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Direct asymmetric aldol reactions catalysed by *trans*-4-hydroxy-(*S*)-prolinamide in solvent-free conditions

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ABSTRACT

Direct asymmetric aldol reactions between 4-nitrobenzaldehyde and cyclohexanone were catalysed by *trans*-4-hydroxy-(*S*)-prolinamide (10 mol %) in the presence of CH_3COOH (10 mol %) as the co-catalyst under solvent-free conditions at 15 °C. (2*S*,4*R*)-4-Hydroxy-*N*-((*S*)-1-phenylethyl)pyrrolidine-2-carboxamide **2** efficiently catalysed the asymmetric aldol reaction to afford the product in >99% yield and with 95% ee with an *anti*/*syn* ratio of 88:12 after 18 h. The additional *trans*-hydroxyl group on (*S*)-prolinamide and (*S*)-1-phenylethylamine both influenced the ee of the predominant *anti* aldol product. Different benzaldehyde derivatives with cyclohexanone gave the corresponding aldol products in 38–89% yields and with 56–94% ee with *anti*/*syn* (100:0–71:29). Catalyst **2** can be used up to 5 continuous cycles for asymmetric aldol reactions between 4-nitrobenzaldehyde and cyclohexanone with overall 91% yield and 86% yield of *anti*-product with *anti*/*syn* (98:2).

1. Introduction

The aldol reaction is one of the most powerful methods for carbon–carbon bond formation. The products (β-hydroxycarbonyls) of direct asymmetric aldol reactions are privileged molecular segments in biologically important molecules required by the pharmaceutical industry. Therefore, the development of suitable organocatalysts for enantioselective aldol reactions is important.[1] Direct asymmetric aldol reactions are highly atom economical compared with other well-established processes using enol or enolate derivatives as the aldol donor.[2] Hajos and Parrish have described organocatalysed aldol reactions using L-proline as the catalyst[3] while the pioneering work by List et al. was published in 2000.[4] After these reports numerous proline-derived organocatalysts such as proline analogues,[5] acyclic amino acids,[6] different types of prolinamides,[7–15] prolinethioamides,[16] sulfonamides,[17] chiral amines,[18] organic salts[19] and recoverable organocatalysts[20] have been designed for direct asymmetric aldol reactions. Chimni et al. used protonated (*S*)-prolinamides derived from proline and different amines such as (*S*)-1-phenylethylamine, (*R*)-phenylethylamine, aniline derivatives.[21] Most methodologies for direct asymmetric aldol reactions use a large excess of nucleophile, high catalyst loading (up to 30 mol %) and non-biodegradable solvents such as DMF and DMSO. To overcome these issues and contribute to the practise of green chemistry, it is beneficial to develop organocatalysts, which can catalyse the reaction using low catalyst loading under solvent-free conditions. Kelleher et al. reported a series of simple 4-hydroxyprolinamides for asymmetric Michael addition reactions for aldehydes to nitroolefins.[22] Herein we report the synthesis of *trans*-4-hydroxy-(*S*)-prolinamides and *cis*-4-hydroxy-(*R*)-prolinamide shown in Figure 1 and their evaluation

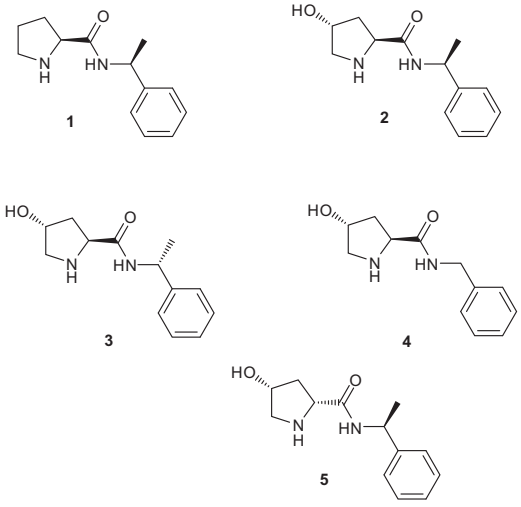

Figure 1. Structure of the organocatalysts (prolinamides) **1**–**5**.

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in the catalysis of direct asymmetric aldol reactions in solvent-free conditions at room temperature.

2. Results and discussion

Organocatalysts **1**–**4** were synthesized by the reaction of *trans*-4-hydroxy-(*S*)-proline or (*S*)-proline with (*S*)-1-phenylethylamine, (*R*)-1-phenylethylamine and benzyl amine (Scheme 1). (*S*)-Proline **6** and *trans*-4-hydroxy-(*S*)-proline **7** were protected as *N*-boc derivatives in quantitative yields. *N*-Boc-*trans*-4-hydroxy-(*S*)-proline **9** was treated with (*S*)-1-phenylethylamine, (*R*)-1-phenylethylamine and benzyl amine in the presence of triethylamine and ethylchloroformate, to give the corresponding *N*-boc-prolinamides **11**–**13** in 74–90% yields. Similarly the reaction of *N*-boc-proline **8** was carried out with (*S*)-1-phenylethylamine to obtain *N*-boc-prolinamide **10**. Deprotection of the *N*-boc group by TFA in dichloromethane at room temperature gave prolinamides **1**–**4**.

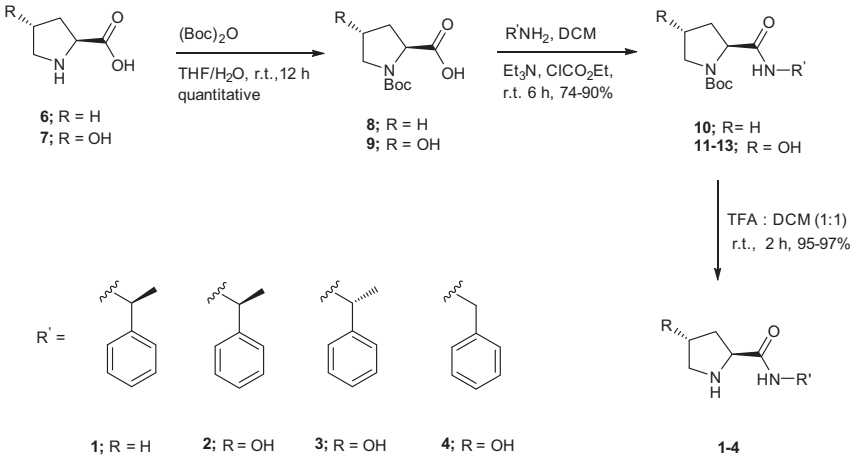
We also synthesized *cis*-4-hydroxy-(*R*)-prolinamide **5** from *cis*-4-hydroxy-(*R*)-proline **14** using the similar procedures used for the prolinamide **2** (Scheme 2). *cis*-4-Hydroxy-L-proline was synthesized according to the literature.[23]

2.1. Optimization of the reaction conditions

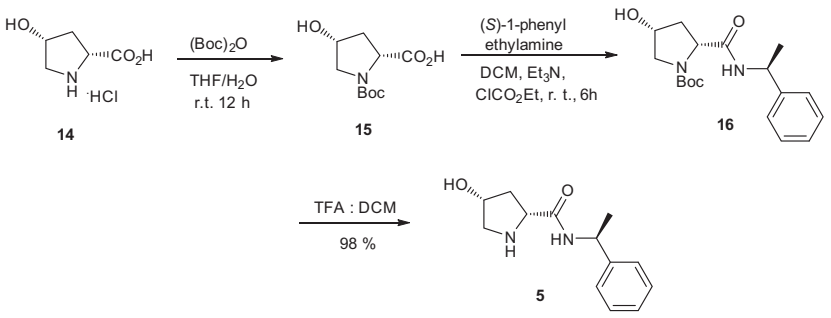
In our initial investigation, we screened different solvents for the direct asymmetric aldol reaction between 4-nitrobenzaldehyde **17** and cyclohexanone using organocatalyst **2** (10 mol %) and benzoic acid (10 mol %) as additives at room temperature (Table 1). Asymmetric aldol reactions in polar solvents such as methanol, DMF, water and brine showed diastereomeric ratios of *anti*/*syn*; 90:10–81:19 and 70–90% conversions to aldol products **18** with 58–90% enantiomeric excesses of the major product *anti*-**18** (90–58%) (Table 1, entries 1–4). Aldol reaction in less polar solvents, such as THF, $CHCl_3$, CH_2Cl_2 and toluene gave 85–91% conversions and *anti*/*syn* ratios of 87:13–86:14 with 70–90% ee of *anti*-products (Table 1, entries 5–8). The ee's of diastereomer *syn*-**18** were found to be better with less polar solvents than polar solvents. Reaction under neat conditions were found to be better than reactions in solvents, conversion of product was >99% and *anti*/*syn* was 84:16 with 97% ee of product (Table 1, entry 9).

After screening different solvents for direct asymmetric aldol reactions, we also screened different additives, catalysts, loadings of the catalyst and reaction temperatures (Table 2). The aldol reaction of 4-nitrobenzaldehyde **17** and cyclohexanone (3 equiv) was carried out using catalyst **2** (10 mol %) with different acids as additives (10 mol %) such as benzoic acid, 4-nitrobenzoic acid, 4-methoxybenzoic acid, triflic acid, trifluoroacetic acid and acetic acid. Acetic acid and benzoic acid were found to be better additives compared to other acids but acetic acid gave better dr (*anti*/*syn*; 88:12) with 95% ee of the product *anti*-**18** (Table 2, entries 1 and 6). We also increased the catalyst loading up to 20 mol % and the product *anti*-**18** was obtained in excellent yield with 92% ee but dr (*anti*/*syn*; 78:22) was poor (Table 2, entry 8). Using less additive (5 mol %) slightly improved the dr, but led to a decrease in the ee (Table 2, entry 9).

The aldol reaction was also carried out at different temperatures; lowering the temperature from 15 °C to 0 °C, improved the dr up to (*anti*/*syn*; 94:6) but decreased the conversion to 57%



Scheme 1. Synthesis of (*S*)-prolinamide and *trans*-4-hydroxy-(*S*)-prolinamides **1**–**4**.



Scheme 2. Synthesis of (2*R*,4*R*)-4-hydroxy-*N*-((*S*)-1-phenylethyl)pyrrolidine-2-carboxamide **5**.

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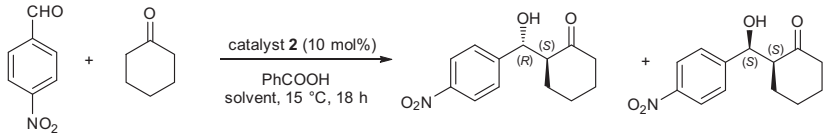
Table 1
Screening of different solvents for direct asymmetric aldol reaction[a]

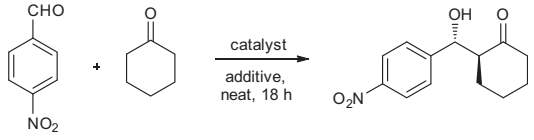


17 (1′S,2R)-*anti*-**18** (1′S,2S)-*syn*-**18**

Entry	Solvent	Conversion[b] (%)	dr (*anti*/*syn*)[c]	ee (%) (*anti*/*syn*)[c,d]
1	Water	70	89:11	90:18
2	DMF	71	81:19	58:32
3	MeOH	90	90:10	86:68
4	Brine	72	85:15	83:55
5	THF	91	86:14	70:54
6	$CHCl_3$	85	86:14	90:79
7	DCM	92	86:14	82:78
8	Toluene	85	87:13	84:78
9	Neat	>99	84:16	97:32

[a] Catalyst **2** (0.1 mmol, 10 mol %), solvent (1 mL), PhCOOH (0.1 mmol, 10 mol %), cyclohexanone (3 mmol) and 4-nitrobenzaldehyde (1 mmol) were stirred at 15 °C for 18 h.
[b] Conversion was determined by HPLC using response factor for 4-nitrobenzaldehyde **17** and product **18**.
[c] Diastereomeric ratio (*anti*/*syn*) and ee were determined by HPLC using chiralpak AD-H column.
[d] The absolute configuration was determined by comparing the specific rotation of product *anti*-**18** with literature values and found to be (1′*S*, 2*R*).

Table 2
Optimization of reaction conditions for asymmetric direct aldol reaction[a]



17 *anti*-**18**

Entry	Catalyst	Catalyst loading (mol %)	Additive	Conversion[b] (%)	dr (*anti*/*syn*)[c]	ee (%) (*anti*)[c]
1	2	10	PhCOOH	>99	84:16	97
2	2	10	*p*-NO_2 PhCOOH	>99	77:23	75
3	2	10	*p*-OMe PhCOOH	>99	77:23	81
4	2	10	Triflic acid	>99	73:27	84
5	2	10	Trifluoroacetic acid	80	48:52	72
6	2	10	CH_3COOH	>99	88:12	95
7	2	5	CH_3COOH	97	85:15	86
8	2	20	CH_3COOH	>99	78:22	92
9	2	10	CH_3COOH[d]	83	89:11	83
10	2	10	CH_3COOH[e]	57	94:6	90
11	2	10	CH_3COOH[f]	97	89:11	80
12	2	10	CH_3COOH[g]	>99	79:21	69
13	1	10	CH_3COOH	72	84:16	68
14	3	10	CH_3COOH	100	88:12	79
15	4	10	CH_3COOH	97	86:14	75
16	5	10	CH_3COOH[h]	>99	86:14	74

[a] Catalyst **2** (0.1 mmol, 10 mol %), additive (0.1 mmol, 10 mol %), cyclohexanone (3 mmol) and 4-nitrobenzaldehyde (1 mmol) were stirred at 15 °C for 18 h.
[b] Conversion was determined by HPLC using response factor for 4-nitrobenzaldehyde **17** and product **18**.
[c] Diastereomeric ratio (*anti*/*syn*) and ee were determined by HPLC using chiralpak AD-H column.
[d] Additive (5 mol %) was used.
[e] Reaction conducted at 0 °C.
[f] Reaction conducted at 40 °C for 6 h.
[g] Reaction conducted at 60 °C for 6 h.
[h] The opposite enantiomer of product *anti*-**18** was obtained.

(Table 2, entry 10). Increasing the temperature from 15 °C to 40 °C and 60 °C took less time to complete the reaction but the ee's decreased (Table 2, entries 11 and 12). We also screened different organocatalysts **1**–**5** and organocatalyst **2** was found to be the best catalyst. The ee's of product *anti*-**18** with organocatalysts **1**–**2** indicated that the *trans*-4-hydroxyl group of (*S*)-prolinamide influenced the ee of product *anti*-**18**, which may be due to intermolecular hydrogen bonding in organocatalyst **2**. *trans*-4-Hydroxy-(*S*)-prolinamides **2** containing (*S*)-1-phenylethylamine were found to be better catalysts compared to (*R*)-1-phenylethylamine and benzyl amine (Table 2, entries 6, 14 and 15). *cis*-4-Hydroxy-(*R*)-prolinamide **5** was also found to be poor compared to catalyst **2** and gave the opposite enantiomer of the product *anti*-**18**. These results show that the absolute configuration is governed by the stereogenic centre of pyrrolidine ring with an amide bond.

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2.2. Transition state for asymmetric aldol reaction

In Figure 2, we proposed a transition state between cyclohexanone, organocatalyst **2** and 4-nitrobenzaldehyde **17**. According to the well-known mechanism of the aldol reaction, cyclohexanone first forms an iminium bond with organocatalyst **2**, then the hydrogen bonding occurs between the hydrogen of the amide of organocatalyst **2** and the oxygen of 4-nitrobenzaldehyde. In this transition state, the two phenyl rings (phenyl ring of organocatalyst **2** and phenyl ring of 4-nitrobenzaldehyde) show π–π interactions (Fig. 2). The double bond of cyclohexene attacks the *Si*-face of 4-nitrobenzaldehyde and gives *anti*-(1′*S*)-2((*R*)-hydroxy(4-nitrophenyl)methyl)cyclohexanone as the major product with 95% ee. Diastereomeric ratios and ee's of the aldol product *anti*-**18** catalysed by organocatalyst **2** (*trans*-4-hydroxy-prolinamide) were found to be better compared to prolinamide **1** in solvent free conditions. These results indicate that the additional effect of the hydroxyl group of prolinamide **2** may take part in intermolecular hydrogen bonding with the two OH groups of the 4-hydroxy proline, which could improve the ee and dr of the product **18** (Fig. 3).

2.3. Scope and limitation of the asymmetric aldol reaction

We also investigated the asymmetric direct aldol reaction of substituted benzaldehydes with cyclohexanone and cyclopentanone catalysed by prolinamide **2** (10 mol %) and co-catalyst CH_3COOH (10 mol %) at 15 °C. Benzaldehyde gave the product in a 50% yield with 76% ee and an *anti*/*syn* ratio of 91:9, while the bulkier naphthaldehyde slightly reduced the *anti*/*syn* ratio, but the ee was slightly improved. An electron withdrawing group such as a nitro on the benzaldehyde improved the reactivity and 2-nitrobenzaldehyde gave 93% ee with a slightly improved *anti*/*syn* ratio compared to 4-nitrobenzaldehyde (Table 2, entry 6 and Table 3, entry 3). Halogenated benzaldehydes required longer reaction times and 2-halogenated benzaldehydes afforded products in better ee compared to 4-halogenated benzaldehydes (Table 3, entries 4–6). Furthermore, the size of halogens affected the ee of the product; when the size increases (F < Cl < Br) the ee's of the corresponding product decreases (F > Cl > Br). Electron donating groups such as methoxy on the benzaldehyde, were found to be less reactive compared to derivatives of electron withdrawing groups. This can be explained by the fact that electron withdrawing groups enhance the electrophilicity of carbonyl carbons in aldehydes, which facilitate the reaction, while electron donating groups lessen the electrophilicity of carbonyl carbons. In the case of 2-(trifluoromethyl)benzaldehyde, it exclusively afforded the *anti*-product with 93% ee (Table 3, entry 12). The ee's of *anti*-aldol products with 2-susbstituted benzaldehydes were found to be better compared to 4-substituted benzaldehydes.

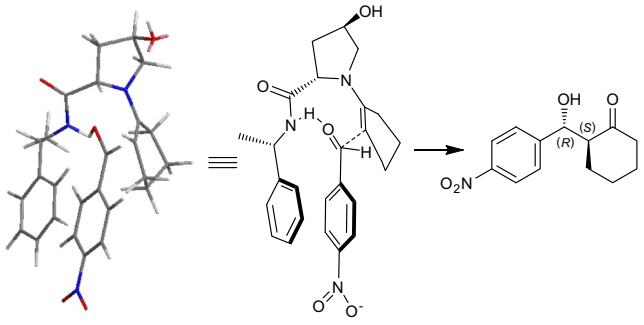
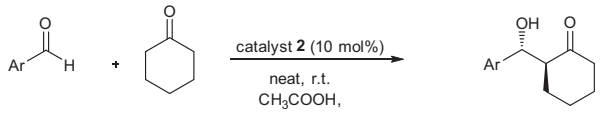


Figure 2. Transition state for the direct asymmetric aldol reaction between cyclohexanone and 4-nitrobenzaldehyde **17** catalysed by prolinamide **2**.

Table 3
Aldol reaction of cyclohexanones with substituted benzaldehydes in the presence of organocatalyst **2**[a]



Entry	Ar	Time (h)	Yield[b] (%)	dr (*anti*/*syn*)[c]	ee (%) (*anti*)[d]
1	Phenyl	24	50	91:9	76
2	1-Naphthyl	36	89	88:12	80
3	2-$NO_2C_6H_4$	12	82	91:9	93
4	2-FC_6H_4	33	88	90:10	94
5	4-FC_6H_4	30	63	86:14	72
6	2-ClC_6H_4	28	65	87:13	93
7	4-ClC_6H_4	26	50	82:18	86
8	2-BrC_6H_4	28	66	85:15	80
9	4-BrC_6H_4	21	78	88:12	84
10	2-$OMeC_6H_4$	30	46	88:12	87
11	4-$OMeC_6H_4$	30	38	79:21	56
12	2-$CF_3C_6H_4$	36	63	100:0	93
13	4-$CF_3C_6H_4$	36	74	85:15	75

[a] Catalyst **2** (0.1 mmol, 10 mol %), CH_3COOH (0.1 mmol, 10 mol %), cyclohexanone (3 mmol) and 4-nitrobenzaldehyde (1 mmol) were stirred at 15 °C for specified time.
[b] Isolated yield after purification by column chromatography.
[c] The diastereomeric ratios were determined by ^1H NMR.
[d] The ee was determined by HPLC using chiralpak AD-H and OD-H columns.

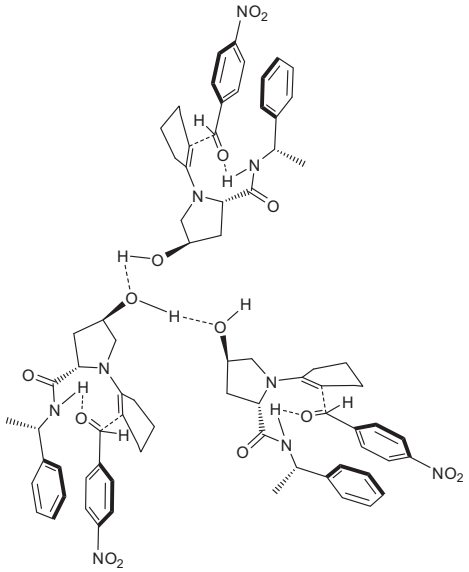
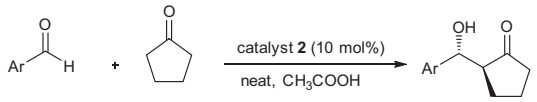


Figure 3. Intermolecular hydrogen bonding in 4-hydroxyprolinamide in the catalytic transition state.

We also studied the direct asymmetric aldol reaction between 2- and 4-substituted benzaldehydes with cyclopentanone catalysed by organocatalyst **2** at 15 °C (Table 4). The reactivity of benzaldehydes with electron withdrawing groups was faster than with electron donating groups. In the case of 4-substituted benzaldehydes, the *anti*/*syn* ratios of the aldol products were poor and the ee of *anti*-products were 51–25%. In the case of 2-halo-benzaldehydes the major products were *syn* with 61–54% ee (Table 4, entries 1, 3, 5 and 7). The diastereomeric ratio and the ee of the *syn*-aldol product of 2-fluorobenzaldehyde were found to be better compared to other benzaldehydes (Table 4, entries 3 and 5).

Table 4
Aldol reaction of cyclopentanone and acetone with substituted benzaldehydes in the presence of organocatalyst **2**[a]



Entry	Ar	Time (h)	Yield[b] (%)	dr (*anti*/*syn*)[c]	ee (%) (*anti*/*syn*)[d]
1	2-$NO_2C_6H_4$	10	83	46:54	76:54
2	4-$NO_2C_6H_4$	10	68	49:51	61:45
3	2-FC_6H_4	33	89	9:91	76:61
4	4-FC_6H_4	33	87	61:39	54:26
5	2-ClC_6H_4	26	83	14:86	85:54
6	4-ClC_6H_4	28	71	51:49	56:33
7	2-$OMeC_6H_4$	36	87	30:70	nd:50
8	4-$OMeC_6H_4$	36	82	44:56	25:0

[a] Catalyst **2** (0.1 mmol, 10 mol %), CH_3COOH (0.1 mmol, 10 mol %), cyclopentanone (3 mmol) and 4-nitrobenzaldehyde (1 mmol) were stirred at 15 °C for specified time.
[b] Isolated yield after purification by column chromatography.
[c] The diastereomeric ratios were determined by ^1H NMR.
[d] The ee was determined by HPLC using chiralpak AD-H and OD-H columns.

2.4. Desymmetrization of prochiral ketone

4-Substituted cyclohexanones are common prochiral ketones; the asymmetric desymmetrization of these compounds may lead to the formation of chiral products with the creation of multiple stereogenic centres. We used 4-*tert*-butylcyclohexanone as the prochiral ketone in the aldol reaction with aromatic aldehydes to provide aldol products with three new stereogenic centres. It is worth mentioning that the prochiral centre C-4 is distant from C-2 of the cyclic ketones where the aldolization takes place. Hence the catalyst should have the ability to control the diastereoselectivity and enantioselectivity and more importantly to distinguish the stereochemistry of C-4 distant from the reactive site at C-2. The reaction of 4-*tert*-butylcyclohexanone was performed in dichloromethane with 3 equiv of ketone, and we observed that the confirmation of cyclohexanone in the *anti*-aldol products was found to be equatorial while the ee was better with 2-nitrobenzaldehyde (Scheme 3). Direct asymmetric aldol reaction between 4-*tert*-butylcyclohexanone as the prochiral substrate and 2-nitro and 4-nitrobenzaldehyde was studied.

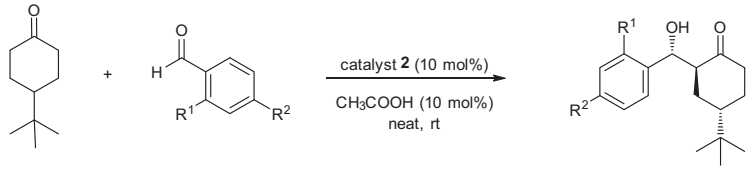
2.5. Continuous use of the catalyst

We carried out 6 successive catalytic cycles for the direct asymmetric aldol reactions between cyclohexanone (1.2 mmol) with *p*-nitrobenzaldehyde **17** (0.4 mmol) using prolinamide **2** as the catalyst (10 mol %) and acetic acid (10 mol %) as the additive at 15 °C. After complete consumption of **17** (TLC and HPLC analysis), cyclohexanone (1.2 mmol) and **17** (0.4 mmol) were added to the reaction mixture without any additional catalyst or additives. After repeating this procedure for another 5 catalytic cycles, the product was obtained in 91% overall yields with a 98:2 dr and 86% ee for the product *anti*-**18**. We also conducted direct asymmetric aldol reactions using large quantities of substrates (substrate/catalyst = 60, catalyst loading is 1.67 mol %) to afford product *anti*-**18** in 79% yield with 87% ee and 93:7 dr. A comparison of the two systems shows the ee values of *anti*-**18** product to be comparable but the diastereomeric ratio was found to better with continuous use of catalyst **2**. The improvement in the dr of *anti*-**18** product may be due to use of excess cyclohexanone (see Table 5).

Table 5
Continuous use of organocatalyst **2** for aldol reactions between cyclohexanone and 4-nitrobenzaldehyde **17**[a]

Cycle	Time (h)	Conversion[b] (%)	ee (%) *anti*[c]
1	18	>99	97
2	18	96	93
3	20	96	87
4	20	95	86
5	20	94	86
6	20	94	86
After purification		91[d]	86

[a] Catalyst **2** (0.04 mmol, 10 mol %), CH_3COOH (0.04 mmol, 10 mol %), cyclohexanone (1.2 mmol) and 4-nitrobenzaldehyde (0.4 mmol) were stirred at 15 °C for specified time.
[b] Conversion was determined by HPLC using response factor for 4-nitrobenzaldehyde **17** and product **18**.
[c] The ee was determined by HPLC using chiralpak AD-H columns.
[d] Isolated yield after purification by column chromatography.



17, $R^2 = NO_2$
19, $R^1 = NO_2$

20, $R^1 = NO_2$, yield 90%, ee 90%
21, $R^2 = NO_2$, yield 80%, ee 85%

Scheme 3. Asymmetric aldol reactions between prochiral ketone (4-*tert*-butylcyclohexanone) and nitrobenzaldehyde.

3. Conclusions

In conclusion we have developed direct asymmetric aldol reactions between benzaldehydes and cycloalkanones catalysed by *trans*-4-hydroxyprolinamide. The reaction between cyclohexanone and 4-nitrobenzaldehyde afforded the *anti*-aldol product as the major product with 95% ee. Benzaldehydes with electron withdrawing groups are more reactive than electron donating groups. The *syn*-aldol was obtained as the major product by the reaction of 2-susbtituted benzaldehydes and cyclopentanone but 4-susbstituted benzaldehydes gave approximately equal distributions of *syn*/*anti* with moderate ee's. Catalyst **2** can be used for 5 continuous cycles for asymmetric aldol reactions between 4-nitrobenzaldehyde and cyclohexanone with a slight loss in ee but an improved dr.

4. Experimental

4.1. General

Benzaldehyde derivatives, cyclohexanone and cyclopentanone were purchased from commercial source and used as such. Proton and carbon nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR, respectively) were recorded on 400 MHz (operating frequencies: ^{1}H, 400.13 MHz; ^{13}C, 100.61 MHz) Jeol-FT-NMR spectrometers at ambient temperature. The chemical shifts (δ) for all compounds are listed in parts per million (ppm) downfield from tetramethylsilane using the NMR solvent as an internal reference. The reference values used for deuterated chloroform ($CDCl_3$) were 7.26 and 77.00 ppm for ^{1}H and ^{13}C NMR spectra, respectively. HRMS analysis was carried out using QSTAR XL Pro system microTOF-Q-II. Infrared spectra were recorded on a Perkin–Elmer FT-IR spectrometer. Thin layer chromatography was carried out using Merck Kieselgel 60 F254 silica gel plates. Column chromatography separations were performed using silica gel 230–400 mesh. The enantiomeric excess was determined on Shimadzu LC-2010HT using chiralcel OD-H and chiralpak AD-H columns. Optical rotations were taken using Rudolph digipol polarimeter. All of the new synthesized compounds were characterized by ^{1}H, ^{13}C NMR and HRMS and known compounds were characterized by ^{1}H and ^{13}C NMR.

4.1.1. (*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidine-2-carboxylic acid 8[25]

To a stirred solution of L-proline **6** (4.76 g, 40 mmol) in dry DCM (60 mL), triethyl amine (7.60 g, 56 mmol) and di-*tert*-butyldicarbonate (12.39 mL, 54 mmol) were added dropwise at 0 °C. The resulting reaction mixture was stirred for 5 h. The reaction mixture was acidified with a saturated solution of citric acid to pH 5–4 and extracted with CH_2Cl_2. The extract was washed with brine and water and dried over anhydrous sodium sulfate. The solvent was evaporated and dissolved in the minimum amount of ethyl acetate, after which hexane and ethyl acetate (6:1) were added and kept at 0 °C for 24 h to give a white solid (7.2 g, 85%). Mp = 136 °C. $[\alpha]_D^{27} = -121.8$ (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.0 (br s, 1H), 4.36–4.18 (m, 1H), 3.57–3.29 (m, 2H), 2.31–1.81 (m, 4H), 1.42 (s, 4.5H), 1.39 (s, 4.5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.75, 175.86, 155.92, 153.89, 81.03, 80.29, 58.90, 46.84, 46.27, 30.77, 28.86, 28.33, 28.21, 24.24, 23.55 ppm.

4.1.2. (2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid 9[24]

trans-4-Hydroxy-L-proline **7** (2.50 g, 19 mmol) was dissolved in 38 mL of THF/H_2O (2:1) and then treated with 10% aqueous NaOH (8 mL) followed by the addition of di-*tert*-butyldicarbonate (6.00 g, 28 mmol). The reaction mixture was stirred at room temperature overnight and then THF was removed by a rotary evaporator. The residue was adjusted to pH 2 by the addition of 10% aqueous $KHSO_4$. The acidic solution was extracted several times with ethyl acetate. The combined organic extracts were washed with H_2O and brine, and dried over anhydrous Na_2SO_4. The solvent was removed by rotavapor to afford compound **9** as a syrup (4.40 g, 100%), which was used without purification for the next step. $[\alpha]_D^{25} = -68.1$ (*c* 1.3, MeOH). IR (film): ν = 3462, 2976, 2934, 1740, 1639 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (br s, 1H), 4.44–4.12 (m, 1H), 3.50–3.32 (m, 2H), 2.10–1.80 (m, 4H), 1.47 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.90, 153.68, 79.51, 68.81, 57.51, 53.14, 30.52, 27.73 ppm.

4.1.3. (*S*)-*tert*-Butyl 2-((*S*)-1-phenylethylcarbamoyl)pyrrolidine-1-carboxylate 10[7]

At first, (*S*)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid **8** (4.50 g, 20.9 mmol) was dissolved in dry dichloromethane (56 mL), after which triethylamine (3.47 g, 24.9 mmol) and ethyl chloroformate [2.36 g, 24.9 mmol, in dichloromethane (11 mL)] were added dropwise at 0 °C. The solution was stirred at the same temperature for 15 min after which a solution of (*S*)-1-phenylethyl amine (2.50 g, 20.9 mmol) in dichloromethane (11 mL) was added slowly. The resulting mixture was warmed to room temperature and stirred for 5 h. The reaction mixture was washed with 10% HCl solution, a saturated $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the residue was recrystallized from ethyl acetate to afford **10** as a white solid (5.78 g, 87%). Mp 81–84 °C. $[\alpha]_D^{25} = -48.0$ (*c* 1.06, MeOH). IR (KBr): ν = 3287, 2978, 1684, 1656 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.26 (m, 5H), 5.51–4.96 (m, 1H), 4.26–4.12 (m, 1H), 3.45–3.26 (m, 1H), 2.11 (d, *J* = 8.39 Hz, 3H), 1.88–1.71 (m, 2H), 1.41 (s, 9H), 1.32–1.21 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.87, 154.80, 143.48, 128.46 (2C), 127.29, 125.99 (2C), 80.44, 61.23, 59.79, 48.16, 30.93, 28.12, 23.55, 21.38 ppm.

4.1.4. (2*S*,4*R*)-*tert*-Butyl-4-hydroxy-2-((*S*)-1-phenylethylcarbamoyl)pyrrolidine-1-carboxylate 11[22]

Compound **9** (2.14 g, 9.3 mmol) was dissolved in dry dichloromethane (25 mL), after which triethylamine (1.54 mL, 11.1 mmol) and ethyl chloroformate (1.05 mL, 11.1 mmol, in dichloromethane (5 mL)) were added slowly at 0 °C and stirred for 15 min. (*S*)-1-Phenylethylamine (1.19 mL, 9.3 mmol) in 5 mL of dichloromethane was added to the above solution and the reaction mixture was allowed to return to room temperature and stirred for 5 h. The reaction mixture was concentrated by a rotary evaporator. The resulting oil was purified on silica gel using 30% ethyl acetate in hexane to give a colourless oil **11** (2.5 g, 81%). $[\alpha]_D^{25} = -97.3$ (*c* 2.0, MeOH). IR (film): ν = 3302, 2976, 1666, 1547 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (br s, 1H), 7.24–7.16 (m, 5H), 5.04–4.95 (m, 1H), 4.53–4.21 (m, 2H), 3.51–3.28 (m, 2H), 2.32–2.19 (m, 1H), 1.93–1.91 (m, 1H), 1.39 (s, 9H), 1.29–1.17 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.77, 155.57, 143.00, 128.12 (2C), 126.61, 125.81 (2C), 80.14, 69.09, 59.39, 54.08, 48.37, 36.36, 27.86, 21.43 ppm.

4.1.5. (2*S*,4*R*)-*tert*-Butyl 2-(benzylcarbamoyl)-4-hydroxypyrrolidine-1-carboxylate 13[22]

Compound **9** (2.14 g, 9.3 mmol) was dissolved in dry dichloromethane (25 mL), after which triethylamine (1.54 mL, 11.1 mmol) and ethyl chloroformate (1.05 mL, 11.1 mmol) were added and then benzyl amine (1.01 mL, 9.3 mmol) was added. The rest of the procedure was followed as the synthesis of compound **10**. Yield (2.67 g, 90%). $[\alpha]_D^{25} = -40.25$ (*c* 0.82, MeOH), IR (film): ν = 3300, 2976, 1685, 1664 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (br s, 1H), 6.75–6.69 (m, 5H), 4.25 (s, 1H), 3.93–3.69 (m, 2H), 3.58–3.54 (m, 1H), 3.06–2.92 (m,1H), 2.73–2.50 (m, 1H), 1.71–1.49 (m,

2H), 0.91–0.69 (m, 9H), ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.03, 153.54, 138.55, 127.43 (2C), 126.88, 126.37 (2C), 78.79, 67.66, 58.87, 54.04, 43.56, 37.12, 29.97 ppm.

4.1.6. (*S*)-*N*-((*S*)-1-Phenylethyl)pyrrolidine-2-carboxamide 1[22]

Compound **10** (2.0 g, 6.2 mmol) was dissolved in dry dichloromethane (2.8 mL) after which trifluoroacetic acid (2.8 mL) was added, then stirred at room temperature for 6 h. Reaction mixture was concentrated in vacuo, dissolved in H_2O (10 mL), and the pH was adjusted to ~8 by adding Et_3N dropwise at 0 °C. The product was then extracted with dichloromethane (3 × 10 mL), dried over $MgSO_4$ and concentrated in vacuo to yield an oil, which was purified by column chromatography using methanol/dichloromethane (10:90), to afford product **1** in 98% yield (1.34 g). $[\alpha]_D^{25} = -71.1$ (*c* 1.10, MeOH). IR (film): ν = 3288, 3087, 1778, 1672, 1666 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (br s, 1H), 7.32–7.19 (m, 5H), 4.91 (d, *J* = 6.9 Hz, 1H), 4.54–4.54 (m, 1H), 3.27–3.26 (m, 2H), 2.40–2.36 (m, 1H), 1.97–1.87 (m, 3H), 1.42 (d, *J* = 6.9 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.73, 142.94, 128.66 (2C), 127.35, 125.29 (2C) 59.84, 50.45, 46.68, 29.87, 24.05, 21.72 ppm. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{13}H_{19}N_2O$: 219.1492; found: 219.1498.

4.1.7. (2*S*,4*R*)-4-Hydroxy-*N*-((*S*)-1-phenylethyl)pyrrolidine-2-carboxamide 2[22]

The compound **11** (2.0 g, 5.98 mmol) was dissolved in dry dichloromethane (2.8 mL), after which trifluoroacetic acid (2.80 mL) was added, then stirred at room temperature for 6 h. The reaction mixture was concentrated in vacuo, dissolved in H_2O (10 mL), and the pH was adjusted to ~8 by adding Et_3N dropwise at 0 °C. The product was then extracted with dichloromethane (3 × 10 mL), dried over $MgSO_4$ and concentrated in vacuo to yield an oil, which was purified by column chromatography using methanol/dichloromethane (10:90), to afford product **2** (1.37 g, 98%). $[\alpha]_D^{25} = -78.7$ (*c* 1.7, MeOH). IR (film): ν = 3298, 3078, 1674, 1660 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (br s, 1H), 6.90–6.78 (m, 5H), 4.6–4.53 (m, 1H), 4.20–4.05 (m, 2H), 2.96–2.91 (m, 2H), 2.10–2.05 (m, 1H), 1.43–1.41 (m, 1H), 1.08–1.01 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.37, 142.87, 127.60 (2C), 126.15, 124.97 (2C), 69.12, 57.53, 53.02, 48.53, 38.18, 21.40 ppm. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{13}H_{19}N_2O_2$: 235.1441; found: 235.1452.

4.1.8. (2*S*,4*R*)-4-Hydroxy-*N*-((*R*)-1-phenylethyl)pyrrolidine-2-carboxamide 3[22]

A similar procedure was followed to that of compound **2**, to give a colourless oil **3** (1.37 g, 98%). $[\alpha]_D^{25} = +25.9$ (*c* 1, MeOH). IR (film): ν = 3298, 3078, 1674, 1660 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (br s, 1H) 6.96–6.08 (m, 5H), 5.10–5.08 (m, 1H), 4.76–4.71 (m, 1H), 4.41–4.27 (m, 2H), 3.13–3.13 (m, 2H), 2.30–2.28 (m, 1H), 1.77–1.75 (m, 1H), 1.22–1.01 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.52, 143.58, 129.92 (2C), 127.27, 126.40 (2C), 70.18, 58.65, 54.10, 49.72, 39.22, 22.22 ppm. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{13}H_{19}N_2O_2$: 235.1441; found: 235.1443.

4.1.9. (2*S*,4*R*)-*N*-Benzyl-4-hydroxypyrrolidine-2-carboxamide 4[22]

Compound **13** (2.00 g, 6.25 mmol) was taken in dry dichloromethane (2.80 mL) with TFA (2.80 mL) using the method as previously described for **2**, to give an oil. The oil was purified on silica gel using methanol/dichloromethane (10:90), yielding the product **4** as an oil (1.35 g, 98%). $[\alpha]_D^{25} = -25.7$ (*c* 1.29 in MeOH), IR (film): ν = 3300, 2976, 1685, 1664 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (br s, 1H), 6.69–6.66 (m, 5H), 3.93–3.79 (m, 4H), 2.82–2.68 (m, 2H), 1.90–1.87 (m, 1H), 1.41–1.37 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.03, 137.08, 127.32 (2C), 126.37 (2C), 126.08, 68.60, 57.26, 52.67, 42.02, 39.96 ppm. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{12}H_{16}N_2O_2$: 221.1290; found: 221.1286.

4.1.10. *cis*-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 15

cis-4-Hydroxy-L-proline hydrochloride **14** (0.50 g, 3.0 mmol) was dissolved in 6 mL of THF/H_2O (2:1) and then treated with 10% aqueous NaOH (1.25 mL) followed by the addition of di-*tert*-butyldicarbonate (0.95 g, 4.42 mmol). The reaction mixture was stirred at room temperature overnight and then THF was removed by rotavapor. The residue was adjusted to pH 2 by the addition of 10% aqueous $KHSO_4$. The acidic solution was extracted several times with ethyl acetate. The combined organic extracts were washed with H_2O and brine, and dried over anhydrous Na_2SO_4. The solvent was removed by a rotary evaporator to afford compound **15** as a syrup (542 mg, 78%), which was used without purification for the next step. $[\alpha]_D^{25} = 15.3$ (*c* 1.02, MeOH). IR (film): ν = 3462, 2976, 2934, 1740, 1639 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (br s, 1H), 5.11–5.09 (m, 2H), 4.94–4.93 (m, 1H), 4.40 (s, 1H), 3.64–3.62 (m, 1H), 3.49–3.44 (m, 2H), 2.27–1.90 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.47, 151.74, 75.81, 67.15, 55.24, 52.27, 35.97, 25.63 ppm. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{10}H_{18}NO_5$: 232.1185; found: 232.1171.

4.1.11. (2*R*,4*R*)-*tert*-Butyl 4-hydroxy-2-((*S*)-1-phenylethylcarbamoyl)pyrrolidine-1-carboxylate 16

Compound **15** (0.542 g, 2.34 mmol) was dissolved in dry dichloromethane (6 mL), after which triethylamine (0.39 mL, 2.79 mmol) and ethyl chloroformate (20.26 mL, 2.79 mmol, in 1 mL dry dichloromethane) were added dropwise at 0 °C. The solution was stirred at the same temperature for 15 min and then (*S*)-1-phenylethyl amine (0.30 mL, 2.34 mmol) was added slowly. The resulting mixture was warmed to room temperature and stirred for 5 h. The reaction mixture was washed with 10% HCl solution, saturated $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the residue was recrystallized from ethyl acetate to afford **16** as a colourless oil (450 mg, 58%). $[\alpha]_D^{25} = -53.8$ (*c* 0.51, MeOH). IR (film): ν = 3298, 3078, 1674, 1660 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (br s, 1H) 7.28–7.19 (m, 5H), 5.00 (t, *J* = 12.97 Hz, 1H), 4.43–4.30 (m, 1H), 3.41–3.38 (m, 1H), 2.32–2.28 (m, 1H), 2.15–2.07 (m, 1H), 2.00–1.93 (m, 1H), 1.44 (d, *J* = 6.87 Hz, 3H), 1.41 (s, 9H), 1.30–1.26 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.04, 155.59, 142.87, 128.59 (2C), 126.99, 125.71 (2C), 80.67, 70.65, 59.67, 56.92, 49.34, 35.54, 28.23, 22.62 ppm. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{27}N_2O_4$: 335.1971; found: 335.1974.

4.1.12. (2*R*,4*R*)-4-Hydroxy-*N*-((*S*)-1-phenylethyl)pyrrolidine-2-carboxamide 5

Compound **13** (400 mg, 1.19 mmol) was taken in dry dichloromethane (0.57 mL) with TFA (0.57 mL) using the method as previously described for **2**, to give an oil. The oil was purified on silica gel using methanol/dichloromethane (10:90), yielding product **5** as an oil (273 mg 98%). $[\alpha]_D^{25} = -24.8$ (*c* 0.58, MeOH). IR (film): 3298, 3078, 1674, 1660 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (br s, 1H) 7.10–7.03 (m, 5H), 4.78–4.73 (m, 1H), 4.23–4.19 (m, 2H), 3.19–3.16 (m, 1H), 3.05–3.01 (m, 1H), 2.34–2.26 (m, 1H), 1.96–1.93 (m, 1H), 1.23–1.20 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.49, 142.77, 128 (2C), 126.65, 125.73 (2C), 68.80, 57.89, 50.04, 49.29, 38.05, 21.42 ppm. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{13}H_{19}N_2O_2$: 235.1441; found: 235.1443.

4.2. General experimental procedure for the aldol reaction

4.2.1. Reaction in solvent

Organocatalyst **2** (23.4 mg, 0.10 mmol) was dissolved in a solvent (1 mL), as described in Table 1, cyclohexanone (0.310 mL, 3 mmol) and acetic acid (6 μL, 0.10 mmol) and was stirred for 20 min at 15 °C after which 4-nitrobenzaldehyde (151 mg,

1 mmol) was added. The reaction mixture was stirred for a specified reaction time period at the same temperature. The solvent was removed by a rotary evaporator under reduced pressure to give a crude aldol adduct, which was purified by flash column chromatography on silica gel (hexane/ethyl acetate (3:1)). The ee and dr of the aldol product were determined by HPLC using chiral column (chiralpak AD-H) using hexane/2-propanol as the mobile phase.

4.2.2. Reaction in solvent free conditions

Organocatalyst **2** (23.4 mg, 0.10 mmol), cyclohexanone (0.310 mL, 3 mmol) and acetic acid (6 μL, 0.10 mmol) were stirred for 20 min at 15 °C, then 4-nitrobenzaldehyde (151 mg, 1 mmol) was added. The reaction mixture was stirred for a specified reaction time period at the same temperature. The crude aldol product was then purified by flash column chromatography on silica gel (hexane/ethyl acetate (3:1)). The diastereomeric ratio was determined by ^{1}H NMR of the crude product. The ee of the aldol product was determined by HPLC using chiral column (chiralpak AD-H and OD-H) using hexane/2-propanol as the mobile phase.

4.2.3. (*S*)-2-((*R*)-Hydroxy(4-nitrophenyl)methyl)cyclohexanone (Table 2, entry 6)[8b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.39 Hz, 2H), 7.44 (d, *J* = 7.93 Hz, 2H), 4.85 (d, *J* = 7.63 Hz, 1H), 2.60–2.53 (m, 1H), 2.43–2.27 (m, 2H), 2.06–2.01 (m, 1H), 1.80–1.74 (m, 1H), 1.69–1.45 (m, 3H), 1.36–1.29 (m, 1H) ppm. HPLC analysis: Chiralpak AD-H (Hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm, 25 °C): t_{minor} = 22.6 min, t_{major} = 30.9 min, ee: 95%.

4.2.4. (*S*)-2-((*R*)-Hydroxy(phenyl)methyl)cyclohexanone (Table 3, entry 1)[8b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.24 (m, 5H), 4.75 (d, *J* = 8.54 Hz, 1H), 2.63–2.56 (m, 1H), 2.46–2.42 (m, 1H), 2.36–2.28 (m, 1H), 2.05–2.02 (m, 1H), 1.75–1.48 (m, 4H), 1.28–1.23 (m,1H) ppm. HPLC analysis: Chiralpak AD-H (Hexane/*i*-PrOH = 80:20, 1.0 mL/min, 254 nm, 25 °C): t_{major} = 15.7 min, t_{minor} = 20.3 min, ee: 76%.

4.2.5. (*S*)-2-((*R*)-Hydroxy(naphthyl)methyl)cyclohexanone (Table 3, entry 2)[8b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 7.63 Hz, 1H), 7.89–7.74 (m, 2H), 7.55–7.43 (m, 4H), 5.57 (d, *J* = 9.16 Hz, 1H), 3.01–3.94 (m, 1H), 2.51–2.32 (m, 2H), 2.04–2.02 (m, 1H), 1.69–1.63 (m, 2H), 1.44–1.24 (m, 3H) ppm. HPLC analysis: Chiralcel OD-H (Hexane/*i*-PrOH = 90:10, .5 mL/min, 280 nm, 25 °C): t_{minor} = 26.8 min, t_{major} = 30.7 min, ee: 80%.

4.2.6. (*S*)-2-((*R*)-Hydroxy(2-nitro-phenyl)methyl)cyclohexanone (Table 3, entry 3)[8b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.39 Hz, 1H), 7.67 (d, *J* = 7.25 Hz, 1H), 7.57 (t, *J* = 7.63 Hz, 1H), 7.37 (t, *J* = 7.63 Hz, 1H), 5.38 (d, *J* = 7.63 Hz, 1H), 2.87–2.82 (m, 1H), 2.43–2.30 (m, 2H), 2.10–2.04 (m, 1H), 1.93–1.86 (m, 1H), 1.79–1.73 (m, 1H), 1.67–1.64 (m, 1H), 1.45–1.34 (m, 1H), 1.01–.97 (m, 1H) ppm. HPLC analysis: Chiralcel OD-H (Hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm, 25 °C): t_{major} = 16.0 min, t_{minor} = 18.4 min, ee: 93%.

4.2.7. (*S*)-2-((*R*)-Hydroxy(2-fluoro-phenyl)methyl)cyclohexanone (Table 3, entry 4)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.39 (m, 1H), 7.19–7.06 (m, 2H), 6.96–6.89 (m, 1H), 5.11 (d, *J* = 9.16 Hz, 1H), 4.14 (br s, 1H), 2.64–2.57 (m, 1H), 2.45–2.26 (m, 2H), 2.09–1.98 (m, 1H), 1.72–1.37 (m, 4H), 1.20–1.16 (m, 1H) ppm. HPLC analysis: Chiralcel OD-H (Hexane/*i*-PrOH = 90:10, 1.0 mL/min, 220 nm, 25 °C): t_{major} = 11.5 min, t_{minor} = 12.0 min, ee: 94%.

4.2.8. (*S*)-2-((*R*)-Hydroxy(4-fluoro-phenyl)methyl)cyclohexanone (Table 3, entry 5)[8b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.24 (m, 2H), 7.02–6.97 (m, 2H), 4.75 (d, *J* = 8.54 Hz, 1H), 2.58–2.51 (m, 1H), 2.44–2.30 (m, 2H), 2.09–2.02 (m, 1H), 1.83–1.54 (m, 3H), 1.30–1.19 (m, 2H) ppm. HPLC analysis: Chiralcel OD–H (Hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, 25 °C): t_{major} = 11.4 min, t_{minor} = 18.1 min, ee: 72%.

4.2.9. (*S*)-2-((*R*)-Hydroxy(2-chloro-phenyl)methyl)cyclohexanone (Table 3, entry 6)[8b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (dd, *J* = 7.93, 1.83 Hz, 1H), 7.24–7.19 (m, 2H), 7.13–7.09 (m, 1H), 5.26 (d, *J* = 7.93 Hz, 1H), 2.62–2.56 (m, 1H), 2.39–2.21 (m, 2H), 1.98–1.96 (m, 1H), 1.73–1.70 (m, 1H), 1.65–1.43 (m, 3H), 1.21–1.17 (m, 1H) ppm. HPLC analysis: Chiralcel OD-H (Hexane/*i*-PrOH = 92:8, 0.5 mL/min, 220 nm, 25 °C): t_{major} = 14.2 min, t_{minor} = 16.6 min, ee: 93%.

4.2.10. (*S*)-2-((*R*)-Hydroxy(4-chloro-phenyl)methyl)cyclohexanone (Table 3, entry 7)[8b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.16 (m, 4H), 4.70 (d, *J* = 12.82 Hz, 1H), 4.15 (br s, 1H), 2.53–2.46 (m, 1H), 2.40–1.34 (m, 2H), 2.00–1.97 (m, 1H), 1.72–1.41 (m, 3H), 1.25–1.16 (m, 2H) ppm. HPLC analysis: Chiralpak AD-H (Hexane/*i*-PrOH = 90:10, 1.0 mL/min, 224 nm, 25 °C): t_{minor} = 13.1 min, t_{major} = 15.6 min, ee: 86%.

4.2.11. (*S*)-2-((*R*)-Hydroxy(2-bromo-phenyl)methyl)cyclohexanone (Table 3, entry 8)[8b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.41 (m, 2H), 7.25 (t, *J* = 7.32 Hz, 1H), 7.06–7.02 (m, 1H), 5.22 (d, *J* = 7.93 Hz, 1H), 2.64–2.57 (m, 1H), 2.36–2.24 (m, 2H), 2.02–1.97 (m, 1H), 1.75–1.47 (m, 4H), 1.20–1.17 (m, 1H) ppm. HPLC analysis: Chiralpak AD-H (Hexane/*i*-PrOH = 90:10, 1.0 mL/min, 220 nm, 25 °C): t_{major} = 6.6 min, t_{minor} = 7.2 min, ee: 80%.

4.2.12. (*S*)-2-((*R*)-Hydroxy(4-bromo-phenyl)methyl)cyclohexanone (Table 3, entry 9)[8b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.39 Hz, 2H), 7.14 (d, *J* = 8.39 Hz, 2H), 4.71 (d, *J* = 8.39 Hz, 1H), 2.55–2.38 (m, 2H), 2.34–2.26 (m, 1H), 2.06–2.01 (m, 1H), 1.76–1.73 (m, 1H), 1.65–1.44 (m, 3H), 1.29–1.22 (m, 1H) ppm. HPLC analysis: Chiralpak AD-H (Hexane/*i*-PrOH = 90:10, 0.3 mL/min, 222 nm, 25 °C): t_{minor} = 45.3 min, t_{major} = 53.6 min, ee: 84%.

4.2.13. (*S*)-2-((*R*)-Hydroxy(2-methoxy-phenyl)methyl)cyclohexanone (Table 3, entry 10)[8b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, *J* = 7.63 Hz, 1H), 7.18 (d, *J* = 8.01 Hz, 1H), 6.89 (d, *J* = 7.63 Hz, 1H), 6.77 (d, *J* = 7.63 Hz, 1H), 5.18 (d, *J* = 8.39 Hz, 1H), 3.72 (s, 3H), 3.33 (br s, 1H), 2.68–2.61 (m, 1H), 2.39–2.25 (m, 2H), 1.97–1.93 (m, 1H), 1.71–1.34 (m, 4H) 1.18–1.16 (m, 1H) ppm. HPLC analysis: Chiralpak OD-H (Hexane/*i*-PrOH = 92:8, 0.5 mL/min, 222 nm, 25 °C): t_{major} = 33.8 min, t_{minor} = 36.1 min, ee: 87%.

4.2.14. (*S*)-2-((*R*)-Hydroxy(4-methoxy-phenyl)methyl)cyclohexanone (Table 3, entry 11)[8b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–7.20 (m, 2H), 6.87–6.85 (m, 2H), 4.73 (d, *J* = 8.54 Hz, 1H), 3.81 (s, 3H), 2.62–2.55 (m, 1H), 2.45–2.33 (m, 2H), 2.07–2.04 (m, 1H), 1.78–1.54 (m, 3H), 1.30–1.23 (m, 2H) ppm. HPLC analysis: Chiralpak AD-H (Hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm, 25 °C): t_{minor} = 20.0 min, t_{major} = 20.9 min, ee: 56%.

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4.2.15. (*S*)-2-((*R*)-Hydroxy(2-trifluoromethyl-phenyl)methyl)-cyclohexanone (Table 3, entry 12)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 7.32 Hz, 1H), 7.51–7.44 (m, 2H), 7.25 (t, J = 7.93 Hz, 1H), 5.17 (d, J = 8.54 Hz, 1H), 2.66–2.59 (m, 1H), 2.39–2.20 (m, 2H), 1.97–1.91 (m, 1H), 1.64–1.13 (m, 5H) ppm. HPLC analysis: Chiralcel AD–H (Hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm, 25 °C): t_{major} = 30.7 min, t_{minor} = 33.5 min, ee: 93%.

4.2.16. (*S*)-2-((*R*)-Hydroxy(4-trifluoromethyl-phenyl)methyl)-cyclohexanone (Table 3, entry 13)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 8.39 Hz, 2H), 7.43 (d, J = 9.16 Hz, 2H), 4.85 (d, J = 8.39 Hz, 1H), 4.09 (br s, 1H), 2.63–2.34 (m, 3H), 2.12–2.06 (m, 1H), 1.82–1.52 (m, 4H), 1.37–1.25 (m, 1H) ppm. HPLC analysis: Chiralpak AD–H (Hexane/*i*-PrOH = 90:10, 0.5 mL/min, 230 nm, 25 °C): t_{minor} = 10.3 min, t_{major} = 13.2 min, ee: 75%.

4.2.17. (2*S*,4*S*)-4-*tert*-Butyl-2-((*R*)-hydroxy-(2-nitrophenyl)methyl)cyclohexanone 20[8b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 8.39 Hz, 1H), 7.71 (d, J = 8.39 Hz, 1H), 7.61 (d, J = 8.39 Hz, 1H), 7.41 (d, J = 9.16 Hz, 1H), 5.45 (d, J = 7.63 Hz, 1H), 2.84–2.78 (m, 1H), 2.40–2.39 (m, 2H), 1.93–1.89 (m, 1H), 1.64–1.47 (m, 4H), 0.76 (s, 9H) ppm; HPLC analysis: Chiralpak AD-H (Hexane/*i*-PrOH = 95:5, .5 mL/min, 254 nm, 25 °C): t_{minor} = 41.0 min, t_{major} = 51.8 min, ee: 90%.

4.2.18. (2*S*,4*S*)-4-*tert*-Butyl-2-((*R*)-hydroxy-(4-nitro-phenyl)methyl)cyclohexanone 21[8b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, J = 9.16 Hz, 1H), 7.47 (d, J = 9.16 Hz, 1H), 4.90 (d, J = 9.92 Hz, 1H), 3.60 (s, 1H), 2.62–2.55 (m, 1H), 2.48–2.30 (m, 2H), 1.93–1.86 (m, 1H), 1.59–1.31 (m, 4H), 0.71 (s, 9H) ppm; HPLC analysis: Chiralpak AD-H (Hexane/*i*-PrOH = 90:10, 0.5 mL/min, 254 nm, 25 °C): t_{major} = 27.7 min, t_{minor} = 36.1 min, ee: 85%.

4.2.19. 2-[Hydroxy(2-nitro-phenyl)methyl]-cyclopentanone (Table 4, entry 1)[8b]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 (d, J = 8.54 Hz, 0.4H), 7.89 (d, J = 7.93 Hz, 1H), 7.83 (d, J = 7.93 Hz, 1H), 7.74 (dd, J = 7.93, 4.27 Hz, 1H), 7.60–7.55 (m, 2H), 7.46 (d, J = 7.93 Hz, 1H), 7.37 (dd, J = 7.93, 3.97 Hz, 1H), 5.80 (s, 1H *syn*), 5.34 (d, J = 7.93 Hz, 1H *anti*), 4.45 (s, .7H), 2.74–2.71 (m, .8H), 2.63–2.59 (m, 1H), 2.49–2.44 (m, .7H), 2.38–2.32 (m, 1H), 2.27–2.24 (m, 1H), 2.13–1.87 (m, 4H), 1.72–1.61 (m, 4H), 1.22–1.17 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ *syn* HPLC analysis Chiralcel OD-H (Hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, 25 °C): *syn*: t_{minor} 11.5 min, t_{major} 14.7 min, ee: 55%; *anti*: t_{major} 20.8 min (*S*, *R*), t_{minor} 22.4 min (*R*, *S*), ee: 77%.

4.2.20. 2-[Hydroxy(4-nitro-phenyl)methyl]-cyclopentanone (Table 4, entry 2)[8b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16–8.06 (m, 3H), 7.45–7.42 (m, 3.6H), 5.48 (d, J = 2.44 Hz, 0.66H *syn*), 4.79 (d, J = 9.16 Hz, 1H *anti*), 3.48–3.32 (m, 1H), 2.99–2.71 (m, 1H), 2.43–2.29 (m, 4H), 2.24–2.01 (m, 1.6H), 1.95–1.84 (m, 2H) 1.65–1.43 (m, 2H) ppm. HPLC analysis Chiralcel AD-H (Hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm, 25 °C): *syn*: t_{major} 14.7 min, t_{minor} 19.1 min, ee: 45%; *anti*: t_{minor} 23.3 min (*R*, *S*), t_{major} 24.6 min (*S*, *R*), ee: 61%.

4.2.21. 2-[Hydroxy(2-fluoro-phenyl)methyl]-cyclopentanone (Table 4, entry 3)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.40 (m, 1H), 7.19–7.10 (m, 1H), 7.04 (t, J = 7.63 Hz, 1.9H), 6.88 (t, J = 8.39 Hz, 1H), 5.48 (d, J = 3.05 Hz, 1H *syn*), 4.99 (d, J = 9.16 Hz, .23 *anti*), 2.49–2.40 (m, 1H), 2.38–2.12 (m, 2H), 2.06–1.97 (m, 1H), 1.93–1.82 (m, 2H), 1.67–1.48 (m, 2.6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ *syn* 220.36, 158.80 (d, J = 245.80 Hz), 129.90 (d, J = 13.42 Hz), 128.39 (d, J = 8.63 Hz), 127.25 (d, J = 3.83 Hz), 123.91 (d, J = 3.83 Hz), 114.73 (d, J = 21.09 Hz), 65.12, 54.43, 38.94, 22.63 20.22; *anti* 222.99, 159.67 (d, J = 252.08 Hz), 130.83 (d, J = 8.63 Hz), 129.12 (d, J = 8.63 Hz), 127.99 (d, J = 3.83 Hz), 124.35 (d, J = 2.88 Hz), 115.02 (d, J = 22.04 Hz), 67.91, 54.86, 38.44, 26.27, 20.22 ppm. HPLC analysis Chiralpak AD-H (Hexane/*i*-PrOH = 95:5, .5 mL/min, 220 nm, 25 °C): *syn*: t_{minor} 11.5 min, t_{major} 14.7 min, ee: 61%; *anti*: t_{major} 20.8 (*S*, *R*) min, t_{minor} 22.4 min (*R*, *S*), ee: 76%.

4.2.22. 2-[Hydroxy-(4-fluoro-phenyl)methyl]-cyclopentanone (Table 4, entry 4)[8b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–7.18 (m, 4H), 6.95–6.90 (m, 3.5H), 5.16 (d, J = 2.29 Hz, 1H *syn*), 4.61 (d, J = 9.16 Hz, 1H *anti*), 2.36–2.26 (m, 3H), 2.23–1.99 (m, 3H), 1.95–1.84 (m, 2H), 1.73–1.54 (m, 3H), 1.44–1.35 (m, 1H), 1.20–1.15 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ *syn* 220.48, 161.82 (d, J = 244.41 Hz), 138.51, 128.10 (d, J = 7.67 Hz, 2C), 115.05 (d, J = 21.09 Hz, 2C), 70.61, 56.11, 39.10, 26.74, 22.53; *anti* 222.88, 162.28 (d, J = 245.37 Hz), 137.17, 127.06 (d, J = 7.67 Hz, 2C), 115.15 (d, J = 21.09 Hz, 2C), 74.37, 55.25, 38.59, 26.74, 20.25 ppm. HPLC analysis: Chiralpak AD-H (Hexane/*i*-PrOH = 90:10, 1.0 mL/min, 222 nm, 25 °C): *syn*: t_{major} 8.0 min, t_{minor} 9.5 min, ee: 26%; *anti*: t_{major} 10.8 min (*S*, *R*), t_{minor} 11.8 min (*R*, *S*), ee: 54%.

4.2.23. 2-[Hydroxy-(2-chloro-phenyl)methyl]-cyclopentanone (Table 4, entry 5)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.40 (m, 1H), 7.19–7.00 (m, 3H), 6.93–6.83 (m, 1H), 5.48 (d, J = 3.05 Hz, 1H *syn*), 4.99 (d, J = 9.16 Hz, 0.29H *anti*), 3.41–3.25 (m, 1H), 2.49–2.42 (m, 1H), 2.38–2.14 (m, 1H), 2.07–1.97 (m, 1H), 1.91–1.81 (m, 2H), 1.67–1.48 (m, 3H), ^{13}C NMR (75 MHz, $CDCl_3$): δ *syn* 220.24, 140.23, 130.75, 129.03, 128.11, 127.38, 126.66, 67.59, 53.36, 38.94, 22.22, 20.23; *anti* 222.76, 138.94, 132.16, 129.11, 128.75, 128.20, 127.19, 70.15, 55.22, 38.50, 26.29, 20.36 ppm. HPLC analysis Chiralpak AD-H (Hexane/*i*-PrOH = 95:5, 1.0 mL/min, 222 nm, 25 °C): *syn*: t_{minor} 7.4 min, t_{major} 8.8 min ee: 54%; *anti*: t_{major} 12.4 min (*S*, *R*), t_{minor} 13.0 min (*R*, *S*), ee: 85%.

4.2.24. 2-[Hydroxy-(4-chloro-phenyl)methyl]-cyclopentanone (Table 4, entry 6)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–7.16 (m, 8.93H), 5.18 (d, J = 2.29 Hz, 1.23H *syn*), 4.61 (d, J = 9.16 Hz, 1H *anti*), 2.38–2.27 (m, 3H), 2.25–2.00 (m, 3H), 1.94–1.83 (m, 3H), 1.71–1.58 (m, 5H), 1.42–1.37 (m, 0.66H), 1.17–1.12 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ *syn* 220.37, 141.26, 132.81, 128.68 (2C), 127.84 (2C), 74.44, 55.17, 38.61, 26.76, 20.35; *anti* 222.79, 139.85, 132.84, 128.37 (2C), 126.88 (2C), 70.62, 56.04, 39.09, 26.76, 22.52 ppm. HPLC analysis Chiralpak AD-H (Hexane/*i*-PrOH = 90:10, 1.0 mL/min, 222 nm, 25 °C): *syn*: t_{major} 7.9 min, t_{minor} 9.6 min, ee: 33%; *anti* t_{major} 11.3 min (*S*, *R*), t_{minor} 12.2 min (*S*, *R*), ee: 56%.

4.2.25. 2-[Hydroxy-(2-methoxy-phenyl)methyl]-cyclopentanone (Table 4, entry 7)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (t, J = 9.92 Hz, 1H), 7.28–7.21 (m, 1H), 6.99–6.94 (m, 2H), 6.85 (t, J = 8.39 Hz, 2H), 5.56 (d, J = 2.29 Hz, 1H *syn*), 5.19 (d, J = 12.21 Hz, 1H *anti*), 3.80 (s, 4.6H), 2.83–2.77 (m, 1H), 2.64–2.58 (m, 1H), 2.51–2.49 (m, 1H), 2.36–2.10 (m, 3H), 2.00–1.96 (m, 2H), 1.72–1.69 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ *syn* 220.80, 155.40, 130.87, 127.90, 126.35, 120.32, 109.75, 66.56, 55.23, 55.01, 39.07, 26.37, 20.34; *anti* 123.14, 156.30, 129.64, 128.55, 127.48, 120.80, 110.36, 68.28, 55.20, 56.68, 38.54, 26.37, 22.81 ppm; HPLC analysis Chiralpak AD-H (Hexane/*i*-PrOH = 95:5, .5 mL/min, 222 nm, 25 °C): *syn*: t_{minor} 11.5 min, t_{major} 14.7 min, ee: 50%.

4.2.26. 2-[Hydroxy-(4-methoxy-phenyl)methyl]-cyclopentanone (Table 4, entry 8)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57–7.51 (m, 0.7H), 7.24–7.20 (m, 2H), 6.93 (d, J = 8.54 Hz, 1H), 6.83 (d, J = 8.54 Hz, 2H), 5.19 (d, J = 3.66 Hz, 1H *syn*), 4.62 (d, J = 12.82 Hz, 0.4 *anti*), 3.82 (s, 0.62), 3.76 (s, 3H), 3.05 (m, 1H), 2.45–2.30 (m, 2H), 2.14–2.13 (m, 1H), 2.02–1.88 (m, 2H), 1.86–1.78 (m, 1H), 1.74–1.61 (m, 1H), 1.47–1.22 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ *syn* 220.72, 159.19, 134.86, 127.69 (2C), 113.68 (2C), 74.64, 56.06, 55.17, 38.69, 26.89, 20.31; *anti* 223.20, 158.70, 133.57, 126.71 (2C), 113.61 (2C), 71.18, 56.06, 55.29, 39.19, 22.84, 24.43 ppm. HPLC analysis Chiralpak AD-H (Hexane/*i*-PrOH = 90:10, 1.0 mL/min, 222 nm, 25 °C): *anti*: t_{major} 17.0 min (*S*, *R*), and t_{minor} 18.6 min (*R*, *S*), ee: 25%.

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