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Highly diastereo- and enantioselective direct aldol reactions of cycloketones with aldehydes catalyzed by a *trans*-4-*tert*-butyldimethylsiloxy-L-proline amide

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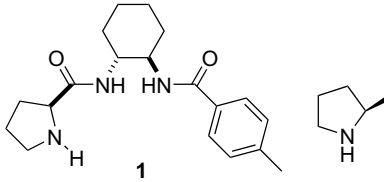
Abstract—An organocatalyst derived from *trans*-4-hydroxy-L-proline and (1*S*,2*S*)-1,2-diphenyl-2-aminoethanol catalyzes the direct aldol reactions of cycloketones with a wide scope of aldehydes in high yields and with excellent diastereoselectivities of up to >99:1 and enantioselectivities of up to >99% ee.

1. Introduction

The development of highly efficient and enantioselective chiral catalysts for the organic transformations that proceed under mild conditions and tolerate a wide scope of substrates is an important area of research. Since the pioneering works of by List and Barbas III et al. in which L-proline was shown to act as a catalyst in the intermolecular direct aldol reaction,[1] a great number of organocatalysts have been designed for the direct aldol reaction and other reactions on the basis of so called 'enamine catalysis'.[2–8] Impressive results for the direct aldol reaction of a wide range of aldehydes with simple ketones, in particular with acetone have been obtained. However, very few organocatalysts have given both high diastereo- and enantioselectivity for the direct aldol reaction of cycloketones with aldehydes, until very recently, where an L-proline amide **1** derived from a chiral diamine[9] and some acyclic amino acids[10] was discovered to catalyze the aldolization of cyclohexanone with high enantioselectivity. Both cases, however, preclude aliphatic aldehydes as acceptors. In addition to this, diastereoselectivities ranging from 6:1 to 37:1 were observed with acylic amino acids[10] and comparably low enantioselectivities (<90% ee) given by L-proline amide **1** for aromatic aldehydes substituted with an electron-donating group[9] require significant improvement.



In our continuous efforts toward developing neworganocatalysis, we found that L-proline amides derived from chiral amino alcohols acted as efficient catalysts for direct asymmetric aldol reactions.[5,6] L-Proline amides **2** and **3** catalyze the direct aldol reactions of both aromatic and aliphatic aldehydes in neat acetone with high enantioselectivities of up to >99% ee.[5,6] However, neither of them catalyze the direct aldol reactions between cyclohexanone and aldehydes with satisfactory stereoselectivity.[5b,6] Extensive studies on

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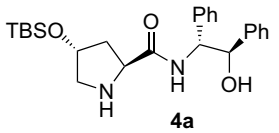
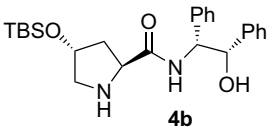
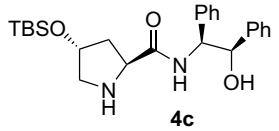
the relationship between the stereogenic centers of the amino alcohol moiety and the stereoselectivity of L-proline amides have revealed that the chirality of each stereogenic center has a considerable effect on the stereocontrol.[5,6] Thus, we envisioned that organocatalyts **4a–d**, which are structurally similar to **2**, but contain an additional stereogenic center, might show distinct catalytic performances from the corresponding L-proline amides. We found that **4d** was an efficient organocatalyst for enantioselective desymmetrizations of the 4-substituted cyclohexanones using the direct aldol reaction.[11] Herein, we report that *trans*-4-*tert*-butyldimethylsiloxy-L-proline-based organocatalysts **4a–d** catalyze the direct aldol reactions of aldehydes with cyclohexanone and its analogues with excellent enantioselectivities of up to >99% and diastereoselectivities of >99:1.



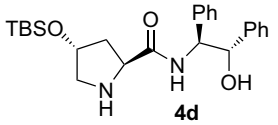
4a



4b



4c



4d

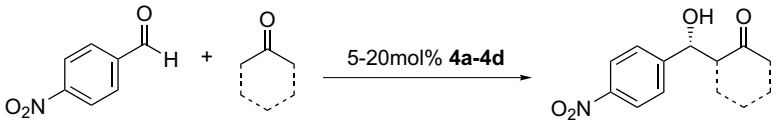
2. Results and discussion

trans-4-*tert*-Butyldimethylsiloxy-L-proline amides **4a–d** were readily prepared from TBS-protected *trans*-4-hydroxy-L-proline and the corresponding enantiomerically pure 1,2-diphenyl-2-aminoethanols. In the presence of 5 mol % **4a–d**, the aldol reaction of 4-nitrobenzaldehyde with acetone was first examined to obtain an optimal reaction conditions. As shown in Table 1, these organic molecules exhibited high catalytic efficiency. The highest enantioselectivity of 65% ee was observed with catalyst **4d** (entry 4). The enantioselectivity increased significantly as the reaction temperature decreased (entry 5). More importantly, **4d** shows much better enantio- and diastereoselectivity for the direct aldol reaction of 4-nitrobenzaldehyde with cyclohexanone than both organocatalysts **2** and **3**.[5,6] When the **4d** catalyzed reaction of cyclohexanone with 4-nitrobenzaldehydes was conducted at −40 °C in dichloromethane, it gave the aldol adduct in a high yield of 95% and with an excellent diastereomeric ratio of >99:1 in favor of the *anti*-diastereomer, as well as a near perfect enantioselectivity of 99% ee (entry 6).

The direct aldol reactions of a variety of aldehydes, including aromatic and aliphatic ones, with cyclohexanone were carried out in the presence of 5 mol % **4d** under the optimal reaction conditions to examine the scope and limitation. The results are summarized in Table 2. The aldol reactions of both aromatic and aliphatic aldehydes with cyclohexanone proceeded smoothly to give the aldol adducts with excellent diastereoselectivities (up to >99:1) and enantioselectivities (up to >99%). Not only did the aromatic aldehydes, which had electron-withdrawing groups lead to the formation of **7aa–ai** with very high diastereoselectivities ranging from 97:3 to >99:1 and enantioselectivities ranging from 82% to >99% ee (entries 1–9), but also the one bearing an electron-donating group gave extremely high diastereoselectivity of >99:1 and enantioselectivity of 99% ee (entry 10). However, neither the acyclic amino acid nor **1** were able to catalyze the aldol reaction between the electron-rich aromatic aldehyde and cycloketone with a similar level of stereoselectivity.[9,10] More importantly, **4d** is also catalytically active for the reactions of aliphatic aldehydes with cyclohexanone, giving *anti*-**7ak** and **7al** in excellent diastereoselectivities of up to >99:1 and enantioselectivities ranging from 99% to >99%ee (entries 11 and 12). These results demonstrate that organocatalyst **4d** is highly diastereo- and enantioselective for a wider scope of aldehydes in direct aldol reactions compared with those reported previously.[3b,9,10]

To investigate further the generality of the current process, aldol reactions between different cycloketones **5a–d** and 4-nitrobenzaldehyde **6a** were examined (Table 3). All the

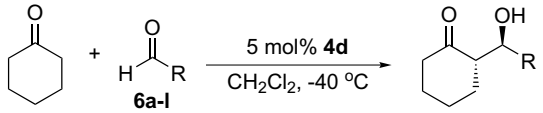
Table 1. *trans*-4-*tert*-Butyldimethylsiloxy-L-proline amides **4a–d** catalyzed direct aldol reaction of acetone and cyclohexanone with 4-nitrobenzaldehyde[a]



Entry	Ketone	Catalyst **4**	Amount of **4** (mol %)	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	Acetone	**4a**	20	0	18	63	40
2	Acetone	**4b**	20	0	18	61	61
3	Acetone	**4c**	20	0	18	75	51
4	Acetone	**4d**	20	0	18	67	65
5	Acetone	**4d**	5	−40	60	57	91
6	Cyclohexanone	**4d**	5	−40	72	95	99[d,e]

[a] The reaction was carried out in neat acetone with a concentration of 0.5 M 4-nitrobenzaldehyde.
[b] Isolated yield.
[c] Ee values were determined by HPLC analysis.
[d] The reaction was carried out in CH_2Cl_2 with a concentration of 0.5 M of 4-nitrobenzaldehyde.
[e] The diastereomeric ratio of *anti*/*syn* is >99:1 on the basis of ^1H NMR analysis.

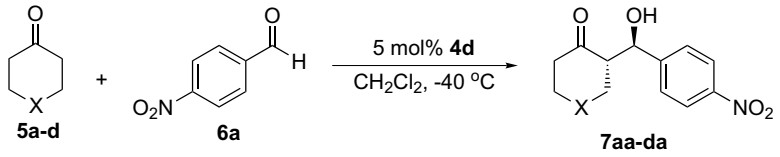
Table 2. The **4d** catalyzed direct intermolecular aldol reactions of cyclohexanone with different aldehydes



Entry	R	Product	Time (h)	Yield[a] (%)	dr[b]	ee[c] (%)
1	4-$NO_2C_6H_4$ **6a**	**7aa**	72	95	>99:1	99
2	2-$NO_2C_6H_4$ **6b**	**7ab**	96	72	99:1	99
3	Ph **6c**	**7ac**	96	49	97:3	98
4	4-CN C_6H_4 **6d**	**7ad**	96	80	>99:1	98
5	4-$CF_3C_6H_4$ **6e**	**7ae**	96	88	>99:1	97
6	2-FC_6H_4 **6f**	**7af**	96	92	97:3	>99
7	2,6-$Cl_2C_6H_3$ **6g**	**7ag**	48	91	>99:1	>99
8	4-ClC_6H_4 **6h**	**7ah**	96	71	98:2	98
9	4-BrC_6H_4 **6i**	**7ai**	96	60	>99:1	96
10	4-MeC_6H_4 **6j**	**7aj**	120	42	>99:1	99
11	*iso*-Propyl **6k**	**7ak**	120	38	>99:1	>99
12	Cyclohexyl **6l**	**7al**	120	40	>99:1	99

[a] Isolated yield after silica-gel column chromatography.
[b] The diastereomeric ratios were determined by ^1H NMR analyses.
[c] The enantiomeric excesses were determined by HPLC analysis.

Table 3. Direct aldol reactions of cycloketones with 4-nitrobenzaldehyde



Entry	Ketone	Product	Yield[a] (%)	dr[b] (*anti*:*syn*)	ee[c] (%)
1	(**5a**)	(**7aa**)	95	>99:1	99
2	(**5b**)	(**7ba**)	90	98:2	94[d]
3	(**5c**)	(**7ca**)	82	98:2	97[d]
4	(**5d**)	(**7da**)	90	96:4	97

[a] Isolated yield.
[b] The diastereoselectivities were determined by NMR analyses.
[c] Ee values were determined by HPLC analysis.
[d] Reactions are carried out at −15 °C.

reactions took place smoothly and furnished the desired aldol adducts **7aa**–**da** in high yield, with excellent diastereomeric ratios of *anti*/*syn* ranging from 96:4 to >99:1 and very high enantioselectivities of up to 99% ee. The diastereo- and enantioselectivities depend to some degree on the structure of the cycloketone. The highest enantio- and

diastereoselectivity were observed for the reaction of cyclohexanone (entry 1). 1,4-Dioxa-spiro[4.5]decan-8-one **5b** gave a comparably lower enantioselectivity than the other cycloketones (entry 2). Notably, **5b** and **5c** seemed less reactive toward the aldehyde than the other two ketones. Thus, the reactions of **5b** and **5c** needed to be conducted at −15 °C in order to ensure the high yields. Interestingly, although **5c** and **5d** are very similar, **5d** is more reactive than **5c**, probably because the sulfur is bulkier than the oxygen. The asymmetric direct aldol reaction catalyzed by **4d** tolerates a wide scope of donors, which will enhance its utility in organic synthesis.

3. Conclusion

In conclusion, we have discovered an organocatalyst **4d**, which catalyzes the direct aldol reactions of cycloketones with a wide range of aldehydes in high yields and with excellent diastereo- and enantioselectivities. The organocatalyst is unique in that it can effectively catalyze the direct aldol reactions of cycloketones with both aromatic and aliphatic aldehydes. Catalyst **4d** seems more efficient than those reported previously since as little as 5 mol % **4d** is enough to efficiently catalyze the direct aldol reaction.

4. Experimental

4.1. General

NMR spectra were recorded on a Brucker-300 MHz spectrometer. Optical rotations were measured on a Perkin–Elmer 241 Polarimeter at 589 nm. HPLC analysis was performed on Waters-Breeze (2487 Dual λ Absorbance Detector and 1525 Binary HPLC Pump). Chiralpak AS, AD, OD and OJ columns were purchased from Daicel Chemical Industries, LTD. Chiral GC analysis was performed on VARIAN CP-3380 with a CP CHIPASIL-DEX column.

4.2. Materials

All starting materials were purchased from Acros and used directly.

4.3. General procedure for aldol reaction

To a solution of the aldehyde (0.5 mmol) and cycloketone (1.0 mL) in anhydrous CH_2Cl_2 (2 mL), L-prolinamide **4d** (11 mg, 0.025 mmol) was added. The resulting mixture was stirred at −40 °C for 72–96 h. The reaction mixture was then treated with saturated ammonium chloride solution, and the layers were separated. The aqueous layer was extracted with ethyl acetate, and dried over anhydrous $MgSO_4$. After removal of solvent, the residue was purified through flash column chromatography on silica gel to give the corresponding aldol products.

4.3.1. 2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclohexanone 7aa. Yield: 95%; *anti*/*syn*: >99:1, *anti*-diastereomer, $[\alpha]_D^{20} = -26.2$ (*c* 0.5, CH_3CO_2Et); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.32 (m, 1H), 1.50–1.57 (m, 3H), 1.76 (m, 1H), 2.04 (m, 1H), 2.32 (m, 2H), 2.58 (m, 1H), 4.06 (br s, 1H), 4.85 (d, $J = 8.3$ Hz, 1H), 7.46 (d, $J = 8.7$ Hz, 2H), 8.16 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 24.606, 27.576, 30.679, 42.601, 57.105, 73.908, 123.488, 126.557, 127.819, 148.345, 214.696; Enantiomeric excess: 99%, determined by HPLC (Daicel Chiralpak OJ, *i*-PrOH/hexane = 35:65), UV 254 nm, flow rate 1.0 mL/min, $t_{Rmajor} = 7.099$ min; $t_{Rminor} = 7.919$ min.

4.3.2. 2-[Hydroxy-(2-nitro-phenyl)-methyl]-cyclohexanone 7ab. Yield: 72%; *anti*/*syn*: = 99:1; *anti*-diastereomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.59–1.74 (m, 5H), 2.03 (m, 1H), 2.31 (m, 2H), 2.72 (m, 1H), 3.75 (br s, 1H), 5.42 (d, $J = 7.1$ Hz, 1H), 7.41 (m, 1H), 7.62 (m, 1H), 7.74 (m, 1H), 7.81 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 24.916, 27.705, 31.050, 42.766, 57.255, 69.692, 124.020, 128.354, 128.962, 133.019, 136.546, 148.692, 214.880; Enantiomeric excess: 99% determined by HPLC (Daicel Chiralpak OJ, *i*-PrOH/hexane = 5:95), UV 254 nm, flow rate 1.0 mL/min, $t_{Rminor} = 19.38$ min; $t_{Rmajor} = 21.07$ min.

4.3.3. 2-[Hydroxy-phenyl-methyl]-cyclohexanone 7ac. Yield: 49%; *anti*/*syn*: = 97:3, *anti*-diastereomer, $[\alpha]_D^{20} = -5.8$ (*c* 0.5, CH_3CO_2Et); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.27–1.31 (m, 1H), 1.32–1.61 (m, 4H), 2.16 (m, 1H), 2.45–2.66 (m, 3H), 3.89 (br s, 1H), 4.76 (d, $J = 8.8$ Hz, 1H), 7.26–7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 24.702, 27.781, 30.822, 42.654, 57.407, 74.731, 127.00, 127.873, 128.353, 140.902, 215.538; Enantiomeric excess: 98% determined by HPLC (Daicel Chiralpak OJ, *i*-PrOH/hexane = 10:90), UV 254 nm, flow rate 1.0 mL/min, $t_{Rmajor} = 9.429$ min; $t_{Rminor} = 11.658$ min.

4.3.4. 2-[Hydroxy-(4-cyano-phenyl)-methyl]-cyclohexanone 7ad. Yield: 80%; *anti*/*syn*: >99:1, *anti*-diastereomer, $[\alpha]_D^{20} = -15.2$ (*c* 0.5, CH_3CO_2Et); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.32–1.63 (m, 5H), 2.08 (m, 1H), 2.34–2.38 (m, 1H), 2.46–2.61 (m, 2H), 4.03 (d, $J = 3.1$ Hz, 1H), 4.81 (dd, $J = 3.1$, 8.4 Hz, 1H); 7.42 (d, $J = 8.1$ Hz, 2H), 7.62 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 24.65, 27.61, 30.70, 42.63, 57.10, 74.19, 111.67, 118.67, 127.74, 132.15, 146.33, 214.81; Enantiomeric excess: 98%, determined by HPLC (Daicel Chiralpak OD, *i*-PrOH/hexane = 10:90), UV 254 nm, flow rate 1.0 mL/min, $t_{Rmajor} = 15.975$ min; $t_{Rminor} = 22.525$ min.

4.3.5. 2-[Hydroxy-(4-trifluoro-phenyl)-methyl]-cyclohexanone 7ae. Yield: 88%; *anti*/*syn*: >99:1 *anti*-diastereomer, $[\alpha]_D^{20} = -13.8$ (*c* 0.5, CH_3CO_2Et); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.30 (m, 1H), 1.36–1.79 (m, 4H), 2.08 (m, 1H), 2.35 (m, 1H), 2.47 (m, 2H), 4.02 (d, $J = 2.9$ Hz, 1H), 4.82 (dd, J=2.9, 8.6 Hz, 1H), 7.43 (d, $J = 8.1$ Hz, 2H), 7.59 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 24.70, 27.69, 30.75, 42.67, 57.25, 74.17, 124.1 ($J = 270$ Hz), 125.28 ($J = 3.4$ Hz), 127.36, 130.06 ($J = 32$ Hz), 144.95, 215.12; IR (KBr) 3359, 2946, 2931, 2865, 1690, 1617, 1449, 1416, 1312, 1285, 844 cm^{-1}; Enantiomeric excess: 97% determined by HPLC (Daicel Chiralpak OD, *i*-PrOH/hexane = 10:90), UV 254 nm, flow rate 1.0 mL/min, $t_{Rminor} = 8.161$ min; $t_{Rmajor} = 9.770$ min.

4.3.6. 2-[Hydroxy-(2-fluoro-phenyl)-methyl]-cyclohexanone 7af. Yield: 92%; *anti*/*syn*: = 97:3 *anti*-diastereomer, $[\alpha]_D^{20} = -14.2$ (*c* 0.5, CH_3CO_2Et); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.44–1.65 (m, 4H), 1.77 (m, 1H), 2.10 (m, 1H), 2.32 (m, 2H), 2.66 (m, 1H), 3.99 (d, $J = 3.2$ Hz, 1H), 5.14 (dd, $J = 2.9$, 8.6 Hz, 1H), 6.96–7.02 (m, 1H), 7.14–7.17 (m, 1H), 7.23–7.26 (m, 1H), 7.46 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 24.63, 27.68, 30.21, 42.52, 56.99, 67.94, 114.91 ($J = 2.2$ Hz), 124.35 ($J = 2.9$ Hz), 128.22 ($J = 3.9$ Hz), 129.05 ($J = 8.2$ Hz), 158.40, 161.65, 215.18; IR (neat) 3512, 2940, 2862, 1698, 1617, 1587, 1492, 1452, 1222, 824, 757; Enantiomeric excess: >99% determined by HPLC (Daicel Chiralpak OD, *i*-PrOH/hexane = 10:90), UV 254 nm, flow rate 1.0 mL/min, $t_{Rminor} = 6.557$ min; $t_{Rmajor} = 8.106$ min.

4.3.7. 2-[Hydroxy-(2,6-2-chloro-phenyl)-methyl]-cyclohexanone 7ag. Yield: 91%; *anti*/*syn*: >99:1; *anti*-diastereomer, $[\alpha]_D^{20} = -80.2$ (*c* 0.5, CH_3CO_2Et); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.24–1.68 (m, 4H), 1.71 (m, 1H), 2.03 (m, 1H), 2.38–2.49 (m, 2H), 3.47 (m, 1H), 3.65 (d, $J = 4.2$ Hz, 1H), 5.80 (dd, $J_1 = 4.2$ Hz, $J_2 = 9.6$ Hz, 1H), 7.11–7.31 (m, 3H), ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 24.655, 27.583, 29.822, 42.403, 53.610, 70.541, 129.302, 134.685, 135.650, 214.364; IR (neat): 3564, 3060, 2964, 2937, 2861, 1695, 1560, 1438, 1131, 794, 762 cm^{-1}; Enantiomeric excess: >99%, determined by HPLC (Daicel Chiralpak OJ, *i*-PrOH/hexane = 5:95), UV 254 nm, flow rate: 1.0 mL/min, $t_{Rminor} = 9.14$ min; $t_{Rmajor} = 10.30$ min.

4.3.8. 2-[Hydroxy-(4-chloro-phenyl)-methyl]-cyclohexanone 7ah. Yield: 71%; *anti*/*syn*: = 98:2 *anti*-diastereomer, $[\alpha]_D^{20} = -5.0$ (*c* 0.5, CH_3CO_2Et); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.26–1.31 (m, 1H), 1.31–1.64 (m, 5H), 2.06 (m, 1H), 2.45–2.55 (m, 3H), 3.98 (d, $J = 2.7$ Hz, 1H), 4.74 (dd, $J = 2.7$, 8.7 Hz, 1H), 7.23 (d, $J = 8.4$ Hz, 2H), 7.30 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 24.695, 27.701, 30.738, 42.647, 57.352, 74.122, 128.368, 128.520, 133.569, 139.490, 215.2; Enantiomeric excess: 98% determined by HPLC (Daicel Chiralpak OJ, *i*-PrOH/hexane = 5:95), UV 254 nm, flow rate 1.0 mL/min, $t_{Rmajor} = 10.892$ min; $t_{Rminor} = 12.615$ min.

4.3.9. 2-[Hydroxy-(4-bromo-phenyl)-methyl]-cyclohexanone 7ai. Yield: 60%; *anti*/*syn*: >99:1, *anti*-diastereomer, $[\alpha]_D^{20} = -5.0$ (*c* 0.5, CH_3CO_2Et); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.25–1.64 (m, 4H), 1.78 (m, 1H), 2.04 (m, 1H), 2.33–2.38 (m, 1H), 2.48–2.55 (m, 2H), 3.97 (d, $J = 2.8$ Hz, 1H), 4.73 (dd, $J = 2.7$, 8.6 Hz, 1H), 7.18 (d, $J = 8.3$ Hz, 2H), 7.44 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 24.699, 27.698, 30.741, 42.646, 57.314, 74.181, 121.707, 128.724, 131.477, 140.017, 215.223; Enantiomeric excess: 96% determined by HPLC (Daicel Chiralpak OJ, *i*-PrOH/hexane = 5:95), UV 254 nm, flow rate 1.0 mL/min, $t_{Rmajor} = 11.857$ min; $t_{Rminor} = 13.832$ min.

4.3.10. 2-[Hydroxy-(4-methyl-phenyl)-methyl]-cyclohexanone 7aj. Yield: 42%; *anti*/*syn*: >99:1; *anti*-diastereomer, $[\alpha]_D^{20} = -3.8$ (*c* 0.5, CH_3CO_2Et); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.25–1.30 (m, 1H), 1.51–1.75 (m, 4H), 2.05 (m, 1H), 2.33–2.36 (m, 3H), 2.36–2.38 (m, 1H), 2.38–2.45 (m, 1H), 2.60 (m, 1H), 3.93 (br s, 1H), 4.73 (d, $J = 8.8$ Hz, 1H), 7.16 (d, $J = 8.0$ Hz, 4H); 7.19 (d, $J = 8.0$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 21.120, 24.68, 27.794, 30.836, 42.635, 57.389, 74.492, 126.887, 129.015, 137.519, 137.903, 215.673; Enantiomeric excess: 99% determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane = 30:70), UV 254 nm, flow rate: 1.0 mL/min, $t_{Rmajor} = 6.137$ min; $t_{Rminor} = 7.047$ min.

4.3.11. 2-[Hydroxy-isopropyl-methyl]-cyclohexanone 7ak. Yield: 38%; *anti*/*syn*: >99:1; *anti*-diastereomer, $[\alpha]_D^{20} = -1.2$ (*c* 0.5, CH_3CO_2Et); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.85–0.94 (m, 3H), 1.62–2.04 (m, 5H), 2.30 (m, 2H), 2.34–2.42 (m, 3H), 3.14 (br s, 1H), 3.48 (dd, $J = 3.9$, 7.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 15.102, 20.043, 24.870, 26.759, 29.090, 30.570, 42.825, 53.565, 75.571, 216.069; IR (Neat): 3541, 2957, 2953, 2870, 1695, 1616, 1398, 1129, 993 cm^{-1}; Enantiomeric excess: >99%, determined by chiral GC analysis (CP CHIRASIL-DEX), Inject Temp 240 °C, Column Temp 100 °C, FID Oven Temp 260 °C, Inlet Pressure 13Psi, $t_{Rmajor} = 20.535$ min; $t_{Rminor} = 21.077$ min.

4.3.12. 2-[Hydroxy-cyclohexyl-methyl]-cyclohexanone 7al. Yield: 40%; *anti*/*syn*: >99:1; *anti*-diastereomer, $[\alpha]_D^{20} = -48$ (*c* 0.5, CH_3CO_2Et); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.14–1.68 (m, 14H), 1.73 (m, 1H), 1.75 (m, 2H), 2.35 (m, 2H), 2.49 (m, 1H), 3.26 (br s, 1H), 3.45 (dd, $J = 3.6$, 7.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 24.967, 25.892, 26.253, 26.376, 26.549, 27.822, 30.308, 30.814, 39.409, 42.936, 52.823, 75.604, 216.210; IR (Neat): 3541, 2927, 2853, 1696, 1448, 1129 cm^{-1}; Enantiomeric excess: 99% determined by HPLC (Daicel Chiralpak AD, *i*-PrOH/hexane = 15:85), UV 280 nm, flow rate 1.0 mL/min, $t_{Rmajor} = 4.47$ min; $t_{Rminor} = 5.62$ min.

4.3.13. 7-[Hydroxy-(4-nitro-phenyl)-methyl]-1,4-dioxa-spiro-[4.5]decan-8-one 7ba. Yield: 90%; *anti*/*syn*: = 98:2; *anti*-diastereomer, $[\alpha]_D^{20} = -2.8$ (*c* 0.5, CH_3CO_2Et); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.48–1.52 (m, 1H), 1.69–1.74 (m, 1H), 1.78–2.04 (m, 2H), 2.47 (m, 1H), 2.71 (m, 1H), 2.98 (m, 1H), 3.86–3.96 (m, 4H), 4.03 (d, $J = 3.1$ Hz, 1H), 4.90 (dd, $J = 3.1$, 8.1 Hz, 1H), 7.48 (d, $J = 8.4$ Hz, 2H), 8.19 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 34.287, 37.750, 38.760, 52.918, 64.627, 73.731, 106.720, 123.552, 126.491, 127.836, 147.853, 213.132; Enantiomeric excess: 94%, determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane = 30:70), UV 254 nm, flow rate 1.0 mL/min, $t_{Rminor} = 12.21$ min; $t_{Rmajor} = 17.87$ min.

4.3.14. 3-[Hydroxyl-(4-nitro-phenyl)-methyl]-tetrahydrothiopyran-4-one 7ca. Yield: 82%; *anti*/*syn*: = 98:2; *anti*-diastereomer, $[\alpha]_D^{20} = -56$ (*c* 0.5, CH_3CO_2Et); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.36–1.39 (m, 1H), 1.40–1.57 (m, 1H), 1.81–1.85 (m, 1H), 2.09 (m, 1H), 2.35–2.39 (m, 1H), 2.48–2.59 (m, 2H), 4.06 (d, $J = 3.1$ Hz, 1H), 4.87 (dd, $J = 3.1$, 8.3 Hz, 1H), 7.49 (d, $J = 8.7$ Hz, 2H), 8.19 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 30.807, 32.814, 44.755, 59.450, 73.186, 123.803, 127.775, 147.597, 147.736, 211.256; Enantiomeric excess: 97%, determined by HPLC (Daicel Chiralpak AS,

i-PrOH/hexane = 30:70), UV 254 nm, flow rate 1.0 mL/min, $t_{Rmajor} = 16.012$ min, $t_{Rminor} = 21.637$ min.

4.3.15. 2-[Hydroxy-(4-nitro-phenyl)-methyl]-tetrahydro-4-*H*-pyran-4-one 7da. Yield: 90%; *anti*/*syn*: = 96:4; *anti*-diastereomer, $[\alpha]_D^{20} = -56.4$ (*c* 0.5, CH_3CO_2Et); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.50–2.54 (m, 1H), 2.66–2.69 (m, 1H), 2.88–2.90 (m, 1H), 3.42–3.49 (t, $J = 9.9$ Hz, 1H), 3.70–3.83 (m, 3H), 4.20 (m, 1H), 4.96 (dd, $J = 3.3$, 8.1 Hz, 1H); 7.50 (d, $J = 8.7$ Hz, 2H), 8.21 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 42.860, 57.219, 68.342, 69.773, 71.328, 123.848, 127.073, 147.368, 127.448, 209.224; IR (neat): 3529, 3105, 2981, 2879, 2844, 1700, 1516, 1348, 1276, 1215, 1098, 1055, 863 cm^{-1}; Enantiomeric excess: 97%, determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane = 30:70), UV 254 nm, flow rate 1.0 mL/min, $t_{Rmajor} = 16.134$ min; $t_{Rminor} = 20.919$ min.

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