Electronic Supplementary Material (ESI) for Chemical Communications
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The Palladium-Catalyzed Cross-Coupling Reactions of Trifluoroethyl Iodide with Aryl and Heteroaryl Boronic Acid Esters

Supporting Information

General Methods. All reactions were performed in dried glass reaction tube equipped with a magnetic stir bar under nitrogen gas atmosphere. Flash column chromatography was performed using silica gel (60-Å pore size, 32-63 μm, standard grade). Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light. Solvents were re-distilled prior to use in the reactions. The transformation progress was indicated by GC-MS using Thermo Fisher Scientific DSQⅡ. Melting point were obtained by XT4A micro Melting-point Measurement Instruments , thermometer was unrevised. The mass spectrum was received via Micromass Q-Tof Micro^{TM} high Resolution mass spectrometer，with ESI as ion source. NMR spectra were obtained on Bruker DPX 400 systems using $CDCl_3$ as solvent, TMS as internal standard substance, with proton and carbon resonances at 400 and 100 MHz, respectively.

Experimental procedures Section. A dried glass reaction tube equipped with a magnetic stir bar was charged with $Pd_2(dba)_3$ (12.9 mg, 0.0125 mmol, 2.5 mol %), XPhos (23.8 mg, 0.05 mmol, 10 mol %), CsF (228.0 mg, 1.5 mmol, 3 equiv), CuCl (49.5 mg, 0.5 mmol, 1.0 equiv), H_2O (72.0 mg, 4.0 mmol, 8.0 equiv), CF_3CH_2I (210.0 mg, 1.0 mmol, 2.0 equiv) and aryl(Het) boronic acid esters (0.5 mmol, 1.0

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equiv); anhydrous DMF (2.0 mL) was added and the mixture was charged with nitrogen gas three times. The reaction mixture was then stirred at 65℃under nitrogen gas until boronic acid esters were consumed. The reaction progress was monitored by GC–MS. The reaction mixture was poured into H_2O after cooling to room temperature and extracted with diethyl ether. The combined organic layer was dried with Na_2SO_4 and filtered through a pad of celite. The filtrate was concentrated in vacuo. The residue was purified by silica gel flash chromatography to produce the desired product. The products were characterized by melting point, ^{1}H NMR, ^{13}C NMR and GC-MS/MS.

Characterization data of compounds.

2-(benzyloxy)-5-(2,2,2-trifluoroethyl)pyridine (3a, yield 53%): White solid. m.p. 65-67℃. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.10(d, *J* = 2.0 Hz, 1H), 7.54(dd, *J* = 8.6, 1.8 Hz, 1H), 7.48(d, *J* = 7.2 Hz, 2H), 7.40(t, *J* = 6.8 Hz, 2H), 7.36-7.32(t, 1H), 6.83(d, *J* = 8.8 Hz, 1H), 5.40(s, 2H), 3.31(q, *J* = 10.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.6(s), 148.0(s), 140.2(s), 137.1(s), 128.5(s), 128.0(d, *J* = 8.2 Hz), 125.5(q, *J* = 275.1 Hz), 118.9(d, *J* = 2.8 Hz), 111.3(s), 67.8(s), 36.8(q, *J* = 30.3 Hz).

2-ethoxy-5-(2,2,2-trifluoroethyl)pyridine (3b, yield 40%): White solid. m.p. 32-34℃. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.05(s, 1H), 7.50(d, *J* = 8.0 Hz, 1H), 6.72(d, *J* = 8.8 Hz, 1H), 4.35(q, *J* = 7.2 Hz, 2H), 3.28(q, *J* = 10.4 Hz, 2H), 1.39(t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.9(s), 148.1(s), 140.1(s), 125.6(q, *J* = 275.0 Hz), 118.5(q, *J* = 2.8 Hz), 111.1(s), 61.9(s), 36.9(q, *J* = 30.4 Hz), 14.6(s).

N,N-dimethyl-5-(2,2,2-trifluoroethyl)pyridin-2-amine (3c, yield 55%): White solid. m.p. 36-38℃. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.05(d, *J* = 1.6 Hz, 1H), 7.37(dd, *J* = 8.8, 1.6 Hz, 1H), 6.49(d, *J* = 8.8 Hz, 1H), 3.21(q, *J* = 10.4 Hz, 2H), 3.08(s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 159.0(s), 149.0(s), 138.6(s), 125.9(q, *J* = 275.0 Hz), 112.8(d, *J* = 2.9 Hz), 105.6(s), 38.1(s), 36.8(q, *J* = 30.0 Hz).

2-phenyl-5-(2,2,2-trifluoroethyl)pyridine (3d, yield 51%): White solid. m.p. 83-85℃. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.62(s, 1H), 8.01-8.00(t, 2H), 7.75-7.69(m, 2H), 7.51-7.42(m, 3H), 3.43(q, *J* = 10.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 157.4(s), 150.9(s), 138.7(s), 138.3(s), 129.3(s), 128.9(s), 126.9(s),

125.4(q, J = 275.4 Hz), 124.3(d, J = 2.7 Hz), 120.3(s), 37.4(q, J = 30.2 Hz).

2-(pyrrolidin-1-yl)-5-(2,2,2-trifluoroethyl)pyridine (3e, yield 57%): White solid. m.p. 50-52℃. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.04(d, J = 1.6 Hz, 1H), 7.36(dd, J = 8.6, 1.4 Hz, 1H), 6.34(d, J = 8.8 Hz, 1H), 3.44(t, J = 6.4 Hz, 4H), 3.21(q, J = 10.8 Hz, 2H), 2.00(m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 157.0(s), 149.4(s), 138.4(s), 125.9(q, J = 275.0 Hz), 112.4(q, J = 2.9 Hz), 106.3(s), 46.7(s), 36.9(q, J = 30.0 Hz), 25.6(s).

1-nitro-4-(2,2,2-trifluoroethyl)benzene (3f, yield 34%): Yellow solid. m.p. 39-41℃. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.23(d, J = 8.8 Hz, 2H), 7.49(d, J = 8.4 Hz, 2H), 3.50(q, J = 10.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 148.0(s), 137.4(d, J = 2.9 Hz), 125.2(q, J = 275.4 Hz), 124.0(s), 40.1(q, J = 30.2 Hz).

1-(4-(2,2,2-trifluoroethyl)phenyl)ethanone (3g, yield 53%): Yellow solid. m.p. 28-30℃. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.95(d, J = 8.0 Hz, 2H), 7.41(d, J = 8.0Hz, 2H), 3.44(q, J = 10.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 196.6(s), 135.9(s), 134.3(d, J = 2.7 Hz), 129.4(s), 127.6(s),124.4(q, J = 275.2 Hz), 39.1(q, J = 29.7 Hz), 25.6(s).

4-(2,2,2-trifluoroethyl)benzonitrile (3h, yield 55%): White solid. m.p. 63-65℃. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.67(d, J = 8.0 Hz, 2H), 7.43(d, J = 8.0Hz, 2H), 3.45(q, J = 10.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 135.3(q, J = 2.9 Hz), 132.4(s), 130.9(s), 125.1(d, J = 275.3 Hz), 118.3(s), 112.4(s), 40.2(q, J = 30.1 Hz).

phenyl(4-(2,2,2-trifluoroethyl)phenyl)methanone (3i, yield 58%): Yellow solid. m.p. 69-71℃. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.80(d, J = 8.0 Hz, 4H), 7.60(t, J = 7.6Hz, 1H), 7.49(t, J = 7.6 Hz, 2H), 7.42(d, J = 8.0 Hz, 2H), 3.46(q, J = 10.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 196.2(s), 137.5(d, J = 4.7 Hz), 134.7(d, J = 2.8 Hz), 132.7(s), 130.5(s), 130.3(s), 130.1(s), 128.5(s), 125.6(q, J = 275.3 Hz), 40.3(q, J = 29.7 Hz).

1-methoxy-4-(2,2,2-trifluoroethyl)benzene (3j, yield 53%): Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.22(d, J = 8.4 Hz, 2H), 6.90(d, J = 8.8Hz, 2H), 3.31(q, J = 10.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 159.4(s), 131.3(s), 125.9(q, J = 274.9 Hz), 122.2(q, J = 3 Hz), 114.1(s), 55.3(s), 39.3(q, J = 29.7 Hz).

methyl 4-(2,2,2-trifluoroethyl)benzoate (3k, yield 60%): Yellow solid. m.p.

42-44℃. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.02(d, *J* = 8.0 Hz, 2H), 7.36(d, *J* = 8.0Hz, 2H), 3.90(s, 3H), 3.41(q, *J* = 10.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.7(s), 135.3(q, *J* =2.8 Hz), 130.4(s), 130.2(s), 129.8(s), 125.6(q, *J* = 275.3 Hz), 77.2(t, *J* = 31.9 Hz), 40.2(q, *J* = 29.6 Hz).

1-(3-(2,2,2-trifluoroethyl)phenyl)ethanone (3l, yield 54%): Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.94(m, 1H), 7.90(s, 1H), 7.49(m, 2H), 3.44(q, *J* = 10.4 Hz, 2H), 2.62(s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 197.6(s), 137.5(s), 134.7(s), 130.8(q, *J* =2.9 Hz), 130.0(s), 129.0(s), 128.2(s), 125.5(q, *J* = 275.1 Hz), 40.1(q, *J* = 29.8 Hz), 26.7(s).

1-methoxy-3-(2,2,2-trifluoroethyl)benzene (3m, yield 31%): Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.27(d, *J* = 8.0 Hz, 1H), 7.23(d, *J* = 5.6 Hz, 1H), 6.87(dd, *J* = 8.0, 1.8 Hz, 1H), 6.83(s, 1H), 3.80(s, 3H), 3.32(q, *J* = 10.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 159.8(s), 131.6(q, *J* = 2.9 Hz), 129.7(s), 125.8(q, *J* = 275.0 Hz), 122.5(s), 116.0(s), 113.5(s), 55.2(s), 40.2(q, *J* = 29.6 Hz).

methyl 4-methyl-3-(2,2,2-trifluoroethyl)benzoate (3n, yield 30%): Yellow solid. m.p. 66-68℃. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.94(s, 1H), 7.90(d, *J* = 8.0 Hz, 1H), 7.29(d, *J* = 8.0, 1H), 3.91(s, 3H), 3.45(q, *J* = 10.4 Hz, 2H), 2.42(s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.7(s), 143.2(s), 132.4(s), 130.9(s), 129.4(s), 129.0(q, *J* = 2.8 Hz), 128.4(s), 125.9(q, *J* = 275.7 Hz), 52.1(s), 37.1(q, *J* = 29.8 Hz), 19.9(s).

2-(benzyloxy)-5-(2,2,3,3,3-pentafluoropropyl)pyridine (3ab, yield 18%): Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.07(d, *J* = 2.1 Hz, 1H), 7.53(dd, *J* = 8.7, 2.1 Hz, 1H), 7.46(d, *J* = 7.2 Hz, 2H), 7.38(t, *J* = 6.8 Hz, 2H), 7.36-7.32(m, 1H), 6.82(d, *J* = 8.8 Hz, 1H), 5.38(s, 2H), 3.26(t, *J* = 18.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.6(s), 148.2(s), 140.6(s), 137.0(s), 128.5(s), 128.0(d, *J* = 7.4 Hz), 114.3(s), 114.0(s), 117.8(s), 111.3(s), 67.8(s), 33.7(t, *J* = 23.0 Hz).