Tetrahedron: *Asymmetry* 23 (2012) 315–328

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

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

Simple and inexpensive threonine-based organocatalysts as highly active and recoverable catalysts for large-scale asymmetric direct stoichiometric aldol reactions on water

Chuanlong Wu [a,b], Xiaoqin Long [b], Shi Li [a], Xiangkai Fu [a,*]

[a] College of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, China
[b] Chongqing Unis Chemical Co., Ltd, Chongqing 402161, China

ARTICLE INFO

Article history:
Received 25 December 2011
Accepted 27 February 2012

ABSTRACT

Nine *O*-acylated threonines were screened as catalysts at loadings of 0.5–5 mol % for the direct asymmetric stoichiometric aldol reaction on water by using variable amounts of water. These threonine-based organocatalyst were simple, inexpensive, highly active and could be synthesized on a large-scale. Among them, the threonine-based organocatalyst **1a** is applicable to the stoichiometric reactions of a wide range of aromatic and heteroaromatic aldehydes with ketones, with the aldol products being obtained with up to 99:1 *anti*/*syn* ratios and >99% ee. The threonine-based organocatalyst **1a** can be easily recovered and reused, and only a slight decrease in the enantioselectivities was observed after six cycles. This novel threonine-based organocatalyst **1a** can be efficiently used in large-scale reactions with the enantioselectivities being maintained at the same level, which offers great possibility for application in industry.

1. Introduction

In spite of the remarkable advances in asymmetric aldol reactions for constructing carbon–carbon bonds, providing high 'atom-economy', there continues to be an increasing demand to explore new, inexpensive, simple, efficient and recoverable organocatalysts.[1] However, organocatalysts are usually used at a loading of 5–30 mol %, and in some cases, higher catalytic loadings have been reported.[2–6] This raises a cost concern when large amounts of organocatalysts are used for large-scale synthesis in industrial applications. For synthetic purposes, the design and development of highly active organocatalysts aimed at lowering the catalytic loading to less than 2 mol % has proven to be a significant challenge and only limited success has been achieved so far. With regards to the direct asymmetric aldol reaction, several examples of organocatalysts have been employed in low catalytic amounts.[7–13] Organocatalysts that are even more complex have also been reported for aldol reactions. A spiro diamine catalyst,[14] the tripeptide H-Pro-Pro-Asp-NH_2,[15] a biphenyl-based axially chiral amino acid,[16] and a very complex dendrimer catalyst[17] were employed in amounts of 0.5–1 mol %. Although these catalysts work at a loading of 0.5–2 mol % to afford aldol products with high levels of stereoselectivity, they are expensive, and for their preparation require demanding procedures, tiresome purification by chromatography and/or use expensive reagents; all of these factors are hurdles for industrial applications, hence these organocatalysts are often only used in research laboratories.

Water has many attractive advantages such as being low cost, safe and environmentally friendly. Many of the reported reactions were carried out in water.[18–20] It has been found that water is able to promote these reactions with high levels of enantio- and diastereo-selectivity and in high yields. Usually, these reactions are carried out with an excess amount of the ketone, from 2 to 10 equiv with respect to the aldehyde, and in the presence of variable amounts of water. It should also be noted that the excess ketone is not easily recycled.[21–24] When an expensive ketone is used in large excess, it is not reassuring for the direct aldol reaction with atom economical 'green' credentials. This raises a cost concern when a large amount of the ketone is used for a large-scale synthesis in industrial applications.[25] In particular, the use of less volatile ketones, such as cyclohexanone (bp 155 °C), in large excess complicates the reaction work-up and product purification.[25] A highly efficient, stereoselective, and atom economical reaction in water is a sought-after goal in synthetic chemistry.[26–31] The use of direct stoichiometric aldol reactions represents an important alternative approach. Armstrong et al. have developed an asymmetric catalytic system in water mediated by sulfated β-CD, which can bind an organocatalyst of *tert*-butylphenoxyproline and associated hydrophobic reactants for direct stoichiometric aldol reactions of cyclohexanone and aryl aldehydes.[24]

For these reasons, the development of a new type of effective asymmetric organocatalysts from a natural chiral pool, with a

* Corresponding author. Tel.: +86 23 8716 1855; fax: +86 23 8716 1874.
E-mail addresses: chuanlong666@yahoo.cn (C. Wu), wcl110@swu. edu.cn (X. Fu).

0957-4166/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetasy.2012.02.023

simple preparation procedure, inexpensive reagents, a highly efficient, stereoselective, green, and atom economical reaction is always desired. An alternative strategy is to design recyclable, simple and inexpensive organocatalysts that promote stoichiometric reactions. Herein, we report novel, simple, inexpensive, recoverable and reusable threonine-based organocatalysts that promote stoichiometric aldol reactions while achieving excellent enantioselectivities. These catalysts can then be used in large-scale reactions with the enantioselectivities being maintained at the same level, thus offering great potential for application on an industrial scale.

2. Results and discussion

Our aim was to find extremely simple and inexpensive organocatalysts that could be used in low loadings (2–0.5 mol %), at room temperature without additives, and that those could catalyze direct asymmetric stoichiometric aldol reactions between cyclic ketones and substituted benzaldehydes with high levels of stereoselectivity. Threonine derivatives have been designed to improve the catalytic activity and stereoselectivity. Barbas et al., Lu et al. and our group have reported a series of threonine derivative organocatalysts for the direct asymmetric aldol reactions of various aromatic aldehydes and ketones, with excellent results being obtained.[32–37] At first, we screened seven new threonine-based derivatives **1a–g** and two known compounds **1h**[36] and **1i**[34,35] (Fig. 1).

The organocatalyzed direct stoichiometric aldol reaction was carried out using cyclohexanone and 4-nitrobenzaldehyde as a model reaction in order to investigate different parameters, such as the catalysts, the solvents, and the loading of the catalysts. In our initial investigations, threonine-based organocatalysts **1a–i** were screened as catalysts. As can be seen from the results in Table 1, catalysts **1a–i** catalyzed the asymmetric direct stoichiometric aldol reaction of 4-nitrobenzaldehyde and cyclohexanone to give the aldol product **2a** in good yields (85–92%) with different ee values (90–98% ee for *anti*) on water (Table 1, entries 1–9). Amongst the nine direct acylated threonine-based derivatives **1a–i**, the catalysts containing a phenyl group gave the best yield (92%) and enantioselectivities (98% ee for *anti*). The threonine-

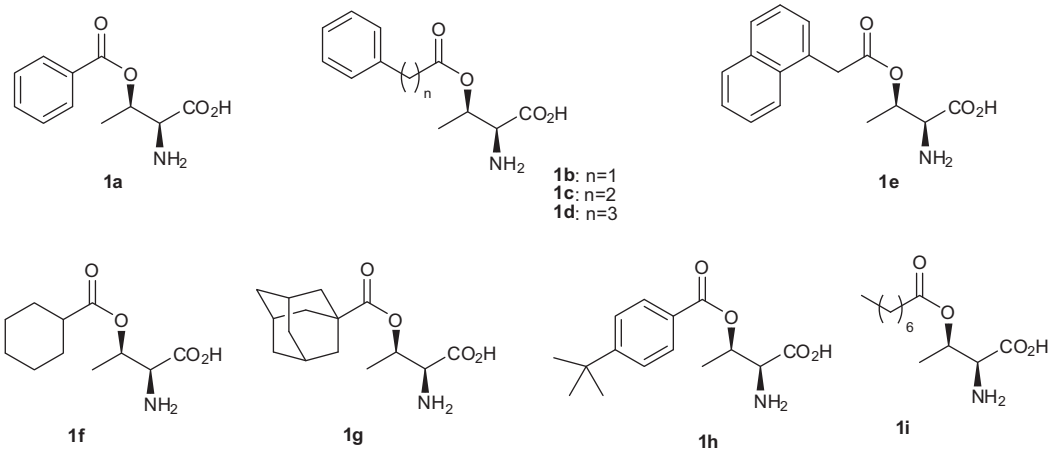
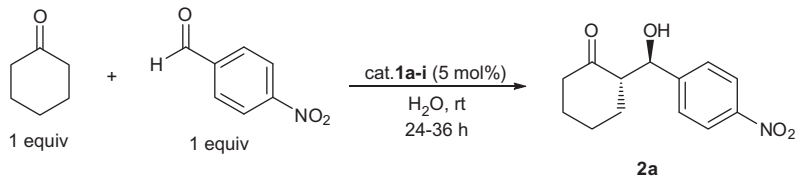


Figure 1. Threonine-based organocatalysts.

Table 1
Screening of organocatalysts **1a–i** for the direct stoichiometric aldol reaction of cyclohexanone with 4-nitrobenzaldehyde on water[a]



Entry	Catalyst	Time (h)	Yield[b] (%)	dr (*anti*/*syn*) [c]	ee (*anti*/*syn*)[c] (%)
1	**1a**	24	92	91:9	98/10
2	**1b**	24	89	90:10	94/23
3	**1c**	24	92	87:13	94/15
4	**1d**	24	91	88:12	94/34
5	**1e**	36	87	70:30	92/40
6	**1f**	24	90	91:9	96/22
7	**1g**	36	93	90:10	94/12
8	**1h**	36	85	88:12	90/21
9	**1i**	36	90	91:9	95/17
10[d]	**1a**	24	91	90:10	96/41

[a] The reactions were carried out using 4-nitrobenzaldehyde (4.0 mmol), cyclohexanone (4.0 mmol) and catalyst (0.2 mmol) on water (2.0 mL).
[b] Isolated yield after chromatography on silica gel.
[c] Determined by chiral HPLC analysis (AD-H).
[d] The reactions were carried out using 4-nitrobenzaldehyde (4.0 mmol), cyclohexanone (4.0 mmol) and catalyst **1a** (0.2 mmol) and sulfated β-cyclodextrin (10 mol %) in water (2.0 mL).

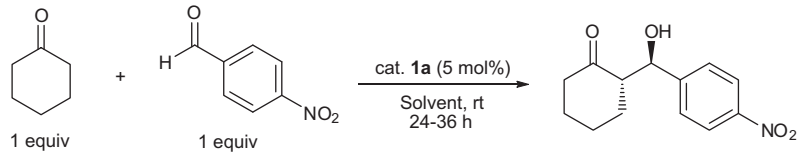
based organocatalyst **1a** turned out to be the most efficient catalyst (Table 1, entry 1). Armstrong et al. have developed an asymmetric catalytic system in water mediated by sulfated β-CD which can bind an organocatalyst of *tert*-butylphenoxyproline and associated hydrophobic reactants for direct stoichiometric aldol reactions of cyclohexanone and aryl aldehydes. We also developed an asymmetric catalytic system in water mediated by sulfated β-CD; although catalyst **1a** can catalyze the asymmetric direct stoichiometric aldol reaction of 4-nitrobenzaldehyde and cyclohexanone, the yield and enantioselectivity did not increase (Table 1, entry 10).

We screened several solvents for the stoichiometric reaction between cyclohexanone and 4-nitrobenzaldehyde (Table 2). Due to its poor solubility in most solvents, reactions mediated by threonine itself were restricted to polar organic solvents such as dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), and *N*-methylpyrrolidone (NMP), while *O*-acylated threonine derived organocatalysts were more soluble than threonine in organic solvents. For the catalyst, we used the most hydrophobic one **1a** (5 mol %). Both the enantioselectivities and yields were not good when DMSO, DMF, NMP, chloroform or toluene were used (Table 2, entries 1–3, 5 and 6). CH_3CN, THF and water/chloroform (v/v = 10:1) showed increased yield and enantioselectivities (Table 2, entries 4, 7 and 8), while water gave the highest stereoselectivity (Table 2, entry 9). This result indicates that water is indispensable for achieving excellent diastereoselectivities and enantioselectivities. The results summarized in Table 2 suggest that the stoichiometric reaction on water is different from that in its absence, and that compared to organic solvents, water has a unique and beneficial effect.

Next, using water as a solvent, and 1a as catalyst, we investigated the effects of catalyst loading on the reactions of cyclohexanone with 4-nitrobenzaldehyde (Table 3). When 0.5 mol % of catalyst was used (Table 3, entry 4), the stoichiometric reaction was slow and the ee value was slightly lower than that using 5 and 2 mol % of catalyst (Table 3, entries 1 and 2). When using only 1 mol % of catalyst after 36 h, the desired aldol product was obtained in 91% yield and with 99% ee for the *anti*-enantiomer (Table 3, entry 3). Thus, the optimized catalyst loading was chosen as 1 mol % of **1a**.

In order to test the substrate generality of this organocatalyzed direct stoichiometric aldol reaction, the reactions of various

Table 2
Effect of the solvent on the direct stoichiometric aldol reaction catalyzed by **1a**[a]

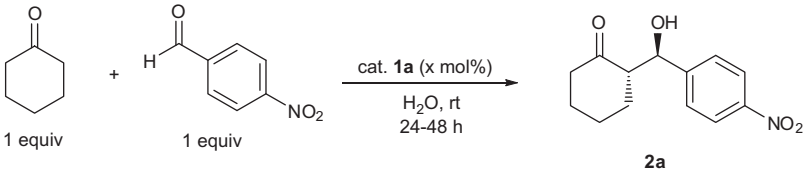


2a

Entry	Solvent	Time (h)	Yield[b] (%)	dr (*anti*/*syn*) [c]	ee (*anti*/*syn*)[c] (%)
1	DMSO	24	70	81:19	42/33
2	DMF	24	68	93:7	25/23
3	NMP	24	86	99:1	58/34
4	CH_3CN	24	82	73:27	90/12
5	$CHCl_3$	36	87	73:27	53/21
6	$PhCH_3$	36	75	80:20	70/34
7	THF	36	78	70:30	88/45
8	$H_2O/CHCl_3$ = 10:1	24	93	90:10	95/16
9	H_2O	24	92	91:9	98/10

[a] The reactions were carried out using 4-nitrobenzaldehyde (4.0 mmol), cyclohexanone (4.0 mmol) and catalyst (0.2 mmol) in a solvent (see Table 2, 2.0 mL).
[b] Isolated yield after chromatography on silica gel.
[c] Determined by chiral HPLC analysis (AD-H).

Table 3
Effect of the catalyst loading on the direct stoichiometric aldol reaction catalyzed by **1a**[a]

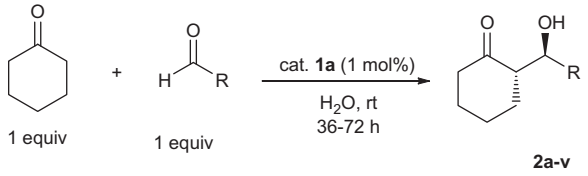


2a

Entry	Catalyst (mol %)	Time (h)	Yield[b] (%)	dr (*anti*/*syn*) [c]	ee (*anti*/*syn*)[c] (%)
1	**5**	24	92	91:9	98/10
2	**2**	36	91	90:10	98/13
3	**1**	36	91	99:1	99/44
4	**0.5**	48	80	93:7	95/14

[a] The reactions were carried out using 4-nitrobenzaldehyde (4.0 mmol), cyclohexanone (4.0 mmol) and catalyst (see Table 3) on water (2.0 mL).
[b] Isolated yield after chromatography on silica gel.
[c] Determined by chiral HPLC analysis (AD-H).

Table 4
Organocatalyst **1a**-catalyzed direct stoichiometric aldol reactions on water[a]

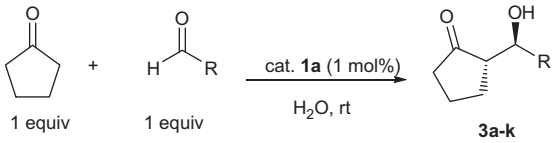


Entry	Product	Time (h)	Yield[b] (%)	dr (*anti*/*syn*) [c]	ee (*anti*/*syn*)[c] (%)
1	**2a** (R = *p*-NO_2-C_6H_4)	36	91	99:1	99/44
2	**2b** (R = *o*-NO_2-C_6H_4)	36	98	97:3	>99/5
3	**2c** (R = *m*-NO_2-C_6H_4)	36	96	97:3	>99/29
4	**2d** (R = *p*-CF_3-C_6H_4)	36	96	90:10	97/10
5	**2e** (R = *p*-CN-C_6H_4)	36	95	87:13	98/23
6	**2f** (R = p-F-C_6H_4)	48	92	89:11	>99/34
7	**2g** (R = *p*-Cl-C_6H_4)	48	90	96:4	98/67
8	**2h** (R = *o*-Cl-C_6H_4)	48	86	98:2	98/8
9	**2i** (R = *m*-Cl-C_6H_4)	48	87	89:11	>99/15
10	**2j** (R = 2,6-Cl-C_6H_4)	48	89	88:12	93/20
11	**2k** (R = *p*-Br-C_6H_4)	48	92	97:3	98/34
12	**2l** (R = *o*-Br-C_6H_4)	48	89	99:1	99/0
13	**2m** (R = *m*-Br-C_6H_4)	48	90	85:15	99/45
14	**2n** (R = *p*-MeO-C_6H_4)	72	68	94:6	98/70
15	**2o** (R = *m*-MeO-C_6H_4)	72	65	94:6	96/21
16	**2p** (R = *p*-Me-C_6H_4)	72	60	95:5	99/10
17	**2q** (R = 1-naphthyl)	72	89	98:2	99/68
18	**2r** (R = 2-naphthyl)	72	92	96:4	>99/6
19	**2s** (R = C_6H_4)	72	65	90:10	97/6
20	**2t** (R = pyridinthyl)	72	90	91:9	98/23
21	**2u** (R = 2-thiophenaldehyde)	36	85	95:5	99/19
22	**2v** (R = 2-furaldehyde)	36	87	80:20	>99/67

[a] The reactions were carried out using aldehyde (4.0 mmol), cyclohexanone (4.0 mmol) and catalyst **1a** (0.04 mmol) on water (2.0 mL).
[b] Isolated yield after chromatography on silica gel.
[c] Determined by chiral HPLC analysis (AD-H, OD-H and OJ-H).

aromatic aldehydes with cyclohexanone were studied under the optimized conditions. The results are summarized in Table 4. It can be seen that a wide range of aromatic and heteroaromatic aldehydes can participate in the stoichiometric aldol reaction. From Table 4, we were able to access aldol adducts **2a**–**v** derived from their corresponding aromatic aldehydes, heteroaromatic aldehydes and cyclohexanone. In the presence of only 1 mol % of catalyst **1a** and 0.5 mL of water, most stoichiometric reactions between cyclohexanone and various aromatic and heteroaromatic aldehydes afforded the aldol products in excellent yields and nearly perfect ee values. In general, the stoichiometric reactions between cyclohexanone and aromatic aldehydes bearing electron-withdrawing substituents

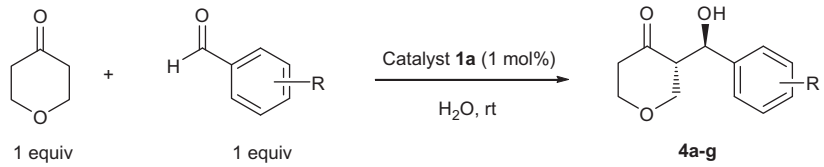
Table 5
The asymmetric stoichiometric aldol reactions of cyclopentanone with various aryl aldehydes on water[a]

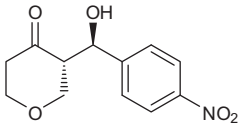
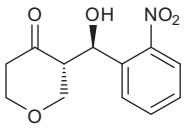
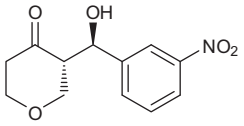
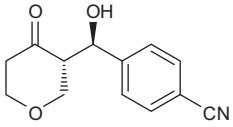
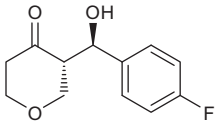
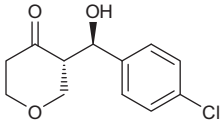
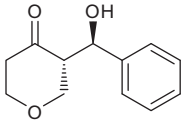


Entry	Product	Time (h)	Yield[b] (%)	dr (*anti*/*syn*) [c]	ee (*anti*/*syn*)[c] (%)
1	**3a** (R = *p*-NO_2-C_6H_4)	36	86	78:22	97/43
2	**3b** (R = *o*-NO_2-C_6H_4)	36	96	85:15	99/50
3	**3c** (R = *m*-NO_2-C_6H_4)	36	98	75:15	98/35
4	**3d** (R = *p*-CF_3-C_6H_4)	36	93	85:15	99/33
5	**3e** (R = *p*-Br-C_6H_4)	48	89	74:26	92/41
6	**3f**(R = *p*-Cl-C_6H_4)	48	90	84:16	99/82
7	**3g** (R = *o*-Cl-C_6H_4)	48	85	83:17	99/96
8	**3h** (R = *m*-MeO-C_6H_4)	72	70	74:26	95/48
9	**3i** (R = *p*-Me-C_6H_4)	72	65	72:28	92/11
10	**3j** (R = 1-naphthyl)	72	75	69:31	94/68
11	**3k** (R = C_6H_4)	72	65	75:25	99/91

[a] The reactions were carried out using aldehyde (4.0 mmol), cyclopentanone (4.0 mmol) and catalyst **1a** (0.04 mmol) on water (2.0 mL).
[b] Isolated yield after chromatography on silica gel.
[c] Determined by chiral HPLC analysis (AD-H, OD-H and OJ-H).

Table 6
The asymmetric stoichiometric aldol reactions of tetrahydro-4*H*-pyran-4-one with various aryl aldehydes on water[a]



Entry	Product	Time (h)	Yield[b] (%)	dr (*anti*/*syn*) [c]	ee (*anti*/*syn*)[c] (%)
1	 **4a**	48	90	94:6	98/99
2	 **4b**	48	92	95:5	99/11
3	 **4c**	48	90	97:3	>99/53
4	 **4d**	48	89	90:10	94/65
5	 **4e**	48	82	91:9	91/34
6	 **4f**	48	80	90:10	92/23
7	 **4g**	72	54	89:11	98/78

[a] The reactions were carried out using aldehyde (4.0 mmol), tetrahydro-4*H*-pyran-4-one (4.0 mmol) and catalyst **1a** (0.04 mmol) on water (2.0 mL).
[b] Isolated yield after chromatography on silica gel.
[c] Determined by chiral HPLC analysis (AD-H and OD-H).

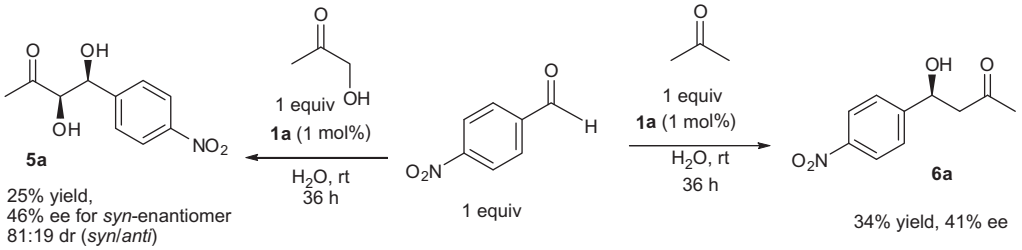
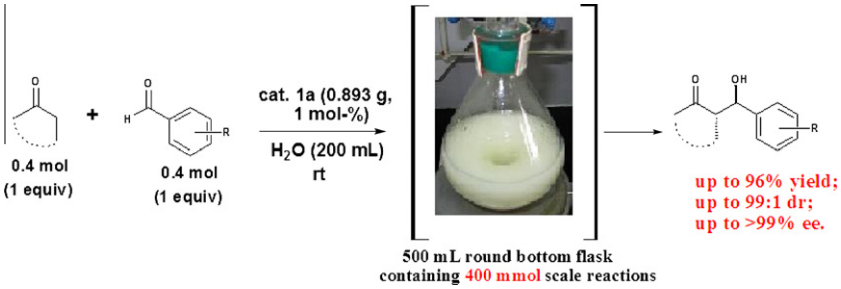


Figure 2. The stoichiometric aldol reactions between 4-nitrobenzaldehyde and water-soluble ketones.

Table 7
Large-scale asymmetric stoichiometric aldol reactions[a]



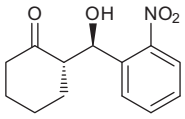
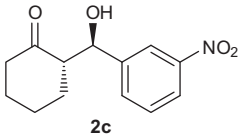
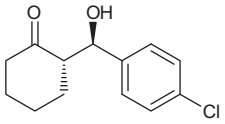
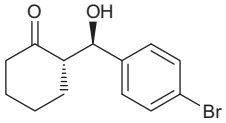
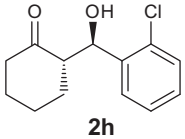
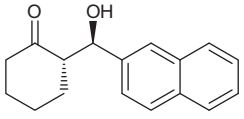
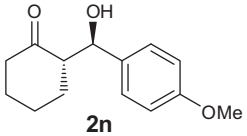
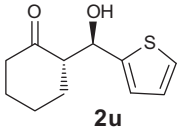
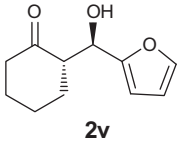
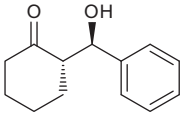
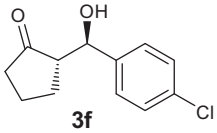
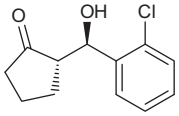
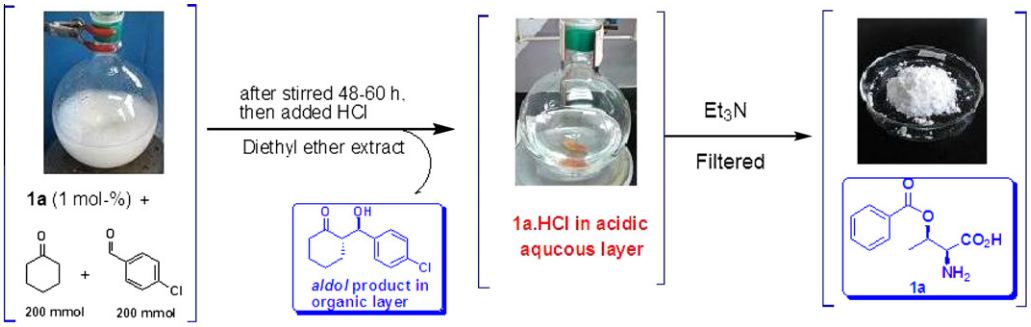
Entry	Product	Time (h)	Yield[b] (%)	dr (*anti*/*syn*) [c]	ee (*anti*/*syn*)[c] (%)
1	 **2b**	24	96	98:2	>99/8
2	 **2c**	24	95	97:3	>99/31
3	 **2g**	30	89	94:6	97/10
4	 **2k**	30	90	92:8	97/30
5	 **2h**	30	85	96:4	97/13
6	 **2r**	30	89	99:1	99/4
7	 **2n**	36	68	97:3	98/75
8	 **2u**	36	85	95:5	99/23
9	 **2v**	36	87	74:26	>99/54

Table 7 (*continued*)

Entry	Product	Time (h)	Yield[b] (%)	dr (*anti*/*syn*) [c]	ee (*anti*/*syn*)[c] (%)
10	 **2s**	48	65	91:9	97/10
11	 **3f**	36	90	70:30	99/85
12	 **3g**	36	85	83:17	99/90

[a] The reactions were carried out using aldehyde (400 mmol), ketone (400 mmol) and catalyst **1a** (4 mmol) on the water (200 mL).
[b] Isolated yield after chromatography on silica gel.
[c] Determined by chiral HPLC analysis (AD-H).

Table 8
Recycling and reuse of catalyst **1a**[a]



Cycle	Time (h)	Yield[b] (%)	*dr* (*anti*/*syn*) [c]	ee (*anti*/*syn*)[c] (%)
1	48	90	99:1	97/0
2	48	90	93:7	97/8
3	48	89	92:8	96/15
4	56	88	92:8	96/19
5	60	87	93:7	96/14
6	60	80	90:10	93/33

[a] The reactions were carried out using 4-chlorobenzaldehyde (200 mmol) and cyclohexanone (200 mmol) on water (100 mL) at room temperature.
[b] Isolated yield after chromatography on silica gel.
[c] Determined by chiral HPLC analysis (AD-H).

furnished β-hydroxy carbonyl aldol products in excellent yields (86–98%) and enantioselectivities (93 to >99% ee for the *anti*-enantiomer) within 36–48 h (Table 4, entries 1–13). In contrast, longer reaction times (72 h) were required for aromatic aldehydes containing an electron-donating groups to give comparatively lower yields (60–68%), but without a decrease in enantioselectivity (Table 3, entries 14–16), in particular the *p*-tolualdehyde (Table 3, entry 16, 95:5 *anti*/*syn* ratio and 99% ee). This can be explained in that electron-withdrawing groups enhance the electrophilicity of the carbonyl carbons in aldehydes, which facilitate the reaction, while electron-donating groups lessen the electrophilicity. Moreover, the direct stoichiometric aldol reactions of neutral aldehydes catalyzed by the threonine-based organocatalyst **1a** also afforded the aldol products in high enantioselectivities and diastereoselectivities (Table 4, entries 17 to 20), especially the 1-naphthyl aldehyde (Table 4, entry 17, 98:2 *anti*/*syn* ratio and 99% ee for the *anti*-enantiomer). Moreover, the heteroaromatic aldehydes 2-furaldehyde and 2-thiophenaldehyde both reacted smoothly with cyclohexanone under the optimal conditions to give the corresponding aldol products in good yields (85–87%) and excellent enantioselectivities (99 to >99%) after 36 h (Table 4, entries 21 and 22). All of the stoichiometric reactions of cyclohexanone with aromatic and heteroaromatic aldehydes provided the corresponding products with excellent enantioselectivities (93 to >99% ee for the *anti*-enantiomer) and excellent diastereoselectivities (*anti*/*syn* 80:20–99:1) (Table 4, entries 1–22).

When aromatic aldehydes and cyclopentanone were employed interesting results were obtained (Table 5), with excellent enantioselectivities being obtained (92–99% ee for the *anti*-enantiomer).

We next investigated threonine-based organocatalyst **1a** as a catalyst in the stoichiometric reaction between aromatic aldehydes and tetrahydro-4*H*-pyran-4-one (Table 6). It can be seen that a wide range of aromatic aldehydes can participate in the stoichiometric aldol reaction, with excellent enantioselectivities. The enantioselectivities ranged from 91 to >99% for the *anti*-enantiomer and diastereoselectivities ranged from 89:11 to 97:3 (*anti*/*syn*).

We also investigated threonine-based organocatalyst **1a** as a catalyst in the stoichiometric aldol reactions between 4-nitrobenzaldehyde and water-soluble ketones (acetone and hydroxyacetone) (Fig. 2). However, when 4-nitrobenzaldehyde and water-ketones were equivalent, we found that the enantioselectivities of aldol reactions products were not high.

We performed large-scale asymmetric stoichiometric aldol reactions with 400 mmol of aromatic aldehydes and 1 equiv of ketones in a 500 mL round bottomed flask. The same catalyst loading of 1 mol % as employed in the experimental scale was used. The large-scale experiments can be easily carried out by using the same procedure as for the experimental scale reactions. As can be seen from the results summarized in Table 7, the enantioselectivities were maintained at the same level for the large-scale reactions. Thus, the threonine-based organocatalyst **1a** is not only simple and easily prepared by a one-step reaction, but the enantioselectivities are maintained at the same level for the large-scale stoichiometric aldol reactions, which offers great possibilities for industrial applications.

In order to verify that the threonine-based organocatalyst **1a** could be recovered and reused, we performed a recycling study of **1a** using the stoichiometric aldol reaction between cyclohexanone and 4-chlorobenzaldehyde in a 500 mL round bottomed flask (Table 8). Catalyst **1a** could be easily recovered from the reaction mixture after completion of the reaction by acid treatment; the aldol product was extracted with diethyl ether (Et_2O), evaporation of the organic solution to give the aldol product. Catalyst **1a** exists in the acidic aqueous layer; an equivalent amount of triethylamine (Et_3N) was added, which resulted in a white suspension that was filtered by vacuum. The white crystals were directly used in subsequent reaction cycles without adding any new catalyst. In each reuse, the same amounts of substrates were used. The recovered catalyst **1a** was used without further purification and retained its catalytic activity; no decrease in enantioselectivity was observed for six cycles (Table 8).

3. Conclusions

In conclusion, our results demonstrate that the direct threonine catalyst **1a**, obtained via a direct O-acylation, is a robust and effective catalyst for highly enantioselective stoichiometric aldol reactions. A wide range of aromatic and heteroaromatic aldehydes with cyclic and acyclic ketones can participate in the direct stoichiometric aldol reactions. Noteworthy features of this catalyst system are; (1) the direct O-acylation of threonine-based organocatalysts **1a**–**i** that can be prepared easily by a one-step reaction from commercially available sources, with both enantiomers being readily available; (2) the direct aldol reactions proceed in the presence of water using simple procedures; (3) only 1 mol % of catalyst **1a** was sufficient to furnish the aldol products in excellent yields (up to 99%) and enantioselectivities (up to >99% ee for the *anti*-enantiomer); (4) aldehydes and cyclic ketones were equivalent, which is reassuring for direct stoichiometric aldol reactions with atom economic 'green' credentials; (5) catalyst **1a** can be readily recovered and reused without a significant loss of catalytic activity or stereoselectivity; (6) this organocatalyzed direct asymmetric stoichiometric aldol reaction can be performed on a large-scale with the enantioselectivity being maintained at the same level, which offers great possibilities for industrial applications.

4. Experimental section

4.1. General information

All reagents were commercial products. The reactions were monitored by TLC (thin layer chromatography). The column and preparative TLC purification was 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 (Bruker Avance 300 Spectrometer). Chemical shifts (δ) are given in ppm relative to TMS as the internal reference, with coupling constants (J) in Hz. IR spectra were recorded on a Bruker Tensor 27 FTIR spectrometer. Melting points were measured on a digital melting point apparatus (TAQ100). Mass spectra (MS) were measured with a Bruker HCT Mass 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) and Chiralcel OJ-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 large-scale preparation of the direct *O*-acylated threonine organocatalysts 1a–g[34–41]

A 1000 mL round bottomed flask was charged with CF_3CO_2H (240 mL) and placed in an ice/water bath. Powdered threonine (500 mmol) was added in small portions with vigorous stirring to give a viscous solution. The reaction mixture was stirred for 40 min, and then the acyl chloride (750 mmol) was added in one portion. After 60 min of stirring, the reaction mixture was removed from the ice/water bath. 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 (500 mL) was added with vigorous stirring over a period of 20 min, slowly at first. The resulting white suspension was stirred at 0–5 °C for 30 min after the complete 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 directly give O-acylation threonine hydrochloride, which was then dissolved in water, and an equivalent amount of triethylamine (Et_3N) added. The resulting white suspension was stirred at room temperature for 10 min after the complete addition, and then filtered by vacuum. The white crystals were washed with two portions of H_2O and dried to give the organocatalysts. These essentially pure materials were used for the next step without further purification.

4.2.1. (2*S*,3*R*)-*O*-(Benzoyloxy)-L-threonine 1a

White microcrystals, yield 101.56 g (455 mmol, 91%); mp 144–145 °C; $[\alpha]_D^{20} = -12.8$ (c 1.02, MeOH). ^{1}H NMR (300 MHz, DMSO): δ = 1.46–1.48 (d, ^3J = 6.6 Hz, 3H, CH_3), 4.35 (br s, 1H, NC*H*), 5.55–5.58 (dq, ^3J = 3.0 and 6.5 Hz, 1H, 3-H, OC*H*), 7.52–7.57(m, 2H, Ph-H), 7.67–7.71 (m, 1H, Ph-H), 8.10–8.13 (m, 2H, Ph-H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 16.7, 55.6, 68.9, 128.7, 129.0, 129.9, 133.9, 164.6, 168.5 ppm. IR (KBr): ν = 2985, 1759, 1716, 1650, 1602, 1586, 1493, 1415, 1157 cm^{-1}. HRMS (FAB): [M+H] calcd for [$C_{11}H_{13}NO_4$] 224.2332, found 224.2340. Anal. Calcd for

$C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.33; H, 5.92; N, 6.30.

4.2.2. (2*S*,3*R*)-*O*-(2-Phenylacetoxy)-L-threonine 1b

White microcrystals, yield 112.7 g (475 mmol, 95%); mp 115–116 °C; $[\alpha]_D^{20} = +28.9$ (*c* 1.26, MeOH). ^{1}H NMR (300 MHz, DMSO): δ = 1.33–1.35 (d, ^3J = 6.6 Hz, 3H, CH_3), 3.70–3.76 (d, ^3J = 16.2 Hz, 2H, CH_2), 4.17 (br s, 1H, NC*H*), 5.27–5.30 (dq, ^3J = 3.9 Hz and 6.3 Hz, 1H, OC*H*), 7.28–7.33 (m, 5H, *Ph-H*) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 16.7, 41.9, 55.4, 68.2, 126.9, 128.1, 129.4, 134.0, 168.4, 170.1 ppm. IR (KBr): ν = 2984, 1739, 1621, 1540, 1493, 1415, 1145 cm^{-1}.. HRMS (FAB): [M+H] calcd for [$C_{12}H_{15}NO_4$] 238.2597, found 238.2587. Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.80; H, 6.40; N, 5.93.

4.2.3. (2*S*,3*R*)-*O*-(3-Phenylpropanoyloxy)-L-threonine 1c

White microcrystals, yield 120.62 g (280 mmol, 96%); mp 112–113 °C; $[\alpha]_D^{20} = +14.6$ (*c* 1.2, MeOH). ^{1}H NMR (300 MHz, DMSO): δ = 1.30–1.32 (d, ^3J = 6.4 Hz, 3H, CH_3), 2.61–2.66 (m, 2H, CH_2), 2.61–2.66 (m, 2H, CH_2), 2.84 (t, J = 7.0 Hz, 2H, CH_2), 4.14 (br s, 1H, NC*H*), 5.25–5.29 (dq, ^3J = 3.8 Hz and 6.3 Hz, 1H, OC*H*), 7.21–7.31 (m, 5H, *Ph-H*) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 20.1, 33.4, 38.4, 58.8, 71.2, 129.5, 131.5, 131.7, 143.7, 171.7, 174.4 ppm. IR (KBr): ν = 2986, 1757, 1731, 1633, 1575, 1493, 1415, 1164 cm^{-1}. HRMS (FAB): [M+H] calcd for [$C_{13}H_{17}NO_4$] 252.2863, found 252.2875. Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.20; H, 6.85; N, 5.64.

4.2.4. (2*S*,3*R*)-*O*-(4-Phenylbutanoyloxy) -L-threonine 1d

White microcrystals, yield 124.16 g (470 mmol, 94%); mp 110–111 °C; $[\alpha]_D^{20} = +14.7$ (*c* 1.0, MeOH). ^{1}H NMR (300 MHz, DMSO): δ = 1.32–1.34 (d, ^3J = 6.5 Hz, 3H, CH_3), 1.76–1.86 (m, 2H, CH_2), 2.24–2.35 (m, 2H, CH_2), 2.50–2.59 (m, 2H, CH_2), 2.61–2.66 (m, 2H, CH_2), 4.13 (br s, 1H, NC*H*), 5.27–5.30 (dq, ^3J = 3.6 Hz and 6.3 Hz, 1H, OC*H*), 7.17–7.19(m, 3H, *Ph-H*), 7.25–7.30(m, 3H, *Ph-H*) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 16.7, 26.1, 33.0, 34.3, 55.4, 67.8, 126.0, 128.4, 128.5, 141.4, 168.5, 171.6 ppm. IR (KBr):ν = 2987, 1758, 1733, 1634, 1540, 1500, 1415, 1156 cm^{-1}; HRMS (FAB): [M+H] calcd for [$C_{14}H_{19}NO_4$] 266.3129, found 266.3137. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.42; H, 7.25; N, 5.32.

4.2.5. (2*S*,3*R*)-*O*-(2-(Naphthalen-1-yl)-L-threonine 1e

White microcrystals, yield 134.54 g (468 mmol, 94%); mp 110–111 °C; $[\alpha]_D^{20} = +27.3$ (*c* 1.3, MeOH). ^{1}H NMR (300 MHz, DMSO): δ = 1.37–1.39 (d, ^3J = 6.4 Hz, 3H, CH_3), 4.20 (br s, 3H, NC*H* and CH_2), 5.30–5.33 (dq, ^3J = 3.6 Hz and 5.9 Hz, 1H, 3-H, OC*H*), 7.46–7.58 (m, 4H, Ph-H), 7.86–7.96 (m, 3H, Ph-H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 17.2, 38.1, 55.9, 68.7, 124.4, 125.9, 126.2, 126.8, 128.1, 128.5, 128.9, 131.0, 132.2, 133.7, 168.8, 170.5 ppm. IR (KBr): ν = 2986, 1755, 1719, 1650, 1602, 1586, 1493, 1415, 1157 cm^{-1}. HRMS (FAB): [M+H] calcd for [$C_{16}H_{17}NO_4$] 288.3184, found 288.3178. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.90; H, 6.99; N, 4.91.

4.2.6. (2*S*,3*R*)-*O*-(Cyclohexylcarbonyl)-L-threonine 1f

White microcrystals, yield 103.28 g (450 mmol, 90%); mp 97–100 °C; $[\alpha]_D^{20} = +15.7$ (*c* 1.1, MeOH). ^{1}H NMR (300 MHz, DMSO): δ = 1.27–1.38 (m, 8H, cyclo-CH_2), 1.42–1.44 (d, ^3J = 6.6 Hz, 3H, CH_3), 1.84–1.88 (m, 2H, cyclo-CH_2), 2.30–2.38 (m, 1H, cyclo-CH_2), 4.22 (br s, 1H, NC*H*), 5.30–5.33 (dq, ^3J = 3.2 Hz and 6.5 Hz, 1H, 3-H, OC*H*) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 16.9, 25.1, 25.2, 25.7, 28.6, 28.7, 42.4, 55.8, 67.9, 168.8, 174.2 ppm. IR (KBr): ν = 3026, 2947, 2929, 2857, 1735, 1629 cm^{-1}. HRMS (FAB): [M+H] calcd for [$C_{11}H_{19}NO_4$] 230.2808, found 230.2823. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.67; H, 8.38; N, 6.13.

4.2.7. (2*S*,3*R*)-*O*-(1-Adamantylcarbonyl)-L-threonine 1g

White microcrystals, yield 126.68 g (450 mmol, 90%); mp 97–100 °C; $[\alpha]_D^{20} = +5.4$ (*c* 1.2, MeOH). ^{1}H NMR (300 MHz, DMSO): δ = 1.28–1.30 (d, ^3J = 6.6 Hz, 3H, CH_3), 1.66 (m, 6H, cyclo-CH_2), 1.81 (m, 6H, cyclo-CH_2), 1.95 (m, 3H, cyclo-CH), 4.19 (br s, 1H, NC*H*), 5.24–5.27 (dq, ^3J = 2.9 Hz and 6.6 Hz, 1H, 3-H, OC*H*) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 15.6, 16.6, 27.7, 36.3, 38.2, 40.5, 55.8, 65.3, 67.8, 168.8, 175.6 ppm. IR (KBr): ν = 3026, 2968, 1758, 1726, 1601, 1575, 1493, 1415, 1157 cm^{-1}. HRMS (FAB): [M+H] calcd for [$C_{15}H_{23}NO_4$] 282.3554, found 282.3569. Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.11; H, 8.28; N, 5.03.

4.3. Representative procedures for the asymmetric stoichiometric aldol reactions of ketones with aldehydes

On water: To a mixture of catalyst **1a** (8.94 mg, 0.04 mmol) and ketone (4.0 mmol) were added the aldehyde (4.0 mmol) and water (2.0 mL). The resulting mixture was stirred at room temperature. The reaction was monitored by TLC. It was then quenched with 8 mL saturated NH_4Cl solution, extracted with EtOAc (5 × 10 mL), and dried over Na_2SO_4. Purification by flash chromatography afforded the corresponding pure products.

4.3.1. (2*S*,10*R*)-2-(Hydroxy-(4-nitrophenyl)methyl)-cyclohexan-1-one 2a[35–37]

Yield 91%, *anti*/*syn* = 99:1, enantiomeric excess: 99% for the *anti*-enantiomer and 44% for the *syn*-enantiomer 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). HRMS (FAB): [M+Na] calcd for [$C_{13}H_{15}NO_4Na$] 272.2522, found 272.2528.

4.3.2. (2*S*,10*R*)-2-(Hydroxy-(2-nitrophenyl)methyl)-cyclohexan-1-one 2b[35–37]

Yield 98%, *anti*/*syn* = 97:3, enantiomeric excess: >99% for the *anti*-diastereomer and 5% for the *syn*-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). HRMS (FAB): [M+Na] calcd for [$C_{13}H_{15}NO_4Na$] 272.2522, found 272.2528.

4.3.3. (2*S*,10*R*)-2-(Hydroxy-(3-nitrophenyl)methyl)-cyclohexan-1-one 2c[35–37]

Yield 96%, *anti*/*syn* = 97:3, enantiomeric excess: >99% for the *anti*-diastereomer and 29% for the *syn*-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). HRMS (FAB): [M+Na] calcd for [$C_{13}H_{15}NO_4Na$] 272.2522, found 272.2528.

4.3.4. (2*S*,10*R*)-2-(Hydroxy-(4-(trifluoromethyl)methyl)-cyclohexan-1-one 2d[35–37]

Yield 96%, *anti*/*syn* = 90:10, enantiomeric excess: 97% for the *anti*-diastereomer and 10% o for the *syn*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; flow rate 0.5 mL/min, 20 °C, *k* = 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). HRMS (FAB): [M+Na] calcd for [$C_{14}H_{15}F_3O_2Na$] 295.2527, found 295.2534.

4.3.5. (2*S*,10*R*)-2-(Hydroxy-(4-cyanophenyl)methyl)-cyclohexan-1-one 2e[35–37]

Yield 95%, *anti*/*syn* = 87:13, enantiomeric excess: 98% for the *anti*-diastereomer and 23% for the *syn*-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). HRMS (FAB): [M+Na] calcd for [$C_{14}H_{15}NO_2Na$] 252.2641, found 252.2637.

4.3.6. (2*S*,10*R*)-2-(Hydroxy-(4-fluor-phenyl)methyl)-cyclohexan-1-one 2f[35–37]

Yield 92%, *anti*/*syn* = 89:11, enantiomeric excess: >99% for the *anti*-diastereomer and 34% for the *syn*-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). HRMS (FAB): [M+Na] calcd for [$C_{13}H_{15}FO_2Na$] 245.2441, found 245.2445.

4.3.7. (2*S*,10*R*)-2-(Hydroxy-(4-chlorophenyl)methyl)-cyclohexan-1-one 2g[35–37]

Yield 90%, *anti*/*syn* = 96:4, enantiomeric excess: 98% for the *anti*-diastereomer and 67% for the *syn*-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 = 37.2 min (*anti*, major), t_R = 32.4 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). HRMS (FAB): [M+Na] calcd for [$C_{13}H_{15}ClO_2Na$] 261.6997, found 261.6992.

4.3.8. (2*S*,10*R*)-2-(Hydroxy-(2-chlorophenyl)methyl)-cyclohexan-1-one 2h[37]

Yield 86%, *anti*/*syn* = 98:2, enantiomeric excess: 98% for the *anti*-diastereomer and 8% for the *syn*-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), 3.88 (s, 1H), 2.65–2.71 (m, 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). HRMS (FAB): [M+Na] calcd for [$C_{13}H_{15}ClO_2Na$] 261.6997, found 261.6992..

4.3.9. (2*S*,10*R*)-2-(Hydroxy-(3-chlorophenyl)methyl)-cyclohexan-1-one 2i[35–37]

Yield 87%, *anti*/*syn* = 89:11, enantiomeric excess: >99% for the *anti*-diastereomer and 15% for the *syn*-diastereomer determined by HPLC (Dicael Chiralpak OD-H column; *i*-PrOH/Hexane = 4:96; flow rate 1.0 mL/min, 20 °C, λ = 221 nm; t_R = 14.8 min (*anti*, major), t_R = 21.2 min (*anti*, minor)). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (s, 1H, Ar), 7.20–7.29 (m, 3H, Ar), 4.80 (d, 1H, *J* = 8.8 Hz), 2.30–2.45 (m, 3H), 1.31–2.08 (m, 6H). HRMS (FAB): [M+Na] calcd for [$C_{13}H_{15}ClO_2$-Na] 261.6997, found 261.6992.

4.3.10. (2*S*,10*R*)-2-(Hydroxy-(2,6-dichlorophenyl)methyl)-cyclohexan-1-one 2j[37]

Yield 89%, *anti*/*syn* = 88:12, enantiomeric excess: 93% for the *anti*-diastereomer and 20% for the *syn*-diastereomer determined by HPLC (Dicael Chiralpak OJ-H column; *i*-PrOH/Hexane = 5:95; flow rate 1.0 mL/min, 20 °C, λ = 221 nm; t_R = 10.2 min (*anti*, major), t_R = 11.9 min (*anti*, minor)). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (d, 2H, *J* = 8.0 Hz) 7.17 (t, 2H, *J* = 8.0 Hz), 5.86 (d, 1H, *J* = 9.6 Hz), 3.69 (br s, 1H), 3.49–3.55 (m, 1H), 2.38–2.55 (m, 2H), 2.07–2.14 (m, 1H), 1.34–1.86 (m, 5H). HRMS (FAB): [M+Na] calcd for [$C_{13}H_{14}Cl_2O_2Na$] 294.1448, found 294.1453.

4.3.11. (2*S*,10*R*)-2-(Hydroxy-(4-bromophenyl)methyl)-cyclohexan-1-one 2k[35–37]

Yield 92%, *anti*/*syn* = 97:3, enantiomeric excess: 98% for the *anti*-diastereomer and 34% for the *syn*-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). HRMS (FAB): [M+Na] calcd for [$C_{13}H_{15}BrO_2Na$] 306.1507, found 306.1513.

4.3.12. (2*S*,10*R*)-2-(Hydroxy-(2-bromophenyl)methyl)-cyclohexan-1-one 2l[36,37]

Yield 89%, *anti*/*syn* = 99:1, enantiomeric excess: 99% for the *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 = 18.4 min (*anti*, major), t_R = 15.3 min (*anti*, minor)). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.54 (m, 2H), 7.33 (t, 1H, *J* = 24.6 Hz), 7.11–7.16 (m, 1H), 5.30 (d, 1H, *J* = 9.6 Hz), 4.02 (s, 1H), 2.64–2.72 (m, 1H), 2.29–2,49 (m, 2H), 2.06–2.12 (m, 1H), 1.49–1.84 (m, 5H). HRMS (FAB): [M+Na] calcd for [$C_{13}H_{15}BrO_2Na$] 306.1507, found 306.1513.

4.3.13. (2*S*,10*R*)-2-(Hydroxy-(3-bromophenyl)methyl)-cyclohexan-1-one 2m[37]

Yield 90%, *anti*/*syn* = 85:15, enantiomeric excess: 99% for the *anti*-diastereomer and 45% for the *syn*-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 = 22.1 min (*anti*, major), t_R = 27.7 min (*anti*, minor)). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (s, 1H, Ar), 7.20–7.29 (m, 3H, Ar), 4.80 (d, 1H, *J* = 8.8 Hz), 2.30–2.45 (m, 3H), 1.31–2.08 (m, 6H). HRMS (FAB): [M+Na] calcd for [$C_{13}H_{15}BrO_2$-Na] 306.1507, found 306.1513.

4.3.14. (2*S*,10*R*)-2-(Hydroxy-(4-methoxy-phenyl)methyl)-cyclohexan-1-one 2n[35–37]

Yield 68%, *anti*/*syn* = 94:6, enantiomeric excess: 98% **for the** *anti*-diastereomer and 70% for the *syn*-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). HRMS (FAB): [M+Na] calcd for [$C_{14}H_{18}O_3Na$] 257.2807, found 257.2812.

4.3.15. (2*S*,10*R*)-2-(Hydroxy-(3-methoxy-phenyl)methyl)-cyclohexan-1-one 2o[35–37]

Yield 65%, *anti*/*syn* = 94:6, enantiomeric excess: 96% for the *anti*-diastereomer and 21% for the *syn*-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). HRMS (FAB): [M+Na] calcd for [$C_{14}H_{18}O_3Na$] 257.2807, found 257.2812.

4.3.16. (2*S*,10*R*)-2-(Hydroxy-(4-tolyl)methyl)-cyclohexan-1-one 2p[35–37]

Yield 60%, *anti*/*syn* = 95:5, enantiomeric excess: 99% for the *anti*-diastereomer and 10% for the *syn*-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). HRMS (FAB): [M+Na] calcd for [$C_{14}H_{18}O_2Na$] 241.2813, found 241.2808.

4.3.17. (2*S*,10*R*)-2-(Hydroxy-(1-naphthyl)methyl)-cyclohexan-1-one 2q[35–37]

Yield 89%, *anti*/*syn* = 98:2, enantiomeric excess: 99% for the *anti*-diastereomer and 68% for the *syn*-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 = 43.2 min (*anti*, major), t_R = 35.3 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). HRMS (FAB): [M+Na] calcd for [$C_{17}H_{18}O_2Na$] 277.3134, found 277.3140.

4.3.18. (2*S*,10*R*)-2-(Hydroxy-(2-naphthyl)methyl)-cyclohexan-1-one 2r[36,37]

Yield 92%, *anti*/*syn* = 96:4, enantiomeric excess: >99% for the *anti*-diastereomer and 6% for the *syn*-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 = 21.9 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). HRMS (FAB): [M+Na] calcd for [$C_{17}H_{18}O_2Na$] 277.3134, found 277.3140.

4.3.19. (2*S*,10*R*)-2-(Hydroxy-(phenyl)methyl)-cyclohexan-1-one 2s[35–37]

Yield 65%, *anti*/*syn* = 90:10, enantiomeric excess: 97% for the *anti*-diastereomer and 6% for the *syn*-diastereomer determined by HPLC (Dicael Chiralpak OD-H column; *i*-PrOH/Hexane = 10:90; flow rate 0.5 mL/min, 20 °C, λ = 221 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 (m, 5H), 4.80 (d, J = 9.0 Hz, 1H), 4.00 (m, 1H), 2.70–2.56 (m, 1H), 2.55–2.44 (m, 1H), 2.34 (td, J = 12.3, 5.4 Hz, 1H), 2.16–2.03 (m, 1H), 1.87–1.73 (m, 1H), 1.72–1.50 (m, 3H), 1.40–1.22 (m, 1H). HRMS (FAB): [M+Na] calcd for [$C_{13}H_{16}O_2Na$] 227.2547, found 227.2553.

4.3.20. (2*S*,10*R*)-2-(Hydroxy-(pyridin-4-yl)methyl)-cyclohexan-1-one 2t[37]

Yield 90%, *anti*/*syn* = 91:9, enantiomeric excess: 98% for the *anti*-diastereomer and 23% for the *syn*-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). HRMS (FAB): [M+H] calcd for [$C_{12}H_{16}NO_2$] 206.2609, found 206.2635.

4.3.21. (*S*)-2-((*R*)-Hydroxy(thiophen-2-yl)methyl)-cyclo-hexanone 2u[37]

Yield 85%, *anti*/*syn* = 95:5, enantiomeric excess: 99% for the *anti*-diastereomer and 19% for the *syn*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; flow rate 1.0 mL/min, 20 °C, λ = 220 nm; t_R = 19.6 min (*anti*, major), t_R = 21.7 min (*anti*, minor)). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (dd, J = 4.8, 0.8 Hz, 1H), 7.00–6.96 (m, 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), 1.30–1.40 (m, 1H). HRMS (FAB): [M+Na] calcd for [$C_{11}H_{14}SO_2Na$] 233.2824, found 233.2829.

4.3.22. (*S*)-2-((*R*)-Furan-2-yl(hydroxy)methyl)-cyclo-hexanone 2v[37]

Yield 87%, *anti*/*syn* = 80:20, enantiomeric excess: >99% for the *anti*-diastereomer and 67% for the *syn*-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 = 7.39 (s, 1H), 6.34–6.30 (m, 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), 1.33–1.43 (m, 1H). HRMS (FAB): [M+Na] calcd for [$C_{11}H_{14}O_3Na$] 217.2168, found 217.2172.

4.3.23. (*S*)-2-(*R*)-Hydroxyl(4-nitrophenyl)methyl)-cyclopentan-1-one 3a[35]

Yield 86%, *anti*/*syn* = 78:22, enantiomeric excess: 97% for the *anti*-diastereomer and 43% for the *syn*-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 = 63.6 min (*anti*, major), t_R = 61.6 min (*anti*, 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). HRMS (FAB): [M+Na] calcd for [$C_{12}H_{13}NO_4Na$] 258.2257, found 258.2252.

4.3.24. (*S*)-2-(*R*)-Hydroxyl(2-nitrophenyl)methyl)-cyclopentan-1-one 3b[35]

Yield 96%, *anti*/*syn* = 85:15, enantiomeric excess: 99% for the *anti*-diastereomer and 50% for the *syn*-diastereomer 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); ^{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). HRMS (FAB): [M+Na] calcd for [$C_{12}H_{13}NO_4Na$] 258.2257, found 258.2252.

4.3.25. (*S*)-2-(*R*)-Hydroxyl(hydroxy-(3-nitrophenyl)methyl)-cyclopentan-1-one 3c[35]

Yield 98%, *anti*/*syn* = 75:25, enantiomeric excess: 98% for the *anti*-diastereomer and 35% for the *syn*-diastereomer 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); ^{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). HRMS (FAB): [M+Na] calcd for [$C_{12}H_{13}NO_4Na$] 258.2257, found 258.2252.

4.3.26. (*S*)-2-(*R*)-Hydroxyl(4-(trifluoromethyl)methyl)-cyclopentanone 3d[42]

Yield 93%, *anti*/*syn* = 85:15, enantiomeric excess: 99% for the *anti*-diastereomer and 33% for the *syn*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; flow rate 1.0 mL/min, 20 °C, λ = 214 nm; t_R = 12.3 min (*anti*, major), t_R = 16.9 min (*anti*, minor); 1H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 5.37 (d, *J* = 2.8 Hz, 0.97H), 4.79 (d, *J* = 9.2 Hz, 0.03H), 2.48–1.69 (m, 8H); HRMS (FAB): [M+Na] calcd for [$C_{13}H_{13}F_3O_3Na$] 274.2357, found 274.2350.

4.3.27. (*S*)-2-(*R*)-Hydroxyl(4-bromophenyl)methyl)-cyclopentanone 3e[42]

Yield 89%, *anti*/*syn* = 74:26, enantiomeric excess: 92% for the *anti*-diastereomer and 41% for the *syn*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 5:95; flow rate 1.0 mL/min, 20 °C, λ = 220 nm; t_R = 27.9 min (*anti*, major), t_R = 20.7 min (*anti*, minor); ^{1}H NMR (300 MHz, CDCl3): δ = 7.36 (s, 1H), 7.29–7.19 (m, 3H), 5.28 (d, *J* = 3.2 Hz, 0.7H), 4.69 (d, *J* = 7.2 Hz, 0.3H), 2.45–1.70 (m, 7H); HRMS (FAB): [M+Na] calcd for [$C_{12}H_{13}BrO_2Na$] 292.1242, found 292.1250.

4.3.28. (*S*)-2-(*R*)-Hydroxyl(4-chlorophenyl)methyl)-cyclopentanone 3f[42]

Yield 90%, *anti*/*syn* = 84:16, enantiomeric excess: 99% for the *anti*-diastereomer and 82% for the *syn*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 5:95; flow rate 1.0 mL/min, 20 °C, λ = 220 nm; t_R = 29.9 min (*anti*, major), t_R = 36.9 min (*anti*, minor); ^{1}H NMR (300 MHz, CDCl3): δ = 7.33–7.26 (m, 4H), 5.28 (d, *J* = 3.2 Hz, 0.73H), 4.70 (d, *J* = 9.2 Hz, 0.27H), 2.46–1.68 (m, 7H); [M+Na] calcd for [$C_{12}H_{13}ClO_2Na$] 247.6732, found 247.6737

4.3.29. (*S*)-2-(*R*)-Hydroxyl(2-chlorophenyl)methyl)-cyclopentanone 3g[42]

Yield 85%, *anti*/*syn* = 83:17, enantiomeric excess: 99% for the *anti*-diastereomer and 96% for the *syn*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 4:96; flow rate 1.0 mL/min, 20 °C, λ = 220 nm; t_R = 17.9 min (*anti*, major), t_R = 19.6 min (*anti*, minor); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (s, 1H), 7.59–7.26 (m, 2H), 7.23–7.18 (m, 1H), 5.69 (d, *J* = 2.8 Hz, 0.96H), 5.3 (d, *J* = 7.2 Hz, 0.04H), 2.70–1.67 (m, 8H); [M+Na] calcd for [$C_{12}H_{13}ClO_2Na$] 247.6732, found 247.6737.

4.3.30. (*S*)-2-(*R*)-Hydroxyl(3-methoxylphenyl)methyl)-cyclopentanone 3h[42]

Yield 70%, *anti*/*syn* = 74:26, enantiomeric excess: 95% for the *anti*-diastereomer and 48% for the *syn*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; flow rate 0.5 mL/min, 20 °C, λ = 270 nm; t_R = 41.3 min (*anti*, major), t_R = 44.0 min *(anti*, minor); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (dd, *J* = 5.2, 5.2 Hz, 2H), 6.89–6.86 (m, 2H), 5.23 (d, *J* = 3.2 Hz, 0.62H), 4.66 (d, *J* = 9.2 Hz, 0.38H), 4.50 (br, 0.38H), 3.80 (s, 3H), 2.46–1.26 (m, 7.62H); HRMS (FAB): [M+Na] calcd for [$C_{13}H_{16}O_3Na$] 243.2541, found 243.2527.

4.3.31. (*S*)-2-(*R*)-Hydroxyl(4-methylphenyl)methyl)-cyclopentanone 3i[42]

Yield 65%, *anti*/*syn* = 72:28, enantiomeric excess: 92% for the *anti*-diastereomer and 11% for the *syn*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; flow rate 0.5 mL/min, 20 °C, λ = 220 nm; t_R = 28.4 min (*anti*, major), t_R = 32.0 min (*anti*, minor)); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.13 (m, 4H), 5.24 (d, *J* = 2.8 Hz, 0.67H), 4.68 (d, *J* = 9.2 Hz, 0.33H), 2.44–1.66 (m, 10H); HRMS (FAB): [M+Na] calcd for [$C_{13}H_{16}O_2Na$] 227.2547, found 227.2541.

4.3.32. (*S*)-2-(*R*)-Hydroxyl(1-naphthyl)methyl)-cyclopentanone 3j[43]

Yield 75%, *anti*/*syn* = 69:31, enantiomeric excess: 94% for the *anti*-diastereomer and 68% for the *syn*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 5:95; flow rate 1.0 mL/min, 20 °C, λ = 264 nm; t_R = 40.0 min (*anti*, major), t_R = 44.1 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), 5.14 (d, *J* = 2.8 Hz, 0.67H), 4.76 (d, *J* = 9.2 Hz, 0.33H), 2.44–1.66 (m, 10H);. HRMS (FAB): [M+Na] calcd for [$C_{16}H_{16}O_2Na$] 263.2868, found 263.2874.

4.3.33. (*S*)-2-(*R*)-Hydroxyl-(phenyl-methyl)-cyclopentanone 3k[42]

Yield 65%, *anti*/*syn* = 75:25, enantiomeric excess: 99% for the *anti*-diastereomer and 91% for the *syn*-diastereomer determined by HPLC (Dicael Chiralpak OD-H column; *i*-PrOH/Hexane = 10:90; flow rate 1.0 mL/min, 20 °C, λ = 213 nm; t_R = 11.6 min (*anti*, major), t_R = 14.0 min (*anti*, minor); 1H NMR (300 MHz, $CDCl_3$): δ 7.37–7.25 (m, 5H), 5.31 (d, *J* = 3.2 Hz, 0.86H), 4.72 (d, *J* = 9.2 Hz, 0.14H), 2.62–1.72 (m, 7H); HRMS (FAB): [M+Na] calcd for [$C_{12}H_{14}O_2Na$] 213.2281, found 213.2278.

4.3.34. (*S*)-3-((*R*)-Hydroxy(4-nitrophenyl)methyl)-tetrahydropyran-4-one 4a[37,43]

Yield 90%, *anti*/*syn* = 94:6, enantiomeric excess: 98% for the *anti* diastereomer and 99% for the *syn*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; 1.0 mL/min, 20 °C, λ = 254 nm) t_R = 16.7 min (*anti*, major) and t_R = 39.4 min (*anti*, minor)). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.24 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.53 ((d, *J* = 8.8 Hz, 2H, Ar-H), 4.99 (d, *J* = 8.0 Hz, 1H), 4.19–4.25(m, 1H), 3.70–3.85 (m, 3H), 3.42–3.49 (m, 1H), 2.88–2.94 (m, 1H), 2.64–2.70 (m, 1H), 2.50–2.57 (m, 1H) ppm. HRMS (FAB): [M+Na] calcd for [$C_{12}H_{13}NO_5$ Na] 274.2251, found 274.2244.

4.3.35. (*S*)-3-((*R*)-Hydroxy(2-nitrophenyl)methyl)-tetrahydropyran-4-one 4b[43]

Yield 92%, *anti*/*syn* = 95:5, enantiomeric excess: 99% for the *anti*-diastereomer and 11% for the *syn*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; 1.0 mL/min, 20 °C, λ = 254 nm) t_R = 66.3 min (*anti*, major) and t_R = 63.2 min (*anti*, minor)). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.93 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.81 (t, *J* = 7.2 Hz, 1H), 7.70–7.66 (m, 1H), 7.49–7.45 (m, 1H), 5.48 (d, *J* = 6.8 Hz, 1H), 4.25–4.20 (m, 1H), 4.06 (br s, 1H), 3.95–3.90 (m, 1H), 3.83–3.75 (m, 2H), 3.10–3.04 (m, 1H), 2.72–2.64 (m, 1H), 2.54–2.49 (m, 1H) ppm. HRMS (FAB): [M+Na] calcd for [$C_{12}H_{13}NO_5Na$] 274.2251, found 274.2244.

4.3.36. (*S*)-3-((*R*)-Hydroxy(3-nitrophenyl)methyl)-tetrahydropyran-4-one 4c[43]

Yield 90%, *anti*/*syn* = 97:3, enantiomeric excess: 99% for the *anti*-diastereomer and 53% for the *syn*-diastereomer determined by HPLC (Dicael Chiralpak OD-H column; *i*-PrOH/Hexane = 10:90;

1.0 mL/min, 20 °C, λ = 254 nm) t_R = 54.6 min (*anti*, major) and t_R = 83.8 min (*anti*, minor)). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.23–8.19 (m, 2H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 4.98 (d, *J* = 8.4 Hz, 1H), 4.25–4.21 (m, 1H), 3.80–3.71 (m, 2H), 3.46 (t, *J* = 8.8 Hz, 1H), 2.97–2.91 (m, 1H), 2.75–2.67 (m, 1H), 2.56–2.52 (m, 1H) ppm. HRMS (FAB): [M+Na] calcd for [$C_{12}H_{13}NO_5Na$] 274.2251, found 274.2244.

4.3.37. 4-((*R*)-Hydroxy((*S*)-4-oxotetrahydro-2*H*-pyran-3-yl)methyl)benzonitrile 4d[43]

Yield 89%, *anti*/*syn* = 90:10, enantiomeric excess: 94% for the *anti*-diastereomer and 65% for the *syn*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; 1.0 mL/min, 20 °C, λ = 220 nm) t_R = 54.3 min (*anti*, major) and t_R = 45.7 min (*anti*, minor)). ^{1}H NMR(300 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 5.6 Hz, 2H), 7.46 (d, *J* = 7.6 Hz, 2H), 4.94 (dd, *J* = 8.0, 3.2 Hz, 1H), 4.16 (s, 1H), 3.87 (s, 1H), 3.80–3.6 8(m, 2H), 3.46–3.41 (m, 1H), 2.85–2.63 (m, 2H), 2.56–2.52 (m, 1H). HRMS (FAB): [M+Na] calcd for [$C_{13}H_{14}NO_3Na$] 254.2370, found 254.2367.

4.3.38. (*S*)-3-((*R*)-Hydroxy(4-fluorophenyl)methyl)-dihydro-2*H*-pyran-4(3*H*)-one 4e[43]

Yield 82%, *anti*/*syn* = 91:9, enantiomeric excess: 91% of *anti*- diastereomer and 34% of *syn*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; 1.0 mL/min, 20 °C, λ = 220 nm) t_R = 38.0 min (*anti*, major) and t_R = 31.2 min (*anti*, minor)). ^{1}H NMR(300 MHz, $CDCl_3$): δ = 7.31–7.28 (m, 2H), 7.06–7.02 (m, 2H), 4.86 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.15–4.10 (m, 1H), 3.80 (br, s, 1H), 3.79–3.73 (m, 1H), 3.65–3.60 (m, 1H), 3.35 (dd, *J* = 11.6, 9.2 Hz, 1H), 2.85–2.79 (m, 1H), 2.66–2.51 (m, 2H). HRMS (FAB): [M+Na] calcd for [$C_{12}H_{14}FO_3Na$] 247.2180, found 247.2183.

4.3.39. (*S*)-3-((*R*)-Hydroxy(4-chlorophenyl)methyl)-dihydro-2*H*-pyran-4(3*H*)-one 4f[43]

Yield 80%, *anti*/*syn* = 90:10, enantiomeric excess: 92% for the *anti*- diastereomer and 23% for the *syn*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; 1.0 mL/min, 20 °C, λ = 220 nm) t_R = 40.6 min (*anti*, major) and t_R = 31.4 min (*anti*, minor)). ^{1}H NMR(300 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 4.85 (d, *J* = 7.2 Hz, 1H), 4.16–4.10 (m, 1H), 3.78 (br s, 1H), 3.77–3.73 (m, 1H), 3.67–3.62 (m, 1H), 3.36 (t, *J* = 9.6 Hz, 1H), 2.84–2.79 (m, 1H), 2.66–2.50 (m, 2H). HRMS (FAB): [M+Na] calcd for [$C_{12}H_{14}ClO_3Na$] 263.6726, found 263.6726.

4.3.40. (*S*)-3-((*R*)-Hydroxy(phenyl)methyl)-tetrahydropyran-4-one 4g[43]

Yield 54%, *anti*/*syn* = 89:11, enantiomeric excess: 98% for the *anti*-diastereomer and 78% for the *syn*-diastereomer determined by HPLC (Dicael Chiralpak AD-H column; *i*-PrOH/Hexane = 10:90; 1.0 mL/min, 20 °C, λ = 220 nm) t_R = 31.7 min (*anti*, major) and t_R = 35.8 min (*anti*, minor). ^{1}H NMR(300 MHz, $CDCl_3$): δ 7.37–7.30 (m, 5H), 4.87 (dd, *J* = 8.8, 3.2 Hz, 1H), 4.10–4.07 (m, 1H), 3.80–3.72 (m, 2H), 3.62 (dd, *J* = 11.2, 5.6 Hz, 1H), 3.36 (dd, *J* = 11.2, 8.8 Hz, 1H), 2.87–2.82 (m, 1H), 2.64–2.51 (m, 2H). HRMS (FAB): [M+Na] calcd for [$C_{12}H_{15}O_3Na$] 229.2287, found 229.2283.

4.3.41. (3*R*,4*S*)-3,4-Dihydroxy-4-(4-nitrophenyl)butan-2-one 5a[41]

Yield 25%, *syn*/*anti* = 81:19, enantiomeric excess: 46% for the *syn*-diastereomer and 57% for the *anti*-diastereomer was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 80:20), 20 °C, λ = 254 nm, 0.8 mL/min; major t_R = 21.7 min(*syn*, major) and t_R = 16.2 min(*syn*, minor). ^{1}HNMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H, CH3), 2.68 (d, *J* = 8.1 Hz, 1H), 3.71 (d, *J* = 4.6 Hz, 1H), 4.40–4.42 (m, 1H), 5.20–5.22 (m, 1H), 7.60–7.63 (m, 2H), 8.24–8.27 (m, 2H). HRMS (FAB): [M+Na] calcd for [$C_{10}H_{11}NO_5Na$] 248.1878, found 248.1883.

4.3.42. 4-Hydroxyl-4-(4-nitrophenyl)-2-butanone 6a[37]

Yield 34%, enantiomeric excess: 41% ee determined by HPLC (Dicael Chiralpak OJ-H column; *i*-PrOH/Hexane = 10:90; 1.0 mL/min, 20 °C, λ = 220 nm) t_R = 21.0 min (major) and t_R = 35.2 min (minor)). 1HNMR (300 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 5.27 (t, *J* = 6.0 Hz, 1H), 3.69 (br, 1H), 2.88 (d, *J* = 6.0 Hz, 2H), 2.20 (s, 3H). HRMS (FAB): [M+Na] calcd for [$C_{10}H_{11}NO_4Na$] 232.1884, found 232.1890.

4.4. General procedure for the large-scale stoichiometric aldol reactions on water

To a mixture of catalyst **1a** (0.893 g, 4 mmol) and ketone (400 mmol) were added aromatic aldehyde (400 mmol) and water (200 mL) in a 500 mL round bottomed flask. The resulting mixture was stirred at room temperature. The stoichiometric reaction was monitored by TLC. It was then quenched with 100 mL of saturated NH_4Cl solution, extracted with EtOAc (3 × 150 mL), and dried over Na_2SO_4. Purification by flash chromatography afforded the corresponding pure aldol products **2b** (95.716 g), **2c** (94.719 g), **2g** (84.981 g), **2k** (95.716 g), **2b** (101.938 g), **2h** (81.161 g), **2r** (90.538 g), **2n** (63.727 g), **2u** (71.498 g), **2v** (67.592 g), **2s** (53.108 g), **3f** (80.885 g), **3g** (76.391 g).

4.5. Procedure for catalyst recovery

To a mixture of catalyst **1a** (0.447 g, 2 mmol) and cyclohexanone (200 mmol) were added 4-chlorobenzaldehyde (28.114 g, 200 mmol) and water (100 mL) in a 500 mL round bottomed flask. The mixture was stirred at room temperature as specified in Table 8. The reaction mixture was quenched with aqueous HCl (2 mmol, 6 mol/L) and then diluted with diethyl ether (200 mL) and the reaction mixture was stirred vigorously for 5 min. The reaction mixture was placed in an ethanol bath (−20 °C) for 1 h. The organic layer was concentrated in vacuo to afford the crude aldol product, which was purified by column chromatography (ethyl acetate/hexane = 1:10 to 1:5). Since catalyst **1a** exists in the acidic aqueous layer, an equivalent amount of triethylamine (Et_3N) was added, and the resulting white suspension was stirred at room temperature for 10 min after the complete addition, and then filtered by vacuum. The white crystals **1a** can be recycled to catalyze subsequent aldol reaction cycles without adding any new catalyst.

Acknowledgement

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

References

1. Mahrwald, R. Modern Aldol Reactions, Vols. 1 and 2, Wiley-VCH, Weinheim, 2004.
2. Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis:From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2005.
3. Dalko, P. I. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, 2007.
4. List, B. *Asymmetric Organocatalysis*; Springer: Berlin, 2010.
5. Mukherjee, S.-J.; Yang, J.-W.; Hoffman, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569.
6. Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416–5470.
7. Vishnumaya, M. R.; Singh, V. K. *Org. Lett.* **2007**, *9*, 2593–2595.
8. Vishnumaya, M. R.; Singh, V. K. *J. Org. Chem.* **2009**, *74*, 4289–4297.
9. Gandhi, S.; Singh, V. K. *J. Org. Chem.* **2008**, *73*, 9411–9416.
10. Jia, Y.-N.; Wu, F.-C.; Ma, X.; Zhu, G.-J.; Da, C.-S. *Tetrahedron Lett.* **2009**, *50*, 3059–3062.
11. Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285–9289.

12. Zhao, J.-F.; He, L.; Jiang, J.; Tang, Z.; Cun, L.-F.; Gong, L.-Z. *Tetrahedron Lett.* **2008**, *49*, 3372–3375.
13. Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Meo, P. L.; Noto, R. *Eur. J. Org. Chem.* **2010**, 5696–5704.
14. Jiang, M.; Zhu, S.-F.; Yang, Y.; Gong, L.-Z.; Zhou, X.-G.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2006**, *17*, 384–387.
15. Krattiger, P.; Kovasy, R.; Revell, J. D.; Ivan, S.; Wennemers, H. *Org. Lett.* **2005**, *7*, 1101–1103.
16. Kano, T.; Tokuda, O.; Maruoka, K. *Tetrahedron Lett.* **2006**, *47*, 7423–7426.
17. Kofoed, J.; Darbre, T.; Reymond, J.-L. *Org. Biomol. Chem.* **2006**, *4*, 3268–3281.
18. Gruttadauria, M.; Giacalone, F.; Noto, R. *Adv. Synth. Catal.* **2009**, *351*, 33–57.
19. Paradowska, J.; Stodulski, M.; Mlynarski, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 4288–4297.
20. Raj, M.; Singh, V. K. *Chem. Commun.* **2009**, 6687–6703.
21. Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 8100–8102.
22. Blackmond, D. G.; Armstrong, A.; Coombe, V.; Wells, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3798–3800.
23. Guillena, G.; Hita, M. C.; Nájera, C.; Viózquez, S. F. *J. Org. Chem.* **2008**, *73*, 5933–5943.
24. Huang, J.; Zhang, X.; Armstrong, D. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 9073–9077.
25. Pihko, P. M.; Laurikainen, K. M.; Usano, A.; Nyberg, A. I.; Kaavi, J. A. *Tetrahedron* **2006**, *62*, 317–328.
26. Tucker, J. L. *Org. Process Res. Dev.* **2006**, *10*, 315–319.
27. Eissen, M.; Metzger, J. O.; Schmidt, E.; Schneidewind, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 414–436.
28. Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686–694.
29. Hailes, H. C. *Org. Process Res. Dev.* **2007**, *11*, 114–120.
30. Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6630–6666.
31. Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997–2011.
32. Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2007**, *129*, 288–289.
33. Wu, X.-Y.; Jiang, Z.-Q.; Shen, H.-M.; Lu, Y.-X. *Adv. Synth. Catal.* **2007**, *349*, 812–816.
34. Wu, C. L.; Fu, X. K.; Ma, X. B.; Li, S. *Tetrahedron Lett.* **2010**, *51*, 5775–5777.
35. Wu, C. L.; Fu, X. K.; Ma, X. B.; Li, S. *Tetrahedron: Asymmetry* **2010**, *21*, 2465–2470.
36. Wu, C. L.; Fu, X. K.; Li, S. *Eur. J. Org. Chem.* **2011**, 1291–1299.
37. Wu, C. L.; Fu, X. K.; Li, S. *Tetrahedron* **2011**, *67*, 4283–4290.
38. Kristensen, T. E.; Hansen, F. K.; Hansen, T. *Eur. J. Org. Chem.* **2009**, 387–395.
39. Kristensen, T. E.; Vestli, K.; Fredriksen, K. A.; Hansen, F. K.; Hansen, T. *Org. Lett.* **2009**, *11*, 2968–2971.
40. Kristensen, T. E.; Vestli, K.; Jakobsen, M. G.; Hansen, F. K.; Hansen, T. *J. Org. Chem.* **2010**, *75*, 1620–1629.
41. Wu, C. L.; Fu, X. K.; Li, S. *Tetrahedron: Asymmetry* **2011**, *22*, 1063–1073.
42. Giacalone, F.; Gruttadauria, M.; Meo, P. L.; Riela, S.; Noto, R. *Adv. Synth. Catal.* **2008**, *350*, 2747–2760.
43. Chen, J. R.; Li, X. Y.; Xing, X. N.; Xiao, W. J. *J. Org. Chem.* **2006**, *71*, 8198–8202.