Highly Enantioselective Direct Aldol Reaction Catalyzed by Organic Molecules

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Supplemental Information

General Methods	2
General Procedure and data for synthesis of catalysts 1a-m	2-5
General procedure for enantioselective aldol reaction	5
Spectra data for aldol products	5-8
HPLC data for chiral aldol products	9-14

Experimental Section

General Methods. ^1H NMR spectra were recorded on 400 MHz spectrometer. Chemical shifts are expressed in ppm downfield from TMS as internal standard, and coupling constants are reported in Hz. Routine monitoring of reaction was performed by TLC, using precoated silica gel TLC plates obtained by E-Merck. IUPAC names of ligands and aldol product were taken from Chem. ultra 8. All the column chromatographic separations were done by using silica gel (Acme's, 60-120 mesh). Petroleum ether used was of boiling range 60-80 °C. Reactions that needed anhydrous conditions were run under the atmosphere of nitrogen or argon using flame-dried glassware. The organic extracts were dried over *anhydrous* sodium sulfate. Evaporation of solvents was performed at reduced pressure. Dichloromethane was distilled over CaH_2 and acetone was dried over *anhydrous* potassium carbonate.

General procedure for the synthesis of catalysts 1a-m.

Triethylamine (0.94 g, 9.3 mmol) was slowly added to a solution of *N*-(*tert*-Benzyloxycarbonyl)-L-proline (2.0 g, 9.3 mmol) in DCM (25 mL) at 0 °C. Ethyl chloroformate (2.4 g, 9.3 mmol) was added drop wise and the solution was stirred at the same temperature for 15 min. Then, optically pure amino alcohol (1 g, 8 mmol) was added and the resulting solution was stirred for 5 h. The whole solution was diluted with some DCM. After filtration and removal of solvent under the reduced pressure, the residue was purified by recrystallisation with ethyl acetate to give *N*-(*tert*-benzyloxycarbonyl)-L-prolinamide.

Formic acid (23 mL) was slowly added to *N*-(*tert*-Benzyloxycarbonyl)-L-prolinamide (2 g, 4.43 mmol) at 0 °C and the resulting solution was stirred for 10 h. Excess formic acid was carefully neutralized by adding solid sodium bicarbonate and the whole mixture was extracted with ethyl acetate. The organic layer was dried and the solvent was removed to obtain pure product.

(*S*)-*N*-(2-Hydroxy-2,2-diphenylethyl)pyrrolidine-2-carboxamide (**1a**).

This was prepared as per our general procedure to afford the product **1a** as a white amorphous solid; yield 85%; mp 200-202 °C; $[\alpha]_D^{25}$ -58.9 (*c* 1.1, CHCl_3). ^1H NMR (CDCl_3 , 400 MHz) δ 1.85-2.05 (m, 4H), 2.48 (m, 1H), 3.42-3.57 (m, 3H), 4.44 (m, 1H), 7.24 (m, 7H), 7.42 (m, 3H), 8.61 (d, J = 10.5 Hz, 1H). Anal. Calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.32; H, 7.20; N, 8.95.

(*S*)-*N*-((*S*)-1-Hydroxy-1,1-diphenylpropan-2-yl)pyrrolidine-2-

carboxamide (**1b**). This was prepared as per our general procedure to afford the product **1b** as a yellowish viscous liquid; yield 79%; $[\alpha]_D^{25}$ -72.0 (*c* 1.3, CHCl_3). ^1H NMR (CDCl_3 , 400 MHz) δ 1.20 (d, J = 6.8 Hz, 3H), 1.33 (m, 1H), 1.49 (m, 2H), 1.90 (m, 1H), 2.62 (m, 1H), 2.82 (m, 1H), 3.49 (dd, J = 9.3, 4.9 Hz, 1H), 4.77 (dt, J = 8.6, 6.8 Hz, 1H), 7.16 (m, 2H), 7.27 (m, 4H), 7.52 (m, 4H), 8.01 (d, J = 8.3 Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) 15.2, 25.7, 30.4, 47.0, 52.9, 60.3, 80.4, 125.6, 125.8, 126.6, 126.7, 128.0, 128.2, 145.1, 146.1, 175.4. Anal. Calcd for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 74.24; H, 7.40; N, 8.55.

(S)-N-((S)-1-Hydroxy-3-methyl-1,1-diphenylbutan-2-yl)pyrrolidine-2-carboxamide (1c). This was prepared as per our general procedure to afford the product **1c** as a white amorphous solid; yield 87%; mp 185-187 °C; $[\alpha]^{25}_D$ -65.3 (*c* 1.1, CHCl₃). ¹H NMR (CDCl₃, 400 MHz) δ 0.79 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 1.26 (m, 1H), 1.54 (m, 1H), 1.64 (m, 1H), 1.84 (m, 2H), 3.01 (m, 2H), 3.79 (m, 1H), 4.86 (d, *J* = 10 Hz, 1H), 7.07-7.28 (m, 6H), 7.54 (m, 4H), 8.10 (d, *J* = 10 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) 17.9, 22.7, 24.1, 28.1, 29.7, 45.7, 58.6, 59.0, 80.9, 124.9, 125.1, 125.9, 127.3, 127.6, 145.5, 147.2, 166.0, 170.4. Anal. Calcd for C₂₂H₂₈N₂O₂: C, 74.97; H, 8.01; N, 7.95. Found: C, 74.76; H, 8.14; N, 7.88.

(S)-N-((S)-1-Hydroxy-4-methyl-1,1-diphenylpentan-2-yl)pyrrolidine-2-carboxamide (1d). This was prepared as per our general procedure to afford the product **1d** as a white amorphous solid; yield 82%; mp 184-187 °C; $[\alpha]^{25}_D$ -45.9 (*c* 1.2, CHCl₃). ¹H NMR (CDCl₃, 400 MHz) δ 0.86 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H), 1.21 (m, 2H), 1.46 (m, 1H), 1.56 (m, 1H), 1.86 (m, 2H), 2.56 (m, 1H), 2.82 (m, 1H), 3.49 (q, *J* = 4.6 Hz, 1H), 4.58 (t, *J* = 8 Hz, 1H), 5.52 (bs, 1H), 7.11-7.32 (m, 6H), 7.55 (m, 4H), 7.96 (d, *J* = 8 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) 21.5, 23.8, 25.4, 25.7, 30.5, 37.3, 47.0, 56.8, 60.2, 80.8, 125.6, 125.7, 126.4, 126.6, 127.9, 128.2, 145.1, 146.6, 176.0. Anal. Calcd for C₂₃H₃₀N₂O₂: C, 75.37; H, 8.25; N, 7.64. Found: C, 75.12; H, 8.34; N, 7.55.

(S)-N-((2S,3S)-1-Hydroxy-3-methyl-1,1-diphenylpentan-2-yl)pyrrolidine-2-carboxamide (1e). This was prepared as per our general procedure to afford the product **1e** as a white amorphous solid; yield 92%; mp 206-208 °C; $[\alpha]^{25}_D$ -86.8 (*c* 1.0, CHCl₃). ¹H NMR (CDCl₃, 400 MHz) δ 0.78 (m, 6H), 0.96 (m, 1H), 1.45 (m, 1H), 1.54 (m, 1H), 1.74 (m, 2H), 1.96 (m, 1H), 2.74 (m, 1H), 2.91 (m, 1H), 3.53 (q, *J* = 4 Hz, 1H), 4.27 (bs, 1H), 4.63 (dd, *J* = 9.5, 3.4 Hz, 1H), 7.11-7.31 (m, 6H), 7.52 (t, *J* = 8 Hz, 4H), 8.15 (d, *J* = 8 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) 11.8, 18.6, 24.7, 25.9, 30.6, 35.5, 47.1, 60.1, 60.4, 81.5, 125.5, 125.7, 126.5, 128.0, 128.1, 145.8, 147.1, 175.1. Anal. Calcd for C₂₃H₃₀N₂O₂: C, 75.37; H, 8.25; N, 7.64. Found: C, 75.16; H, 8.35; N, 7.70.

(S)-N-((S)-1-Hydroxy-1,1,3-triphenylpropan-2-yl)pyrrolidine-2-carboxamide (1f). This was prepared as per our general procedure to afford the product **1f** as a white amorphous solid; yield 85%; mp 178-180 °C; $[\alpha]^{25}_D$ -121.0 (*c* 1.1, CHCl₃). ¹H NMR (CDCl₃, 400 MHz) δ 1.62 (m, 2H), 1.80 (m, 1H), 2.77-2.94 (m, 2H), 3.05 (m, 2H), 3.24 (m, 1H), 4.24 (d, *J* = 4.6 Hz, 1H), 4.84 (m, 1H), 7.08-7.38 (m, 10H), 7.61 (m, 5H), 7.89 (bs, 1H). Anal. Calcd for C₂₆H₂₈N₂O₂: C, 77.97; H, 7.05; N, 6.99. Found: C, 77.76; H, 7.21; N, 6.91.

(S)-N-((S)-2-Hydroxy-1,2,2-triphenylethyl)pyrrolidine-2-carboxamide

(1g). This was prepared as per the general procedure to afford the product **1g** as a white amorphous solid; yield 79%; mp 221-224 °C; $[\alpha]_D^{25}$ -6.4 (*c* 1.0, CHCl₃). ¹H NMR (CDCl₃, 400 MHz) δ 1.60 (m, 3H), 1.94 (m, 1H), 2.88 (m, 2H), 3.56 (m, 1H), 5.90 (d, *J* = 9.3 Hz, 1H), 6.99-7.24 (m, 11H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.60 (d, *J* = 7.8 Hz, 2H), 8.65 (d, *J* = 8.8 Hz, 1 H); ¹³C NMR (DMSO-*d*₆, 100 MHz) 25.6, 30.2, 46.7, 58.5, 60.1, 79.9, 126.1, 126.3, 126.5, 126.8, 127.3, 127.7, 129.0, 139.8, 145.4, 146.4, 173.4. Anal. Calcd for C₂₅H₂₆N₂O₂: C, 77.69; H, 6.78; N, 7.25. Found: C, 77.54; H, 6.70; N, 7.30.

(S)-N-((R)-2-Hydroxy-1,2,2-triphenylethyl)pyrrolidine-2-carboxamide

(1h). This was prepared as per our general procedure to afford the product **1h** as a white amorphous solid; yield 75%; mp 205-208 °C; $[\alpha]_D^{25}$ +112.7 (*c* 1.0, CHCl₃). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 1.08 (m, 1H), 1.38 (m, 2H), 1.78 (m, 1H), 2.33 (m, 1H), 2.69 (m, 1H), 3.45 (m, 1H), 5.77 (d, *J* = 9.8 Hz, 1H), 7.06 (m, 8H), 7.30 (m, 3H), 7.28 (t, *J* = 7.4 Hz, 2H), 7.50 (d, *J* = 7.8 Hz, 2H), 8.75 (d, *J* = 9.5 Hz, 1H); ¹³C NMR (DMSO-*d*₆, 100 MHz) 29.9, 35.1, 51.2, 63.6, 64.8, 85.3, 131.2, 131.3, 131.6, 132.1, 132.5, 132.9, 134.3, 144.6, 150.3, 151.4, 169.6, 177.0. Anal. Calcd for C₂₅H₂₆N₂O₂: C, 77.69; H, 6.78; N, 7.25. Found: C, 77.44; H, 6.94; N, 7.20.

(S)-N-((S)-2-Ethyl-2-hydroxy-1-phenylbutyl)pyrrolidine-2-

carboxamide (1i). This was prepared as per our general procedure to afford the product **1i** as a white amorphous solid; yield 60%; mp 158-163 °C; $[\alpha]_D^{25}$ -1.5 (*c* 1.0, CHCl₃). ¹H NMR (CDCl₃, 400 MHz) δ 0.82 (t, *J* = 7.4 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H), 1.14 (m, 1H), 1.29 (m, 1H), 1.60 (m, 4H), 1.77 (m, 1H), 2.05 (m, 1H), 2.17 (bs, 2H), 2.89 (m, 1H), 2.99 (m, 1H), 3.76 (dd, *J* = 9.0, 5.4 Hz, 1H), 4.88 (d, *J* = 9.5 Hz, 1H), 7.27 (m, 5H), 8.56 (d, *J* = 9.0 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) 7.5, 8.0, 26.0, 27.3, 28.4, 30.6, 47.2, 57.4, 60.6, 76.9, 127.3, 128.1, 128.2, 139.6, 174.1. Anal. Calcd for C₁₇H₂₆N₂O₂: C, 70.31; H, 9.02; N, 9.65. Found: C, 70.12; H, 9.14; N, 9.60.

(S)-N-((S)-2-Hydroxy-1-phenylethyl)pyrrolidine-2-carboxamide (1j).

This was prepared as per our general procedure to afford the product **1j** as yellowish viscous liquid; yield 75%. ¹H NMR (CDCl₃, 400 MHz) δ 1.67 (m, 2H), 1.82 (s, *J* = 6 Hz, 1H), 2.08 (m, 1H), 2.87 (m, 1H), 2.95 (m, 1H), 3.51 (bs, 2H), 3.76 (m, 3H), 4.99 (m, 1H), 7.28 (m, 5H), 8.37 (d, *J* = 7.8 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) 25.9, 30.5, 47.0, 55.3, 60.3, 66.2, 126.4, 127.4, 128.5, 139.3, 175.5. Anal. Calcd for C₁₃H₁₈N₂O₂: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.40; H, 7.64; N, 11.88.

(S)-N-((S)-4-Ethyl-4-hydroxy-2-methylhexan-3-yl)pyrrolidine-2-

carboxamide (1k). This was prepared as per our general procedure to afford the product **1k** as a white amorphous solid; yield 65%; mp 99-102 °C; $[\alpha]_D^{25}$ -94.3 (*c* 1.1, CHCl₃). ¹H

NMR (CDCl₃, 400 MHz) δ 0.89 (m, 12H), 1.39-1.64 (m, 5H), 1.75 (m, 2H), 1.97 (m, 1H), 2.13 (m, 2H), 2.95 (m, 1H), 3.05 (m, 1H), 3.80 (dd, J = 10.5, 2.0 Hz 1H), 7.97 (d, J = 8.5 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) 7.6, 8.0, 17.1, 22.4, 26.2, 27.7, 27.8, 28.7, 31.2, 47.4, 56.4, 60.8, 77.6, 175.5. Anal. Calcd for C₁₄H₂₈N₂O₂: C, 65.59; H, 11.01; N, 10.93. Found: C, 65.34; H, 11.09; N, 10.85.

(*S*)-*N*-((*S*)-2-Benzyl-2-hydroxy-4-methyl-1-phenylpentan-3-

yl)pyrrolidine-2-carboxamide (**1l**). This was prepared as per our general procedure to afford the product **1l** as a white amorphous solid; yield 71%; mp 145-150 °C; $[\alpha]_D^{25}$ -30.5 (*c* 1.0, CHCl₃). ¹H NMR (CDCl₃, 400 MHz) δ 0.83 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H), 1.67 (m, 3H), 1.87 (qn, J = 5.9 Hz, 1H), 2.08 (m, 1H), 2.34 (sd, J = 6.6, 1.9 Hz, 1H), 2.72-3.01 (m, 7H), 3.61 (dd, J = 9.3, 5.2 Hz, 1H), 3.85 (dd, J = 9.7, 1.9 Hz, 1H), 7.24 (m, 10H), 7.98 (d, J = 10.1 Hz, 1H). Anal. Calcd for C₂₄H₃₂N₂O₂: C, 75.75; H, 8.48; N, 7.36. Found: C, 75.52; H, 8.61; N, 7.30.

(*S*)-*N*-((*S*)-1-Hydroxy-1,1-bis(4-methoxyphenyl)-3-methylbutan-

2-yl)pyrrolidine-2-carboxamide (**1m**). This was prepared as per the general procedure to afford the product **1m** as a white amorphous solid; yield 62%; mp 188-190 °C; $[\alpha]_D^{25}$ -190.0 (*c* 1.0, CHCl₃). ¹H NMR (CDCl₃, 400 MHz) δ 1.02 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H), 1.65 (m, 3H), 2.25 (m, 1H), 2.86 (m, 1H), 3.19 (m, 1H), 3.40 (m, 1H), 3.75 (s, 3H), 3.74-3.79 (m, 1H), 3.79 (s, 3H), 4.43 (d, J = 4.8 Hz, 1H), 6.73 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 7.04 (d, J = 8.5 Hz, 2H), 7.12 (d, J = 8.7 Hz, 2H), 8.05 (bs, 1H). Anal. Calcd for C₂₄H₃₂N₂O₄: C, 69.88; H, 7.82; N, 6.79. Found: C, 69.52; H, 7.96; N, 6.70.

General Procedure for the Enantioselective Direct Aldol Reaction. A solution of a catalyst **1** (0.1 mmol) in dry acetone (1 mL) was stirred at a suitable temperature (Tables) for half an hour. An aldehyde (1 mmol) was added and the resulting mixture was stirred at the same temperature for 24 - 48 h. After completion of the reaction, the reaction mixture was treated with saturated aqueous ammonium chloride solution and the whole mixture was extracted with ethyl acetate. The organic layer was washed with brine. It was dried and the solvent was removed to give a crude residue. After purification by column chromatography over silica gel using hexane-ethyl acetate (3:2), the pure product was obtained.

(*R*)-4-Hydroxy-4-phenylbutan-2-one (**2a**)¹. It was obtained in a maximum of >99% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 90.0:10.0]; flow rate 1.0mL/min; t_R = 9.16 min (*R*), 10.06 min (*S*); $[\alpha]_D^{25}$ +60.3 (*c* 1.0, CHCl₃) [lit.¹ (98% ee); $[\alpha]_D^{22}$ +74.8 (*c* 0.61, CHCl₃)].

(*R*)-4-(4-Chlorophenyl)-4-hydroxybutan-2-one (**2b**)¹. It was obtained in a maximum of >99% ee. The optical purity was determined by HPLC on chiralpak AD-H

column [hexane/2-propanol 95.0:5.0]; flow rate 1.0 mL/min; t_R = 16.43 min (*R*), 17.72 min (*S*); $[\alpha]^{25}_D +52.0$ (*c* 1.5, CHCl₃) [lit.¹ (99% ee); $[\alpha]^{22}_D +70.5$ (*c* 0.5, CHCl₃)].

(*R*)-4-(4-Fluorophenyl)-4-hydroxybutan-2-one (2c)¹. It was obtained in a maximum of >99% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 90.0:10.0]; flow rate 1.0 mL/min; t_R = 13.23 min (*R*), 14.27 min (*S*); $[\alpha]^{25}_D +58.7$ (*c* 1.0, CHCl₃) [lit.¹ (97% ee); $[\alpha]^{22}_D +69.8$ (*c* 0.47, CHCl₃)].

(*R*)-4-(3-Chlorophenyl)-4-hydroxybutan-2-one (2d). It was obtained in a maximum of >99% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 90.0:10.0]; flow rate 1.0 mL/min; t_R = 8.81 min (*R*), 9.84 min (*S*); $[\alpha]^{25}_D +33.2$ (*c* 2.1, CHCl₃). ¹H NMR (CDCl₃, 400 MHz) δ 2.17 (s, 3H), 2.80 (m, 2H), 3.68 (bs, 1H), 5.09 (m, 1H), 7.21 (m, 3H), 7.34 (s, 1H). Anal. Calcd for C₁₀H₁₁ClO₂: C, 60.46; H, 5.58. Found: 60.25; H, 5.68.

(*R*)-4-Hydroxy-4-(3-methoxyphenyl)butan-2-one (2e)². It was obtained in a maximum of >99% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 90.0:10.0]; flow rate 1.0 mL/min; t_R = 13.13 min (*R*), 14.73 min (*S*); $[\alpha]^{25}_D +30.5$ (*c* 1.3, CHCl₃) [lit.¹ (98% ee); $[\alpha]^{22}_D +74.8$ (*c* 0.61, CHCl₃)].

(*R*)-4-(2-Chloro-6-fluorophenyl)-4-hydroxybutan-2-one (2f). It was obtained in a maximum of >99% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 95.0:5.0]; flow rate 1.0 mL/min; t_R = 18.37 min (*R*), 20.38 min (*S*); $[\alpha]^{25}_D +13.7$ (*c* 1.9, CHCl₃). ¹H NMR (CDCl₃, 400 MHz) δ 2.24 (s, 3H), 2.81 (dd, *J* = 17.4, 2.9 Hz, 1H), 3.34 (dd, *J* = 17.6, 10 Hz, 2H), 5.75 (dd, *J* = 9.7, 2.9 Hz, 1H), 6.99 (m, 1H), 7.21 (m, 2H). Anal. Calcd for C₁₀H₁₀FCIO₂: C, 55.44; H, 4.65. Found: C, 55.51; H, 4.55.

(*R*)-4-(3-Chloro-4-fluorophenyl)-4-hydroxybutan-2-one (2g). It was obtained in a maximum of 99% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 95.0:5.0]; flow rate 1.0 mL/min; t_R = 14.26 min (*R*), 16.12 min (*S*); $[\alpha]^{25}_D +42.6$ (*c* 1.5, CHCl₃). ¹H NMR (CDCl₃, 400 MHz) δ 2.19 (s, 3H), 2.81 (m, 2H), 3.68 (bs, 1H), 5.10 (dd, *J* = 8.3, 3.7 Hz, 1H), 7.10 (t, *J* = 8.5 Hz, 1H), 7.20 (m, 1H), 7.41 (dd, *J* = 7.1, 1.8 Hz, 1H). Anal. Calcd for C₁₀H₁₀FCIO₂: C, 55.44; H, 4.65. Found: C, 55.62; H, 4.76.

(*R*)-4-Hydroxy-4-(4-nitrophenyl)butan-2-one (2h)¹. It was obtained in a maximum of 99% ee. The optical purity was determined by HPLC on chiralpak AS-H

column [hexane/2-propanol 70.0:30.0]; flow rate 1.0 mL/min; t_R = 10.75 min (*R*), 13.84 min (*S*); $[\alpha]^{25}_D +14.0$ (*c* 1.0, CHCl₃) [lit.¹ (99% ee); $[\alpha]^{22}_D +66.2$ (*c* 0.5, CHCl₃)].

(*R*)-4-Hydroxy-4-(3-methylphenyl)butan-2-one (2i)². It was obtained in a maximum of 99% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 90.0:10.0]; flow rate 1.0 mL/min; t_R = 9.06 min (*R*), 9.65 min (*S*); $[\alpha]^{25}_D +58.8$ (*c* 1.0, CHCl₃) [lit.¹ (98% ee); $[\alpha]^{22}_D +74.8$ (*c* 0.61, CHCl₃)].

(*R*)-4-(3-Fluorophenyl)-4-hydroxybutan-2-one (2j). It was obtained in a maximum of 98% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 90.0:10.0]; flow rate 1.0 mL/min; t_R = 7.99 min (*R*), 9.04 min (*S*); $[\alpha]^{25}_D +44.8$ (*c* 2.1, CHCl₃). ¹H NMR (CDCl₃, 400 MHz) δ 2.19 (s, 3H), 2.82 (m, 2H), 3.52 (d, *J* = 2.9 Hz, 1H), 5.14 (m, 1H), 6.96 (td, *J* = 8.3, 2.4 Hz, 1H), 7.09 (m, 2H), 7.29 (m, 1H). Anal. Calcd for C₁₀H₁₁FO₂: C, 65.92; H, 6.09. Found: C, 65.68; H, 6.16.

(*R*)-4-(2,5-Difluorophenyl)-4-hydroxybutan-2-one (2k). It was obtained in a maximum of 98% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 90.0:10.0]; flow rate 1.0 mL/min; t_R = 8.05 min (*R*), 9.29 min (*S*); $[\alpha]^{25}_D +80.9$ (*c* 2.7, CHCl₃). ¹H NMR (CDCl₃, 400MHz) δ 2.19 (s, 3H), 2.75 (m, 1H), 2.88 (m, 1H), 3.79 (bs, 1H), 5.37 (d, *J* = 9.0 Hz, 1H), 6.91 (m, 2H), 7.24 (m, 1H). Anal. Calcd for C₁₀H₁₀F₂O₂: C, 60.00; H, 5.04. Found: C, 60.35; H, 5.20.

(*R*)-4-(2,3-Difluorophenyl)-4-hydroxybutan-2-one (2l). It was obtained in a maximum of 97% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 90.0:10.0]; flow rate 1.0 mL/min; t_R = 8.02 min (*R*), 9.25 min (*S*); $[\alpha]^{25}_D +67.5$ (*c* 1.4, CHCl₃). ¹H NMR (CDCl₃, 400 MHz) δ 2.21 (s, 3H), 2.87 (m, 2H), 3.83 (bs, 1H), 5.43 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.07 (m, 2H), 7.29 (m, 1H). Anal. Calcd for C₁₀H₁₀F₂O₂: C, 60.00; H, 5.04. Found: C, 60.24; H, 5.15.

(*R*)-4-(2-Chlorophenyl)-4-hydroxybutan-2-one (2m)¹. It was obtained in a maximum of 98% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 95.0:5.0]; flow rate 1.0 mL/min; t_R = 12.95 min (*R*), 15.97 min (*S*); $[\alpha]^{25}_D +112.6$ (*c* 1.9, CHCl₃) [lit.¹ (96% ee); $[\alpha]^{22}_D +101.7$ (*c* 0.58, CHCl₃)].

(*R*)-4-(3-Bromophenyl)-4-hydroxybutan-2-one (2n). It was obtained in a maximum of 97% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 95.0:5.0]; flow rate 1.0 mL/min; t_R = 14.81 min (*R*), 16.51 min (*S*); $[\alpha]^{25}_D +36.7$ (*c* 1.2, CHCl₃). ¹H NMR (CDCl₃, 400 MHz) δ 2.21 (s, 3H), 2.83 (m,

2H), 3.43 (d, $J = 2.9\text{Hz}$, 1H), 5.12 (m, 1H), 7.23 (m, 2H), 7.41 (d, $J = 7.6\text{Hz}$, 1H), 7.53 (s, 1H). Anal. Calcd for $\text{C}_{10}\text{H}_{11}\text{BrO}_2$: C, 49.41; H, 4.56. Found: C, 49.36; H, 4.57.

(R)-4-Cyclohexyl-4-hydroxybutan-2-one (2o)¹. It was obtained in a maximum of 99% ee. The optical purity was determined by HPLC on chiralpak AD-H column (U.V $\lambda = 280\text{nm}$); [hexane/2-propanol 95.0:5.0]; flow rate 1.0 mL/min; $t_R = 10.99$ min (*R*), 12.83 min (*S*); $[\alpha]_D^{25} +40.3$ (c 1.1, CHCl_3) [lit.¹ (97% ee); $[\alpha]_D^{18} +46.8$ (c 0.24, CHCl_3)].

References:

- 1) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2005**, *127*, 928.
- 2) Ingfried, S.; Frank, W.; Juergen, G. *Chem. Ber.* **1989**, *122*, 371.

2a (Racemic) **2a (Chiral)** **DEMO REPORT**

Peak #	Component Name	Time [min]	Area [$\mu\text{V}\cdot\text{s}$]	Height [μV]	Area [%]
1		8.412	2078983.00	152957.20	99.76
2		9.156	4949.50	525.18	0.24
			2083932.50	153482.38	100.00

2b (Racemic) **2b (Chiral)**

DEMO REPORT

Peak #	Component Name	Time [min]	Area [$\mu\text{V}\cdot\text{s}$]	Height [μV]	Area [%]
1		16.427	2440154.50	95095.13	99.85
2		17.721	3582.00	170.32	0.15
			2443736.50	95265.46	100.00

2c (Racemic) **2c (Chiral)** **DEMO REPORT**

Peak #	Component Name	Time [min]	Area [$\mu\text{V}\cdot\text{s}$]	Height [μV]	Area [%]
1		13.140	2029408.00	73434.71	100.00
			2029408.00	73434.71	100.00

2d (Racemic) **2d (Chiral)** **DEMO REPORT**

Peak #	Component Name	Time [min]	Area [$\mu\text{V}\cdot\text{s}$]	Height [μV]	Area [%]
1		8.774	4270382.22	244750.06	99.69
2		9.681	13430.50	1250.96	0.31
			4283812.72	246001.02	100.00

2e (Racemic) **2e (Chiral)**

DEMO REPORT

Peak #	Component Name	Time [min]	Area [$\mu\text{V}\cdot\text{s}$]	Height [μV]	Area [%]
1		13.150	17440094.50	741454.78	99.78
2		14.598	39324.00	2492.60	0.22
		17479418.50	743947.38	100.00	

2f(Racemic)

2f (Chiral)

DEMO REPORT

Peak #	Component Name	Time [min]	Area [$\mu\text{V}\cdot\text{s}$]	Height [μV]	Area [%]
1		19.071	3098252.37	97660.98	99.85
2		21.158	4694.50	195.36	0.15
			3102946.87	97856.34	100.00