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Direct asymmetric aldol reaction catalyzed by simple prolinamide phenols

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Abstract—Simple prolinamides **1a**–**f** were synthesized, and their catalytic effects on the direct asymmetric aldol reactions in organic solvents and in water were evaluated. Prolinamide phenols **1a**–**d** were found to be effective catalysts for the reaction of aromatic aldehydes with cyclohexanone in neat ketone and in water. The *anti*-aldol products were obtained with up to 98/2 *anti*/*syn* ratio and 96% ee in neat ketone, 98/2 *anti*/*syn* ratio and 99% ee in water, respectively.

1. Introduction

The asymmetric aldol reaction is one of the most powerful methods for the construction of complex chiral polyol architectures. Consequently, a large number of catalysts and reagents have been developed in order to achieve an efficient aldol addition with high diastereo- and enantioselectivities.[1] Since the early discovery by List et al. that L-proline can mimic type I aldolase to enantioselectively catalyze intermolecular aldol reactions,[2] the concept of small organic molecules as catalysts (termed organocatalysts) has received much attention.[3] Several organocatalysts have been synthesized and applied to highly enantioselective direct aldol reactions over the past few years, for example, 4-substituted-L-proline,[4] *N*-sulfonylcarboxamides,[5a] tetrazole,[5b,c] diamine-protonic acid,[5d] axially chiral amino acids,[5e,f] small peptides,[5g] 3-pyrrolidinecarboxylic acid,[5h] and prolinamides.[6,7] However, highly efficient catalytic systems, which give high enantioselectivity for a broad range of substrates with low catalyst loading, are still limited. Therefore, the development of new and inexpensive organocatalysts or catalytic systems is still a frontier research topic in asymmetric synthesis.

Stereoselective reactions in water/aqueous media are another important issue because water is an environmentally friendly, safe medium, which avoids the problems of pollution that are inherent with organic solvents.[8] Although some organocatalysts for the direct aldol reaction in water/aqueous media have been developed in recent years,[5c,7b,9] highly efficient organocatalysts are still rare.[9f,g]

Considering that multiple-step acid–base catalysis is thought to be involved in the formation and reaction of enamine intermediates,[3] and inspired by the work of Gong,[6] we presumed that prolinamide **1** may also induce the asymmetric aldol reaction. The chirality, rigidity, and capability of forming hydrogen bond within this class of compounds would be responsible for enantioselectivity. Additionally, the acidity of the amide and hydroxyl groups can be easily adjusted through the modification of the aromatic ring.

2. Results and discussion

Prolinamides **1a**–**f** were prepared from the commercially available L-proline or *trans*-4-hydroxy-L-proline and corresponding 2-aminophenol, 1-amino-2-naphthol or *N*-(2-aminophenyl)-4-methylbenzenesulfonamide according to the synthetic route shown in Scheme 1. The crystal structure of **1a** was determined, with the molecular structure as shown in Figure 1. 2-Amino-4,6-di-*tert*-butylphenol **3** was prepared by the nitration of 2,4-di-*tert*-butylphenol with 6% nitric acid followed by the catalytic hydrogenation with 10% Pd–C in ethanol in 36% overall yield. *N*-(2-Aminophenyl)-4-methylbenzenesulfonamide was prepared by

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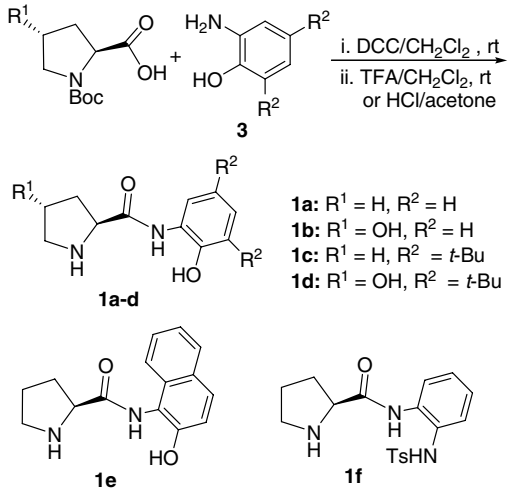


Scheme 1. Synthesis of prolinamides **1a**–**f**.

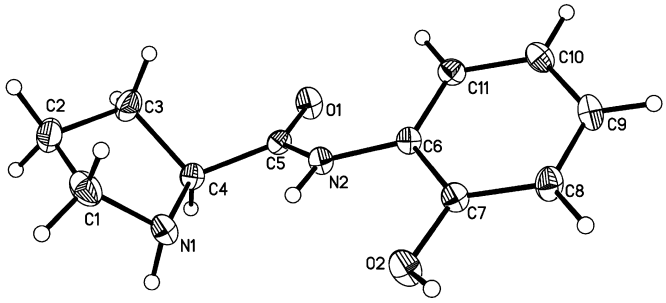


Figure 1. Crystal structure of compound **1a**.

the reaction of *o*-phenylene diamine with *p*-TsCl in $CH_2Cl_2/Na_2CO_3/H_2O$.

Initially, the catalytic effects of **1a**–**f** were tested in the model reaction of *o*-nitrobenzaldehyde with neat acetone in the presence of 20 mol % catalyst at room temperature in air. The best catalytic efficiency was observed with **1a** (Table 1, entry 1, 53% yield and 73% ee). Compounds **1b**–**d** exhibited lower catalytic activity and moderate enantioselectivity (entries 2–5, 16–36% yields and 47–68% ee). The enantioselectivities of the reactions utilizing **1e** and **1f** as catalysts were poor (entries 5 and 6). When the loading of catalyst **1a** was decreased, and the reaction was run at lower temperature, both the yield and enantioselectivity were improved upon (entries 1, 9 and 10, 75% yield and 78% ee was obtained in the presence of 10 mol % **1a** at 0 °C).

In order to increase the range of substrates, we investigated cyclohexanone as an aldol donor in neat ketone at room temperature, and the results are summarized in Table 2. The catalytic efficiency of **1a**–**f** was first evaluated using *o*-nitrobenzaldehyde as an aldol acceptor. The results indicated that **1a**–**f** promoted this reaction, and the *anti*-isomers were obtained with moderate to high yields, as well as good to excellent diastereoselectivity and enantioselectivity (entries 1–6). Compounds **1b**, **1c**, and **1d** generated better stereoselectivities than other catalysts (entries 2–4). When **1b** or **1d** was used to catalyze the model reaction, the aldol products were obtained with high yields (94–98%), and with good to excellent diastereoselectivities (*anti*/*syn* ratio 80:20–97:3) and enantioselectivities (95–96% ee, entries 2 and 4). Compound **1c** gave the highest stereoselectivity (entry 3, the *anti*/*syn* ratio and enantiomeric excess were up to 98:2 and 96%, respectively). However, the catalytic activity of **1c** was lower than that of **1b** and **1d** (entry 3 vs 2, 4; entry 8 vs 7, 9). When *o*-chlorobenzaldehyde was used as the aldol acceptor, **1d** exhibited better catalytic activity than **1b** (entries 10 vs 11). Other aldehydes generated aldol products in moderate yields and stereoselectivities (entries 13–16).

In view of the good stereoselectivity in neat ketone, as well as the amphiphilic character of **1a**–**d** (there are hydrophilic groups and hydrophobic groups simultaneously in the molecules), we presumed that the asymmetric aldol reaction may proceed in water. Cyclohexanones as aldol donors, which react with aromatic aldehydes were tested, and the results are summarized in Table 3.

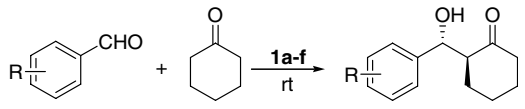
The application of these prolinamide phenol compounds **1a**–**d** as catalysts to the aldol reaction of cyclohexanone with *o*-nitrobenzaldehyde in water made the reaction proceed efficiently. The *anti*-aldol products were obtained with good to excellent stereoselectivities (entries 1–4). Especially when **1c** was used, the *anti*-aldol product was obtained in high yield (99%) with excellent diastereoselectivity (*anti*/

Table 1. Direct aldol reaction of aromatic aldehydes with acetone catalyzed by **1a**–**f**

Entry	Aldehyde	Cat.	Cat. loading (mol %)	*T* (°C)	Time (h)	Yield[a] (%)	ee[b] (%)
1	*o*-$NO_2C_6H_4CHO$	**1a**	20	rt	48	53	73
2	*o*-$NO_2C_6H_4CHO$	**1b**	20	rt	48	36	59
3	*o*-$NO_2C_6H_4CHO$	**1c**	20	rt	72	16	68
4	*o*-$NO_2C_6H_4CHO$	**1d**	20	rt	72	32	47
5	*o*-$NO_2C_6H_4CHO$	**1e**	20	rt	72	69	23
6	*o*-$NO_2C_6H_4CHO$	**1f**	20	rt	17	63	1
7	*p*-$NO_2C_6H_4CHO$	**1a**	20	rt	48	21	62
8	C_6H_5CHO	**1a**	20	rt	72	10	68[c]
9	*o*-$NO_2C_6H_4CHO$	**1a**	10	rt	48	62	75
10	*o*-$NO_2C_6H_4CHO$	**1a**	10	0	48	75	78

[a] Isolated yields after thin layer chromatography on silica gel.
[b] The ee values were determined by chiral HPLC, and the major enantiomer was assigned to be (*R*) according to $[\alpha]_D^{20}$ and Ref. 2.
[c] In the literature the aldol product was obtained in 31% yield with 39% ee (determined by specific rotation).[10]

Table 2. Direct aldol reaction of aldehydes with cyclohexanone catalyzed by 10 mol % **1a–f** in neat ketone

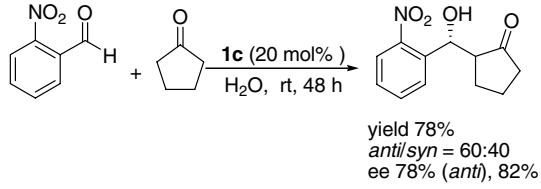


Entry	Cat.	R	Time (h)	Yield[a] (%)	*anti*/*syn*[b]	ee (%) (*anti*)[c]
1	**1a**	*o*-NO_2	48	79	85:15	90
2	**1b**	*o*-NO_2	48	98	97:3	95
3	**1c**	*o*-NO_2	48	37	98:2	96
4	**1d**	*o*-NO_2	48	94	80:20	96
5	**1e**	*o*-NO_2	48	74	63:37	66
6	**1f**	*o*-NO_2	48	33	82:18	89
7	**1b**	*p*-NO_2	48	96	83:17	70
8	**1c**	*p*-NO_2	48	70	78:22	82
9	**1d**	*p*-NO_2	24	92	74:26	74
10	**1b**	*o*-Cl	96	51	89:11	90
11	**1d**	*o*-Cl	48	71	91:9	87
12	**1d**	*m*-NO_2	72	66	79:21	68
13	**1d**	*p*-Cl	72	31	87:13	63
14	**1d**	*m*-Br	72	57	89:11	73
15	**1d**	*m*-Cl	72	40	85:15	56
16	**1d**	*p*-F	72	28	75:25	53

[a] Isolated yields for (*anti* + *syn*) after thin layer chromatography on silica gel.
[b] Determined by analysis of ^{1}H NMR spectra of the mixture of *anti*- and *syn*-products.
[c] Determined by chiral HPLC on a chiralcel OD-H column.

syn ratio up to 96:4) and enantiomeric excess (ee >99%). Even if the catalyst loading was reduced from 20 to 5 mol %, excellent results were still obtained (entries 3, 5, and 6, *anti*/*syn* = 92:2 and 92% ee for *anti*-isomer were obtained with 5 mol % of **1c**). High diastereoseslectivity and enantioselectivity were also achieved in the presence of only 5 mol % of **1d** (entry 8, 98:2 of *anti*/*syn* and 92% ee). *p*-Nitro and *m*-nitrobenzaldehyde were more reactive in the presence of 20 mol % of **1c** than *o*-nitrobenzaldehyde and halo-substituted benzaldehydes, while the enantioselectivities were in the moderate to good range (entries 3, 9–15). Most of the halo-substituted benzaldehydes furnished the corresponding aldol products in high yields with good diastereoselectivities and high enantioselectivities (entries 11–15, 86–94% ee). This result is much better than that achieved in an organic solvent (Table 2). For the emulsion that existed in the reaction mixture (the emulsion was more stable in the case of **1c** and **1d** as catalysts than the cases of **1a** and **1b**), we reasoned that this type of catalysts, **1a–d**, could aggregate with reactants in water through hydrophobic interactions and sequester the transition state from water. Therefore, the reaction proceeded more efficiently in the aggregated organic phase, than in organic solvent, to afford the aldol products with higher enantioselectivities through a transition state similar to that in organic solvent.

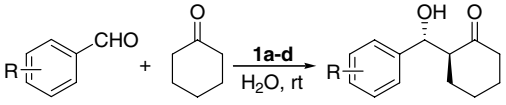
Cyclopentanone was finally explored as an aldol donor. The reaction of cyclopentanone with *o*-nitrobenzaldehyde proceeded smoothly in water to give the corresponding aldol product in 78% yield. The diastereomeric ratio of *anti*/*syn* was 60:40. An enantioselectivity of 78% ee and 82% ee was observed for *anti*-isomers and *syn*-isomers, respectively (Eq. 1).



(1)

Previous experiments showed that if there was no *ortho*-hydroxyl group attached to the amide in **1a**, it catalyzed the reaction of *p*-nitrobenzaldehyde with acetone at room

Table 3. Direct aldol reaction of cyclohexanone with aldehydes catalyzed by **1a–d** in water at room temperature



Entry	Cat.	R	Cat. loading (mol %)	Time (h)	Yield[a] (%)	*anti*/*syn*[b]	ee (*anti*, %)[c]
1	**1a**	*o*-NO_2	20	48	80	79:21	86
2	**1b**	*o*-NO_2	20	48	77	86:14	85
3	**1c**	*o*-NO_2	20	48	99	96:4	>99
4	**1d**	*o*-NO_2	20	48	98	90:10	90
5	**1c**	*o*-NO_2	10	72	96	94:6	93
6	**1c**	*o*-NO_2	5	72	95	92:8	92
7	**1d**	*o*-NO_2	10	72	90	94:6	92
8	**1d**	*o*-NO_2	5	72	80	98:2	92
9	**1c**	*p*-NO_2	20	24	98	89:11	45
10	**1c**	*m*-NO_2	20	24	98	85:15	89
11	**1c**	*o*-Cl	20	72	85	93:7	76
12	**1c**	*m*-Cl	20	72	90	78:22	86
13	**1c**	*p*-Cl	20	72	94	86:14	88
14	**1c**	*m*-Br	20	72	90	81:19	90
15	**1c**	*p*-F	20	72	80	92:8	94

[a] Isolated yields for (*anti* + *syn*) after thin layer chromatography on silica gel.
[b] Determined by analysis of ^{1}H NMR spectra of the mixture of *anti* and *syn* products.
[c] Determined by chiral HPLC on a chiralcel OD-H column.

temperature with only 37% ee.[6c] Therefore, we assumed that the hydroxyl group participated in the catalytic process. Analogous to the proline-catalyzed aldol reaction[2] and the Gong's prolinamide alcohol-catalyzed aldol reaction,[6] the mechanism through enamine intermediate was proposed, and a model of the transition state is depicted in Figure 2a. Theoretical calculations have been carried out for the simple model reaction of benzaldehyde with acetone to understand the high enantioselectivity (all calculations were implemented in the Gaussian 03 program). Transition Structures in the stereo-controlling C–C bond formation step were studied using Hartree–Fock method at 6-31G (d) level. The best transition structure shown in Figure 2b corresponds to the channel with the lowest active energy; therefore, leading to the formation of the (*R*)-aldol product. Both the amide and the hydroxyl groups are hydrogen-bonded with the aldehyde. The hydroxyl group appears to be the better hydrogen-bond donor as indicated by the shorter hydrogen bond. This model is in agreement with the above experimental results and the proposed mechanism.

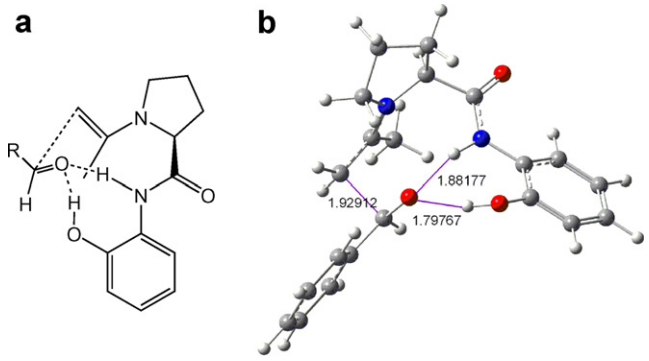


Figure 2. Transition structure of the aldol reaction of benzaldehyde with acetone catalyzed by **1a**: (a) proposed transition structure model and (b) calculated transition structure.

3. Conclusion

In conclusion, a series of prolinamides **1a–f** derived from L-proline were synthesized and evaluated for their ability to catalyze the direct aldol reaction of aldehydes with ketone in neat ketone and in water. Compounds **1c** and **1d** demonstrated good to excellent reactivity, diastereoselectivity, and enantioselectivity on the reaction of arylaldehydes with cyclohexanone both in neat ketone and in water. Further studies on the influences of organic solvents, generality of more substrates and the application of **1a–d** in other reactions are ongoing and will be reported in due course.

4. Experimental

4.1. 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 the internal reference. FT-IR spectra were determined on a Thermo Nicolet IR200 unit. High resolution mass spectra (HR-MS) were obtained on a Waters Micromass Q-Tof Micro™ 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 Elmer341 polarimeter. The single crystal structure was determined on a Bruker CCD 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.

4.2. General procedure for the preparation of 1a–f

Compound **1a** is referred to as an example: To a stirred solution of *N*-Boc-L-proline **2** (430 mg, 2.0 mmol) and 2-aminophenol **3** (240 mg, 2.2 mmol) in dichloromethane (10 mL) was added dicyclohexylcarbodiimine (DCC, 453 mg, 2.2 mmol) at room temperature. After stirring for about 5 h, the mixture was filtered. The filtrate was concentrated and recrystallized from chloroform to afford *N*-Boc protected prolinamide phenol as a white solid. Deprotection of the Boc group was performed using 30% TFA in dichloromethane for 2 h at room temperature. After evaporation of the solvent, the resulting residue was neutralized with aqueous Na_2CO_3 solution, and extracted with *n*-butanol. The organic layer was dried over Na_2SO_4, filtered, and concentrated followed by column chromatography on silica gel (MeOH/$CHCl_3$ = 1:10, v/v) to give a semi-solid product, which was recrystallized from methanol-chloroform to furnish **1a** as a colorless crystal.

4.2.1. (*S*)-*N*-(2-Hydroxyphenyl)pyrrolidine-2-carboxamide 1a. Colorless crystals, 312 mg, yield 76%; mp 166–167 °C; $[\alpha]_D^{20} = -41.0$ (*c* 1.41, EtOH); IR (KBr, cm^{-1}): 3311, 3224, 2983, 2741, 2570, 1667, 1618, 1602, 1549, 1458, 1199, 1183, 1142, 748; ^{1}H NMR (D_2O) δ: 1.97 (m, 2H, CH_2), 2.09 (m, 1H, C*H*HCH), 2.41 (m, 1H, CH*H*CH), 3.25–3.36 (m, 2H, NCH_2), 4.43 (m, 1H, CH), 6.84 (t, J = 8.0 Hz, 1H, Ar–H), 6.87 (d, J = 8.0 Hz, 1H, Ar–H), 7.08 (t, J = 8.0 Hz, 1H, Ar–H), 7.32 (d, J = 8.0 Hz, 1H, Ar–H); ^{13}C NMR (D_2O) δ: 25.3, 31.3, 48.0, 61.6, 117.8, 121.9, 124.5, 127.0, 129.5, 150.8, 170.4; HR MS; ESI; *m*/*z*: calcd for $C_{11}H_{15}N_2O_2$ $(M+H)^+$ 207.1134, found 207.1136.

Crystals suitable for X-ray analysis were obtained by recrystallization from chloroform/methanol at room temperature.

CCDC-603255 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.

4.2.2. (2*S*,4*R*)-4-Hydroxy-*N*-(2-hydroxyphenyl)pyrrolidine-2-carboxamide 1b. White solid, 275 mg, yield 62%: mp 136–138 °C, $[\alpha]_D^{20} = -20.0$ (*c* 1.36, EtOH); IR (KBr,

cm^{-1}): 3286, 3200, 3061, 2978, 2942, 2923, 2871, 2746, 2705, 1662, 1600, 1546, 1509, 1455, 755; ^{1}H NMR (D_2O) δ: 2.00 (m, 1H, CHC*H*HCH), 2.22 (m, 1H, CHCH*H*CH), 2.95–3.09 (m, 2H, NCH_2), 4.14 (t, $J = 8.4$ Hz, 1H, CH), 4.45 (m, 1H, CH), 6.82–6.89 (m, 2H, Ar–H), 7.08 (m, 1H, Ar–H), 7.43 (dd, $J = 8.0$, 1.2 Hz, 1H, Ar–H); ^{13}C NMR (D_2O) δ: 38.6, 53.9, 59.3, 72.0, 116.6, 119.6, 124.0, 124.5, 127.4, 150.0, 174.6; HR MS; ESI; *m*/*z*: calcd for $C_{11}H_{15}N_2O_3$ $(M+H)^+$ 223.1083, found 223.1084.

4.2.3. (*S*)-*N*-(3,5-Di-*tert*-butyl-2-hydroxyphenyl)pyrrolidine-2-carboxamide 1c. White solid, 504 mg, yield 79%; mp 217–218 °C; $[\alpha]_D^{20} = -36.8$ (*c* 1.18, EtOH); IR (KBr, cm^{-1}): 3200, 2960, 2756, 1702, 1660, 1595, 1558, 1482, 1390, 1362, 1227, 874; ^{1}H NMR ($CDCl_3$) δ: 1.22 (s, 9H, *t*-Bu), 1.35 (s, 9H, *t*-Bu), 1.76–1.93 (m, 3H, CH_2C*H*HCH), 2.15 (m, 1H, CH*H*CH), 3.21–3.31 (m, 2H, NCH_2), 5.04 (m, 1H, CH), 7.07 (d, $J = 2.4$ Hz, 1H, Ar–H), 7.17 (d, $J = 2.4$ Hz, 1H, Ar–H), 7.95 (s, 1H, NH), 9.44 (s, 1H, NHCO), 10.04 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ: 24.1, 29.8 ($3CH_3$), 30.2, 31.5 ($3CH_3$), 34.2, 35.2, 46.8, 60.3, 120.5, 122.5, 124.1, 138.3, 142.3, 146.7, 169.4; HR MS; ESI; *m*/*z*: calcd for $C_{19}H_{31}N_2O_2$ $(M+H)^+$ 319.2385, found 319.2381.

4.2.4. (2*S*,4*R*)-4-Hydroxy-*N*-(3,5-di-*tert*-butyl-2-hydroxyphenyl)pyrrolidine-2-carboxamide 1d. White solid, 514 mg, yield 77%; mp 78.4–80.1 °C; $[\alpha]_D^{20} = -16.2$ (*c* 1.07, EtOH); IR (KBr, cm^{-1}): 3386, 3199, 2955, 1685, 1659, 1596, 1560, 1519, 1481, 1456, 1362, 1225, 1032, 869; ^{1}H NMR (DMSO-d_6) δ: 1.24 (s, 9H, *t*-Bu), 1.36 (s, 9H, *t*-Bu), 1.78–1.84 (m, 1H, CHC*H*HCH), 2.04–2.09 (m, 1H, CHCH*H*CH), 2.84–2.92 (m, 2H, NCH_2), 3.40 (s, 1H, OH), 3.96 (t, $J = 8.0$ Hz, 1H, CH), 4.24 (m, 1H, CH), 4.74 (s, 1H, OH), 7.03 (d, $J = 2.0$ Hz, 1H, ArH), 7.41 (d, $J = 2.0$ Hz, 1H, ArH), 8.83 (s, 1H, CONH), 10.13 (s, 1H, ArO*H*); ^{13}C NMR (DMSO-d_6) δ: 29.9 ($3CH_3$), 31.5 ($3CH_3$), 34.2, 35.0, 39.5, 55.2, 59.9, 71.6, 117.4, 119.5, 127.7, 138.5, 141.7, 144.5, 174.9; HR MS; ESI; *m*/*z*: calcd for $C_{19}H_{31}N_2O_3$ $(M+H)^+$ 335.2334, found 335.2324.

4.2.5. (*S*)-*N*-(2-Hydroxynaphthalen-1-yl)pyrrolidine-2-carboxamide 1e. White solid, 370 mg; yield 74%; mp: 179–181 °C, $[\alpha]_D^{20} = -28.3$ (*c* 0.64, MeOH). IR (KBr disc) cm^{-1}: 3344, 3294, 3268, 3208, 3064, 2983, 2884, 1677, 1627, 1575, 1505, 1280, 752; ^{1}H NMR (DMSO-d_6) δ: 1.70–1.79 (m, 2H, CH_2), 1.90–1.94 (m, 1H, C*H*H), 2.09–2.14 (m, 1H, CH*H*), 2.98 (m, 2H, NCH_2), 3.87 (dd, $J = 8.8$, 5.6 Hz, 1H, NCH), 7.20 (d, $J = 8.8$ Hz, 1H, Ar–H), 7.31 (t, $J = 7.6$ Hz, 1H, Ar–H), 7.45 (t, $J = 7.6$ Hz, 1H, Ar–H), 7.62 (d, $J = 8.4$ Hz, 1H, Ar–H), 7.72 (d, $J = 8.8$ Hz, 1H, Ar–H), 7.82 (d, $J = 8.0$ Hz, 1H, Ar–H), 9.77 (br, 2H, NHCO, OH); ^{13}C NMR (DMSO-d_6) δ: 26.2, 30.9, 47.0, 60.8, 116.8, 119.1, 121.9, 123.1, 126.4, 127.7, 128.1, 128.3, 130.9, 149.7, 174.9; HRMS; ESI; *m*/*z*: calcd for $C_{15}H_{16}N_2O_2^+$; $M+H^{+\cdot}$; 257.1290, found 257.1291.

4.2.6. (*S*)-*N*-(2-(4-Methylphenylsulfonamido)phenyl)pyrrolidine-2-carboxamide 1f. Yellow-white powder: mp 62.7–64.4 °C; $[\alpha]_D^{20} = -60.8$ (*c* 0.88, EtOH); IR (KBr, cm^{-1}): 3376, 3243, 3064, 2971, 2875, 1672, 1597, 1525, 1453, 1333, 1161, 1092, 815, 760, 661, 565; ^{1}H NMR ($CDCl_3$) δ: 1.76–1.81 (m, 2H, CH_2), 1.95–1.98 (m, 1H, C*H*HCH), 2.18–2.22 (m, 1H, CH*H*CH), 2.39 (s, 3H, CH_3), 2.97–3.01 (m, 1H, C*H*HNH), 3.06–3.11 (m, 1H, CH*H*NH), 3.94–3.98 (m, 1H, C*H*CO), 5.10 (s, 3H, 3NH), 7.06–7.10 (m, 1H, Ar–H), 7.15–7.21 (m, 2H, Ar–H), 7.20 (d, $J = 8.4$ Hz, 2H, Ar′–H), 7.43 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.56 (d, $J = 8.4$ Hz, 2H, Ar′–H); ^{13}C NMR ($CDCl_3$) δ: 21.5, 26.0, 30.5, 47.0, 60.5, 123.3 (Ar–C), 125.9 (Ar–C), 127.1 (2Ar′–C), 127.3 (Ar–C), 127.5 (Ar–C), 128.5 (Ar–C), 129.4 (2Ar′–C), 132.5 (Ar–C), 137.1 (Ar′–C), 143.4 (Ar′–C), 173.4 (C=O); HRMS; ESI; *m*/*z*: calcd for $C_{18}H_{22}N_3O_3S$ $(M+H^+)$ 360.1382, found: 360.1379.

4.3. General procedure for the preparation of aldol products

4.3.1. General procedure for the aldol reaction of acetone with aldehydes in neat acetone. To a stirred mixture of 0.5 mmol aldehyde and 1.0 mL acetone was added the catalyst at the indicated temperature. The mixture was stirred for the indicated time, then was purified by thin layer chromatography on silica gel (petroleum ether/ethyl acetate).

4.3.1.1. 4-Hydroxyl-4-(2-nitrophenyl)-butan-2-one. ^{1}H NMR ($CDCl_3$) δ: 2.24 (s, 3H), 2.74 (dd, $J = 17.8$, 9.4 Hz, 1H), 3.13 (dd, $J = 17.8$, 1.8 Hz, 1H), 3.89 (s, 1H), 5.68 (dd, $J = 9.4$, 1.8 Hz, 1H), 7.44 (t, $J = 8.0$ Hz, 1H), 7.67 (t, $J = 8.0$ Hz, 1H), 7.80 (d, $J = 8.0$ Hz, 1H), 7.96 (d, $J = 8.0$ Hz 1H); HPLC: Chiralcel OD-H, UV 254, *i*-PrOH/hexane = 15/85, flow rate 0.5 mL/min, (*S*)-isomer, t_R 17.8 min, (*R*)-isomer, t_R 20.4 min.

4.3.1.2. 4-Hydroxyl-4-(4-nitrophenyl)-butan-2-one. ^{1}H NMR ($CDCl_3$) δ: 2.24 (s, 3H), 2.87 (d, $J = 6.0$ Hz, 2H), 3.61 (s, 1H), 5.28 (t, 1H, $J = 6.0$ Hz), 7.55 (d, $J = 8.8$ Hz, 2H), 8.20 (dd, $J = 8.8$, 2.0 Hz, 2H); HPLC: Chiralcel OD-H, UV 254, *i*-PrOH/hexane = 10/90; flow rate 0.5 mL/min, (*R*)-isomer, t_R 37.8 min, (*S*)-isomer, t_R 40.3 min.

4.3.1.3. 4-Hydroxyl-4-phenyl-butan-2-one. ^{1}H NMR ($CDCl_3$) δ: 2.13 (s, 3H), 2.74 (dd, $J = 17.2$, 3.2 Hz, 1H), 2.85 (dd, $J = 17.2$, 9.6 Hz, 1H), 3.63 (s, 1H), 5.10 (dd, $J = 9.6$, 3.2 Hz, 1H), 7.24–7.32 (m, 5H); HPLC: Chiralpak AD, *i*-PrOH/hexane = 5/95, flow rate 0.6 mL/min, (*R*)-isomer, t_R 23.4 min, (*S*)-isomer, t_R 25.6 min.

4.3.2. General procedure for the aldol reaction of cyclohexanone with aldehydes

4.3.2.1. Reaction in neat ketone. Catalyst (0.05 mmol) was added to a solution of 0.5 mmol of aldehyde in 1.0 mL cyclohexanone. After being stirred 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 product after thin layer chromatographic purification on silica gel (petroleum ether/ethyl acetate).

4.3.2.2. Reaction in water. Aldehyde (0.33 mmol) was added to the mixture of 0.4 mL cyclohexanone, 1.0 mL water, and 0.067 mmol of catalyst. After being stirred at room temperature for the indicated time, the mixture was treated the same as that of the step in neat ketone.

4.3.2.3. 2-(Hydroxyl(4-nitrophenyl)methyl)cyclohexanone. ^{1}H NMR ($CDCl_3$) δ: *syn*-isomer: 1.50–1.88 (m, 5H), 2.09–2.15 (m, 1H), 2.37–2.52 (m, 2H), 2.62–2.66 (m, 1H), 3.10 (s, 1H), 5.49 (d, $J = 1.6$ Hz, 1H), 7.49 (d, $J = 8.4$ Hz, 2H), 8.22 (d, $J = 8.4$ Hz, 2H); *anti*-isomer: 1.36–1.44 (m, 1H), 1.51–1.73 (m, 3H), 1.83 (m, 1H), 2.10–2.15 (m, 1H), 2.33–2.46 (m, 1H), 2.50 (m, 1H), 2.57–2.63 (m, 1H), 3.80 (s, 1H), 4.90 (d, $J = 8.4$ Hz, 1H), 7.51 (d, $J = 8.4$ Hz, 2H), 7.22 (d, $J = 8.4$ Hz, 2H); HPLC (for *anti*-isomer): Chiralcel OD-H, UV 254, *i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, t_R 33.8 min (major), t_R 44.7 min (minor).

4.3.2.4. 2-(Hydroxyl(2-nitrophenyl)methyl)cyclohexanone. ^{1}H NMR ($CDCl_3$) δ: *syn*-isomer: 1.53–1.87 (m, 5H), 2.10 (m, 1H), 2.42–2.47 (m, 2H), 2.90 (dd, $J = 13.2$, 4.8 Hz, 1H), 3.15 (s, 1H), 5.96 (d, $J = 1.6$ Hz, 1H), 7.46 (dt, $J = 0.8$, 8.0 Hz, 1H), 7.66 (dt, $J = 0.8$, 8.0 Hz, 1H), 7.84 (dd, $J = 8.0$, 0.8 Hz, 1H), 8.02 (dd, $J = 8.0$, 0.8 Hz, 1H); *anti*-isomer: 1.61–1.87 (m, 5H), 2.10 (m, 1H), 2.34–2.47 (m, 2H), 2.77 (m, 1H), 3.95 (s, 1H), 5.45 (d, $J = 7.2$ Hz, 1H), 7.44 (dt, $J = 0.8$, 8.0 Hz, 1H), 7.66 (dt, $J = 0.8$, 8.0 Hz, 1H), 7.78 (dd, $J = 8.0$, 0.8 Hz, 1H), 7.86 (dd, $J = 8.0$, 0.8 Hz, 1H); HPLC (for *anti*-isomer): Chiralcel OD-H, UV 254, *i*-PrOH/hexane = 5/95, flow rate 0.5 mL/min, t_R 38.1 min (major), t_R 47.6 min (minor).

4.3.2.5. 2-(Hydroxyl(2-chlorophenyl)methyl)cyclohexanone. ^{1}H NMR ($CDCl_3$) δ: *syn*-isomer: 1.53–1.71 (m, 4H), 1.81–1.84 (m, 1H), 2.08 (m, 1H), 2.33–2.42 (m, 1H), 2.48 (m, 1H), 2.81 (m, 1H), 3.95 (s, 1H), 5.72 (d, $J = 2.0$ Hz, 1H), 7.20–7.34 (m, 3H), 7.56 (d, $J = 8.0$ Hz, 1H); *anti*-isomer: 1.53–1.84 (m, 5H), 2.05–2.13 (m, 1H), 2.31–2.39 (m, 1H), 2.46–2.49 (m, 1H), 2.65–2.71 (m, 1H), 3.88 (s, 1H), 5.35 (d, $J = 8.0$ Hz, 1H), 7.20–7.34 (m, 3H), 7.56 (d, $J = 8.4$ Hz, 1H); HPLC (for *anti*-isomer): Chiralcel OD-H, UV 220, *i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, t_R 10.0 min (major), t_R 12.9 min (minor).

4.3.2.6. 2-(Hydroxyl(4-chlorophenyl)methyl)cyclohexanone. ^{1}H NMR ($CDCl_3$) δ: *syn*-isomer: 1.42–2.11 (m, 6H), 2.32–2.45 (m, 2H), 2.53–2.56 (m, 1H), 3.05 (s, 1H), 5.36 (d, $J = 2.0$ Hz, 1H), 7.24 (d, $J = 8.4$ Hz, 2H), 7.32 (d, $J = 8.4$ Hz, 2H); *anti*-isomer: 1.27–1.31 (m, 1H), 1.53–1.82 (m, 4H), 2.07–2.11 (m, 1H), 2.35–2.56 (m, 3H), 4.76 (d, $J = 8.8$ Hz, 1H), 7.26 (d, $J = 8.0$ Hz, 2H), 7.32 (d, $J = 8.0$ Hz, 2H); HPLC (for *anti*-isomer): Chiralcel OD-H, UV 220, *i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, t_R 13.9 min (major), t_R 21.5 min (minor).

4.3.2.7. 2-(Hydroxyl(3-nitrophenyl)methyl)cyclohexanone. ^{1}H NMR ($CDCl_3$) δ: *syn*-isomer: 1.48–2.10 (m, 6H), 2.33–2.48 (m, 2H), 2.62–2.66 (m, 1H), 3.16 (s, 1H), 5.48 (d, $J = 2.0$ Hz, 1H), 7.52 (t, $J = 8.0$ Hz, 1H), 7.66 (d, $J = 1.4$ Hz, 1H), 8.11 (d, $J = 8.0$ Hz, 1H), 8.20 (d, $J = 8.0$ Hz, 1H); *anti*-isomer: 1.33–2.10 (m, 6H), 2.32–2.48 (m, 2H,), 2.70 (m, 1H), 3.16 (s, 1H), 4.91 (d, J = 8.4 Hz, 1H), 7.54 (t, $J = 8.0$ Hz, 1H), 7.68 (d, $J = 0.8$ Hz, 1H), 8.15 (m, $J = 8.0$ Hz, 1H), 8.20 (d, $J = 8.0$ Hz, 1H); HPLC (for *anti*-isomer): Chiralcel OD-H, UV 254, *i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, t_R 22.4 min (major), t_R 31.2 min (minor).

4.3.2.8. 2-(Hydroxyl(3-chlorophenyl)methyl)cyclohexanone. ^{1}H NMR ($CDCl_3$) δ: *syn*-isomer: 1.45–2.11 (m, 6H), 2.32–2.45 (m, 2H), 2.53–2.56 (m, 1H), 3.05 (s, 1H), 5.50 (d, $J = 2.0$ Hz, 1H), 7.21–7.30 (m, 3H, Ar), 7.37 (s, 1H, Ar); *anti*-isomer: 1.31–2.08 (m, 6H), 2.30–2.45 (m, 3H), 4.80 (d, $J = 8.8$ Hz, 1H), 7.20–7.29 (m, 3H, Ar), 7.37 (s, 1H, Ar); HPLC (for *anti*-isomer): Chiralcel OD-H, UV 220, *i*-PrOH/hexane = 1/30, flow rate 1.0 mL/min, t_R 14.2 min (major), t_R 19.1 min (minor).

4.3.2.9. 2-(Hydroxyl(3-bromophenyl)methyl)cyclohexanone. ^{1}H NMR ($CDCl_3$) δ: *syn*-isomer: 1.50–2.08 (m, 6H), 2.31–2.61 (m, 3H), 5.36 (d, $J = 2.0$ Hz, 1H), 7.20–7.23 (m, 2H), 7.39–7.50 (m, 2H); *anti*-isomer: 1.30–2.08 (m, 6H), 2.30–2.45 (m, 3H), 4.74 (d, $J = 8.8$ Hz, 1H), 7.20–7.23 (m, 2H), 7.39–7.50 (m, 2H). HPLC (for *anti*-isomer): Chiralcel OD-H, UV 254, *i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, t_R 12.3 min (major), t_R 16.5 min (minor).

4.3.2.10. 2-(Hydroxyl(4-fluorophenyl)methyl)cyclohexanone. ^{1}H NMR ($CDCl_3$) δ: *syn*-isomer: 1.50–1.87 (m, 5H), 1.84–1.88 (m, 1H), 2.36–2.56 (m, 3H), 3.05 (br, 1H), 5.36 (d, $J = 1.6$ Hz, 1H), 7.00–7.05 (m, 2H), 7.25–7.29 (m, 2H); *anti*-isomer: 1.24–1.33 (m, 1H), 1.53–1.82 (m, 4H), 2.07–2.12 (m, 1H), 2.35–2.59 (m, 3H), 4.01 (s, 1H), 4.77 (d, $J = 8.8$ Hz, 1H), 7.01–7.05 (m, 2H), 7.27–7.31 (m, 2H); HPLC (for *anti*-isomer): Chiralcel OD-H, UV 254, *i*-PrOH/hexane = 5/95, flow rate 0.5 mL/min, t_R 23.6 min (major), t_R 40.2 min (minor).

4.3.2.11. 2-(Hydroxy(2-nitrophenyl)methyl)cyclopentanone. ^{1}H NMR ($CDCl_3$) δ: *syn*-isomer: 1.70–1.78 (m, 2H), 2.03–2.19 (m, 3H), 2.37 (dd, $J = 8.0$, 1.6 Hz, 1H), 2.60 (br, 1H), 2.74 (m, 1H), 5.92 (d, $J = 2.4$ Hz, 1H) 7.44 (td, $J = 8.0$, 0.8 Hz, 1H, Ar–H), 7.66 (t, $J = 8.0$ Hz, 1H, Ar–H), 7.89 (d, $J = 8.0$ Hz, 1H, Ar), 8.02 (d, $J = 8.0$ Hz, 1H, Ar–H); *anti*-isomer: 1.70–2.03 (m, 4H), 2.19–2.38 (m, 2H), 2.68 (d, $J = 7.6$ Hz, 1H), 2.90 (br, 1H), 5.21 (d, $J = 7.2$ Hz, 1H), 7.44 (t, $J = 8.0$ Hz, 1H, Ar–H), 7.66 (t, $J = 8.0$ Hz, 1H, Ar–H), 7.89 (d, $J = 8.0$ Hz, 1H), 8.00 (dd, $J = 8.0$, 0.8 Hz, 1H); HPLC: *syn*-isomer: Chiralcel OD-H, UV 254, *i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, t_R 17.5 min (major), t_R 13.7 min (minor); *anti*-isomer: Chiralcel OD-H, UV 254, *i*-PrOH/hexane = 5/95, flow rate 1.0 mL/min, t_R 22.6 min (major), t_R 25.6 min (minor).

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