Tetrahedron: *Asymmetry* 21 (2010) 2465–2470

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

One-step, efficient synthesis of combined threonine–surfactant organocatalysts for the highly enantioselective direct aldol reactions of cyclic ketones with aromatic aldehydes in the presence of water

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ARTICLE INFO

Article history:
Received 20 July 2010
Accepted 6 September 2010
Available online 8 November 2010

ABSTRACT

In this work, a new class of organocatalysts have been designed and synthesized in one step by a rational combination of threonine with acyl chlorides at room temperature in trifluoroacetic acid to make a series of novel combined threonine-surfactant organocatalysts readily available on a large-scale. No protecting groups or chromatographic techniques are involved in the procedures, while certain combined threonine-surfactant organocatalysts mediate the direct aldol reactions of cyclic ketones with aromatic aldehydes to provide the aldol products in good yields with enantioselectivities of up to 99%.

1. Introduction

Asymmetric organocatalysis has become an important area of research in organic synthesis.[1] The asymmetric aldol reaction is one of the most powerful methods for constructing carbon–carbon bonds in organic synthesis.[2] The past decade has witnessed the extraordinary success of amines, especially the use of chiral primary amino acids and their derivatives which is an important area of research in enantioselective aldol reactions.[3] It has been reported that primary amino acid catalyzed aldol reactions[3k,q,r] can only afford high enantioselectivity in solvents such as dimethylsulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF); these polar solvents often create additional hurdles for product isolation. Water is an ideal solvent for chemical reactions due to its low cost, safety, and environmentally benign nature. As water offers several advantages over organic solvents, reactions in aqueous media have received a great deal of attention in recent years.[4] However, the vast majority of organocatalytic reactions yield racemic products if the reactions take place in the presence of water.[5] Recently, it was shown by Takabe et al., Barbas et al. and Hayashi et al. that the direct asymmetric aldol reaction and the Michael reaction could be catalyzed by the proline-derived hydrophobic catalysts in the presence of water.[3n,o,6] Our group recently reported that the 4-phenoxy substituted and the 4-*tert*-butyl-dimethylsiloxy-substituted prolinamides catalyze the direct aldol reactions between cyclic ketones and aromatic aldehydes in the presence of water.[7] Lu et al. reported that the siloxy theronine and serine derivatives are highly efficient organocatalysts for asymmetric aldol reactions of ketones in the presence of water.[8] Although these amino acids were not efficient organocatalysts in direct aldol reactions between cyclohexanone and benzaldehyde in water, their hydrophobic derivatives (e.g., *O*-TBS-threonine) proved to be very efficient catalysts. The desired aldol products were obtained in excellent yields (up to 99%), with nearly perfect enantiomeric control (up to 99% ee). However, it should be noted that among all the reported asymmetric organocatalysts, most of them were prepared with a laborious procedure, tiresome purification of chromatography, and/or need some expensive reagents, which created additional hurdles for industrial production. As a result these organocatalysts are often only used in research laboratories. Therefore, the development of a new type of effective asymmetric organocatalysts from the chiral pool, with simple preparation procedures, and using inexpensive reagents is urgently needed and is a significant challenge. Herein, we disclose our findings that simple, natural L-threonine derivatives are excellent organocatalysts for the direct aldol reactions in aqua.

For the design of novel catalysts **1·HCl**, we are particularly interested in organocatalysts that can be easily derived from the crude chiral pool. We hypothesized and deduced that the incorporation of a hydrophobic group into hydrophilic natural amino acids, which are usually abundant in the chiral pool, which could enhance their hydrophobic capability, consequently their interaction with organic substrates may be favorable in aqueous media.[9] With the properly designed catalysts, water can be sequestered from the transition state and high stereocontrol may be expected. This approach is particularly attractive in view of the ready availability of natural amino acids and the variety of chiral structural scaffolds that they can offer.

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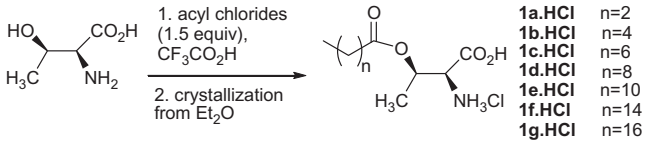
doi:10.1016/j.tetasy.2010.09.006

Threonine seems to be good chiral structural scaffolds, as its hydroxy group allows for the easy attachment of various hydrophobic groups such as alkyl, acyl, and so on.[10a–c,8] In this work we show how an O-acylation of L-threonine with acyl chlorides at room temperature in trifluoroacetic acid in one step makes a series of novel L-threonine derivatives readily available on large-scale (Scheme 1).[10d,e] No protecting groups or chromatographic techniques are involved in the procedures, and certain combined threonine-surfactant organocatalysts mediate the direct aldol reaction of cycloheaxanone with 4-nitrobenzaldehyde in the presence of water (Table 1).



Scheme 1. Synthetic scheme for acyloxythreonines 1: (1) acyl chlorides, CF_3CO_2H, 0 °C to room temperature; (2) crystallization from Et_2O.

2. Results and discussion

Emulsions may be the ideal reaction medium for achieving effective mixing, as demonstrated by Kobayashi et al. for several surfactant-combined organometallic catalysts, which promote organic reactions in the presence of water.[6c,11] Natural threonine was not an efficient organocatalyst in the presence of water (Table 1, entry 1).[8] The incorporation of hydrophobic acylation groups into threonine resulted in effective organocatalysts capable of catalyzing the direct aldol reaction in the presence of water (Table 1, entries 2–9 and entry 11). From the seven threonine–surfactant derivatives synthesized obtained by the O-acylation of L-threonine with acyl chlorides, it was found that the chain length (n) dramatically affected the yields and enantioselectivities. Neither very long (n = 8, 10, 14, 16) nor very short carbon chains (n = 2, 4) were effective, whereas catalyst **1c·HCl** containing the n-octanoic group (n = 6) gave the best yield (98%), diastereoselectivity (*anti*/*syn* = 92:8), and enantioselectivity (98% ee) (Table 1, entry 4). When only with 5 mol % catalyst **1c·HCl**, the desired aldol product was obtained in about 97% yield and with 99% ee in the presence of water (Table 1, entry 9). When the reaction was carried out neat, both the diastereoselectivity and the enantioselectivity decreased (Table 1, entry 10). This result provides evidence that the reaction proceeds in the organic phase, created inside the emulsion when the reaction is performed in the presence of water.

Having optimized the reaction conditions, the combined threonine–surfactant organocatalyst **1c·HCl** catalyzed direct aldol reactions in the presence of water that were extended to a series of aromatic aldehydes to explore the generality of this catalytic system. The results are summarized in Table 2.

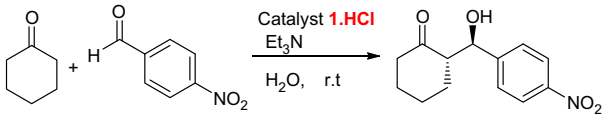
In the presence of only 5 mol % of catalyst **1c·HCl**, most reactions between cyclohexanone and various aromatic aldehydes afforded the aldol products in excellent yields and nearly perfect enantioselectivities in water. The more reactive aromatic aldehydes underwent the catalytic process to afford the products in excellent enantioselectivities and with good diastereoselectivities (Table 2, entries 1–10). In contrast, the enantioselectivities obtained for a representative electron rich aromatic aldehydes gave excellent enantioselectivity, especially the *p*-tolualdehyde (Table 2, entry 11, 85:15 *anti*/*syn* ratio and >99% ee), although the yield was moderate (Table 2, entries 11–13). Moreover, the direct aldol reaction of neutral aromatic aldehydes catalyzed by the catalyst **1c·HCl** also afforded the products in high enantioselectivities and diastereoselectivities (Table 2, entries 14–17).

Cyclopentanone and 4-methylclohexanone were also explored as aldol donors with nitrobenzaldehydes (*o*-nitrobenzaldehyde, *m*-nitrobenzaldehyde, *p*-nitrobenzaldehyde) under the same conditions. As shown in Table 3, the aldol products were obtained in high yields (up to 98%) with excellent enantioselectivities (up to 99% ee).

3. Conclusion

In conclusion, we have designed and synthesized a new series of combined threonine–surfactant organocatalysts in one step for the first time, which were prepared from commercially available and

Table 1
Screening of organocatalysts[a]

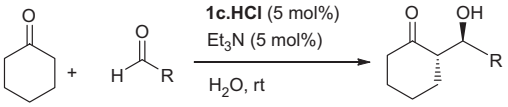


2

Entry	Catalyst	Catalyst loading (%)	Time (h)	Yield[b] (%)	*Anti*/*syn*[c]	ee[d] (%)
1[e]	L-Thr	10	48	<5	—	—
2	**1a·HCl**	10	24	92	75:25	90
3	**1b·HCl**	10	24	95	80:20	97
4	**1c·HCl**	**10**	**20**	**98**	**92:8**	**98**
5	**1d·HCl**	10	24	96	85:15	94
6	**1e·HCl**	10	24	94	89:11	93
7	**1f·HCl**	10	24	87	72:28	81
8	**1g·HCl**	10	24	80	81:19	75
9[f]	**1c·HCl**	**5**	**24**	**97**	**92:8**	**99**
10[g]	**1c·HCl**	5	24	97	88:12	96
11[h]	**1c·HCl**	2	24	90	89:11	93

[a] The reactions were performed with 4-nitrobenzaldehyde (1 mmol), cyclohexanone (2.5 mmol), Et_3N (0.1 mmol), and catalyst **1·HCl** (0.1 mmol) in the presence of water (11 mmol) at room temperature.
[b] Isolated yield.
[c] The *anti* to *syn* ratio was determined by ^1H NMR analysis of the crude product and by HPLC.
[d] The ee value of the *anti*-isomer was determined by chiral HPLC analysis.
[e] See Ref. 8.
[f] Aldehyde/cyclohexanone/water/Et_3N/catalyst ratio was 1:2.5:11:0.05:0.05.
[g] The reaction was performed neat.
[h] Aldehyde/cyclohexanone/water/Et_3N/catalyst ratio was 1:2.5:11:0.02:0.02.

Table 2
Organocatalyst **1c·HCl**-catalyzed direct aldol reactions in the presence of water[a]



Entry	Product	Time (h)	Yield[b] (%)	*Anti*/*syn*[c]	ee[d] (%)
1	**2** (R = *p*-NO_2-C_6H_4)	24	97	92:8	99
2	**3** (R = *o*-NO_2-C_6H_4)	20	99	96:4	>99
3	**4** (R = *m*-NO_2-C_6H_4)	20	99	99:1	99
4	**5** (R = 2,4-dinitrophenyl)	20	98	97:3	97
5	**6** (R = *p*-CN-C_6H_4)	24	97	84:16	95
6	**7** (R = *p*-CF_3-C_6H_4)	24	92	82:18	96
7	**8** (R = *p*-Br-C_6H_4)	30	98	93:7	97
8	**9** (R = *p*-Cl-C_6H_4)	30	92	85:15	97
9	**10** (R = *o*-Cl-C_6H_4)	30	92	93:7	98
10	**11** (R = *p*-F-C_6H_4)	24	92	93:7	97
11	**12** (R = *p*-CH_3-C_6H_4)	36	63	85:15	>99
12	**13** (R = *p*-OMe-C_6H_4)	36	68	98:2	98
13	**14** (R = *m*-OMe-C_6H_4)	36	65	94:6	96
14	**15** (R = 2-naphthyl)	30	76	86:14	>99
15	**16** (R = 1-naphthyl)	30	86	95:5	96
16	**17** (R = C_6H_5)	48	62	91:9	97
17	**18** (R = pyridinthyl)	24	96	90:10	98

[a] The reactions were performed with aldehyde (1 mmol), cyclohexanone (2.5 mmol), Et_3N (0.05 mmol), and **1c·HCl** (0.05 mmol) in the presence of water (11 mmol) at room temperature.
[b] Isolated yield.
[c] The *anti* to *syn* ratio was determined by ^1H NMR analysis of the crude product and by HPLC.
[d] The ee value of the *anti*-isomer was determined by chiral HPLC analysis.

inexpensive threonine and acyl chlorides. No protecting groups or chromatographic techniques were involved in the procedures. For the asymmetric direct aldol reactions of cyclic ketones with aromatic aldehydes, high isolated yields (up to 99%) and enantioselectivities (up to 99% ee) were obtained by using catalyst **1c·HCl**. The reactions described in this report are highly enantioselective, environmentally benign, and operationally simple. Our findings represent a novel application of primary amino acids derivatives as asymmetric organocatalysts in aqueous organic reactions. Mechanistic studies, the development of catalytic systems applicable to a broader range of substrates and the extension of our catalysts to other organic transformations are currently being investigated, and will be reported in due course.

4. Experimental

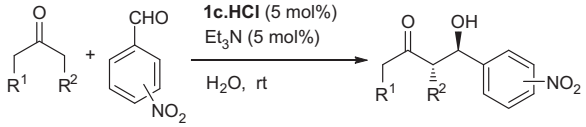
4.1. General information

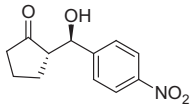
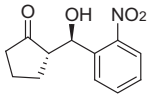
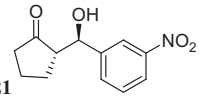
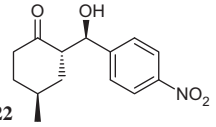
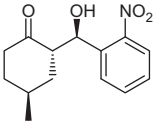
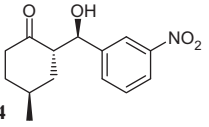
All reagents were commercial products. The reactions were monitored by TLC (thin layer chromatography). The column and preparative TLC purifications were carried out using silica gel. Flash column chromatography was performed on silica gel (200–300 mesh). NMR spectra were recorded on a 300 MHz instrument. Chemical shifts (δ) are given in ppm relative to TMS as the internal reference, coupling constants (J) in hertz. 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) columns. Optical rotations were measured on a JASCO P-1010 Polarimeter at λ = 589 nm.

4.2. Typical experimental procedure for the preparation of combined threonine–surfactant 1a·HCl–1g·HCl (Scheme 1):[10d,e]

A 500 ml round bottom flask was charged with CF_3CO_2H (120 mL) and placed in an ice/water bath. Powdered L-threonine (29.78 g, 250 mmol, dried at 70–75 °C for 24 h) was added in small portions under vigorous stirring to give a viscous solution (leaving some small pieces of undissolved material). The reaction mixture was stirred for 15 min, and then removed from the ice/water bath. After 5 min of stirring, acyl chloride (375 mmol) was added in one portion. The reaction flask was fitted with a loose glass stopper, and the reaction mixture was stirred at room temperature without any external temperature adjustment for 6 h, to give a clear and colorless solution. The reaction flask was then cooled in an ice/water bath, and Et_2O (360 mL) was added under vigorous stirring over a period of 20 min, slowly at first. The resulting white suspension was stirred at 0–5 °C for 15 min after completed addition, and then filtered by vacuum. The crystals were washed with two portions of Et_2O and dried at room temperature for 23 h in a ventilated hood to give *O*-acyl-L-threonine hydrochloride **1**, as a fine white powder. This essentially pure material was used for the next step without further purification.

Table 3
Direct asymmetric aldol reactions between cyclic ketones and nitrobenzaldehydes in the presence of water, catalyzed by **1c·HCl**[a]



Entry	Product	Time (h)	Yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	 **19**	20	98	63:37	95/57
2	 **20**	20	96	52:48	99/81
3	 **21**	20	98	75:25	98/31
4	 **22**	24	95	93:7	96
5	 **23**	24	98	99:1	99
6	 **24**	24	97	96:4	95

[a] The reactions were performed with nitrobenzaldehydes (1 mmol), cyclohexanone (2.5 mmol), Et_3N (0.05 mmol), and **1c·HCl** (0.05 mmol) in the presence of water (11 mmol) at room temperature.
[b] Isolated yield.
[c] The *anti* to *syn* ratio was determined by ^1H NMR analysis of the crude product and by HPLC.
[d] The ee value of the *anti*-isomer was determined by chiral HPLC analysis.

4.2.1. *O*-(*n*-Butyl)-L-threonine hydrochloride 1a·HCl

Yield: 96%; white solid; mp: 120–121 °C; $[\alpha]_D^{20} = +16.1$ (c 1, MeOH); ^1H NMR (300 MHz, DMSO): δ 0.84–0.92 (m, 3H), 1.32–1.34 (d, J = 6.5 Hz, 3H), 1.45–1.60 (m, 2H), 2.26–2.31(m, 2H), 4.13 (d, J = 2.7 Hz, 1H), 5.26–5.29 (dq, J = 3.5 Hz and 6.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO): δ 13.4, 16.7, 17.9, 35.4, 55.4, 67.7, 168.4,

171.7. MS (ESI) m/z calcd for ($C_8H_{15}NO_4$): 189.51 (M^+). FT-IRν_{max} (neat)/cm^{-1}: 2968, 1754, 1737, 1588, 1493, 1415, 1167, 1124, 1056, 747, 709.

4.2.2. *O*-(*n*-Hexanoyl)-L-threonine hydrochloride 1b·HCl

Yield: 97%; white solid; mp: 126–127 °C; $[\alpha]_D^{20} = +15.0$ (c 1, MeOH); ^{1}H NMR (300 MHz, DMSO): δ 0.84–0.88 (m, 3H),1.05–1.26(m, 4H), 1.32–1.34 (d, J = 6.5 Hz, 3H), 1.45–1.60 (m, 2H), 2.27–2.32 (m, 2H), 4.13 (d, J = 2.7 Hz, 1H), 5.25–5.28 (dq, J = 3.6 Hz and 6.0 Hz, 1H); ^{13}C NMR(75 MHz, DMSO): δ 13.9, 16.7, 21.8, 24.0, 30.6, 33.4, 55.4, 67.7, 168.5, 171.9; MS(ESI) m/z calcd for ($C_{10}H_{19}NO_4$): 217.51 (M^+). FT-IRν_{max} (neat)/cm^{-1}: 2959, 1759, 1737, 1413, 1340, 1166, 1125, 1057, 783, 715.

4.2.3. *O*-(*n*-Octanoyl)-L-threonine hydrochloride 1c·HCl

Yield: 95%; white solid; mp: 127–128 °C; $[\alpha]_D^{20} = +13.2$ (c 1, MeOH); ^{1}H NMR (300 MHz, DMSO): δ 0.86–0.90 (m, 3H), 1.27 (br s, 8H), 1.34–1.36 (d, J = 6.6 Hz, 3H), 1.51–1.55 (m, 2H), 2.29–2.34 (m, 2H), 4.15 (d, J = 2.7 Hz, 1H), 5.27–5.30 (dq, J = 3.6 Hz and 6.0 Hz, 1H); ^{13}C NMR (75 MHz, DMSO): δ 13.997, 16.703, 22.102, 24.294, 28.381, 31.147, 33.449, 55.378, 67.629, 168.510, 171.820. MS (ESI) m/z calcd for ($C_{12}H_{23}NO_4$): 245.56 (M^+). FT-IRν_{max} (neat)/cm^{-1}: 2957, 1758, 1737, 1413, 1383, 1208, 1164, 1122, 1055, 789, 635.

4.2.4. *O*-(*n*-Decanoyl)-L-threonine hydrochloride 1d·HCl

Yield: 96%; white solid; mp: 128–129 °C; $[\alpha]_D^{20} = +13.0$ (c 1, MeOH); ^{1}H NMR (300 MHz, DMSO): δ 0.84–0.86 (m, 3H), 1.24 (br s, 12H), 1.32–1.34 (d, J = 6.3 Hz, 3H), 1.40–1.42 (m, 2H), 2.27–2.31 (m, 2H), 4.15 (d, J = 2.7 Hz, 1H), 5.26–5.27 (dq, J = 3.6 Hz and 6.0 Hz, 1H); ^{13}C NMR (75 MHz, DMSO): δ 14.0, 16.7, 22.19, 24.3, 28.5, 28.8, 28.8, 28.9, 31.4, 33.5, 55.4, 67.7, 168.5, 171.8; MS (ESI) m/z calcd for ($C_{14}H_{27}NO_4$): 273.55 (M^+). FT-IRν_{max} (neat)/cm^{-1}: 2923, 2854, 1753, 1412, 1353, 1159, 1141, 1076, 744, 705.

4.2.5. *O*-(*n*-Dodecanoyl)-L-threonine hydrochloride 1e·HCl

Yield: 94%; white solid; mp: 127–128 °C; $[\alpha]_D^{20} = +11.6$ (c 1, MeOH); ^{1}H NMR (300 MHz, DMSO): δ 0.84–0.86 (m, 3H), 1.24 (br s, 16H), 1.31–1.33 (d, J = 6.6 Hz, 3H), 1.39–1.41 (m, 2H), 2.26–2.31 (m, 2H), 4.13 (d, J = 2.6 Hz, 1H), 5.25–5.28 (dq, J = 3.6 Hz and 6.3 Hz, 1H); ^{13}C NMR (75 MHz, DMSO): δ 14.1, 16.8, 22.3, 24.4, 28.5, 28.8, 28.9, 29.0, 29.2, 31.4, 33.5, 55.5, 67.7, 168.6, 171.9; MS (ESI) m/z calcd for ($C_{16}H_{31}NO_4$): 301.59 (M^+). FT-IRν_{max} (neat)/cm^{-1}: 2922, 2852, 1753, 1717, 1412, 1353, 1159, 1141, 1076, 744, 705.

4.2.6. *O*-(*n*-Palmitoyl)-L-threonine hydrochloride 1f·HCl

Yield: 90%; white solid; mp: 129–130 °C; $[\alpha]_D^{20} = +7.8$ (c 1, MeOH); ^{1}H NMR (300 MHz, DMSO): δ 0.82–0.84 (m, 3H), 1.22 (br s, 24H), 1.30–1.32 (d, J = 6.5 Hz, 3H), 1.49 (m, 2H), 2.25–2.30 (m, 2H), 4.11 (d, J = 2.6 Hz, 1H), 5.23–5.26 (dq, J = 3.5 Hz and 6.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO): δ 13.9, 16.6, 22.1, 22.1, 24.3, 28.4, 28.7, 28.9, 29.0, 29.1, 31.3, 33.4, 55.4, 67.6, 168.4, 171.7. MS (ESI) m/z calcd for ($C_{20}H_{39}NO_4$): 357.71 (M^+). FT-IRν_{max} (neat)/cm^{-1}: 2920, 2851, 1753, 1716, 1412, 1353, 1159, 1141, 1076, 744, 705.

4.2.7. *O*-(*n*-Stearoyl)-L-threonine hydrochloride 1g·HCl

Yield: 85%; white solid; mp: 129–130 °C; $[\alpha]_D^{20} = +8.0$ (c 1, MeOH); ^{1}H NMR (300 MHz, DMSO): δ 0.82–0.86 (m, 3H), 1.22 (br s, 28H), 1.30–1.32 (d, J = 6.5 Hz, 3H), 1.49 (m, 2H), 2.25–2.30 (m, 2H), 4.12 (d, J = 2.6 Hz, 1H), 5.23–5.26 (dq, J = 3.7 Hz and 5.9 Hz, 1H); ^{13}C NMR (75 MHz, DMSO): δ 14.0, 16.7, 22.2, 24.3, 28.5, 28.8, 29.0, 29.0, 29.1, 29.2, 31.4, 33.5, 55.4, 67.6, 168.5, 171.8; MS (ESI) m/z calcd for ($C_{22}H_{43}NO_4$): 385.72 (M^+). FT-IRν_{max} (neat)/cm^{-1}: 2920, 2851, 1753, 1717, 1412, 1353, 1159, 1141, 1076, 744, 705.

4.3. General procedure for the aldol reaction of cyclohexanone with aromatic aldehydes

4.3.1. Reactions in neat cyclohexanone

Cyclohexanone (0.25 mL, 2.5 mmol) was added to a mixture of *p*-nitrobenzaldehyde (0.1512 g, 1 mmol), catalyst **1c·HCl** (14.05 mg, 0.05 mmol) and Et_3N (0.05 mmol). 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 a 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 the known literature values.

4.3.2. Reactions in the presence of water

To a mixture of catalyst **1c·HCl** (14.05 mg, 0.05 mmol), Et_3N (0.05 mmol), and aldehyde in the presence of water (0.2 mL) was added the ketone under air in a closed system. After being stirred at room temperature for the indicated time, the mixture was treated in the same manner as shown above.

4.3.3. (2*S*,10*R*)-2-(Hydroxy-(4-nitrophenyl)methyl) cyclohexan-1-one 2

Yield 97%, *anti*/*syn* = 92:8, enantiomeric excess: 99% of *anti* diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 20:80; flow rate 0.5 mL/min, 20 °C, λ = 254 nm; t_R = 42.5 min (*anti*, major), t_R = 32.8 min (*anti*, minor)). ^{1}H 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).

4.3.4. (2*S*,10*R*)-2-(Hydroxy-(2-nitrophenyl)methyl) cyclohexan-1-one 3

Yield 99%, *anti*/*syn* = 96:4, enantiomeric excess: >99% of *anti*-diastereomer determined by HPLC (Dicael Chiralpak OD-H column; *i*-PrOH/Hexane = 5:95; flow rate 0.5 mL/min, 20 °C, λ = 254 nm; t_R = 41.9 min (*anti*, major), t_R = 50.7 min (*anti*, minor)). ^{1}H 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).

4.3.5. (2*S*,10*R*)-2-(Hydroxy-(3-nitrophenyl)methyl) cyclohexan-1-one 4

Yield 99%, *anti*/*syn* = 99:1, enantiomeric excess: 99% of *anti*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 20:80; flow rate 0.5 mL/min, 20 °C, λ = 254 nm; t_R = 41.9 min (*anti*, major), t_R = 32.4 min (*anti*, minor)). ^{1}H 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).

4.3.6. (2*S*,10*R*)-2-(Hydroxy-(2,4-dinitro-phenyl)methyl) cyclohexan-1-one 5

Yield 98%, *anti*/*syn* = 97:3, enantiomeric excess: 97% of *anti*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 15:85; flow rate 1.0 mL/min, 20 °C, λ = 254 nm; t_R = 27.6 min (*anti*, major), t_R = 24.5 min (*anti*, minor)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.75 (d, J = 2.4 Hz, 1H), 8.48 (dd, J = 8.4,

2.0 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 5.53(s, 1H), 4.31(d, *J* = 4.0 Hz, 1H) 2.31–2.82 (m, 3H), 2.11–2.16 (m, 1H), 1.63–1.94 (m, 5H).

4.3.7. (2*S*,10*R*)-2-(Hydroxy-(4-cyanophenyl)methyl) cyclohexan-1-one 6

Yield 97%, *anti*/*syn* = 84:16, enantiomeric excess: 95% of *anti*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 20:80, flow rate 0.5 mL/min, 20 °C, λ = 254 nm; t_R = 22.5 min (*anti*, major), t_R = 18.1 min (*anti*, minor)). ^{1}H 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).

4.3.8. (2*S*,10*R*)-2-(Hydroxy-(4-(trifluoromethyl)methyl) cyclohexan-1-one 7

Yield 92%, *anti*/*syn* = 82:18, enantiomeric excess: 96% of *anti*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; flow rate 0.5 mL/min, 20 °C, λ = 254 nm; t_R = 34.4 min (*anti*, major), t_R = 26.9 min (*anti*, minor)). ^{1}H 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).

4.3.9. (2*S*,10*R*)-2-(Hydroxy-(4-bromophenyl)methyl) cyclohexan-1-one 8

Yield 98%, *anti*/*syn* = 93:7, enantiomeric excess: 97% of *anti*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; flow rate 0.8 mL/min, 20 °C, λ = 221 nm; t_R = 27.0 min (*anti*, major), t_R = 22.4 min (*anti*, minor)). ^{1}H 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).

4.3.10. (2*S*,10*R*)-2-(Hydroxy-(4-chlorophenyl)methyl) cyclohexan-1-one 9

Yield 92%, *anti*/*syn* = 85:15, enantiomeric excess: 97% of anti diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; flow rate 0.5 mL/min, 20 °C, λ = 221 nm; t_R = 39.2 min (*anti*, major), t_R = 33.4 min (*anti*, minor)). ^{1}H 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).

4.3.11. (2*S*,10*R*)-2-(Hydroxy-(2-chlorophenyl)methyl) cyclohexan-1-one 10

Yield 92%, *anti*/*syn* = 93:7, enantiomeric excess: 98% of *anti*-diastereomer determined by HPLC (Dicael Chiralpak OD-H column; *i*-PrOH/Hexane = 5:95; flow rate 1.0 mL/min, 20 °C, λ = 221 nm; t_R = 9.7 min (*anti*, major), t_R = 12.3 min (*anti*, minor)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, 1H, *J* = 8.4 Hz,) 7.20–7.34 (m, 3H), 5.35 (d, 1H, *J* = 8.0 Hz), 2.65–2.71 (m, 1H), 3.88 (s, 1H), 2.46–2.49 (m, 1H), 2.31–2.39 (m, 1H), 2.05– 2.13 (m, 1H), 1.53–1.84 (m, 5H).

4.3.12. (2*S*,10*R*)-2-(Hydroxy-(4-fluor-phenyl)methyl) cyclohexan-1-one 11

Yield 92%, *anti*/*syn* = 93:7, enantiomeric excess: 97% of *anti*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 5:95; flow rate 1.0 mL/min, 20 °C, λ = 221 nm; t_R = 28.3 min (*anti*, major), t_R = 24.7 min (*anti*, minor)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.32 (m, 2H), 7.00–7.07 (m, 2H), 4.77 (d, *J* = 8.8 Hz, 1H), 3.99 (br, 1H), 2.45–2.56 (m, 2H), 2.34–2.48 (m, 1H), 2.06–2.11 (m, 1H), 1.77–1.82 (m, 1H), 1.51–1.68 (m, 3H), 1.25–1.30 (m, 1H).

4.3.13. (2*S*,10*R*)-2-(Hydroxy-(4-tolyl)methyl)cyclohexan-1-one 12

Yield 63%, *anti*/*syn* = 85:15, enantiomeric excess: >99% of *anti*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; flow rate 0.5 mL/min, 20 °C, λ = 221 nm; t_R = 32.8 min (*anti*, major), t_R = 44.5 min (*anti*, minor)). ^{1}H 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).

4.3.14. (2*S*,10*R*)-2-(Hydroxy-(4-methoxy-phenyl)methyl) cyclohexan-1-one 13

Yield 68%, *anti*/*syn* = 98:2, enantiomeric excess: 98% of *anti*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; flow rate 0.8 mL/min, 20 °C, λ = 221 nm; t_R = 32.5 min (*anti*, major), t_R = 30.8 min (*anti*, minor)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (dd, *J* = 13.2, 8.4 Hz, 3H), 6.90 (d, *J* = 8.8 Hz, 3H), 4.76 (d, *J* = 7.6 Hz, 1H), 3.94 (s, 1H), 3.83 (s, 3H), 2.34–2.65 (m, 3H), 2.08–2.14 (m, 1H), 1.55–1.82 (m, 6H), 1.20–1.40 (m, 2H).

4.3.15. (2*S*,10*R*)-2-(Hydroxy-(3-methoxy-phenyl)methyl) cyclohexan-1-one 14

Yield 65%, *anti*/*syn* = 96:4, enantiomeric excess: 96% of *anti*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; flow rate 0.5 mL/min, 20 °C, λ = 221 nm; t_R = 56.3 min (*anti*, major), t_R = 51.1 min (anti, minor)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.33 (m, 1H), 6.80–7.00 (m, 3H), 4.80 (d, *J* = 8.7 Hz, 1H), 3.85 (s, 3H), 2.30–2.75 (m, 3H), 2.00–2.15 (m, 1H), 1.55–1.90 (m, 4H), 1.20–1.40 (m, 1H).

4.3.16. (2*S*,10*R*)-2-(Hydroxy-(2-naphthyl)methyl) cyclohexan-1-one 15

Yield 76%, *anti*/*syn* = 86:14, enantiomeric excess: >99% of *anti*-diastereomer determined by HPLC (Dicael Chiralpak OD-H column; *i*-PrOH/Hexane = 10:90; flow rate 1.0 mL/min, 20 °C, λ = 221 nm; t_R = 15.7 min (*anti*, major), t_R = 22.2 min (anti, minor)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70–7.90 (m, 4H), 7.40–7.55 (m, 3H), 5.01 (d, *J* = 8.7 Hz, 1H), 4.10 (s, 1H), 2.71–2.78 (m, 1H), 2.37–2.55 (m, 2H), 2.09–2.14 (m, 1H), 1,52–1.80 (m, 5H), 1.28–1.42 (m, 2H).

4.3.17. (2*S*,10*R*)-2-(Hydroxy-(1-naphthyl)methyl) cyclohexan-1-one 16

Yield 86%, *anti*/*syn* = 95:5, enantiomeric excess: 96% of *anti*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 5:95; flow rate 1.0 mL/min, 20 °C, λ = 254 nm; t_R = 45.9 min (*anti*, major), t_R = 36.7 min (anti, minor)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24–8.27 (m, 1H), 7.84–7.89 (m, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.57 (d, *J* = 6.3 Hz, 1H), 7.45–7.53 (m, 3H), 5.58 (dd, *J* = 8.7, 2.9 Hz, 1H), 4.15 (d, *J* = 2.9 Hz, 1H), 2.95–3.04 (m, 1H), 2.49–2.54 (m, 1H), 2.35–2.45 (m, 1H), 2.05–2.12 (m, 1H), 1.61–1.74 (m, 2H), 1.33–1.51 (m, 3H).

4.3.18. (2*S*,10*R*)-2-(Hydroxy-(phenyl)methyl) cyclohexan-1-one 17

Yield 62%, *anti*/*syn* = 91:9, enantiomeric excess: 97% of *anti*-diastereomer determined by HPLC (Dicael Chiralpak OD-H column; *i*-PrOH/Hexane = 10:90; flow rate 0.5 mL/min, 20 °C, λ = 220 nm; t_R = 19.6 min (*anti*, major), t_R = 30.6 min (anti, minor)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.28 (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).

4.3.19. (2*S*,10*R*)-2-(Hydroxy-(pyridin-4-yl)methyl) cyclohexan-1-one 18

Yield 96%, *anti*/*syn* = 90:10, enantiomeric excess: 98% of *anti*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; flow rate 1.0 mL/min, 20 °C, λ = 254 nm; t_R = 27.5 min (*anti*, major), t_R = 25.0 min (anti, minor)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.53–8.55 (d, *J* = 6.0 Hz, 2H), 7.25–7.28 (d, *J* = 6.0 Hz, 2H), 4.80 (d, *J* = 8.4 Hz, 1H), 4.29 (br, 1H), 2.31–2.63 (m, 3H), 2.07–2.12 (m, 1H), 1.81–1.84 (m, 1H), 1.61–1.71 (m, 4H), 1.30–1.41 (m, 1H).

4.3.20. (2*S*,10*R*)-2-(Hydroxy-(4-nitrophenyl) methyl)-cyclopentan-1-one 19

Yield 98%, *anti*/*syn* = 63:37, enantiomeric excess: 95% of *anti*-isomer and 57% syn-isomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 5:95; flow rate 1.0 mL/min, 20 °C, λ = 254 nm; t_R = 58.4 min (*anti*, major), t_R = 55.4 min (*anti*, minor)); t_R = 30.8 min (*syn*, major), t_R = 43.9 min (*syn*, minor)). ^{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* = 9.2 Hz), 4.76 (s, 1H), 2.54–2.18 (m, 3H), 2.08–1.95 (m, 1H), 1.81–1.48 (m, 3H).

4.3.21. (2*S*,10*R*)-2-(Hydroxy-(2-nitrophenyl) methyl)-cyclopentan-1-one 20

Yield 96%, *anti*/*syn* = 52:48, enantiomeric excess: 99% of *anti*-isomer and 81% syn-isomer determined by HPLC (Dicael Chiralpak OD-H column; *i*-PrOH/Hexane = 5:95; flow rate 1.0 mL/min, 20 °C, λ = 254 nm; t_R = 39.8 min (*anti*, major), t_R = 43.2 min (*anti*, minor); t_R = 20.7 min (*syn*, major), t_R = 23.1 min (*syn*, minor)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 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).

4.3.22. (2*S*,10*R*)-2-(Hydroxy-(3-nitrophenyl) methyl)-cyclopentan-1-one 21

Yield 98%, *anti*/*syn* = 75:25, enantiomeric excess: 98% of *anti*-isomer and 31% syn-isomer determined by HPLC (Dicael Chiralpak AD-H column; i-PrOH/Hexane = 8:92; flow rate 1.0 mL/min, 20 °C, λ = 254 nm; t_R = 29.4 min (*anti*, major), t_R = 43.3 min (*anti*, minor); t_R = 20.7 min (*syn*, major), t_R = 23.1 min (*syn*, minor)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17–8.18 (m, 1H), 8.10 (ddd, *J* = 8.1, 2.3, 1.1 Hz, 1H), 7.62–7.65 (m, 1H), 7.47 (t, *J* = 7.9 Hz, 1H), 4.77 (d, 1H, *J* = 9.3 Hz), 4.72 (s, 1H), 2.16–2.47 (m, 3H), 1.92–2.01 (m, 1H), 1.61–1.78 (m, 2H), 1.50–1.55 (m, 1H).

4.3.23. ((2*S*,4*S*)-2-((*R*)-Hydroxy(4-nitrophenyl)methyl)-4-methylcyclohexan-1-one 22

Yield 95%, *anti*/*syn* = 93:7, enantiomeric excess: 96% of *anti*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; flow rate 1.0 mL/min, 20 °C, λ = 254 nm; t_R = 36.3 min (*anti*, major), t_R = 41.3 min (*anti*, minor)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18–8.23 (m, 2H), 7.47–7.52 (m, 2H), 4.92 (d, 1H, *J* = 8.6 Hz), 3.82 (br, 1H), 2.72–2.78 (m, 1H), 2.48–2.50 (m, 1H), 2.36–2.43 (m, 1H), 2.07–2.09 (m, 1H), 1.89–1.93 (m, 1H), 1.78–1.81 (m, 1H), 1.54–1.60 (m, 1H), 1.33 (m, 1H), 1.05 (d, *J* = 6.9 Hz, 3H).

4.3.24. (2*S*,4*S*)-2-((*R*)-Hydroxy(2-nitrophenyl)methyl)-4-methylcyclohexan-1-one 23

Yield 98%, *anti*/*syn* = 99:1, enantiomeric excess: 99% of *anti*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; flow rate 0.8 mL/min, 20 °C, λ = 254 nm; t_R = 32.5 min (*anti*, major), t_R = 34.7 min (*anti*, minor)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81–7.84 (m, 1H), 7.72–7.74 (m, 1H), 7.62 (m, 1H), 7.40–7.45 (m, 1H), 5.42 (d, 1H, *J* = 7.2 Hz), 3.95 (br, 1H), 2.89–2.92 (m, 1H), 2.44–2.46 (m, 1H), 2.33–2.39 (m, 2H), 2.09–2.11 (m, 1H), 1.74–1.93 (m, 3H), 1.52 (m, 1H), 1.07 (d, *J* = 6.9 Hz, 3H).

4.3.25. (2*S*,4*S*)-2-((*R*)-Hydroxy(2-nitrophenyl)methyl)-4-methylcyclohexan-1-one 24

Yield 97%, *anti*/*syn* = 96:4, enantiomeric excess: 95% of *anti*-diastereomer determined by HPLC(Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; flow rate 0.5 mL/min, 20 °C, λ = 254 nm; t_R = 63.4 min (*anti*, major), t_R = 46.5 min (*anti*, minor)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (s, 1H, Ar), 7.53–7.86 (m, 3H, Ar), 5.20 (d, 1H, *J* = 8.4 Hz), 3.93 (br, 1H), 2.85–2.90 (m, 1H), 2.45–2.47 (m, 1H), 2.35–2.42 (m, 2H), 2.38–2.79 (m, 2H), 1.90–1.93 (m, 1H), 1.64–1.75 (m, 3H), 1.43 (m, 1H), 1.06 (d, *J* = 6.9 Hz, 3H).

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**, *116*, 5248–5286; (b) Berkssel, A.; Groger, H. In *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, 2005.
2. (a)For reviews on direct aldol reactions, see: *Modern Aldol Additions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; (b) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Eur. J.* **2002**, *8*, 36–44; (c) Machajewski, T. D.; Wong, C. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352–1374.
3. For reviews, see: (a) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580–591; (b) Mukherjee, S.; Yang, J. W.; Hoffman, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569; (c) Liu, X. H.; Lin, L. L.; Feng, X. M. *Chem. Commun.* **2009**, *41*, 6145–6158; (d) Raj, M.; Singh, V. K. *Chem. Commun.* **2009**, *42*, 6687–6703; (e) Xu, L. W.; Luo, J.; Lu, Y. X. *Chem. Commun.* **2009**, 1807–1821; (f) Xu, L. W.; Lu, Y. X. *Org. Biomol. Chem.* **2008**, *6*, 2047–2053; (g) Peng, F. Z.; Shao, Z. H. *J. Mol. Catal. A* **2008**, *285*, 1–13; (h) Chen, Y. C. *Synlett* **2008**, 1919–1930; (i) Bartoli, G.; Melchiorre, P. *Synlett* **2008**, 1759–1771; For selected examples of *anti*-aldol reactions, see: (j) Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1343–1345; (k) Córdova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W. W. *Chem. Commun.* **2005**, 3586–3588; (l) Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 3359–3363; (m) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983–1986; (n) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F., ; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 734–735; (o) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958–961; (p) Samanta, S.; Liu, J.; Dodda, R.; Zhao, C. G. *Org. Lett.* **2005**, *7*, 5321–5323; (q) Córdova, A.; Zou, W.; Dziedzic, P.; Ibrahem, I.; Reyes, E.; Xu, Y. *Chem. Eur. J.* **2006**, *12*, 5383–5397; (r) Hayashi, Y.; Itoh, T.; Nagae, N.; Ohkubo, M.; Ishikawa, H. *Synlett* **2008**, 1565–1570.
4. (a)*Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie: 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.
5. (a) Córdova, A.; Notz, W.; Barbas, C. F., III *Chem. Commun.* **2002**, 3024–3025; (b) Akthivel, K. S.; Notz, W.; Bui, T.; Barbas, C. F., III *J. Am. Chem. Soc* **2001**, *123*, 5260–5267.
6. (a) Monika, R.; Vinod, S. K. *Chem. Commun.* **2009**, *44*, 6687–6692; (b) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 4966–4967; (c) Hayashi, Y.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5527–5529.
7. (a) Zhang, S. P.; Fu, X. K.; Fu, S. D.; Pan, J. F. *Cat. Commun.* **2009**, *10*, 401–405; (b) Zhang, S. P.; Fu, X. K.; Fu, S. D. *Tetrahedron Lett.* **2009**, *50*, 1172–1173; (c) Fu, S. D.; Fu, X. K.; Zhang, S. P.; Zou, X. C.; Wu, X. J. *Tetrahedron: Asymmetry* **2009**, *20*, 2390–2396.
8. Wu, X. Y.; Jiang, Z. Q.; Shen, H. M.; Lu, Y. X. *Adv. Synth. Catal.* **2007**, *349*, 812–816.
9. For the use of hydrophobicity in organic synthesis, see: (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; (c) Breslow, R. *Acc. Chem. Res.* **2004**, *37*, 471–478.
10. (a) Siyutkin, D. E.; Kucherenko, A. S.; Zlotin, S. G. *Tetrahedron* **2009**, *65*, 1366–1372; (b) Dziedzic, P.; Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2008**, *49*, 803–807; (c) Chen, L. L.; Han, X.; Huang, M. H.; Wong, M. W.; Lu, Y. X. *Chem. Commun.* **2007**, *40*, 4143–4145; (d) Kristensen, T. E.; Hansen, F. K.; Hansen, T. *Eur. J. Org. Chem.* **2009**, *3*, 387–395; (e) Kristensen, T. E.; Vestli, K.; Fredriksen, K. A.; Hansen, F. K.; Hansen, T. *Org. Lett.* **2009**, *11*, 2968–2971.
11. (a) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209–217; (b) Hamada, T.; Manabe, K.; Kobayashi, S. *J. Syn. Org. Chem. Jpn.* **2003**, *61*, 445–448.