiral surfactant that can assemble on the interface of water and oil and enhances the reactivity and stereoselectivity.

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Herein, we report our work on the design and synthesis of novel proline derivatives bearing long alkyl chain groups via ether bonds, which is more stable than ester bond, and their catalytic activities on the aldol reactions in organic solvents and in water.

2 Experimental

2.1 General

All chemicals were used as received unless otherwise noted. Reagent grade solvents were distilled prior to use. All reported ^{1}H NMR spectra were collected on a Bruker DPX 400 NMR spectrometer with TMS as internal reference. IR spectra were determined on a Thermo Nicolet IR200 unit. High resolution mass spectra (HRMS) were obtained on a Waters Micromass Q-Tof Micro^{TM} instrument using the ESI technique. Chromatography was performed on silica gel (200–300 mesh). Melting points were determined using a XT5A apparatus and are uncorrected. Optical rotations were determined on a Perkin Elmer 341 polarimeter. Single crystal structure was carried out on a Rigaku R-AXIS-IV area detector. Enantiomeric excess was measured by chiral HPLC at room temperature using JASCO PU-1580 pump equipped with JASCO UV-1575 ultra detector (or Syltech 500 pump equipped with a UV 500 version 4.1 ultra-violet detector) with Chiralpak AD (4.6 mm × 250 mm) or Chiralcel OD-H (4.6 mm × 250 mm) columns.

2.2 General Procedure for the Preparation of **4a** and **4b**

Compound **3** was prepared according to [33]. Under argon atmosphere, compound **3** (2.65 g, 10 mmol) and anhydrous DMF (20 mL) were added to a three-necked flask. The mixture was stirred and cooled down to 0 °C, then 60% NaH (1 g, 25 mmol) was added. After stirring for 30 min, $C_{12}H_{25}Br$ (6.5 mL, 27.1 mmol) was added dropwise slowly (about 30 min). Then the mixture was warmed to room temperature and stirred overnight. The reaction system was acidified with 5 mol/L aqueous HCl to pH $\sim$2 followed by extraction with diethyl ether. The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated to afford the crude product, which was purified through column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 5:1, v/v) to provide the product **4a**. Similar procedure gave compound **4b**.

2.2.1 *(2S,4R)-1-Benzyl-2-dodecyloxy-4-(dodecyloxy)pyrrolidine-1,2-dicarboxylate* ***4a***

Pale yellowish oil (2.64 g, 44%); IR (KBr, cm^{-1}): 2924, 2854, 1748, 1715, 1498, 1465, 1415, 1353, 1191, 1117, 768, 697; ^{1}H NMR ($CDCl_3$) δ: 0.88 (t, 6H, $J = 7.2$ Hz, $2CH_3$), 1.26–1.30 (m, 36H, $18CH_2$), 1.47–1.63 (m, 4H, $2CH_2CH_2O$), 2.05–2.10 (m, 1H, C*H*HCHCO), 2.28–2.40 (m, 1H, CH*H*CHCO), 3.36–3.40 (m, 2H, NCH_2), 3.53–3.69 (m, 2H, $CHOCH_2$), 3.95 (m, 1H, OCH), 4.06–4.14 (2H, m, $COOCH_2$), 4.42 (m, 1H, NCHCO), 5.04–5.17 (2H, m, CH_2Ph), 7.30 (m, 5H, 5Ar-H); ^{13}C NMR ($CDCl_3$) (2 conformational isomers) δ: 14.1 ($2CH_3$), 22.7 ($2CH_2$), 25.7 and 25.8 (CH_2), 26.1 (CH_2), 28.3–29.7 ($14CH_2$), 31.8 ($2CH_2$), 35.6 and 36.7 ($CHCH_2$), 51.6 and 51.9 (NCH_2), 57.9 and 58.1 (NCH), 65.2 and 65.3 ($COOCH_2$), 67.0 (OCH_2Ph), 69.4 (OCH_2), 76.3 and 76.9 (OCH), 127.7–128.4 (5Ar-C), 136.3 and 136.5 (Ar-C), 154.3 and 154.8 (NCO), 172.6 and 172.8 (COO); HRMS (ESI) *m/z*: calcd. for $C_{37}H_{63}NO_5Na$ $(M + Na)^+$ 624.4604, found 624.4601.

2.2.2 *(2S,4R)-1-Benzyl-2-hexyl-4-(hexyloxy)pyrrolidine-1,2-dicarboxylate* ***4b***

Pale yellowish oil (1.689 g, 39%); IR (KBr, cm^{-1}): 2955, 2931, 1741, 1714, 1498, 1415, 768, 697; ^{1}H NMR ($CDCl_3$) δ: 0.88 (t, $J = 7.2$ Hz, 6H, 2CH3), 1.24–1.34 (m, 12H, $6CH_2$), 1.47–1.64 (m, 4H, $2CH_2CH_2O$), 2.04–2.10 (m, 1H, CHCHHCH), 2.31–2.34 (m, 1H, CHCHHCH), 3.37–3.41 (m, 2H, OCH_2), 3.57–3.66 (m, 2H, NCH_2), 3.96 (t, $J = 6.8$ Hz, 1H, CHHOC=O), 4.06 (m, 1H, $CHOCH_2$), 4.13 (t, $J = 6.8$ Hz, 1H, CHHOC=O), 4.41–4.47 (m, 1H, NCHC=O), 5.04–5.16 (m, 2H, $PhCH_2$), 7.26–7.34 (m, 5H, 5ArH); ^{13}C NMR ($CDCl_3$) δ (2 conformational isomers): 13.9 and 14.0 ($2CH_3$), 22.5 and 22.6 ($2CH_2$), 25.5 and 25.8 ($2CH_2$) 28.5 and 28.6 (CH_2), 29.8 (CH_2), 31.4 and 31.6 ($2CH_2$), 35.8 and 36.9 ($CHCH_2$), 51.8 and 52.1 (NCH_2), 58.1 and 58.3 (NCH), 65.3 ($COOCH_2$), 67.1 ($PhCH_2$), 69.5 (OCH_2), 76.4 (OCH), 127.8–128.5 (5Ar-C), 136.6 and 136.8 (Ar-C), 154.5 and 155.0 (NCO), 172.6 and 172.8 (COO). HRMS (ESI) *m/z*: calcd for $C_{25}H_{39}NO_5Na$ $(M + Na)^+$ 456.2726, found 456.2735.

2.3 General Procedure for the Preparation of **1a** and **1b**

To the mixture of compound **4a** (1.20 g, 2 mmol), methanol and water (10 mL, 1/1, v/v) was added NaOH (0.8 g, 20 mmol). After stirring at room temperature for 24 h, the mixture was acidified to pH $\sim$2 with 2 mol/L aqueous HCl, and extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated and purified through column chromatography on silica gel (eluent: ethanol/ethyl acetate = 1:3, v/v) to give a pale yellow oil **5a** in yield 82%. Then **5a** (0.5 g, 1.15 mmol) was put to catalytic hydrogenation in ethanol (30 mL) with Pd/C (10%, 0.2 g) as catalyst under 3 atm of hydrogen at room temperature. After removing the solvent, the crude product was recrystallized in ethanol to afford **1a** as white solid. Similar procedure gave compound **1b** as colorless crystal.

2.3.1 *(2S,4R)-4-(Dodecyloxy)pyrrolidine-2-carboxylic acid **1a***

White solid (0.250 g, 84%), mp 148–150 °C; $[\alpha]_D^{20} = -15.2$ (c 0.4, $CHCl_3$); IR (KBr, cm^{-1}): 3431, 2953, 2922, 1629, 1576, 1392, 1094; ^1H NMR ($CDCl_3$) δ: 0.88 (t, $J = 7.2$ Hz, 3H, CH_3), 1.28 (m, 18H, $9CH_2$), 1.51 (m, 2H, CH_2), 2.07 (m, 1H, CHHCHCO), 2.37 (m, 1H, CHHCHCO), 3.23 (m, 1H, NCHH), 3.35(m, 2H, OCH_2), 3.64 (m, 1H, NCHH), 4.11 (m, 2H, 2CH). 5.40–9.40 (br, 2H, NH and COOH); ^{13}C NMR ($CDCl_3$) δ: 14.1 (CH_3), 22.7 (CH_2), 26.1 (CH_2), 29.4–29.7 ($6CH_2$), 31.9 (CH_2), 35.1 ($CHCH_2$), 50.3 (NCH_2), 60.5 (NCH), 69.4 (OCH_2), 77.5 (OCH), 173.7 (C=O); HRMS (ESI) *m/z*: calcd for $C_{17}H_{33}NO_3Na$ $(M + Na)^+$ 322.2353, found 322.2336.

2.3.2 *(2S,4R)-4-(Hexyloxy)pyrrolidine-2-carboxylic acid **1b***

Colorless crystal (0.357 g, 83%); mp 173–174 °C, $[\alpha]_D^{20} = -35.1$ (c 0.5, $CHCl_3$). IR (KBr, cm^{-1}) : 2958, 2933, 2854, 2794, 2410, 1621, 1578, 1447, 1386, 1124; ^1H NMR ($CDCl_3$) δ: 0.88 (t, $J = 6.8$ Hz, 3H, CH_3), 1.23–1.30 (m, 6H, $3CH_2$), 1.49–1.54 (m, 2H, CH_2), 2.11–2.17 (m, 1H, CHHCHCO), 2.36–2.41 (m, 1H, CHHCHCO), 3.35–3.41 (m, 3H, OCH_2 and NCHH), 3.51–3.56 (m, 1H, NCHH), 4.12–4.20 (m, 2H, 2CH); ^{13}C NMR ($CDCl_3$) δ: 14.0 (CH_3), 22.6 (CH_2), 25.7 (CH_2), 29.6 (CH_2), 31.7 (CH_2), 35.4 (CH_2), 50.0 (NCH_2), 60.2 (NCH), 69.5 (OCH_2), 78.0 (OCH), 173.7 (C=O); HRMS (ESI) *m/z*: calcd for $C_{11}H_{21}NO_3Na$ $(M + Na)^+$ 238.1419, found 238.1417.

Crystals suitable for X-ray analysis were obtained by recrystallization from ethyl acetate at room temperature. CCDC-299797 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2.4 Preparation and Determination of Diastereoselective Ratios and Enantiomeric Excess of Aldol Products

2.4.1 *Reactions in Organic Solvents*

Aldehyde (0.33 mmol) and ketone (0.4 mL) were added to solvent (1.2 mL) at room temperature in aerial atmosphere followed by addition of catalyst. The mixture was then stirred for 24–48 h. When acetone was used as aldol donor, the reaction mixture was directly put to separate through thin layer chromatography on silica gel after reaction to give pure aldol product (eluent: mixture of petroleum ether and ethyl acetate). When cyclohexanone was used, the reaction mixture was treated with saturated ammonium chloride aq. solution, extracted with ethyl acetate, dried ($MgSO_4$), filtered and concentrated to give pure aldol product through thin layer chromatography on silica gel (petroleum ether/ethyl acetate). 1 mL cyclohexanone was used in the reaction in neat cyclohexanone. The *anti*/*syn* ratio were obtained by isolated yields or determined by chiral HPLC. The enantiomeric excesses were determined by chiral HPLC [30].

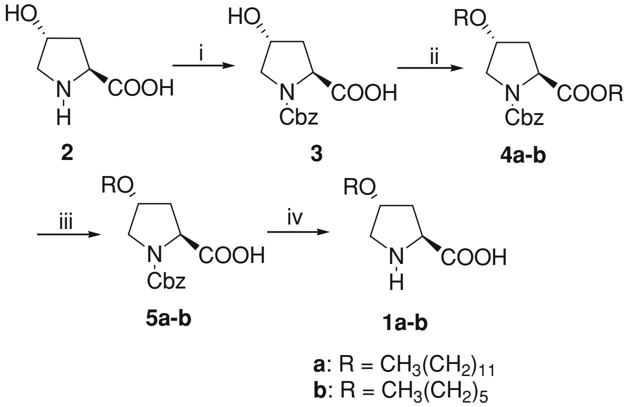
2.4.2 *Reactions in Water*

0.33 mmol of aldehyde was added to the mixture of indicated amounts of ketone, water and catalyst. After being stirred at indicated temperature for the indicated time, the mixture was treated with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and concentrated to give pure aldol products through thin layer chromatography on silica gel (petroleum ether/ethyl acetate). The *anti*/*syn* ratio were obtained by isolated yields or determined by chiral HPLC. The enantiomeric excesses were determined by chiral HPLC [30].

3 Results and Discussion

3.1 Synthesis of **1a** and **1b**

1a–b were readily prepared from (2*S*,4*R*)-4-hydroxyproline by the procedure shown in Scheme 1. Commercially available (2*S*,4*R*)-4-hydroxyproline **2** was firstly converted to compound **3** using BTC (bis(trichloromethyl) carbonate) and benzyl alcohol [33]. **4a–b** were prepared by the



Scheme 1 Synthesis of compounds **1a–b**. Reagents and conditions: (i) BTC, BnOH; then aq. Na_2CO_3; (ii) RBr, NaH, DMF; (iii) NaOH/MeOH/H_2O, rt, then HCl (aq); (iv) H_2, Pd/C, EtOH

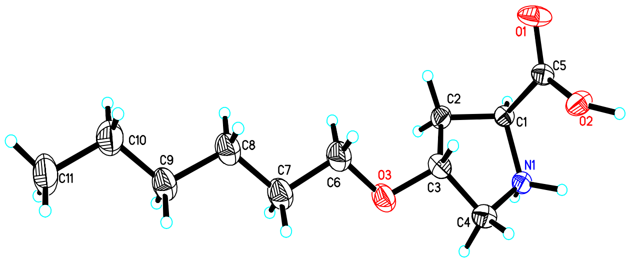


Fig. 1 Crystal structure of compound **1b**

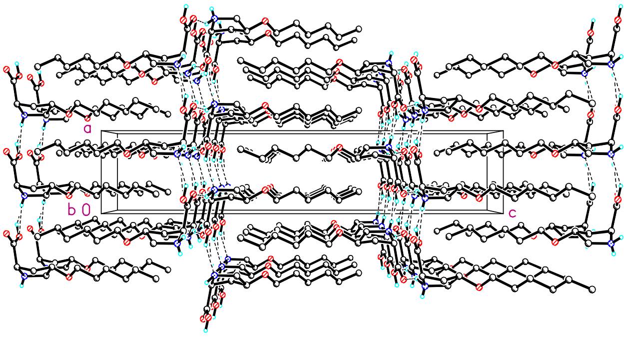


Fig. 2 Packing diagram of compound **1b**

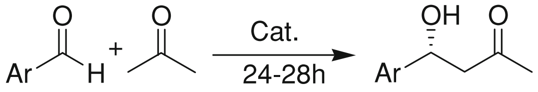
reaction of compound **3** with corresponding alkyl bromide in the presence of NaH in dry DMF. After hydrolysis of **4a–b** in NaOH/H_2O/MeOH solution followed by catalytic hydrogenation with Pd/C, **1a** and **1b** were obtained in good yields. The single crystal structure of **1b** was analyzed, and the molecular structure was shown in Fig. 1. The packing diagram shown in Fig. 2 demonstrates the existence of strong hydrophobic/hydrophilic interaction in the molecular stack.

3.2 Aldol Reactions Catalyzed by 1a–b in Organic Solvents

The catalytic activities of **1a** and **1b** on the aldol reaction in organic solvents were firstly evaluated. The results of the reactions between acetone and different aromatic aldehydes are summarized in Table 1. In the presence of 20 mol% catalysts, **1a** and **1b** showed similar enantioselectivity, but **1a** showed higher catalytic activity than **1b** (entries 1–8). This might be attributed to the better lipophilicity of **1a** with longer chain than that of **1b** with shorter one. If the loading of catalyst **1a** went down to 5 mol%, *o*-nitrobenzaldehyde and *p*-nitrobenzaldehyde gave aldol products in high yields with 84% and 79% enantiomeric excess, respectively (entries 9–10). These results were better than that of 30 mol% of proline itself being used, in which case the enantiomeric excesses of the aldol products *p*-4-hydroxyl-4-(4′-nitrophenyl)-butan-2-one were 76% (in DMSO) and 67% (in acetone), respectively (entry 11) [34]. Additionally, acetone is much easier to be removed than DMSO after reaction.

In order to scope the substrate, cyclohexanone was then used as aldol donor, and the results are summarized in Table 2. The effects of solvents were investigated firstly

Table 1 Direct asymmetric aldol reactions of acetone and various aldehydes catalyzed by **1a** and **1b** in neat acetone



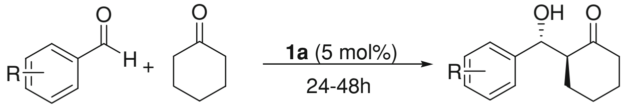
Entry	Ar	Catalyst	Cat. loading (mol%)	Yield (%)[a]	ee (%)[b]	Config.
1	*o*-$NO_2C_6H_4$	**1a**	20	80	77	*R*
2	*o*-ClC_6H_4	**1a**	20	83	58	*R*
3	*o*-$NO_2C_6H_4$	**1b**	20	72	79	*R*
4	*o*-ClC_6H_4	**1b**	20	69	60	*R*
5	*p*-$NO_2C_6H_4$	**1a**	20	78	77	*R*
6	*m*-ClC_6H_4	**1a**	20	92	63	*R*
7	*m*-$NO_2C_6H_4$	**1a**	20	88	72	*R*
8	*o*-$MeOC_6H_4$	**1a**	20	61	63	*R*
9	*o*-$NO_2C_6H_4$	**1a**	5	88	84	*R*
10	*p*-$NO_2C_6H_4$	**1a**	5	82	79	*R*
11	*p*-$NO_2C_6H_4$	L-proline (30 mol%)	20	68	76 (67)[c]	*R*

[a] Isolated yield after thin layer chromatography on silica gel

[b] The ee values were determined by HPLC on chiralpak AD or chiralcel OD-H column by comparison with authentic sample, and the major enantiomer was assigned to be *R* according to [33]

[c] Reported in literature [33], DMSO or acetone (in parentheses) was used as solvent

Table 2 Direct aldol reaction of cyclohexanone with aromatic aldehydes catalyzed by **1a** in organic solvents



Entry	R	Solvent	*T*	Yield (%)[a]	*Anti*/*syn*[b]	ee for *anti* (%)[c]
1	*o*-NO_2	THF	rt	53 (27)[d]	89:11	93
2	*o*-NO_2	THF	0	43 (26)[d]	83/17	89
3	*o*-NO_2	CH_2Cl_2	rt	51 (29)[d]	83:17	92
4	*o*-NO_2	CH_2Cl_2	0	37 (37)[d]	77:23	91
5	*o*-NO_2	DMF	rt	52	84:16	92
6	*o*-NO_2	DMF	0	60	88:12	89
7	*o*-NO_2	Cyclohexanone	rt	98	94:6	91
8	*o*-NO_2	Cyclohexanone	0	99	98:2	96
9	*m*-NO_2	Cyclohexanone	0	97	96:4	80
10	*p*-NO_2	Cyclohexanone	0	98	98:2	69
11	*o*-Cl	Cyclohexanone	0	99	94:6	59
12	*m*-Cl	Cyclohexanone	0	99	94:6	62
13	*p*-Cl	Cyclohexanone	0	93	90:10	70
14	*m*-Br	Cyclohexanone	0	97	65:35	73
15[e]	*o*-NO_2	Cyclopentanone	0	91	55:54	58 (94)[f]

[a] Isolated yield after TLC on silica gel

[b] Isolated or determined by HPLC

[c] Determined by chiral HPLC

[d] Recovered aldehyde in parentheses

[e] Cyclopentanone was used

[f] Value for *syn*-isomer

using the reaction of *o*-nitrobenzaldehyde with cyclohexanone as model. In the presence of 5 mol% of **1a** at room temperature or 0 °C, the *anti*-aldol products were all the major products and the enantioselectivities were all high for the examined solvents (entries 1–8, 89–96% ee for *anti*-isomer). The reaction at 0 °C was slower than the reaction at room temperature, but the enantioselectivity was similar. Remarkably, the reaction in cyclohexanone was much faster than that in other solvents (entries 7–8), and the aldol product was obtained in 99% yield with 98% *anti*-isomer and 96% ee at 0 °C in 24 h (entry 8). Under this condition, other aldehydes were almost quantitatively transformed into aldol products with high to excellent diastereoselectivity and moderate to good enantioselectivity (entries 10–14).

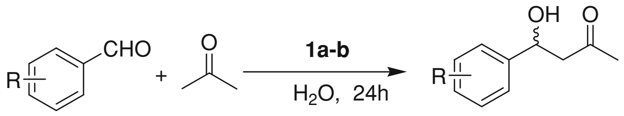
The reaction of cyclopentanone with *o*-nitrobenzaldehyde catalyzed by 5 mol% of **1a** was also tested. The aldol product was obtained in 91% yield with 55:45 of *anti*/*syn* ratio, 94% ee for *syn*-isomer and 58% ee for *anti*-isomer (Table 2, entry 15). This result is different from the case of cyclohexanone, in which the *anti*-isomers are the major with high enantioselectivities.

3.3 Aldol Reactions Catalyzed by **1a–b** in Water

It has been reported that an anionic surfactant sodium dodecyl sulfate (SDS) could accelerate the proline-catalyzed aldol reaction of aldehyde with acetone in water and gave racemic aldol product [22]. Considering that the amphiphilic compounds **1a** and **1b** can be seen as chiral ampholytic surfactants and catalysts, we induce that they may promote the aldol reaction enantioselectively in water. Their catalytic efficiency on the aldol reaction of acetone with aromatic aldehydes in water were tested primarily according to the method cited in the literature [22], and the results are summarized in Table 3. When *o*-nitrobenzaldehyde, acetone and 20 mol% of **1a** in water were put to react at 20 °C for 24 h, the aldol product was obtained in 23% yield with 33% ee. Although the enantioselectivity was moderate, the result was still encouraging compared with the results reported in the literature (Table 3, entry 1) [22]. When this reaction was performed at 40 °C, both the yield and the enantioselectivity increased distinctively (Table 3, entry 2). When *m*-nitrobenzaldehyde was used as aldol acceptor, the aldol product was also obtained enantioselectively with moderate enantioselectivity (Table 3, entry 4). The enantioselectivity for the aldol product of *p*-nitrobenzaldehyde with acetone was poor (18% ee, Table 3, entry 3), but surprisingly, the configuration of the major enantiomer of the aldol product was (*S*) retro to that in organic solvents (which was (*R*)). This phenomenon was only reported as Zn-proline was used as catalyst [35]. When the loading of catalyst **1a** decreased, the reaction rate slowed somewhat, but the enantioselectivity enhanced obviously (entries 2, 7, and 8). Even if the loading of catalyst decreased to 5 mol%, the aldol product could still be obtained in 46% yield with up to 62% ee. Both the reactivity and enantioselectivity of **1b** on the aldol reaction in water were lower than that of **1a** (Table 3, entries 5 and 6).

Although the primary experiments demonstrated that **1a** could catalyze the aldol reaction enantioselectively in water, the yield and enantiomeric excess were still moderate. Considering that the amount of water may affect the reaction, we then investigated the influence of the amount of water on the aldol reaction using *o*-nitrobenzaldehyde as aldol acceptor in the presence of 5 mol% **1a**. For operational simplicity, the reactions were performed at room temperature, and the results are shown in Table 4. From the results we can see that the amount of water affected both the reactivity and the enantioselectivity. As the amount of

Table 3 Direct aldol reactions of acetone and aromatic aldehydes catalyzed by **1a** and **1b** in water[a]



Entry	R	Catalyst	Cat. loading (mol%)	Temp (°C)	Yield (%)[b]	ee (%)[c]	Config.[d]
1	*o*-NO_2	**1a**	20	20	23	33	*R*
2	*o*-NO_2	**1a**	20	40	64	44	*R*
3	*p*-NO_2	**1a**	20	40	48	18	*S*
4	*m*-NO_2	**1a**	20	40	53	48	*R*
5	*o*-NO_2	**1b**	20	40	42	3	*R*
6	*p*-NO_2	**1b**	20	40	32	11	*S*
7	*o*-NO_2	**1a**	10	40	53	54	*R*
8	*o*-NO_2	**1a**	5	40	46	62	*R*

[a] 0.33 mmol aldehyde, 0.5 mL acetone and 2 mL water were used

[b] Isolated yield after thin layer chromatography on silica gel

[c] Determined by chiral HPLC

[d] Determined according to [33]

Table 4 Direct aldol reaction of *o*-nitrobenzaldehyde and acetone catalyzed by 5 mol% **1a** at room temperature

Entry	H_2O/ketone (V)[a]	Yield (%)[b]	ee (%)[c]	Config.[d]
1	0	88	84	*R*
2	0.5	58	1	*S*
3	1.0	42	9	*S*
4	2.0	32	69	*R*
5	4.0	28	77	*R*

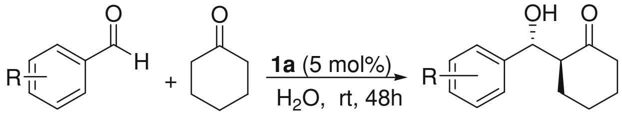
[a] 0.33 mmol aldehyde, 0.4 mL acetone were used

[b] Isolated yield after thin layer chromatography on silica gel

[c] Determined by chiral HPLC

[d] Determined according to [33]

Table 5 Direct aldol reaction of aldehydes with cyclohexanone catalyzed by **1a** in water[a]



Entry	R	H_2O/ketone (V)	Yield (%)[b]	*Anti*/*syn*[c]	ee (%)[d]
1	*o*-NO_2	0	98	94:6	91
2	*o*-NO_2	0.5	98	95:5	99
3	*o*-NO_2	1.0	89	97:3	96
4	*o*-NO_2	2.0	99	99/1	90
5	*o*-NO_2	4.0	92	97:3	76
6	*m*-NO_2	0.5	93	97:3	98
7	*p*-NO_2	0.5	92	97:3	98
8	*o*-Cl	0.5	93	94:6	99
9	*m*-Cl	0.5	97	96:4	98
10	*p*-Cl	0.5	96	94:6	98
11	*p*-F	0.5	85	82:18	98
12	*m*-Br	0.5	96	93:7	83
13	*o*-CH_3O	0.5	67	98:2	98

[a] 0.33 mmol of aldehyde, 0.4 mL of ketone was used

[b] Yield refers to the combined yield of isolated diastereomers

[c] Isolated or determined on HPLC

[d] Determined by chiral HPLC

water increased from 0 to 1.6 mL, the yield decreased from 88% to 28% (Table 4, entries 1–5). In the absence of water, the configuration of the major enantiomer of the aldol product was *R*, and the enantiomeric excess was 84%. But when 0.2 mL of water was used, the aldol products were almost racemic (entry 2). If the amount of water increased to 0.4 mL, the (*S*)-aldol product was excess with 9% ee (entry 3). As the amount of water increased to 0.8 or 1.6 mL, however, (*R*)-product was furnished with good enantiomeric excess (entries 4 and 5, up to 77% ee). To clarify this phenomenon, we repeated the reaction with different amount of water (from 0.1 to 0.9 mL), and similar results were obtained. However, when *p*-nitrobenzaldehyde was used as aldol acceptor, the aldol products were obtained with 11–37% enantiomeric excess for (*S*)-enantiomer in the presence of 0.1–0.9 mL water. From the accepted enamine mechanism of L-proline-catalyzed aldol reaction we know the (*R*)-aldol product would be furnished, and the reversed configuration may not be obtained directly. This phenomenon remains unclear at present. We consider that the reason for this phenomenon may attribute to the retro-aldol reaction with some enantioselectivity, which can enrich the minor enantiomer of the aldol product, or water molecules participate in the formation of the transition state. Further studies are in progress in our laboratory now.

To scope the substrates, we then tested other ketones such as cyclic ketones as aldol donors. Five mol% of **1a** was used as catalyst. Remarkably, when cyclohexanone was employed as aldol donor, the reaction mixture presents an emulsion under vigorous stirring, and the *anti*-aldol products were obtained with high yields, excellent diastereo- and enantioselectivities. Additionally, the influences of the amount of water were different compared with the cases of acetone as donor (Table 5). As the amount of water increased from 0.2 to 1.6 mL, the yields were all high (>90%), but the enantioselectivity decreased slightly (entries 2–5). The best result was obtained as 0.2 mL of water (water/ketone = 1/2) was used (entry 2, 98% yield, 95% dr and 99% ee). According to [31, 32, 36, 37], the reason for the difference between cyclohexanone and acetone as donors was proposed as follows: the catalyst acts as a chiral surfactant. Cyclohexanone is more lipophilic than acetone and could assemble with catalyst and aldehyde in water (independent of the amount of water) through hydrophobic interactions and sequester the transition state from water. Therefore, the reaction proceeded efficiently in the aggregated organic phase to afford the aldol products with higher yield and enantioselectivity through a transition state similar to that in organic solvent. Whereas acetone is mutual soluble with water, so it could not efficiently combined with catalyst and aldehyde, and this lead to the decrease of the yield as the amount of water increased.

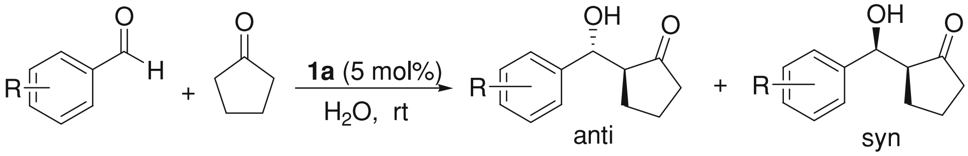
Under this optimal condition (water/ketone = 1/2, 5% mol catalyst), other aldehydes also gave *anti*-aldol product in high yield (most between 93 and 97%) with 94–98% dr and 98–99% ee (entries 6–11). Even the reaction of *o*-methoxybenzaldehyde gave the aldol product in 67% yield, 98% dr and 98% ee after 5 days (entry 13). The yields, diastereoselectivity, and enantioselectivity are comparable to the results reported by Li et al. [32], but the catalyst loading in the present study (5 mol%) was much less than the reported work where 15 mol% of catalyst was used.

When cyclopentanone was used as aldol donor, the *anti*-aldol products were also obtained in excellent enantioselectivity (Table 6, 97% and 92% ee were achieved for *o*-nitrobenzaldehyde and *m*-nitrobenzaldehyde as acceptor, respectively), although the diastereoselectivities were not so high as that of cyclohexanone.

4 Conclusion

In summary, a novel simple amphiphilic proline derived catalyst bearing long alkyl chain on the 4-position via stable ether bond has been developed. In comparison with the parent proline, the catalytic activities with 5 mol% of **1a** are better than that with 30 mol% of proline itself being used both in organic solvents and in water. Especially with cyclic ketones as aldol donors in water, high yields, excellent enantioselectivities, and *anti*-diastereoselectivities are achieved for a broad range of aromatic aldehydes at room temperature. The catalytic role of this novel amphiphilic chiral molecule is more like an enzyme process than that of proline itself does. Besides, we have observed first that the configuration of aldol product of acetone with aldehyde catalyzed by substituted proline is related to the amount of water. Further studies on the catalytic mechanism in water and the application of this kind of catalysts in other related reactions are in progress.

Table 6 Direct aldol reaction of aldehydes with cyclopentanone catalyzed by **1a** in water[a]



Entry	R	Yield (%)[b]	*Anti/syn*[c]	ee (%)[d]
1	*o*-NO_2	96	82:20	97 (16)
2	*m*-NO_2	95	54:46	92 (77)

[a] 0.33 mmol of aldehyde, 0.4 mL of ketone was used

[b] Yield refers to the combined yield of isolated diastereomers

[c] Determined by chiral HPLC

[d] Determined by chiral HPLC

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