B-Alkyl Suzuki couplings for the stereoselective synthesis of substituted pyrans

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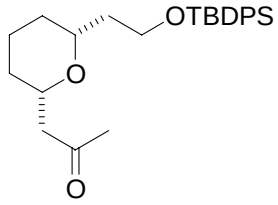
General: All reactions were carried out under Ar in flame-dried glassware. IR: Nicolet FT-7199 spectrometer, wavenumbers ($\tilde{\nu}$) in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: Finnigan MAT 95, accurate mass determinations: Bruker APEX III FT-MS (7 T magnet). The solvents used were purified by distillation over the drying agents indicated and were transferred under Argon: THF, Et_2O (Mg-anthracene), CH_2Cl_2, MeCN, Et_3N (CaH_2), DMF (Desmodur®, dibutyltin dilaurate), MeOH (Mg), toluene (Na/K). Flash chromatography: Merck silica gel 60 (230-400 mesh). NMR: Spectra were recorded on a Bruker AV 400, or DMX 600 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm, coupling constants (J) in Hz. The solvent signals were used as references (CD_2Cl_2: $\delta_C \equiv 54.0$ ppm; residual CH_2Cl_2 in CD_2Cl_2: $\delta_H \equiv 5.32$ ppm; C_6D_6: $\delta_C \equiv 128.0$ ppm; residual C_6H_6 in C_6D_6: $\delta_H \equiv 7.15$ ppm; $CDCl_3$: $\delta_C \equiv 77.0$ ppm; residual $CHCl_3$ in $CDCl_3$: $\delta_H \equiv 7.26$ ppm). ***Where indicated, the signal assignments are unambiguous***; the numbering scheme is arbitrary and is shown in the inserts. The assignments are based upon 1D and 2D spectra recorded using the following pulse sequences from the Bruker standard pulse program library: DEPT; COSY (*cosygs* and *cosydqtp*); HSQC (*invietgssi*) optimized for ^1J(C,H) = 145 Hz; HMBC (*inv4gslplrnd*) for correlations via ^nJ(C,H); HSQC-TOCSY (*invietgsml*) using an MLEV17 mixing time of 120 ms.

Pyran 7

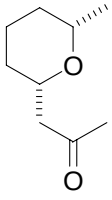


To a solution of 9-BBN dimer (274 mg, 1.123 mmol, 2.0 eq) in THF (2.8 ml) at room temperature was added alcohol **6** (175 mg, 0.562 mmol, 1.0 eq) and the resulting solution was stirred for 6 h (no starting material by TLC). To the borane thus obtained was added a degassed solution of NaOH (1.0 M, 1.68 ml, 3.0 eq) and the

mixture was stirred for 10 min. The resulting boronate solution was transferred via syringe to a Schlenk tube containing iodide **5** (218 mg, 1.120 mmol, 2.0 eq), $PdCl_2$(dppf) (41 mg, 0.056 mmol, 0.1 eq), and $AsPh_3$ (17 mg, 0.056 mmol, 0.1 eq) in degassed THF (2.8 ml) and the mixture was stirred at ambient temperature overnight. The reaction was quenched with aq. NH_4Cl (15 ml) and extracted with EtOAc (2 x 15 ml). The combined organic extracts were stirred with HCl (1.0 M, 30 ml) for 50 min, the layers were separated, and the organic phase dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (10:1 to 4:1, hexanes:EtOAc) afforded pyran **7** as a mixture of diastereomers[1] (148 mg, 62%, d.r > 10:1).

$[\alpha]_D^{20}$ = +10.0 (*c* 2.0, CH_2Cl_2). IR (ATR) 2921, 2858, 1697, 1468, 1450, 1410, 1387, 1360, 1326, 1298, 1251, 1167, 1107, 1083, 1006, 977 701, 673 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 4H), 7.45 – 7.34 (m, 6H), 3.81 – 3.67 (m, 3H), 3.52 (m, 1H), 2.60 (dd, *J* = 15.1, 7.5 Hz, 1H), 2.39 (dd, *J* = 15.1, 5.2 Hz, 1H), 2.11 (s, 3H), 1.80 (m, 1H), 1.74 – 1.50 (m, 5H), 1.23 – 1.11 (m, 2H), 1.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8, 135.5, 134.0, 129.5, 127.6, 74.7, 74.3, 60.4, 50.5, 39.3, 31.5, 31.4, 30.9, 26.9, 23.5, 19.2. HRMS (ESI+): calcd. for $C_{26}H_{36}O_3NaSi$ $(M + Na)^+$: 447.2323; found 447.2326.

Pyran 9



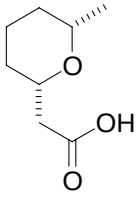
To a solution of 9-BBN dimer (92 mg, 0.377 mmol, 2.1 eq) in THF (0.9 ml) at room temperature was added alcohol **8** (15 mg, 0.180 mmol, 1.0 eq) and the resulting solution was stirred for 4 h. To the borane thus obtained was added a degassed solution of NaOH (1.0 M, 0.54 ml, 3.0 eq) and the mixture was stirred for 10 min. The resulting boronate solution was transferred via syringe to a Schlenk tube containing iodide **5** (53 mg, 0.270 mmol, 1.5 eq), $PdCl_2$(dppf) (13 mg, 0.018 mmol, 0.1 eq), and $AsPh_3$ (6 mg, 0.018 mmol, 0.1 eq) in degassed THF (0.9 ml) and the mixture was stirred at ambient temperature overnight. The reaction was quenched with aq. NH_4Cl (15 ml) and extracted with EtOAc (2 x 15 ml). The combined organic extracts were stirred with HCl (1.0 M, 30 ml) for 50 min

[1] Diastereomeric ratios determined by NMR analysis.

and the layers were separated. The organic phase was stirred with a pH = 7 buffer solution (15 ml) and 30% H_2O_2 (5 ml) for 30 min. The layers were separated and the organic phase dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (4:1, hexanes:EtOAc) afforded pyran **9** (20 mg, 73%, d.r > 10:1) as an oil.

$[\alpha]_D^{20}$ = –31.8 (*c* 0.5, CH_2Cl_2). IR (ATR) 1699, 1466, 1371, 1244, 1204, 1091, 1073, 973, 929 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.77 (m, 1H), 3.45 (ddd, *J* = 12.5, 8.0, 6.3 Hz, 1H), 2.68 (dd, *J* = 15.5, 7.6 Hz, 1H), 2.42 (dd, *J* = 15.5, 5.2 Hz, 1H), 2.18 (s, 3H), 1.84 – 1.76 (m, 1H), 1.63 – 1.47 (m, 3H), 1.21 – 1.10 (m, 2H), 1.13 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7, 74.1, 74.0, 50.4, 33.0, 31.2, 31.0, 23.5, 22.1. HRMS (ESI+): calcd. for $C_9H_{16}O_2H^+$ $(M + H)^+$: 157.1226; found 157.1228.

(+)-(*S,S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid (10)



To a solution of pyran **9** (46 mg, 0.293 mmol) in dioxane (2.3 ml) at room temperature was added a sodium hypobromite solution (4.6 ml) (freshly prepared from bromine (1.1 ml), aqueous sodium hydroxide (10%, 28.3 ml) and dioxane (6.67 ml)) and the mixture was stirred vigorously for 3 h. The reaction was quenched with aqueous sodium sulfite (10%, 2.0 ml) and acidified to pH = 1 with HCl (3 M). The mixture was extracted with methyl *tert*-butyl ether (2 x 15 ml) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (4:1 to 2:1 to 1:1, hexanes:EtOAc) afforded **10** (30 mg, 65%) as an oil.

$[\alpha]_D^{20}$ = +19.1 (*c* 1.0, $CHCl_3$) [lit.,[2] $[\alpha]_D^{20}$ +18.6 (*c* 2.77, $CHCl_3$)] . IR (ATR) 2930, 1714, 1440, 1079, 1040 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.82 – 3.72 (m, 1H), 3.64 – 3.52 (m, 1H), 2.56 (m, 1H), 2.54 (m, 1H), 1.89 – 1.81 (m, 1H), 1.68 – 1.47 (m, 3H), 1.32 – 1.18 (m, 2H), 1.22 (d, *J* = 6.19 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 74.8, 73.9, 40.9, 32.7, 30.7, 23.0, 22.0. HRMS (ESI+): calcd. for $C_8H_{14}O_3Na$ $(M + Na)^+$: 158.0943; found 158.0942.

[2] P. R. Auburn, P. B. Mackenzie and B. Bosnich, *J. Am. Chem. Soc.*, 1985, **107**, 2033.