Chem Biol Drug Des 2010; **76:** 181–186

doi: 10.1111/j.1747-0285.2010.00998.x

Research Letter

The Mimic of Type II Aldolases Chemistry: Asymmetric Synthesis of β-Hydroxy Ketones by Direct Aldol Reaction

Zhijin Lu[1], Haibo Mei[1], Jianlin Han[1,*] and Yi Pan[1,2,*]

[1]*School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, China*
[2]*State Key Laboratory of Coordination Chemistry, Nanjing University, Nanjing 210093, China*
**Corresponding authors: Jianlin Han, molab@nju.edu.cn; Yi Pan, yipan@nju.edu.cn*

An efficient direct aldol reaction has been developed for the synthesis of chiral β-hydroxy ketone using a combination of C_1-symmetric chiral prolinamides based on *o*-phenylenediamine and zinc triflate as catalyst. The reaction was convenient to carry out in aqueous media with up to 98% chemical yields and up to 94% ee values. The current strategy can be regarded as the analogue of aldolase type II, which suggests a new pathway for the designing of new organocatalysts.

Key words: aldol reaction, chiral prolinamides, zinc triflate, β-hydroxy ketone

Received 15 December 2009, revised 7 May 2010 and accepted for publication 7 May 2010

The development of stereoselective and enantioselective aldol reaction has become an interesting and challenging topic in modern organic and medicinal chemistry (1–3), because the resulting chiral β-hydroxy ketones belong to an extremely important class of biological compounds. In fact, β-hydroxy ketones can serve as versatile building block for the asymmetric synthesis of carbohydrates, amino acids and many other biomolecules (4–6). They also provide privileged structural functionalities that exist in many important natural products (7–12). For example, the β-hydroxy ketones functionalities exist in macrolide classes of antibiotics such as telithromycin and cethromycin which are targeted primarily against Gram-positive bacterial strains including *Streptococcus pneumoniae* and *S. pyogenes*, fastidious Gram-negative strains including *Haemophilus influenzae* and *Moraxella catarrhalis*, atypicals *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophilia* (13). They were also found in conagenin that can improve the antitumor efficacy of adriamycin and mitomycin C against murine leukemias, which suggest its potential utility for cancer chemotherapy (14).

In virtue of the importance of chiral β-hydroxy ketones, several approaches aiming to prepare them have been reported in the last decade (15–27). Among all the catalytic direct aldol, the most attractive one is the mimic of the actions of the enzymes. Although the direct catalytic aldol systems which were assumed to proceed through an enamine mechanism by mimic of aldolase type I have been well explored (28–32), the direct aldol systems by using the methods analogue to the actions of aldolase type II containing a zinc cofactor have still remained challenging. In fact, there were only a few reports for direct aldol reactions promoted by the zinc complexes with N-donor ligands in the presence of water until now (33–38). Herein, we reported a chiral ligands and zinc triflate catalyzed asymmetric direct aldol reaction with water as solvent. To our knowledge, this is the first example that mimics type II aldolase utilizing C_1-symmetric organic molecular based on *o*-phenylenediamine as chiral ligand.

Results and Discussions

According to the mechanism of type II aldolase (33–38), we designed and prepared a series of chiral ligands (Figure 1). These chiral ligands **1–6** were easily prepared from proline and aniline or *o*-phenylenediamine in high yields. Most of these ligands have C_1 symmetry, expect compound **4**, which is a C_2-symmetric ligand. Then, all these compounds were used in the direct aldol reactions. The reactions were carried out between cyclohexanone and *p*-nitro-

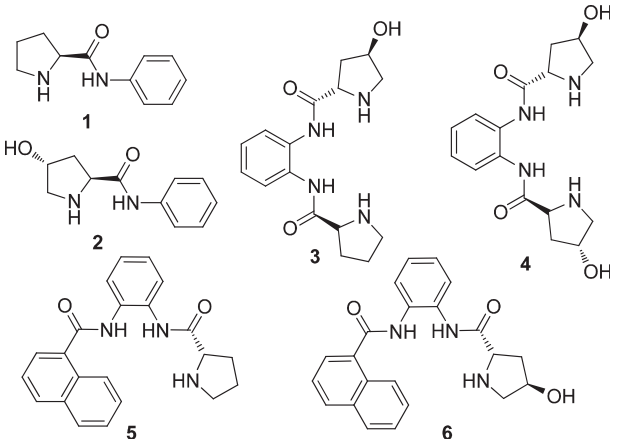


Figure 1: Structure of the catalysts **1**–**6**.

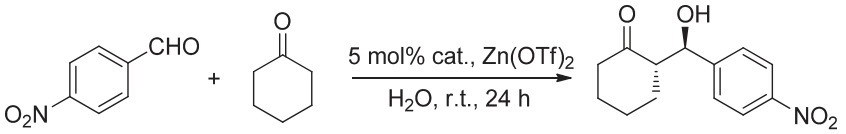
benzaldehyde in aqueous media (Table 1). As shown by Table 1, all the designed chiral prolinamide derivatives worked well in the direct aldol reactions and gave the desired β-hydroxy ketone in good yields and good enantioselectivities. Addition of zinc trifluoromethanesulfonate could obviously improve the diastereoselectivities and enantioselectivities (entry 10 versus entry 9). Good result was obtained when the combined catalyst of zinc triflate and the C_2-symmetric prolinamide ligand **4** containing two amino acid moities was used (Table 1, entry 8). However, the best result with respect to yield and enantioselectivity was observed with C_1-symmetric prolinamide ligand **5** and $Zn(OTf)_2$ as additive (96% yield and 93% ee, Table 1, entry 10). The loading amount of $Zn(OTf)_2$ in the reaction was also investigated. The use of 5 mmol% of $Zn(OTf)_2$ seemed best for the reaction (Table 1, entry 10). Although lower loading of $Zn(OTf)_2$ slightly decreased both yields and selectivities (Table 1, entries 15 and 16), no improvement was detected when more than 10 mmol% catalyst was used (Table 1, entries 13 and 14).

From Table 1, it was also found that the prolinamides and zinc triflate combined catalyst can work very well in aqueous media. Then, the solvents used for this reaction were examined (Table 2). The chemical yields were increased by the use of water as co-solvent (Table 2, entries 3–5). The best result was observed when the ratio of cyclohexanone to water was 5:1, and 96% chemical yield and 93% ee value were obtained (Table 2, entry 5). Almost no desired product was detected when DMSO was used as solvent (Table 2, entry 7), and only medium yield and enantioselectivity were found with neat cyclohexanone (Table 2, entry 6) or tetrahydrofuran (Table 2, entry 2) as solvent. It is obvious that water is helpful to form product and control the stereoselectivity of the reaction. Reaction temperature was also found to have some effect on the current catalytic system. When the temperature was increased to 50 °C, both the diastereoselectivity and the enantioselectivity decreased (Table 2, entry 8). Decreasing the temperature to 3 °C still did not show any improvement on diastereoselectivity (Table 2, entry 10). From the results above, we found that these new chiral ligands together with zinc triflate could act as catalysts for direct aldol in aqueous media. Both zinc triflate and chiral prolineamides were essential for the catalytic system. In this respect, the combined catalysts could be regarded as mimic of type II aldolase, and an enamine was presumed to be formed in the active site (33–38).

After the optimized reaction conditions was obtained, several aldol reactions under the above-mentioned conditions were carried out to check their catalytic activities, and the results are summarized in Table 3. Several aromatic aldehydes were suitable substrates for the reaction and gave corresponding β-hydroxy ketone with good to excellent yields. Especially for aldehydes with strong electron-withdrawing group (NO_2) on the aromatic ring, the reaction gave excellent yields, high enantioselectivities (Table 3, entries 1–3). However, for the aldehyde substituted with a CF_3 group, only moderate diastereoselectivity was found (*anti*:*syn* = 59:41, Table 3, entry 7). In the cases of the aldehydes with electron-donating group (OMe) on the aromatic ring, such as 4-methoxybenzaldehyde and 4-methylbenzaldehyde, only a trace amout of desired products were observed even after the reaction time had been extended to 72 h.

Acetone was also used as substrate in the direct aldol reaction with *p*-nitrobenzaldehyde under the same reaction condition

Table 1: Screening of catalysts in the reaction between cyclohexanone and *p*-nitrobenzaldehyde[a]

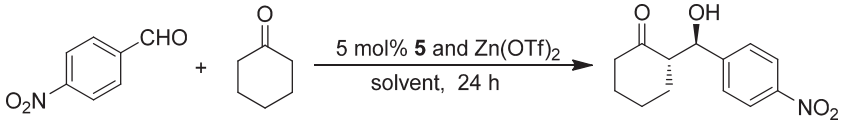


anti-**7a**

Entry	Ligand	$Zn(OTf)_2$ (mol%)	Yield (%)[b]	*Anti*/*syn*[c]	ee (%)[c]
1	**1**	0	88	85:15	80
2	**1**	5	85	90:10	87
3	**2**	0	90	87:13	80
4	**2**	5	88	88:12	85
5	**3**	0	92	78:22	71
6	**3**	5	95	78:22	78
7	**4**	0	90	72:28	77
8	**4**	5	88	83:17	86
9	**5**	0	95	73:27	78
10	**5**	5	96	83:17	93
11	**6**	0	94	69:31	77
12	**6**	5	95	75:25	92
13	**5**	20	30	61:39	89
14	**5**	10	92	60:40	82
15	**5**	2.5	88	62:38	88
16	**5**	1.25	90	60:40	73

[a]Reaction conditions: aldehyde (75.5 mg, 0.5 mmol), cyclohexanone (1 mL), ligand (5 mol%), water (0.2 mL), room temperature.
[b]Isolated yield.
[c]Determined by chiral HPLC (Chiralpak AD-H). This system seems to be selective for the formation of the R configuration.

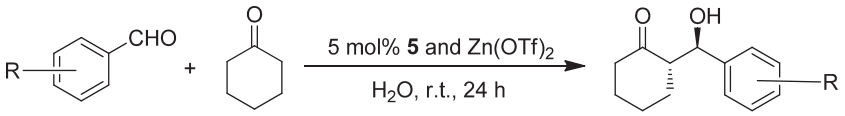
Table 2: The optimization of the current aldol reaction conditions[a]



Entry	Solvent	T (°C)	Yield (%)[b]	*Anti/syn*[c]	ee (%)[c]
1	Water	25	95	74:26	79
2	THF/H_2O = 9:1	25	50	83:17	89
3	cyclo/H_2O = 9:1	25	98	68:32	88
4	Cyclo/H_2O = 1:1	25	97	72:28	87
5	Cyclo/H_2O =5:1	25	96	83:17	93
6	Cyclohexanone	25	60	58:42	69
7	DMSO	25	<10%	–	–
8	Cyclo/H_2O = 5:1	50	98	64:36	79
9	Cyclo/H_2O = 5:1	30	98	88:12	94
10	Cyclo/H_2O = 5:1	3	90	73:27	96

[a]Reaction conditions: aldehyde (75.5 mg, 0.5 mmol), cyclohexanone (260 μL, 2.5 mmol), 5 mmol% 5 and 5 mmol% $Zn(OTf)_2$ in 1 mL solvent.
[b]Isolated yield.
[c]Determined by chiral HPLC (Chiralpak AD-H). This system seems to be selective for the formation of the R configuration.

Table 3: Catalytic aldol reaction between cyclohexanone and aryl aldehydes[a]



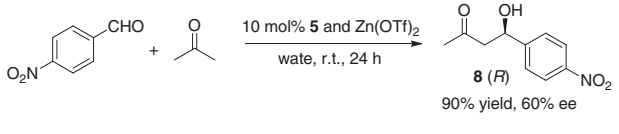
anti-**7**

Entry	R	Product	Yield (%)[b]	*Anti/syn*[c]	ee (%)[c]
1	4-NO_2	**7a**	98	88:12	94
2	3-NO_2	**7b**	92	60:40	87
3	2-NO_2	**7c**	90	90:10	95
5	2-naphthyl	**7d**	34	82:18	84
6	4-CN	**7e**	83	46:54	74
7	4-CF_3	**7f**	92	59:41	85

[a]Reaction conditions: aldehyde (0.5 mmol), cyclohexanone (1 mL), water (0.2 mL), room temperature.
[b]Isolated yield.
[c]Determined by chiral HPLC (Chiralpak AD-H, OD-H and AS-H). This system seems to be selective for the formation of the R configuration.

(Scheme 1). The corresponding product **8** was formed with excellent chemical yield (90% yield). However, It was obvious that acetone gave a little bit lower enantioselectivity compared to the cyclohexanone substrates, and only 60% ee value was obtained.

The mechanism of this catalytic system is believed to be similar to that of previous reported zinc-proline complex catalyzed aldol reactions (39,40), which can be assumed as the mimic of Type II aldolases. The Zn^{2+} ion may co-ordinate to ketone and can promote the formation of ketone-enolate. Although the asymmetric ligand provides a chiral environment, resulting in the enantioselectivity of the current system.



Scheme 1: Aldol reaction with acetone.

In summary, a series of C_1-symmetric chiral prolinamides based on *o*-phenylenediamine were designed and were successfully used as chiral ligands in metal-assisted asymmetric direct aldol reactions in aqueous media for the first time. This catalytic direct aldol provides an easy access to the chiral β-hydroxy ketones with good diastereoselectivities (dr up to 88:12) and high enantioselectivities (up to 96% ee). This catalytic results were really good in the area of mimicking the type II aldolase. These new C_1-symmetric chiral prolinamides based on *o*-phenylenediamine explore an interesting area of direct aldol reaction catalyzed by zinc salt and organocatalysts in aqueous media.

Experimental Section

General remarks

Cyclohexanone was distilled and *p*-nitrobenzaldehyde was sublimated before use. All reagents not listed were used as received from common commercial sources. NMR spectra were obtained on Bruker 300 or 500 MHz spectrometer in DMSO-d_6 or $CDCl_3$, and chemical shifts are reported in ppm using tetramethylsilane as internal standard. IR and ESI-MS spectra were measured on Bruker Vector 22 as KBr pellets and Finnigan Mat TSQ 7000 instruments (Finnigan, San Jose, CA, USA), respectively. Microanalyses were obtained on Perkin-Elmer 240 instruments (PerkinElmer, CT, USA), and melting points (mp) were determined with a digital electrothermal apparatus without further correction. Optical rotation measurements were determined at RT using HPLC-grade solvents. Analytical HPLC measurements were carried out on the Perkin-Elmer machine. Compound **1** was prepared according to the reported method (41).

General procedure for the synthesis of 2–6 (Data S2)

2: (*2S,4R*)-4- hydroxypyrrolidine-2-carboxylic acid (1.15 g, 5 mmol) and TEA (0.61 g, 6 mmol) were dissolved in THF (20 mL). To the solution was added dropwise ethylchloroformate (0.65 g, 6 mmol) at 0 °C. After the solution was stirred for 15 min, aniline (0.46 g, 5 mmol) was added. The resulting solution was stirred at 0 °C for 1 h, at room temperature for 16 h, detected by TLC. The reaction mixture was filtered and washed with THF, and the filtrate was evaporated to dryness. The residue was purified through chromatography on a silica gel column eluted with methanol and dichloromethane to give colorless oil. The colorless product were dissolved in CH_2Cl_2 (12 mL) and F_3CCOOH (3 mL) and stirred for 2 h; the reaction was treated by ammonia solution (10 mL) for 0.5 h; the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and removal of the solvent gave a white solid **2** with 90% yield $[\alpha]_D^{20}$ = −29.3 (c = 1.0, CH_3OH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.79 (s, 1H), 7.61-7.58 (m, 2H), 7.36-7.31 (m, 2H), 7.14-7.09 (m, 1H), 4.49-4.47 (t, *J* = 3.2 Hz 1H), 4.18-4.13 (t, *J* = 8.6 Hz 1H), 3.14-3.09 (dd, *J* = 1.5, 12.2 Hz 1H), 2.92-2.87 (dd, *J* = 3.0, 12.6 Hz, 1H), 2.42-2.34 (m, 1H), 2.09-2.00 (m, 1H).^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 137.6, 129.0, 124.2, 119.5, 73.2, 60.2, 55.3, 39.8. IR (KBr disc): 3450 cm^{-1}.ESI-MS: *m/z* = 207.24[M + H$^+$]. Anal. Calcd (%) for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58; Found: C, 64.03; H, 6.85; N, 13.55.

3: (*2S,4R*)-4-hydroxypyrrolidine-2-carboxylic acid (1.15 g, 5 mmol) and TEA (0.61 g, 6 mmol) were dissolved in THF (20 mL). To the solution was added dropwise ethylchloroformate (0.65 g, 6 mmol) at 0 °C. After the solution was stirred for 15 min, *o*-phenylenediamine (0.54 g, 5 mmol) was added. The resulting solution was stirred at 0 °C for 1 h, at room temperature for 16 h, detected by TLC. The reaction mixture was filtered and washed with THF, and the filtrate was evaporated to dryness. The residue was purified through chromatography on a silica gel column eluted with methanol and dichloromethane to give colorless oil ((*2S,4R*)-N-(2-aminophenyl)-4-hydroxypyrrolidine-2-carboxamide) with 72% yield.

Boc-protected proline (0.65 g, 3 mmol) and TEA (0.31 g, 3 mmol) were dissolved in THF (20 mL). To the solution was added dropwise ethylchloroformate (0.38 g, 3.5 mmol) at 0 °C. After the solution was stirred for 15 min, the intermedia obtained above (0. 96 g, 3 mmol) was added. The resulting solution was stirred at 0 °C for 1 h, at room temperature for 16 h, detected by TLC. The reaction mixture was filtered and washed with THF, and the filtrate was evaporated to dryness. The residue was purified through chromatography on a silica gel column eluted with methanol and dichloromethane to give colorless oil ((R)-tert-butyl 2-((2-((*2S,4R*)-4-hydroxypyrrolidine-2-carboxamido)phenyl)carbamoyl)pyrrolidine-1-carboxylate) with 65% yield. Then, the Boc-protect **3** was dissolved in CH_2Cl_2 (12 mL) and CF_3COOH (3 mL) and stirred for 2 h; the reaction was treated by ammonia solution (10 mL) for 0.5 h; the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and removal of the solvent gave brown oil **3** (0.61 g, 38% yield overall steps). $[\alpha]_D^{20}$ = −30.1 (c = 1.0, CH_3OH). ^{1}H NMR (300 MHz, DMSO-d_6): ^{1}H δ 9.87 (s, 1H), 7.67-7.61 (m, 2H), 7.15-7.12 (m, 2H), 4.22-4.21 (m, 2H), 3.92-3.87 (m, 2H), 3.74-3.69 (m, 2H), 2.95-2.78 (m, 4H), 2.10-1.98 (m, 2H), 1.88-1.78 (m, 2H), 1.71-1.59 (m, 2H).^{13}C NMR (75 MHz, DMSO-d_6): δ 174.4, 174.4, 131.0, 130.7, 125.4, 125.3, 124.4,.124.1, 71.9, 61.1, 60.3, 55.5, 47.2, 40.25, 30.9, 26.4. IR (KBr disc): 3422, 3332, 3234 cm^{-1}. ESI-MS: *m/z* = 319.33 [M + H$^+$]. Anal. Calcd (%) for $C_{16}H_{22}N_4O_3$ C, 60.36; H, 6.97; N, 17.60; Found: C, 60.29; H, 7.01; N, 17.55.

4: (*2S,4R*)-4-hydroxypyrrolidine-2-carboxylic acid (2.32 g, 10 mmol) and TEA (1.22 g, 6 mmol) were dissolved in THF (30 mL). To the solution was added dropwise ethylchloroformate (1.31 g, 12 mmol) at 0 °C. After the solution was stirred for 15 min, *o*-phenylenediamine (0.54 g, 5 mmol) was added. The resulting solution was stirred at 0 °C for 1 h, at room temperature for 16 h, detected by TLC. The reaction mixture was filtered and washed with THF, and the filtrate was evaporated to dryness. The residue was purified through chromatography on a silica gel column eluted with methanol and dichloromethane to give colorless oil (Bco-protect **4**) with 62% yield. Then, colorless Bco-protected **4** were dissolved in CH_2Cl_2 (12 mL) and CF_3COOH (3 mL) and stirred for 2 h. The reaction was treated by ammonia solution (10 mL) for 0.5 h; the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and removal of the solvent gave brown oil **4** (0.71 g, 42% yield overall steps).$[\alpha]_D^{20}$ = −45.7 (c = 1.0, CH_3OH). ^{1}H NMR (300 MHz, DMSO-d6): δ 9.88 (s, 1H), 7.65-7.62 (m, 2H), 7.15-7.11 (m, 2H), 4.22-4.20 (m, 2H), 3.92-3.87 (m, 2H), 2.83-2.82 (d, 2H), 2.07-2.00 (m, 2H), 1.88-1.80 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 174.4, 130.9, 125.4, 124.3, 71.9, 60.3, 55.5, 40.2. IR (KBr disc): 3434, 3340, 3201 cm^{-1}. ESI-MS: *m/z* = 335.33 [M + H$^+$]. Anal. Calcd (%) for $C_{16}H_{22}N_4O_4$ C, 57.47; H, 6.63; N, 16.76; Found: C, 57.55; H, 6.59; N, 16.72.

5: The *o*-phenylenediamine (1.08 g, 10 mmoL) and pyridine (0.96 g,12 mmol) were dissolved in the THF (20 mL). To the solution was added dropwise 1-naphthoyl chloride in THF (20 mL) in 30 min; the resulting solution was stirred at room temperature for 4 h, detected by TLC. Then, the mixture was filtered to get the solution of N-(2-aminophenyl)-1-naphthamide.

Boc-protected proline (1.61 g, 8 mmol) and TEA (0.82 g, 8 mmol) were dissolved in THF (20 mL). To the solution was added dropwise ethylchloroformate (1.08 g, 10 mmol) at 0 °C. After the solution was stirred for 15 min, the prepared solvent mentioned above was added. The resulting solution was stirred at 0 °C for 1 h at room temperature for 16 h and detected by TLC. The reaction mixture was filtered and washed with THF, and the filtrate was evaporated to dryness. The residue was purified through chromatography on a silica gel column eluted with methanol and dichloromethane to give colorless oil as Boc-protect **5**. Then, the colorless Boc-protect **5** was dissolved in CH_2Cl_2 (12 mL) and CF_3COOH (3 mL), and stirred for 2 h; the reaction was treated by ammonia solution (10 mL) for 0.5 h; the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and removal of the solvent gave brown oil **5** (2.34 g, 65% yield overall steps). $[\alpha]_D^{20}$ = 3.03 (c = 1.0, CH_3OH). ^1H NMR (300 MHz, DMSO-d_6): δ 10.38 (s, 1H), 10.33 (s, 1H), 8.46-8.44 (d, 1H), 8.19-8.16 (d, 1H), 8.14-8.11 (d, 1H), 8.06-8.03 (m, 1H), 7.98-7.96 (d, 1H), 7.68-7.61 (m, 3H), 7.46-7.44 (m,1H), 7.36-7.30 (m, 1H), 7.22-7.17 (m, 1H), 3.80-3.76 (m, 1H), 2.92-2.84 (m, 1H), 2.75-2.68 (m, 1H), 2.12-2.00 (m, 1H), 1.89-1.78 (m, 1H), 1.68-1.56 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 174.1, 168.5, 134.3, 134.2, 133.7, 131.0, 128.8, 128.4, 127.7, 126.4, 126.0, 125.4, 124.3, 122.0, 61.4, 47.2, 30.9, 26.4. IR (KBr disc): 3464, 3249 cm^{-1}. ESI-MS: *m/z* = 360.25 [M + H^+].Anal. Calcd (%) for $C_{22}H_{21}N_3O_2$ C, 73.52; H, 5.89; N, 11.69; Found: C, 73.46; H, 5.61; N, 11.64.

6: The *o*-phenylenediamine (1.08 g, 10 mmol) and pyridine (0.96 g,12 mmol) were dissolved in the THF (20 mL). To the solution was added dropwise 1-naphthoyl chloride in THF (20 mL) in 30 min, the resulting solution was stirred at room temperature for 4 h and detected by TLC. Then, the mixture was filtered to get the solution of N-(2-aminophenyl)-1-naphthamide.

(*2S,4R*)-4-Hydroxypyrrolidine-2-carboxylic acid (1.95 g, 8 mmol) and TEA (0.82 g, 8 mmol) were dissolved in THF (30 mL). To the solution was added dropwise ethylchloroformate (1.08 g, 10 mmol) at 0 °C. After the solution was stirred for 15 min, the solution obtained above (0.54 g, 5 mmol) was added. The resulting solution was stirred at 0 °C for 1 h, at room temperature for 16 h and detected by TLC. The reaction mixture was filtered and washed with THF, and the filtrate was evaporated to dryness. The residue was purified through chromatography on a silica gel column eluted with methanol and dichloromethane to give colorless oil as Boc-protected **6**. Then, the colorless Boc-protected **6** was dissolved in CH_2Cl_2 (12 mL) and CF_3COOH (3 mL) and stirred for 2 h; the reaction was treated by ammonia solution (10 mL) for 0.5 h; the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and removal of the solvent gave brown oil **6** (1.73 g, 46% yield overall steps). $[\alpha]_D^{20}$ = −30.4 (c = 1.0, CH_3OH). ^1H NMR (300 MHz, DMSO-d6): δ 10.34 (s, 1H), 10.29 (s, 1H), 8.42-8.39 (m, 1H), 8.15-8.10 (m, 2H), 8.05-8.02 (m, 1H), 7.96-7.93 (m, 1H), 7.67-7.59 (m, 3H), 7.45-7.42 (m,1H), 7.34-7.29 (m, 1H), 7.21-7.12 (m, 2H), 3.98-3.87 (m, 1H), 2.82-2.68 (m, 3H), 2.10-2.03 (m, 1H), 1.84-1.76 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 174.0, 168.5, 134.3,134.1, 133.7, 131.0, 130.3, 129.1, 128.8, 128.4, 127.6, 127.4, 127.2, 126.9, 126.4, 126.2, 125.9, 125.5, 124.4, 122.1. 71.9, 60.6, 55.4, 40.2, 28.6. IR (KBr disc): 3422, 3338 cm^{-1}; ESI-MS: *m/z* = 376.25 [M + H^+] Anal. Calcd (%) for $C_{22}H_{21}N_3O_3$ C, 70.38; H, 5.64; N, 11.19; Found: C, 70.30; H, 5.60; N, 11.25.

Typical procedure for the direct aldol reaction

Catalyst **5** (5 mol%, 0.025 mmol, 8.99 mg) and $Zn(OTf)_2$ (5 mol%, 0.025 mmol, 9.08 mg) were stirred in the solvent (1.2 mL, cyclohexanone:H_2O = 5:1) for 10 min. The 4-nitrobenzaldehyde (0.5 mmoL, 75.5 mg) was then added and the resulted mixture was stirred for the given time and temperature. The aqueous layer was decanted from the precipitated products and extracted with ether. The desired products **7** and **8** were obtained by flash chromatography and have been characterized to be identical to those of known samples (42) (Data S1).

Acknowledgments

We gratefully acknowledge National Natural Science Foundation of China (Grant No. 20772056) and Jiangsu 333 program (for Pan) for the generous financial support. The research funds for Pan from the Qing-Lan program of Jiangsu Province and the Kua-Shi-Ji program of the Education Ministry of China are also acknowledged.

References

1. Heathcock C.H. (1991) In: Trost B.M., Fleming I., Heathcock C.H., editors. Comprehensive Organic Synthesis, Vol. 2. Oxford: Pergamon; 133 p.
2. Carreira E.M. (1999) In: Jacobsen E.N., Pfaltz A., Yamamoto H., editors. Comprehensive Asymmetric Catalysis, Vol. 3, Chapter 29.1. Berlin, Germany: Springer; p 997–1066.
3. Shibasaki M., Yoshikawa N., Matsunaga S. (2003) In: Jacobsen E.N., Pfaltz A., Yamamoto H., editors. Comprehensive Asymmetric Catalysis, Supp. 1, Chapter 29.4. Berlin, Germany: Springer; p 135–142.
4. Machajewski T.D., Wong C.H. (2000) The catalytic asymmetric aldol reaction. Angew Chem Int Ed;39:1352–1374.
5. Heathcock H. (1984) In: Morrison J.D., editor. Asymmetric Synthesis, Vol. 3, Chapter 2. New York: Academic Press; p 111–212.
6. Masamune S., Choy W., Petersen J.S., Sita L.R. (1985) Double asymmetric synthesis and a new strategy for stereochemical control in organic synthesis. Angew Chem Int Ed Engl;24:1–30.
7. West L.M., Northcote P.T. (2000) Peloruside A: a potent cytotoxic macrolide isolated from the new Zealand marine sponge *mycale* sp. J Org Chem;65:445–449.
8. Höfle G., Bedorf N., Steinmetz H., Schomburg D., Gerth K., Reichenbach H. (1996) Epothilone A and B-novel 16-membered macrolides with cytotoxic activity: Isolation, crystal structure, and conformation in solution. Angew Chem Int Ed Engl;35: 1567–1569.
9. Ghosh A.K., Kass J., Anderson D.D., Xu X.M., Marian C. (2008) L-selectride-mediated highly diastereoselective asymmetric reductive aldol reaction: access to an important subunit for bioactive molecules. Org Lett;10:4811–4814.
10. Raghavan S., Rathore K. (2009) Asymmetric synthesis of (–)-tetrahydrolipstatin. Tetrahedron;65:10083–10092.

11. Dias L.C., Goncalves C.D.C.S. (2008) Total synthesis of (–)-basiliskamide B. Adv Synth Catal;350:1017–1021.
12. Malathong V., Rychnovsky S.D. (2009) Polyol synthesis with β-oxyanionic alkyllithium reagents: syntheses of aculeatins A, B, and D. Org Lett;11:4220–4223.
13. Magee T.V., Ripp S.L., Flanagan M.E. (2009) Discovery of azetidinyl ketolides for the treatment of susceptible and multidrug resistant community-acquired respiratory tract infections. J Med Chem;52:7446–7457.
14. Matsukawa Y., Isobe M., Kotsuki H., Ichikawa Y. (2005) Synthesis of (+)-conagenin. J Org Chem;70:5339–5341.
15. Aratake S., Itoh T., Okano T., Usui T., Shoji M., Hayashi Y. (2007) Small organic molecule in enantioselective, direct aldol reaction ''in water''. Chem Commun;2524–2526.
16. Gruttadauria M., Giacalone F., Marculescu A.M., Noto R. (2008) Novel prolinamide-supported polystyrene as highly stereoselective and recyclable organocatalyst for the aldol reaction. Adv Synth Catal;350:1397–1405.
17. Zu L.S., Wang J., Li H., Wang W. (2006) A recyclable fluorous (*S*)–pyrrolidine sulfonamide promoted direct, highly enantioselective Michael addition of ketones and aldehydes to nitroolefins in water. Org Lett;8:3077–3079.
18. Zu L., Xie H., Li H., Wang J., Wang W. (2008) Highly enantioselective aldol reactions catalyzed by a recyclable fluorous (*S*) pyrrolidine sulfonamide on water. Org Lett;10:1211–1214.
19. Guizzetti S., Benaglia M., Raimondi L., Celentano G. (2007) Enantioselective direct aldol reaction ``on water'' promoted by chiral organic catalysts. Org Lett;9:1247–1250.
20. Zhu M., Xu X., Gong L. (2008) Organocatalytic asymmetric syn-aldol reactions of aldehydes with long-chain aliphatic ketones on water and with dihydroxyacetone in organic solvents. Adv Synth Catal;350:1390–1396.
21. Chimni S.S., Singh S., Mahajan D. (2008) Protonated (*S*)-prolinamide derivatives-water compatible organocatalysts for direct asymmetric aldol reaction. Tetrahedron Asymmetry;19:2276–2284.
22. Zhang S.P., Fu X.K., Fu S.D. (2009) Rationally designed 4-phenoxy substituted prolinamide phenols organocatalyst for the direct aldol reaction in water. Tetrahedron Lett;50:1173–1176.
23. Chimni S.S., Singh S., Kumar A. (2009) The pH of the reaction controls the stereoselectivity of organocatalyzed direct aldol reactions in water. Tetrahedron Asymmetry;20:1722–1724.
24. Trost B.M., Fettes A., Shireman B.T. (2004) Direct catalytic asymmetric aldol additions of methyl ynones. Spontaneous reversal in the sense of enantioinduction. J Am Chem Soc; 126:2660–2661.
25. Trost B.M., Yeh V.S.C. (2002) A dinuclear Zn catalyst for the asymmetric nitroaldol (Henry) reaction. Angew Chem Int Ed Engl;41:861–863.
26. Yamada Y.M.A., Yoshikawa N., Sasai H., Shibasaki M. (1997) Direct catalytic asymmetric aldol reactions of aldehydes with unmodified ketones. Angew Chem Int Ed Engl;36:1871–1873.
27. Yoshikawa N., Yamada Y.M.A., Das J., Sasai H., Shibasaki M. (1999) Direct catalytic asymmetric aldol reaction. J Am Chem Soc;121:4168–4178.
28. List B., Lerner R.A., Barbas C.F. III (2000) Proline-catalyzed direct asymmetric aldol reactions. J Am Chem Soc;122:2395–2396.
29. Mukherjee S., Yang J.W., Hoffmann S., List B. (2007) Asymmetric enamine catalysis. Chem Rev;107:5471–5569.
30. Dalko P.I., Moisan L. (2001) Enantioselective organocatalysis. Angew Chem Int Ed Engl;40:3726–3748.
31. Dalko P.I., Moisan L. (2004) In the golden age of organocatalysis. Angew Chem Int Ed;43:5138–5175.
32. Northrup A.B., MacMillan D.W.C. (2002) The first direct and enantioselective cross-aldol reaction of aldehydes. J Am Chem Soc;124:6798–6799.
33. Paradowska J., Stodulski M., Mlynarskia J. (2007) Direct catalytic asymmetric aldol reactions assisted by zinc complex in the presence of water. Adv Synth Catal;349:1041–1046.
34. Darbe T., Machuqueiro M. (2003) Zn-proline catalyzed direct aldol reaction in aqueous media. Chem Commun;1090–1091.
35. Kofoed J., Machuqueiro M., Reymond J.L., Darbre T. (2004) Zinc-proline catalyzed pathway for the formation of sugars. Chem Commun;1540–1541.
36. Itoh S., Kitamura M., Yamada Y., Aoki S. (2009) Chiral catalysts dually functionalized with amino acid and Zn2+ complex components for enantioselective direct aldol reactions inspired by natural aldolases: design, synthesis, complexation properties, catalytic activities, and mechanistic study. Chem Eur J;15:10570–10584.
37. Mlynarski J., Paradowska J. (2008) Catalytic asymmetric aldol reactions in aqueous media. Chem Soc Rev;37:1502–1511.
38. Paradowska J., Stodulski M., Mlynarski J. (2009) Catalysts based on amino acids for asymmetric reactions in water. Angew Chem Int Ed;48:4288–4297.
39. Kofoed J., Darbre T., Reymond J.L. (2006) Dual mechanism of zinc-proline catalyzed aldol reactions in water. Chem Commun;1482–1484.
40. Fernandez-Lopez R., Kofoed J., Machuqueiro M., Darbre T. (2005) A selective direct aldol reaction I aqueous media catalyzed by zinc-proline. Eur J Org Chem;5268–5276.
41. Luo S.Z., Xu H., Li J.Y., Zhang L., Mi X.L., Zheng X.X., Cheng J.P. (2007) Facile evolution of asymmetric organocatalysts in water assisted by surfactant Brønsted acids. Tetrahedron;63:11307–11314.
42. Tang Z., Jiang F., Cui X., Gong L.Z., Mi A.Q., Jiang Y.Z., Wu Y.D. (2004) Enantioselective direct aldol reactions catalyzed by L-prolinamide derivatives. Proc Natl Acad Sci U S A;101:5755–5760.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Procedure and some HPLC spectrums for **7** and **8**.

Data S2. ^{1}H and ^{13}C NMR spectrums compounds **2–6**.

Please note: Wiley-Blackwell is not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.