

Aryl bromide /triflate selectivities reveal mechanistic divergence in palladium-catalysed couplings; the Suzuki-Miyaura anomaly

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Synthetic aspects; numbering follows the main manuscript.

*Synthesis of triflate (7)*¹

A Schlenk tube was charged with 2-bromo-4,5-difluorophenol (1.64 ml, 3g, $1.44 \cdot 10^{-2}$ mol) under nitrogen and 9 ml of pyridine. The stirred solution is cooled to 0° C and then trifluoromethanesulfonic anhydride, 2.67 ml, is added very slowly through the rubber stopper via a syringe. The temperature is maintained at 0° C for 5 min and then allowed to warm to room temperature and stirred overnight (20-25 h).

The resulting mixture was poured into water and extracted with ethyl ether. The ether extract (upper phase) was washed sequentially with water, 10% aqueous hydrochloric acid solution (2x), water, and a concentrated sodium chloride solution, dried (MgSO₄), and concentrated to yield an oil. Chromatography (flash column, petroleum spirit 40-60°C / EtOAc, 20:1) and solvent removing (rotavapor, 40° C, high vacuum, 3h, to remove all the EtOAc) afforded the desired product, **7**, as a colourless liquid (3.2 g, 65%)

¹H-NMR (CDCl₃, 400 MHz) δ ppm: 7.56 (t, J=8.46, 8.46 Hz, 1H); 7.28 (dd, J=6.85, 9.51 Hz, 1H). ¹³C{¹H}-NMR (CDCl₃, 101 MHz) δ ppm: 149.5 (dd, ³J_{FC}=12.9, ¹J_{FC}=256.1 Hz, 1C, C-F); 149.3 (dd, ³J_{FC}=13.6, ¹J_{FC}=254.8 Hz, 1C, C-F); 142.4 (dd, ³J_{FC}=3.9, 8.2 Hz, 1C, C-OTf); 122.3 (d, ²J_{FC}=21.4 Hz, 1C, C-H); 118.5 (q, ¹J_{FC}=320.8 Hz, 1C, CF₃); 112.8 (d, ²J_{FC}=21.9 Hz, 1C, C-H); 110.8 (dd, J=4.6, 7.5 Hz, 1C, C-Br).

¹⁹F{¹H}-NMR (CDCl₃, 377 MHz) δ ppm: -72.9 (s, 3F, CF₃); -131.5 (d, ³J_{FF}=21.3 Hz, 1F, C-F); -132.3 (d, ³J_{FF}=21.3 Hz, 1F, C-F).

MS CI+(m/z) Found 339.8801 ([M]⁺); C₇H₂BrF₅O₂S requires 339.8828.

Triflate (**2**)² was prepared similarly from 3-bromophenol as a light-coloured oil; MS CI+(m/z) Found 339.8801 ([M]⁺); C₇H₂BrF₅O₂S requires 339.8828.

¹ W. Zhang, R. Gorny, and P. Dowd, *Synth. Commun.*, 1999, **29**, 2903.

² K. S. Petrakis, T. L. Nagabhushan, *J. Am. Chem. Soc.* 1987, **109**, 2831.

Catalytic Experiments

All the catalytic experiments were carried out under nitrogen in Schlenk tubes. Products were analyzed by ^{19}F NMR and GC-MS spectroscopy.

Suzuki reaction

In a typical experiment, a Schlenk tube was charged with 4-methoxyphenylboronic acid (47 mg, 0.308 mmol, 5% excess), K_3PO_4 (124.4 mg, 0.586 mmol), LiBr (25 mg, 0.293 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (11 mg, 0.0147 mmol, 5% molar to aryl halide). Then, the schlenk tube was evacuated and refilled with nitrogen three times. Afterwards, it was charged with aryl halide-triflate (**7**) (100 mg, 0.293 mmol) under a nitrogen atmosphere and 3 ml of toluene and then heated at reflux temperature overnight (22 h). The resulting mixture was cooled and then filtered. Finally, the crude was analyzed by ^{19}F NMR and GC/MS.

Suzuki double-coupling experiments

In the first experiment, previous procedure was followed but the amount of aryl halide-triflate (**7**) was halved to ensure (1:2) molar rate with regard to the boronic acid (50 mg, 0.147 mmol). 4-methoxyphenylboronic acid (47 mg, 0.308 mmol, 5% excess), K_3PO_4 (124.4 mg, 0.586 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (11 mg, 0.0147 mmol, 5% molar to aryl halide)

Kumada reaction

In a typical experiment, a Schlenk tube was charged with PhMgBr (0.117 mL, 3M solution, 0.352 mmol, 20% excess), LiBr (26 mg, 0.293 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (11 mg, 0.0147 mmol, 5% molar to aryl halide). Then, the Schlenk tube was evacuated and refilled with nitrogen three times. Afterwards, it was charged with aryl halide-triflate (**7**) (100 mg, 0.293 mmol) under a nitrogen atmosphere and 3 ml of toluene and then heated

at reflux temperature overnight (22 h). The resulting mixture was cooled and then filtered. Finally, the crude was analyzed by ^{19}F NMR and GC/MS.

Heck reaction

In a typical experiment, a Schlenk tube was charged with sodium carbonate (47 mg, 0.440 mmol), dppp (12 mg, 0.0293 mmol, 10% molar to aryl halide) and $\text{Pd}_2(\text{dba})_3$ (13 mg, 0.0147 mmol, 5% molar to aryl halide). Then, the Schlenk tube was evacuated and refilled with nitrogen three times. Afterwards, it was charged with 3 ml of toluene, buthyl acrylate (56 mg, 0.440 mmol) and aryl halide-triflate (**7**) (100 mg, 0.293 mmol), both through a rubber septum under a nitrogen atmosphere and then the mixture was heated at reflux temperature overnight (22 h). The resulting mixture was cooled and then filtered. Finally, the reaction was analyzed by ^{19}F NMR and GC/MS.

Amination

In a typical experiment, a Schlenk tube was charged with sodium tert-butoxide (39 mg, 0.410 mmol), dppp (6 mg, 0.0150 mmol, 10% molar to aryl halide) and $\text{Pd}_2(\text{dba})_3$ (6.7 mg, 0.0073 mmol, 5% molar to aryl halide). Then, the Schlenk tube was evacuated and refilled with nitrogen three times. Afterwards, it was charged with 3 ml of toluene, morpholine (31 mg, 0.352 mmol) and aryl halide-triflate (**7**) (100 mg, 0.293 mmol), both through a rubber septum under a nitrogen atmosphere and then the mixture was heated at 80° C (22 h). The resulting mixture was cooled and then filtered. Finally, the crude was analyzed by ^{19}F NMR and GC/MS.

(8) $\text{C}_{14}\text{H}_9\text{O}_4\text{F}_5\text{S}$ GC-MS CI+(m/z): calcd for $([\text{M} + \text{NH}_4]^+)$: 368.0142, found: 368.0147; $^{19}\text{F}\{^1\text{H}\}$ -NMR (377 MHz, CDCl_3) δ ppm: -73.8 (s, 3F, CF_3); -134.8 (d, $^3\text{J}_{\text{FF}} = 21.8$ Hz, 1F, C-F); -136.0 (d, $^3\text{J}_{\text{FF}} = 21.8$ Hz, 1F, C-F).

(9) $\text{C}_{13}\text{H}_9\text{BrF}_2\text{O}$ GC-MS CI+(m/z): calcd for $([\text{M}]^+)$: 297.9805, found: 297.9798; $^{19}\text{F}\{^1\text{H}\}$ -NMR (377 MHz, CDCl_3) δ ppm: -137.7 (d, $^3\text{J}_{\text{FF}} = 21.3$ Hz, 1F); -138.8 (d, $^3\text{J}_{\text{FF}} = 20.9$ Hz, 1F) (minor product).

(10) $C_{20}H_{16}O_2F_2$ GC-MS CI+(m/z): calcd for $([M]^+)$: 326.1118, found: 326.1117; $^{19}F\{^1H\}$ -NMR (377 MHz, $CDCl_3$) δ ppm: -140.9 (s, 2F, C-F) (minor product).

(11) $C_{13}H_7O_3F_5S$ GC-MS CI+(m/z): calcd for $([M]^+)$: 338.0036, found: 338.0031; $^{19}F\{^1H\}$ -NMR (377 MHz, $CDCl_3$) δ ppm: -73.4 (s, 3F, CF_3); -133.0 (d, $^3J_{FF} = 21.8$ Hz, 1F, C-F); -134.9 (d, $^3J_{FF} = 21.8$ Hz, 1F, C-F); 1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.7-7.3 (m, 7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 149.6 (dd, $J = 252.0, 12.4$ Hz, C-F, 1C); 149.1 (dd, $J = 253.9, 14.2$ Hz, C-F, 1C); 141.3 (dd, $J = 8.2, 3.3$ Hz, C-OTf, 1C); 134.8 (t, $J = 6.3, 6.3$ Hz, C-Ph, 1C); 133.9 (s, C^i -Ph, 1C); 129.3 (s, C^o -Ph, 2C); 129.0 (s, C^p -Ph, 1C); 128.8 (s, C^m -Ph, 2C); 119.7 (d, $J = 19.20$ Hz, C-H, 1C); 118.3 (q, $J = 320.7, 320.7, 320.6$ Hz, CF_3 , 1C); 112.3 (d, $J = 21.1$ Hz, C-H, 1C).

(12) $C_{13}H_7O_3F_5S$ $^{19}F\{^1H\}$ -NMR (377 MHz, $CDCl_3$) δ ppm: -137.1 (d, $^3J_{FF} = 21.7$ Hz, 1F, C-F); -138.6 (d, $^3J_{FF} = 21.7$ Hz, 1F, C-F) (minor product).

(13) $C_{18}H_{12}F_2$ GC-MS CI+(m/z): calcd for $([M]^+)$: 266.0907, found: 266.0909; $^{19}F\{^1H\}$ -NMR (377 MHz, $CDCl_3$) δ ppm: -140.2 (s, 2F, C-F). (minor product).³

(15) $C_{10}H_{10}BrF_2NO$ GC-MS CI+(m/z): calcd for $([M]^+)$: 276.9914, found: 276.9904; $^{19}F\{^1H\}$ -NMR (377 MHz, $CDCl_3$) δ ppm: -135.5 (d, $^3J_{FF} = 21.9$ Hz, 1F, C-F); -141.1 (d, $^3J_{FF} = 21.9$ Hz, 1F, C-F).

(16) $C_{13}H_{13}BrF_2O_2$ GC-MS CI+(m/z): calcd for $([M+H]^+)$: 319.0145, found: 319.0134; $^{19}F\{^1H\}$ -NMR (377 MHz, $CDCl_3$) δ ppm: -131.5 (d, $^3J_{FF} = 22.2$ Hz, 1F, C-F); -136.6 (d, $^3J_{FF} = 22.2$ Hz, 1F, C-F).

³ (a) P. Singh and R. Kumar, *J. Enzyme Inhib.*, 1998, 13, 409. (b) D. C. England, E. A. Donald, and F. J. Weigert, *J. Org. Chem.*, 1981, 46, 144.