**Stannane-Free Chemoselective
Hydrodehalogenation of 4-Halo-
Tetrahydropyrans: Scope and Application to
Natural Product Synthesis**

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Supplementary Material

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Supporting Information

General Methods

Experiments involving moisture and/or air sensitive components were performed in oven-dried glassware. Commercial solvents and reagents were used without further purification with the following exceptions: Hexane, dichloromethane, ethyl acetate and diethylether were fractionally distilled. Azeotropic drying of starting materials or reagents was performed by the addition of the stated amount of anhydrous tetrahydrofuran, ensued by azeotropic removal of tetrahydrofuran with traces of moisture *in vacuo* followed by purging with nitrogen. Methanol was passed through Linde type 4Å molecular sieve before distillation.

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate, followed by heating on a hot plate.

Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use.

Infrared spectra were recorded on a Shimadzu IR Prestige-21 FT-IR Spectrometer. Liquid samples were examined as film between NaCl salt plates.

Proton nuclear magnetic resonance spectra (^1H NMR) were recorded on a Bruker Avance 400 and 500 spectrophotometers (CDCl_3 as solvent). Chemical shifts for ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0 ppm) and relative to the signal of chloroform-*d* (δ

7.2600, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); ddd (doublets of doublets of doublet); dt (doublets of triplet); td (triplets of doublet); tdd (triplets of doublets of doublets); tt (triplets of triplets) or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a *J* value in Hz. Carbon nuclear magnetic resonance spectra (¹³C NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe₄ (δ 0.0 ppm) and relative to the signal of chloroform-*d* (δ 77.03 ppm, triplet). The proportion of diastereomers and geometric isomers was determined from the integration of ¹H NMR and ¹³C NMR spectra.

Mass spectral analyses (HRMS) were carried out on a Thermo Finnigan MAT 95 XP mass spectrophotometer. Mass spectral data were reported in units of mass to charge (*m/z*).

Optical rotation was measured using a JASCO P-1030 Polarimeter equipped with a sodium vapor lamp at 589 nm. Concentration is denoted as *c* and was calculated as grams per milliliters (g / 100 mL) whereas the solvent was indicated in parentheses (*c*, solvent).

Experimental

General Method for the Synthesis of de-halo-tetrahydropyran

To a 25 ml round-bottom flask equipped with a magnetic stirring bar was charged 10% Pd in carbon (0.122 g, 0.11 mmol, 0.4 equiv.) in methanol (2.57 mL). 4-Halo-6-cyclohexyl-tetrahydro-2*H*-pyran (0.28 mmol) in ethyl acetate (0.28ml) was added to the mixture and was allowed to stir under hydrogen atmosphere for 8 h. Sodium bicarbonate (47 mg, 0.56 mmol) was added to the reaction mixture and was stirred under hydrogen atmosphere for another 16 hours. The mixture was filtered through celite and was then concentrated *in vacuo*. The residue was diluted with ethyl acetate (5 mL) prior to washing with water (2 × 5 mL) followed by brine solution (2 × 5 mL). The organic layer was dried with anhydrous MgSO₄ and concentrated *in vacuo*. The residual crude product was purified *via* flash column chromatography to afford the dehalo-tetrahydropyran.

2-(4-Chloro-6-cyclohexyl-tetrahydro-2*H*-pyran-2-yl)ethanol (1a)

Colourless oil (54 mg, 79% yield).

¹H NMR (400 MHz, CDCl₃): δ 4.00 (tt, *J* = 11.8, 4.5 Hz, 1H), 3.80-3.75 (m, 2H), 3.58-3.51 (m, 1H), 3.09 (ddd, *J* = 11.3, 6.3, 1.7 Hz, 1H), 2.68 (br s, 1H), 2.14 (tdd, *J* = 12.7, 4.2, 2.0 Hz, 1H), 2.08 (tdd, *J* = 12.7, 4.6, 2.4 Hz, 1H), 1.86-1.77 (m, 1H), 1.76-1.67 (m, 5H), 1.67-1.61 (m, 2H), 1.45-1.34 (m, 1H), 1.27-1.14 (m, 4H), 1.05-0.92 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 81.4, 76.9, 61.1, 56.0, 42.5, 42.5, 39.3, 37.5, 28.8, 28.8, 26.4, 26.0, 25.9.

FTIR (neat) ν_{max} : 3373, 2924, 2851, 1449, 1080, 1051, 760, 606 cm⁻¹.

HRMS (EI) *m/z* Calcd for C₁₃H₂₃ClO₂ [M⁺] = 246.1381. Found: 246.1338

2-(6-Cyclohexyl-tetrahydro-2H-pyran-2-yl)ethanol (1b)

Colourless oil (55 mg, 92% yield).

^1H NMR (400 MHz, CDCl_3): δ 3.78 (t, J = 4.8 Hz, 2H), 3.58-3.50 (m, 1H), 3.20 (br s, 1H), 3.07 (ddd, J = 11.2, 6.4, 1.9 Hz, 1H), 1.88-1.78 (m, 3H), 1.76-1.66 (m, 5H), 1.65-1.55 (m, 4H), 1.52-1.46 (m, 3H), 1.31-1.23 (m, 2H), 0.97-0.88 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 82.6, 79.2, 62.0, 43.0, 37.8, 31.7, 29.0, 29.0, 28.1, 26.5, 26.2, 26.1, 23.6.

FTIR (neat) ν_{max} : 3370, 2928, 2853, 1449, 1084, 1042, 733 cm^{-1} .

HRMS (EI) m/z Calcd for $\text{C}_{13}\text{H}_{24}\text{O}_2$ [M^+] = 212.1771. Found: 212.1763

2-(2-(Benzyloxy)ethyl)-6-cyclohexyl-tetrahydro-2H-pyran (1c)

Colourless oil (63 mg, 74% yield).

^1H NMR (400 MHz, CDCl_3): δ 7.37-7.31 (m, 4H), 7.31-7.27 (m, 1H), 4.53 and 4.49 (ABq, J = 11.8 Hz, 2H), 3.68-3.54 (m, 2H), 3.46-3.37 (m, 1H), 2.94 (ddd, J = 10.7, 7.6, 1.8 Hz, 1H), 1.98-1.91 (m, 1H), 1.87-1.78 (m, 1H), 1.78-1.71 (m, 3H), 1.70-1.67 (m, 1H), 1.66-1.56 (m, 3H), 1.31-1.25 (m, 2H), 1.24-1.15 (m, 4H), 1.15-1.13 (m, 2H), 1.01-0.82 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 138.7, 128.3, 127.6, 127.4, 82.2, 74.6, 73.0, 67.0, 43.2, 36.8, 32.0, 29.3, 28.9, 28.6, 26.7, 26.3, 26.1, 23.9.

FTIR (neat) ν_{max} : 3435, 3107, 3086, 3063, 3028, 2826, 2853, 1494, 1450, 1089, 1043, 733, 696 cm^{-1} .

HRMS (EI) m/z Calcd for $\text{C}_{20}\text{H}_{30}\text{O}_2$ [M^+] = 302.2240. Found: 302.2243.

(4-Chloro-6-cyclohexyl-tetrahydro-2H-pyran-2-yl)methanol (2a)

Colourless oil (42 mg, 65% yield).

^1H NMR (400 MHz, CDCl_3): δ 4.03 (tt, $J = 11.9, 4.7$ Hz, 1H), 3.65-3.58 (m, 1H), 3.59-5.51 (m, 1H), 3.48-3.41 (m, 1H), 3.10 (ddd, $J = 11.2, 6.4, 1.6$ Hz, 1H), 2.15 (tdd, $J = 12.6, 4.5, 2.1$ Hz, 1H), 2.08-1.99 (m, 2H), 1.93-1.83 (m, 1H), 1.78-1.64 (m, 4H), 1.57-1.51 (m, 1H), 1.47-1.40 (m, 1H), 1.30-1.13 (m, 4H), 1.08-0.93 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 81.0, 76.9, 65.7, 56.1, 42.7, 39.4, 38.3, 28.9, 28.6, 26.5, 26.1, 26.0.

FTIR (neat) ν_{max} : 3412, 2926, 2853, 1450, 1087, 1065, 1043, 764, 738, 610 cm^{-1} .

HRMS (EI) m/z Calcd for $\text{C}_{12}\text{H}_{21}\text{ClO}_2$ [M^+] = 232.1225. Found: 232.1229.

2-(Benzyloxymethyl)-6-cyclohexyl-tetrahydro-2H-pyran (2c)

Colourless oil (38 mg, 47% yield).

^1H NMR (400 MHz, CDCl_3): δ 7.38-7.31 (m, 4H), 7.30-7.24 (m, 1H), 4.61 and 4.56 (ABq, $J = 12.1$ Hz, 2H), 3.54-3.48 (m, 2H), 3.44-3.39 (m, 1H), 3.09-2.99 (m, 1H), 2.01-1.92 (m, 1H), 1.91-1.82 (m, 1H), 1.79-1.72 (m, 1H), 1.72-1.68 (m, 2H), 1.68-1.65 (m, 1H), 1.46-1.40 (m, 1H), 1.39-1.32 (m, 1H), 1.30-1.18 (m, 5H), 1.18-1.10 (m, 2H), 1.05-0.91 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 138.7, 128.3, 127.7, 127.4, 82.3, 77.2, 73.9, 73.3, 43.1, 29.3, 28.7, 28.6, 28.2, 26.7, 26.3, 26.2, 23.5.

FTIR (neat) ν_{max} : 3113, 3088, 3063, 3030, 2926, 2853, 1497, 1450, 1113, 1086, 737, 698 cm^{-1} .

HRMS (EI) m/z Calcd for $\text{C}_{19}\text{H}_{28}\text{O}_2$ [M^+] = 288.2084. Found: 288.2082.

4-(4-Chloro-6-cyclohexyl-tetrahydro-2H-pyran-2-yl)butan-1-ol (3a)

Colourless oil (46 mg, 60% yield).

^1H NMR (400 MHz, CDCl_3): δ 3.99 (tt, $J = 11.7, 4.5$ Hz, 1H), 3.65 (t, $J = 6.3$ Hz, 2H), 3.28-3.19 (m, 1H), 2.97 (ddd, $J = 11.2, 7.1, 1.3$ Hz, 1H), 2.15 (tdd, $J = 12.3, 4.5, 2.1$ Hz, 1H), 2.10 (tdd, $J = 2.2, 4.6, 12.7$ Hz, 1H), 1.97-1.87 (m, 1H), 1.78-1.69 (m, 2H), 1.68-1.54 (m, 6H), 1.51-1.35 (m, 7H), 1.27-1.14 (m, 2H), 1.01-0.92 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 81.1, 76.5, 62.8, 56.8, 42.8, 42.7, 39.7, 35.5, 32.5, 29.2, 28.7, 26.5, 26.1, 26.0, 21.8.

FTIR (neat) ν_{max} : 3418, 2930, 2853, 1450, 1265, 1086, 1065, 738, 704, 608 cm^{-1} .

HRMS (EI) m/z Calcd for $\text{C}_{15}\text{H}_{27}\text{ClO}_2$ [M^+] = 274.1694. Found: 274.1698.

2-(4-(Benzyloxy)butyl)-6-cyclohexyl-tetrahydro-2H-pyran (3c)

Colourless oil (61 mg, 66% yield).

^1H NMR (400 MHz, CDCl_3): δ 7.37-7.31 (m, 4H), 7.30-7.23 (m, 1H), 4.50 (s, 2H), 3.47 (t, $J = 6.7$ Hz, 2H), 3.24-3.14 (m, 1H), 2.92 (ddd, $J = 11.2, 7.8, 1.6$ Hz, 1H), 2.04-1.96 (m, 1H), 1.86-1.78 (m, 1H), 1.75-1.67 (m, 2H), 1.55-1.49 (m, 3H), 1.41-1.37 (m, 4H), 1.33-1.22 (m, 7H), 1.18-1.07 (m, 3H), 0.92-0.82 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 138.7, 128.3, 127.6, 127.4, 82.4, 77.7, 72.8, 70.5, 43.2, 36.4, 32.0, 29.7, 29.4, 28.9, 28.6, 26.7, 26.2, 26.1, 23.9, 22.3.

FTIR (neat) ν_{max} : 3109, 3088, 3063, 3030, 2910, 2851, 1495, 1092, 1045, 733, 696 cm^{-1} .

HRMS (EI) m/z Calcd for $\text{C}_{22}\text{H}_{34}\text{O}_2$ [M^+] = 330.2553. Found: 330.2547.

2,6-Dicyclohexyl-tetrahydro-2H-pyran (4)

Colourless oil (55 mg, 79% yield).

^1H NMR (400 MHz, CDCl_3) δ 2.89 (ddd, $J = 11.0, 7.9, 1.4$ Hz, 2H), 2.07-1.96 (m, 2H), 1.88-1.80 (m, 1H), 1.74-1.71 (m, 2H), 1.71-1.66 (m, 3H), 1.66-1.60 (m, 4H), 1.30- 1.22 (m, 6H), 1.22-1.12 (m, 6H), 1.01-0.84 (m, 4H).

^{13}C NMR (100 MHz, CDCl_3): δ 82.4, 43.3, 29.4, 29.0, 28.9, 26.7, 26.3, 26.1, 24.0.

FTIR (neat) ν_{max} : 2920, 2849, 1449, 1263, 1084, 1072, 1045, 743 cm^{-1} .

HRMS (EI) m/z Calcd for $\text{C}_{17}\text{H}_{30}\text{O}$ [M^+]: 250.2297. Found: 250.2291.

2-Cyclohexyl-6-phenyl-tetrahydro-2H-pyran (5)

Colourless oil (45 mg, 66% yield).

^1H NMR (400 MHz, CDCl_3): δ 7.40-7.30 (m, 4H), 7.26-7.21 (m, 1H), 4.35 (dd, $J = 11.1, 1.8$ Hz, 1H), 3.24 (ddd, $J = 11.1, 6.2, 1.7$ Hz, 1H), 2.01-1.93 (m, 2H), 1.90-1.82 (m, 1H), 1.79-1.72 (m, 3H), 1.71-1.62 (m, 3H), 1.52-1.42 (m, 2H), 1.35-1.17 (m, 4H), 1.15-1.02 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 144.0, 128.1, 126.9, 125.7, 82.5, 79.4, 43.3, 33.9, 29.1, 28.7, 27.8, 26.7, 26.4, 26.3, 24.2.

FTIR (neat) ν_{max} : 3088, 3061, 3028, 2927, 2851, 1497, 1450, 1092, 1043, 749, 698 cm^{-1} .

HRMS (EI) m/z Calcd for $\text{C}_{17}\text{H}_{24}\text{O}$ [M^+] = 244.1822. Found: 244.1830.

Procedures and Characterization of Intermediates of (+)-SCH 351448

Methyl 2-((2R,4S,6R)-6-(2-(benzyloxy)ethyl)-4-bromo-tetrahydro-2H-pyran-2-yl)-2-methylpropanoate (7): To a solution of homoallylic alcohol **6** (0.88 g, 5 mmol) in dichloromethane (50 mL) was added InBr_3 (0.18 g, 0.5 mmol, 0.1 equiv.) at 0 °C. The solution was allowed to cool to -78 °C and trimethylsilyl bromide (0.78 mL, 6 mmol, 1.2 equiv.) was added dropwise. The solution was stirred for 1 minute and was treated with a solution of 3-(benzyloxy)propanal in dichloromethane (5 mL). The reaction mixture was allowed to stir at -78 °C for 4 hours, and was allowed to warm up gradually to room temperature. The reaction was allowed to proceed for another 12 hours prior to quenching with saturated sodium bicarbonate solution (15 mL). The aqueous layer was extracted with diethyl ether (3 $\times$ 30 mL), and the combined organic extracts were washed with water (50 mL) and brine (50 mL) and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (hexane / ether, 25:1) to afford the 4-bromo-THP product as colorless oil (1.30 g, 65% yield, 91% *ee*).

R_f = 0.59 (4:1 hexane/ethyl acetate).

^1H NMR (500 MHz, CDCl_3): δ 7.33 (m, 5H), 4.47, (s, 2H), 4.15, (tt, J = 12.0, 4.4 Hz, 1H), 3.64 (s, 3H), 3.55-3.51 (m, 1H) 3.51 (dd, J = 11.7, 4.1 Hz, 1H), 3.50 (t, J = 5.7 Hz, 2H), 2.19 (tdd, J = 12.4, 4.4, 2.1 Hz, 1H), 2.12 (tdd, J = 12.4, 4.4, 2.1 Hz, 1H), 1.77-1.67 (m, 4H), 1.17 (s, 3H), 1.12 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3): δ 176.6, 138.4, 128.4, 127.7, 127.6, 81.5, 74.6, 73.1, 66.5, 51.9, 47.0, 46.5, 43.4, 37.6, 35.9, 20.8, 20.6.

FTIR (neat) ν_{max} : 2949, 1732, 1275, 1194, 1070, 737, 698 cm^{-1} .

HRMS (EI) m/z Calcd for $\text{C}_{19}\text{H}_{27}\text{BrO}_4$ [M^+] = 398.1087. Found: 398.1077.

$[\alpha]_D^{23} = +4.2$ (c = 1.65, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel ODH column (*n*-hexane : *i*-propanol 99:1, 1.0 mL/min): t_1 = 8.5 min (minor), t_2 = 14.1 min (major).

Methyl 2-((2*R*,6*S*)-tetrahydro-6-(2-hydroxyethyl)-2*H*-pyran-2-yl)-2-methylpropanoate (8): To an oven-dried 100 mL round-bottom flask equipped with a magnetic stirring bar was added Pd/C (10% w/w, 2.22 g, 0.3 equiv.) and was flushed with nitrogen before cooling to 0 °C. Methanol (63 mL) was added slowly to the solid while stirring at a minimum speed of 500 rpm. The suspension was allowed to warm up to room temperature and was added an ethyl acetate (7 mL) solution of 4-bromo-THP methyl ester **7** (2.80 g, 7 mmol). The mixture was allowed to proceed under a H₂ atmosphere introduced through a balloon for 8 hours. The reaction mixture was subsequently treated with NaHCO₃ (1.76 g, 21 mmol, 3 equiv.) and was allowed to stir under H₂ atmosphere for another 16 hours. The mixture was filtered through a pad of Celite and flushed with 300 mL of dichloromethane. The solution was concentrated *in vacuo* and was dissolved in 50 mL diethyl ether. The organic layer was washed with H₂O (3 × 20 mL) and brine (20 mL) and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (hexane / ethyl acetate, 8:1) to afford the debromo-THP-alcohol as colorless oil (1.10 g, 68% yield).

R_f = 0.13 (4:1 hexane/ethyl acetate).

¹H NMR (500 MHz, CDCl₃): δ 3.73-3.69 (m, 2H), 3.68 (s, 3H), 3.58-3.52 (m, 2H), 2.80 (br s, 1H), 1.90-1.84 (m, 1H), 1.77-1.73 (m, 1H), 1.71-1.67 (m, 2H), 1.53-1.47 (m, 2H), 1.31-1.23 (m, 2H), 1.16 (s, 3H), 1.12 (s, 3H).

¹³C-NMR (125 MHz, CDCl₃): δ 177.5, 83.0, 79.3, 61.6, 51.9, 46.6, 38.0, 31.5, 24.8, 23.4, 21.9, 19.7.

FTIR (neat) $\nu_{\max}$: 3446, 2943, 2860, 1732, 1437, 1271, 1088, 1047 cm⁻¹.

HRMS (EI) m/z Calcd for C₁₂H₂₂O₄ [M⁺] = 230.1513. Found 230.1507.

$$[\alpha]_{\text{D}}^{23} = +8.8 \text{ } (c = 1.55, \text{CH}_2\text{Cl}_2)$$