# A highly asymmetric direct aldol reaction catalyzed by chiral proline amide – thiourea bifunctional catalysts

**Yun Li, Qing-chuan Yang, Xiao-Ying Xu, Yong Zhou, Jian-fei Bai, Fei-ying Wang, and Li-xin Wang**



**Abstract:** A series of chiral proline amide – thiourea bifunctional catalysts derived from L-proline and chiral diamine were prepared and successfully applied to highly enantioselective direct aldol reactions of cyclohexanone with various aldehydes in excellent yields (85%–97%), diastereoselectivities (anti/syn > 20:1) and enantioselectivities (up to 91% ee).

*Key words:* aldol reaction, bifunctional catalyst, proline, amide–thiourea.

**Résumé :** On a préparé une série de catalyseurs chiraux bifonctionnels amide de la proline – thiourée dérivés de la L-proline et d'une diamine chirale et on l'a appliquée avec succès à la réaction d'aldolisation directe hautement énantiosélective de la cyclohexanone avec divers aldéhydes, avec d'excellents rendements (85 %–97 %), et des diastéréosélectivités (anti/syn > 20 : 1) et énantiosélectivités (allant jusqu'à 91 % ee) élevées.

*Mots-clés :* réaction aldolique, catalyseur bifonctionnel, proline, amide–thiourée.

[Traduit par la Rédaction]

## Introduction

The aldol reaction is considered one of the most important carbon–carbon bond-forming reactions that creates the β-hydroxy ketones frequently found in many biologically active compounds and drugs.[1,2] Since pioneering work discovered that L-proline is a highly efficient catalyst for asymmetric direct aldol reactions,[3] great advances have been made for this reaction.[2–4] The direct aldol reaction involving cyclohexanone principally generates β-hydroxyketone as a mixture of regio-, diastereo-, and enantio-isomers, and it is quite difficult to obtain a single isomer. As a result, many efforts have been made on this conversion. Xiao and co-workers[5a] developed a kind of L-prolinamide derived from L-proline and chiral diamine to catalyze this reaction and provide high entioselectivities, anti-disastereoselectivities, and yields. Since then, a series of L-prolinamides[5] have been prepared and applied to this transformation, and impressive results have been made. As well, L-proline[6] and L-prolinamides,[5] tetrazole,[7] 3-pyrrolidinecarboxylic acid,[8] 4-substituted L-proline,[9] cinchona-derived primary amines,[10] chiral phosphinyl oxide pyrrolidines,[11] prolinethioamides,[12] sulfonamide,[13] 6-APA,[14] *cis*-diamine derivatives,[15] and acyclic amino acids[16] have also been evaluated for this reaction. To the best of our knowledge, L-proline amide – thiourea bifunctional catalysts have not been reported for the catalysis of the aldol reaction of cyclohexanone with aldehydes.

Recently, chiral thiourea organocatalysts have been widely used in asymmetric catalysis because of their effective activation of carbonyl and nitro groups through double-hydrogen-bonding interactions.[17] Among them, secondary amines, especially L-proline and its structural analogues, are powerful tools for the activation of aldehydes and ketones via an enamine or imine transition state.[2,18] However, the chiral proline amide – thiourea catalysts **4a**–**4d** with two catalytic sites of chiral thiourea and L-prolic amide skeleton have not drawn enough attention.[19] Based on this background, we expected to expand the scope of the application for these bifunctional catalysts and wanted to see if these catalysts may catalyze the asymmetric direct aldol reaction of cyclohexanone with aldehydes.

Aldol reactions are typically performed in organic solvents such as DMSO, DMF, or chloroform. In recent years, water has been widely used as a substitute for conventional organic solvents in asymmetric reactions because it is safe, economical, and environment friendly.[20] Therefore, asymmetric aldol reactions using an organocatalyst in water have received considerable attention[21] since Barbas and co-workers[21a] and Hayashi et al.[9] reported the first example of a small molecule catalyzed by direct an asymmetric Aldol reaction in pure water.

As a part of our continuing interest in asymmetric synthesis,[22,23] herein, we wish to report examples of chiral proline

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amide – thiourea bifunctional catalyst promoted enantioselective direct aldol reaction of cyclohexanone with various aldehydes in DMSO with water as a co-solvent in excellent yields, as well as high anti-diastereoselectivities (dr > 20:1) and enantioselectivities (up to 91%). These catalysts are illustrated in Fig. 1.

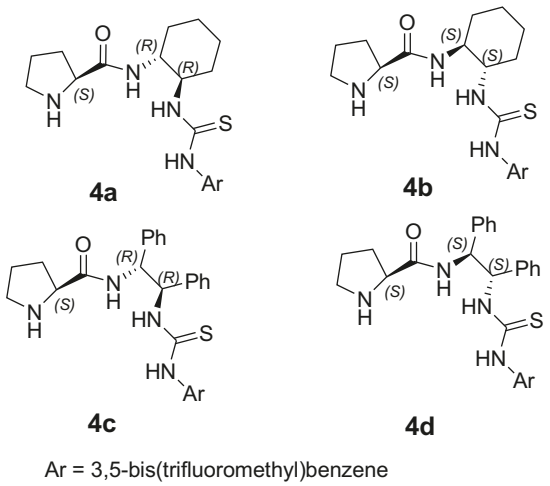
## Results and discussion

Chiral catalysts **4a**–**4d** may be similarly prepared as the reported procedures[19] and the catalytic activities of **4a**–**4d** were investigated in the model reaction of cyclohexanone with *p*-nitrobenzaldehyde, and the results are summarized in Table 1, which shows that chiral catalysts with different stereocompatibility and chiral centers have great effects on reactivities and selectivities. Comparatively, catalysts **4a** and **4c** gave better yields and enantioselectivities (Table 1, entries 1 and 3 versus 2 and 4). This is probably due to the compatibility of the two catalytic chiral centers. The less compatible chiral centers in **4b** and **4d** probably exert no synergic or negative effects on enantioselectivity. Catalyst **4a**, bearing a R,R linker, afforded the desired products in excellent yield (97%) and good enantioselectivity (75% ee) and was chosen for further optimization. Next, a range of solvents was screened for the model reaction catalyzed by **4a** at room temperature. As shown in Table 1, the enantioselectivities and yields were highly variable with different solvents. All the solvents delivered good yields (60%–94%), moderate to good enantioselectivities (15%–78% ee), and anti-diastereoselectivities (1:1 to 24:1). Less polar aprotic solvents such as hexane, toluene, and DCM gave good yields and moderate enantioselectivities (Table 1, entries 5–10). Protic solvents such as *i*-PrOH and water separately seemed to have an adverse influence on enantioselectivities (Table 1, entries 14 and 15). Relatively, DMSO gave an excellent yield (92%) and a good enantioselectivity (78%) and was chosen for further investigation (Table 1, entry 12).

To further improve the results, a series of additives were studied and the results are listed in Table 2. Additives have remarkable effects on catalytic activity and enantioselectivity, and the reaction time was reduced to 7 h (entries 1–8). When AcOH was used, the yield increased to 92% and the enantioselectivity was 86% ee (Table 2, entry 8). Interestingly, when water was used as a co-solvent, the reaction rate was dramatically accelerated and the reaction was completed within half an hour with increases in diastereoselectivity (Table 2, entries 9 and 10) and 81% and 87% ee were obtained. Particularly, when the volume ratio of DMSO to water reached 1:2, excellent yield (97%), good enantioselectivity (87% ee), and diastereoselectivity (96:4) were achieved (Table 2, entry 10). Through extensive screening, the optimized reaction conditions were found to be 20 mol% of catalyst **4a** and 10 equiv cyclohexanone in DMSO and water ($V_{DMSO}$:$V_{H_2O}$ = 1:2) at 25 °C (Table 2, entry 10).

Having established optimized conditions for the model reaction, the scope and the limitations of the reaction with different aldehydes were examined, and the results are summarized in Table 3. All the aldehydes bearing electron-withdrawing groups in the aromatic ring either at ortho (Table 3, entries 6–8), meta (Table 3, entry 5), or para positions (Table 3, entries 1–4) gave excellent yields, diastereoselectivities, and enantioselectivities. Particularly, the strong electron-withdrawing substituents at the ortho position in the benzene ring afforded the best enantioselectivities (up to 91% ee; Table 3, entries 6 and 7). The para position also gave high yields and excellent diastereoselectivities and enantioselectivities (up to 90% ee; Table 3, entries 2 and 3). Cyclopentanone was also investigated under these optimized conditions and gave 94% yield and 71% ee.

**Fig. 1.** Chiral proline amide – thiourea bifunctional catalysts.




## Conclusion

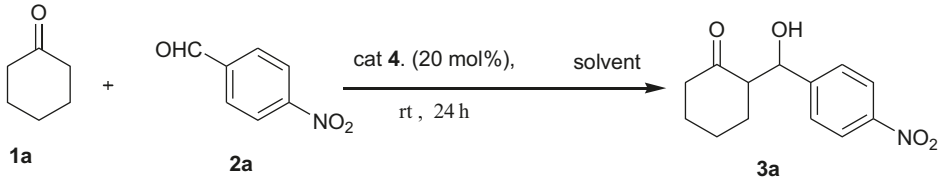
In conclusion, we have successfully applied the chiral proline amide – thiourea bifunctional catalysts **4a**–**4d** for the catalysis of the direct asymmetric aldol reaction of cyclohexanone with various aldehydes in the presence of water in excellent yields (85%–97%) and high anti-diastereoselectivities (dr > 20:1) and enantioselectivities (up to 91% ee). Further studies of the newly developed catalyst model and related catalysts in other organocatalyses are currently underway.

## Experimental section

### General

All reagents were purchased from a commercial supplier without further purification. Commercial grade solvent was dried and purified by standard procedures as specified in the *Purification of Laboratory Chemicals*;[24] NMR spectra were recorded with tetramethylsilane as the internal standard (δ = 0.0 ppm). $^1$H NMR spectra were recorded at 300 MHz, and $^{13}$C NMR spectra were recorded at 75 MHz (Bruker Avance). Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) for $^1$H NMR and relative to the central $CDCl_3$ resonance (δ = 77.0 ppm) for $^{13}$C NMR spectroscopy. Flash column chromatography was carried out using silica gel eluting with ethyl acetate and petroleum ether. Reactions were monitored by TLC and visualized with UV light. Melting points were measured on a Büchi B-545 melting point apparatus. Enantioselectivities (ee) were determined by HPLC using Daicel Chiralpak AD, OD, WHELK, or AS

**Table 1.** Screening of catalysts **4a**–**4d** and solvents.




**1a** **2a** **3a**

| Entry | Catalyst | Solvent | Yield (%)[a] | Anti / syn[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | **4a** | Neat | 97 | 14:1 | 75 |
| 2 | **4b** | Neat | 85 | 11:1 | 41 |
| 3 | **4c** | Neat | 87 | 32:1 | 55 |
| 4 | **4d** | Neat | 35 | 4:1 | 41 |
| 5 | **4a** | Toluene | 94 | 2:1 | 41 |
| 6 | **4a** | hexane | 66 | 2:1 | 54 |
| 7 | **4a** | DCM | 70 | 2:1 | 44 |
| 8 | **4a** | $CHCl_3$ | 87 | 9:1 | 62 |
| 9 | **4a** | $Et_2O$ | 86 | 2:1 | 48 |
| 10 | **4a** | THF | 94 | 2:1 | 37 |
| 11 | **4a** | $CH_3CN$ | 88 | 2:1 | 39 |
| 12 | **4a** | DMSO | 92 | 3:1 | 78 |
| 13 | **4a** | DMF | 60 | 24:1 | 64 |
| 14 | **4a** | *i*-PrOH | 91 | 1:1 | 15 |
| 15 | **4a** | $H_2O$ | 80 | 4:1 | 57 |

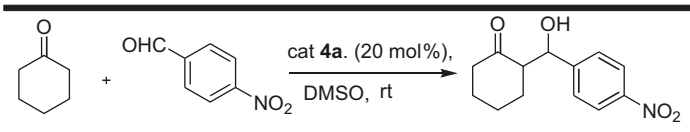
**Note:** Unless otherwise specified, all reactions were carried out with catalysts **4** (0.02 mmol), **1a** (2 mmol), and **2a** (0.1 mmol) in the specified solvent (0.2 mL) at room temperature.

[a]Isolated yield.

[b]Determined by $^1$H NMR.

[c]ee values were determined via HPLC with a Chiralpak-AD column.

**Table 2.** The effect of additives.




**1a** **2a** **3a**

| Entry | Additive (20 mol%) | Time (h) | Yield (%)[a] | Anti/syn[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | 4-$OHC_6H_4CO_2H$ | 7 | 84 | 65:35 | 75 |
| 2 | Phenol | 7 | 80 | 85:15 | 75 |
| 3 | $PhCO_2H$ | 7 | 97 | 76:24 | 72 |
| 4 | 4-$NO_2C_6H_4CO_2H$ | 7 | 94 | 87:13 | 71 |
| 5 | $PhCH_2CO_2H$ | 7 | 93 | 60:40 | 68 |
| 6 | $H_2O$ | 7 | 99 | 79:21 | 66 |
| 7 | $C_6H_4(CO_2H)_2$ | 7 | 80 | 80:20 | 78 |
| 8 | AcOH | 7 | 92 | 74:26 | 86 |
| 9[d] | AcOH | 0.5 | 92 | 91:9 | 81 |
| 10[e] | AcOH | 0.5 | 97 | 96:4 | 87 |

**Note:** Unless otherwise specified, all reactions were carried out with catalysts **4a** (0.02 mmol), **1a** (2 mmol), and **2a** (0.1 mmol) in DMSO (0.2 mL) at room temperature.

[a]Isolated yield.

[b]Determined by $^1$H NMR.

[c]ee values were determined via HPLC with a Chiralpak-AD column.

[d]The solvent was DMSO–$H_2O$ (2:1).

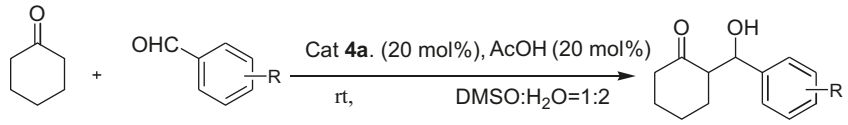
[e]The solvent was DMSO–$H_2O$ (1:2).

columns with *i*-PrOH–hexane as the eluent. All compounds in this manuscript are known compounds. All physical and spectral data were found to be consistent with those reported.[19,22]

### (*S*)-*N*-((1*R*,2*R*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl) thioureido)cyclohexyl)pyrrolidine-2-carboxamide (4a)[19]

Enantiomerically pure **4a** was obtained after a single recrystallization from petroleum ether – EtOAc (*v*/*v* 1:100).

**Table 3.** The reaction of cyclohexanone with various aldehydes under optimized conditions.




1a 2 3

| Entry | R | Time (h) | Product | Yield (%)[a] | ee (%)[b] | Anti/syn[c] |
|---|---|---|---|---|---|---|
| 1 | 4-$NO_2$ | 0.5 | **3a** | 97 | 87 | >20:1 |
| 2 | 4-Br | 2 | **3b** | 88 | 71 | 15:85 |
| 3 | 4-CN | 2 | **3c** | 97 | 90 | >20:1 |
| 4 | 4-F | 2 | **3d** | 90 | 63 | >20:1 |
| 5 | 3-$NO_2$ | 2 | **3e** | 93 | 90 | >20:1 |
| 6 | 2-Br | 2 | **3f** | 97 | 91 | >20:1 |
| 7 | 2-$NO_2$ | 2 | **3g** | 94 | 91 | >20:1 |
| 8 | 2-CN | 2 | **3h** | 85 | 87 | >20:1 |

**Note:** Unless otherwise specified, all reactions were carried out with catalysts **4a** (0.02 mmol), **1a** (2 mmol), and **2** (0.1 mmol) in a mixture of DMSO and water (*v*/*v* = 1:2).

[a]Isolated yield.

[b]ee values were determined by HPLC using a chiral stationary phase.

[c]Determined by $^1$H NMR.



Colorless solid, mp 176–177 °C. $R_f$ (10% MeOH – EtOAc) 0.23. $^1$H NMR (300 MHz $CDCl_3$) δ (ppm): 9.89–9.84 (m, 1H), 8.21 (d, $J$ = 10.0 Hz, 1H), 8.15 (d, $J$ = 10.8 Hz, 2H), 7.79 (d, $J$ = 9.5 Hz, 1H), 7.55 (s, 1H), 4.63–4.60 (m, 1H), 3.74–3.67 (m, 2H), 3.01–2.96 (m, 2H), 1.99–1.94 (m, 1H), 1.68–1.22 (m, 12H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 180.9, 176.6, 141.3, 132.1, 128.6, 124.9, 122.1, 121.3, 117.7, 60.3, 56.8, 53.7, 47.1, 32.9, 32.2, 30.9, 25.8, 25.3, 24.7. HRMS (ESI-TOF) calcd for $C_{20}H_{25}F_6N_4OS$ ([M + H]$^+$): 483.1648; found: 483.1660. All physical and spectral data were found to be consistent with those reported.[19,22]

### (*S*)-*N*-((1*S*,2*S*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl) thioureido)cyclohexyl)pyrrolidine-2-carboxamide (4b)[19]

Enantiomerically pure **4b** was obtained after a single recrystallization from petroleum ether – EtOAc (*v*/*v* 1:100). Colorless solid, mp 149–151 °C. $R_f$ (10% MeOH – EtOAc) 0.26. $^1$H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.03–1.35 (m, 2H), 1.47–1.57 (m, 3H), 1.63–1.70 (m, 2H), 1.89–2.01 (m, 7H), 2.97–3.03 (m,2H), 3.69–3.73 (m, 2H), 4.59–4.62 (d, $J$ = 9 Hz, 1H), 7.55 (s, 1H), 7.77–7.80 (d, $J$ = 9 Hz, 1H), 8.13 (s, 2H), 8.19–8.22 (d, $J$ = 9 Hz, 1H), 9.88–9.89 (br, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 180.9, 176.7, 141.4, 132.2, 128.6, 125.0, 122.1, 121.4, 117.0, 60.3, 56.9, 53.7, 47.1, 32.9, 30.9, 25.8, 25.9, 24.7. HRMS (ESI-TOF) calcd for $C_{20}H_{25}F_6N_4OS$ ([M + H]$^+$): 483.1648; found: 483.1658. All physical and spectral data were found to be consistent with those reported.[19,22]

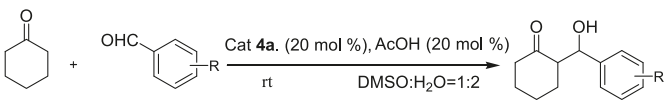
### (*S*)-*N*-((1*R*,2*R*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl) thioureido)-1,2-diphenylethyl)pyrrolidine-2-carboxamide (4c)[19]

Enantiomerically pure **4c** was obtained after a single recrystallization from petroleum ether – EtOAc (*v*/*v* 1:80). Colorless solid, mp 166–168 °C. $R_f$ (10% MeOH – EtOAc) 0.28. $^1$H NMR (300 MHz $CDCl_3$) δ (ppm): 8.92–8.89 (m, 1H), 8.50–8.48 (m, 1H), 8.07 (s, 2H), 7.60 (s, 1H), 7.28–7.12 (m, 10 H), 6.40 (m, 1H), 5.45–5.38 (t, 1H), 3.74–3.69 (m, 1H), 3.14–3.10 (m, 1H), 3.10–2.98 (m, 1H), 2.05–1.64 (m, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ (ppm): 181.5, 176.5, 141.0, 138.0, 131.7, 123.2, 129.0, 128.6, 128.4, 127.9, 127.7, 122.9, 122.1, 117.7, 61.9, 60.5, 58.6, 47.2, 31.1, 26.1. HRMS (ESI-TOF) calcd for $C_{28}H_{27}F_6N_4OS$ ([M + H]$^+$): 581.1804; found: 581.1823. All physical and spectral data were found to be consistent with those reported.[19,22]

### (*S*)-*N*-((1*S*,2*S*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl) thioureido)-1,2-diphenylethl)pyrrolidine-2-carboxamide (4d)[19]

Enantiomerically pure **4d** was obtained after a single recrystallization from petroleum ether – EtOAc (*v*/*v* 1:80). Colorless solid, mp 147–148 °C. $R_f$ (10% MeOH – EtOAc) 0.30. $^1$H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.25–1.63 (m, 2H), 1.83–1.85 (m, 1H), 2.09–2.13 (m, 2H), 2.74–2.78 (m, 1H), 2.98–3.02 (m, 1H), 3.83–3.88 (m, 1H), 5.23–5.29 (t, $J$ = 8.4 Hz, 9.8 Hz, 1H), 6.53–6.55 (d, $J$ = 6 Hz, 1H), 7.08–7.19 (m, 12H), 7.43 (s, 1H), 8.65–8.68 (d, $J$ = 9 Hz, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ (ppm): 181.6, 176.4, 140.8, 137.8, 131.8, 129.0, 128.6, 128.2, 127.9, 127.7, 127.5, 123.1, 123.4, 122.1, 118.0, 62.9, 60.6, 59.4, 46.9, 30.4, 25.7. HRMS (ESI-TOF) calcd for $C_{28}H_{27}F_6N_4OS$ ([M + H]$^+$): 581.1804; found: 581.1812. All physical and spectral data were found to be consistent with those reported.[19,22]

### Asymmetric direct aldol reactions of cyclohexanone with various aldehydes




1a 2 3

**General procedure for direct aldol reaction of cyclohexanone with various aldehydes (Table 3)**

A mixture of **2** (0.1 mmol, 1 equiv), **1a** (2 mmol, 20 equiv), **4a** (0.02 mmol, 0.2 equiv), and water–DMSO (0.2 mL, *v*/*v* 2:1) was stirred for 0.5–2 h. Then the crude product was directly purified by silica gel chromatography without workup using a mixture of EtOAc–hexanes (from 1:5 to 1:6) as the eluent and fractions were collected and concentrated in vacuo to provide the desired product.

**Spectroscopic data of final products 3**

***2-[Hydroxy(4-nitrophenyl)methyl]cyclohexanone (3a)***

The title compound was prepared according to the general procedure, as described previously, in 97% yield. HPLC (Chiralcel AD-H, *i*-PrOH–hexane = 20:80, flow rate = 1.0 mL/min, λ = 254 nm): $t_{minor}$ = 11.25 min, $t_{major}$ = 14.19 min, ee = 87%, dr > 20:1. Pure anti-product was obtained by silica gel chromatography (eluent: $V_{hexane}/V_{ethyl\ acetate}$ = 6:1). Furthermore, enantiomerically pure anti-product was obtained after a single recrystallization from petroleum ether – EtOAc (*v*/*v* 1.5:2). Colorless solid, mp 149–150 °C. (lit.[25] mp 149–151 °C). $R_f$ (50% EtOAc – petroleum ether) 0.40. $^1$H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.24–1.39 (m, 1H), 1.53–1.65 (m, 3H), 1.81–1.85 (m, 1H), 2.08–2.09 (m, 1H), 2.35–2.39 (m, 1H), 2.47–2.59 (m, 2H), 4.09 (br, 1H), 4.87–4.90 (d, *J* = 9 Hz, 1H), 7.49–7.52 (d, *J* = 9 Hz, 2H), 8.19–8.22 (d, *J* = 9 Hz, 2H). All physical and spectral data were found to be consistent with those reported.[5a,9,21a,25]

***2-[(4-Bromophenyl)hydroxy-methyl]cyclohexanone (3b)***

The title compound was prepared according to the general procedure, as described previously, in 88% yield. HPLC (Chiralpak AD-H, *i*-PrOH–hexane = 10:90, flow rate = 1.0 mL/min, λ = 220 nm): $t_{minor}$ = 12.98 min, $t_{major}$ = 14.96min, ee = 71%, dr > 85:15. Pure anti-product was obtained by silica gel chromatography (eluent: $V_{hexane}/V_{ethyl\ acetate}$ = 6:1). Furthermore, enantiomerically pure anti-product was obtained after a single recrystallization from petroleum ether – EtOAc (*v*/*v* 1.8:2). Yellow solid, mp 126–128 °C. (lit.[25] mp 126–127 °C). $R_f$ (25% EtOAc – petroleum ether) 0.27. $^1$H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.25–1.31 (m, 1H), 1.51–1.69 (m, 4H), 2.07–2.08 (m, 1H), 2.34–2.38 (m, 3H), 2.45–2.58 (m, 1H), 4.73–4.76 (d, *J* = 9 Hz, 1H), 7.17–7.26 (q, *J* = 15.39 Hz, 8.28 Hz, 5.4 Hz, 2H), 7.44–7.48 (m, 2H). All physical and spectral data were found to be consistent with those reported.[5a,9,21a,25]

***2-[Hydroxy(4-oxo-cyclohexyl)methyl]benzonitrile (3c)***

The title compound was prepared according to the general procedure, as described previously, in 97% yield. HPLC (Chiralcel AD-H, *i*-PrOH–hexane = 10:90, flow rate = 1.0 mL/min, λ = 220 nm): $t_{minor}$ = 20.48 min, $t_{major}$ = 25.34 min, ee = 90%, dr >20:1. Pure anti-product was obtained by silica gel chromatography (eluent: $V_{hexane}/V_{DCM}$ = 1:1). Furthermore, enantiomerically pure anti-product was obtained after a single recrystallization from petroleum ether – EtOAc (*v*/*v* 1.6:2). Yellow solid, mp 72–74 °C. $R_f$ (50% EtOAc – petroleum ether) 0.33. $^1$H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.24–1.37 (m, 1H), 1.52–1.64 (m, 3H), 2.08–2.09 (m, 2H), 2.34 (m, 1H), 2.46–2.52 (m, 2H), 2.56–2.58 (br, 1H), 4.81–4.84 (d, *J* = 9 Hz, 1H), 7.40–7.45 (m, 2H), 7.63–7.65 (d, *J* = 6 Hz, 2H). All physical and spectral data were found to be consistent with those reported.[5a,21a]

***2-[Hydroxy(4-fluorophenyl)methyl]cyclohexanone (3d)***

The title compound was prepared according to the general procedure, as described previously, in 90% yield. HPLC (Chiralpak WHELK, *i*-PrOH–hexane = 20:80, flow rate = 1.0 mL/min, λ = 220 nm): $t_{minor}$ = 9.08 min, $t_{major}$ = 7.48 min, ee = 63%, dr > 20:1. Pure anti-product was obtained by silica gel chromatography (eluent: $V_{hexane}/V_{ethyl\ acetate}$ = 6:1). Furthermore, enantiomerically pure anti-product was obtained after single recrystallization from petroleum ether – EtOAc (*v*/*v* 1:2). Colorless solid, mp 84–85 °C. (lit.[25] mp 84–85 °C). $R_f$ (25% EtOAc – petroleum ether) 0.39. $^1$H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.26–1.30 (m, 1H), 1.52–1.68 (m, 4H), 2.07 (m, 1H), 2.34–2.57 (m, 3H), 3.99 (s, 1H), 4.76–4.78 (d, *J* = 6 Hz, 1H), 6.99–7.06 (m, 2H), 7.26–7.31 (m, 2H). All physical and spectral data were found to be consistent with those reported.[21a,26,25]

***2-[Hydroxy(3-nitrophenyl)methyl]cyclohexanone (3e)***

The title compound was prepared according to the general procedure, as described previously, in 93% yield. HPLC (Chiralcel OD-H, *i*-PrOH–hexane = 10:90, flow rate = 0.8 mL/min, λ = 220 nm): $t_{minor}$ = 18.77 min, $t_{major}$ = 14.69 min, ee = 90%, dr >20:1. Pure anti-product was obtained by silica gel chromatography (eluent: $V_{hexane}/V_{ethyl\ acetate}$ = 6:1). Furthermore, enantiomerically pure anti-product was obtained after single recrystallization from petroleum ether – EtOAc (*v*/*v* 1:3). Yellow solid, mp 102–104 °C (no literature data reported). $R_f$ (50% EtOAc – petroleum ether) 0.50. $^1$H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.39–1.41 (m, 1H), 1.54–1.65 (m, 3H), 1.81–1.84 (m, 1H), 2.09 (m, 1H), 2.36–2.62 (m, 3H), 4.10–4.11 (s, *J* = 3 Hz, 1H), 4.87–4.91 (m, 1H), 7.49–7.54 (t, *J* = 7.89 Hz, 7.92 Hz, 1H), 7.65–7.68 (m, 1H), 8.13–8.20 (m, 2H). All physical and spectral data were found to be consistent with those reported.[5a,9,21a]

***2-[(2-Bromophenyl)hydroxy-methyl]cyclohexanone (3f)***

The title compound was prepared according to the general procedure, as described previously, in 91% yield. HPLC (Chiralpak AD-H, *i*-PrOH–hexane = 10:90, flow rate = 1.0 mL/min, λ = 220 nm): $t_{minor}$ = 11.86 min, $t_{major}$ = 10.28 min, ee = 87%, dr > 20:1. Pure anti-product was obtained by silica gel chromatography (eluent: $V_{hexane}/V_{ethyl\ acetate}$ = 6:1). Furthermore, enantiomerically pure anti-product was obtained after single recrystallization from petroleum ether – EtOAc (*v*/*v* 1.5:2). Brown solid, mp 105–106 °C (no literature data reported). $R_f$ (50% EtOAc – petroleum ether) 0.39. $^1$H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.57–1.72 (m, 6H), 2.33–2.45 (m, 2H), 2.70 (m, 1H), 4.03–4.05 (d, *J* = 6 Hz, 1H), 5.28–5.32 (m, 1H), 7.13–7.16 (m, 1H), 7.35–7.37 (m, 1H), 7.51–7.54 (m, 2H). All physical and spectral data were found to be consistent with those reported.[27]

***2-[Hydroxy(2-nitrophenyl)methyl]cyclohexanone (3g)***

The title compound was prepared according to the general procedure, as described previously, in 94% yield. HPLC (Chiralcel AD-H, *i*-PrOH–hexane = 10:90, flow rate = 1.0 mL/min, λ = 220 nm): $t_{minor}$ = 18.44 min, $t_{major}$ =

17.34 min, ee = 91%, dr >20:1. Pure anti-product was obtained by silica gel chromatography (eluent: $V_{hexane}/V_{ethyl\ acetate}$ = 6:1). Furthermore, enantiomerically pure anti-product was obtained after single recrystallization from petroleum ether – EtOAc (*v*/*v* 1.3:2). Gray solid, mp 111–113 °C. (lit.[28] mp 126–127 °C). $R_f$ (50% EtOAc – petroleum ether) 0.21. $^1$H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.60–1.76 (m, 4H), 2.32–2.44(m, 4H), 2.73–2.76 (m, 1H), 3.68–3.75 (br, 1H), 5.43–5.46 (d, $J$ = 9 Hz, 1H), 7.42–7.45 (m, 1H), 7.629–7.63 (m, 1H), 7.75–7.78 (m, 1H), 7.83–7.86 (m, 1H). All physical and spectral data were found to be consistent with those reported.[5a,21a,28]

### *2-[Hydroxy(2-oxo-cyclohexyl)methyl]benzonitrile (3h)*

The title compound was prepared according to the general procedure, as described previously, in 85% yield. HPLC (Chiralcel AS-H, *i*-PrOH–hexane = 5:95, flow rate = 1.0 mL/min, λ = 220 nm): $t_{minor}$ = 41.79 min, $t_{major}$ = 44.53 min, ee = 87%, dr >20:1. Pure anti-product was obtained by silica gel chromatography (eluent: $V_{hexane}/V_{ethyl\ acetate}$ = 6:1). Furthermore, enantiomerically pure anti-product was obtained after single recrystallization from petroleum ether – EtOAc (*v*/*v* 1:2). Yellow solid, mp: 185–186 °C (no literature data reported). $R_f$ (50% EtOAc – petroleum ether) 0.50. $^1$H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.52–1.58 (m, 4H), 1.83–1.85 (m, 2H), 2.34–2.38 (m, 1H), 2.47–2.53 (m, 1H), 2.67–2.70 (m, 1H), 4.22–4.23 (d, $J$ = 3 Hz, 1H), 5.21–5.23 (d, $J$ = 3.18 Hz, 8.55 Hz, 1H), 7.37–7.43 (m, 1H), 7.59–7.65 (m, 3H). All physical and spectral data were found to be consistent with those reported.[29]

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