

Enantioselective Organo–Cascade Catalysis

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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. Ethyl acetate was pre-dried with 4Å molecular sieves 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, KMnO₄ or *p*-anisaldehyde stain.

¹H and ¹³C 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 ¹H 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 ¹³C 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) or β-DM (30 m 0.25 mm) column. High performance liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatographs using Chiralcel AD column (1.6 x 25 cm) and AD guard (1.6 x 5 cm),

Chiralcel OD-H (1.6 x 25 cm) and OD guard (1.6 x 5 cm), or Chiralcel AS (1.6 x 25 cm) and AS guard (1.6 x 5 cm) as noted.

General Procedure: To a 2-dram vial equipped with a magnetic stir bar and charged with (2*S*, 5*S*)-5-(1-benzyl-1*H*-indol-3-yl)-2-*tert*-butyl-3-methyl-imidazolidin-4-one (0.05 mmol) was added ethyl acetate (0.25 mL) and trifluoroacetic acid (0.05 mmol), and then it was placed in a bath at the indicated temperature. The solution was stirred for 5 min before addition of aldehyde (0.75 mmol) followed by the nucleophile (0.25 mmol) and 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (0.5 mmol). The resulting solution was stirred at constant temperature until the reaction was determined to be complete by TLC or GLC analysis. The reaction was quenched by filtration through Iatrobeds eluting with ethyl ether, and concentrated in vacuo under an ice bath. The diastereoselectivity was determined by ¹H-NMR or GLC analysis. The resulting residue was purified by Iatrobeds chromatography (solvents noted) and fractions carefully concentrated in vacuo under an ice bath to provide the title compounds. The enantioselectivity was determined by chiral GLC or HPLC analysis.

(2*R*,3*S*)-2-Chloro-3-(5-methyl-furan-2-yl)-butyraldehyde (Table 2, entry 1): Prepared according to the general procedure from 2-methyl furan (22.6 μ L, 0.25 mmol), crotonaldehyde (62 μ L, 0.75 mmol) and 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (150 mg, 0.5 mmol) for 36 h to provide the title compound as a colorless oil (40.2 mg, 86% yield, 14:1 dr, 99% ee) after Iatrobeds chromatography (3% ethyl ether/ pentane). IR (film) 2982, 2924, 1733, 1567, 1455, 1383, 1218 cm^{-1} ; ¹H NMR (300 MHz, CDCl₃) δ 9.49 (d, 1H, *J* = 2.75 Hz **CHO**), 6.02 (d, 1H, *J* = 2.75 Hz, **CCHCH**), 5.88 (dq, 1H, *J* = 2.76, 1.10 Hz, **CCHCH**), 4.40 (dd, 1H, *J* = 2.75, 5.5 Hz, **ClCHCHO**), 3.52 (penta, 1H, *J* = 6.60, **CH₃CHCHCl**), 2.25 (d, 3H, *J* = 1.10, **COCH₃**), 1.35 (d, *J* = 7.8 Hz, 3H, **CHCH₃**); ¹³C NMR (75 MHz, CDCl₃) δ 194.65, 152.00, 151.65, 107.68, 106.18, 66.98, 35.66, 14.14, 13.53; HRMS (CI) exact mass calculated for (C₉H₁₀ClO₂) requires *m/z* 185.0369, found *m/z* 185.0373. $[\alpha]_D = +48.4$ (*c* = 1.35, CH₂Cl₂). The diastereomeric and enantiomeric ratio was determined by GLC using a Bodman Chiraldex β -DM (30 m x

0.25 mm) column (100 °C isotherm, 1 mL/min); (2*S*, 3*R*) isomer t_r = 20.6 min, (2*R*, 3*S*) isomer t_r = 20.8 min, (2*R*, 3*R*) isomer t_r = 22.0 min, (2*S*, 3*S*) isomer t_r = 22.9 min.

(2*R*,3*S*)-2-Chloro-3-(5-methyl-furan-2-yl)-hexanal (Table 2, entry 2):

Prepared according to the general procedure from 2-methyl furan (22.6 μ L, 0.25 mmol), 2-hexenal (87 μ L, 0.75 mmol) and 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (150 mg, 0.5 mmol) for 60 h to provide the title compound as a colorless oil (39.7 mg, 74% yield, 13:1 dr, 99% ee) after Iatrobeds chromatography (3% ethyl ether/ pentane). IR (film) 2960, 2932, 1733, 1694, 1581, 1561, 1218, 1112 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 9.38 (d, 1H, J = 3.30 Hz **CHO**), 6.03 (d, 1H, J = 3.03 Hz, **CCHCH**), 5.87 (m, 1H, **CCHCH**), 4.29 (dd, 1H, J = 3.30, 6.60 Hz, **ClCHCHO**), 3.28 (q, 1H, J = 7.32, **CH₂CHCHCl**), 2.24 (d, 3H, J = 1.10, **COCH₃**), 1.77 (dt, 2H, J = 6.60, 7.98 Hz, **CH₂CH₂CH₃**), 1.26 (m, 2H, **CH₂CH₂CH₃**), 0.90 (t, 3H, J = 8.43, **CH₂CH₂CH₃**); ^{13}C NMR (75 MHz, CDCl_3) δ 194.19, 151.82, 150.29, 108.95, 106.16, 66.03, 41.82, 31.99, 20.29, 13.80, 13.57; HRMS (CI) exact mass calculated for ($\text{C}_{11}\text{H}_{15}\text{ClO}_2$) requires m/z 214.0761, found m/z 214.0767. $[\alpha]_D = +17.5$ (c = 1.25, CH_2Cl_2). The diastereomeric and enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ -TA (30 m x 0.25 mm) column (80 °C isotherm, 1 mL/min); (2*R*, 3*S*) isomer t_r = 68.2 min, (2*S*, 3*R*) isomer t_r = 70.8 min, (2*S*, 3*S*) isomer t_r = 77.8 min, (2*R*, 3*R*) isomer t_r = 86.4 min.

(2*R*,3*S*)-3-Chloro-2-(5-methyl-furan-2-yl)-4-oxo-butyrac acid methyl ester

(Table 2, entry 3): Prepared according to the general procedure from 2-methyl furan (22.6 μ L, 0.25 mmol), *trans*-4-oxo-but-2-enoic acid methyl ester (34 mg, 0.3 mmol) and 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (90 mg, 0.3 mmol) for 36 h to provide the title compound as a colorless oil (48.9 mg, 80% yield, 22:1 dr, >99% ee) after Iatrobeds chromatography (10% ethyl acetate/ hexanes). IR (film) 2956, 2925, 1739, 1560, 1437, 1232, 1163 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 9.53 (d, 1H, J = 2.39 Hz **CHO**), 6.27 (d, 1H, J = 3.19 Hz, **CCHCH**), 5.97 (m, 1H, **CCHCH**), 4.75 (dd, 1H, J = 7.97, 2.39 Hz, **ClCHCHO**), 4.43 (d, 1H, J = 7.97, **CHCO₂CH₃**), 3.81 (s, 3H, **CO₂CH₃**), 2.92 (s, 3H, **COCH₃**); ^{13}C NMR (75 MHz, CDCl_3) δ 192.33, 168.34, 153.04, 144.32, 110.71, 106.84, 61.27, 53.00, 48.50, 13.54; HRMS (CI) exact mass calculated for

(C₁₀H₁₁ClO₄) requires m/z 230.0346, found m/z 230.0339. $[\alpha]_D = -27.9$ ($c = 1.27$, CH₂Cl₂). The diastereomeric and enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ -TA (30 m x 0.25 mm) column (100 °C isotherm, 25 min, ramp to 180 °C via 5 °C/min, 1 mL/min); (2*S*, 3*R*) isomer $t_r = 35.1$ min, (2*R*, 3*S*) isomer $t_r = 35.3$ min, (2*R*, 3*R*) isomer $t_r = 36.2$ min, (2*S*, 3*S*) isomer $t_r = 36.5$ min.

(2*R*,3*S*)-Acetic acid 3-chloro-2-(5-methyl-furan-2-yl)-4-oxo-butyl ester (Table 2, entry 4): Prepared according to the general procedure from 2-methyl furan (22.6 μ L, 0.25 mmol), acetic acid 4-oxo-but-2-enyl ester (51.3 mg, 0.4 mmol) and 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (120 mg, 0.4 mmol) for 18 h to provide the title compound as a colorless oil (50.2 mg, 82% yield, 11:1 dr, >99% ee) after Iatrobeads chromatography (10% ethyl acetate/ hexanes). IR (film) 2924, 2853, 1743, 1368, 1232, 1042 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.56 (d, 1H, $J = 2.12$ Hz CHO), 6.14 (d, 1H, $J = 4.09$ Hz, CCHCH), 5.94 (m, 1H, CCHCH), 4.57 (dd, 1H, $J = 5.05, 2.12$ Hz, ClCHCHO), 4.48 (m, 2H, CH₂O), 3.88 (m, 1H, CHCH₂O), 2.29 (s, 3H, COCH₃), 2.07 (s, 3H, OCOCH₃); ¹³C NMR (75 MHz, CDCl₃) δ 194.31, 170.20, 152.26, 147.28, 109.04, 106.43, 63.87, 61.58, 41.07, 20.76, 13.50; HRMS (CI) exact mass calculated for (C₁₁H₁₃ClO₄) requires m/z 244.0502, found m/z 244.0494. $[\alpha]_D = +24.3$ ($c = 1.10$, CH₂Cl₂). The diastereomeric and enantiomeric ratio was determined by GLC analysis of a bis-trifluoroacetate derivative (DIBAL reduction, followed by bis-trifluoroacetylation) using a Bodman Chiraldex Γ -TA (30 m x 0.25 mm) column (100 °C isotherm, 60 min, 1 mL/min); (2*R*, 3*S*) isomer $t_r = 39.8$ min, (2*S*, 3*S*) isomer $t_r = 40.6$ min, (2*S*, 3*R*) isomer $t_r = 42.0$ min, (2*R*, 3*R*) isomer $t_r = 44.0$ min.

(2*R*,3*S*)-2-Chloro-3-(1-methyl-1*H*-indol-3-yl)-3-phenyl-propionaldehyde

(Table 2, entry 5): Prepared according to the general procedure from 1-methyl indole (32 μ L, 0.25 mmol), *trans*-cinnamaldehyde (50.4 μ L, 0.4 mmol) and 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (120 mg, 0.4 mmol) for 36 h to provide the title compound as a colorless oil (61.8 mg, 83% yield, 9:1 dr, 99% ee) after Iatrobeads chromatography (15% ethyl acetate/ hexanes). IR (film) 3058, 2932, 2826, 1732, 1674, 1474, 1454, 1373, 1332 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.36 (d, 1H, $J = 3.30$ Hz

CHO), 7.38 (m, 8H, PhH and IndH), 7.07 (m, 2H, PhH and IndH), 4.81 (m, 2H, ClCHCHO and IndCHPh), 3.76 (s, 3H, NCH₃); ¹³C NMR (75 MHz, CDCl₃) δ 193.14, 139.27, 136.82, 128.66, 128.51, 127.28, 126.95, 122.25, 119.51, 118.85, 112.64, 109.43, 65.91, 45.09, 32.90; HRMS (CI) exact mass calculated for (C₁₈H₁₆ClNO) requires *m/z* 297.0920, found *m/z* 297.0923. [α]_D = +5.8 (c = 0.62, CH₂Cl₂). The diastereomeric ratio was determined by NMR. The enantiomeric ratio was determined by HPLC of the NaBH₄ reduced alcohol using a Chiracel AD and AD guard column (8% *i*-propanol/hexanes, 1 mL/min); (2*S*, 3*R*) isomer *t*_r = 15.9 min, (2*S*, 3*S*) isomer *t*_r = 18.0 min, (2*R*, 3*S*) isomer *t*_r = 20.3 min, (2*R*, 3*R*) isomer *t*_r = 22.0 min.

(2*R*,3*S*)-2-Chloro-4-methyl-3-(1-methyl-1*H*-indol-3-yl)-pentanal (Table 2, entry 6): Prepared according to the general procedure from 1-methyl indole (32 μL, 0.25 mmol), *trans*-4-methyl-pent-2-enal (46.5 μL, 0.4 mmol) and 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (120 mg, 0.4 mmol) for 24 h to provide the title compound as a colorless oil (44.2 mg, 67% yield, 12:1 dr, >99% ee) after Iatrobeads chromatography (6% ethyl acetate/ hexanes). IR (film) 3058, 2932, 2826, 1732, 1674, 1474, 1454, 1373, 1332 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.18 (d, 1H, *J* = 5.52 Hz CHO), 7.62 (dt, 1H, *J* = 7.97, 1.07 Hz, IndH), 7.29 (m, 1H, IndH), 7.16 (m, 1H, IndH), 6.88 (s, 1H, IndH), 4.47 (dd, 1H, *J* = 9.83, 4.26 Hz, ClCHCHO), 3.81 (s, 3H, NCH₃) 3.50 (dd, 1H, *J* = 9.57, 5.31 Hz, CHCHClCHO), 2.55 (m, 1H, CH(CH₃)₂), 0.94 (d, 6H, *J* = 6.91 Hz, CH(CH₃)₂); ¹³C NMR (75 MHz, CDCl₃) δ 193.47, 136.57, 128.41, 127.80, 122.00, 119.42, 119.08, 109.62, 109.36, 65.36, 44.51, 32.96, 28.31, 21.70, 17.70; HRMS (CI) exact mass calculated for (C₁₅H₁₈ClNO) requires *m/z* 263.1077, found *m/z* 263.1069. [α]_D = +11.3 (c = 0.80, CH₂Cl₂). The diastereomeric ratio was determined by NMR. The enantiomeric ratio was determined by HPLC of the NaBH₄ reduced alcohol using a Chiracel AD and AD guard column (5% *i*-propanol/ hexanes, 1 mL/min); (2*S*, 3*S*) isomer *t*_r = 17.8 min, (2*S*, 3*R*) isomer *t*_r = 20.7 min, (2*R*, 3*S*) isomer *t*_r = 22.5 min, (2*R*, 3*R*) isomer *t*_r = 29.1 min.

(2*R*,3*S*)-2-Chloro-3-(5-methoxy-thiophen-2-yl)-butyraldehyde (Table 3, entry 2): Prepared according to the general procedure from 2-methoxy thiophene (25 μL, 0.25

mmol), crotonaldehyde (62 μL , 0.75 mmol) and 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (150 mg, 0.5 mmol) for 36 h to provide the title compound as a colorless oil (42.1 mg, 77% yield, 11:1 dr, 99% ee) after Iatrobeads chromatography (10% ethyl ether/ pentane). IR (film) 2927, 2852, 1732, 1560, 1505, 1431, 1379, 1207 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 9.43 (d, 1H, $J = 3.03$ Hz **CHO**), 6.51 (dd, 1H, $J = 3.85, 0.82$ Hz, **SCCHCH**), 6.01 (d, 1H, $J = 3.85$ Hz, **SCCHCH**), 4.23 (dd, 1H, $J = 6.32, 3.02$ Hz, **ClCHCHO**), 3.85 (s, 3H, **CH₃O**), 3.58 (penta, 1H, $J = 6.88$ Hz, **CH₃CHCHCl**), 1.41 (d, 3H, $J = 6.88$ Hz, **CHCH₃**); ^{13}C NMR (75 MHz, CDCl_3) δ 194.27, 165.48, 129.72, 122.63, 103.03, 68.70, 60.21, 37.88, 17.89; HRMS (CI) exact mass calculated for ($\text{C}_9\text{H}_{11}\text{ClO}_2\text{S}$) requires m/z 218.0168, found m/z 218.0159. $[\alpha]_{\text{D}} = -3.4$ ($c = 2.17$, CH_2Cl_2). The diastereomeric and enantiomeric ratio was determined by GLC using a Bodman Chiraldex Γ -TA (30 m x 0.25 mm) column (120 $^\circ\text{C}$ isotherm, 1 mL/min); (2*R*, 3*R*) isomer $t_{\text{r}} = 27.5$ min, (2*S*, 3*S*) isomer $t_{\text{r}} = 27.9$ min, (2*S*, 3*R*) isomer $t_{\text{r}} = 28.6$ min, (2*R*, 3*S*) isomer $t_{\text{r}} = 29.4$ min.

(2*R*,3*S*)-2-Chloro-3-((2*S*)-2-methyl-5-oxo-2,5-dihydro-furan-2-yl)-

butyraldehyde (Table 3, entry 3): Prepared via a sequential addition fashion: To a 2 dram vial equipped with a magnetic stir bar and charged with (2*S*, 5*S*)-5-(1-benzyl-1*H*-indol-3-yl)-2-*tert*-butyl-3-methyl-imidazolidin-4-one (18.1 mg, 0.05 mmol) and trifluoroacetic acid (3.85 μL , 0.05 mmol), ethyl acetate (0.25 mL) was added and the solution cooled to -55 $^\circ\text{C}$. The solution was cooled for 5 minutes and crotonaldehyde (41.4 μL , 0.5 mmol) was added in one portion followed by trimethyl-(5-methyl-furan-2-yloxy)-silane (46 μL , 0.25 mmol). The mixture was stirred for 24 hours and 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (150 mg, 0.5 mmol) was added. The resulting solution was stirred until reaction is determined to be complete by TLC. The reaction was quenched by filtration through Iatrobeads (8 g) eluting with ethyl ether, and carefully concentrated *in vacuo* with an ice bath. The resulting residue is purified by Iatrobeads chromatography (20% ethyl acetate/ hexanes) to provide the title compound as a colorless oil (36 mg, 71% yield, >25:1 dr, >99% ee). IR (film) 2986, 1754, 1603, 1452, 1378, 1228, 1126, 1099, 953 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 9.44 (d, 1H, $J = 0.55$ Hz, **CHO**), 7.50 (d, 1H, $J = 5.78$ Hz, **CH=CHC=O**), 6.06 (d, 1H, $J = 5.78$ Hz, **CH=CHC=O**),

4.30 (dd, 1H, $J = 2.21, 0.55$ Hz, ClCHCHO), 2.93 (dq, 1H, $J = 2.20, 6.88$ Hz, CHCHCl), 1.53 (s, 3H, CH₃CO), 1.07 (d, 3H, $J = 6.88$ Hz, CH₃CHCl); ¹³C NMR (75 MHz, CDCl₃) δ 194.44, 171.62, 158.55, 121.17, 89.25, 63.92, 41.38, 24.07, 21.08, 11.28; HRMS (CI) exact mass calculated for (C₉H₁₁ClO₃) requires m/z 202.0397, found m/z 202.0386. $[\alpha]_D = +114.4$ ($c = 1.04$, CH₂Cl₂). NMR showed only one of the four possible diastereomers. The enantiomeric ratio was determined by GLC analysis using a Bodman Chiraldex Γ-TA (30 m x 0.25 mm) column (150 °C isotherm, 1 mL/min); minor enantiomer $t_r = 29.2$ min, major enantiomer $t_r = 32.2$ min.

(2R,3S)-3-(1-Benzyl-1H-indol-3-yl)-2-chloro-butylaldehyde (Table 3, entry 4): Prepared according to the general procedure from 1-benzyl indole (52 mg, 0.25 mmol), crotonaldehyde (25 μL, 0.3 mmol) and 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (90 mg, 0.3 mmol) for 48 h. The desired product was isolated as the corresponding alcohol after NaBH₄ reduction (58.8 mg, 75% yield, 9:1 dr, >99% ee) after silica gel chromatography (20% ethyl acetate/ hexanes). IR (film) 3381, 2972, 2934, 1467, 1454, 1376, 1355, 1178 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.63 (dt, 1H, $J = 8.25, 1.37$ Hz, IndH), 7.17 (m, 8H, PhH and IndH), 7.00 (s, 1H, IndH), 5.29 (s, 2H, CH₂Ph), 4.30 (ddd, 1H, $J = 6.88, 8.25, 3.85$ Hz, ClCHCHO), 3.69 (m, 2H, CHClCH₂OH), 3.46 (penta, 3H, $J = 6.88$ Hz, CH₃CHCHCl), 1.56 (d, 3H, $J = 6.88$ Hz, CHCH₃); ¹³C NMR (75 MHz, CDCl₃) δ 137.42, 136.68, 128.83, 127.87, 126.96, 126.69, 125.72, 122.09, 119.39, 119.27, 116.96, 110.00, 70.83, 65.95, 50.04, 34.61, 18.69; HRMS (CI) exact mass calculated for (C₁₉H₂₀ClNO) requires m/z 313.1233, found m/z 313.1225. $[\alpha]_D = +9.3$ ($c = 0.79$, CH₂Cl₂). The diastereomeric and enantiomeric ratio was determined by HPLC of the corresponding alcohol after NaBH₄ reduction using a Chiracel AD and AD guard column (2.5% *i*-propanol/ hexanes, 1 mL/min); (2*S*, 3*S*) isomer $t_r = 80.6$ min, (2*S*, 3*R*) isomer $t_r = 89.0$ min, (2*R*, 3*R*) isomer $t_r = 92.4$ min, (2*R*, 3*S*) isomer $t_r = 97.6$ min.

(2R,3S)-2-chloro-3-((S)-4,5-dihydro-4-methyl-5-oxo-2-phenyloxazol-4-yl)butanal (Table 3, entry 5).³ To a 1-dram vial equipped with a magnetic stir bar and charged with (2*R*)-2-*tert*-butyl-3-methyl-imidazolidin-4-one TCA salt (16 mg, 0.05 mmol) and 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (300 mg, 1.0 mmol),

acetonitrile (1.0 mL) and H₂O (9 μL, 0.5 mmol) were added. The vial was cooled immediately to -40 °C. After 3 minutes, crotonaldehyde (124 μL, 1.5 mmol) and 4-methyl-2-phenyl-5-triisopropylsilanyloxy-oxazole (0.166 g, 0.50 mmol) were added *via* syringe. After 4 h, the reaction was flushed through an Iatrobeds plug with Et₂O and concentrated. The title compound was isolated as the hydrate in 75% yield (0.112 g, 0.38 mmol) after chromatography on Iatrobeds (0-2-4-7% Et₂O/hex to 4:11:85 to 4:13:83 EtOAc/Et₂O/hex); 9:1 *syn:anti*, 99% ee. Product ratios were determined by GLC (Bodman Γ-TA column, 140 °C, 20 min; 1 °C/min gradient, 145 °C, 20 min; 1 °C/min gradient, 150 °C, 20 min 23 psi); (2*R*, 3*S*) *syn* isomer t_r = 59.9 min, (2*S*, 3*R*) *syn* isomer t_r = 62.7 min, *anti* isomers t = 64.0 min. IR (film) 3045, 2939, 1822, 1724, 1654, 1004 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.76 (m, 2H, ArH), 7.43 (m, 3H, ArH), 5.26 (d, *J* = 4.1 Hz, 1H, CH(OH)₂), 4.34 (dd, *J* = 4.1, 9.2 Hz, 1H, CHCl), 2.77 (m, 1H, CHCH₃), 2.06 (s, 3H, CH₃), 1.40 (d, *J* = 7.2 Hz, 3H, CHCH₃). ¹³C NMR (300 MHz, CDCl₃) δ 202.8, 182.7, 163.6, 135.0, 131.2, 128.5, 128.0, 82.1, 70.2, 62.4, 48.3, 23.3, 11.2; HRMS (FAB) exact mass calcd for (C₁₄H₁₅ClNO₃) requires *m/z* 280.0744, found *m/z* 280.0744; [α_D] = -2.1 (c = 1.0, CHCl₃).

(2*S*,3*R*)-2-Chloro-3-phenyl-butyraldehyde (Equation 3): To a 2 dram vial equipped with a magnetic stir bar and charged with (2*R*)-2-*tert*-butyl-3-methylimidazolidin-4-one TCA salt (16 mg, 0.05 mmol), chloroform (1 mL) was added 3-phenyl-but-2-enal (36.5 mg, 0.25 mmol), and the solution cooled to the -40 °C. The solution was cooled for 5 minutes and di-*tert*-butyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (92.2 mg, 0.3 mmol) was added in one portion. The mixture was stirred for 24 hours and 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (150 mg, 0.5 mmol) was added in one portion. The resulting solution was stirred until the reaction is determined to be complete by TLC. The reaction was quenched by filtration through Iatrobeds (8 g) eluting with ethyl ether, and carefully concentrated *in vacuo* with an ice bath. The resulting residue is purified by Iatrobeds chromatography (3% ethyl ether/pentane) to provide the title compound as a colorless oil (25.6 mg, 70% yield, 8:1 dr, 99% ee). The product was analyzed according to reported procedure, and its spectral data match the literature values.⁴

(2R, 3R)-2-Chloro-3-phenyl-butyraldehyde (Equation 4): To a 2 dram vial equipped with a magnetic stir bar and charged with (2R)-2-*tert*-butyl-3-methylimidazolidin-4-one TCA salt (16 mg, 0.05 mmol), chloroform (1 mL) was added 3-phenyl-but-2-enal (36.5 mg, 0.25 mmol), and the solution cooled to the $-20\text{ }^{\circ}\text{C}$. The solution was cooled for 5 minutes and di-*tert*-butyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (92.2 mg, 0.3 mmol) was added in one portion. The mixture was stirred for 24 hours and *N*-fluorobenzenesulfonamide (0.394 g, 1.25 mmol) was added in one portion followed by THF:*i*PrOH (9:1) (1.25 mL). The resulting solution was stirred until the reaction is determined to be complete by TLC (30 h). The reaction was cooled to $-78\text{ }^{\circ}\text{C}$, diluted with Et₂O and filtered through a pad of Davisil[®] Silica Gel, eluting with Et₂O and concentrated in vacuo. The reaction was dissolved in Et₂O and Me₂S was added forming a white precipitate. The resulting mixture was washed with sat. NaHCO₃, dried over MgSO₄, filtered and concentrated in vacuo. Enantiomeric and diastereomeric ratios were determined by GLC (1:3 dr, 99% ee) using a CP-Chirasil-Dex-CB (50 m x 0.25 mm) column (90 °C isotherm); (2*S*, 3*R*) *anti* isomer $t_r = 40.1\text{ min}$, (2*R*, 3*S*) *anti* isomer $t_r = 37.3\text{ min}$, (2*R*, 3*R*) *syn* isomer $t_r = 36.1\text{ min}$, (2*R*, 3*R*) *syn* isomer $t_r = 35.0\text{ min}$. The resulting aldehyde was taken up in EtOH (5 mL) and NaBH₄ (58.3 mg, 1.54 mmol) was added. The reaction was allowed to stir for 1 hour, then quenched with H₂O, and basified to pH 12-13 and extracted with Et₂O. The combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo. Purification on silica gel (10-50% Et₂O/pentane) afforded (2*R*,3*R*)-2-fluoro-3-phenylbutan-1-ol as a colorless liquid (25.1 mg, 60% yield).

(2*S*, 3*R*)-2-Fluoro-3-phenyl-butyraldehyde (Equation 5): To a 20 mL vial equipped with a magnetic stir bar was added 3-phenyl-but-2-enal (45 mg, 0.31 mmol) and di-*tert*-butyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (114.3 mg, 0.37 mmol). This mixture was dissolved in chloroform (0.25 mL) and cooled to $-20\text{ }^{\circ}\text{C}$. After stirring for 10 min, a solution of (2*R*)-2-*tert*-butyl-3-methylimidazolidin-4-one TCA salt (7.4 mg, 23.1 μmol) in chloroform (0.25 mL) was added. The reaction was allowed to stir for 30 h then *N*-fluorobenzenesulfonamide (0.485 g, 1.54 mmol) was added followed by a solution of (*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one

dichloroacetic acid salt (32.1 mg, 92.4 μmol) in THF:*i*PrOH (9:1) (1.25 mL). The vial was then placed in a $-10\text{ }^{\circ}\text{C}$ bath and allowed to stir for 12 h. The reaction was cooled to $-78\text{ }^{\circ}\text{C}$, diluted with Et_2O and filtered through a pad of Davisil[®] Silica Gel, eluting with Et_2O and concentrated in vacuo. The reaction was dissolved in Et_2O and Me_2S was added forming a white precipitate. The resulting mixture was washed with sat. NaHCO_3 , dried over MgSO_4 , filtered and concentrated in vacuo. Enantiomeric and diastereomeric ratios were determined by GLC (16:1 dr, 99% ee) using a CP-Chirasil-Dex-CB (50 m x 0.25 mm) column ($90\text{ }^{\circ}\text{C}$ isotherm); (2*S*, 3*R*) *anti* isomer $t_r = 40.1$ min, (2*R*, 3*S*) *anti* isomer $t_r = 37.3$ min, (2*R*, 3*R*) *syn* isomer $t_r = 36.1$ min, (2*R*, 3*R*) *syn* isomer $t_r = 35.0$ min.

The aldehyde product was taken up in EtOH (5 mL) and NaBH_4 (58.3 mg, 1.54 mmol) was added. The reaction was allowed to stir for 1 hour, then quenched with H_2O , and basified to pH 12-13 and extracted with Et_2O . The combined organic extracts were dried over MgSO_4 , filtered and concentrated in vacuo. Purification on silica gel (10-50% Et_2O /pentane) afforded (2*S*,3*R*)-2-fluoro-3-phenylbutan-1-ol as a colorless liquid (42.1 mg, 81% yield). IR (film) 3367, 2934, 1494, 1453, 1021, 845, 762, 701 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.36-7.19 (m, 5H, ArH), 4.70-4.45 (dddd, 1H, $J = 3.0, 6.0, 11.7, 48.9$ Hz, FCH), 3.66-3.44 (m, 2H, CH_2OH), 3.08 (ddq, 1H, $J = 6.0, 11.7, 23.7$ Hz, CHCH₃), 1.72 (bs, 1H, OH), 1.40 (d, 3H, $J = 6.9$ Hz, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 142.0 (d, $J = 8.3$ Hz), 128.8, 127.6, 127.0, 98.0 (d, $J = 173.7$ Hz), 63.4 (d, $J = 21.7$ Hz), 41.0, (d, $J = 20.3$ Hz), 17.4 (d, $J = 4.6$ Hz); HRMS (EI+) exact mass calculated for ($\text{C}_{10}\text{H}_{13}\text{OF}$) requires m/z 168.0950, found m/z 168.0947. $[\alpha]_D = -15.1$ ($c = 1.0, \text{CHCl}_3$).

(2*R*, 3*R*)-2-Fluoro-3-phenyl-butyraldehyde (Equation 6): To a 20 mL vial equipped with a magnetic stir bar was added 3-phenyl-but-2-enal (45 mg, 0.31 mmol) and di-*tert*-butyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (114.3 mg, 0.37 mmol). This mixture was taken up in chloroform (0.25 mL) and cooled to $-20\text{ }^{\circ}\text{C}$. After stirring for 10 min, a solution of (2*R*)-2-*tert*-butyl-3-methyl-imidazolidin-4-one TCA salt (7.4 mg, 23.1 μmol) in chloroform (0.25 mL) was added. The reaction was allowed to stir for 30 h then *N*-fluorobenzenesulfonamide (0.485 g, 1.54 mmol) was added followed by a solution of (*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one dichloroacetic acid salt (32.1 mg, 92.4 μmol) in THF:*i*PrOH (9:1) (1.25 mL). The vial was kept in the $-20\text{ }^{\circ}\text{C}$

bath and allowed to stir for 30 h. The reaction was cooled to $-78\text{ }^{\circ}\text{C}$, diluted with Et_2O and filtered through a pad of Davisil[®] Silica Gel, eluting with Et_2O and concentrated in vacuo. The reaction was dissolved in Et_2O and Me_2S was added forming a white precipitate. The resulting mixture was washed with sat. NaHCO_3 , dried over MgSO_4 , filtered and concentrated in vacuo. Enantiomeric and diastereomeric ratios were determined by GLC (1:9 dr, 99% ee) using a CP-Chirasil-Dex-CB (50 m x 0.25 mm) column ($90\text{ }^{\circ}\text{C}$ isotherm); (2*S*, 3*R*) *anti* isomer $t_r = 40.1$ min, (2*R*, 3*S*) *anti* isomer $t_r = 37.3$ min, (2*R*, 3*R*) *syn* isomer $t_r = 36.1$ min, (2*R*, 3*R*) *syn* isomer $t_r = 35.0$ min.

The resulting aldehyde was taken up in EtOH (5 mL) and NaBH_4 (58.3 mg, 1.54 mmol) was added. The reaction was allowed to stir for 1 hour, then quenched with H_2O , and basified to pH 12-13 and extracted with Et_2O . The combined organic extracts were dried over MgSO_4 , filtered and concentrated in vacuo. Purification on silica gel (10-50% Et_2O /pentane) afforded (2*R*,3*R*)-2-fluoro-3-phenylbutan-1-ol as a colorless liquid (32.1 mg, 62% yield). IR (film) 3368, 2931, 1494, 1452, 1045, 853, 761, 700 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.36-7.20 (m, 5H, ArH), 4.78-4.56 (dtd, 1H, $J = 3.0, 6.6, 48.6$ Hz, FCH), 3.80-3.60 (m, 2H, CH_2OH), 3.08 (dq, 1H, $J = 7.2, 19.8$ Hz, CHCH₃), 1.75 (bs, 1H, OH), 1.35 (d, 3H, $J = 7.5$ Hz, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 142.0 (d, $J = 8.3$ Hz), 128.5, 127.9, 126.8, 97.0 (d, $J = 172.6$ Hz), 63.4 (d, $J = 22.3$ Hz), 40.9, (d, $J = 19.4$ Hz), 17.4 (d, $J = 6.5$ Hz); HRMS (EI+) exact mass calculated for ($\text{C}_{10}\text{H}_{13}\text{OF}$) requires m/z 168.0950, found m/z 168.0957. $[\alpha]_D = -1.07$ ($c = 0.8, \text{CHCl}_3$).

Absolute and relative configuration was assigned by chemical correlation by derivatization to the known epoxide⁴: **(*S,S*)-2-Methyl-5-(1-oxiranyl-ethyl)-furan**: Prepared via a one-pot fashion: To a 3 dram vial equipped with a magnetic stir bar and charged with (2*S*, 5*S*)-5-(1-benzyl-1*H*-indol-3-yl)-2-*tert*-butyl-3-methyl-imidazolidin-4-one (18.1 mg, 0.05 mmol) and trifluoroacetic acid (3.85 μL , 0.05 mmol), ethyl acetate (0.25 mL) was added and the solution cooled to $-40\text{ }^{\circ}\text{C}$. The solution was cooled for 5 minutes and crotonaldehyde (124 μL , 1.5 mmol) was added in one portion followed by 2-methyl furan (45 μL , 0.5 mmol) and 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (301 mg, 1 mmol). The resulting solution was stirred at $-40\text{ }^{\circ}\text{C}$ for 36 hours and was diluted with ethanol (1 mL), followed by addition of NaBH_4 (75.6 mg, 2 mmol). The

resulting white suspension was warmed to +4 °C and stirred for 20 minutes. Aqueous NaOH solution (50% w/w, 3 mL) was then added. The bi-phase mixture was rigorously stirred for 30 minutes. The reaction was quenched with saturated aqueous NaHCO₃ solution and extracted three times with dichloromethane. The organic layers were combined, dried and concentrate *in vacuo* with an ice bath. The resulting residue is purified by silica gel chromatography (solvents noted) and fractions carefully concentrated *in vacuo* with an ice bath to provide the title compound (47.2 mg, 62% yield, 99% ee). The minor diastereomer structure was confirmed by comparison with literature reported data.⁵ The major diastereomer structure was assigned accordingly. $[\alpha]_D = -29.0$ (c = 1.35, CH₂Cl₂).

¹ Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; 3rd ed., Pergamon Press, Oxford, 1988.

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³The absolute and relative configuration for the initial iminium reaction has been determined independently. Details of this work will be published at a later date.

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