Supporting Information

Pd-Assisted Room Temperature Nucleophilic Substitution of an Unactivated Aryl Fluoride

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General Procedures:

All operations with air- and moisture- sensitive compounds were performed in a nitrogen-filled Innovative Technology glove box. All solvents were degassed and stored under high-purity nitrogen and activated 4Å molecular sieves. All deuterated solvents were stored under high-purity nitrogen on 3Å molecular sieves. Commercially available reagents (Aldrich, Strem and Acros) were used as received. The NMR spectra were recorded on Bruker AC 200MHz, Bruker Avance 400MHz and Bruker Avance III 400MHz spectrometers. ^{1}H and ^{13}C NMR signals are reported in ppm downfield from TMS. ^{1}H signals are referenced to the residual proton of a deuterated solvent 7.26 ppm for $CDCl_3$ and 7.15 ppm for C_6D_6. ^{13}C signals are referenced to the solvent signal at 77.36 ppm for $CDCl_3$ and 128.06 ppm for C_6D_6. ^{31}P chemical shifts are reported in ppm downfield from H_3PO_4 and referenced to an external 85% phosphoric acid sample. ^{19}F chemical shifts are reported in ppm downfield from $CClF_3$. All measurements were performed at 22ºC in $CDCl_3$ unless stated otherwise. Elemental analysis was performed in the laboratory for microanalysis at the Hebrew University of Jerusalem. Mass Spectra were recorded on a VG-Autospec M-250 instrument. Complex [Pd(4-FC_6H_4)I(tmeda)] was prepared by the slightly modified literature procedure.[1]

Synthesis of 8-fluoro-2-methylquinoline:[2]

A toluene solution (20 ml) of 2-fluoroaniline (1 ml, 10 mmol), HCl (80 ml, 10M), tetra-n-butylammonium bromide (TBAB) (210 mg, 0.65 mmol) and crotonaldehyde (3 ml, 35 mmol) was refluxed at 90^{o}C for 2 hrs. The mixture was extracted with $CHCl_3$, washed with brine and dried over $MgSO_4$. Column purification (5:1, hexane:ethyl acetate) gave the product as a yellow oil (1.53 gr, 95% yield). ^{1}H NMR 8.06 (dd, J = 8.6, 1.6 Hz, Ar-H, 1H), 7.55 (dd, J = 7.1, 1.6 Hz, Ar-H, 1H), 7.43-7.32 (m, Ar-H, 3H), 7.18 (m, Ar-H, 1H), 2.79 (s, CH_3, 3H); $^{13}C\{^{1}H\}$ 159.41 (s), 158.75 (s), 137.95 (s), 135.77 (s), 128.10 (s), 125.25 (s), 123.03 (d, J_{FC} = 16.9 Hz), 113.39 (d, J_{FC} = 18.5 Hz), 25.45 (s, CH_3); $^{19}F\{^{1}H\}$ -126.74 (s).

Synthesis of **1:**

To a THF solution (5 ml) of 8-fluoro-2-methylquinoline (400 mg, 25 mmol) at -78ºC was slowly added lithium diisopropylamide (LDA) (1.2 equiv.). The mixture was left to stir at -78ºC for 2

hrs after which di-tertbutylchlorophosphine was added dropwise and the mixture was left to stir overnight at RT. The reaction was quenched with methyl alcohol and washed with degassed brine. Removal of the solvent *in vacuo* gave the product as brown oil (400 mg, 52% yield). ^{1}H NMR 7.98 (dd, Ar-H , J = 8.6, 1.5 Hz, 1H), 7.65 (d, J = 8.6 Hz, Ar-H, 1H), 7.47 (m, Ar-H, 1H), 7.30 (m, Ar-H, 2H), 3.26 (d, J_{PH} = 3.5 Hz, CH_2-P, 2H), 1.13 (d, J_{PH} = 11.2 Hz, ^{t}Bu, 18H); ^{19}F{^{1}H} -126.64 (s); ^{31}P{^{1}H} 35.74 (s).

Synthesis of **2**:

An acetone solution (5 ml) of **1** (342 mg, 1.1 mmol) and [(tetramethylethylenediamine)(4-fluorophenyl)iodopalladium(II)] (0.9 eq) was stirred for 5 days at RT. Precipitation of the product from the crude is visible within 1 day. Filtration followed by washing with n-pentane gave the product as a bright yellow solid (639 mg, 84% yield). ^{1}H NMR 8.26 (d, J = 8.5 Hz, Ar-H, 1H), 7.65 (m, Ar-H, 1H), 7.61-7.51 (m, Ar-H, 4H), 7.48 (d, J = 8.5 Hz, 1H), 6.78 (t, J = 9.0 Hz, 2H), 3.84 (d, J_{PH} = 7.9 Hz, CH_2-P, 2H), 1.31 (d, J_{PH} = 13.9 Hz, ^{t}Bu, 18H); ^{13}C{^{1}H} 162.71 (s), 160.33 (s), 139.83 (s), 139.23 (br.s), 137.56 (s), 129.09 (d, J = 12.8 Hz), 126.31 (s), 123.16 (d, J = 4.9 Hz), 120.89 (d, J = 5.6 Hz), 119.98 (s), 117.18 (d, J = 21.8 Hz), 116.72 (d, J = 4.5 Hz), 113.92 (s), 113.25 (d, J = 20.4 Hz), 111.13 (s), 110.37 (s), 56.59 (s, OCH_3), 36.60 (d, J_{PC} = 10.8 Hz, CH_2-P), 29.93 (s, $(CH_3)_3$C-P); ^{19}F{^{1}H} -102.05 (s), -124.45 (s); ^{31}P{^{1}H} 60.71 (s). HRMS M^+ (Calc. for $C_{24}H_{29}F_2NPPd$) 506.104 (506.104).

Synthesis of **3**:

To a THF suspension (2 ml) of **2** (30 mg, 0.047 mmol) was added sodium methoxide (26 mg, 0.47 mmol). Within seconds, the mixture turned clear red and the reaction was complete within 1h at RT. The crude solution was filtered over celite and filtrate was evaporated to yield an orange solid. The solid was then washed with benzene and filtered over celite. The solvent was removed *in vacuo* to give the product as a dark orange solid (100% yield). ^{1}H NMR (C_6D_6) 7.62 (dt, Ar-H, 2H), 7.00 (t, J = 7.0 Hz, Ar-H, 2H), 6.73 (dd, J = 8.9,2.4 Hz, Ar-H, 2H), 6.53 (d, J = 9.4 Hz, Ar-H, 1H), 6.39 (d, J = 7.8 Hz, Ar-H, 1H), 6.08 (d, J = 8.0 Hz, Ar-H, 1H), 3.35 (d, J_{PH} = 6.0 Hz, CH-P, 1H), 2.87 (s, OCH_3, 3H), 1.26 (d, J_{PH} = 14.0 Hz, ^{t}Bu, 18H) ; ^{13}C{^{1}H} 164.49 (d, J = 14.6 Hz), 163.25 (s), 160.88 (s), 152.44 (s), 149.86 (s), 140.12 (s), 138.87 (d, J = 2.9 Hz), 131.55 (s), 122.07 (s), 121.70 (s), 120.08 (d, J = 18.7 Hz), 115.70 (s), 114.41 (d, J = 18.7 Hz),

114.04 (s), 110.34 (s), 67.20 (d, J_{PC} = 59.5 Hz, CH-P), 56.71 (s, OCH_3), 37.60 (d, J_{PC} = 28.7 Hz, $(CH_3)_3C$-P), 29.38 (d, J_{PC} = 4.2 Hz, $(CH_3)_3C$-P); $^{19}F\{^1H\}$ -120.73 (s); $^{31}P\{^1H\}$ 89.83 (s). Elemental analysis: Found (Calc.): C 58.02 (57.98), H 6.10 (6.03).

Complex **3** can also be prepared in a quantitative yield within 1 hr by adding 5-fold excess of NaOMe or KOt-Bu to the THF solution of **5** followed by the standard purification protocol.

Synthesis of **4**:

To a THF solution (10 ml) of 8-methoxy-2-methylquinoline (500 mg, 2.9 mmol) at -30^{o}C was slowly added LDA (4.3 ml, 3 eq). The reaction was left to stir at RT for 8 hrs after which di-tertbutylchlorophosphine (0.5 ml, 0.9 eq) was added dropwise and the mixture was left to stir for overnight. The reaction was quenched with methyl alcohol and washed with degassed brine. Removal of the solvent *in vacuo* gave the product as brown oil (609 mg, 70% yield). ^1H NMR 7.86 (d, J = 7.8 Hz, Ar-H, 1H), 7.58 (d, Ar-H, 1H), 7.19(m, Ar-H, 2H), 6.86 (d, J = 7.2 Hz, Ar-H, 1H), 3.90 (s, OCH_3, 3H), 3.23 (d, J = 3.6 Hz, CH_2-P, 2H), 1.06 (d, ^{t}Bu, J_{PH} = 11.0 Hz, 18H); $^{13}C\{^1H\}$ 162.22 (d, J = 16.5 Hz), 155.39 (s), 139.76 (s), 135.85 (s), 127.88 (s), 125.74 (s), 123.20 (d, J = 11.8 Hz), 119.76 (s), 108.21 (s), 56.42 (s, OCH_3), 41.11 (d, J_{PC} = 10.3 Hz, CH_2-P), 37.23 (s, $(CH_3)_3C$-P), 28.95 (d, J_{PC} = 7.8 Hz, $(CH_3)_3C$-P); $^{31}P\{^1H\}$ 34.58 (s).

Synthesis of **5**:

A benzene solution (4 ml) of **4** (185 mg, 0.6 mmol) and [(tetramethylethylenediamine)(4-fluorophenyl)iodopalladium(II)] (233 mg, 0.5 mmol) was stirred for 3 days at RT. Precipitation of the product from the crude is visible within few hours. Evaporation of the reaction solvent following n-Pentane washes gave the product as a yellow solid (289 mg, 75% yield). ^1H NMR 8.12 (dd, J = 8.5, 0.5 Hz, Ar-H, 1H), 7.59 (d, J = 8.5 Hz, Ar-H, 1H), 7.48 (m, Ar-H, 2H), 7.41 (d, J = 7.9 Hz, 1H), 7.34 (dd, J = 7.9, 1.3 Hz, Ar-H, 2H), 6.71 (t, J = 9.0 Hz, Ar-H, 2H), 3.92 (s, OCH_3, 3H), 3.91 (d, J_{PH} = 7.1 Hz, CH_2-P, 2H), 1.22 (d, J_{PH} = 14.4 Hz, ^{t}Bu, 18H); $^{13}C\{^1H\}$ 162.32 (s), 159.62 (s), 158.66 (s), 155.30 (s), 139.23 (s), 139.17 (s), 138.93 (s), 134.46 (s), 128.82 (s), 128.28 (s), 121.41 (d, J = 7.5 Hz), 120.07 (s), 114.01 (s), 113.83 (s), 111.26 (s), 56.68 (s, OCH_3), 37.85 (d, J_{PC} = 21.8 Hz, $(CH_3)_3C$-P), 37.26 (d, J_{PC} = 13.5 Hz, $(CH_3)_3C$-P), 29.89 (s, $(CH_3)_3C$-P); $^{19}F\{^1H\}$ -122.89 (s); $^{31}P\{^1H\}$ 73.01 (s).

Synthesis of **6**:

To a CH_2Cl_2 solution (2 ml) of **5** (8 mg, 12μmol) was added silver tetrafluoroborate (1 equiv.). The mixture was stirred in the dark at RT for 12 hrs. The mixture was filtered over celite which was then washed with CH_2Cl_2. The combined filtrate was evaporated giving the product as a yellow solid in 100% yield. ^{1}H NMR 8.45 (dd, J = 8.8, 1.0 Hz, Ar-H, 1H), 8.24 (d, J = 8.8 Hz, Ar-H, 1H), 7.74-7.58 (m, Ar-H, 2H), 7.52 (m, Ar-H, 2H), 7.41-7.32 (m, Ar-H, 1H), 6.98 (t, J = 8.9 Hz, Ar-H, 2H), 4.32 (d, J_{PH} = 9.5 Hz, CH_2-P, 2H), 3.73 (s, OCH_3, 3H), 1.44 (d, J_{PH} = 16.3 Hz, ^{t}Bu, 18H); ^{19}F{^{1}H} -118.26 (s, 1F), -152.70 (s, BF_4^-, 4F); ^{31}P{^{1}H} 92.43 (s).

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2- Reynolds, K. A.; Young, D. J.; Loughlin, W. A. *Synthesis* **2010**, *21*, 3645.