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Protonated (*S*)-prolinamide derivatives—water compatible organocatalysts for direct asymmetric aldol reaction

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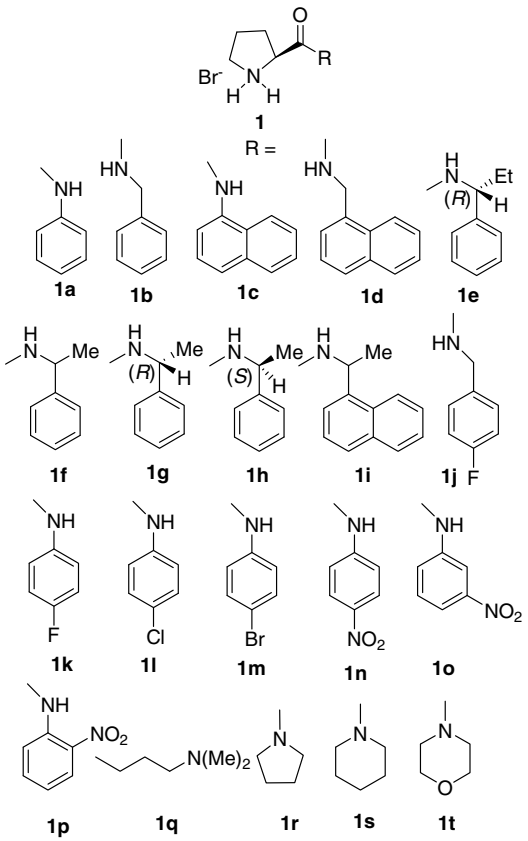
ABSTRACT

Protonated chiral (*S*)-prolinamide derivatives have been developed as water compatible highly efficient organocatalysts for a direct enantioselective aldol reaction. A simple protonated (*S*)-prolinamide organocatalyst prepared from L-proline and 3-nitroaniline catalyzes the aldol reaction of unmodified ketones and a variety of aromatic aldehydes yielding aldol product in high yield with enantioselectivities of up to 98% and diastereoselectivity of up to >99:1.

1. Introduction

The main challenge in developing asymmetric catalysis lies in the mimicking of natural enzymes. Designed enzyme models should be both efficient and capable of accepting a broad range of substrates. Aldolase enzymes[1] (Types I and II) and antibodies[2] are known to catalyze aldol reactions in aqueous media. In recent years, L-proline and its derivatives have been shown to mimic the enzymatic activity of aldolase Type I enzymes in organic solvents, resulting in the formation of an aldol product with high enantioselectivity.[3] The L-proline catalysis of aldol reactions in water leads to racemic products.[4] This is probably due to interruption of the H-bonding and other ionic interactions in the transition state that are critical for any enantioselective reaction.[5] Alternately, Hayashi has obtained enantioselective aldol product with wet proline.[6] However, over the last two years there have been very few reports of organocatalysts that provide satisfactory enantio- and diastereoselectivities in water.[7,5a] Using water as a solvent and (*S*)-prolinamide derivatives as catalysts, our group has reported the first enantioselective direct aldol reaction.[8] Our interest was to design simple proline-based organocatalysts that catalyze the aldol reaction to yield the aldol product in high enantio- and diastereoselectivity. The evidence gathered from studies on natural aldolases shows that the active center in the aldolase enzyme is the protonated ε-amino group of a lysine residue that lies in a hydrophobic pocket composed of long chain peptides with perturbed pK_a.[9] We envisaged that protonated prolinamides,[8] containing aromatic rings, will act as ideal models for an aldolase Type I enzyme, where on the one hand the aromatic group provides suitable hydrophobic interactions,[10] and on the otherhand, the amidic –NH group provides appropriate hydrogen bonding[11] for suitable orientation of the substrate. In the case of amines, Spencer et al. observe that nucleophilic catalysis in water becomes increasingly effective as the base strength of the amine catalyst is decreased.[12] This can be easily achieved by the protonation of the amine with an acid.



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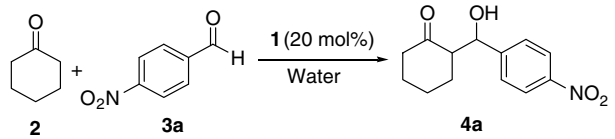
Herein, we report the use of protonated (*S*)-prolinamide derivatives as water compatible organocatalysts for direct aldol reaction of ketones with aromatic aldehydes.

2. Result and discussion

In our preliminary study, the aldol reaction of cyclohexanone **2** and 4-nitrobenzaldehyde **3a** was carried out with catalyst **1a** using water as a solvent. The aldol product **4a** was isolated with a yield of 81%, a diastereomeric ratio of 95:5 (*anti*:*syn*) and ee of 88% for the major *anti*-product (Table 1, entry 1). Initially, the reaction mixture was biphasic, consisting of an upper thin layer of cyclohexanone and a lower bulky layer of water containing dissolved protonated catalyst, as well as undissolved aldehyde at the bottom. After a few hours of stirring, an organic layer appeared at the bottom of the reaction vessel, which upon investigation was found to consist of product **4a**. The screening of other catalysts for the aldol reaction provided **4a** in moderate to good diastereoselectivity and enantioselectivity. Increasing the hydrophobicity of the catalyst, via introduction of the naphthyl group as in **1c**, had a very minor effect on the enantioselectivity (Table 1, entry 3). The introduction of a CH_2 spacer between the aromatic group and nitrogen gave lower diastereoselectivities and enantioselectivities (Table 1, entries 2 and 4). To explore the possibility of a match and mismatch effect of the stereogenic centers on the catalysts, diastereomeric prolinamide catalysts **1f**, **1g**, and **1h** were prepared. However, they yielded **4a** with lower diastereoselectivities and moderate enantioselectivities (Table 1, entries 6–8). Moderate enantio- and diastereoselectivities were observed with catalysts **1e** and **1i** (Table 1, entries 5 and 9). The catalysts **1k** to **1o**, having an electron-withdrawing group in the aromatic ring, afford **4a** with good enantioselectivity on the one hand, but moderate diastereoselectivity on the other (Table 1, entries 11–15).

Table 1
Screening of various organocatalysts for direct aldol reaction[a]



2 **3a** **4a**

Entry	Catalyst	Time (h)	Yield[b] (%)	dr[c] *anti*:*syn*	ee[d] (%)
1	**1a**	29	81	95:5	88
2	**1b**	30	81	90:10	85
3	**1c**	72	79	93:7	90
4	**1d**	72	81	90:10	74
5	**1e**	48	76	69:31	81
6	**1f**	50	70	87:13	85
7	**1g**	17	87	78:22	83
8	**1h**	17	85	83:17	76
9	**1i**	29	82	92:8	67
10	**1j**	27	83	85:15	83
11	**1k**	19	90	78:22	87
12	**1l**	19	88	80:20	87
13	**1m**	19	89	75:25	82
14	**1n**	24	89	82:12	89
15	**1o**	18	81	87:13	90
16	**1p**	24	73	82:18	41
17	**1q**	14	89	71:29	75
18	**1r**	20	88	69:31	76
19	**1s**	22	85	76:24	84
20	**1t**	24	81	73:27	66

[a] Reaction conditions: 1 mL of water, 10 mmol of ketone, 2 mmol of aldehyde, 20 mol % catalyst, 27 °C.
[b] Yields determined after chromatographic purifications.
[c] Diastereomeric excess determined by NMR of crude reaction mixture.
[d] Enantiomeric excess determined by chiral HPLC for *anti*-diastereomer.

Catalyst **1p**, with an electron-withdrawing group at the *ortho*-position, affords **4a** with lower enantio- and diastereoselectivity (Table 1, entry 16). This is perhaps due to the steric hindrance caused by the nitro group in the transition state. The catalysts **1j**, **1q**, **1r**, **1s**, and **1t** provide **4a** with moderate enantioselectivity (Table 1, entries 10 and 17–20).

The two catalysts **1c** and **1o** that provided **4a** in 90% ee were selected for further optimization of the reaction conditions. Catalyst **1c** has a naphthyl as a hydrophobic group, whereas **1o** has 3-nitrophenyl as an electron-deficient hydrophobic group. In order to determine if the change in the volume of water has any effect on their catalytic efficiency, we initially performed a direct aldol reaction using catalyst **1c**, because it has a large hydrophobic group. The results indicate that while the volume of water does not have much effect on the enantiomeric excess, it does affect the diastereomeric excess. The highest diastereomeric excess was obtained by using 2.5 mL of water (Table 2), and thus, all further reactions were performed using this volume of water.

Table 2
Variation of amount of water using catalyst **1c**[a]

Entry	Water (mL)	Time (h)	Yield[b] (%)	dr[c] *anti*:*syn*	ee[d] (%)
1	0.1	30	88	79:21	87
2	0.5	30	81	85:15	87
3	1.5	30	84	85:15	87
4	2.5	30	89	93:7	88
5	5	30	87	87:13	79

[a] Reaction conditions: 2.5 mL of water, 5 mmol of ketone, 1 mmol of aldehyde, 20 mol % catalyst, 27 °C.
[b] Yields determined after chromatographic purifications.
[c] Diastereomeric excess determined by NMR of crude reaction mixture.
[d] Enantiomeric excess determined by chiral HPLC for *anti*-diastereomer.

We further planned to vary the amount of ketone because for the development of an eco-friendly process, it is prudent to use stoichiometric amounts of reactants. A high enantiomeric excess of 93% was obtained using 5 equiv of cyclohexanone (Table 3, entry 2), while using a lower amount led to loss of enantioselectivity as well as decrease in the yield of **4a**. These conditions were then taken as the standard for all subsequent cross aldol reactions.

Table 3
Variation in amount of cyclohexanone using catalyst **1c**[a]

Entry	**2** (mmol)	Time (h)	Yield[b] (%)	dr[c] *anti*:*syn*	ee[d] (%)
1	10	30	84	85:15	91
2	5	30	85	88:12	93
3	3	41	67	93:7	82
4	2	41	60	84:16	80
5	1.5	41	62	81:19	75

[a] Reaction conditions: 2.5 mL of water, 5 mmol of ketone, 1 mmol of aldehyde, 20 mol % catalyst, 27 °C.
[b] Yields determined after chromatographic purifications.
[c] Diastereomeric excess determined by NMR of crude reaction mixture.
[d] Enantiomeric excess determined by chiral HPLC for *anti*-diastereomer.

The standard conditions of 2.5 mL of water and 5 equiv of **2** were used to perform a direct aldol reaction with **1o**, since in the initial screening this also afforded a similar level of enantioselectivity as catalyst **1c** (Table 1). Catalyst **1o** yielded **4a** in 95% ee under these conditions. The enantioselectivity of **4a**, using both catalysts **1c** and **1o**, was observed to be higher under these conditions. In addition to this, the diastereoselectivity obtained for *anti*-product in the case of catalyst **1o** was very good (Table 4, entry 1). Further optimization was then carried out using **1o,** as it was found to afford **4a** with the highest enantioselectivity.

The lowering of catalyst loading led to a slight decrease in the enantio- as well as diastereoselectivity and also an increase in

Table 4
Effect of catalyst loading and protonation on the enantio- and diastereoselectivity of **4a** using catalyst **1o**[a]

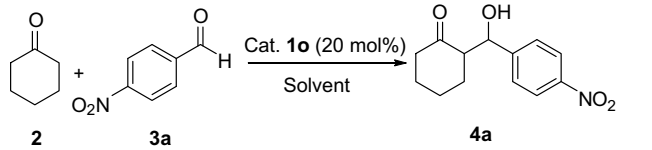
Entry	Catalyst (mol %)	Water (mL)	Time (h)	Yield[b] (%)	dr[c] *anti*:*syn*	ee[d] (%)
1	20	2.5	24	92	94:6	95
2	10	2.5	45	87	86:14	94
3	5	2.5	49	86	82:18	92
4	1	2.5	4 days	82	79:21	92
5[f]	1	16.5	4 days	81	84:16	90
6[g]	20 (C_1)	2.5	24	87	86:14	94
7[h]	20 (C_2)	2.5	24	43	94:6	95
8[e]	20	2.5	7	73	70:30	38
9	20	—	38	72	58:42	55
10[e]	20	—	7	79	73:27	58

[a] Reaction conditions: 2.5 mL of water, 5 mmol of ketone, 1 mmol of aldehyde, 20 mol % catalyst, 27 °C.
[b] Yield determined after chromatographic purification.
[c] Diastereomeric excess determined by NMR of crude reaction mixture.
[d] Enantiomeric excess determined by chiral HPLC for *anti*-diastereomer.
[e] Reaction was performed without protonation of the catalyst.
[f] Reaction was performed using 1 g of 4-nitrobenzaldehyde.
[g] The reaction was performed using recovered catalyst (Cycle 1).
[h] The reaction was performed using recovered catalyst from first cycle and 0.5 mmol of **3a** (Cycle 2).

the reaction time (Table 4, entries 2 and 3). Interestingly, enantioselectivity of 92% and yield of 82% were observed by using 1 mol % of this catalyst (Table 4, entry 4). One of the most intriguing aspects of developing an industrial process is the scaling up of the reaction and recyclability of the catalysts. A gram scale reaction was performed using 1 g of aldehyde and employing only 1 mol % of catalyst **1o**. This provided **4a** in 81% yield and 90% ee (Table 4, entry 5). No loss in the activity of the catalysts was observed even after two cycles. The product obtained exhibited nearly similar enantioselectivity (Table 4, entries 6 and 7).

In order to determine the role of water, a reaction was performed in the absence of water under solvent-free conditions. This resulted in longer reaction time, and afforded **4a** with low diastereo- and enantioselectivity (Table 4, entry 9). On the other hand, the reaction was very fast when using deprotonated catalyst **1k** in both water and solvent-free conditions, but **4a** obtained exhibited poor enantio- and diastereoselectivity (Table 4, entries 8 and 10). Furthermore, the catalytic efficiency of **1o** was also determined in organic solvents (Table 5). The aldol reaction performed in CH_3CN and THF provided **4a** with ee of 90% and 94%, respectively, but the yield of **4a** was low (Table 5, entries 3 and 5). The yield increased when performing the reaction in a THF-water mixture (Table 5, entry 6). Thus, this study substantiates the superiority of water as solvent for obtaining aldol product in high enantioselectivity and diastereoselectivity using **1o** as catalyst.

Table 5
Effect of organic solvents on the enantio- and diastereoselectivity of **4a** using catalyst **1o**[a]



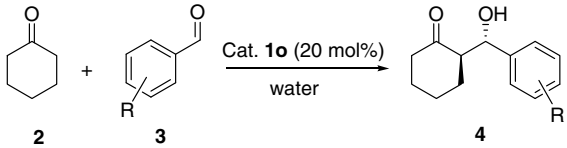
2 **3a** **4a**

Entry	Solvent	Time (h)	Yield[b] (%)	dr[c] *anti*:*syn*	ee[d] (%)
1	DMSO	24	—	—	—
2	DMF	24	—	—	—
3	CH_3CN	24	51	93:7	90
4	Hexane	24	—	—	—
5	THF	24	73	92:8	94
6	THF:Water (1:1)	24	80	94:6	94
7	MeOH	24	—	—	—

[a] Reaction conditions: 2.5 mL of water, 5 mmol of ketone, 1 mmol of aldehyde, 20 mol % catalyst, 27 °C.
[b] Yields determined after chromatographic purification.
[c] Diastereomeric excess determined by NMR of crude reaction mixture.
[d] Enantiomeric excess determined by chiral HPLC for *anti*-diastereomer.

In order to evaluate the general scope of catalyst **1o**, the aldol reaction of **2** was performed with different aromatic aldehydes (Table 6). The results reflect the catalytic versatility of **1o**. It catalyzes the aldol reaction of a variety of substituted aromatic aldehydes with cyclohexanone providing aldol products **4a** to **4n** in moderate to high enantioselectivity and diastereoselectivity. The aldol reaction of 2,6-dichlorobenzaldehyde **3h** provides **4h** in >99:1 diastereoselectivity and 98% ee (Table 6, entry 8). The 4-substituted benzaldehydes **3a**, **3d**, **3e**, **3g** afford the aldol product in ee of >90% (Table 6, entries 1, 4, 5, and 7), except for 4-bromobenzaldehyde **3f**. The same trend is observed in 2-substituted benzaldehydes **3j**, **3k**, and **3l**. The reaction with benzaldehyde **3m** and naphthaldehyde **3n** provides lower enantioselectivity.

Table 6
Direct aldol reaction of different aldehydes using catalyst **1o**[a]



2 **3** **4**

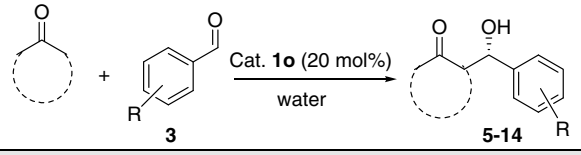
Entry	ArCHO	Time (h)	Yield[b] (%)	dr[c] *anti*:*syn*	ee[d] (%)
1	4-$NO_2C_6H_4$ **3a**	24	92	94:6	95
2	3-$NO_2C_6H_4$ **3b**	24	83	88:12	86
3	2-$NO_2C_6H_4$ **3c**	30	86	92:8	94
4	4-FC_6H_4 **3d**	24	61	93:7	92
5	4-ClC_6H_4 **3e**	24	73	92:8	95
6	4-BrC_6H_4 **3f**	24	61	93:7	87
7	4-CNC_6H_4 **3g**	24	71	88:12	90
8	2,6-$Cl_2C_6H_3$ **3h**	24	89	>99:1	98
9	3,4-$Cl_2C_6H_4$ **3i**	24	82	72:28	84
10	2-FC_6H_4 **3j**	24	71	87:13	93
11	2-ClC_6H_4 **3k**	24	69	98:2	91
12	2-BrC_6H_4 **3l**	24	73	86:14	82
13	C_6H_5 **3m**	24	62	87:13	82
14	2-Naph **3n**	27	35	93:7	79

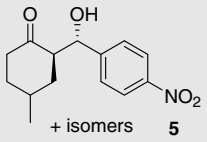
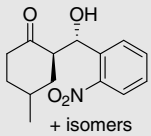
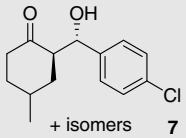
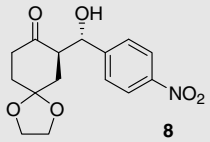
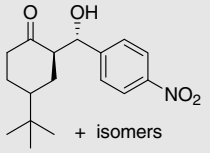
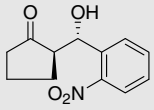
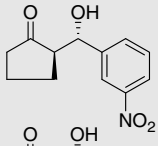
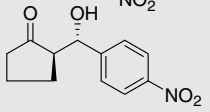
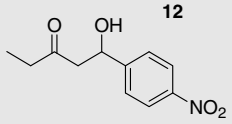
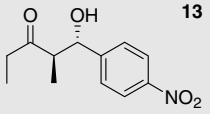
[a] Reaction conditions: 2.5 mL of water, 5 mmol of ketone, 1 mmol of aldehyde, 20 mol % catalyst, 27 °C.
[b] Yields determined after chromatographic purification.
[c] Diastereomeric excess determined by NMR of the crude reaction mixture.
[d] Enantiomeric excess determined by chiral HPLC for *anti*-diastereomer.

Finally, a number of ketones were also screened using catalyst **1o** providing aldol products in moderate to excellent enantioselectivities using optimized conditions (Table 7). Cyclic ketones having a six membered ring provide higher enantioselectivity of the aldol product as compared to five membered cyclic ketones (Table 7). In case of acyclic ketones, moderate enantioselectivity and yield were obtained along with prolonged reaction time (Table 7, entries 9 and 10).

The stereochemistry of the aldol reaction can be rationalized through the proposed transition state[13] (Fig. 2). Here the enamine attacks the aldehyde on the *re* face and leads to the formation of the favored *anti*-diastereomer as the major product. The carbonyl group of the aldehyde is activated by H-bonding with the amide N–H. The role of the amide N–H in the hydrogen bonding is confirmed by the increase in the rate of reaction and also by the enantioselectivity of the product in the case of catalysts with an electron-withdrawing group on the aromatic ring. Further, we believe that hydrophobic interactions[14] also play an important role in

Table 7
Direct aldol reaction of different ketones using catalyst **1o**[a]



Entry	Aldol product	Time (h)	Yield[b]	dr[c] *anti*:*syn*	ee[d] (%)
1	 + isomers **5**	24	88	—	95
2	 + isomers **6**	24	85	—	95
3	 + isomers **7**	24	80	—	97
4[e]	 **8**	24	70	85:15	91
5[e]	 + isomers **9**	24	90	—	92
6	 **10**	26	69	70:30	90
7	 **11**	24	78	52:48	80
8	 **12**	24	74	56:44	73
9[f]	 **13**	3 days	63	—	50
10	 **14**	3 days	21	50:50	48

[a] Reaction conditions: 2.5 mL of water, 5 mmol of ketone, 1 mmol of aldehyde, 20 mol % catalyst, 27 °C.
[b] Yields determined after chromatographic purification.
[c] Diastereomeric excess determined by NMR of crude reaction mixture.
[d] Enantiomeric excess determined by chiral HPLC for *anti*-diastereomer.
[e] Mixture of water and THF (1:1) was used as solvent.
[f] Linear and branched regioisomers[17] were formed in a ratio of 2:3.

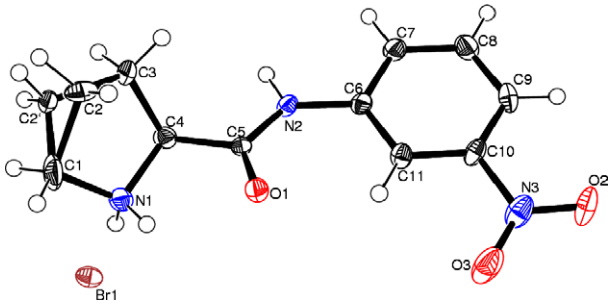


Figure 1. X-ray structure of catalyst **1o**.

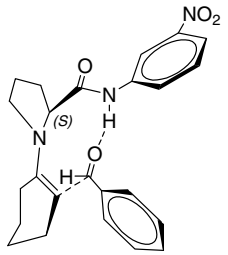


Figure 2. Plausible transition state.

providing rigidity to the transition state, and this in turn increases the enantioselectivity of the aldol product.

Catalyst **1o** has an orthorhombic crystal lattice as shown by the X-ray crystal structure (Fig. 1).[15] There are two NH–Br hydrogen bonds between bromine ion and the pyrrolidine NH of successively stacked molecules (2.358 Å and 2.704 Å) and one amidic NH–Br hydrogen bond (2.681 Å) with the molecule stacked in the adjacent molecular stacking. The *m*-nitro group on the aromatic ring is positioned on the same side as the carbonyl oxygen; having an intramolecular CH–O distance of 2.288 Å between the ortho H atom and the carbonyl group. The aromatic ring was placed nearly orthogonal to the pyrrolidine ring.

3. Conclusion

In summation, we have successfully demonstrated that very simple protonated (*S*)-prolinamide derivatives efficiently catalyze aldol reaction in water. The methodology developed is very simple, environmentally benign, and highly enantioselective. We believe that our findings will open up new avenues for the design of structurally simple organocatalysts that would be highly effective under aqueous reaction conditions.

4. Experimental

4.1. General methods

NMR spectra were obtained at 300 MHz (Jeol AL-300) using either $CDCl_3$ or D_2O as solvents with Me_4Si in $CDCl_3$ as the internal standard. The chemical shifts are reported in δ values relative to TMS and coupling constants (*J*) are expressed in hertz. Spectral patterns are designated as s = singlet; d = doublet; dd = doublet of doublets; q = quartet; t = triplet; br = broad; m = multiplet. When necessary, assignments were aided by DEPT-135 and decoupling experiments. Analytical thin-layer chromatography (TLC) was performed on either (i) aluminum sheets pre-coated with silica gel $60F_{254}$ (Merck, India) or (ii) glass plates (7.5 × 2.5 cm) coated with silica gel GF-254 (Spectrochem, India) containing 13% calcium

sulfate as binder and various combinations of ethyl acetate and hexane were used as eluents. Visualization of the spots was accomplished by exposing to UV light or iodine vapors. Column chromatography was performed on 60–120 mesh silica (Spectrochem, India) using 1–8% methanol in dichloromethane and mixture of hexane and ethylacetate as eluents. Organic substrates, aryl, and alkyl amines were obtained from either Aldrich or S.d. fine-chem. Ltd., India and L-proline, Dicyclohexylcarbodiimide and benzylchloroformate (Cbz) as 50% solution in toluene were procured from Spectrochem, India and used as received.

4.2. General procedure for the synthesis of catalysts 1a–m

Catalysts were synthesized by a standard procedure reported earlier[8b] and the spectroscopic data were similar to those reported. The experimental data for the new catalysts are given below.

4.2.1. (*S*)-2-(1′-Naphthmethylcarbamoyl)pyrrolidinium bromide 1d

Yield, 52%; dark brown solid; mp: 190–192 °C; R_f 0.3 (methanol/chloroform, 4:96); MS (*m*/*z*) FAB: 255 (M^+); $[\alpha]_D^{20} = -22.6$ (*c* 0.41, MeOH); ^{1}H NMR (D_2O, 300 MHz): δ 1.63–1.81 (m, 3H, CH_2), 2.02–2.11 (m, 1H, CH_2), 3.09–3.20 (m, 2H, CH_2), 4.07–4.12 (m, 1H, CH_2), 4.39–4.44 (d, 1H, *J* = 15 Hz, CH), 7.16–7.34 (m, 4H, ArH), 7.56–7.65 (m, 3H, ArH); ^{13}C NMR (D_2O, 300 MHz): δ 24.3, 30.4, 41.8, 47.1, 60.3, 123.5, 126.6, 127.1, 128.8, 129.2, 131.1, 133, 134, 168.8, 169.4.

4.2.2. (*S*)-2-(4′-Fluorobenzylcarbamoyl)pyrrolidinium bromide 1j

Yield, 60%; light brown liquid; R_f 0.3 (methanol/chloroform, 5:95); MS (*m*/*z*) FAB: 223 (M^+); $[\alpha]_D^{20} = -22.4$ (*c* 0.49, MeOH); ^{1}H NMR (D_2O, 300 MHz): δ 2.01–2.14 (m, 3H, CH_2), 2.45–2.54 (m, 1H, CH_2), 3.38–3.48 (m, 2H, CH_2), 4.34–4.49 (m, 3H, CH and CH_2), 7.10–7.16 (m, 2H, ArH), 7.32–7.36 (m, 2H, ArH); ^{13}C NMR (D_2O, 300 MHz): 24.4, 30.41, 43.2, 50, 60.4, 115.9, 116.1, 129.7, 129.8, 133.9, 170; Anal. Calcd for $C_{12}H_{16}ON_2BrF$: C, 47.54; H, 5.32; N, 9.24. Found: C, 47.56; H, 6.05; N, 9.63.

4.2.3. (*S*)-2-(4′-Fluorophenylcarbamoyl)pyrrolidinium bromide 1k

Yield, 57%, brown solid; mp: 177–179 °C; R_f 0.2 (methanol/chloroform, 2:98); MS (*m*/*z*) FAB: 209 (M^+); $[\alpha]_D^{20} = -38.8$ (*c* 1.0, MeOH); ^{1}H NMR (D_2O, 300 MHz): δ 2.14–2.32 (m, 3H, CH_2), 2.62–2.76 (m, 1H, CH_2), 3.52–3.68 (m, 2H, CH_2), 4.62–4.70 (m, 1H, CH), 7.16–7.23 (m, 2H, ArH), 7.49–7.56 (m, 2H, ArH); ^{13}C NMR (D_2O, 300 MHz): δ 26.4, 32.4, 49.2, 62.6, 118, 118.2, 125.6, 125.7, 134.8, 170.5.

4.2.4. (*S*)-2-(4′-Chlorophenylcarbamoyl)pyrrolidinium bromide 1l

Yield, 60%, white solid; mp: 183–185 °C; R_f 0.2 (methanol/chloroform, 2:98); MS (*m*/*z*) FAB: 225(M^+); $[\alpha]_D^{20} = -36.4$ (*c* 1.0, MeOH); ^{1}H NMR (D_2O, 300 MHz): δ 1.82–1.96 (m, 3H, CH_2), 2.33–2.41 (m, 1H, CH_2), 3.25–3.33 (m, 2H, CH_2), 4.36–4.40 (m, 1H, CH), 6.99–7.02 (d, 2H, *J* = 8.7 Hz, ArH), 7.16–7.18 (d, 2H, *J* = 8.4 Hz, ArH); ^{13}C NMR (D_2O, 300 MHz): δ 24.5, 30.7, 47.4, 60.8, 122.8, 129.5, 130.4, 135.7, 168.

4.2.5. (*S*)-2-(4′-Bromophenylcarbamoyl)pyrrolidinium bromide 1m

Yield, 42%, brown solid; mp: 188–189 °C; R_f 0.2 (methanol/chloroform, 2:98); MS (*m*/*z*) FAB: 270 (M^+); $[\alpha]_D^{20} = -37.4$ (*c* 1.0, MeOH); ^{1}H NMR (D_2O, 300 MHz): δ 1.80–2.01 (m, 3H, CH_2), 2.25–2.42 (m, 1H, CH_2), 3.20–3.35 (m, 2H, CH_2), 4.30–4.38 (m, 1H, CH), 7.12–7.15 (d, 2H, *J* = 9 Hz, ArH), 7.21–7.24 (d, 2H, *J* = 8.7 Hz, ArH); ^{13}C NMR (D_2O, 300 MHz): δ 24.5, 30.5, 47.3, 60.8, 118.4, 123.3, 132.5, 136.1, 168.3.

4.2.6. (*S*)-2-(4′-Nitrophenylcarbamoyl)pyrrolidinium bromide 1n

Yield, 47%, light pale yellow solid; mp: 187–189 °C; R_f 0.2 (methanol/chloroform, 1:99); MS (*m*/*z*) FAB: 236 (M^+); $[\alpha]_D^{20} = -36.3$ (*c* 0.71, MeOH); ^{1}H NMR (D_2O, 300 MHz): δ 1.89–2.10 (m, 3H, CH_2), 2.32–2.44 (m, 1H, CH_2), 3.21–3.38 (m, 2H, CH_2), 4.34–4.39 (m, 1H, CH), 7.50–7.55 (m, 2H, ArH), 8.04–8.09 (m, 2H, ArH); ^{13}C DEPT NMR (D_2O, 300 MHz): δ 24.4 (−ve), 30.2 (−ve), 47.2 (−ve), 61 (+ve), 120.8 (+ve), 125.6 (+ve), 143.5, 168.9; Anal. Calcd for $C_{11}H_{14}O_3N_3Br$: C, 41.79; H, 4.46; N, 13.29. Found C, 42.33; H, 4.82; N, 13.32.

4.2.7. (*S*)-2-(3′-Nitrophenylcarbamoyl)pyrrolidinium bromide 1o

Yield, 52%; light pale yellow solid, mp: 180–182 °C; R_f 0.2 (methanol/chloroform, 1:99); MS (*m*/*z*) FAB: 236 (M^+); $[\alpha]_D^{20} = -38.1$ (*c* 0.94, MeOH); ^{1}H NMR (D_2O, 300 MHz): δ 2.10–2.32 (m, 3H, CH_2), 2.50–2.62 (m, 1H, CH_2), 3.44–3.58 (m, 2H, CH_2), 4.56–4.61 (m, 1H, CH), 7.59–7.64 (m, 1H, ArH), 7.78–7.81 (m, 1H, ArH), 8.05–8.08 (m, 1H, ArH), 8.40–8.41 (m, 1H, ArH); ^{13}C NMR (D_2O, 300 MHz): δ 26.2, 32.1, 49.1, 62.7, 117.6, 122.4, 129.2, 132.5, 139.9, 150.2, 170.5; Anal. Calcd for $C_{11}H_{14}O_3N_3Br$: C, 41.79; H, 4.46; N, 13.29. Found: C, 41.50; H, 4.73; N, 13.18.

4.2.8. (*S*)-2-(2′-Nitrophenylcarbamoyl)pyrrolidinium bromide 1p

Yield, 40%; dark brown solid; mp: 181–183 °C; R_f 0.2 (methanol/chloroform, 5:95); MS (*m*/*z*) FAB: 236 (M^+); $[\alpha]_D^{20} = -29.7$ (*c* 0.21, MeOH); ^{1}H NMR (D_2O, 300 MHz): δ 1.85–2.11 (m, 3H, CH_2), 2.34–2.46 (m, 1H, CH_2), 3.20–3.35 (m, 2H, CH_2), 4.46–4.52 (m, 1H, CH), 7.21–7.26 (t, 1H, *J* = 7.5 Hz, ArH), 7.46–7.55 (m, 2H, ArH), 7.83–7.85 (d, 1H, *J* = 6 Hz, ArH); ^{13}C NMR (D_2O, 300 MHz): δ 24.4, 30.1, 47.3, 60.9, 126.1, 127, 127.9, 129.9, 135.7, 142.6, 169.4.

4.2.9. (*S*)-2-[3′-(*N*,*N*-Dimethylamonium)propyl carbamoyl]prrolidinium dibromide 1q

Yield, 57%, light brown solid; mp: 192–194 °C; R_f 0.4 (methanol/chloroform, 5:95); MS (*m*/*z*) FAB: 197 (M^+); $[\alpha]_D^{20} = -27.05$ (*c* 0.32, MeOH); ^{1}H NMR (D_2O, 300 MHz): δ 0.94–1.14 (m, 6H, CH_3), 1.38–1.90 (m, 8H, CH_2), 2.10–2.32 (m, 1H, CH_2), 3.10–3.24 (m, 2H, CH_2), 3.42–3.43 (m, 1H, CH_2), 4.08–4.12 (m, 1H, CH); ^{13}C NMR (D_2O, 300 MHz): δ 24.5, 24.9, 25.5, 30.7, 32.4, 47.2, 50.1, 60.4, 168.9.

4.3. General procedure for the enantioselective aldol reaction

To a solution of water (2.5 mL) and catalyst (0.2 mmol), cyclohexanone (5 mmol) was added at 27 °C, and the mixture was allowed to stir for 5 min followed by addition of aldehyde (1 mmol). The reaction mixture was stirred for 9–48 h and was monitored with TLC at regular intervals. On completion of the reaction, water (5 mL) was added to it and the resulting mixture was extracted with dichloromethane (3 × 10 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and evaporated to obtain crude aldol product. The ^{1}H NMR of the crude reaction mixture was recorded to determine the diastereomeric excess. The column chromatography on silica gel (mesh 60–120) gave pure aldol product. The HPLC of the pure aldol product was performed using Diacel Chiralpak AS-H, OD-H, and AD-H columns using mixture of hexane–isopropanol as eluting solvents.

4.3.1. 2-[1′-Hydroxy-1′-(4″-nitrophenyl)methyl] cyclohexan-1-one[16a] 4a

Yield: 92%; *anti*/*syn* = 94:6; enantiomeric excess: 95% determined by HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH 85:15; flow rate 0.3 mL min^{-1}, λ = 254 nm; t_R (*syn*, major) = 43.86 min, t_R (*anti*, major) = 48.23, t_R (*anti*, minor) = 59.0 min, t_R (*syn*, minor) = 66.56 min; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.53–1.85 (m, 4H, CH_2), 2.05–2.13 (m, 1H, CH_2), 2.33–2.56 (m, 4H, CH_2 and CH), 3.90–4.20 (br s, 1H, OH), 4.85–4.88 (d, 1H, *J* = 9 Hz, CH (*anti*)), 5.48 (s, 1H, CH (*syn*)), 7.45–7.49 (m, 2H, ArH), 8.15–8.19 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 24.5, 24.6, 25.8, 27.5, 27.6, 30.6, 42.4, 42.5, 56.7, 57.0, 69.9, 73.8, 123.3, 123.4, 126.5, 127.8, 147.4, 148.3, 149.2, 213.9, 214.6.

4.3.2. 2-[1′-(Hydroxy-1′-(3″-nitrophenyl)methyl] cyclohexan-1-one[16a] 4b

Yield: 83%; *anti*/*syn* = 88:12; enantiomeric excess: 86% determined by HPLC (Diacel Chiralpak AD-H, hexane/*i*-PrOH 95:5, flow rate 0.8 mL/min; λ = 254 nm; t_R (*syn*, major) = 35.09 min, t_R = (*syn*, minor) = 40.14 min, t_R (*anti*, major) = 43.79 min, t_R (*anti*, minor) = 56.53 min; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.57–1.74 (m, 5H, CH_2), 1.98–2.10 (m, 1H, CH_2), 2.39–2.46 (m, 2H, CH_2), 2.61–2.70 (m, 1H, CH), 3.20–3.32 (br s, 1H, OH (*syn*)), 4.13–4.30 (br s, 1H, OH (*anti*)), 4.92–4.95 (d, 1H, *J* = 9 Hz, CH (*anti*)), 5.47–5.48 (d, 1H, *J* = 2.4 Hz, CH (*syn*)), 7.49–7.56 (m, 1H, ArH), 7.69–7.70 (m, 1H, ArH), 8.06–8.22 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 24.5, 25.8, 27.5, 27.7, 30.6, 42.5, 56.6, 57.0, 69.7, 73.9, 120.8, 122, 122.7, 129, 129.2, 131.9, 133.1, 143.2, 148.1, 214.7.

4.3.3. 2-[1′-Hydroxy-1′-(2″-nitrophenyl)methyl] cyclohexan-1-one[16a] 4c

Yield: 86%; *anti*/*syn* = 92:8; enantiomeric excess: 94% determined by HPLC (Diacel Chiralpak AD-H; hexane/*i*-PrOH 95:5; flow rate 0.3 mL/min; λ = 254 nm; t_R (*anti*, major) = 65.04 min, t_R (*anti*, minor) = 69.86 min; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.51–1.82 (m, 5H, CH_2), 1.91–2.20 (m, 1H, CH_2), 2.25–2.50 (m, 2H, CH_2), 2.70–2.80 (m, 1H, CH), 4.20–4.89 (br s, 1H, OH), 5.42–5.45 (d, 1H, *J* = 3 Hz, CH (*anti*)), 5.92 (s, 1H, CH (*syn*)), 7.30–7.45 (m, 1H, ArH), 7.55–7.68 (m, 1H, ArH), 7.70–7.82 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 24.6, 26.3, 27.6, 29.5, 30.9, 42.4, 42.6, 54.7, 57.1, 61.4, 66.4, 69.5, 123.9, 124.3, 128.3, 128.9, 129.4, 132.9, 133.6, 133.9, 136.4, 137, 146.9, 148.6, 213.7, 214.8.

4.3.4. 2-[1′-Hydroxy-1′-(4″-fluorophenyl)methyl] cyclohexan-1-one[7f] 4d

Yield: 61%; *anti*/*syn* = 93:7; enantiomeric excess: 92% determined by HPLC (Diacel Chiralpak AD-H, hexane/*i*-PrOH 90:10; flow rate 0.3 mL/min; λ = 208 nm; t_R (*syn*, major) = 27.9 min, t_R (*syn*, minor) = 31.7, t_R (*anti*, major) = 40.8 min, t_R (*anti*, minor) = 44.9 - min; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41–1.87 (m, 5H, CH_2), 1.91–2.21 (m, 1H, CH_2), 2.26–2.49 (m, 3H, CH_2 and CH), 3.01–3.20 (br s, 1H, OH (*syn*)), 3.88–3.92 (br s, 1H, OH (*anti*)), 4.70–4.73 (d, 1H, *J* = 9 Hz, CH (*anti*)), 5.29 (s, 1H, CH (*syn*)), 6.96–7.00 (m, 2H, ArH), 7.20–7.23 (br s, 2H, ArH); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 24.6, 24.8, 26.0, 27.7, 27.9, 30.7, 42.6, 53.4, 57.1, 57.4, 70.1, 74.1, 114.8, 115.3, 127.2, 128.6, 214.7.

4.3.5. 2-[1′-Hydroxy-1′-(4″-chlorophenyl)methyl] cyclohexan-1-one[16a] 4e

Yield: 73%; *anti*/*syn* = 92:8; enantiomeric excess: 95% determined by HPLC (Diacel Chiralpak AD-H; hexane/*i*-PrOH 90:10; flow rate 0.3 mL/min; λ = 224 nm; t_R (*syn*, major) = 32.7 min, t_R (*syn*, minor) = 37.9, t_R (*anti*, major) = 48.7 min, t_R (*anti*, minor) = 55.4 - min; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.55–1.87 (m, 5H, CH_2), 1.98–2.09 (m, 1H, CH_2), 2.33–2.55 (m, 3H, CH_2 and CH), 3.00 (br s, 1H, OH (*syn*)), 3.91 (bs, 1H, OH (*anti*)), 4.71–4.74 (d, 1H, *J* = 9 Hz, CH (*anti*)), 5.33 (s, 1H, CH (*syn*)), 7.20–7.30 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 24.6, 24.8, 25.9, 27.7, 27.9, 30.7, 42.6, 57.0, 57.3, 70.1, 74.1, 127.1, 128.2, 128.3, 128.5, 132.6, 133.5, 139.4, 140, 214.6, 215.3.

4.3.6. 2-[1′-Hydroxy-1′-(4″-bromophenyl)methyl] cyclohexan-1-one[16a] 4f

Yield: 61%; *anti*/*syn* = 93:7; enantiomeric excess: 87% determined by HPLC (Diacel Chiralpak AD-H; hexane/*i*-PrOH 90:10; flow rate 0.3 mL/min; λ = 222 nm; t_R (*syn*, major) = 30.0 min, t_R (*syn*, minor) = 35.5, t_R (*anti*, major) = 46.3 min, t_R (*anti*, minor) = 53.8 min; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.50–1.87 (m, 5H, CH_2), 2.05–2.11 (m, 1H, CH_2), 2.33–2.57 (m, 3H, CH_2 and CH), 3.05 (br s, 1H, OH (*syn*), 3.93 (bs, 1H, OH (*anti*)), 4.70–4.73 (d, 1H, *J* = 9 Hz, CH (*anti*)), 5.30 (br s, 1H, CH (*syn*)), 7.14–7.18 (m, 2H, ArH), 7.42–7.46 (m, 2H, ArH).

4.3.7. 2-[1′-Hydroxy-1′-(4″-cyanophenyl)methyl] cyclohexan-1-one[16a] 4g

Yield: 71%; *anti*/*syn* = 88:12; enantiomeric excess: 90% determined by HPLC (Diacel Chiralpak AD-H; hexane/*i*-PrOH 90:10; flow rate 0.3 mL/min, λ = 234 nm; t_R (*syn*, major) = 53.2 min, t_R (*syn*, minor) = 62.9, t_R (*anti*, major) = 72.7 min, t_R (*anti*, minor) = 91.6 - min; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.25–1.84 (m, 5H, CH_2), 2.08–2.13 (m, 1H, CH_2), 2.28–2.58 (m, 3H, CH_2 and CH) 3.12 (br s, 1H, OH (*syn*)), 3.95 (br s, 1H, OH (*anti*)), 4.78–4.81 (d, 1H, *J* = 9 Hz, CH (*anti*)), 5.39 (s, 1H, CH (*syn*)), 7.39–7.40 (m, 2H, ArH), 7.60–7.63 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 24.5, 25.7, 27.5, 30.6, 42.5, 56.6, 57.0, 70.74, 111.5, 118.7, 126.4, 127.6, 128.6, 130.4, 132, 146.3, 147, 213.9, 214.7.

4.3.8. 2-[1′-Hydroxy-1′-(2″,6″-dichlorophenyl)methyl] cyclohexan-1-one[16a] 4h

Yield: 89%; *anti*/*syn* = >99:1; enantiomeric excess: 98% determined by HPLC (Diacel Chiralpak AS-H; hexane/*i*-PrOH 95:5; flow rate 0.5 mL/min; λ = 220 nm; t_R (*anti*, minor) = 20.69 min, t_R (*anti*, major) = 25.03 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25–1.45 (m, 1H, CH_2), 1.46–1.86 (m, 4H, CH_2), 2.05–2.15 (m, 1H, CH_2), 2.30–2.58 (m, 2H, CH_2), 3.43–3.54 (m, 1H, CH), 3.68–3.69 (d, 1H, *J* = 4.2 Hz OH), 5.80–5.87 (m, 1H, CHOH), 7.12–7.17 (m, 1H, ArH), 7.26–7.32 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 24.5, 27.4, 29.7, 42.2, 53.4, 70.3, 129.1, 134.5, 135.4, 214.1.

4.3.9. 2-[1′-Hydroxy-1′-(3″,4″-dichlorophenyl)methyl] cyclohexan-1-one 4i

Yield: 82%; *anti*/*syn* = 72:28; enantiomeric excess: 84% determined by HPLC(Diacel Chiralpak AD-H; hexane/*i*-PrOH 90:10; flow rate 0.3 mL/min; λ = 215 nm; t_R (*anti*, major) = 36.45 min, t_R (*anti*, minor) = 38.76 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30–1.45 (m, 1H, CH_2), 1.52–1.98 (m, 5H, CH_2), 2.15–2.18 (m, 1H, CH_2), 2.30–2.60 (m, 2H, CH and CH_2), 3.23 (s, 1H, OH (*syn*)), 4.06 (s, 1H, OH (*anti*)), 4.72–4.75 (dd, 1H, C*H*OH (*anti*), 5.32 (s, 1H, C*H*OH (*anti*)), 7.07–7.22 (m, 1H, ArH), 7.35–7.50 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 24.5, 24.6, 25.8, 27.5, 27.7, 30.6, 42.5, 56.7, 57.1, 69.5, 73.6, 125, 126.3, 127.8, 128.9, 130, 130.1, 130.7, 131.6, 132.4, 141.2, 141.9, 214.1, 214.9.

4.3.10. 2-[1′-Hydroxy-1′-(2″-fluorophenyl)methyl] cyclohexan-1-one[16a] 4j

Yield: 71%; *anti*/*syn* = 87:13; enantiomeric excess: 93% determined by HPLC (Diacel Chiralpak AS-H; hexane/*i*-PrOH 90:10; flow rate 0.8 mL/min; λ = 215 nm; t_R (*anti*, major) = 15.63 min, t_R (*anti*, minor) = 17.05 min; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.37–1.92 (m, 5H, CH_2), 2.07–2.20 (m, 1H, CH_2), 2.25–2.50 (m, 2H, CH_2), 2.55–2.73 (m, 1H, CH)), 3.82–4.08 (br s, 1H, OH), 5.14–5.16 (d, 1H,

J = 6 Hz, CH (*anti*)), 6.96–7.02 (t, 1H, *J* = 9 Hz, ArH), 7.12–7.28 (m, 2H, ArH), 7.43–7.48 (t, 1H, *J* = 7.5 Hz, ArH).

4.3.11. 2-[1′-Hydroxy-1′-(2″-chlorophenyl)methyl] cyclohexan-1-one[16d] 4k

Yield: 69%; *anti*/*syn* = 98:2; enantiomeric excess: 91% determined by HPLC (Diacel Chiralpak AD-H; hexane/*i*-PrOH 90:10; flow rate 0.3 mL/min; λ = 225 nm; t_R (*syn*, major) = 11.08 min, t_R (*syn*, minor) = 12.10, (*anti*, major) = 19.35 min, t_R (*anti*, minor) = 21.89 min; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.55–1.82 (m, 5H, CH_2), 2.07–2.11 (m, 1H, CH_2), 2.27–2.48 (m, 2H, CH_2), 2.59–2.62 (m, 1H, CH), 3.96 (br s, 1H, OH), 5.29–5.31 (d, 1H, *J* = 6 Hz, CH (*anti*)), 5.67 (s, 1H, CH (*syn*)), 7.17–7.32 (m, 3H, ArH), 7.51–7.54 (d, 1H, ArH). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 24.7, 25.8, 27.8, 42.5, 53.5, 67.6, 126.5, 128.1, 128.4, 129.1, 130.7, 138.5, 214.7.

4.3.12. 2-[1′-Hydroxy-1′-(2″-bromophenyl)methyl] cyclohexan-1-one 4l

Yield: 73%; *anti*/*syn* = 86:14; enantiomeric excess: 82% determined by HPLC (Diacel Chiralpak AD-H, hexane/*i*-PrOH 90:10; flow rate 0.3 mL/min; λ = 225 nm; t_R (*anti*, major) = 37.2 min, t_R (*anti*, minor) = 42.9 min; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.25–1.86 (m, 5H, CH_2), 2.07–2.11 (m, 1H, CH_2), 2.27–2.48 (m, 2H, CH_2), 2.60–2.69 (m, 1H, CH), 3.98 (br s, 1H, OH), 5.25–5.28 (d, 1H, *J* = 9 Hz, CH (*anti*)), 7.09–7.17 (m, 1H, ArH), 7.25–7.35 (m, 1H, ArH), 7.48–7.52 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 24.8, 27.7, 30.4, 42.6, 57.5, 72.7, 123.2, 127.7, 128.4, 129, 132.4, 140.6, 215.

4.3.13. 2-[1′-Hydroxy-1′-phenylmethyl]cyclohexan-1-one[16a] 4m

Yield: 62%; *anti*/*syn* = 87:13; enantiomeric excess: 82% determined by HPLC (Diacel Chiralpak AD-H; hexane/*i*-PrOH 95:5; flow rate 1 mL/min; λ = 211 nm; t_R (*syn*, major) = 12.1 min, t_R (*syn*, minor) = 13.4, t_R (*anti*, major) = 14.6 min, t_R (*anti*, minor) = 16 min; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.25–1.86 (m, 5H, CH_2), 1.98–2.09 (m, 1H, CH_2), 2.29–2.56 (m, 3H, CH_2 and CH), 2.96 (br s, 1H, OH (*syn*)), 3.89 (br s, 1H, OH (*anti*)), 4.74–4.77 (d, 1H, *J* = 9 Hz, CH (*anti*)), 5.36 (s, 1H, CH (*syn*)), 7.21–7.29 (m, 5H, ArH).

4.3.14. 2-[1′-Hydroxy-1′-(naphthalene-2-yl)methyl] cyclohexan-1-one[16e] 4n

Yield: 35%; *anti*/*syn* = 93:7; enantiomeric excess: 79% determined by HPLC (Diacel Chiralpak AS-H; hexane/*i*-PrOH 90:10; flow rate 0.5 mL/min; λ = 225 nm; t_R (*syn*, major) = 19.13 min, t_R (*syn*, minor) = 21.41, t_R (*anti*, major) = 25.0 min, t_R (*anti*, minor) = 27.98 - min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40–1.90 (m, 5H, CH_2), 2.07–2.26 (m, 1H, CH_2), 2.28–2.58 (m, 2H, CH_2), 2.62–2.79 (m, 1H, CH), 3.20 (br s, 1H, OH (*syn*)), 4.06 (br s, 1H, OH (*anti*)), 4.94–4.97 (d, 1H, *J* = 9 Hz, C*H*OH (*anti*)), 5.55 (s, 1H, C*H*OH (*syn*)), 7.36–7.49 (m, 3H, ArH), 7.74–7.84 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 24.5, 24.7, 25.9, 27.6, 27.8, 30.8, 42.5, 56.9, 57.3, 70.6, 74.7, 123.8, 124.4, 124.5, 125.5, 125.8, 125.9, 126, 126.1, 127.5, 127.6, 127.7, 127.8, 128.1, 132.5, 133, 133.1, 138.2, 138.8, 214.7, 215.4.

4.3.15. 2-[1′-Hydroxy-1′-(4″-nitrophenyl)methyl]-4-methylcyclohexan-1-one 5[16b]

Yield: 88%, enantiomeric excess: 95% of major diastereomer determined by HPLC (Diacel Chiralpak AS-H; hexane/*i*-PrOH 70:30; flow rate 0.8 mL/min; λ = 254 nm; t_R (major) = 13.23 min, t_R (minor) = 18.45 min; ^{1}H NMR (mixture of isomers) ($CDCl_3$, 300 MHz): δ 0.90–0.94 (m, 1H, CH_3), 1.04–1.07 (m, 2H, CH_3) 1.30–1.60 (m, 2H, CH_2), 1.77–2.11 (m, 3H, CH and CH_2), 2.32–2.79 (m, 3H, CH_2), 4.00 (br s, 1H, OH), 4.93 (d, 0.7H, *J* = 8.7 Hz, C*H*OH), 5.47 (s, 0.3H, C*H*OH), 7.47–7.52 (m, 2H, ArH), 8.19–8.22 (m, 2H, ArH); ^{13}C NMR (mixture of isomers) ($CDCl_3$, 300 MHz): δ 18.0, 18.2, 20.8, 21, 26.5, 30.9, 31.3, 32.6, 32.9, 33.4, 34.6, 35.4, 35.9, 38, 38.4, 40.6, 41.5, 52, 53, 53.3, 55.6, 69.7, 70.2, 73.8, 123.2, 123.3, 123.4, 126.4, 127.6, 127.7, 146.8, 147.4, 148.5, 149.2, 213.9, 214.6.

4.3.16. 2-[1′-Hydroxy-1′-(2″-nitrophenyl)methyl]-4-methylcyclohexan-1-one 6[16b]

Yield: 85%, enantiomeric excess: 95% of major diastereomer determined by HPLC (Diacel Chiralpak AD-H; hexane/*i*-PrOH 80:20; flow rate 0.8 mL/min; λ = 225 nm; t_R (minor) = 9.41 min, t_R (major) = 9.98 min; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.81–1.10 (m 3H, CH_3), 1.35–1.60 (m, 1H, CH), 1.67–2.01 (m, 3H, CH_2), 2.05–2.25 (m, 1H, CH_2), 2.27–2.65 (m, 2H, CH_2), 2.80–3.10 (m, 1H, CH), 5.42–5.44 (d, 0.9H, *J* = 6 Hz, C*H*OH), 5.94 (bd, 0.1H, *J* = 2.7 Hz, C*H*OH), 7.40–7.46 (m, 1H, ArH), 7.60–7.66 (m, 1H, ArH) 7.72–7.76 (m, 1H, ArH) 7.82–7.85 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 20.2, 22.1, 23, 26.6, 29, 30.9, 34.5, 38.2, 38.4, 38.8, 40.6, 54.9, 55.9, 64.9, 69.9,74, 120.4, 121.4, 122, 122.7, 126.7, 127.3, 128.3, 129.1, 129.3, 131.5, 132.6, 143.5, 145.2, 148.1, 219.6, 222.2.

4.3.17. 2-[1′-Hydroxy-1′-(4″-chlorophenyl)methyl]-4-methylcyclohexan-1-one 7[16b]

Yield: 80%, enantiomeric excess 97% of major diastereomer determined by HPLC (Diacel Chiralpak AS-H; hexane/*i*-PrOH 90:10; flow rate 0.8 mL/min; λ = 225 nm; t_R (*anti*, major) = 15.78 min, t_R (*anti*, minor) = 25.20 min; ^{1}H NMR (mixture of isomers) ($CDCl_3$, 300 MHz): δ 0.92–1.04 (m, 3H, CH_3), 1.25–1.50 (m, 2H, CH and CH_2), 1.71–1.76 (m, 1H, CH_2), 1.89–2.06 (m, 2H, CH_2), 2.25–2.57 (m, 2H, CH_2), 2.65–2.78 (m, 1H, CH), 3.32 (br, 1H, OH), 4.72–4.75 (d, 0.8H, *J* = 9 Hz, C*H*OH), 5.31–5.34 (m, 0.2H, C*H*OH), 7.21–7.36 (m, 4H, ArH); ^{13}C NMR (of three isomers) ($CDCl_3$, 300 MHz): δ 14.0, 18.5, 21.2, 26.6, 29.6, 31.5, 33.2, 33.6, 35.6, 36.1, 38.1, 41.7, 53.4, 55.9, 69.8, 74.1, 127.1, 128.2, 128.6, 129.4, 130.8, 133.6, 139.6, 215.2.

4.3.18. 7-[1′-Hydroxy-1′-(4″-nitrophenyl)methyl]-1,4-dioxa-spiro-[4.5]decan-8-one 8[16a]

Yield: 70%, *anti*/*syn* = 85:15; enantiomeric excess: 91% of *anti* diastereomer determined by HPLC (Diacel Chiralpak AS-H, hexane/*i*-PrOH 70:30, flow rate 1.0 mL/min; λ = 254 nm; t_R (*anti*, minor) = 10.61 min, t_R (*anti*, major) = 14.99 min; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.45–1.55 (m, 1H, CH_2), 1.90–2.13 (m, 3H, CH_2), 2.41–2.51 (m, 1H, CH_2), 2.64–2.81 (m, 1H, CH_2), 2.93–3.03 (m, 1H, CH), 3.09 (d, 1H, *J* = 6 Hz, OH (*syn*)), 3.84–3.96 (m, 4H, CH_2), 4.04–4.05 (d, 1H, *J* = 3 Hz, OH (*anti*)), 4.92 (d, 1H, *J* = 7.8 Hz, C*H*OH (*anti*)), 5.52 (m, 1H, C*H*OH (*syn*)), 7.46–7.51 (m, 2H, ArH), 8.19–8.22 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 33.0, 34.2, 37.7, 38.4, 38.7, 52.9, 64.5, 64.6, 64.7, 69.5, 76.5, 106.7, 107.2, 123.5, 123.6, 126.4, 127.8, 148.5.

4.3.19. 2-[1′-Hydroxy-1′-(4″-nitrophenyl)methyl]-4-*tert*-butylcyclohexan-1-one 9[16c]

Yield: 90%, enantiomeric excess: 92% of major diastereomer determined by HPLC (Diacel Chiralpak OD-H; hexane/*i*-PrOH 92:8; flow rate 0.5 mL/min; λ = 280 nm; t_R (major) = 21.76 min, t_R (minor) = 24.70 min; ^{1}H NMR (mixture of isomers) ($CDCl_3$, 300 MHz): δ 0.78, 0.81, 0.82 (3s, 9H, CH_3), 1.40–1.67 (m, 4H, CH and CH_2), 2.09–2.15 (m, 1H, CH_2), 2.40–2.52 (m, 2H, CH_2), 2.65–2.67 (m, 1H, CH), 3.14–3.15 (br s, 1H, OH), 4.95–4.98 (d, 0.3H, *J* = 9 Hz, C*H*OH), 5.48 (s, 0.7H, C*H*OH), 7.47–7.55 (m, 2H, ArH), 8.19–8.25 (m, 2H, ArH); ^{13}C NMR (mixture of isomers) ($CDCl_3$, 300 MHz): δ 26.7, 27.4, 27.5, 28.4, 28.5, 31.7, 32.4, 32.5, 41.8, 42, 46.4, 46.5, 55.8, 56, 70.1, 74.1, 123.4, 123.5, 126.5, 127.7, 147, 147.4, 148.4, 149.1.

4.3.20. 2-[1′-Hydroxy-1′-(2″-nitrophenyl)methyl] cyclopent-1-one 10[7a]

Yield: 69%; *anti*/*syn* = 70:30; enantiomeric excess: 90% of *anti* diastereomer determined by HPLC (Diacel Chiralpak AS-H; hexane/*i*-PrOH 95:5; flow rate 1.0 mL/min, λ = 225 nm; t_R (*syn*, minor) = 22.75 min, t_R (*syn*, major) = 36.83, t_R (*anti*, major) = 28.22 min, t_R (*anti*, minor) = 31.09 min; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.69–1.81 (m, 2H, CH_2), 1.95–2.26 (m, 2H, CH_2), 2.26–2.60 (m, 2H, CH_2), 2.65–2.85 (m, 1H, CH), 4.50 (br s, 1H, OH), 5.41–5.44 (d, 1H, J = 8.4 Hz, C*H*OH (*anti*)), 5.89–5.90 (d, 1H, J = 3 Hz, CHOH (*syn*)), 7.38–7.57 (m, 1H, ArH), 7.59–7.72 (m, 1H, ArH), 7.78–7.81 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 20.1, 20.4, 22.8, 26.5, 38.6, 54.7, 55.3, 66.4, 69.0, 123.9, 124.4, 127.9, 128.5, 128.6, 128.9, 133.1, 133.3, 138.6, 146.9, 219.1.

4.3.21. 2-[1′-Hydroxy-1′-(3″-nitrophenyl)methyl] cyclopent-1-one 11[16c]

Yield: 78%; *anti*/*syn* = 52:48; enantiomeric excess: 80% of *anti* diastereomer determined by HPLC (Diacel Chiralpak OD-H; hexane/*i*-PrOH 93:7; flow rate 0.5 mL/min, λ = 254 nm; t_R (*syn*, minor) = 35.02 min, t_R (*syn*, major) = 42.60, t_R (*anti*, major) = 45.47 min, t_R (*anti*, minor) = 53.98 min; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.50–1.89 (m, 2H, CH_2), 1.90–2.58 (m, 4H, CH and CH_2), 2.89–3.12 (m, 1H, CH), 4.82–4.85 (d, 1H, J = 9 Hz, C*H*OH (*anti*)), 5.42–5.43 (d, 1H, J = 2.7Hz, C*H*OH (*syn*)), 7.38–7.89 (m, 2H, ArH), 8.11–8.30 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 18.3, 26.8, 33.2, 36.6, 38.5, 53.1, 69.7, 124.0, 128.4, 128.8, 133.1, 136.7, 148.7, 214.9.

4.3.22. 2-[1′-Hydroxy-1′-(4″-nitrophenyl)methyl] cyclopent-1-one 12[16c]

Yield: 74%; *anti*/*syn* = 56:44; enantiomeric excess: 73% of *anti* diastereomer determined by HPLC (Diacel Chiralpak AD-H; hexane/*i*-PrOH 95:5; flow rate 1.0 mL/min, λ = 254 nm; t_R (*syn*, major) = 22.46 min, t_R (*syn*, minor) = 29.77, t_R (*anti*, minor) = 35.27 min, t_R (*anti*, major) = 36.74 min; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.45–1.82 (m, 2H, CH_2), 1.85–2.52 (m, 4H, CH and CH_2), 2.92–3.07 (m, 1H, CH), 2.88 (br s, 1H, OH (*syn*)), 4.63 (s, 1H, OH (*anti*)), 4.80–4.83 (d, 1H, J = 9 Hz, C*H*OH (*anti*)), 5.39 (s, 1H, C*H*OH (*syn*)), 7.49–7.52 (m, 2H, ArH), 8.17–8.20 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 24.3, 24.6, 25.5, 27.5, 30.2, 42.5, 56.3, 57.0, 69.8, 73.5, 123.0, 126.5, 127.2, 147.4, 147.9, 149.2, 213.5, 214.6.

4.3.23. 1-Hydroxy-1-(4′-nitrophenyl)pentan-3-one 13[16f]

Yield 63%, enantiomeric excess: 50% determined by HPLC (Diacel Chiralpak AS-H; hexane/*i*-PrOH 70:30; flow rate 0.5 mL/min, λ = 260 nm; t_R (major) = 16.15 min, t_R (minor) = 22.85; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.07 (t, 3H, J = 7.2 Hz, CH_3), 2.46 (q, 2H, J = 7.2 Hz, CH_2), 2.75–2.79 (m, 2H, CH_2), 5.25–5.29 (m, 1H, CH), 7.50 (d, 2H, J = 8.6 Hz, ArH), 8.17 (d, 2H, J = 8.6 Hz, ArH); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 7.47, 36.8, 50.2, 69.1, 123.7, 126.4, 126.8, 127.5, 147.3, 150.2, 211.3.

4.3.24. 1-Hydroxy-2-methyl-1-(4′-nitrophenyl)pentan-3-one 14[16g]

Yield 21%, *anti*/*syn* = 1:1, enantiomeric excess: 48% of *anti* diastereomer determined by HPLC (Diacel Chiralpak AD-H; hexane/*i*-PrOH 98:2; flow rate 1.5 mL/min; λ = 260 nm; t_R (*anti*, major) = 40.09 min, t_R (*anti*, minor) = 66.45 min; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.96–1.08 (m, 6H, 2 × CH_3), 2.33–2.89 (m, 3H, CH and CH_2), 4.81 (d, 1H, CH (*anti*)), 5.18 (d, 1H, CH (*syn*)), 7.47 (d, J = 8.8 Hz, 2H, ArH), 8.16 (d, J = 8.8 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 7.2 (+ve), 7.3 (+ve), 9.9 (+ve), 14.1 (+ve), 35.0 (−ve), 36.2 (−ve), 51.5 (+ve), 52.1 (+ve), 72.0 (+ve), 75.3 (+ve), 123.2 (+ve), 123.4 (+ve), 126.7 (+ve), 127.3, 147.2, 149.3, 149.6, 215.4, 216.8.

4.4. Procedure for regeneration of the catalyst 1o

After workup of reaction, the aqueous portion was separated and neutralized with saturated solution of sodium carbonate. The neutralized aqueous solution was extracted with dichloromethane (3 × 10 mL), dried over anhydrous Na_2SO_4, and distilled to obtained gummy material. It was titurated with equivalent amount of 50% aqueous HBr and used for the aldol reaction.

Crystal suitable for X-ray analysis was obtained by recrystallization from dichloromethane/methanol (95/5) at room temperature. CCDC 688390 contains the supplementary cystallography data for this compound.

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