Tetrahedron: *Asymmetry* 20 (2009) 2390–2396

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Highly diastereo- and enantioselective direct aldol reactions by 4-*tert*-butyldimethylsiloxy-substituted organocatalysts derived from *N*-prolylsulfonamides in water

Shao-dong Fu [a], Xiang-kai Fu [a,*], Shu-peng Zhang [b], Xiao-chuan Zou [a], Xiao-ju Wu [a]

[a] College of Chemistry and Chemical Engineering, Research Institute of Applied Chemistry Southwest University, The Key Laboratory of Applied Chemistry of Chongqing Municipality, Key Laboratory of Eco-environments in Three Gorges Reservoir Region (Ministry of Education), Chongqing 400715, People's Republic of China
[b] School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210091, China

ARTICLE INFO

Article history:
Received 26 August 2009
Accepted 10 September 2009
Available online 28 October 2009

ABSTRACT

A new set of 4-*tert*-butyldimethylsiloxy-substituted organocatalysts derived from *N*-prolylsulfonamide has been designed and proved to be effective in catalyzing the direct aldol reactions of cyclic ketones with a series of aromatic aldehydes. Furthermore, to the best of our knowledge, there are no reports on the aldol reaction generating the products in very good yields (>99%) and with excellent diastereoselectivities up to >99:1 and enantioselectivities up to >99% by using lower catalyst loadings (only 3 mol %), without using any additives in a large amount of water under mild conditions.

1. Introduction

Over the last decade, asymmetric organocatalysis has become an important area of research in organic synthesis. Organocatalysts, which are metal-free small organic molecules, are able to function as efficient and selective catalysts making many organocatalytic reactions superior to those carried out using more conventional methods;[1] among these reactions, the aldol reaction which is recognized as one of the most powerful carbon–carbon bond-forming reactions in modern organic synthesis, creating the β-hydroxy carbonyl structural unit found in many natural products and drugs, has received much attention in recent years.[2,3]

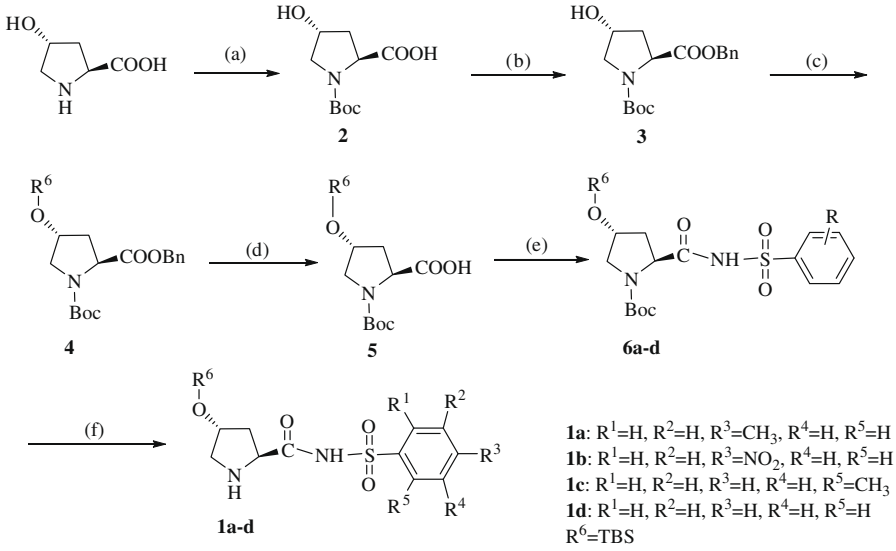
Since the early reports in the 1970s that L-proline catalyzed intramolecular aldol reactions[4a,b] and the discovery by List et al. that L-proline could mimic a type I aldolase to enantioselectively catalyze intermolecular aldol reactions,[4c] many organocatalysts have been synthesized with the aim of increasing their reactivity and stereoselectivity.[1a,b,5] However, unlike enzymatic reactions in nature that occur in water, enantioselective organocatalytic processes have typically been carried out in organic solvents, such as DMSO, DMF, and chloroform, under mild conditions.[6] Hence the main challenge in developing asymmetric catalysis lies in the mimic of natural enzymes.

Water as a substitute for conventional organic solvents is an ideal solvent for chemical reactions due to its low cost, safety, and environmentally benign nature.[7,8] However, the vast majority of organocatalytic reactions would yield racemic products if the reactions took place in water,[9] because water interferes with the organocatalysts and disrupts hydrogen bonds as well as other polar interactions in many cases deteriorating the catalytic activity and stereocontrol. Hence it should be noted that among all of the reported systems,[6,8,10,13] some use more catalyst loadings or work in mixed aqueous organic solvent, or require the use of additives, and others are supported or dendritic systems, whose preparation requires chemical manipulation, only a portion of which really seems to work without any additives in the presence of a large amount of water with lower catalyst loadings. Therefore, highly efficient catalytic systems, which give high enantioselectivity for a broad range of substrates in water, are still limited and currently a sought-after goal in modern chemistry.

In consideration of the proposed, very efficient, mechanism of an enamine-based proline of this reaction,[4c] the electronic and steric effects of the catalysts and the position of the hydroxyl moiety could be important in affecting the enantioselectivity. In addition, inspired by the works of Berkessel and Ley,[11a,b] herein we report a new system of 4-*tert*-butyldimethylsiloxy-substituted organocatalysts derived from *N*-prolylsulfonamides, which will also result in a functional group of comparable acidity to the carboxylic acid function of proline (Scheme 1) and in this Letter water has been found to improve the performance of the catalysts to catalyze the direct aldol reaction with excellent diastereoselectivities up to >99:1 and enantioselectivities up to >99% by using lower catalyst loadings (only 3 mol %) without any additives.

* Corresponding author. Tel.: +86 23 6825 3704; fax: +86 23 6825 4000.
E-mail address: fxk@swu.edu.cn (X.-k. Fu).

0957-4166/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2009.09.019



Scheme 1. Synthesis of catalysts **1a–d**. Reagents and conditions (catalyst **1a** is referred to as an example): (a) $(Boc)_2O$, $KHCO_3$; (b) BnBr, TEA; (c) TBS–Cl, TEA; (d) H_2, Pd/C, MeOH, rt; (e) *p*-toluenesulfonamide, EDCI, DMAP, CH_2Cl_2, rt; (f) CF_3COOH, CH_2Cl_2, rt. EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, and DMAP = 4-dimethylaminopyridine.

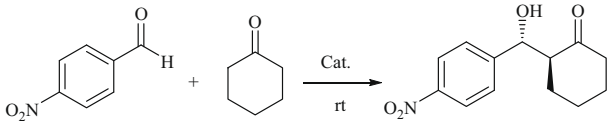
2. Results and discussion

Catalysts **1a–d** were prepared from the commercially available *trans*-4-hydroxy-L-proline and the corresponding *p*-toluenesulfonamide, *o*-toluenesulfonamide, *p*-nitrobenzene-sulfonamide, and benzenesulfonamide according to the synthetic route shown in Scheme 1. These compounds were purified by flash column chromatography and characterized by ^1H NMR, ^{13}C NMR, and mass spectrometry. All the results were in full agreement with the proposed structures.

Initially, the catalytic activities of **1a–b** for the direct asymmetric aldol reaction were investigated by performing a model reaction using stoichiometric amounts of 4-nitrobenzaldehyde with neat cyclohexanone in the presence of 10 mol % catalyst at room temperature and the results are summarized in Table 1.

The *anti*-aldol products were obtained as the major products in good to excellent yields with high diastereoselectivities and enantioselectivities. The best catalytic efficiency was observed with **1a** (entry 1, >99% yield, 97/3 dr, and 97% ee), while catalyst **1d** exhibited lower stereoselectivity (entry 4, 71/29 dr and 75% ee). Although compounds **1b** and **1c** showed moderate stereoselectivity, 81/17 dr, 91% ee and 92/8 dr, 91% ee, respectively, the reaction time was short, especially catalyst **1b**, which completed the reaction within 2.5 h. When the reactions were carried out at a lower temperature, both the diastereo- and enantioselectivities were improved (entries 5 and 6). Interestingly, the reaction gave a higher stereoselectivity by decreasing the catalyst loadings (entries 7–12). When the loadings of **1b** and **1c** were reduced to 3 mol %, the *anti*-aldol products were obtained with excellent enantioselectivity (97% ee, entries 9 and 10).

Table 1
Direct asymmetric aldol reaction of *p*-nitrobenzaldehyde catalyzed by **1a–d** in neat cyclohexanone[a]

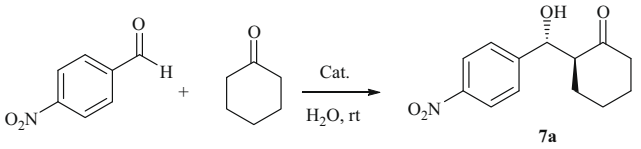


Entry	Cat.	Loading (mol %)	T (°C)	Time (h)	Yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	**1a**	10	25	17	>99	97/3	97
2	**1b**	10	25	2.5	>99	81/19	91
3	**1c**	10	25	5	>99	92/8	91
4	**1d**	10	25	3.5	>99	71/29	75
5	**1b**	10	0	6	>99	87/13	95
6	**1c**	10	0	10	>99	94/6	95
7	**1b**	5	25	4	>99	87/13	94
8	**1c**	5	25	5	>99	93/7	95
9	**1b**	3	25	6	>99	93/7	97
10	**1c**	3	25	8	>99	96/4	97
11	**1b**	1	25	15	>99	96/4	97
12	**1c**	1	25	15	>99	96/4	96

[a] The reaction was performed with *p*-nitrobenzaldehyde (0.2 mmol) and cyclohexanone (2 mmol) at room temperature with vigorous stirring.
[b] The combined isolated yield of the diastereomers.
[c] Determined by ^1H NMR of the crude product and by HPLC.
[d] Determined by chiral HPLC.

In view of the good stereoselectivities in neat cyclohexanone, as well as the unique properties (there were hydrophilic groups and hydrophobic groups simultaneously in the molecules[12]), and to test the initial focus and find the optimal reaction parameters, our working hypothesis was that the *tert*-butyldimethylsiloxy moiety might build a hydrophobic pocket where the reactions would take place. The catalytic performances of **1b** and **1c** were evaluated in the direct asymmetric aldol reaction of cyclohexanone to *p*-nitrobenzaldehyde using 3 mol % as a model reaction in water, and the influence of the amount of water and cyclohexanone on the direct asymmetric aldol reaction was investigated. The results are summarized in Table 2.

Table 2
Screening of efficient catalysts in the direct asymmetric aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde in the presence of water[a]

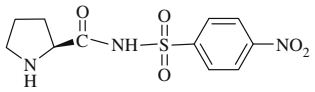


7a

Entry	Cat. (3%)	Water (mL)	Time (h)	Yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	**1b**	0.1	12	>99	94/6	96
2	**1c**	0.1	12	>99	97/3	97
3	**1b**	0.2	12	>99	93/7	97
4	**1c**	0.2	12	>99	97/3	96
5	**1b**	0.3	12	>99	95/5	97
6	**1c**	0.3	12	>99	98/2	96
7	**1b**	0.4	12	>99	97/3	98
8	**1c**	0.4	12	>99	98/2	98
9	**1b**	0.5	12	>99	97/3	99
10	**1c**	0.5	12	>99	97/3	97
11	**1b**	0.8	12	96	96/4	98
12	**1c**	0.8	12	95	97/3	97
13	**1b**	1.0	12	95	95/5	98
14	**1c**	1.0	12	93	96/4	97
15	**1e**	0.5	12	84	93/7	94
16[e]	**1b**	0.5	12	91	90/10	95
17[f]	**1b**	0.5	12	90	89/11	93

[a] The reaction was performed with *p*-nitrobenzaldehyde (0.2 mmol) and cyclohexanone (2 mmol) in the presence of water at room temperature with vigorous stirring and the reaction time is indicated.
[b] The combined isolated yield of the diastereomers.
[c] Determined by ^{1}H NMR of the crude product and by HPLC.
[d] Determined by chiral HPLC.
[e] Cyclohexanone (0.103 mL, 5 equiv) and water (0.5 mL) were used in this reaction.
[f] Cyclohexanone (0.042 mL, 2 equiv) and water (0.5 mL) were used in this reaction.

The aldol products were obtained in the indicated times of the reactions in different equivalents of water (from 0.1 mL, 28 equiv to 1.0 mL, 280 equiv). Initial experiments were performed in 0.2 mL:0.1 mL mixture of cyclohexanone and water (entries 1–2) at room temperature. As expected, catalysts **1b** and **1c** showed much better reactivity and higher selectivity (entries 1 and 2) in water than those in neat cyclohexanone. Increasing the amount of water (from 0.2 mL to 0.5 mL) allowed the reaction to give product **7a** with a high enantioselectivitiy of 99% ee (entry 9) and excellent diastereoselectivities ranging from 93/7 to 98/2 (entries 3–10). When increasing the amount of water from 0.8 mL to 1.0 mL, the direct aldol reactions catalyzed by the catalysts **1b** and **1c** took place smoothly with excellent enantioselectivity, although the yields and diastereoselectivities did decrease to some extent (entries 11–14). In order to better understand the role of the 4-*tert*-butyldimethylsiloxy in catalyzing the direct asymmetric aldol reaction in water, catalyst **1e** was synthesized (Scheme 2) and evaluated in the model reaction (entry 15). In contrast to the

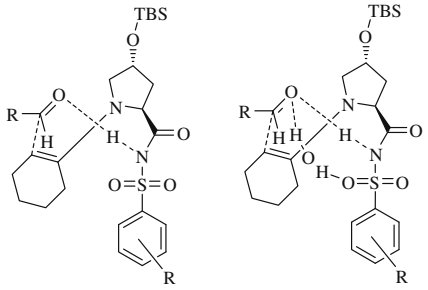


1e

Scheme 2. Structure of catalyst **1e** (according to the Ref. 11a.).

known reaction using large excess of donor, with only 2 or 5 equiv of donor to the aldehyde used, the reactions proceeded smoothly to afford the aldol product in good results but showed a decrease in stereocontrol (entries 16 and 17).

This fact showed us that the catalysts increased the stereoselectivity of the direct aldol reaction in water more efficiently than in an organic solvent (neat cyclohexanone) to afford the aldol products with excellent diastereoselectivities up to >99:1 and enantioselectivities up to >99%. Furthermore, we did not use any acids, surfactants, etc. We considered[6,10b,c] that the *tert*-butyldimethylsiloxy could mimic the aldolase antibodies to form a pocket, which shaped the hydrophobic active site in the presence of water and concentrated the organocatalyst and reactants, assembled substrates, diminished contacts between bulk water and the reaction transition states, and made the reactions occur in the hydrophobic pocket. The role of water was to bring the hydrophobic catalyst and reactants closer together and to form tiny 'oil' droplets floating on water during the vigorous stirring of the reaction mixture.[8a–c,10k,13] Furthermore, since we considered transition state model **TS 2** of the aldol reaction possibly as well as **TS 1** (Scheme 3),[10k,11a,c] it was possible that the reaction efficiencies of catalysts in water were much better than those in neat cyclohexanone.

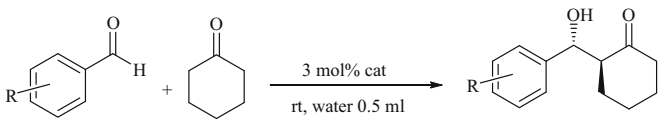


Scheme 3. Proposed transition state models of aldol reaction.

In order to broaden the range of substrates, we found the best catalytic efficiency for the optimized conditions of the reaction with **1b** (entry 9, >99% yields and 99% ee). Thus, direct aldol reactions of various substituted benzaldehydes with cyclohexanone were carried out in the presence of 3 mol % of **1b** under optimum reaction conditions for the subsequent studies (Table 3).

As can be seen from the results summarized in Table 3, the processes proceeded smoothly with 3 mol % loadings of catalyst **1b** which gave rise to enantio-enriched adducts in goods yields ranging from 70% to >99%. Notably, in most cases, the *anti*-aldol products were obtained with excellent diastereoselectivity and enantioselectivity regardless of the electronic nature of the aromatic aldehydes. For some benzaldehydes with electron-withdrawing substrates, the reaction could be completed within 12 h in high yields and stereoselectivities (entries 1 and 2). In contrast, the neutral and electron-rich aromatic aldehydes were much less reactive as seen from the longer reaction times; however, excellent diastereo- and enantioselectivities were obtained in indicated times (entries 5–11). When 4-substituted benzaldehydes were used as the aldol acceptor (entries 1 and 4–8), the aldol products exhibited excellent stereoselectivity, especially the *p*-cyanobenzaldehyde (entry 4, >99:1 *anti*/*syn* ratio and >99% ee) and *p*-chloro-

Table 3
Results of reaction of various aldehydes with cyclohexanone catalyzed by **1b** in water[a]



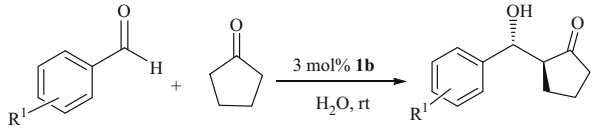
Entry	R	Cat. (%)	Product	Time (h)	Yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	4-NO_2	3	**7a**	12	>99	97/3	99
2	3-NO_2	3	**7b**	12	99	96/4	98
3	2-NO_2	3	**7c**	48	99	98/2	98
4	4-CN	3	**7d**	48	70	>99/1	>99
5	4-Cl	3	**7e**	96	86	>99/1	>99
6	4-CF_3	3	**7f**	96	67	97/3	>99
7	4-CH_3	3	**7g**	96	72	95/5	>99
8	4-Br	3	**7h**	96	74	97/3	>99
9	2-Cl	3	**7i**	96	80	98/2	>99
10	3-Cl	3	**7j**	96	83	96/4	99
11	H	3	**7k**	96	75	93/7	98

[a] The reaction was performed with aldehyde (0.2 mmol), ketone (2.0 mmol), **1b** (3 mol %), and H_2O (0.5 mL) at room temperature.
[b] The combined isolated yield of the diastereomers.
[c] Determined by ^1H NMR of the crude product and by HPLC.
[d] Determined by chiral HPLC.

benzaldehyde (entry 5, >99:1 *anti*/*syn* ratio and >99% ee). The results showed that the aldol reactions of *para*-substituted and electron-deficient aromatic aldehydes exhibited higher enantioselectivities than those of *ortho*- and *meta*-substituted aldehydes. In fact, catalyst **1b** could efficiently catalyze the direct aldol reactions of cyclohexanone with aromatic aldehydes generating the products with excellent diastereoselectivity and enantioselectivity on electron-withdrawing or electron-rich systems, there being no obvious change in the catalytic activities.

Cyclopentanone was finally explored as an aldol donor with *o*-nitrobenzaldehyde and *p*-nitrobenzaldehyde under the same conditions. As shown in Table 4, the aldol products were obtained in high yields (94% and 99%, respectively) with excellent enantioselectivities (96% ee and >99% ee), although the diastereoselectivities decreased, especially product **7m**.

Table 4
Reactions of cyclopentanone with *o*-nitrobenzaldehyde and *p*-nitrobenzaldehyde catalyzed by **1b**[a]



Entry	R^1	Product	Time (h)	Yield[b] (%)	*anti*/*syn*[c]	ee[d] % (*syn*)
1	*o*-NO_2	**7l**	12	94	92/8	96 (82)
2	*p*-NO_2	**7m**	12	99	88/12	>99 (69)

[a] The reaction was performed with aldehyde (30 mg, 0.2 mmol), water (0.5 mL), and ketone (0.2 mL, 10 equiv).
[b] Combined yields of isolated diastereomers.
[c] Determined by ^1H NMR of the crude product and by HPLC.
[d] Determined by chiral-phase HPLC analysis of the *anti*/*syn* product.

3. Conclusion

Herein we have succeeded in designing a new system of 4-*tert*-butyldimethylsiloxy substituted organocatalysts derived from *N*-prolylsulfonamides, and studied their catalytic effect on the corresponding direct asymmetric aldol reaction in water. Based on the basic amphiphilic character, catalyst **1b** was found to be the best catalyst for the direct asymmetric aldol reactions of cyclic ketones with a series of aromatic aldehydes in water under the optimal reaction conditions, excellent diastereoselectivities up to >99:1 and enantioselectivities up to >99% with very good yields (>99%) were obtained by using as little as 3 mol % of **1b**. It is noteworthy that we did not use any additives. Further studies focusing on the mechanistic studies, application to a broader range of substrates, and the extension of **1a**–**d** in other reactions are currently under investigation and will be reported in due course.

4. Experimental

4.1. General

The starting reagents with the sulfonylamido group used during the course of preparing organocatalysts **1a**–**d** including *p*-toluenesulfonamide, *o*-toluenesulfonamide, benzenesulfonamide, and *p*-nitrobenzenesulfonamide were purchased from the Aldrich Company. All chemicals were used as received unless otherwise noted. Reagent grade solvents were distilled prior to use. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates visualized with UV light and/or by staining with ethanolic phosphomolybdic acid (PMA) and/or ninhydrin both in ethanol stain. THF was freshly distilled from sodium-benzophenone ketyl radical under an argon atmosphere immediately prior to use, DMF was distilled after drying over anhydrous $MgSO_4$ and stored over 4 Å molecular sieves. Flash column chromatography was performed on silica gel (200–300 mesh). NMR spectra were recorded on a 300 MHz instrument. Chemical shifts (δ) are given in ppm relative to TMS as the internal reference, coupling constants (J) in Hz. IR spectra were recorded on a spectrometer. Melting points were measured on a digital melting point apparatus. Mass spectra (MS) were measured with a spectrometer. Analytical high performance liquid chromatography (HPLC) was carried out on Agilent 1200 instrument using Chiralpak AD (4.6 mm × 250 mm), Chiralcel OD-H (4.6 mm × 250 mm), or Chiralcel OJ-H (4.6 mm × 250 mm) columns. Optical rotations were measured on a JASCO P-1010 Polarimeter at λ = 589 nm.

4.1.1. *N*-Boc-*trans*-4-hydroxy-L-proline 2

A solution of *trans*-4-hydroxy-L-proline (4 g, 30.4 mmol) in 40 mL solvents [V (dioxane)/V (H_2O) = 1:1] and satd aq $NaHCO_3$ solution (80 mL) at 0 °C was treated by the dropwise addition of $(Boc)_2O$ (60.8 mmol). The solution was stirred overnight at room temperature. The pH was maintained at 3 by the addition of 2 M aq HCl and the reaction mixture was extracted with AcOEt and dried over Na_2SO_4. After evaporation of the solvent and flash chromatography on silica gel, pure **2** was isolated (6.8 g, 29.4 mmol, 97%). Colorless waxes; FT-IR ν_{max} (neat)/cm^{-1} 3421, 2979, 2361, 1681, 1419, 1160. ^1H NMR ($CDCl_3$): 11.0 (br, 1H, COOH), 4.46–4.36 (m, 1H, C*H*), 4.16–4.09 and 3.71–3.49 (m, 3H, NCH_2 and CH_2CH), 2.32–2.29 (m, 1H), 2.11–2.05 (m, 1H), 1.26 and 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$, *cis* and *trans* conformers): 177.0, 175.6, 155.6, 154.4, 81.1, 80.9, 69.5, 69.1, 60.4, 60.4, 57.8, 57.5, 38.7, 37.7, 28.2, 28.1.

4.1.2. *N*-Boc-*trans*-4-hydroxy-L-proline benzyl ester 3

Triethylamine (1.87 mL, 13.4 mmol, 1.1 equiv) was added to a solution of (2*S*,4*R*)-1-Boc-4-hydroxyl-L-proline (2.82 g, 12.2 mmol, 1 equiv) and benzyl bromide (1.59 mL, 13.4 mmol, 1.1 equiv) in tetrahydrofuran (15 mL) at 0 °C. After the mixture was stirred for 18 h at room temperature, the solvent was evaporated in vacuo. The residue was dissolved in 30 mL of CH_2Cl_2, washed with HCl

(1 N), H_2O, Na_2CO_3 (5%), and H_2O, and then dried over Na_2SO_4 overnight. Evaporation of the solvent under reduced pressure yielded a light yellow oil, which was almost pure after standing overnight under high vacuum. It was further purified by flash chromatography (eluent, AcOEt/petroleum ether = 1:2) to give **3** as a light yellow oil. Yield: 90%. FT-IR ν_{max} (neat)/cm^{-1} 3438, 3034, 1748, 1679, 1413, 1157, 735. ^1H NMR ($CDCl_3$): 7.32–7.30 (m, 5H), 5.13–5.07 (m, 2H), 4.45–4.39 (m, 1H), 4.15 (s, 1H), 3.56 (m, 2H), 2.27–2.25 (m, 1H, CH_2-H_a), 2.02–1.99 (m, 1H, CH_2-H_b), 1.43 and 1.31 (s, 9H). ^{13}C NMR (*cis* and *trans* conformers): 172.7, 172.4, 154.3, 153.7, 135.2, 134.9, 128.2, 128.0, 127.9, 127.9, 127.7, 127.6, 80.0, 79.8, 69.1, 68.5, 66.3, 57.7, 57.4, 54.2, 54.1, 38.6, 37.8, 27.9, 27.7.

4.1.3. *N*-Boc-*cis*-4-*tert*-butyldimethylsiloxy-L-proline benzyl ester 4[14]

To a stirred of solution of *N*-Boc-*trans*-4-hydroxy-L-proline benzyl ester 3 (3.5 g, 11 mmol, 1 equiv) in DMF (20 mL), NEt_3 (1.67 mL, 1.1 equiv) was added, and then under a dry Ar atmosphere, the mixture was chilled to 0 °C in ice bath, after which 1.641 g (1 equiv) TBS–Cl was added to the solution, and stirred for 1 h. Then the solution was allowed to warm up to 50 °C and was stirred for 2 days. The solution was diluted with 30 mL EtOAC and the solution was washed by 15 mL distilled water and dried over anhydrous Na_2SO_4 overnight. The solvent was evaporated under reduced pressure and the residue was chromatographed (eluent, AcOEt/petroleum ether = 1:16) to give the *N*-Boc-*cis*-4-*tert*-butyldimethylsiloxy-L-proline benzyl ester **4** as a light yellow oil. Yield: 76%; FT-IR ν_{max} (neat)/cm^{-1}: 2887.32, 2857.84, 1749.73, 1703.90, 1609.54, 1587.87, 1497.79, 1256.15, 1064.94, 754.36, 698.24; 1H NMR ($CDCl_3$): 7.34 (s, 5H), 5.07–5.27 (m, 2H), 4.34–4.47 (m, 2H), 3.58–3.62 (m, 1H), 3.38–3.41 (m, 1H), 2.14–2.18 (m, 1H), 1.98–2.02 (m, 1H), 1.36 and 1.45 (s, 9H), 0.85 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$): 172.8, 172.5, 154.4, 153.7, 135.7, 135.4, 128.3, 127.9, 79.8, 69.8, 66.5, 57.8, 54.4, 39.1, 28.1, 25.5, 17.7, −5.0; MS(ESI): 458.07 $(M+Na)^+$.

4.1.4. General procedure for the preparation of 6a–d

Compound **6a** is referred to as an example: *N*-Boc-*cis*-4-*tert*-butyldimethylsiloxy-L-proline benzyl ester **4** (3.0 g, 7 mmol, 1 equiv) and 10% Pd/C (0.3 g) in methanol (35 mL) were stirred under an atmosphere of hydrogen at room temperature for 12 h. After this time, the mixture was filtered through Celite and the filtrate evaporated in vacuo to give the compound *N*-Boc-*cis*-4-*tert*-butyldimethylsiloxy-L-proline **5** as an off-white wax. The crude product may be used directly in the next step. Under a dry Ar atmosphere, to a stirred solution of *N*-Boc-*cis*-4-*tert*-butyldimethylsiloxy-L-proline 5 (400 mg, 1 mmol, 1 equiv), DMAP (42 mg, 0.3 equiv), EDCI (244 mg, 1.1 equiv), and *p*-toluenesulfonamide (159 mg, 0.8 equiv) were dissolved in dichloromethane (10 mL). The resulting mixture was stirred at room temperature for 2 days. Then the mixture was concentrated to half the volume in vacuo and the resulting mixture was partitioned between EtOAc (100 mL) and 1 M aqueous HCl (50 mL). The organic layer was washed with half-saturated brine (25 mL), dried (Na_2SO_4), filtered, and concentrated followed by flash column chromatography (AcOEt/petroleum ether = 1:6) to give compound **6a**.

4.1.4.1. *N*-Boc-*cis*-4-*tert*-butyldimethylsiloxy-L-proline amide 6a.

White solid. Yield: 52%; mp: 175–176 °C; FT-IR ν_{max} (neat)/cm^{-1}; 3435.39, 3105.33, 2887.87, 1727.61, 1666.69, 1586.26, 1468.41, 1366.38, 1255.22, 1087.76, 776.14, 688.70; ^1H NMR (DMSO): 12.20 (s, 1H), 7.81 (d, 2H, J = 7.0 Hz), 7.41 (d, 2H, J = 6.9 Hz), 4.14–4.31 (m, 2H), 3.16 (d, 1H, J = 10.4 Hz), 2.37 (s, 3H), 2.02 (d, 1H, J = 7.0 Hz), 1.58–1.71 (m, 1H), 1.32 and 1.10 (s, 9H), 0.80 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$): 170.4, 169.1, 157.3, 144.8, 135.9, 129.4, 128.2, 81.7, 69.7, 59.8, 55.0, 39.6, 35.4, 28.2, 255, 21.5, 17.7, −5.1; MS(ESI): 498.84 (M^+).

4.1.4.2. *N*-Boc-*cis*-4-*tert*-butyldimethylsiloxy-L-proline amide 6b.

Light yellow solid. Yield: 47%; mp: 161–162 °C FT-IR ν_{max} (neat)/cm^{-1}; 3448.00, 3109.25, 2888.60, 1736.25, 1650.58, 1535.43, 1478.56, 1369.12, 1256.97, 1087.12, 838.29; ^1H NMR ($CDCl_3$):11.01 (s, 1H), 8.37 (d, 2H, J = 8.3 Hz), 8.26 (d, 2H, J = 8.3 Hz), 4.31–4.36 (m, 2H), 3.30–3.37 (m, 2H), 2.37–2.41 (m, 1H), 1.88–1.90 (m, 1H), 1.49 (s, 9H), 0.83 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$): 170.8, 169.4, 157.4, 154.6, 150.6, 144.2, 129.7, 123.9, 82.3, 69.7, 59.1, 55.2, 35.6, 29.4, 25.5, 17.8, −5.0; MS(ESI): 528.19 $(M-H)^+$.

4.1.4.3. *N*-Boc-*cis*-4-*tert*-butyldimethylsiloxy-L-proline amide 6c.

Light yellow solid. Yield: 41%; mp: 98–99 °C; FT-IR ν_{max} (neat)/cm^{-1}: 3378.70, 3108.11, 2887.27, 1685.22, 1649.83, 1566.95, 1474.46, 1367.12, 1255.70, 1094.79, 775.80; ^1H NMR ($CDCl_3$): 10.88 (s, 1H), 8.20 (d, 1H, J = 7.8 Hz), 7.50–7.55 (t, 1H, $J1$ = 7.1 Hz, $J2$ = 7.3 Hz), 7.37–7.42 (t, 1H, $J1$ = 7.6 Hz, $J2$ = 7.4 Hz), 7.32 (d, 1H, J = 7.6 Hz), 4.31–4.44 (m, 2H), 3.31–3.41 (m, 2H), 2.68 (s, 3H), 2.42–2.46 (m, 1H), 1.88 (m, 1H), 1.53 (s, 9H), 0.86 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$): 168.9, 157.7, 137.7, 133.7, 132.3, 131, 126.2, 82.2, 69.8, 59.1, 55.0, 35.2, 28.2, 25.6, 20.1, 17.8, −4.9; MS(ESI): 397.70 $(M-H)^+$.

4.1.4.4. *N*-Boc-*cis*-4-*tert*-butyldimethylsiloxy-L-proline amide 6d.

White solid. Yield: 46%; mp: 151–152 °C. FT-IR ν_{max} (neat)/cm^{-1}: 3455.33, 3076.64, 2891.30, 1734.88, 1659.99, 1599.43, 1477.96, 1368.92, 1255.16, 1087.92, 838.28; ^1H NMR ($CDCl_3$): 8.04 (d, 2H, J = 5.8 Hz), 7.15–7.61 (m, 3H), 4.31 (s, 2H), 3.30–3.49 (m, 2H), 1.86–2.36 (m, 2H), 1.23 and 1.47 (s, 9H), 0.82 (s, 9H), 0.02 (s, 6H), N–H was not determined; ^{13}C NMR ($CDCl_3$): 170.5, 169.1, 157.3, 138.7, 133.6, 128.5, 81.7, 69.7, 59.84, 55.0, 39.6, 35.3, 28.0, 25.5, 17.7, −5.0; MS(ESI): 482.66 $(M-H)^+$.

4.1.5. General procedure for the preparation of 1a–d

Compound **1a** is referred to as an example: To a stirred solution of *N*-Boc-*cis*-4-*tert*-butyldimethylsiloxy-L-proline amide **6a** (430 mg, 1 mmol) in dichloromethane (10 mL), TFA (4.3 mL) was added and stirred at room temperature for 5 h. After evaporation of the solvent, the resulting residue was neutralized with 10% NaOH aqueous solution, and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated followed by flash column chromatography on silica gel ($MeOH/CHCl_3$ = 1:10, v/v) to give **1a** as a light yellow solid.

4.1.5.1. *cis*-4-*tert*-Butyldimethylsiloxy-L-proline amide 1a.

Light yellow solid. Yield: 89%; mp: 114–115 °C; $[\alpha]_D^{20} = -6.2$ (c 0.005, $CHCl_3$) FT-IR ν_{max} (neat)/cm^{-1}: 3470.53, 3063.88, 2857.05, 1599.67, 1495.82, 1364.06, 1257.25, 1085.19, 837.20; ^1H NMR ($CDCl_3$): 7.8 (d, 2H, J = 5.6 Hz), 7.20 (d, 2H, J = 5.4 Hz), 4.42 (s, 2H), 3.52 (d, 2H), 3.24 (d, 2H, J = 10.8 Hz), 2.38 (s, 3H), 2.28 (s, 2H), 2.00 (s, 2H), 0.83 (s, 9H), 0.03 (s, 6H), N–H was not determined; ^{13}C NMR ($CDCl_3$): 170.8, 142.3, 140.1, 128.1, 126.8, 70.9, 60.8, 53.4, 38.8, 25.6, 20.8, 17.6, −5.1; MS(ESI):399.70 $(M+H)^+$.

4.1.5.2. *cis*-4-*tert*-Butyldimethylsiloxy-L-proline amide 1b.

Light yellow solid. Yield: 82%; mp: 125–126 °C; $[\alpha]_D^{20} = -12.4$ (c 0.005, $CHCl_3$); FT-IR ν_{max} (neat)/cm^{-1}: 3452.21, 3105.00, 2857.77, 1605.01, 1528.73, 1469.58, 1260.92, 1087.02, 836.73; ^1H NMR ($CDCl_3$): 8.26 (d, 2H, J = 8.0 Hz), 8.09 (d, 2H, J = 8.1 Hz), 4.50 (m, 2H), 3.57 (d, 1H, J = 10.4 Hz), 3.34 (d, 1H, J = 11.7 Hz), 2.27–2.29 (m, 1H), 1.99–2.02 (m, 1H), 0.82 (s, 9H), 0.04 (s, 6H), N–H was not determined; ^{13}C NMR ($CDCl_3$): 174.1, 149.4, 148.5, 27.9, 123.7, 71.2, 62.0, 54.7, 39.2, 25.5, 17.8, −5.0; MS(ESI): 428.01 $(M-H)^+$.

4.1.5.3. *cis*-4-*tert*-Butyldimethylsiloxy-L-proline amide 1c. Light yellow solid. Yield: 79%; mp: 131–132 °C; $[\alpha]_D^{20} = -2.54$ (*c* 0.005, $CHCl_3$) FT-IR ν_{max} (neat)/cm^{-1}: 3428.82, 3061.41, 2857.29, 1601.43, 1470.08, 1363.60, 1257.22, 1064.35, 756.70; ^1H NMR ($CDCl_3$): 7.90–7.99 (m, 1H), 7.33–7.38 (m, 1H), 7.25 (d, 2H, *J* = 7.6 Hz), 4.40–4.47 (m, 2H), 3.47 (d, 1H, *J* = 11.4 Hz), 3.16 (d, 1H, *J* = 12.0 Hz), 2.68 (s, 3H), 2.28–2.34 (m, 1H), 1.92–1.96 (m, 1H), 0.85 (s, 9H), 0.05 (s, 6H), N–H was not determined; ^{13}C NMR ($CDCl_3$): 173.2, 141.2, 137.0, 131.9, 131.5, 127.7, 125.5, 71.1, 61.7, 54.3, 39.7, 25.7, 20.6, 17.9, −4.9; MS(ESI): 397.72 $(M-H)^+$.

4.1.5.4. *cis*-4-*tert*-Butyldimethylsiloxy-L-proline amide 1d. Light yellow solid. Yield: 82%; mp: 106–107 °C; $[\alpha]_D^{20} = -8.6$ (*c* 0.005, $CHCl_3$); FT-IR ν_{max} (neat)/cm^{-1}: 3444.37, 3065.66, 2857.12, 1603.00, 1470.07, 1364.47, 1258.91, 1086.61, 753.88, 719.49; ^1H NMR ($CDCl_3$): 7.91 (d, 2H, *J* = 6.4 Hz), 7.43 (d, 2H, *J* = 7.4 Hz), 4.40–4.48 (m, 2H), 3.47 (d, 2H, *J* = 9.9 Hz), 3.19 (d, 2H, *J* = 11.6 Hz), 2.28–2.30 (m, 1H), 1.96–2.05 (m, 1H), 0.83 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$): 173.7, 143.0, 131.5, 128.4, 126.4, 71.2, 61.8, 54.3, 39.4, 25.6, 17.9, −4.9; MS(ESI): 383.21 $(M-H)^+$.

4.2. General procedure for the preparation of aldol products

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

4.2.1.1. Reactions in neat ketone. Cyclohexanone (0.206 mL) was added to a mixture of 0.2 mmol of aldehyde and catalyst. 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 flash column chromatography (silica gel, petroleum ether/ethyl acetate). The absolute configuration of aldol products was extrapolated by comparison of the HPLC data with known literature values.

4.2.1.2. Reactions in water. To a mixture of catalyst (7.15 mg, 0.02 mmol) and aldehyde in water (0.2 mL), the ketone was added under air in a closed system. After being stirred at room temperature for the indicated time, the mixture was treated the same manner as shown above.

4.2.2. (2*S*, 1′*R*)-2-(Hydroxy-(4-nitrophenyl) methyl) cyclohexan-1-one 7a

$[\alpha]_D^{25} = +12.8$ (*c* 1.85, $CHCl_3$), 99% ee. ^1H NMR (300 MHz, $CDCl_3$): δ 8.21 (d, 2H, *J* = 8.7 Hz), 7.51 (d, 2H, *J* = 8.7 Hz), 4.90 (dd, 1H, *J* = 8.4, 3.0 Hz), 4.09 (d, 1H, *J* = 3.0 Hz), 2.65–2.45 (m, 2H), 2.36 (td, 1H, *J* = 13.2, 5.7 Hz), 2.17–2.06 (m, 1H), 1.87–1.78 (m, 1H), 1.67–1.51 (m, 3H), 1.45–1.31 (m, 1H). IR (film): 3730, 2924, 1699, 1519, 1346, 854 cm^{-1}. Enantiomeric excess was determined by HPLC with a Chiralpak AD column (hexane/2-propanol = 80/20), 21 °C, 254 nm, 0.5 mL/min; major enantiomer t_R = 41.9 min and minor enantiomer t_R = 32.4 min.

4.2.3. (2*S*, 1′*R*)-2-(Hydroxy-(3-nitrophenyl) methyl) cyclohexan-1-one 7b

$[\alpha]_D^{24} = +32.5$ (*c* 1.35, $CHCl_3$), 98% ee. ^1H NMR (300 MHz, $CDCl_3$): δ 8.12 (s, 1H), 8.16 (d, 1H, *J* = 7.8 Hz), 7.68 (d, 1H, *J* = 7.5 Hz), 7.53 (t, 1H, *J* = 7.8 Hz), 4.90 (dd, 1H, *J* = 8.7, 3.0 Hz), 4.15 (d, 1H, *J* = 3.0 Hz), 2.68–2.58 (m, 1H), 2.54–2.46 (m, 1H), 2.38 (td, 1H, *J* = 12.3, 5.4 Hz), 2.17–2.07 (m, 1H), 1.87–1.78 (m, 1H), 1.67–1.53 (m, 3H), 1.46–1.31 (m, 1H). IR (film, cm^{-1}): 3512, 2939, 1701, 1529, 1351, 736. Enantiomeric excess was determined by HPLC with a Chiralpak AD column (hexane/2-propanol = 90/10), 20 °C, 254 nm, 0.5 mL/min; major enantiomer t_R = 49.2 min and minor enantiomer t_R = 63.2 min.

4.2.4. (2*S*, 1′*R*)-2-(Hydroxy-(2-nitrophenyl) methyl) cyclohexan-1-one 7c

$[\alpha]_D^{24} = +19.8$ (*c* 1.60, $CHCl_3$), 98% ee. ^1H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, 1H, *J* = 8.1 Hz), 7.77 (d, 1H, *J* = 7.8 Hz), 7.63 (t, 1H, *J* = 7.5 Hz), 7.43 (t, 1H, *J* = 7.8 Hz), 5.45 (d, 1H, *J* = 6.6 Hz), 3.90 (br, 1H), 2.82–2.70 (m, 1H), 2.50–2.40 (m, 1H), 2.34 (td, 1H, *J* = 12.3, 5.7 Hz), 2.15–2.06 (m, 1H), 1.90–1.55 (m, 4H). IR (film, cm^{-1}): 3512, 2940, 1699, 1526, 1351, 855 cm^{-1}. Enantiomeric excess was determined by HPLC with a Chiralpak OD column (hexane/2-propanol = 95/5), 20 °C, 254 nm, 0.5 mL/min; major enantiomer t_R = 37.9 min and minor enantiomer t_R = 45.7 min.

4.2.5. (2*S*, 1′*R*)-2-(Hydroxy-(4-cyanophenyl) methyl) cyclohexan-1-one 7d

$[\alpha]_D^{22} = +23.3$ (*c* 1.55, $CHCl_3$), >99% ee. ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, 2H, *J* = 8.1 Hz), 7.45 (d, 2H, *J* = 8.1 Hz), 4.85 (dd, 1H, *J* = 8.1, 3.0 Hz), 4.11 (d, 1H, *J* = 3.0 Hz), 2.65–2.44 (m, 2H), 2.37 (td, 1H, *J* = 12.9, 6.0 Hz), 2.17–2.06 (m, 1H), 1.88–1.77 (m, 1H), 1.72–1.47 (m, 3H), 1.44–1.31 (m, 1H). IR (film, cm^{-1}): 3509, 2932, 2227, 1701, 1609, 841 cm^{-1}. Enantiomeric excess was determined by HPLC with a Chiralpak AD column (hexane/2-propanol = 80/20), 21 °C, 254 nm, 0.5 mL/min; major enantiomer t_R = 34.8 min and minor enantiomer t_R = 27.9 min.

4.2.6. (2*S*, 1′*R*)-2-(Hydroxy-(4-chlorophenyl) methyl) cyclohexan-1-one 7e

$[\alpha]_D^{25} = +21.7$ (*c* 1.00, $CHCl_3$), >99% ee. ^1H NMR (300 MHz, $CDCl_3$): δ 7.29 (dd, 4H, *J* = 20.4, 8.4 Hz), 4.76 (dd, 1H, *J* = 8.7, 2.7 Hz), 3.99 (d, 1H, *J* = 3.0 Hz), 2.61–2.44 (m, 2H), 2.35 (td, 1H, *J* = 12.9, 5.4 Hz), 2.15–2.05 (m, 1H), 1.85–1.75 (m, 1H), 1.70–1.50 (m, 3H), 1.37–1.20 (m, 1H). IR (film, cm^{-1}): 3491, 2934, 1698, 1489, 830. Enantiomeric excess was determined by HPLC with a Chiralpak AD column (hexane/2-propanol = 90/10), 21 °C, 220 nm, 0.5 mL/min; major enantiomer t_R = 39.9 min and minor enantiomer t_R = 33.6 min.

4.2.7. (2*S*, 1′*R*)-2-(Hydroxy-(4-(trifluoromethyl) phenyl) methyl) cyclohexan-1-one 7f

$[\alpha]_D^{25} = +2.3$ (*c* 1.00, $CHCl_3$), >99% ee. ^1H NMR (300 MHz, $CDCl_3$): δ 7.74–7.55 (m, 3H), 7.40 (t, 1H, *J* = 7.2 Hz), 5.30 (d, 1H, *J* = 9.3 Hz), 4.03 (t, 1H, *J* = 3.0 Hz), 2.81–2.69 (m, 1H), 2.55–2.45 (m, 1H), 2.37 (td, 1H, *J* = 12.9, 4.8 Hz), 2.15–2.03 (m, 1H), 1.81–149 (m, 3H), 1.48–1.23 (m, 1H). IR (film, cm^{-1}): 3512, 2943, 1701, 1453, 1312, 768 cm^{-1}. Enantiomeric excess was determined by HPLC with a Chiralpak AD column (hexane/2-propanol = 90/10), 21 °C, 254 nm, 0.5 mL/min; major enantiomer t_R = 34.4 min and minor enantiomer t_R = 26.9 min.

4.2.8. (2*S*, 1′*R*)-2-(Hydroxy-(4-tolyl) methyl) cyclohexan-1-one 7g

$[\alpha]_D^{24} = +12.9$ (*c* 0.17, $CHCl_3$), >99% ee. ^1H NMR (300 MHz, $CDCl_3$): δ 7.18 (dd, 4H, *J* = 17.1, 8.4 Hz), 4.75 (dd, 1H, *J* = 9.0, 2.7 Hz), 3.91 (d, 1H, *J* = 2.7 Hz), 2.66–2.54 (m, 1H), 2.51–2.43 (m, 1H), 2.35 (td, 1H, *J* = 13.2, 6.0 Hz), 2.34 (s, 3H), 2.14–2.03 (m, 1H), 1.82–1.72 (m, 1H), 1.70–1.50 (m, 3H), 1.38–1.18 (m, 1H). IR (film, cm^{-1}): 3513, 2926, 1701, 1449, 820. Enantiomeric excess was determined by HPLC with a Chiralpak AD column (hexane/2-propanol = 90/10), 21 °C, 220 nm, 0.5 mL/min; major enantiomer t_R = 32.7 min and minor enantiomer t_R = 44.5 min.

4.2.9. (2*S*,1′*R*)-2-(Hydroxy-(4-bromophenyl) methyl) cyclohexan-1-one 7h

$[\alpha]_D^{24} = +22.6$ (*c* 0.70, $CHCl_3$), >99% ee. ^1H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, 2H, *J* = 8.1 Hz), 7.20 (d, 2H, *J* = 8.7 Hz), 4.75 (dd, 1H, *J* = 8.7, 2.7 Hz), 3.99 (d, 1H, *J* = 3.0 Hz), 2.61–2.44 (m, 2H), 2.35 (td, 1H, *J* = 12.9, 6.3 Hz), 2.15–2.04 (m, 1H), 1.85–1.75 (m, 1H), 1.70–1.50 (m, 3H), 1.37–1.20 (m, 1H). IR (film, cm^{-1}): 3361,

2928, 1692, 1460, 825. Enantiomeric excess was determined by HPLC with a Chiralpak AD column (hexane/2-propanol = 90/10), 21 °C, 220 nm, 0.5 mL/min; major enantiomer t_R = 43.1 min and minor enantiomer t_R = 35.5 min.

4.2.10. (2*S*,1′*R*)-2-(Hydroxyl (2-chlorophenyl)methyl) cyclohexan-1-one 7i

>99% ee. ^{1}H NMR (300 MHz, $CDCl_3$) 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); Enantiomeric excess was determined by HPLC with Chiralcel OD-H (hexane/*i*-PrOH = 95/5), 21 °C, 220 nm, flow rate 1.0 mL/min, major enantiomer t_R = 10.5 min and minor enantiomer t_R = 13.7 min.

4.2.11. (2*S*,1′*R*)-2-(Hydroxyl (3-chlorophenyl) methyl) cyclohexan-1-one 7j

99% ee. ^{1}H NMR (300 MHz, $CDCl_3$) 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); Enantiomeric excess was determined by HPLC with Chiralcel OD-H (hexane/*i*-PrOH = 96/4), 21 °C, 220 nm, flow rate 1.0 mL/min, major enantiomer t_R = 14.8 min and minor enantiomer t_R = 21.2 min.

4.2.12. (2*S*, 1′*R*)-2-(Hydroxy (phenyl) methyl) cyclohexan-1-one 7k

$[\alpha]_D^{22} = +23.3$ (*c* 1.55, $CHCl_3$), 98% ee. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50–7.24 (5H, m), 4.80 (d, 1H, J = 9.0 Hz), 4.00 (m, 1H), 2.70–2.56 (m, 1H), 2.55–2.44 (m, 1H), 2.34 (td, 1H, J = 12.3, 5.4 Hz), 2.16–2.03 (m, 1H), 1.87–1.73 (m, 1H), 1.72–1.50 (m, 3H), 1.40–1.22 (m, 1H). IR (film, cm^{-1}): 3508, 2932, 1697, 1451, 702. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (hexane/2-propanol = 90/10), 20 °C, 220 nm, 0.5 mL/min; major enantiomer t_R = 19.6 min and minor enantiomer t_R = 30.6 min.

4.2.13. (2*S*, 1′*R*)-2-(Hydroxy(2-nitrophenyl)methyl) cyclopentan-1-one 7l

Anti-isomer: 96% ee. ^{1}H NMR (300 MHz, $CDCl_3$): 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); Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (hexane/2-propanol = 95/5), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 27.4 min, minor enantiomer t_R = 22.9 min, syn-isomer: 82% ee. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (hexane/2-propanol = 95/5), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 20.3 min and minor enantiomer t_R = 17.2 min.

4.2.14. (2*S*, 1′*R*)-2-(Hydroxy-(4-nitrophenyl) methyl) cyclopentan-1-one 7m

$[\alpha]_D^{22} = -30.6$ (*c* 0.56, $CHCl_3$), anti-isomer: >99% ee. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (d, 2H, J = 8.7 Hz), 7.54 (d, 2H, J = 9.0 Hz), 4.85 (d, 1H, J = 9.0 Hz), 4.74 (s, 1H), 2.54–2.18 (m, 3H), 2.08–1.95 (m, 1H), 1.81–1.48 (m, 3H). IR (film, cm^{-1}): 3442, 2966, 1737, 1604, 1519, 1347, 857 cm^{-1}. Enantiomeric excess was determined by HPLC with a Chiralpak AD column (hexane/2-propanol = 95/5), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 59.8 min, minor enantiomer t_R = 56.8 min. syn-isomer: 69% ee. Enantiomeric excess was determined by HPLC with a Chiralpak AD column (hexane/2-propanol = 95/5), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 31.1 min and minor enantiomer t_R = 44.7 min.

Acknowledgment

Authors are grateful to Southwest University of China for financial support.

References

1. (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175; (b) List, B. *Chem. Commun.* **2006**, 819–824; (c) Guillena, G.; Ramón, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1456–1492; (d) Mukherjee, S.; Yang, J. W.; Hoffman, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569.
2. For a review: *Modern Aldol Reactions*; Mahrwald, R., Ed.2004; Wiley-VCH: Weinheim, Germany; Vols. 1 and 2.
3. (a) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325–345; (b) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573–575; (c) Cordova, A.; Notz, W.; Barbas, C. F., III *Chem. Commun.* **2002**, *24*, 3024–3025; (d) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475–2479; (e) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152–2154; (f) Tang, Z.; Jiang, F.; Cui, X.; Gong, L. Z.; Mi, A. Q.; Jiang, Y. Z.; Wu, Y. D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5755–5760; (g) Ender, D.; Grondal, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1210–1212; (h) Kazmaier, U. *Angew. Chem., Int. Ed.* **2005**, *44*, 2186–2188; (i) He, L.; Tang, Z.; Cun, L. F.; Mi, A. Q.; Jiang, Y. Z.; Gong, L. Z. *Tetrahedron* **2006**, *62*, 346–351; (j) Xu, X. Y.; Tang, Z.; Wang, Y. Z.; Luo, S. W.; Cun, L. F.; Gong, L. Z. *J. Org. Chem.* **2007**, *72*, 9905–9913; (k) Russo, A.; Botta, G.; Lattanzi, A. *Tetrahedron* **2007**, *63*, 11886–11892.
4. (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed.* **1971**, *10*, 496–497; (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621; (c) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
5. For selected reviews on the aldol and other reactions using asymmetric organocatalysis, see: (a) Guillena, G.; Najera, C.; Ramón, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249–2293; (b) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724; (c) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580–591; (d) List, B. *Acc. Chem. Res.* **2004**, *37*, 548–557; (e) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558–569; (f) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638–4660.
6. Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 734–735.
7. (a) Garner, P. P. In *Organic Synthesis in Water*; Blackie Academic & Professional: London, 1998; (b) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751–2772; (c) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095–3166; (d) Pirrung, M. C. *Chem. Eur. J.* **2006**, *12*, 1312–1317.
8. (a) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417–4420; (b) Guizzetti, S.; Benaglia, M.; Raimondi, L.; Celentono, G. *Org. Lett.* **2007**, *9*, 1247–1250; (c) Siyutkin, D. E.; Kucherenko, A. S.; Struchkova, M. I.; Zlotin, S. G. *Tetrahedron Lett.* **2008**, *49*, 1212–1216.
9. (a) Cordova, A.; Notz, W.; Barbas, C. F., III *Chem. Commun.* **2002**, 3024–3025; (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267.
10. For some selected references on the aldol reaction in/on water via asymmetric organocatalysis, see: (a) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958–961; (b) Aratake, S.; Itoh, T.; Okano, T.; Nagae, N.; Sumiya, T.; Shoji, M.; Hayashi, Y. *Chem. Eur. J.* **2007**, *13*, 10246–10256; (c) Hayashi, Y.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5527–5529; (d) Guizzetti, S.; Benaglia, M.; Raimondi, L.; Celentano, G. *Org. Lett.* **2007**, *9*, 1247–1250; (e) Huang, J. M.; Zhang, X. T.; Armstrong, D. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 9073–9077; (f) Luo, S.; Mi, X.; Liu, S.; Xu, H.; Cheng, J.-P. *Chem. Commun.* **2006**, 3687–3689; (g) Font, D.; Jimeno, C.; Pericas, M. A. *Org. Lett.* **2006**, *8*, 4653–4655; (h) Guillena, G.; Hita, M.; Najera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1493–1497; (i) Dziedzic, P.; Zou, W.; Hafren, J.; Cordova, A. *Org. Biol. Chem.* **2006**, *4*, 38–40; (j) Chimni, S. S.; Mahajan, D. *Tetrahedron: Asymmetry* **2006**, *17*, 2108–2119; (k) Zhang, S. P.; Fu, X. K.; Fu, S. D.; Pan, J. F. *Catal. Commun.* **2008**, *10*, 401–405; (l) Chimni, S. S.; Singh, S.; Mahajan, D. *Tetrahedron: Asymmetry* **2008**, *19*, 2276–2284; (m) Zhang, S. P.; Fu, X. K.; Fu, S. D. *Tetrahedron Lett.* **2009**, *50*, 1173–1176.
11. (a) Berkessel, A.; Koch, B.; Lex, J. *Adv. Synth. Catal.* **2004**, *346*, 1141–1146; (b) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84–96; (c) Gandhi, S.; Singh, V. K. *J. Org. Chem.* **2008**, *73*, 9411–9416.
12. (a) Lindstrom, U. M.; Andersson, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 548–551; (b) Otto, S.; Engberts, J. B. F. N. *Org. Biomol. Chem.* **2003**, *1*, 2809–2820.
13. (a) Maya, V.; Raj, M.; Singh, V. K. *Org. Lett.* **2007**, *9*, 2593–2595.
14. Ohtake, H.; Imada, Y.; Murahashi, S. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2737–2754.