Tetrahedron 64 (2008) 9585–9591

Contents lists available at ScienceDirect

Tetrahedron

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

Proline-based dipeptides with two amide units as organocatalyst for the asymmetric aldol reaction of cyclohexanone with aldehydes

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ARTICLE INFO

Article history:
Received 22 December 2007
Received in revised form 13 July 2008
Accepted 15 July 2008
Available online 18 July 2008

Keywords:
Dipeptide
Aldol reaction
Organocatalyst
Enantioselectivity

ABSTRACT

A series of proline-based dipeptide organocatalysts with two amide units (**1**–**16**) have been developed and evaluated in the direct catalytic asymmetric aldol reactions of aldehydes with cyclohexanone. These catalysts showed good solubility in organic solvents compared with their corresponding carboxyl terminal dipeptides. The robust amide bond formation allowed structural modifications and fine tuning of catalyst properties by varying the stereo and electronic effects of the terminal amide to affect the ability of hydrogen bonding formation between the catalysts and the substrates. The reactions proceeded smoothly in high yields (up to 99%), enantioselectivities (up to 98% ee) and anti-diastereoselectivities (up to 99:1) in the presence of bifunctional organocatalyst **4** under the optimal reaction conditions.

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1. Introduction

The aldol reaction is one of the most important carbon–carbon bond-forming reactions in modern organic synthesis. Direct aldol reaction does not require pre-formed enolate, and therefore, it is more convenient to carry out and is highly atomically economic. A lot of efforts have been devoted to the development of this reaction, and a great success has been achieved in this field.[1] Shibasaki has reported the first example of a direct asymmetric aldol reaction catalyzed by heterobimetallic complexes.[2] Since List and Barbas discovered that L-proline may be used as the catalyst for the enantioselective direct aldol reaction,[3,9g] many groups have developed proline,[4] proline-derivatives including L-prolinamides,[5] proline *N*-sulfonyl amides,[6] substituted L-prolines,[7] diamines,[8] L-proline-based small peptides,[9] and other organocatalysts[10] for the direct asymmetric aldol reaction. Among them, N-terminal prolyl dipeptides are effective for the direct catalytic asymmetric aldol reaction.[9c,g] However, those dipeptides have low solubility in most of organic solvents and hence highly polar solvents such as DMSO and DMF are often used in the organocatalytic reactions. Such high-boiling point solvents are difficult to remove. Tomasini and Gong groups had tried to use N-terminal prolyl dipeptides esters to catalyze the aldol reaction.[9d,f] Those soluble dipeptide esters gave moderate results due to the decrease of the stereoselectivity control ability arising from the weak carboxyl hydrogen bonding between the catalysts and the substrate in the transition state. Xiao et al. have shown that L-prolinamide derivatives are able to efficiently catalyze intermolecular cyclohexanone aldolisation with high enantioselectivity.[5b,g] However, those catalysts were prepared from L-proline and unnatural enantiopure (*R*,*R*)- or (*S*,*S*)-1,2-diaminocyclohexane. Inspired by these observations, we designed a new series of proline-based dipeptides as chiral organic catalysts with two amide units. These catalysts may have the following merits: (1) the solubility of the dipeptides in organic solvents could be significantly improved by converting carboxyl into the corresponding amide; (2) the robust amide bond formation allowed structural modifications, therefore, fine tuning of catalyst properties by varying the stereo and electronic effects of the terminal amide to affect the ability of hydrogen bonding formation between the catalysts and substrates. Intrigued by the potential structural diversity and motivated by our interest in stereoselective organocatalysis, herein, we report a series of proline-based dipeptides **1**–**16** (Fig. 1) with two amide units as tunable and bifunctional organocatalysts in attaining the direct asymmetric aldol reaction with high efficiency.

2. Results and discussion

As shown in Figure 1, a variety of proline-based dipeptides **1**–**16** were prepared from commercially available proline, the corresponding amino acids and amine derivatives. The catalytic activity of these new catalysts was then evaluated in the direct asymmetric aldol reaction of 4-nitrobenzaldehyde with cyclohexanone. The results are summarized in Table 1. Preliminary tests showed that

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doi:10.1016/j.tet.2008.07.051

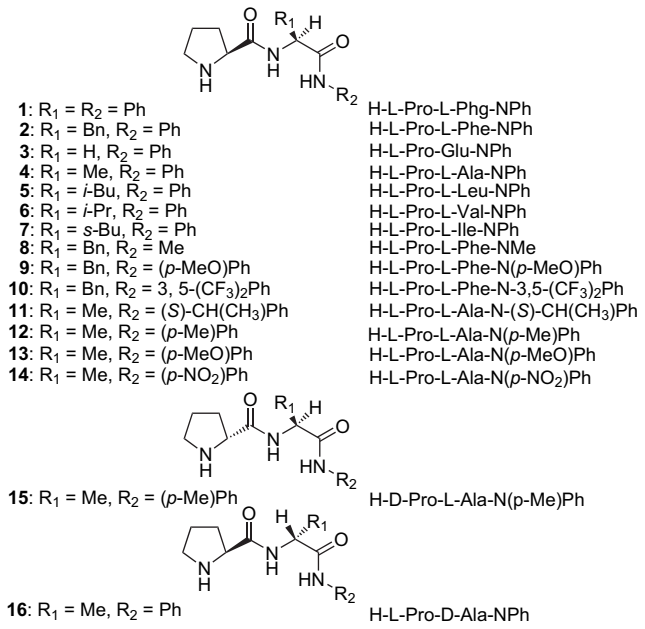
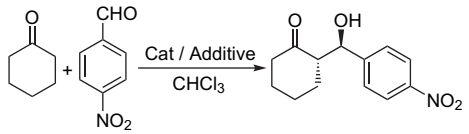


Figure 1. Proline-based dipeptides **1**–**16**.

the presence of a BrΦnsted acid enhanced both reactivity and selectivity using **4** as the catalyst (Table 1, entries 4–7). The same phenomenon was also observed in Xiao's catalytic system.[5b] Without the BrΦnsted acid additive, both reactivity and selectivity decreased sharply, only 35% yield and 60% ee were obtained after 24 h (Table 1, entry 4). The ratio of catalyst to additive was then optimized and we found that the best ratio of acid additive to catalyst is 1:1 (Table 1, entry 6). In addition, when the catalyst load was reduced from 20% to 10%, reactivity, enantioselectivity, and diastereoselectivity all decreased dramatically (Table 1, entries 6, 8). Then, we used 20 mol % of catalysts and 20 mol % of AcOH to test the catalytic activity (Table 1, entries 1–3, 11–22). We also optimized the temperature using **4** as the catalyst and found that reaction ran at −20 °C afforded the product in high yield and better enantioselectivity (Table 1, entries 6, 9, 10). At −10 °C, the reaction was complete quantitatively in >99% yield, but the ee of the major product was 87% (Table 1, entry 9). When lowering the temperature further to −30 °C, 88% ee was obtained, but the yield dropped from 99% to 38.4% (Table 1, entry 10). We then tested other catalysts in the reaction. The catalytic activities and steroselectivities were significantly influenced by both R_1 and R_2 in catalysts **1**–**16**. When R_2 was phenyl and R_1 changed to benzyl from phenyl, the ee of the product slightly increased from 87% up to 92% (Table 1, entries 1, 2). The best enantioselectivity (93% ee) was obtained when R_1 was methyl (Table 1, entry 6). With further changes of R_1 into *iso*-butyl, *iso*-propyl, and *sec*-butyl, respectively, the ee of the products varied from 79% to 90% (Table 1, entries 11–13). Particularly, when R_1 was hydrogen, the catalytic activity was very low. This may be caused by its poor solubility in the reaction system (Table 1, entry 3). We also investigated the influence of R_2 on the reaction. When R_1 was benzyl, R_2 was changed from phenyl to methyl, both yields and ee of the products decreased and from 99% yield, 92% ee down to 77% yield, 89% ee (Table 1, entries 2, 14). Electron-withdrawing or electron-donating substitutes on the phenyl showed slight influence on the reaction (Table 1, entries 2, 15, 16). When R_1 was methyl, the similar electronic and steric effects of R_2 were observed as when R_1 was benzyl (Table 1, entries 6, 17–20). With electron-withdrawing *p*-nitro on the phenyl, the reactivity was reduced dramatically to yield only 60% of the product (Table 1, entry 20). With *p*-methoxyl on the phenyl, the reactivity was also reduced and the yield was 72% (Table 1, entry 19). The chirality of R_2 had slight influence on the reactivity and enantioselectivity (Table 1, entry 17). Among the catalytic systems examined, the best catalyst was **4**, which gave good selectivity (*anti*/*syn* 91/9; 93% ee) and 98% yield (Table 1, entry 6) under the same conditions. The product with the opposite configuration was obtained when L-proline moiety in the catalyst was replaced by D-proline (Table 1, entries 18, 21). On the contrary, when L-alanine was changed into D-alanine, the configuration of the product didn't vary. Only the ee value decreased slightly from 92% to 89% (Table 1, entries 6, 22). This indicated that the stereoselectivity was controlled by the proline part of the dipeptide. When proline was used as catalyst in the same conditions, only 11.2% yield of the product was obtained with 92% ee (Table 1, entry 23).

A series of solvents were also screened, and the results are summarized in Table 2. Good yields and enantiomeric excesses were obtained in moderate polar aprotic solvents such as CH_2Cl_2, THF, Et_2O, $CHCl_3$, $PhCH_3$ (Table 2, entries 1–3, 7, 8), and the best result was achieved in $CHCl_3$ (Table 2, entry 7). On the other hand,

Table 1
Direct asymmetric aldol reaction of 4-nitrobenzaldehyde with cyclohexanone catalyzed by prolinamide derivatives **1**–**16**



Entry	Cat.	Additive	*T* (°C)	Time (h)	Yield[a] (%)	*anti*/*syn*[b]	ee[c] (%)
1	**1** (20%)	AcOH (20%)	−20	24	>99	91/9	87
2	**2** (20%)	AcOH (20%)	−20	24	>99	85/15	92
3	**3** (20%)	AcOH (20%)	−20	24	<10	—	—
4	**4** (20%)	None	−20	24	35.2	82/18	60
5	**4** (20%)	AcOH (10%)	−20	24	75.2	79/21	85
6	**4** (20%)	AcOH (20%)	−20	24	98	98/2	93
7	**4** (20%)	AcOH (40%)	−20	24	>99	88/12	92
8	**4** (10%)	AcOH (10%)	−20	48	64	88/12	88
9	**4** (20%)	AcOH (20%)	−10	24	>99	84/16	86
10	**4** (20%)	AcOH (20%)	−30	24	38.4	89/11	88
11	**5** (20%)	AcOH (20%)	−20	24	98	78/22	83
12	**6** (20%)	AcOH (20%)	−20	24	77	81/19	79
13	**7** (20%)	AcOH (20%)	−20	24	97	92/8	90
14	**8** (20%)	AcOH (20%)	−20	24	77	97/3	89
15	**9** (20%)	AcOH (20%)	−20	24	82	71/29	92
16	**10** (20%)	AcOH (20%)	−20	24	93	93/7	90
17	**11** (20%)	AcOH (20%)	−20	24	82	88/12	90
18	**12** (20%)	AcOH (20%)	−20	24	96	92/8	92
19	**13** (20%)	AcOH (20%)	−20	24	72	87/13	89
20	**14** (20%)	AcOH (20%)	−20	24	60	87/13	89
21	**15** (20%)	AcOH (20%)	−20	24	99	98/2	−89
22	**16** (20%)	AcOH (20%)	−20	24	92	92/8	89
23	Pro (20%)	AcOH (20%)	−20	24	11.2	93/7	92

[a] Isolated yield.
[b] Determined by ^{1}H NMR of the crude product.
[c] Determined by chiral HPLC.

Table 2
The effect of solvents on the direct aldol reaction of 4-nitrobenzaldehyde with cyclohexanone by **4** (20 mol %) and AcOH (20 mol %)

Entry	Solvent	Yield[a] (%)	*anti*/*syn*[b]	ee[c] (%)
1	CH_2Cl_2	85	88/12	90
2	THF	77	90/10	82
3	Et_2O	75	87/13	86
4	DMF	44	96/4	70
5	CH_3CN	38	79/21	75
6	MeOH	36	73/27	83
7	$CHCl_3$	98	98/2	93
8	Tol	87	81/19	83

[a] Isolated yield.
[b] Determined by ^{1}H NMR of the crude product.
[c] Determined by chiral HPLC.

reactions in more polar solvents such as DMF, CH_3CN, and protic MeOH led to a decrease both in yields and in enantioselectivities (Table 2, entries 4–6).

Pyrrolidine-based organocatalysts catalyze the aldol reaction is presumed to proceed via enamine intermediate.[4y] The overall rate of the reaction would be improved by any factors, which could promote the enamine formation.[4x,8a,d,e,11] Pihko[4x] and Gryko[10r] have thoroughly studied the influence of additives on the reactions and found that an appropriate acid could effectively enhance the activity of the catalysts. This influence is susceptible to subtle changes in the catalyst structures and reaction conditions. In order to find proper acid additive to match our catalyst, we have studied the influence of acid additive on the reactivity (Table 3). When stronger acids were used, the reaction was almost completely suppressed (Table 3, entries 1, 4, 8). This is somewhat same as what was observed in Gryko's L-prolinethioamide catalyst system. Benzoic acid, substituted benzoic acid, and acetic acid gave similar good yields and enantioselectivities (Table 3, entries 3, 5, 11, 12). Acetic acid gave the optimal performance, where all the yield, chemoselectivity, and enantioselectivity were the most satisfactory (Table 3, entry 12). The same enantioselectivity was observed when 2-methylbenzoic acid was used. Use of H_2O and AcOH in the ratio of 1:1 as additive only slightly decreased the yield and selectivity (Table 3, entry 2 vs entry 12).

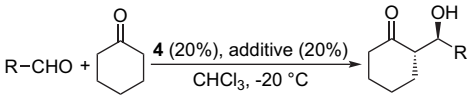
Table 3
The effect of additives on the direct aldol reaction of 4-nitrobenzaldehyde with cyclohexanone by **4** (20 mol %) in chloroform

Entry	Additive (20%)	Yield[a] (%)	*anti*/*syn*[b]	ee[c] (%)
1	CF_3COOH	Trace	—	—
2	AcOH, H_2O	94	92/8	92
3	PhCOOH	98	91/9	92
4	PTSA·H_2O	<10	—	88
5	2-FPhCOOH	95	91/9	92
6	*n*-Octylic acid	79	86/14	87
7	$ClCH_2COOH$	79	91/9	90
8	2,4,6-Trinitrophenol	<10	—	95
9	4-Nitrophenol	39	84/16	71
10	Phenol	38	92/8	67
11	2-MePhCOOH	87	87/13	93
12	AcOH	98	98/2	93

[a] Isolated yield.
[b] Determined by ^1H NMR of the crude product.
[c] Determined by chiral HPLC.

With the optimal conditions in hand, we investigated a variety of aromatic aldehydes and the results are summarized in Table 4. High yields and enantioselectivities (up to 98% ee) were obtained for aromatic aldehydes with electron-withdrawing group on the benzene ring (Table 4, entries 1–8, 12–17). The additive 2-MePhCOOH (pK_a=4.36) is superior to AcOH (pK_a=4.76) for most substrates and better yield or enantioselectivity (Table 4, entries 5–8, 16–17) was achieved. Besides the slight difference in their pK_a value, the counter ion of BrΦnsted acid may also cause steric effect on the reaction and different enantioselectivity was observed when they were used independently to co-catalyze the same substrate. The reaction of benzaldehyde proceeded very slowly at −20 °C and only 27% yield was obtained with 90% ee after 24 h (Table 4, entry 9), whereas good yield (98%) and enantioselectivity (84% ee) were

Table 4
Scope of the aldehydes for the direct aldol reaction with cyclohexanone under optimal conditions



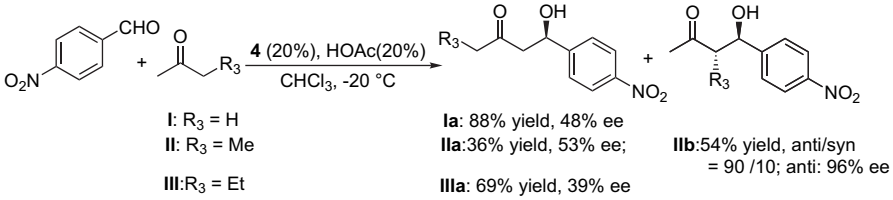
Entry	R	Additive[a]	Yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	4-$NO_2C_6H_4$	A	98	98/2	93
2	4-$NO_2C_6H_4$	B	87	87/13	93
3	3-$NO_2C_6H_4$	A	99	82/18	94
4	3-$NO_2C_6H_4$	B	94	87/13	96
5	2-$NO_2C_6H_4$	A	60	82/18	94
6	2-$NO_2C_6H_4$	B	85	90/10	95
7	4-BrC_6H_4	A	75	91/9	93
8	4-BrC_6H_4	B	75	90/10	98
9	Ph	A	27	81/19	90
10	Ph	B	29	94/6	52
11[e]	Ph	B	98	81/19	87
12	2,4-$Cl_2C_6H_4$	A	93	99/1	97
13	2,4-$Cl_2C_6H_4$	B	93	99/1	96
14	2-ClC_6H_4	A	61	94/6	94
15	2-ClC_6H_4	B	81	98/2	93
16	2-BrC_6H_4	A	73	95/5	94
17	2-BrC_6H_4	B	86	91/9	94

[a] A=AcOH, B=2-MePhCOOH.
[b] Isolated yield.
[c] Determined by ^1H NMR of the crude product.
[d] Determined by chiral HPLC.
[e] The reaction was carried out at −10 °C.

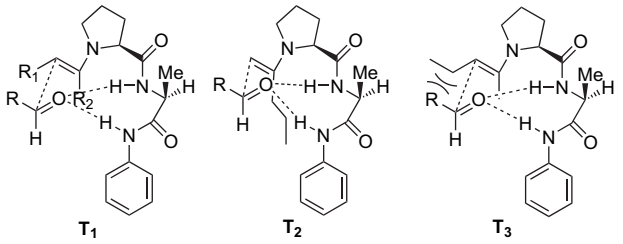
obtained when this reaction was carried out at −10 °C (Table 4, entry 11). This is possibly due to its electron-rich character and hence has showed lower reactivity.

The reactions of 4-nitrobenzaldehyde with acetone (**I**), butanone (**II**), and 2-pentanone (**III**) using **4** as catalyst were also investigated. As shown in Scheme 1, acetone gave the desired product in 88% yield with 48% ee. The reaction with butanone also worked well and preferentially occurred at the C-3 position of butanone to give the desired product (**IIb**) (54% yield) in good diastereoselectivity (90:10) and enantioselectivity (96% ee), and the minor product (**IIa**) (36% yield) with only 53% ee. On the contrary, the reaction of 2-heptanone only occurred at its C-1 position gave the corresponding product (**IIIa**) with low enantioselectivity (20% ee) in 69% yield.

According to the stereochemical outcome in the above direct aldol reactions catalyzed by **4**, we propose that the proline-based dipeptides could catalyze the direct asymmetric aldol reactions between ketones and aldehydes via the plausible six-membered chair-like transition state $\mathbf{T_1}$ (Scheme 2).[5f,10k] The aldehyde could be activated by hydrogen bonding with the two NH of the catalyst in a manner such that C–C bond formation could take place from its *re* face. When 2-heptanone was used as the substrate, the reaction only took place at its C-1 position. This may be explained by transition states $\mathbf{T_2}$ and $\mathbf{T_3}$. If the reaction took place at its C-3 position, the strong-nonbonding interaction between R group and ethyl group would have had been disfavored as shown in transition state $\mathbf{T_3}$. When butanone was used as the substrate, the nonbonding interaction between R group and methyl group was weaker, so two products **IIa** and **IIb** were obtained.



Scheme 1.



Scheme 2.

3. Conclusion

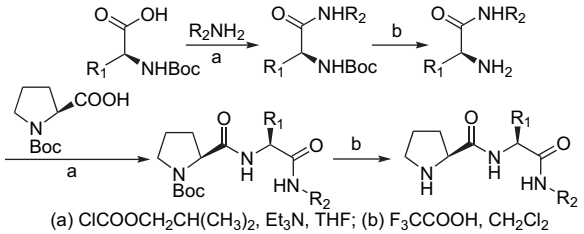
We have developed a series of new proline-based dipeptides catalysts with two amide units for asymmetric direct aldol reaction. High yields (up to 99%), enantioselectivities (up to 98% ee) and anti-diastereoselectivities (up to 99:1) were obtained using this catalytic system. Based on the L-proline catalysis model, we believe that the two amide units play a key role in stabilizing the transition state by forming hydrogen bonds between the catalysts and the aldehydes, and these two tunable functionalities not only activate the aldol acceptor but also favor one-face of the acceptor to the attack of the enamine. The extension of the catalysts to other organic transformations is currently being investigated in our laboratory and will be reported in due course.

4. Experimental

4.1. General

Unless otherwise indicated, all reagents were purchased from commercial suppliers and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates visualized with UV light and/or by staining with ethanol phosphomolybdic acid (PMA). Flash column chromatography was performed on silica gel H (10–40 μm). NMR spectra were recorded on 300 MHz instruments. Chemical shifts (δ) are given in parts per million relative to TMS, coupling constants (J) in hertz. IR spectra were recorded on a Perkin Elmer-GX spectrometer. Melting points were determined on an X-6 digital melting-point apparatus and were uncorrected. Optical rotations were measured on a Perkin Elmer 341 Polarimeter at λ=589 nm. Analytical high performance liquid chromatography (HPLC) was carried out on WATERS 510 instrument (2487 Dual λ Absorbance Detector and 515 HPLC Pump) using chiral column.

4.2. General procedure for the synthesis of catalysts[12]



4.2.1. H–L-Pro–L-Ala–NPh (*4*)

N-Boc-L-alanine (1.1 g, 5.8 mmol) and TEA (1.2 mL, 9.1 mmol) were dissolved in dry THF (30 mL). The solution was cooled down to −15 °C. Ethylchloroformate (0.88 mL, 7.0 mmol) was added dropwise and the resulting mixture was stirred for 20 min. Aniline (0.56 g, 6 mmol) was added and the resulting mixture was stirred for another 1 h, then the reaction mixture was warmed to room temperature slowly and stirred overnight. $NaHCO_3$ solution (5%, 10 mL) was added and the resulting mixture was stirred for 30 min. The aqueous solution was extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with 1.0 M hydrochloric acid (20 mL), brine (30 mL), and dried over Na_2SO_4. The solvent was evaporated to give a residue (white solid, 1.2 g). The solid was dissolved in CH_2Cl_2 (2 mL) and TFA (2 mL) was added. The mixture was stirred overnight at room temperature. Then diluted with ethyl acetate (100 mL) and washed with 10% sodium hydroxide solution (20 mL). The organic layer was washed with brine (20 mL) and dried over Na_2SO_4. The solvent was evaporated to give *L-Ala–NHPh* (0.80 g, 4.8 mmol).

N-Boc-L-proline (0.86 g, 4.0 mmol) and TEA (0.70 mL, 5.0 mmol) were dissolved in dry THF (30 mL). The solution was cooled down to −15 °C. Ethylchloroformate (0.60 mL, 4.8 mmol) was added dropwise and the reaction mixture was stirred for 20 min, *L-Ala–NHPh* (0.80 g, 4.8 mmol) was added and the reaction mixture was stirred for another 1 h, then slowly warmed to room temperature and stirred overnight. $NaHCO_3$ solution (5%, 10 mL) was added and the mixture was stirred for 30 min. The aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with 1.0 M hydrochloric acid (20 mL), brine (30 mL), and dried over Na_2SO_4. The solvent was evaporated to give a residue and flash column chromatography on silica afforded *Boc-4* as white solid. The solid was dissolved in CH_2Cl_2 (2 mL) and TFA (2 mL) was added. The mixture was stirred overnight at room temperature. Then diluted with ethyl acetate (100 mL), the mixture was washed with 10% sodium hydroxide solution (20 mL). The organic layer was washed with brine (20 mL) and dried over Na_2SO_4. The solvent was evaporated to give **4** (1.0 g) as a white solid; yield (97%). $[\alpha]_D^{rt}$ −169.2 (*c* 0.52, $CHCl_3$); mp 172–173 °C; IR (KBr): ν=3309, 3269, 3205, 3142, 3101, 2979, 2871, 1697, 1647, 1613, 1556, 1515, 1447, 1375, 1322, 1251, 1215, 763, 733, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ=9.15 (s, 1H), 8.20 (d, J=7.41 Hz, 1H), 7.56 (d, J=7.80 Hz, 2H), 7.28 (t, J=7.11 Hz, 2H), 7.06 (t, J=7.35 Hz, 1H), 4.60–4.67 (m, 1H), 3.75–3.80 (q, 1H), 2.99–3.07 (m, 1H), 2.88–2.96 (m, 1H), 2.12–2.22 (m, 1H), 2.05 (s, 1H), 1.90–1.96 (m, 1H), 1.68–1.78 (m, 2H), 1.46 (d, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 176.2, 170.2, 138.2, 128.8, 123.9, 119.7, 60.3, 49.2, 47.2, 30.6, 26.2, 16.9 ppm. MS (ESI): 261.71 (M^+).

4.2.2. H–L-Pro–L-Phg–NPh (*1*)

White solid; $[\alpha]_D^{rt}$ +54.3 (*c* 0.49, $CHCl_3$); mp 176–177 °C; IR (KBr): ν=3283, 3206, 3141, 3092, 2970, 2871, 1693, 1652, 1603, 1551, 1500, 1443, 1369, 1330, 1247, 758, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ=9.35 (s, 1H), 9.06 (d, J=8.0 Hz, 1H), 7.47–7.58 (m, 4H), 7.22–7.33 (m, 5H), 7.04 (t, J=7.3 Hz, 1H), 6.01 (d, J=8.12 Hz, 1H), 3.81–3.85 (q, 1H), 2.94–3.09 (m, 2H), 2.09–2.19 (m, 2H), 1.89–1.99 (m, 1H), 1.67–1.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 175.5, 168.5, 138.2, 137.9, 128.9, 128.8, 128.1, 127.0, 124.1, 119.7, 60.5, 57.2, 47.3, 30.7, 26.2 ppm. MS (ESI): 323.85 (M^+).

4.2.3. H–L-Pro–L-Phe–NPh (*2*)

White solid; $[\alpha]_D^{rt}$ −57.4 (*c* 1.0, $CHCl_3$); mp 141.7–143.5 °C; IR (KBr): ν=3443, 3315, 3063, 2970, 1690, 1648, 1534, 1499, 1445, 1368, 1313, 1204, 1135, 750, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ=8.90 (s, 1H), 8.29 (d, J=7.83 Hz, 1H), 7.47 (d, J=7.88 Hz, 1H), 7.21–7.49 (m, 7H), 7.06 (t, J=7.35 Hz, 1H), 4.75–4.82 (m, 1H), 3.70–3.74 (q, 1H), 3.25–3.32 (m, 1H), 3.02–3.10 (m, 1H), 2.87–2.93 (m, 1H), 2.65–2.69 (m, 1H), 2.16 (s, 1H), 1.97–2.04 (m, 1H), 1.63–1.73 (m, 1H), 1.50–1.60 (m, 1H), 1.27–1.41 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 176.3, 169.2, 137.8, 136.8, 129.2, 128.8, 128.5, 126.8, 124.1, 119.8, 60.1, 54.7, 47.0, 37.0, 30.5, 25.7 ppm. MS (ESI): 337.87 (M^+).

*4.2.4. H–L-Pro–Glu–NPh (**3**)*

White solid; $[\alpha]_D^{rt}$ −39.8 (*c* 0.5, MeOH); mp 99–103 °C; IR (KBr): *ν*=3348, 3318, 3268, 3075, 2939, 2869, 1693, 1636, 1601, 1560, 1521, 1500, 1444, 1423, 1372, 1310, 1260, 1213, 1100, 750, 689 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz): *δ*=7.54 (d, *J*=7.88 Hz, 2H), 7.30 (t, *J*=7.68 Hz, 2H), 7.08 (t, *J*=7.37 Hz, 1H), 4.90 (s, 3H), 4.03 (d, *J*=3.57 Hz, 2H), 3.72–3.76 (m, 1H), 2.90–3.04 (m, 2H), 2.09–2.21 (m, 1H), 1.71–1.88 (m, 3H); ^{13}C NMR (CD_3OD, 75.5 MHz): 178.0, 169.4, 139.5, 129.8, 125.2, 121.1, 61.5, 47.9, 43.6, 31.9, 27.0 ppm. MS (ESI): 247.68 (M^+).

*4.2.5. H–L-Pro–L-Leu–NPh (**5**)*

White solid; $[\alpha]_D^{rt}$ −70.2 (*c* 1, MeOH); mp 92.0–93.5 °C; IR (KBr): *ν*=3279, 3139, 3084, 2960, 2870, 1694, 1648, 1603, 1544, 1523, 1502, 1442, 1313, 1251, 1107, 756, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ*=9.13 (s, 1H), 8.15 (d, *J*=7.91 Hz, 1H), 7.53 (d, *J*=7.91 Hz, 2H), 7.26 (t, *J*=6.88 Hz, 2H), 7.05 (t, *J*=7.34 Hz, 1H), 4.57–4.60 (m, 1H), 3.75–3.80 (m, 1H), 2.98–3.06 (m, 1H), 2.86–2.94 (m, 1H), 2.09–2.22 (m, 1H), 2.04 (s, 1H), 1.62–1.96 (m, 6H), 0.97 (d, *J*=6.14 Hz, 3H), 0.92 (d, *J*=6.25 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 176.3, 170.1, 138.1, 128.7, 123.9, 119.7, 60.2, 51.9, 47.2, 39.7, 30.7, 26.2, 24.9, 22.9, 21.9 ppm. MS (ESI): 303.83 (M^+).

*4.2.6. H–L-Pro–L-Val–NPh (**6**)*

White solid; $[\alpha]_D^{rt}$ −64.6 (*c* 0.5, MeOH); mp 210.9–212.7 °C; IR (KBr): *ν*=3278, 3140, 2959, 2870, 1694, 1648, 1603, 1546, 1523, 1503, 1442, 1312, 1251, 1107, 756, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ*=8.90 (s, 1H), 8.38 (d, *J*=8.85 Hz, 1H), 7.57 (d, *J*=7.80 Hz, 2H), 7.28 (t, *J*=7.65 Hz, 2H), 7.07 (t, *J*=7.33 Hz, 1H), 4.39–4.43 (br, 1H), 3.80 (dd, *J*=9.15 Hz, 4.89 Hz, 1H), 2.94–3.04 (m, 2H), 2.13–2.29 (m, 3H), 1.95–1.99 (m, 1H), 1.71–1.76 (m, 2H), 0.99–1.04 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 175.9, 169.7, 138.0, 128.8, 124.1, 119.9, 60.4, 59.1, 47.3, 30.9, 30.3, 26.1, 19.5, 18.2 ppm. MS (ESI): 289.78 (M^+).

*4.2.7. H–L-Pro–L-Ile–NPh (**7**)*

White solid; $[\alpha]_D^{rt}$ −108.8 (*c* 0.48, $CHCl_3$); mp 154–155 °C; IR (KBr): *ν*=3305, 3216, 2962, 2856, 1645, 1602, 1541, 1445, 1377, 1197, 750, 716 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ*=9.29 (s, 1H), 8.40 (d, *J*=9.12 Hz, 1H), 7.58 (d, *J*=7.89 Hz, 2H), 7.26 (t, *J*=7.65 Hz, 2H), 7.05 (t, *J*=7.35 Hz, 1H), 4.54 (t, *J*=8.43 Hz, 1H), 3.75–3.80 (q, 1H), 2.92–3.01 (m, 2H), 2.29 (s, 1H), 2.11–2.18 (m, 1H), 1.90–2.04 (m, 2H), 1.67–1.76 (m, 2H), 1.52–1.63 (m, 1H), 1.07–1.20 (m, 1H), 1.00 (d, *J*=6.7 Hz, 3H), 0.91 (t, *J*=7.36 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 175.7, 170.0, 138.1, 128.7, 123.9, 119.9, 60.3, 58.0, 47.2, 36.9, 30.9, 26.1, 24.8, 15.6, 11.1 ppm. MS (ESI): 303.86 (M^+).

*4.2.8. H–L-Pro–L-Phe–NMe (**8**)*

White solid; $[\alpha]_D^{rt}$ −77.1 (*c* 0.55, $CHCl_3$); mp 148–149 °C; IR (KBr): *ν*=3282, 3099, 3028, 2961, 2909, 1643, 1596, 1501, 1414, 1328, 1162, 1099, 747, 713 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ*=8.10 (d, *J*=8.04 Hz, 1H), 7.18–7.30 (m, 5H), 6.33 (s, 1H), 4.54–4.57 (m, 1H), 3.64–3.69 (q, 1H), 3.15–3.22 (q, 1H), 2.87–3.04 (m, 2H), 2.65–2.74 (m, 4H), 1.91–1.99 (m, 2H), 1.53–1.67 (m, 2H), 1.33–1.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 175.8, 171.6, 137.0, 129.1, 128.4, 126.8, 60.2, 53.8, 47.1, 37.5, 30.5, 26.1, 25.8 ppm. MS (ESI): 275.74 (M^+).

*4.2.9. H–L-Pro–L-Phe–N(p-MeO)Ph (**9**)*

White solid; $[\alpha]_D^{rt}$ −52.2 (*c* 0.46, $CHCl_3$); mp 100–101 °C; IR (KBr): *ν*=3286, 3063, 2957, 1659, 1609, 1553, 1511, 1410, 1241, 1174, 1109, 1032, 830, 742, 700, 653 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ*=8.64 (s, 1H), 8.27 (d, *J*=7.83 Hz, 1H), 7.36 (d, *J*=8.82 Hz, 2H), 7.21–7.29 (m, 5H), 6.80 (d, *J*=8.84 Hz, 2H), 4.71–4.78 (q, 1H), 3.77 (s, 3H), 3.68–3.73 (m, 1H), 3.24–3.30 (m, 1H), 3.02–3.10 (m, 1H), 2.87–2.95 (m, 1H), 2.63–2.70 (m, 1H), 1.94–2.04 (m, 2H), 1.62–1.73 (m, 1H), 1.52–1.60 (m, 1H), 1.30–1.39 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 176.3, 168.9, 156.2, 136.9, 130.9, 129.2, 128.5, 126.8, 121.5, 113.9, 60.1, 55.4, 54.6, 47.0, 37.1, 30.5, 25.8 ppm. MS (ESI): 367.86 (M^+).

*4.2.10. H–L-Pro–L-Phe–N–3,5-$(CF_3)_2$Ph (**10**)*

White solid; $[\alpha]_D^{rt}$ −63.7 (*c* 0.52, $CHCl_3$); mp 132–134 °C; IR (KBr): *ν*=3294, 3190, 3117, 2971, 2877, 1653, 1580, 1525, 1472, 1444, 1385, 1280, 1172, 1133, 886, 741, 700, 682 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ*=9.87 (s, 1H), 8.41 (d, *J*=7.34 Hz, 1H), 7.99 (s, 2H), 7.53 (s, 1H), 7.19–7.28 (m, 5H), 4.77–4.84 (m, 1H), 3.74–3.79 (m, 1H), 3.28–3.34 (m, 1H), 3.05–3.10 (m, 1H), 2.91–2.99 (m, 1H), 2.64–2.71 (m, 1H), 2.01–2.08 (m, 1H), 1.56–1.76 (m, 3H), 1.33–1.38 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 177.0, 169.9, 139.5, 136.3, 132 (q), 129.1, 128.7, 127.1, 124.9, 121.2, 119.4, 117.0, 60.1, 55.0, 47.1, 36.9, 30.6, 25.8 ppm. MS (ESI): 473.87 (M^+).

*4.2.11. H–L-Pro–L-Ala–N–(S)-CH(CH_3)Ph (**11**)*

White solid; $[\alpha]_D^{rt}$ −146 (*c* 0.55, $CHCl_3$); mp 208–209 °C; IR (KBr): *ν*=3297, 2968, 1641, 1554, 1534, 1449, 1380, 1218, 1158, 754, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ*=8.13 (s, 1H), 7.36–7.22 (m, 5H), 7.16 (s, 1H), 5.00–5.09 (m, 1H), 4.45–4.49 (m, 1H), 3.71–3.76 (m, 1H), 2.97–3.05 (m, 1H), 2.86–2.94 (m, 1H), 2.28 (s, 1H), 2.06–2.16 (m, 1H), 1.82–1.93 (m, 1H), 1.65–1.74 (m, 2H), 1.44 (d, *J*=6.90 Hz, 3H), 1.34 (d, *J*=6.93 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 175.4, 171.2, 143.4, 128.6, 127.1, 126.0, 60.3, 48.8, 48.5, 47.2, 30.6, 26.1, 22.1, 17.9 ppm. MS (ESI): 289.82 (M^+).

*4.2.12. H–L-Pro–L-Ala–N(p-Me)Ph (**12**)*

White solid; $[\alpha]_D^{rt}$ −166.9 (*c* 0.45, $CHCl_3$); mp 168–169 °C; IR (KBr): *ν*=3359, 3305, 3268, 3201, 3133, 2972, 2869, 1684, 1645, 1610, 1547, 1511, 1448, 1405, 1315, 1248, 821, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ*=9.03 (d, *J*=19.8 Hz, 1H), 8.19 (s, 1H), 7.44 (d, *J*=7.95 Hz, 2H), 7.08 (d, *J*=8.1 Hz, 2H), 4.60–4.67 (m, 1H), 3.72–3.79 (q, 1H), 2.98–3.06 (m, 1H), 2.88–2.95 (m, 1H), 2.29 (s, 3H), 2.11–2.21 (m, 1H), 1.87–1.99 (m, 2H), 1.68–1.77 (m, 2H), 1.45 (d, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 176.0, 170.1, 135.6, 133.5, 129.3, 119.6, 60.2, 49.1, 47.2, 30.6, 26.2, 20.8, 17.3, 17.2 ppm. MS (ESI): 275.75 (M^+).

*4.2.13. H–L-Pro–L-Ala–N(p-MeO)Ph (**13**)*

White solid; $[\alpha]_D^{rt}$ −95.8 (*c* 1, MeOH); mp 184–186 °C; IR (KBr): *ν*=3360, 3308, 3267, 3200, 3133, 2970, 1685, 1646, 1611, 1546, 1512, 1446, 1403, 1316, 1247, 1204, 1106, 937, 821, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ*=8.99 (s, 1H), 8.20 (d, *J*=7.56 Hz, 1H), 7.46 (d, *J*=8.93 Hz, 2H), 6.82 (d, *J*=8.96 Hz, 2H), 4.60–4.64 (m, 1H), 3.74–3.79 (m, 4H), 3.01–3.07 (m, 1H), 2.88–2.99 (m, 1H), 2.04–2.20 (m, 2H), 1.88–1.94 (m, 1H), 1.68–1.77 (m, 2H), 1.44 (d, *J*=6.94 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 176.1, 169.9, 156.1, 131.3, 121.3, 113.9, 60.3, 55.4, 49.1, 47.2, 30.6, 26.2, 17.1 ppm. MS (ESI): 291.75 (M^+).

*4.2.14. H–L-Pro–L-Ala–N(p-NO_2)Ph (**14**)*

Yellow oil; $[\alpha]_D^{rt}$ −115.6 (*c* 0.5, $CHCl_3$); IR (KBr): *ν*=3287, 3158, 3094, 2969, 2874, 1705, 1650, 1619, 1597, 1563, 1509, 1451, 1409, 1340, 1301, 1258, 1198, 1174, 1153, 1111, 855, 751, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ*=10.07 (s, 1H), 8.34 (d, *J*=6.93 Hz, 1H), 8.14 (d, *J*=9.03 Hz, 2H), 7.71 (d, *J*=9.03 Hz, 2H), 4.64–4.71 (m, 1H), 3.82–3.87 (q, 1H), 3.04–3.12 (m, 1H), 2.92–2.99 (m, 1H), 2.16–2.29 (m, 2H), 1.89–1.97 (m, 1H), 1.72–1.81 (m, 2H), 1.48 (d, *J*=6.86 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 176.6, 170.9, 144.2, 143.1, 124.8, 119.0, 60.2, 49.6, 47.2, 30.6, 26.2, 17.0 ppm. MS (ESI): 306.8 (M^+).

*4.2.15. H–D-Pro–L-Ala–N(p-Me)Ph (**15**)*

White solid; $[\alpha]_D^{rt}$ −50.9 (*c* 1.0, $CHCl_3$); mp 183.8–185.6 °C; IR (KBr): *ν*=3447, 3297, 3071, 2962, 1652, 1602, 1544, 1500, 1444, 1380, 1313, 1243, 1200, 1058, 1031, 935, 900, 746, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ*=8.93 (s, 1H), 8.15 (d, *J*=7.29 Hz, 1H), 7.41 (d,

J=8.31 Hz, 2H), 7.10 (d, J=8.22 Hz, 2H), 4.57–4.64 (m, 1H), 3.80 (dd, J=9.16 Hz, 5.25 Hz, 1H), 2.96–3.02 (m, 1H), 2.86–2.93 (m, 1H), 2.29 (s, 3H), 2.10–2.22 (m, 1H), 1.82–1.93 (m, 2H), 1.63–1.72 (m, 2H), 1.46 (d, J=6.96 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 176.4, 170.0, 135.6, 133.5, 129.3, 119.7, 60.3, 49.1, 47.2, 30.9, 26.1, 20.8, 16.7 ppm. MS (ESI): 275.73 (M^+).

4.2.16. H–L-Pro–D-Ala–NPh (**16**)

White solid; $[\alpha]_D^{rt}$ +56.3 (c 1.0, $CHCl_3$); mp 174–176 °C; IR (KBr): ν=3311, 3276, 3209, 3148, 3106, 2977, 2935, 2874, 1691, 1645, 1613, 1558, 1519, 1447, 1378, 1348, 1318, 1298, 1252, 1179, 1145, 1081, 1062, 997, 941, 759, 735, 693 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=9.12 (s, 1H), 8.19 (d, J=5.67 Hz, 1H), 7.54 (d, J=7.87 Hz, 2H), 7.29 (t, J=7.63 Hz, 2H), 7.07 (t, J=7.33 Hz, 1H), 4.61–4.68 (m, 1H), 3.81 (dd, J=9.15 Hz, 5.27 Hz, 1H), 2.97–3.05 (m, 1H), 2.87–2.94 (m, 1H), 2.10–2.22 (m, 1H), 2.06 (s, 1H), 1.83–1.94 (m, 1H), 1.64–1.73 (m, 2H), 1.47 (d, J=6.96 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 176.3, 170.2, 138.2, 128.8, 123.9, 119.7, 60.3, 49.2, 47.2, 30.8, 26.1, 16.8 ppm. MS (ESI): 261.73 (M^+).

4.3. General procedure for aldol reaction of cyclohexanone with aldehyde

The catalyst (0.1 mmol) and AcOH (0.1 mmol) were stirred in 2 mL chloroform/cyclohexanone (1:1) for 20 min at −20 °C. The corresponding aldehyde (0.5 mmol) was added and the mixture was stirred for 24–72 h. The reaction mixture give pure aldol adduct after flash column chromatography on silica gel. The enantiomeric excess was determined by chiral HPLC with Daicel Chiralpak AS-H, AD-H, or OD-H.

4.3.1. (2S,1′R)-2-(Hydroxy-(p-nitrophenyl)methyl) cyclohexan-1-one[3d]

Yield: 98%; $[\alpha]_D^{rt}$ +11.3 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.22 (d, J=9.3 Hz, 2H), 7.52 (d, J=9.3 Hz, 2H), 4.90 (d, J=6.2 Hz, 1H), 4.10 (s, 1H), 2.48–2.60 (m, 2H), 2.32–2.42 (m, 1H), 2.09–2.15 (m, 1H), 1.20–1.85 (m, 5H); ee: 96%, determined by HPLC (Daicel Chiralpak AD-H, i-PrOH/hexane 5/95), 254 nm, flow rate 1.0 mL/min, t_{major}=46.6 and t_{minor}=63.3.

4.3.2. (2S,1′R)-2-(Hydroxy-(m-nitrophenyl)methyl) cyclohexan-1-one[8e]

Yield: 94%; $[\alpha]_D^{rt}$ 37.6 (c 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.09–8.20 (m, 2H), 7.66 (d, J=7.7 Hz, 1H), 7.49–7.55 (m, 1H), 4.89 (d, J=8.49 Hz, 1H), 4.12–4.15 (m, 1H), 2.58–2.67 (m, 1H), 2.36–2.52 (m, 2H), 2.08–2.14 (m, 1H), 1.70–1.85 (m, 1H), 1.53–1.70 (m, 3H), 1.35–1.44 (m, 1H); ee: 96%, determined by HPLC (Daicel Chiralpak AD-H, i-PrOH/hexane 5/95), 254 nm, flow rate 1.0 mL/min, t_{major}=41.5 and t_{minor}=55.6.

4.3.3. (2S,1′R)-2-(Hydroxy-(o-nitrophenyl)methyl) cyclohexan-1-one[8e]

Yield: 85%; $[\alpha]_D^{rt}$ 18.0 (c 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.84 (d, J=7.62 Hz, 1H), 7.77 (d, J=7.31 Hz, 1H), 7.63 (t, 1H), 7.42 (t, 1H), 5.44 (d, J=5.9 Hz, 1H), 3.87 (br, 1H), 2.75 (d, J=5.1 Hz, 1H), 2.33–2.47 (m, 2H), 2.07 (s, 1H), 1.25–1.86 (m, 5H); ee: 95%, determined by HPLC (Daicel Chiralpak AD-H, i-PrOH/hexane 1/9), 254 nm, flow rate 0.5 mL/min, t_{major}=45.5 and t_{minor}=49.6.

4.3.4. (2S,1′R)-2-(Hydroxy-(p-bromophenyl)methyl) cyclohexan-1-one[8e]

Yield: 75%; $[\alpha]_D^{rt}$ +11.3 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.46–7.49 (m, 2H), 7.17–7.21 (m, 2H), 4.75 (d, J=8.70 Hz, 1H), 4.00 (s, 1H), 2.46–2.57 (m, 2H), 2.34–2.40 (m, 1H), 2.06–2.12 (m, 1H), 1.77–1.82 (m, 1H), 1.51–1.69 (m, 3H), 1.20–1.35 (m, 1H); ee: 98%, determined by HPLC (Daicel Chiralpak AD-H, i-PrOH/hexane 10/90), 254 nm, flow rate 0.5 mL/min, t_{minor}=32.4 and t_{major}=39.1.

4.3.5. (2S,1′R)-2-(Hydroxy-(2,4-dichlorophenyl)methyl) cyclohexan-1-one[6b]

Yield: 93%; $[\alpha]_D^{rt}$ 22.9 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.50 (d, J=8.40 Hz, 1H), 7.35 (d, J=1.95 Hz, 1H), 7.27–7.31 (m, 1H), 5.27–5.31 (m, 1H), 4.05 (d, J=3.96 Hz, 1H), 2.58–2.66 (m, 1H), 2.45–2.49 (m, 1H), 2.28–2.39 (t, 1H), 2.07–2.13 (m, 1H), 1.83–1.85 (m, 1H), 1.52–1.76 (m, 4H); ee: 97%, determined by HPLC (Daicel Chiralpak AS-H, i-PrOH/hexane 10/90), 254 nm, flow rate 0.5 mL/min, t_{minor}=15.2 and t_{major}=16.8.

4.3.6. (2S,1′R)-2-(Hydroxy-(o-chlorophenyl)methyl) cyclohexan-1-one[5b]

Yield: 81%; $[\alpha]_D^{rt}$ +4.8 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.54–7.56 (m, 1H), 7.18–7.34 (m, 3H), 5.35 (d, J=8.10 Hz, 1H), 4.04 (s, 1H), 2.64–2.70 (m, 1H), 2.29–2.49 (m, 2H), 2.06–2.12 (m, 1H), 1.80–1.84 (m, 1H), 1.50–1.75 (m, 4H); ee: 97%, determined by HPLC (Daicel Chiralpak OD-H, i-PrOH/hexane 5/95), 220 nm, flow rate 1 mL/min, t_{major}=9.4 and t_{minor}=12.1.

4.3.7. (2S,1′R)-2-(Hydroxy-(o-bromophenyl)methyl) cyclohexan-1-one

Yield: 86%; $[\alpha]_D^{rt}$ +20.1 (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.50–7.54 (m, 2H), 7.33 (t, J=24.6 Hz, 1H), 7.11–7.16 (m, 1H), 5.30 (d, J=9.60 Hz, 1H), 4.02 (s, 1H), 2.64–2.73 (m, 1H), 2.29–2.49 (m, 2H), 2.06–2.12 (m, 1H), 1.49–1.84 (m, 5H); ee: 97%, determined by HPLC (Daicel Chiralpak OD-H, i-PrOH/hexane 5/95), 220 nm, flow rate 1 mL/min, t_{major}=9.8 and t_{minor}=12.5.

4.3.8. (2S,1′R)-2-(Hydroxy(phenyl)methyl) cyclohexan-1-one[8e]

Yield: 98%; $[\alpha]_D^{rt}$ +22.9 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.25–7.38 (m, 5H), 4.79 (d, J=9.3 Hz, 1H), 4.00 (m, 1H), 2.63–2.67 (m, 1H), 2.35–2.47 (m, 2H), 2.07 (m, 1H), 1.52–1.78 (m, 4H), 1.20–1.22 (m, 1H); ee: 84%, determined by HPLC (Daicel Chiralpak OD-H, i-PrOH/hexane 5/95), 220 nm, flow rate 1 mL/min, t_{major}=12.3 and t_{minor}=19.5.

4.3.9. (R)-1-Hydroxy-1-(4-nitrophenyl) pentan-3-one[8e]

Yield: 36%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.20 (d, J=8.7 Hz, 2H), 7.55 (d, J=8.6 Hz, 2H), 5.26–5.29 (q, 1H), 3.69 (s, 1H), 2.81–2.84 (m, 2H), 2.45–2.52 (q, 2H), 1.06–1.11 (t, 3H); ee: 53%, determined by HPLC (Daicel Chiralpak AS-H, i-PrOH/hexane 30/70), 254 nm, flow rate 1 mL/min, t_{major}=6.7 and t_{minor}=8.7.

4.3.10. (3S,4R)-4-Hydroxy-3-methyl-4-(4-nitrophenyl) butan-2-one[8e]

Yield: 54%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.22 (d, J=8.7 Hz, 2H), 7.53 (d, J=8.7 Hz, 2H), 4.88 (d, J=8.7 Hz, 1H), 2.86–2.94 (q, 1H), 2.21 (s, 3H), 1.03 (d, J=7.3 Hz, 3H); ee: 96%, determined by HPLC (Daicel Chiralpak AS-H, i-PrOH/hexane 30/70), 254 nm, flow rate 1 mL/min, t_{major}=6.3 and $t_{mino\ r}$=7.1.

4.3.11. (4R)-4-Hydroxy-4-(4-nitrophenyl) butan-2-one[8e]

Yield: 88%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.21 (d, J=8.7 Hz, 2H), 7.54 (d, J=8.7 Hz, 2H), 5.25–5.29 (t, 1H), 3.60 (s, 1H), 2.84–2.87 (t, 2H), 2.23 (s, 3H); ee: 48%, determined by HPLC (Daicel Chiralpak AS-H, i-PrOH/hexane 30/70), 254 nm, flow rate 1 mL/min, t_{major}=9.8 and t_{minor}=12.2.

4.3.12. (1R)-1-Hydroxy-1-(4-nitrophenyl) hexan-3-one

Yield: 69%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.21 (d, J=8.7 Hz, 2H), 7.54 (d, J=8.7 Hz, 2H), 5.25–5.29 (m, 1H), 2.80–2.83 (t, 2H), 2.41–2.46 (t, 2H), 1.57–1.69 (m, 2H), 0.85–0.95 (t, J=7.38 Hz, 3H); ee: 20%, determined by HPLC (Daicel Chiralpak AS-H, i-PrOH/

hexane 30/70), 254 nm, flow rate 1 mL/min, t_{major}=6.3 and t_{minor}=7.5.

Acknowledgements

This work was supported by the Natural Science Foundation of China (NSFC 20572087), the Ministry of Education, PR China (No. 106141) and the Program for New Century Excellent Talents (NCET-06-0772) in University.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.07.051.

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