Distinguishing Between Pathways for Transmetallation in the Suzuki-Miyaura Reaction

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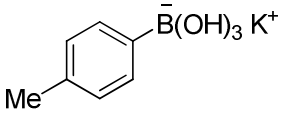
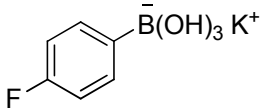
Supporting information.

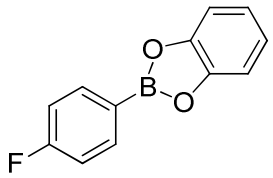
General methods. All manipulations were conducted in an inert atmosphere dry box or using standard Schlenk techniques unless otherwise specified. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer; ^{13}C NMR spectra were recorded at 125 MHz with external $CDCl_3$ as a reference; $^{31}P\{^{1}H\}$ NMR spectra were recorded at 160 or 200 MHz with external H_3PO_4 as a reference; $^{19}F\{^{1}H\}$ NMR spectra were recorded at 375 MHz with external $CFCl_3$ as a reference; $^{11}B\{^{1}H\}$ NMR spectra were recorded at 130 MHz with external $BF_3{\cdot}Et_2O$ as a reference. The complexes $[(Ph_3P)Pd(Ph)(\mu\text{-}OH)]_2$ (**1**),[1] $(Cy_3P)_2Pd(Ph)(OH)$ (**5**),[2] $(Ph_3P)_2Pd(Ph)(I)$ (**2**),[3] and $(Ph_3P)_2Pd(Ph)(Br)$ (**3**)[3] were prepared by published procedures. Tetrahydrofuran and pentane used for the preparation of palladium complexes were dried with a solvent purification system by percolation through neutral alumina under positive pressure of argon. All other reagents and solvents were obtained from commercial sources and used without further purification.



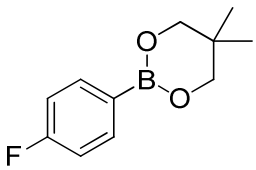
Potassium *p*-tolyltrihydroxyborate. Powdered potassium hydroxide (56 mg, 1.0 mmol) and *p*-tolylboronic acid (136 mg, 1.00 mmol) were weighed into a vial, and THF (5 mL) was added. The mixture was sonicated for 20 min. Upon reduction of the solvent volume to ~1 mL by evaporation under vacuum a white solid precipitated. Hexane (15 mL) was added, and after stirring for 5 min the white solid was filtered, washed with pentane (2x2 mL) and dried to afford 160 mg of product (83%). ^{1}H NMR (D_2O, 400 MHz) δ 7.28 (d, J = 7.2 Hz, 2H), 6.96 (d, J = 7.6 Hz, 2H), 2.10 (s, 3H); ^{13}C NMR (D_2O, 125 MHz) δ 149.73 (br), 138.43, 134.20, 130.50, 22.78; $^{11}B\{^{1}H\}$ NMR (D_2O, 130 MHz) δ 4.8; Anal. Calc'd for $C_7H_{10}BKO_3$: C, 43.77; H, 5.25. Found: C, 43.74; H, 4.95.



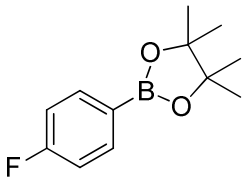
Potassium 4-fluorophenyltrihydroxyborate. 4-fluorophenylboronic anhydride (122 mg, 0.333 mmol) and powdered potassium hydroxide (56 mg, 1.0 mmol) were weighed into a vial. Water (18 μL) and THF (5 mL) were added, and the mixture was sonicated for 20 min. Upon reduction of the solvent volume to ~2 mL by evaporation under vacuum a white solid precipitated. Hexane (15 mL) was added, and after stirring for 30 min the white solid was filtered, washed with pentane (2x2 mL) and dried to afford 139 mg of product (71%). ^{1}H NMR (D_2O, 400 MHz) δ 7.38 (t, J = 6.4 Hz, 2H), 6.84 (t, J = 8.8 Hz, 2H); ^{13}C NMR (D_2O, 125 MHz) δ 164.46 (d, J = 240 Hz), 147.53 (br), 135.70, 116.21 (d, J = 18.6 Hz); ^{19}F{^{1}H} NMR (D_2O, 375 MHz) δ -117.95; ^{11}B{^{1}H} NMR (D_2O, 130 MHz) δ 6.2; Anal. Calc'd for $C_6H_7BFKO_3$: C, 36.76; H, 3.60. Found: C, 36.62; H, 3.41.



4-fluorophenylboronic acid catechol ester. 4-fluorophenylboronic anhydride (185 mg, 0.506 mmol) and 1,2-dihydroxybenzene (167 mg, 1.50 mmol) were weighed into a flask. Water (20 μL) and benzene (5 mL) were added, and the mixture was refluxed with a Dean-Stark trap for 1 h. The solvent was evaporated to dryness. The residue was dissolved in hexane (10 mL), filtered through a plug of Celite, and the filtrate was evaporated under vacuum to dryness. The residue was dissolved in hot hexane (2 mL) and then cooled to -20 °C for 3 h. The resulting crystalline precipitate was filtered, washed with cold pentane (2x2 mL) and dried to afford 212 mg (65%) of product as colorless needles. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (dd, J = 8.4, 6.0 Hz, 2H), 7.31 (dd, J = 5.7, 3.6 Hz, 2H), 7.19 (t, J = 8.4 Hz, 2H), 7.14 (dd, J = 5.6, 3.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.72 (d, J = 253 Hz), (C-B is broad, not observed), 148.45, 137.33 (d, J = 8.8 Hz), 122.82, 115.57 (d, J = 20.5 Hz), 112.54; ^{19}F{^{1}H} NMR ($CDCl_3$, 375 MHz) δ -106.51; ^{11}B{^{1}H} NMR ($CDCl_3$, 130 MHz) δ 31.6; Anal. Calc'd for $C_{12}H_8BFO_2$: C, 67.35; H, 3.77. Found: C, 67.48; H, 3.70.



4-fluorophenylboronic acid neopentyl glycol ester. 4-fluorophenylboronic anhydride (183 mg, 0.500 mmol) and neopentyl glycol (156 mg, 1.50 mmol) were weighed into a flask. Water (20 μL) and benzene (5 mL) were added, and the mixture was refluxed with a Dean-Stark trap for 1 h. Solvent was concentrated to dryness affording the product as a colorless solid (312 mg) in quantitative yield. ^{1}H and ^{13}C NMR chemical shifts matched literature values.[4]



4-fluorophenylboronic acid pinacol ester. 4-fluorophenylboronic anhydride (200 mg, 0.547 mmol) and pinacol (194 mg, 1.64 mmol) were weighed into a flask. Water (20 μL) and benzene (5 mL) were added, and the mixture was refluxed with a Dean-Stark trap for 1 h. The solution was passed through a silica plug and washed with 50 mL of hexane/ethyl acetate (3:1). The filtrate was evaporated affording 255 mg (70%) of product as a pale tan liquid. ^{1}H and ^{13}C NMR chemical shifts matched literature values.[5]

Reaction of $[(Ph_3P)Pd(Ph)(\mu\text{-}OH)]_2$ (1) with *p*-tolylboronic acid (Eq 1). A solution of p-tolylboronic acid (10 mg, 0.075 mmol) in THF/H_2O (0.25 mL/10 μL) was added by to a vial containing **1** (7.0 mg, 7.6 μmol), PPh_3 (12 mg, 0.045 mmol), and *n*-tetradecane (5.0 μL, 0.019 mmol, internal standard) in THF (0.25 mL). The resulting solution was stirred at room temperature. Aliquots of the reaction mixture (50 μL) were diluted in ethyl acetate (0.75 mL), passed through a silica plug, and the yield of 4-methylbiphenyl was determined by gas chromatography.

Reaction of $(Ph_3P)_2Pd(Ph)(I)$ (2) with potassium *p*-tolyltrihydroxyborate (Eq 2). A solution of potassium *p*-tolyltrihydroxyborate (15 mg, 0.078 mmol) and 18-crown-6 (20 mg, 0.075 mmol) in THF/H_2O (0.25 mL/10 μL) was added to a vial containing **2** (13 mg, 0.15 mmol), PPh_3 (8 mg, 0.03 mmol), and *n*-tetradecane (5.0 μL, 0.019 mmol, internal standard) in THF (0.25 mL). The resulting solution was stirred at room temperature. Aliquots of the reaction mixture (50 μL) were diluted in ethyl acetate (0.75 mL), passed through a silica plug, and the yield of 4-methylbiphenyl was determined by gas chromatography.

Reaction of iodobenzene with *p*-tolylboronic acid (Eq 3). Iodobenzene (20 mg, 0.10 mmol), *p*-tolylboronic acid (16 mg, 0.12 mmol), potassium carbonate (35 mg, 0.25 mmol), and $Pd(PPh_3)_4$ (1 mg, 0.001 mmol) were weighed into a small vial. THF (0.50 mL), and *n*-tetradecane (15 μL, 0.076 mmol, internal standard) were added, and the vial was sealed with a septum cap. Water (0.25 mL) was added by syringe, and the mixture was stirred vigorously at 80 ^{o}C. Aliquots of the reaction mixture (20 μL) were diluted in ethyl acetate (0.75 mL), passed through a silica plug, and the yield of 4-methylbiphenyl was determined by gas chromatography.

Representative procedure for determination of *K* for reaction of 4-fluorophenylboronic acid with potassium carbonate (Eq 4). A stock solution of 4-fluorophenylboronic anhydride (0.020 M) in a 50:50 acetone/H_2O mixture was prepared. A portion of the resulting solution of 4-fluorophenylboronic acid (0.50 mL, 0.030 mmol) was added to a small vial, followed by addition of aqueous K_2CO_3 (15 μL, 75 μmol, 5.0 M) by microliter syringe. The mixture was transferred to an NMR tube. The ratio of boronic acid and trihydroxyborate was calculated from the observed time-averaged ^{11}B and ^{19}F NMR chemical shifts at 20 ^{o}C (^{19}F{^{1}H} NMR (375 MHz) δ -116.2; ^{11}B{^{1}H} NMR (130 MHz) δ 13.8), relative to pure 4-fluorophenylboronic acid (^{19}F{^{1}H} NMR (375 MHz) δ -110.9; ^{11}B{^{1}H} NMR (130 MHz) δ 28.7) and potassium 4-fluorophenyltrihydroxyborate (^{19}F{^{1}H} NMR (375 MHz) δ -119.7; ^{11}B{^{1}H} NMR (130 MHz) δ 3.5) at the same concentration and solvent ratio.

Representative procedure for determination of *K* for reaction of $[(Ph_3P)Pd(Ph)(\mu\text{-}OH)]_2$ (1) with halide salt (Eq 5). A stock solution of **1** (40 mg, 0.043 mmol) and PPh_3 (115 mg, 0.438 mmol) in THF (2.0 mL) was prepared. Separately, a stock solution of $N(butyl)_4I$ (32 mg, 0.087 mmol) in THF/H_2O (25:1, 1.04 mL) was prepared. The palladium solution (0.50 mL) and halide solution (0.52 mL) were combined in a small vial then transferred to an NMR tube and sealed with a septum. The relative ratios of **1**, $(Ph_3P)_2Pd(Ph)(OH)$, and $(PPh_3)_2Pd(Ph)(I)$ (**2**) were subsequently determined by ^{31}P NMR spectroscopy at 20 ^{o}C.

Representative procedure for determination of *K* for reaction of $(Cy_3P)_2Pd(Ph)(OH)$ (5) with halide salt (Eq 6 and 7). A stock solution of **5** (40 mg, 0.052 mmol) in THF (2.0 mL) was

prepared. Separately, a stock solution of N(butyl)$_4$I (19 mg, 0.051 mmol) in THF/H_2O (25:1, 2.08 mL) was prepared. The palladium solution (0.50 mL) and halide solution (0.52 mL) were combined in a small vial then transferred to an NMR tube and sealed with a septum. The relative ratios of **5** and $(Cy_3P)_2Pd(Ph)(I)$ (**6**) were subsequently determined by ^{31}P NMR spectroscopy at 20 ^oC.

Procedure for kinetic experiments: reaction of [(Ph$_3$P)Pd(Ph)(μ-OH)]$_2$ (1) with *p*-tolylboronic acid (Fig 1). A stock solution of **1** (14 mg, 0.015 mmol) and PPh_3 (40 mg, 0.15 mmol) in THF (0.5 mL) was prepared. The solution containing palladium complex and ligand (0.25 mL) was transferred to an NMR tube. A sealed capillary containing a 1.0 M solution of PBu_4Br in DMF was also placed in the NMR tube as a ^{31}P NMR external reference. The NMR tube was sealed with a septum. A stock solution of *p*-tolylboronic acid (20 mg, 0.15 mmol) in THF/H_2O (25:1, 0.52 mL) was prepared. The NMR tube was cooled to -50 ^oC, and the solution of boronic acid (0.26 mL) was added by syringe. The resulting solution was placed in the NMR probe cooled to -40 ^oC. ^{31}P NMR spectra were acquired at fixed time intervals throughout the length of experiment with the aid of an automated data collection program.

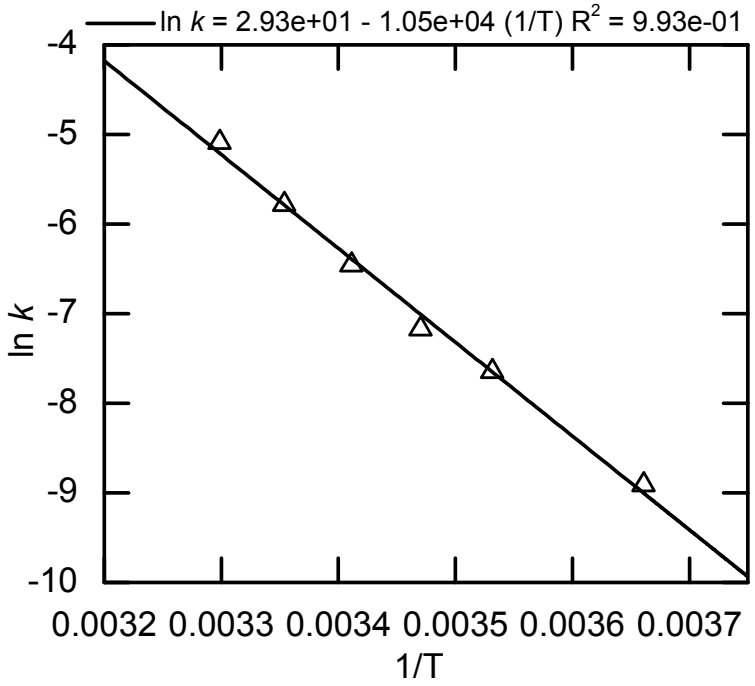


Figure S1. Arrhenius plot for the reaction of **3** (0.030 M) in the presence of potassium *p*-tolyltrihydroxyborate (0.15 M), PPh_3 (0.15 M), and 18-crown-6 in THF/H_2O (50:1) at 0-30 ^oC as monitored by ^{31}P NMR spectroscopy.

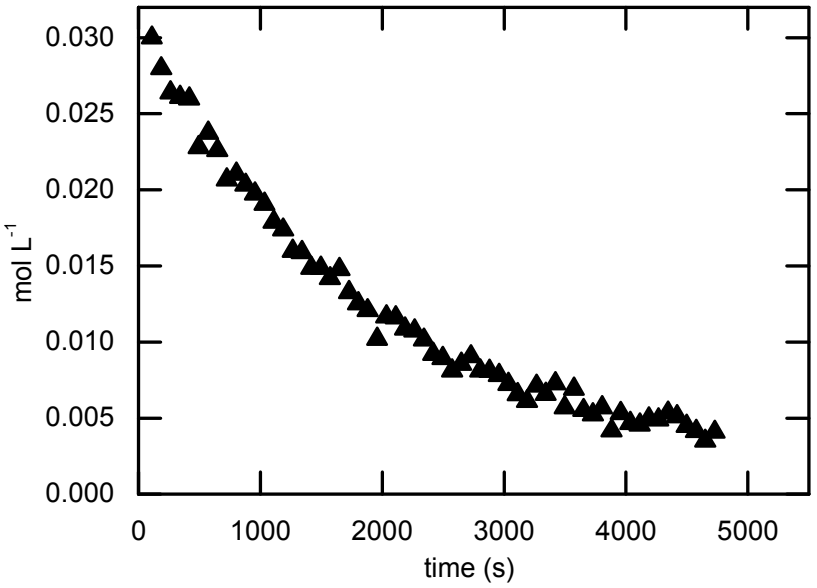


Figure S2. Decay of **3** (0.030 M) in the presence of PPh_3 (0.15 M), potassium *p*-tolyltrihydroxyborate (0.15 M), and 18-crown-6 in THF/H_2O (50:1) at 10 ^oC as monitored by ^{31}P NMR spectroscopy.

Representative procedure for the kinetic experiment for reaction of $(Ph_3P)_2Pd(Ph)(Br)$ (3) with potassium *p*-tolyltrihydroxyborate (Fig S2). A stock solution of **3** (24 mg, 0.030 mmol) and PPh_3 (40 mg, 0.15 mmol) in THF (0.5 mL) was prepared. The solution containing palladium complex and ligand (0.25 mL) was transferred to an NMR tube. A sealed capillary containing a 1.0 M solution of PBu_4Br in DMF was also placed in the NMR tube as a ^{31}P NMR external reference. The NMR tube was sealed with a septum. A stock solution of potassium *p*-tolyltrihydroxyborate (29 mg, 0.15 mmol) and 18-crown-6 (40 mg, 0.15 mmol) in THF/H_2O (25:1, 0.52 mL) was prepared. The NMR tube was cooled to 0 ^oC, and the solution of trihydroxyborate (0.26 mL) was added by syringe. The resulting mixture was placed in the NMR probe that was cooled to 10 ^oC. ^{31}P NMR spectra were acquired at fixed time intervals throughout the length of experiment with the aid of an automated data collection program.

Representative procedure for the reaction of $[(Ph_3P)Pd(Ph)(\mu\text{-}OH)]_2$ (1) with 4-fluorophenylboronic acid esters (Scheme 3). A stock solution of **1** (14 mg, 0.015 mmol) and PPh_3 (40 mg, 0.15 mmol) in THF (0.5 mL) was prepared. The solution containing palladium complex and ligand (0.25 mL) was transferred to an NMR tube. A stock solution of 4-

fluorophenylboronic acid neopentyl glycol ester (32 mg, 0.15 mmol) in THF/H_2O (25:1, 0.52 mL) was prepared. The NMR tube was cooled to -78 ^oC, and the solution of boronic ester (0.26 mL) was added by syringe. The resulting solution was placed in the NMR probe chilled to -55 ^oC. ^{31}P NMR spectra were acquired at fixed time intervals throughout the length of experiment with the aid of an automated data collection program.

References

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(3) Fitton, P.; Johnson, M. P.; McKeon, J. E. *Chem. Comm.* **1968**, 6-7.

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