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A Green and Efficient Asymmetric Aldol Reaction Catalyzed by a Chiral Anion Modified Ionic Liquid

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Keywords: Asymmetric synthesis / Ionic liquids / Organocatalysis / Aldol reactions / Chirality

A chiral anion modified ionic liquid derived from L-proline proves as a green and efficient asymmetric organocatalyst for direct asymmetric aldol reactions in $[BMIm]BF_4$ at room temperature. The corresponding aldol products with moderate to good isolated yields (up to 99%), *anti*-diastereoselectivities (up to 97:3), and excellent enantioselectivities (up to 99% *ee*) were afforded. Recycling of the catalyst and solvent ($[BMIm]BF_4$) was possible up to four runs with a slight reduction in activity.

Introduction

The asymmetric aldol reaction is one of the most important carbon–carbon bond-forming reactions in organic synthesis[1] for the production of enantiomerically enriched β-hydroxy ketones. Since List and Barbas III[2] reported the direct aldol reaction catalyzed by (*S*)-proline under mild conditions, the use of small organic molecules as catalysts has received great attention. Over the past few years, (*S*)-proline and its structural analogues have been continuously developed for direct asymmetric aldol reactions.[3,4] However, the enantio- and diastereoselectivities were not good enough for their restricted substrate applicability in some cases. In addition, the organic solvents employed in this reaction, DMSO and DMF, are not environmentally friendly and make recycling of the catalyst difficult.

Over the last decade, room-temperature ionic liquids (ILs) have attracted much attention as an environmentally benign reaction media because of their fascinating and characteristic properties.[5] They have also been used as a substitution for organic solvents in direct aldol reactions mainly as green and recoverable solvents.[4c,6] Furthermore, chiral ionic liquids (CILs) have recently emerged as a hot research focus.[7] Due to their facile chemical modification, ILs with chiral cations derived from (*S*)-proline were successfully utilized as highly enantioselective organocatalysts[4a,8] for aldol reactions, whereas there are only a few CILs modified on the anion structure.[9] In 2007, Han[10] developed a functional ionic liquid by using L-proline as an anion, but the enantiomeric excess values were less than 10% when the CIL was applied to direct aldol reactions.

Previously, we reported that the anion-modified CIL 1-ethyl-3-methylimidazolium-(*S*)-2-pyrrolidinecarboxylic acid salt [EMIm][Pro][11] (**1**) could efficiently catalyze the asymmetric Michael addition reaction through an enamine mechanism with a catalyst loading of 200 mol-%.[12] Herein, as a continuation of our work, we would like to disclose the application of **1** as a green and efficient organocatalyst for direct asymmetric aldol reactions. Compared to the (*S*)-proline-catalyzed aldol reaction in organic solvent,[2b] more convincing results were obtained. When a catalyst loading of 30 mol-% was used, the corresponding aldol products were obtained in moderate to excellent yields (up to 99%), low to high diastereoselectivities (up to 97:3), and good to excellent enantiomeric excesses (up to 99%). As $[BMIm]BF_4$ was used as the solvent, a green and efficient system was developed, and it could be reused up to four times with only a slight decrease in activity. To the best of our knowledge, this is the first asymmetric aldol reaction induced by an anion modified CIL with satisfactory enantioselectivities, which may greatly expand the scope of the design and application of CILs.

Results and Discussion

Originally, the model reaction of 4-nitrobenzaldehyde with cyclohexanone (3 equiv.) was carried out in various solvents at room temperature by using **1** (30 mol-%) as the catalyst (Table 1).

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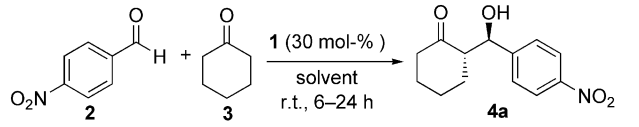
Table 1. Optimization of reaction conditions.



Entry	Solvent	Yield[a][%]	*dr*[b] (*syn*/*anti*)	*ee*[b][%](*syn*/*anti*)
1	DMSO	95	46:54	*rac*/–11
2	DMF	87	55:45	4/–11
3	cyclohexanone	98	58:42	*rac*
4	hexane	82	36:64	*rac*
5	toluene	90	46:54	–10/–18
6	CH_3OH	75	52:48	–20/–30
7	CH_2Cl_2	87	45:55	–21/–27
8	H_2O	85	37:63	16/4
9	[BMIm]PF_6	77	39:61	–6/–9
10	[BMIm]BF_4	95	22:78	94/97
11[c]	[BMIm]BF_4	97	26:74	77/93
12[d]	[BMIm]BF_4	97	25:75	86/93
13[e]	[BMIm]BF_4	90	22:78	89/93
14[f]	[BMIm]BF_4	90	33:67	80/91

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] Water (100 mol-%) was added. [d] Cyclohexanone (2 equiv.) was used. [e] Cyclohexanone (5 equiv.) was used. [f] 20 mol-% of catalyst **1** was used.

When the reaction was performed in DMSO or DMF, which are usually used in aldol reaction, almost racemic aldol product **4a** was obtained, although an excellent yield was obtained after 12 h (Table 1, Entries 1 and 2). Other organic solvents and solvent-free conditions were also tested, but no good results were acquired (Table 1, Entries 3–7). Reactions occurring in toluene, CH_3OH, or CH_2Cl_2 exhibited inverted enantioselectivities compared with proline-catalyzed reactions; the diastereoselectivities and *ee* values were far from satisfactory (Table 1, Entries 5–7). At best, only a slight improvement in the diastereoselectivities was observed with water and [BMIm]PF_6, and the enantioselectivities were still disappointing.

However, dramatic changes occurred when the ionic liquid [BMIm]BF_4 was employed in conjunction with catalyst **1**: the aldol adduct was afforded in 98% yield with moderate diastereoselectivity (78:22) and excellent *ee* value (97%/94%) for both isomers. Moreover, no inverted enantioselectivity was observed with the use of [BMIm]BF_4. Thus, the unique ionic liquid [BMIm]BF_4 when used as a solvent plays a crucial role in the stereoselectivity of this reaction. Although the solvent effect between [BMIm][BF_4] and [BMIm][PF_6] was not clear at this stage, we proposed that because BF_4^- was more electronegative than PF_6^-, the BF_4^- ion has a much stronger ionicity, which could stabilize the enamine transition state. Water was added to improve the diastereoselectivity, but no obvious effect was detected (Table 1, Entry 11). Examination of the ratio of the reactants indicated that 3 equivalents of donor cyclohexanone to 1 equivalent of acceptor aldehyde gave the best results (Table 1, Entries 12 and 13). Reducing the catalyst loading to 20 mol-% resulted in a lower *dr* value (33:67; Table 1, Entry 14).

To broaden the scope of this transformation, a variety of aromatic aldehydes were tested with cyclohexanone under the optimized conditions. As illustrated in Table 2, the reaction of various substituted benzaldehydes bearing an electron-withdrawing group proceeded smoothly in moderate to good diastereoselectivities (up to 3:97) and excellent enantioselectivities (up to 98%) to furnish the *anti* isomer of the aldol adducts (Table 2, Entries 1–8), whereas for the neutral and electron-rich aromatic aldehydes (Table 2, Entries 9–11), the reactions commonly required a longer time (108 h). Lower isolated yields and enantioselectivities were obtained for *p*-tolualdehyde and anisaldehyde (Table 2, Entries 10 and 11). Other aromatic aldehydes, such as, 2-furaldehyde, 2-thenaldehyde, and 2-pyridinylaldehyde, underwent the aldol reactions as well and generated the corresponding adducts with good enantioselectivities for the major isomer. Dramatically, the reaction with furfural primarily produced the *syn* isomer, whereas the diastereoselectivity was disappointingly low for 2-pyridinylaldehyde (Table 2, Entries 12–14).

To further investigate the generality of the current process, several different cycloketones were examined with 4-nitrobenzaldehyde (Table 2, Entries 15–19). Each reaction gave the aldol product in good yield except cycloheptanone (Table 2, Entry 16). Although the diastereoselectivities were not satisfactory, moderate to excellent enantioselectivities were attained in almost all cases. When applying 4-methylcyclohexanone in the present reaction, one more chiral center was introduced into the structure of the product (Table 2, Entry 19). Predominantly one single *syn* isomer with excellent enantioselectivity (99%*ee*) was obtained with a ratio of 71:29 to all other isomers. Reaction with acetone was also carried out, and the adduct was produced with a similar *ee* value (74%) compared to that[2a] obtained with the proline-catalyzed reaction (Table 2, Entry 20). Significantly, no dehydrated products were produced in any of the reactions listed in Table 2.

After completion of the reaction and subsequent extraction of the product with ether, catalyst **1** remaining in [BMIm]BF_4 can be reused directly in subsequent reactions. Table 3 showed that the catalyst and the solvent could be recycled together four times with a slight decrease in activity and stereoselectivity.

A proline–imidazole conjugate catalysis has also been proposed as a probable transition state of the asymmetric aldol reaction (Figure 1). As major product **4a** had (2*S*,1′*R*)[2b] absolute stereochemistry, the enamine intermediate of

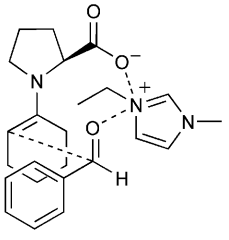
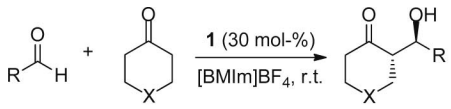
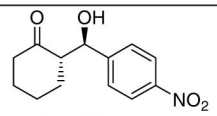
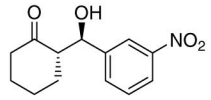
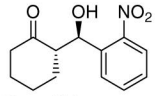
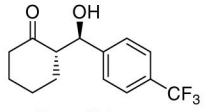
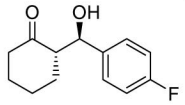
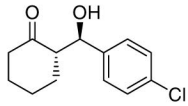
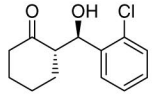
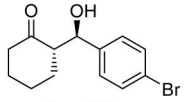
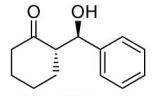
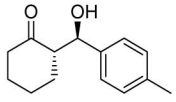
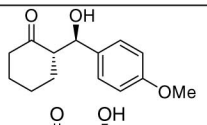
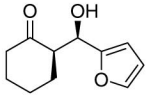
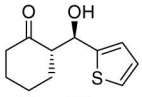
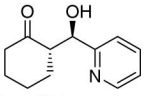
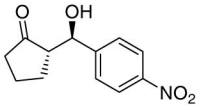
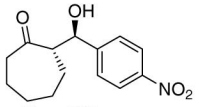
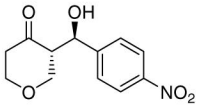
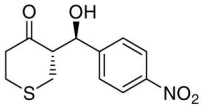
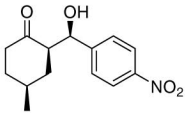
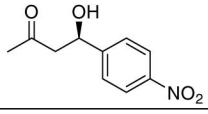


Figure 1. Proposed transition state.

Table 2. Screening of different aromatic aldehydes with cyclic ketones.



Entry	Product	*t* [h]	Yield[a] [%]	*dr*[b,c] (*syn*/*anti*)	*ee*[b][%] (*syn*/*anti*)
1		6	95	22:78	94/97
2		12	92	19:81	64/96
3		24	88	3:97	–[d]/98
4		24	85	26:74	29/91
5		48	73	6:94	–/95
6		48	84	18:82	–/94
7		24	90	3:97	–/97
8		48	85	22:78	87/96
9		108	41	7:93	–/95
10		108	39	24:76	–/88

Entry	Product	*t* [h]	Yield[a] [%]	*dr*[b,c] (*syn*/*anti*)	*ee*[b][%] (*syn*/*anti*)
11		108	34	18:82	–/74
12		72	76	85:15[e]	93/–
13		72	57	19:81	20/88
14		6	99	44:56	84/93
15		12	98	66:34	54/75
16		72	31	5:95	/28
17		12	99	54:46	76/78
18		12	97	46:54	62/69
19		24	85	71:29[e]	99/97
20		12	91	–	74

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] Determined by ^{1}HNMR spectroscopic analysis. [d] Not detected. [e] Inverted diastereoselectivity was observed.

Table 3. Recycling study of [EMIm][Pro] (**1**) using the model reaction.

Entry	Reuse	*t* [h]	Yield[a][%]	*dr*[b] (*syn*/*anti*)	*ee*[b] [%] (*syn*/*anti*)
1		6	95	22:78	94/97
2	1	12	90	30:70	69/91
3	2	12	91	33:67	75/87
4	3	24	89	40:60	56/79
5	4	24	93	32:68	70/85

[a] Isolated yield. [b] Determined by chiral HPLC analysis.

the reaction favored *Re* facial attack on the arylaldehyde. An electrostatic interaction between the aromatic aldehyde and the imidazolium moiety of the catalyst is expected to stabilize the transition state and make the selectivity possible.

Conclusions

To conclude, we have applied the anion-modified CIL [EMIm][Pro] (**1**) as a green and efficient asymmetric organocatalyst in direct aldol condensation reactions. It broadly expands the substrate applicability with close to perfect diastereo- and enantioselectivities. The employment of the ionic liquid as either a catalyst or the solvent made

the aldol process environmentally benign and more atom economical. Moreover, the system can be reused over four runs with only a slight decrease in activity. As a result, this procedure was proved to be a green and attractive alternative to the existing methods for the synthesis of β-hydroxy ketones. Further investigations on the design of similar CILs that may influence the outcome of asymmetric reactions are underway.

Experimental Section

General Methods: Commercial reagents were used as received, unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded with either a Bruker-DPX 300 or AV-400 spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. HPLC analysis was performed with a Shimadzu CTO-10AS by using a Chiralpak AD-H or OD-H column purchased from Daicel Chemical Industries.

Typical Procedure for Direct Asymmetric Aldol Reaction: Cyclohexanone (29.5 mg, 0.3 mmol) was injected into a vial containing catalyst **1** (6.7 mg, 0.03 mmol) in [BMIm]BF_4 (0.25 mL) at room temperature. The mixture was then stirred for 30 min before *p*-nitrobenzaldehyde (15.1 mg, 0.1 mmol) was added. The mixture was vigorously stirred and monitored by TLC. When the reaction was complete, the mixture was extracted with diethyl ether and then purified by flash silica gel chromatography (ethyl acetate/hexane, 1:3) to afford the product as a white solid. Yield: 23.6 mg (95%); 22:78 *dr* (determined by HPLC) and 94:97% *ee*. HPLC (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R (*syn* isomer) = 21.85 (minor), 19.04 min (major); t_R (*anti* isomer) = 24.25 (minor), 32.28 min (major).

(2*S*,1′*R*)-2-[Hydroxy(*p*-nitrophenyl)methyl]cyclohexan-1-one:[13–15] Yield: 23.6 mg, 95% (Table 2, Entry 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 7.9 Hz, 2 H, Ar), 7.51 (d, *J* = 8.0 Hz, 2 H, Ar), 4.90 (d, *J* = 7.9 Hz, 1 H, CH), 4.09 (s, 1 H, OH), 2.58–2.62 (m, 1 H, CH), 2.49–2.52 (m, 1 H, CH), 2.36–2.41 (m, 1 H, CH), 2.11–2.14 (m, 1 H, CH), 1.35–1.85 (m, 5 H, CH, CH_2) ppm. HPLC (Chiralpak AD-H column, hexane/2-propanol = 90:10, ow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 24.25 (minor), 32.28 min (major).

(2*S*,1′*R*)-2-[Hydroxy(*m*-nitrophenyl)methyl]cyclohexan-1-one:[13–15] Yield: 22.8 mg, 92% (Table 2, Entry 2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (m, 1 H, Ar), 8.16–8.18 (m, 1 H, Ar), 7.67–7.69 (m, 1 H, Ar), 7.52–7.56 (m, 1 H, Ar), 4.90 (d, *J* = 8.5 Hz, 1 H, CH), 4.14 (br. s, 1 H, OH), 2.59–2.68 (m, 1 H, CH), 2.49–2.53 (m, 1 H, CH), 2.34–2.42 (m, 1 H, CH), 2.10–2.15 (m, 1 H, CH), 1.82–1.87 (m, 1 H, CH), 1.52–1.77 (m, 3 H, CH, CH_2), 1.37–1.44 (m, 1 H, CH) ppm. HPLC (Chiralpak AD-H column, hexane/2-propanol = 92:8, ow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 24.61 (major), 31.29 min (minor).

(2*S*,1′*R*)-2-[Hydroxy(*o*-nitrophenyl)methyl]cyclohexan-1-one:[14,18] Yield: 21.9 mg, 88% (Table 2, Entry 3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76–7.86 (m, 2 H, Ar), 7.66 (m, 1 H, Ar), 7.43–7.45 (m, 1 H, Ar), 5.45 (d, *J* = 6.5 Hz, 1 H, CH), 4.14 (br. s, 1 H, OH), 2.74–2.78 (m, 1 H, CH), 2.44–2.46 (m, 1 H, CH), 2.31–2.37 (m, 1 H, CH), 1.84–1.87 (m, 1 H, CH), 1.53–1.78 (m, 5 H, CH, CH_2) ppm. HPLC (Chiralpak AD-H column, hexane/2-propanol = 92:8, ow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 24.76 (major), 26.92 min (minor).

(2*S*,1′*R*)-2-{Hydroxy[*p*-(trifluoromethyl)phenyl]methyl}cyclohexan-1-one:[14,18] Yield: 23.1 mg, 85% (Table 2, Entry 4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 7.8 Hz, 2 H, Ar), 7.44 (d, *J* = 7.9 Hz, 2 H, Ar), 4.84 (d, *J* = 8.2 Hz, 1 H, CH), 4.04 (br. s, 1 H, OH), 2.32–2.62 (m, 3 H, CH, CH_2), 2.08–2.12 (m, 1 H, CH), 1.49–1.82 (m, 4 H, CH_2), 1.28–1.38 (m, 1 H, CH) ppm. HPLC (Chiralpak AD-H column, hexane/2-propanol = 90:10, ow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 10.52 (minor), 12.86 min (major).

(2*S*,1′*R*)-2-[Hydroxy(*p*-fluorophenyl)methyl]cyclohexan-1-one:[14,18] Yield: 16.2 mg, 73% (Table 2, Entry 5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.30 (m, 2 H, Ar), 7.01–7.06 (m, 2 H, Ar) 4.78 (d, *J* = 8.8 Hz, 1 H, CH), 4.00 (br. s, 1 H, OH), 2.32–2.62 (m, 3 H, CH, CH_2), 2.08–2.12 (m, 1 H, CH), 1.57–1.89 (m, 4 H, CH_2), 1.23–1.34 (m, 1 H, CH) ppm. HPLC (Chiralpak AD-H column, hexane/2-propanol = 90:10, ow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 12.93 (minor), 13.98 min (major).

(2*S*,1′*R*)-2-[Hydroxy(*p*-chlorophenyl)methyl]cyclohexan-1-one:[15,18] Yield: 19.9 mg, 84% (Table 2, Entry 6). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.33 (m, 2 H, Ar), 7.23–7.27 (m, 2 H, Ar), 4.76 (d, *J* = 8.7 Hz, 1 H, CH), 4.01 (s, 1 H, OH), 2.32–2.59 (m, 3 H, CH, CH_2), 2.08–2.12 (m, 1 H, CH), 1.49–1.87 (m, 4 H, CH_2), 1.24–1.34 (m, 1 H, CH) ppm. HPLC (Chiralpak AD-H column, hexane/2-propanol = 90:10, ow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 13.65 (minor), 15.58 min (major).

(2*S*,1′*R*)-2-[Hydroxy(*o*-chlorophenyl)methyl]cyclohexan-1-one:[14] Yield: 21.4 mg, 90% (Table 2, Entry 7). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.56 (m, 2 H, Ar), 7.22–7.34 (m, 2 H, Ar), 5.36 (d, *J* = 7.7 Hz, 1 H, CH), 4.04 (s, 1 H, OH), 2.34–2.71 (m, 3 H, CH, CH_2), 2.10–2.12 (m, 1 H, CH), 1.57–1.84 (m, 5 H, CH, CH_2) ppm. HPLC (Chiralpak AD-H column, hexane/2-propanol = 90:10, ow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 12.96 (minor), 11.43 min (major).

(2*S*,1′*R*)-2-[Hydroxy(*p*-bromophenyl)methyl]cyclohexan-1-one:[14,18] Yield: 23.9 mg, 85% (Table 2, Entry 8). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.49 (m, 2 H, Ar), 7.17–7.21 (m, 2 H, Ar), 4.75 (dd, *J* = 8.7, 2.4 Hz, 1 H, CH), 4.01 (s, 1 H, OH), 2.31–2.59 (m, 3 H, CH, CH_2), 2.07–2.13 (m, 1 H, CH), 1.49–1.87 (m, 4 H, CH_2), 1.25–1.34 (m, 1 H, CH) ppm. HPLC (Chiralpak AD-H column, hexane/2-propanol = 90:10, ow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 14.73 (minor), 17.04 min (major).

(2*S*,1′*R*)-2-[Hydroxy(phenyl)methyl]cyclohexan-1-one:[13–15] Yield: 8.3 mg, 41% (Table 2, Entry 9). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.36 (m, 5 H, Ar), 4.79 (d, *J* = 8.6 Hz, 1 H, CH), 3.97 (s, 1 H, OH), 2.33–2.67 (m, 3 H, CH, CH_2), 2.07–2.11 (m, 1 H, CH), 1.51–1.81 (m, 4 H, CH_2), 1.23–1.37 (m, 1 H, CH) ppm. HPLC (Chiralpak OD-H column, hexane/2-propanol = 95:5, ow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 17.26 (minor), 12.29 min (major).

(2*S*,1′*R*)-2-[Hydroxy(*p*-tolyl)methyl]cyclohexan-1-one:[16,18] Yield: 8.5 mg, 39% (Table 2, Entry 10). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15–7.22 (m, 4 H, Ar), 4.79 (d, *J* = 8.5 Hz, 1 H, CH), 3.93 (s, 1 H, OH), 2.40–2.64 (m, 3 H, CH, CH_2), 2.34 (s, 3 H, CH_3), 2.09–2.10 (m, 1 H, CH), 1.60–1.80 (m, 4 H, CH, CH_2), 1.27–1.34 (m, 1 H, CH) ppm. HPLC (Chiralpak OD-H column, hexane/2-propanol = 90:10, ow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 9.18 (minor), 7.46 min (major).

(2*S*,1′*R*)-2-[Hydroxy(*p*-methoxyphenyl)methyl]cyclohexan-1-one:[13,18] Yield: 7.9 mg, 34% (Table 2, Entry 11). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.24 (m, 2 H, Ar), 6.88–6.90 (m, 2 H, Ar), 4.75 (d, *J* = 8.3 Hz, 1 H, CH), 3.94 (s, 1 H, OH), 3.81 (s, 3 H, OCH_3), 2.33–2.63 (m, 3 H, CH, CH_2), 2.08–2.11 (m, 1 H, CH), 1.57–1.80 (m, 4 H, CH_2), 1.24–1.32 (m, 1 H, CH) ppm. HPLC

(Chiralpak AD-H column, hexane/2-propanol = 95:5, ow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 31.38 (minor), 33.01 min (major).

(2*R*,1′*R*)-2-[Hydroxy(furan-2-yl)methyl]cyclohexan-1-one:[18] Yield: 14.7 mg, 76% (Table 2, Entry 12). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 1 H, Ar), 6.25–6.32 (m, 2 H, Ar), 5.29 (br. s, 1 H, CH), 4.05 (s, 1 H, OH), 2.32–2.95 (m, 3 H, CH, CH_2), 2.04–2.17 (m, 1 H, CH), 1.60–1.89 (m, 4 H, CH_2), 1.30–1.44 (m, 1 H, CH) ppm. HPLC (Chiralpak AD-H column, hexane/2-propanol = 95:5, ow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 20.45 (minor), 22.59 min (major).

(2*S*,1′*R*)-2-[Hydroxy(thien-2-yl)methyl]cyclohexan-1-one:[17,21] Yield: 11.9 mg, 57% (Table 2, Entry 13). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.3 (m, 1 H, Ar), 6.93–6.96 (m, 2 H, Ar), 5.09 (d, J = 8.2 Hz, 1 H, CH), 4.11 (s, 1 H, OH), 2.33–2.70 (m, 3 H), 2.10–2.13 (m, 1 H), 1.63–1.86 (m, 4 H), 1.34–1.40 (m, 1 H) ppm. HPLC (Chiralpak AD-H column, hexane/2-propanol = 90:10, ow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 14.65 (minor), 13.25 min (major).

(2*S*,1′*R*)-2-[Hydroxy(pyrid-2-yl)methyl]cyclohexan-1-one:[19] Yield: 20.2 mg, 99% (Table 2, Entry 14). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53–8.55 (m, 1 H, Ar), 7.68–7.72 (m, 1 H, Ar), 7.48 (d, J = 7.8 Hz, 1 H, Ar), 7.17–7.21 (m, 1 H, Ar), 4.91 (br. s, 1 H, CH), 4.31 (s, 1 H, OH), 2.97–3.10 (m, 1 H, CH), 2.33–2.49 (m, 2 H, CH_2), 2.07–2.10 (m, 1 H, CH), 1.82–1.89 (m, 1 H, CH), 1.46–1.77 (m, 4 H, CH_2) ppm. HPLC (Chiralpak AD-H column, hexane/2-propanol = 99:1, ow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 68.24 (minor), 66.12 min (major).

(2*S*,1′*R*)-2-[Hydroxy(*p*-nitrophenyl)methyl]cyclopentan-1-one:[13–15] Yield: 23.0 mg, 98% (Table 2, Entry 15). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, J = 8.7 Hz, 2 H, Ar), 7.51 (d, J = 8.6 Hz, 2 H, Ar), 4.85 (d, J = 9.2 Hz, CH), 4.79 (s, 1 H, OH), 2.34–2.51 (m, 2 H, CH_2), 1.96–2.18 (m, 2 H, CH_2), 1.53–1.77 (m, 3 H, CH, CH_2) ppm. HPLC (Chiralpak AD-H column, hexane/2-propanol = 95:5, ow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 44.18 (minor), 44.91 min (major).

(2*S*,1′*R*)-2-[Hydroxy(*p*-nitrophenyl)methyl]cycloheptan-1-one:[15,18] Yield: 8.1 mg, 31% (Table 2, Entry 16). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, J = 8.7 Hz, 2 H, Ar), 7.53 (d, J = 8.6 Hz, 2 H, Ar), 4.92 (dd, J = 6.4, 5.0 Hz, CH), 3.72–3.74 (s, 1 H, OH), 2.96–3.00 (m, 1 H, CH), 2.44–2.60 (m, 2 H, CH_2), 1.26–1.90 (m, 8 H, CH_2) ppm. HPLC (Chiralpak AD-H column, hexane/2-propanol = 90:10, ow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 18.89 (minor), 45.66 min (major).

(2*S*,1′*R*)-2-[Hydroxy(*p*-nitrophenyl)methyl]tetrahydro-4-*H*-pyran-4-one:[16] Yield: 26.4 mg, 99% (Table 2, Entry 17). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, J = 8.7 Hz, 2 H, Ar), 7.52 (d, J = 8.6 Hz, 2 H, Ar), 5.00 (d, J = 7.7 Hz, CH) 4.19–4.27 (s, 1 H, OH), 3.71–3.88 (m, 3 H, CH, CH_2), 3.46 (t, J = 10.54, 10.54 Hz, 1 H, CH), 2.46–2.95 (m, 3 H, CH, CH_2) ppm. HPLC (Chiralpak AD-H column, hexane/2-propanol = 90:10, ow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 47.41 (minor), 56.11 min (major).

(2*S*,1′*R*)-2-[Hydroxy(*p*-nitrophenyl)methyl]tetrahydrothiopyran-4-one:[15,16] Yield: 25.8 mg, 97% (Table 2, Entry 18). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, J = 8.7 Hz, 2 H, Ar), 7.54 (d, J = 8.6 Hz, 2 H, Ar), 5.05 (dd, J = 8.0, 3.6 Hz, CH), 3.64 (d, J = 3.8 Hz, 1 H, OH), 2.65–3.05 (m, 6 H, CH, CH_2), 2.51–2.53 (m, 1 H, CH) ppm. HPLC (Chiralpak AD-H column, hexane/2-propanol = 90:10, ow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 59.88 (minor), 71.04 min (major).

(2*R*,4*S*)-2-[(*R*)-Hydroxy(*p*-nitrophenyl)methyl]-4-methylcyclohexanone:[20] Yield: 22.3 mg, 85% (Table 2, Entry 19). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, J = 8.7 Hz, 2 H, Ar), 7.49 (d, J = 8.6 Hz, 2 H, Ar), 5.48 (br. s, 1 H, CH), 3.15 (s, 1 H, OH), 2.66–2.72 (m, 1 H, CH), 2.37–2.56 (m, 2 H, CH_2), 2.02–2.06 (m, 1 H, CH), 1.77–1.97 (m, 2 H, CH_2) 1.57–1.63 (m, 1 H, CH), 1.36–1.52 (m, 1 H, CH), 0.93 (d, J = 6.5 Hz, 3 H, CH_3) ppm. HPLC (Chiralpak AD-H column, hexane/2-propanol = 92:8, ow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 23.58 (minor), 22.54 min (major).

(*R*)-4-Hydroxy-4-(*p*-nitrophenyl)butan-2-one:[3,15] Yield: 19.0 mg, 91% (Table 2, Entry 20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, J = 8.7 Hz, 2 H, Ar), 7.54 (d, J = 8.7 Hz, 2 H, Ar), 5.26 (d, J = 8.0 Hz, 1 H, CH), 3.60 (s, 1 H, OH), 2.82–2.85 (m, 2 H, CH_2), 2.20 (s, 3 H, CH_3) ppm. HPLC (Chiralpak AD-H column, hexane/2-propanol = 90:10, ow rate = 0.6 mL min^{-1}, λ = 254 nm): t_R = 25.86 (minor), 26.81 min (major).

Supporting Information (see footnote on the first page of this article): Selected ^{1}H NMR spectroscopic data for diastereoisomers and HPLC data for enantiomers of aldol adducts.

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