Direct and Enantioselective Organocatalytic α-Chlorination of Aldehydes

Michael P. Brochu, Sean P. Brown, and David W. C. MacMillan*

Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

Supporting Information

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chloroform was distilled from calcium hydride prior to use. Chromatographic purification of products was accomplished using forced-flow chromatography on Iatrobeads 6RS–8060 according to the method of Still.[2] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or anisaldehyde stain. Gas liquid chromatography (GLC) assays to determine enantiometric excess were developed using racemic samples.

^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury 300 (300 MHz and 75 MHz respectively) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of Technology Mass Spectral facility. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 Series gas chromatography equipped with a split-mode capillary injection system and flame ionization detectors using a Bodman Chiraldex Γ-TA (30 m 0.25 mm) column.

General Procedure: A 10 mL round-bottom flask equipped with a magnetic stir bar and charged with (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one (16.6 mg, 0.05

mmol) and acetone (2 mL) is allowed to cool to –30 °C for five minutes prior to addition of 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (361 mg, 1.2 mmol). The aldehyde substrate (1 mmol) was added to the yellow homogenous solution. The resulting mixture was stirred at –30 °C until the reaction is determined to be complete by GLC, upon which time the mixture is a pale yellow heterogeneous solution. The reaction was then eluted with Et_2O and passed through Iatrobeads (8 g), and the resulting organics were carefully concentrated *in vacuo* (using an ice bath). The resulting residue was purified by Iatrobeads chromatography (solvents noted) and organics carefully concentrated *in vacuo* with an ice bath to provide the title compounds. The enantioselectivity was determined by chiral GLC analysis.

5-Methoxymethoxy-pentanal: To a flask containing 1,5-pentanediol (34 mL, 330 mmol) and NEt_3 (13.7 mL, 99 mmol) in CH_2Cl_2 (150 mL) was slowly added chloromethyl methyl ether (5.0 ml, 65.8 mmol) at 0 °C. The solution was allowed to warm to room temperature and stirred for 4 hours. The reaction was then treated with saturated aqueous NH_4Cl, extracted with CH_2Cl_2 (2 × 100 mL), dried over Na_2SO_4, and concentrated. Iodobenzene diacetate (8.4 g, 26.2 mmol) was then added to a solution of the crude product (3.5 g, 24 mmol) and TEMPO (0.37 g, 2.4 mmol) in CH_2Cl_2 (50 mL).[3] The reaction was stirred for 12 hours and then diluted with CH_2Cl_2 (250 mL). The mixture was washed with a saturated aqueous solution of $Na_2S_2O_3$ (150 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (150 mL), dried over $NaSO_4$, and concentrated *in vacuo*. The resulting residue is purified by silica gel chromatography (40% Et_2O/ pentane) and the organics carefully concentrated *in vacuo* with an ice bath to provide the title compound. IR (film) 2941, 2871, 2720, 1725, 1454, 1383, 1353, 1262, 1201, 1138, 1122, 1078, 1035, 991.9, 905.0, 868.3, 814.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, 1H, J = 1.5 Hz, CHO), 4.58 (s, 2H, CH_2OMe), 3.51 (t, 2H, J = 6.5 Hz, $CH_2C\mathbf{H_2}O$), 3.33 (s, 3H, CH_3), 2.46 (td, J = 1.5, 7.3 Hz, 2H), 1.76- 1.54 (m, 4H, $(C\mathbf{H_2})_2CH_2CHO$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 96.4, 67.1, 55.1, 43.5, 29.1, 18.9; HRMS (CI) exact mass calculated for ($C_7H_{13}O_3$) requires m-1/z 145.0865, found m-1/z 145.0862.

(*S*)-2-Chloro-octanal (Table 3, entry 1): Prepared according to the general procedure from octylaldehyde (156 μL, 1.00 mmol) for 6 h to provide the title compound as a colorless oil (115.2 mg, 71% yield, 92% ee) after Iatrobeads chromatography (2.5% Et_2O/ pentane). IR (film) 3385, 2957, 2927, 2858, 1458, 1400, 1378, 1343, 1138, 1102, 1069, 879.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.52 (d, 1H, J = 2.7 Hz CHO), 4.19 (ddd, 1H, J = 2.7, 5.6, 8.2 Hz, CHCl), 2.06- 1.95 (m, 1H, ClCC**H**$_2$), 1.90- 1.79 (m, 1H, ClCC**H**$_2$), 1.62- 1.26 (m, 8H, (C**H$_2$**)$_4$CH$_3$), 0.92 (t, J = 6.9 Hz, 3H, C**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 64.0, 32.1, 31.5, 28.6, 25.5, 22.5, 14.0; HRMS (CI) exact mass calculated for ($C_8H_{15}ClO$) requires m/z 162.0811, found m/z 167.0812. $[\alpha]_D$ = –35.47 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex β-TA (30 m x 0.25 mm) column (50 °C isotherm, 1 mL/min); (*R*) isomer t_r = 75.5 min and (*S*) isomer t_r = 81.4 min.

(*S*)-2-Chloro-7-octenal (Table 3, entry 2): Prepared according to the general procedure from oct-7-enal (126 mg, 1.00 mmol) for 8 h to provide title compound as a colorless oil (114 mg, 76% yield, 92% ee) after Iatrobeads chromatography (2% Et_2O/ pentane). IR (film) 3853, 3676, 3406, 2970, 2928, 2855, 2357, 2325, 1279, 1102, 1076, 905.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.45 (d, 1H, J = 2.2 Hz, CHO), 5.83-5.69 (m, 1H, CH_2C**H**=CH_2), 4.97 (dd, 2H, J = 1.7, 10.1 Hz, CH=C**H$_2$**), 4.13 (ddd, 1H, J = 2.2, 6.7, 7.1 Hz, CHCl), 2.09-1.99 (m, 2H, C**H$_2$**CH=CH_2), 2.02-1.93 (m, 1H, ClCC**H**$_2$), 1.88-1.76 (m, 1H, ClCC**H**$_2$) 1.62-1.38 (m, 4H, CH_2(C**H$_2$**)$_2$$CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5, 138.4, 115.1, 64.1, 33.5, 32.1, 28.4, 25.2; HRMS (CI) exact mass calculated for ($C_8H_{13}ClO$) requires m/z [M-Cl] =127.0759, found m/z 127.0759. $[\alpha]_D$ = –40.59 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex β-TA (30 m x 0.25 mm) column (50 °C isotherm, 1 mL/min); (*R*) isomer t_r = 89.3 min and (*S*) isomer t_r = 91.4 min.

(*S*)-Chloro-cyclohexyl-acetaldehyde (Table 3, entry 3): Prepared according to the general procedure from cyclohexyl-acetaldehyde[3] (138 μL, 1.00 mmol) for 8 h to provide the title compound as a colorless oil (139.8 mg, 87% yield, 94% ee) after Iatrobeads chromatography (2.5% Et_2O/ pentane). IR (film) 3374, 2930, 2855, 1451,

1378, 1112, 1080, 890.3, 733.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 9.50 (d, 1H, *J* = 3.5 Hz, CHO), 4.00 (dd, 1H, *J* = 3.5, 6.4 Hz, CHCl), 2.07- 1.92 (m, 1H, ClCC**H**), 1.90- 1.66 (m, 4H), 1.43- 1.11 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) □ 195.8, 69.4, 40.2, 29.7, 28.3, 25.9, 25.8, 25.6; HRMS (CI) exact mass calculated for ($C_7H_{12}Cl$) requires *m/z* 131.0628, found *m/z* 131.0626. [□]$_D$ = –6.01 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex □-TA (30 m x 0.25 mm) column (60 °C isotherm, 1 mL/min); (*R*) isomer t_r = 101.3 min and (*S*) isomer t_r = 111.0 min.

(*S*)-Chloro-tricyclo[3.3.1.1^{0,0}]dec-1-yl-acetaldehyde (Table 3, entry 4): Prepared according to the general procedure from tricyclo[3.3.1.1^{0,0}]dec-1-yl-acetaldehyde[4] (174 *μ*L, 1.00 mmol) at –40 °C using (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one (66.4 mg, 0.2 mmol) for 24 h to provide the title compound as a colorless oil (136.5 mg, 85% yield, 95% ee). The excess 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one was consumed by addition of propionaldehyde (29 *μ*L, 0.40 mmol). The reaction was quenched by filtration through Iatrobeads (8 g) eluting with Et_2O and concentrated *in vacuo*. The resulting residue was purified by Iatrobeads chromatography (2.5% Et_2O/ pentane). IR (film) 2905, 2851, 1730, 1456, 1345, 1106, 1064, 1004, 976.2, 762.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 9.52 (d, 1H, *J* = 4.8 Hz, CHO), 3.70 (d, 1H, *J* = 4.8 Hz, CHCl), 2.10- 2.02 (m, 3H), 1.81-1.63 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) □ 195.7, 73.8, 38.8, 37.1, 36.5, 28.0; HRMS (CI) exact mass calculated for ($C_{12}H_{17}ClO$) requires *m/z* 212.0968, found *m/z* 212.0970. [□]$_D$ = +30.02 (c = 1.0, $CHCl_3$). Reduction of the title compound to the corresponding alcohol and cyclization with aqueous 50% KOH provided the epoxide 2-tricyclo[3.3.1.1^{0,0}]dec-1-yl-oxirane which matched literature data.[5] The enantiomeric ratio of the epoxide was determined by GLC using a Bodman Chiraldex □-TA (30 m x 0.25 mm) column (100 °C isotherm, 1 mL/min); (*S*) isomer t_r = 49.3 min and (*R*) isomer t_r = 51.6 min.

(*S*)-2-Chloro-hydrocinnamaldehyde (Table 3, entry 5): Prepared according to the general procedure from hydrocinnamaldehyde (62 mg, 0.50 mmol) in d_6-acetone for 6 h. To reaction flask was added benzyl methyl ether (61 mg, 0.50 mmol). The title compound was provided (92% NMR yield, 92% ee) then isolated as a colorless oil (80%

ee) after Iatrobeads chromatography (2% Et_2O/ pentane). The title compound was identical in all respects to the known literature compound with regards to NMR and HRMS data.[6] IR (film) 3511, 2360, 2341, 1717, 1653, 1540, 1417, 1377, 1277, 1191, 1111, 767.7, 701.6 cm^{-1}; $[\alpha]_D$ = –8.84 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (60 °C isotherm, 1 mL/min); (*R*) isomer t_r = 234.3 min and (*S*) isomer t_r = 245.4 min.

(*S*)-2-Chloro-5-methoxymethoxy-pentanal (Table 3, entry 6): Prepared according to the general procedure from 5-methoxymethoxy-pentanal (170 μL, 1.00 mmol) at –40 °C for 12 h to provide the title compound as a colorless oil (139.8 mg, 94% yield, 93% ee) after Iatrobeads chromatography (40% Et_2O/ pentane). IR (film) 3401, 2932, 2885, 2826, 1736, 1445, 1386, 1346, 1149, 1110, 1040, 919.5, 775.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.53 (d, 1H, *J* = 2.1 Hz, CHO), 4.62 (s, 2H, CH_2OMe), 4.26 (ddd, 1H, *J* = 2.1, 5.1, 8.5 Hz, CHCl), 3.59 (t, 2H, *J* = 5.8 Hz, $CH_2C\mathbf{H_2}O$), 3.37 (s, 3H, $C\mathbf{H_3}$), 2.22- 2.09 (m, 1H), 2.00- 1.68 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.0, 96.4, 66.5, 63.7, 55.3, 29.1, 25.8; HRMS (CI) exact mass calculated for ($C_7H_{14}ClO_3$) requires *m/z* 181.0632, found *m/z* 181.0632. $[\alpha]_D$ = –12.68 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (50 °C isotherm, 1 mL/min); (*R*) isomer t_r = 260.4 min and (*S*) isomer t_r = 267.5 min.

(*S*)-2-Chloro-6-oxo-heptanal (Table 3, entry 7): Prepared according to the general procedure from 6-oxo-heptanal[7] (128 mg, 1.0 mmol) for 12 h to provide title compound as a colorless oil (134 mg, 78% yield, 87% ee) after Iatrobeads chromatography (35% Et_2O/ pentane). IR (film) 3420, 2933, 2855, 2360, 1732, 1715, 1418, 1363, 1162 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.47 (d, 1H, *J* = 2.3 Hz, CHO), 4.16 (dd, 1H, *J* = 2.2, 7.2 Hz, CHCl), 2.47 (t, 2H, *J* = 7.2 CH_2CO), 2.12 (s, 3H, $C\mathbf{H}_3$), 2.03-1.93 (m, 1H), 1.85-1.57 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9, 195.1, 63.8, 42.7, 31.4, 30.1, 19.9; HRMS (CI) exact mass calculated for ($C_7H_{15}ClO2$) requires *m/z* =160.0655, found *m/z* 160.0658. $[\alpha]_D$ = –49.93 (c = 1.0, $CHCl_3$). The enantiomeric ratio

was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (75 °C isotherm, 1 mL/min); (*R*) isomer t_r = 144.1 min and (*S*) isomer t_r = 149.3 min.

(*R*)-2-Chloro-(*R*)-3-phenylbutyraldehyde (Equation 3): Prepared according to the general procedure from (*S)*-3-phenylbutyraldehyde (74 mg, 0.50 mmol) for 6 h to provide the title compound as a colorless oil (65 mg, 71% yield, 7:1 *anti:syn*, 98% ee) after Iatrobeads chromatography (1% Et_2O/ pentane). IR (film) 3821 3751, 2973, 2831, 1733, 1495, 1455, 762.5, 700.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.37 (d, 1H, *J* = 3.0 Hz, CHO), 7.37-7.23 (m, 5H, ArH), 4.29 (dd, 1H, *J*= 3.0, 6.6 CHCl), 3.47 (qd, *J* = 6.6, 7.2 Hz, 1H, C**H**CH_3), 1.46 (d, *J* = 7.2 Hz, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.2, 140.3, 129.9, 128.8, 128.5, 128.4, 127.9, 127.7, 68.7, 42.3, 18.7; HRMS (CI) exact mass calculated for ($C_{10}H_{11}ClO$) requires *m/z* =182.0502, found *m/z* 182.0498. $[\alpha]_D$ = –3.86 (c = 1.0, $CHCl_3$). Product ratio was determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (75 °C isotherm, 1 mL/min); *anti* adduct (2*R*, 3*R*) t_r = 115.5 min, *syn* adduct (2*S*, 3*R*) t_r = 189.2 min.

(*S*)-2-Chloro-(*R*)-3-phenylbutyraldehyde (Equation 4): Prepared according to the general procedure from (*S)*-3-phenylbutyraldehyde (74 mg, 0.50 mmol) for 6 h to provide pure title compound as a colorless oil (72 mg, 79% yield, 24:1 *syn:anti*, 98% ee) after Iatrobeads chromatography (1% Et_2O/ pentane). IR (film) 3821 3751, 2973, 2831, 1733, 1495, 1455, 762.5, 700.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.37 (d, 1H, *J* = 3.0 Hz CHO), 7.37-7.23 (m, 5H, ArH), 4.29 (dd, 1H, J = 3.0, 6.6 Hz, CHCl), 3.47 (qd, 1H, *J* = 6.6, 7.2 Hz, C**H**CH_3), 1.4 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ195.2, 140.3, 129.9, 128.8, 128.5, 128.4, 127.9, 127.7, 68.7, 42.3, 18.7; HRMS (CI) exact mass calculated for ($C_{10}H_{11}ClO$) requires *m/z* =182.0502, found *m/z* 182.0498. $[\alpha]_D$ = –2.31 (c = 1.0, $CHCl_3$). The enantiomeric and diastereomeric ratios were determined by GLC using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (75 °C isotherm, 1 mL/min); *syn* adduct (2*S*, 3*R*) t_r = 111.8, *anti* adduct (2*R*, 3*R*) t_r = 190.2 min.

Stereochemical Analysis

Procedure for Conversion to Epoxide: To a solution of (*S*)-2-chloroaldehyde (0.5 mmol) in CH_2Cl_2 (0.5 mL) and absolute ethanol (0.5 mL) was added sodium borohydride (0.5 mmol) at 0 °C. After 15 min, the resulting solution was treated with saturated aqueous $NaHCO_3$ and the mixture was extracted with CH_2Cl_2. The crude mixture was then concentrated *in vacuo*. The resultant yellow oil was then added to a round-bottom flask equipped with a magnetic stir bar. To the flask was added a solution of aqueous 50% KOH (2 mL) and allowed to stir at room temperature for 4 hours. At this time the resulting mixture was washed with Et_2O (3 x 5 mL) before the organics were concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (5% Et_2O/ pentane).

(*R*)-Benzyl oxirane: Prepared according to the procedure for conversion to epoxide from (*S*)-2-chloro-hydrocinnamaldehyde (77 mg, 0.5 mmol) to afford the title compound as a colorless oil (37 mg, 55% yield). The title compound was identical in all respects to the known literature compound. $[\alpha]_D$ = +10.1 (c = 1.94, EtOH); reported rotation for (*S*)-benzyl oxirane $[\alpha]_D$ = -17.3 (c = 1.94, EtOH).[8]

(*R*)-2-Hexyloxirane: Prepared according to the procedure for conversion to epoxide from (*S*)-2-chloro-octanal (81 mg, 0.5 mmol) to afford the title compound as a colorless oil (42 mg, 66% yield). The title compound was identical in all respects to the known literature compound. $[\alpha]_D$ = +6.2 (c = 1.8, $CHCl_3$); reported rotation for (*R*)-2-hexyloxirane $[\alpha]_D$ = +7.4 (c = 4.5, $CHCl_3$).[9]

(*R*)-2-Cyclohexyloxirane: Prepared according to the procedure for conversion to epoxide from (*S*)-chloro-cyclohexyl-acetaldehyde (80 mg, 0.5 mmol) to afford the title compound as a colorless oil (24 mg, 38% yield). The title compound was identical in all respects to the known literature compound. $[\alpha]_D$ = –2.1 (c = 0.88, $CHCl_3$); reported rotation for (*S*)-2-cyclohexyloxirane $[\alpha]_D$ = +2.1 (c = 0.88, $CHCl_3$).[10]

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