SUPPORTING INFORMATION

Organocatalysis in Radical Chemistry. Enantioselective α-Oxyamination of Aldehydes

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General Experimental Procedures. Methylene chloride was distilled from calcium hydride prior to use. Aldehydes **7**, **11**, and **19** were purchased from Aldrich Chemical company. TEMPO and ferrocenium tetrafluoroborate were also purchased from Aldrich chemical company. Aldehyde **18** was purchased from Alfa Aesar. The ligands **10a-f** were synthesized according to methods reported in the literature. Powdered molecular sieves 4Å (MS 4Å) was purchased from Aldrich Chemical and dried at 250-300 °C under vacuum before use. Flash chromatography was performed using EM Science silica gel 60 (230-400 mesh). All glassware was oven dried, assembled hot, and cooled under a stream of dry nitrogen before use. Reactions with air sensitive materials were carried out by standard syringe techniques.

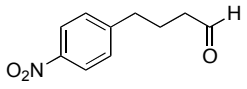
Melting points were recorded on a Fisher-Johns melting point apparatus and are uncorrected. ^{1}H NMR was recorded on a Varian Unity/Inova-500 NB (500 MHz), or a Varian Mercury-400 (400 MHz). Chemical shifts are reported in parts per million (ppm) down field from TMS, using residual $CDCl_3$ (7.27 ppm) as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q =

quartet, qn = quintet, dd = doublets of doublets, dt = doublets of triplets, dq = doublets of quartets, m = multiplet, br = broad, AB sys = AB system), coupling constant(s) and integration. ^{13}C NMR was recorded on a Varian Unity/Inova-500 NB (125 MHz) or a Varian Mercury-400 (100 MHz) spectrometers using broad band proton decoupling. Chemical shifts are reported in parts per million (ppm) down field from TMS, using the middle resonance of $CDCl_3$ (77.23 ppm) as an internal standard. HPLC analyses were carried out on Waters 515 HPLC pump and a 2487 dual λ absorbance detector connected to a PC with millennium workstation. Rotations were recorded on a JASCO-DIP-370 instrument. High-resolution mass spectra (HRMS) [EI+ or FAB] were obtained from the Mass Spectrometry Laboratory, North Dakota State University, Fargo, North Dakota.

Preparation of the starting materials:

The following aldehydes have already been described in the literature: 4-phenylbutyradehyde (**12**)[1], 4-(4-methoxyphenyl)butyraldehyde (**13**)[2], 3-(3,4-dimethoxyphenyl)propionaldehyde (**14**)[3], 3-(2-furyl)propionaldehyde (**16**).[4]

Synthesis of 4-(4-nitrophenyl)butyraldehyde (15)

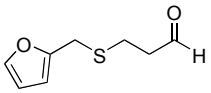


To a solution of 4-(4-nitrophenyl)-1-butanol (1.00 g, 5.12 mmol) in Et_2O (20 ml), cooled to 0 °C, was added Dess-Martin periodinane (3.911 g, 9.22 mmol). The resulting suspension was warmed to room temperature and stirred for approximately 1 hour until the reaction was judged to be complete by TLC. The reaction mixture was poured into 50 mL of 1.0 N NaOH. The aqueous layer was extracted with Et_2O (10 ml x 3) and the combined organic layers were dried over $MgSO_4$,

filtered and concentrated *in vacuo*. The residue was purified by silica-gel chromatography (40 % Et_2O /heptane) to afford the title compound as an yellow oil (704.0 mg, 3.65 mmol, 71% yield).

704.0 mg, 71 % yield (yellow oil); ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.92-2.04 (m, 2H), 2.48 (dt, *J* = 1.3, 7.2 Hz, 2H), 2.73 (t, *J* = 7.2 Hz, 2H), 7.30-7.32 (m, 2H), 8.11-8.13 (m, 2H), 9.76 (t, *J* = 1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 23.3, 35.0, 43.1, 124.0, 129.4, 146.8, 149.3, 201.7; IR (neat) ν = 2889, 1723 and 1391 cm^{-1}; HRMS Exact mass calcd for $C_{10}H_{12}NO_3$ $[M + H]^+$: 194.0817; Found: 194.0814.

Synthesis of 3-(furfurylthio)propionaldehyde (17)



To a solution of ethyl 3-(furfurylthio)-propionate (1.00 g, 4.67 mmol) in THF (10 mL), cooled to 0 °C, was added $LiAlH_4$ (177 mg, 4.67 mmol). The resulting suspension was warmed to room temperature and stirred for approximately 60 minutes until the reaction was judged to be complete by TLC. The reaction mixture was added into 0.5 mL of H_2O and 1.0 N NaOH (1.5 ml). This mixture was filtered by celite and the organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. To the residue in Et_2O (15 ml), cooled to 0 °C, was added Dess-Martin periodinane (1.98 g, 4.67 mmol). The resulting suspension was warmed to room temperature and stirred for approximately 1 hour until the reaction was judged to be complete by TLC. The reaction mixture was poured into 50 mL of 1.0 N NaOH. The aqueous layer was extracted with Et_2O (10 ml x 3) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica-

gel chromatography (10 % Et_2O /heptane) to afford the title compound as an yellow oil (554.5 mg, 3.26 mmol, 70% yield).

554.5 mg, 70 % yield (yellow oil); ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 2.69 (t, J = 7.1 Hz, 2H), 2.80 (t, J = 7.1 Hz, 2H), 3.75 (s, 2H), 6.20 (m, 1H), 6.32 (m, 1H), 7.37 (m, 1H), 9.75 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 24.3, 28.8, 43.7, 107.9, 110.7, 142.5, 151.5, 200.6; IR (neat) ν = 2921, 1721 and 1590 cm^{-1}; HRMS Exact mass calcd for $C_8H_{10}O_2SNa$ $[M + Na]^+$: 193.0299; Found: 193.0301.

Preparation of organocatalysts:

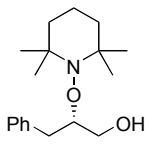
The catalysts **10a**-**10c**[5] and **10e**[6] were synthesized according to methods reported by MacMillan and co-workers. The catalyst **10d**[7] and **10f**[8] was synthesized according to methods reported in the literature.

General Procedure for the organocatalyst reaction:

A mixture of aldehyde (0.50 mmol), TEMPO (1.0 mmol), $NaNO_2$ (0.15 mmol) and organocatalyst (0.10 mmol) in DMF (0.50 mL) was stirred at room temperature for 5 min. $FeCl_3$ (0.10 mmol) and oxygen (introduced via syringe (10 mL) was added and the mixture was stirred at room temperature or -10 °C for 2 or 24 hours. The reaction was monitored by TLC (10% EtOAc in hexane) and when judged complete was quenched with 5 mL of aq-NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (10 ml x 3) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. This extra drying under vacuum removes excess TEMPO by sublimation. To the residue in THF (5 ml), cooled to 0 °C, was added $NaBH_4$ (37.8 mg, 1.00 mmol). The resulting

suspension was warmed to room temperature and stirred for approximately 1 hour until the reaction was judged to be complete by TLC. The reaction mixture was poured into 10 mL of aq-NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (10 ml x 3) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica-gel chromatography (hexane/ethyl acetate) to afford the products.

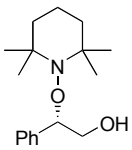
3-Phenyl-2-(2,2,6,6-tetramethylpiperidin-1-oxy)-propane-1-ol (9)



99.3 mg, 68 % yield (colorless oil); $[\alpha]_D^{25}$ = -53.5 (*c* 0.40, CH_2Cl_2); The enantiomeric purity was determined by HPLC (210 nm, 25 °C) t_R = 6.4 min (major); t_R = 7.4 min (minor) [Chiralcel ODH (0.46 cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98/2, 1.0mL/min] as 82% ee.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.96 (s, 3H), 1.10 (s, 3H), 1.19 (s, 3H), 1.28 (s, 3H), 1.32-1.59 (m, 6H), 2.57 (dd, *J* = 5.5, 13.7 Hz, 1H), 2.71 (dd, *J* = 7.1, 13.70 Hz, 1H), 3.64 (br d, 1H), 3.95 (dd, *J* = 9.4, 11.9 Hz, 1H), 4.42-4.48 (m, 1H), 5.61 (br s, 1H), 7.15-7.28 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 17.3, 20.4, 20.8, 32.6, 34.7, 37.8, 40.1, 40.5, 68.0, 81.4, 126.4, 128.3, 129.6, 138.5; IR (neat) ν = 3418, 2920, 1258, 1040 and 749 cm^{-1}; HRMS Exact mass calcd for $C_{18}H_{30}NO_2$ $[M + H]^+$: 292.2277; Found: 292.2280.

2-Phenyl-2-(2,2,6,6-tetramethylpiperidin-1-oxy)-ethane-1-ol (20)

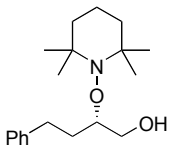


101.6 mg, 74 % yield (yellow oil); $[\alpha]_D^{25}$ = -6.9 (*c* 0.13, CH_2Cl_2); The enantiomeric purity was determined by HPLC (210 nm, 25 °C) t_R = 5.0 min (minor); t_R = 6.0 min (major) [Chiralcel OJH (0.46 cm x 25cm) (from Daicel

Chemical Ind., Ltd.) hexane/*i*-PrOH, 98/2, 1.0 mL/min] as 32% ee.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.17 (s, 3H), 1.24 (s, 3H), 1.27-1.63 (m, 12H), 3.74 (m, 1H), 4.24 (dd, *J* = 9.5, 14.8 Hz, 1H), 5.31 (dd, *J* = 2.7, 9.5 Hz, 1H), 5.79 (br d, 1H), 7.28-7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 17.4, 20.7, 21.0, 33.0, 34.9, 40.5, 40.7, 70.0, 83.9, 127.0, 128.1, 128.6, 139.2; IR (neat) ν = 3410, 2871, 1364, 1082 and 756 cm^{-1}; HRMS Exact mass calcd for $C_{17}H_{28}NO_2$ $[M+H]^+$: 278.2120; Found: 278.2123

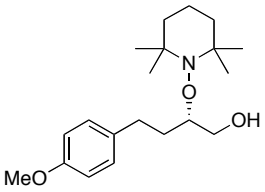
4-Phenyl-2-(2,2,6,6-tetramethylpiperidin-1-oxy)-butane-1-ol (21)



98.0 mg, 64 % yield (yellow oil); $[\alpha]_D^{25}$ = -42.7 (*c* 0.89, CH_2Cl_2); the enantiomeric purity was determined by HPLC (210 nm, 25 °C) t_R = 10.2 min (minor); t_R = 11.6 min (major) [Chiralcel ODH (0.46 cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98/2, 1.0 mL/min] as 82% ee.

^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.15 (s, 3H), 1.21 (s, 3H), 1.27 (s, 3H), 1.36 (s, 3H), 1.46-1.77 (m, 8H), 2.66-2.72 (m, 1H), 2.80-2.86 (m, 1H), 3.61 (br t, 1H), 4.03 (dd, *J* = 10.0, 11.5 Hz, 1H), 4.28-4.32 (m, 1H), 5.97 (br d, 1H), 7.16-7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 17.4, 20.6, 20.7, 32.3, 32.7, 33.1, 34.7, 40.1, 40.6, 68.8, 79.5, 126.1, 128.58, 128.61, 142.2; IR (neat) ν = 2871, 1380, 1032 and 749 cm^{-1}; HRMS Exact mass calcd for $C_{19}H_{32}NO_2$ $[M+H]^+$: 306.2433; Found: 306.2433.

4-(4-Methoxyphenyl)-2-(2,2,6,6-tetramethylpiperidin-1-oxy)-butane-1-ol (22)

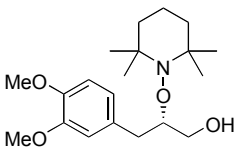


108.0 mg, 64 % yield (colorless oil); $[\alpha]_D^{25}$ = -37.1 (*c* 0.54, CH_2Cl_2); the enantiomeric purity was determined by HPLC (210 nm, 25 °C) t_R = 29.9 min (major); t_R = 31.9 min (minor) [Chiralcel ADH (1 cm x

25cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99/1, 2.0 mL/min] as 86% ee.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.11 (s, 3H), 1.17 (s, 3H), 1.24 (s, 3H), 1.31 (s, 3H), 1.36-1.71 (m, 8H), 2.56-2.63 (m, 1H), 2.69-2.76 (m, 1H), 3.56 (br t, 1H), 3.76 (s, 3H), 4.03 (dd, *J* = 9.8, 11.9 Hz, 1H), 4.22-4.28 (m, 1H), 5.95 (br d, *J* = 9.6 Hz, 1H), 6.79-6.82 (m, 2H), 7.08-7.11 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 17.4, 20.7, 31.4, 32.7, 33.3, 34.7, 40.1, 40.6, 55.5, 60.1, 61.8, 68.7, 79.5, 114.0, 129.4, 134.3, 158.0 (note that the quaternary carbons are non equivalent); IR (neat) ν = 3290, 2871, 1465, 1245 and 1133 cm^{-1}; HRMS Exact mass calcd for $C_{20}H_{34}NO_3$ $[M + H]^+$: 336.2539; Found: 336.2538.

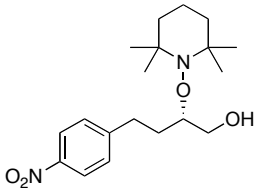
3-(3,4-Dimethoxyphenyl)-2-(2,2,6,6-tetramethylpiperidin-1-oxy)-propane-1-ol (23)



111.6 mg, 64 % yield (colorless oil); $[\alpha]_D^{25}$ = -47.6 (*c* 0.50, CH_2Cl_2); the enantiomeric purity was determined by HPLC (210 nm, 25 °C) t_R = 10.7 min (minor); t_R = 12.7 min (major) [Chiralcel AD (0.46 cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 96/4, 1.0 mL/min] as 84% ee.

^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.10 (s, 3H), 1.12 (s, 3H), 1.21 (s, 3H), 1.30 (s, 3H), 1.32-1.35 (m, 2H), 1.43-1.47 (m, 2H), 1.51-1.56 (m, 2H), 2.54 (dd, *J* = 5.2, 13.9 Hz, 1H), 2.66 (dd, *J* = 7.1, 13.9 Hz, 1H), 3.64 (brd, 1H), 3.85 (s, 3H), 3.86 (s, 3H), 3.96 (dd, *J* = 9.5, 11.9 Hz, 1H), 4.41-4.46 (m, 1H), 5.65 (brs, 1H), 6.71-6.79 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 17.4, 20.6, 20.8, 32.7, 34.8, 37.5, 40.1, 40.5, 56.0, 56.1, 68.1, 81.5, 111.2, 113.0, 121.6, 131.2, 147.7, 148.8; IR (neat) ν =3382, 2873, 1453, 1262 and 1158 cm^{-1}; HRMS Exact mass calcd for $C_{20}H_{34}NO_4$ $[M + H]^+$: 352.2488; Found: 352.2480.

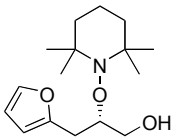
4-(4-Nitrophenyl)-2-(2,2,6,6-tetramethylpiperidin-1-oxy)-butane-1-ol (24)



131.3 mg, 75 % yield (yellow oil); $[\alpha]_D^{25}$ = -35.7 (*c* 0.40, CH_2Cl_2); the enantiomeric purity was determined by HPLC (210 nm, 25 °C) t_R = 28.3 min (minor); t_R = 30.2 min (major) [Chiralcel ODH (1 cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 96/4, 2.0 mL/min] as 82% ee.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.10 (s, 3H), 1.16 (s, 3H), 1.23 (s, 3H), 1.31 (s, 3H), 1.37-1.78 (m, 8H), 2.74-2.82 (m, 1H), 2.87-2.94 (m, 1H), 3.57 (br, 1H), 4.00 (dd, *J* = 9.7, 12.0 Hz, 1H), 4.23-4.28 (m, 1H), 5.85 (br d, 1H), 7.33-7.35 (m, 2H), 8.11-8.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 17.3, 20.7, 32.3, 32.5, 32.7, 34.7, 40.1, 40.6, 60.2, 61.8, 68.5, 79.3, 123.9, 129.4, 146.6, 150.1; IR (neat) ν = 3386, 2931, 1517, 1131, and 855 cm^{-1}; HRMS Exact mass calcd for $C_{19}H_{31}N_2O_4$ $[M + H]^+$: 351.2284; Found: 351.2285.

3-Furyl-2-(2,2,6,6-tetramethylpiperidin-1-oxy)-propane-1-ol (25)

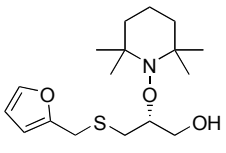


93.1 mg, 66 % yield (colorless oil); $[\alpha]_D^{25}$ = -44.7 (*c* 0.45, CH_2Cl_2); The enantiomeric purity was determined by HPLC (210 nm, 25 °C) t_R = 6.5 min (major); t_R = 8.3 min (minor) [Chiralcel AS (0.46 cm x 25cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99/1, 1.0 mL/min] as 90% ee.

^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.09 (s, 3H), 1.10 (s, 3H), 1.29 (s, 6H), 1.34-1.36 (m, 2H), 1.43-1.59 (m, 4H), 2.64 (dd, *J* = 6.4, 15.1 Hz, 1H), 2.79 (dd, *J* = 6.4, 15.1 Hz, 1H), 3.66-3.71 (m, 1H), 3.96 (dd, *J* = 9.3, 11.9 Hz, 1H), 4.50-4.55 (m, 1H), 5.50 (br s, 1H), 6.06-6.07 (m, 1H), 6.28-6.29 (m, 1H), 7.30-7.31 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 17.4, 20.4, 20.6, 30.0, 32.7, 34.7, 40.2, 40.6, 67.8, 79.2, 107.0, 110.5, 141.0, 152.1; IR

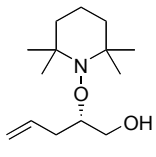
(neat) ν = 3402, 2873,1598, 1243 and 1179 cm^{-1}; HRMS Exact mass calcd for $C_{16}H_{28}NO_3$ $[M + H]^+$: 282.2069; Found: 282.2061.

3-Furfurylthio-(2,2,6,6-tetramethylpiperidin-1-oxy)- propane -1-ol (26)



81.3 mg, 50 % yield (yellow oil); $[\alpha]_D^{25}$ = +1.43 (*c* 0.56, CH_2Cl_2); the enantiomeric purity was determined by HPLC (210 nm, 25 °C) t_R = 11.4 min (major); t_R = 13.7 min (minor) [Chiralcel AS (0.46 cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99/1, 1.0 mL/min] as 85% ee. ^1H NMR ($CDCl_3$, 500 MHz) δ = 1.13 (s, 3H), 1.19 (s, 3H), 1.30 (s, 3H), 1.32 (s, 3H), 1.44-1.61 (m, 6H), 2.43 (dd, *J* = 5.8, 13.7 Hz, 1H), 2.60 (dd, *J* = 6.2, 13.7 Hz, 1H), 3.68-3.71 (m, 1H), 3.76 (d, *J* = 14.7 Hz, 1H), 3.80 (d, *J* = 14.7 Hz, 1H), 3.99 (dd, *J* = 8.9, 11.9 Hz, 1H), 4.36-4.40 (m, 1H), 5.30 (br d, 1H), 6.20 (d, *J* = 20.0 Hz, 1H), 6.31-6.32 (m, 1H), 7.36 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 17.4, 20.7, 20.8, 29.6, 32.2, 32.8, 34.8, 40.2, 40.6, 67.3, 81.0 107.0, 110.6, 142.5, 151.8; IR (neat) ν = 3420, 2850, 1594, 1245 and 1181 cm^{-1}; HRMS Exact mass calcd for $C_{17}H_{30}NO_3S$ $[M + H]^+$: 328.1946; Found: 328.1948.

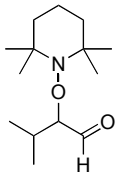
2-(2,2,6,6-tetramethylpiperidin-1-oxy)-4- pentene -1-ol (27)



70.3 mg, 58 % yield (colorless oil); $[\alpha]_D^{25}$ = -46.4 (*c* 0.55, CH_2Cl_2); the enantiomeric purity was determined by HPLC (210 nm, 25 °C) t_R = 8.6 min (major); t_R = 10.2 min (minor) [Chiralcel AS + AS-H (0.46 cm x 25cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98/2, 1.0 mL/min] as 90% ee.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.09 (s, 3H), 1.15 (s, 3H), 1.28 (s, 3H), 1.30 (s, 3H), 1.47-1.56 (m, 6H), 2.04 (m, 1H), 2.18 (m, 1H), 3.59 (dd, *J* = 2.0, 12.0 Hz, 1H), 3.94 (dd, *J* = 9.6, 12.0 Hz, 1H), 4.28 (m, 1H), 5.03 (m, 2H), 5.64 (br s, 1H), 5.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 17.4, 20.5, 20.6, 32.7, 34.8, 35.9, 40.2, 40.5, 68.1, 80.1, 117.0, 134.7; IR (neat) ν = 3389, 2890, 2873, 1642 and 1364 cm^{-1}; HRMS Exact mass calcd for $C_{14}H_{28}NO_2$ $[M + H]^+$: 242.2120; Found: 242.2120.

3-Methyl-2-(2,2,6,6-tetramethylpiperidin-1-oxy)-butanal (28)



89.2 mg, 74 % yield (colorless oil); ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 0.95 (dd, *J* = 1.2, 6.9 Hz, 3H), 1.04 (dd, *J* = 1.2, 6.9 Hz, 3H), 1.17 (s, 12H), 1.29-1.57 (m, 6H), 2.13 (m, 1H), 3.85 (m, 1H), 9.85 (dd, *J* = 1.0, 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 17.3, 18.0, 18.7, 20.6, 30.3, 34.3, 34.6, 40.3, 40.5, 92.0, 205.5; IR (neat) ν = 2875 and 1729 cm^{-1}; HRMS Exact mass calcd for $C_{14}H_{27}NO_2Na$ $[M + Na]^+$: 264.1939; Found: 264.1928.

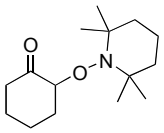
The enantiomeric purity was determined by chiral-phase GC (CP-Chirasil-DexCB (30 m × 0.25 mm) column): [T_{inj} = 275 °C, T_{det} = 275 °C, flow = 1.0 ml/min, t_i = 100 °C; retention times: t_{maj} = 80.3, t_{min} = 82.5] as 0 %ee. Additional ee analysis was carried out by converting the oxyamination product to 3-methyl-1,2-butanediol.

Oxyamination of cyclohexanone

A mixture of cyclohexanone (4.00 mmol), TEMPO (0.50 mmol), $NaNO_2$ (0.15 mmol) and organocatalyst (0.10 mmol) in DMF (0.50 mL) was stirred at room temperature for 5 min. $FeCl_3$ (0.10 mmol) and oxygen (introduced via syringe) was added and the mixture

was stirred at rt for 20 hours. The reaction was monitored by TLC (10% EtOAc in hexane) and when judged complete was quenched with silica gel, concentrated. The silica gel purified by silica gel chromatography (hexane/ethyl acetate = 10/1 v/v) to give the products.

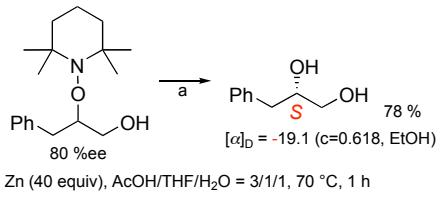
2-(2,2,6,6-tetramethylpiperidin-1-oxy)cyclohexane-1-one



108.6 mg, 86 % yield (colorless oil); ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.12-1.16 (m, 12H), 1.43-1.63 (m, 7H), 1.74-1.79 (m, 1H), 1.86-1.90 (m, 2H), 1.98-2.04 (m, 1H), 2.10-2.12 (m, 1H), 2.26 (m, 1H), 2.76 (m, 1H), 4.15 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 17.3, 20.4, 22.3, 28.7, 33.7, 34.2, 35.0, 40.5, 41.2, 89.4, 212.0; IR (neat) ν = 2869 and 1725 cm^{-1};HRMS Exact mass calcd for $C_{15}H_{28}NO_2$ $[M + H]^+$: 254.2120; Found: 254.2119.

The enantiomeric ratio was determined by chiral-phase GC (CP-Chirasil-DexCB (30 m × 0.25 mm) column): [T_{inj} = 275 °C, T_{detj} = 275 °C, flow = 1.1 ml/min, t_i = 150 °C; retention times: t_{maj} = 17.3, t_{min} = 18.7] as 0 %ee

Absolute Stereochemistry Analysis



[a] Zn (40 equiv), AcOH/THF/H_2O = 3/1/1, 70 °C, 1 h

(*R*)-3-Phenyl-propane-1,2-diol
$[\alpha]_D$ = +25.5 (c=1.0, EtOH)[b]

[b] S. P. Brown; M. P. Brochu; C. J. Sinz; D. W. C. MacMillan *J. Am. Chem. Soc.*, **2003**, *125*, 10808

By modification of Boger's method[9], deprotection of the 3-Phenyl-2-(2,2,6,6-tetramethylpiperidin-1-oxy)-propane-1-ol to 3-phenyl-propane-1,2-diol was achieved with Zn/AcOH at 50 °C (Scheme).

References

1) Saphier, S.; Sinha, S. C.; Keinan, E. *Angew. Chem. Int. Ed.* **2003**, *42*, 1378-1381.

2) McCalmont, W. F.; Patterson, J. R.; Lindenmuth, M. A.; Heady, T. N.; Haverstick, D. M.; Gray, L. S.; Macdonald, T. L. *Bioorg. Med. Chem.* **2005**, *13*, 3821-3839.

3) Pedrosa, R.; Andres, C.; Iglesias, J. M. *J. Org. Chem.,* **2001**, *66*, 243 -250.

4) Richter, F.; Bauer, M.; Perez, C.; Maichle-Mossmer, C.; Maier, M. E. *J. Org. Chem.* **2002**, *67*, 2474 -2480.

5) (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243 (b) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874

6) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894

7) Hubert, C.; Garrigues, B. *Can. J. Chem.* **1998**, *76*, 234

8) (a) Zhenghong, Z.; Yilong, T.; Lixin, W.; Guofeng, Z.; Qilin, Z.; Chuchi, T. *Synthesis* **2004**, 217 (b) Yanagi, T.; Kikuchi, K.; Takeuchi, H.; Ishikawa, T.; Nishimura, T.; Kubota, M.; Yamamoto, I. *Chem. Pharm. Bull.* **2003***, 51*, 221

9) Boger, D. L.; Garbaccio, R. M.; Jin, Q. *J. Org. Chem.* **1997**, *62*, 8875