Supporting Information

New Air-Stable Catalysts for General and Efficient Suzuki-Miyaura Cross-Coupling Reactions of Heteroaryl Chlorides

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EXPERIMENTAL

General. All experiments were performed under nitrogen atmosphere. All reagents including di-tert-butylphosphine, Pd_2dba_3 , $\text{PdCl}_2(\text{COD})$, aryl halides, arylboronic acids, and inorganic bases were purchased from commercial sources and used as received. Anhydrous, sure-seal grade organic solvents including toluene, tetrahydrofuran (THF), and pentane were used as purchased. Distilled water purged with nitrogen was used. Stock solutions of catalysts were used for high TON experiments. Commercially available pre-packed silica gel plugs and hexanes/ethylacetate solvents were used for column chromatographic purification of organic products. Isolated yields correspond to products of > 95 % purity as determined by GC, LC and NMR. GC yields correspond to calibrated GC yields using a standard. All NMR (^1H , ^{13}C , ^{31}P , and ^{19}F) chemical shifts are reported in parts per million (ppm) and all coupling constants are reported in Hertz (Hz).

Synthesis of $\text{PdCl}_2\{\text{P}^t\text{Bu}_2(\text{Ph-R})\}_2$ (A: R = *p*- CF_3 ; B: R = H; C: R = *p*- NMe_2) complexes. A toluene solution of di-tert-butyl phosphine (1.0 equiv.), aryl bromide (1.0 equiv.) and Pd_2dba_3 (1 mol %) was stirred at 90 °C for 12 h. The reaction was cooled to ambient temperature and filtered through a short silica gel plug. The silica gel plug was rinsed with toluene and the combined filtrate was concentrated under vacuum. The residue was dissolved in THF followed by the addition of solid $\text{PdCl}_2(\text{COD})$ (0.35 equiv.) and the reaction mixture was stirred at ambient temperature for 12 h. The reaction mixture was filtered, and the yellow solid was washed with pentane and dried under vacuum. Isolated yields of about 85 % of the desired complexes were typically observed.

$\text{PdCl}_2\{\text{P}^t\text{Bu}_2(\text{Ph-}p\text{-CF}_3)\}_2$ (A; MG-2): ^1H NMR (CDCl_3): δ 8.00 (s br, 4H, ArH), 7.59 (d, J = 7.9, 4H, ArH), 1.62 (t, J_{PH} = 7.0, 36H, ^tBu). ^{31}P NMR (CDCl_3): δ 55.7. ^{19}F NMR (CDCl_3): δ - 63.4. **Elemental Analysis:** Calc. C 54.07, H 7.45; Found C 53.87, H 7.59.

PdCl₂{P'Bu₂(Ph)}₂ (B): ¹H NMR (CD₂Cl₂): δ 7.9 – 7.8 (m, 4H, ArH), 7.36 – 7.30 (m, 6H, ArH), 1.56 (t, J_{PH} = 6.9, 36H, 'Bu). ³¹P NMR (CD₂Cl₂): δ 54.4.

PdCl₂{P'Bu₂(Ph-*p*-NMe₂)}₂ (C; MG-1): ¹H NMR (CDCl₃): δ 7.5 (s br, 4H, ArH), 6.42 (d, J = 8.3, 4H, ArH), 2.75 (s, 12H, NMe₂), 1.38 (t, J_{PH} = 6.6, 36H, 'Bu). ³¹P NMR (CDCl₃): δ 52.1.

General procedure for the Suzuki-Miyaura cross-coupling reactions. A mixture of arylhalide (0.5 mmol, 1.0 equiv.), arylboronic acid (0.6 mmol, 1.2 equiv.), K₂CO₃ (1.0 mmol, 2.0 equiv.) and catalyst (1 mol %) in toluene/water (2.5 mL/0.25 mL) solution was stirred at reflux for 12 h. The reaction was cooled to ambient temperature and extracted in ether (25 mL). The ether extract was washed with aqueous NaOH (1N, 10 mL, only entries 1 – 7), water (10 mL), brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated under vacuum. The crude material was purified by column chromatography on silica gel using hexanes and hexane/ethylacetate (1/4 and 1/1) as eluents. High TON experiments were stirred at reflux for 24 h. Anhydrous toluene was used as solvent for entry 12. K₃PO₄ base was used for entries 15 – 17.

2-(*o*-Tolyl)-3-pyridinamine (entry 1). This compound was isolated as a white solid (93 % yield) from the reaction of 2-chloro-3-pyridinamine and *o*-tolylboronic acid using the general procedure. ¹H NMR (CDCl₃): δ 8.08 (d, J = 4.5, 1H, ArH), 7.29-7.26 (m, 4H, ArH), 7.08-7.00 (m, 2H, ArH), 3.59 (s br, 2H, NH₂), 2.17 (s, 3H, ArCH₃). ¹³C NMR (CDCl₃): δ 146.0, 140.3, 139.2, 137.4, 136.7, 130.7, 129.1, 128.5, 126.3, 123.2, 121.9, 19.3.

2-(*p*-Tolyl)-3-pyridinamine (entry 2). This compound was isolated as a white solid (95 % yield) from the reaction of 2-chloro-3-pyridinamine and *p*-tolylboronic acid using the general procedure. ¹H NMR (CDCl₃): δ 8.1 (d/d, J = 4.1/1.8, 1H, ArH), 7.55 (d, J = 8.2, 2H, ArH), 7.26 (d, J = 7.8, 2H, ArH), 7.04 – 6.98 (m, 2H, ArH), 3.84 (s br, 2H, NH₂), 2.39 (s, 3H, ArCH₃). ¹³C NMR (CDCl₃): δ 145.1, 140.0, 139.9, 138.0, 135.7, 129.4, 128.3, 122.8, 122.6, 21.3.

2-{4-(Trifluoromethyl)phenyl}-3-pyridinamine (entry 3). This compound was isolated as a white solid (92 % yield) from the reaction of 2-chloro-3-pyridinamine and 4-(trifluoromethyl)phenylboronic acid using the general procedure. $^1\text{H NMR}$ (CDCl_3) δ : 8.12 (d/d, $J = 4.5/1.6$, 1H, ArH), 7.81 (d, $J = 8.0$, 2H, ArH), 7.71 (d, $J = 8.3$, 2H, ArH), 7.10 – 7.02 (m, 2H, ArH), 3.85 (s br, NH_2). $^{13}\text{C NMR}$ (CDCl_3) δ : 143.1, 142.3, 140.2, 130.1 (q, $J_{\text{CF}} = 32.5$, CF_3), 128.9, 125.7, 125.5, 123.8, 123.2, 122.8.

2-(4-Methoxyphenyl)-3-pyridinamine (entry 4). This compound was isolated as a white solid (93 % yield) from the reaction of 2-chloro-3-pyridinamine and 4-methoxyphenylboronic acid using the general procedure. $^1\text{H NMR}$ (CDCl_3): δ 8.08 (d/d, $J = 3.7/1.1$, 1H, ArH), 7.60 (d, $J = 8.4$, 2H, ArH), 7.01 – 6.96 (m, 4H, ArH), 3.85 (s br, 2H, NH_2 , partially overlap with OCH_3 signal), 3.82 (s, 3H, OCH_3). $^{13}\text{C NMR}$ (CDCl_3): δ 159.5, 144.8, 140.1, 139.8, 131.1, 129.8, 122.7, 122.6, 114.2, 55.4.

2-(4-Fluorophenyl)-4-pyridinamine (entry 5). This compound was isolated as a white solid (93 % yield) from the reaction of 2-chloro-4-pyridinamine and 4-fluorophenylboronic acid using the general procedure. $^1\text{H NMR}$ (CDCl_3): δ 7.46 – 7.42 (m, 2H, ArH), 7.14 – 7.10 (m, 2H, ArH), 6.97 – 6.92 (m, 3H, ArH), signal for NH_2 protons not observed. $^{13}\text{C NMR}$ (CDCl_3): δ 162.5, 160.0, 142.3, 129.6, 127.0, 126.54, 123.73, 122.1, 114.76 (d, $J_{\text{CF}} = 21.5$, ArF).

2-{4-(Trifluoromethyl)phenyl}-4-pyridinamine (entry 6). This compound was isolated as a white solid (90 % yield) from the reaction of 2-chloro-4-pyridinamine and 4-(trifluoromethyl)phenylboronic acid using the general procedure. $^1\text{H NMR}$ (CDCl_3): δ 8.31 (d, $J = 5.4$, 1H, ArH), 8.0 (d, $J = 8.2$, 2H, ArH), 7.67 (d, $J = 8.2$, ArH), 6.93 (s, 1H, ArH), 6.51 (d, $J = 5.5$, 2H, ArH), 4.39 (s br, 2H, NH_2). $^{13}\text{C NMR}$ (CDCl_3): δ 156.8, 153.7, 150.3, 143.2, 130.5 (q, $J_{\text{CF}} = 32.2$, CF_3), 127.2, 125.5, 122.9, 109.0, 106.9.

2-Mesityl-4-pyridinamine (entry 7). This compound was isolated as a white solid (98 % yield) from the reaction of 2-chloro-4-pyridinamine and 4-mesitylboronic acid using the

general procedure except 2 mol % catalyst was used. $^1\text{H NMR}$ (CDCl_3): δ 8.02 (d, J = 5.5, 1H, ArH), 6.75 (s, 2H, ArH), 6.23 (d, J = 5.4, 1H, ArH), 6.20 (s, 1H, ArH), 4.57 (s br, 2H, NH_2), 2.17 (s, 3H, p -Ar CH_3), 1.90 (s, 6H, o -Ar CH_3). $^{13}\text{C NMR}$ (CDCl_3): δ 159.0, 152.7, 148.4, 137.1, 135.9, 134.5, 127.0, 109.1, 106.8, 20.0, 18.9.

4-(4-Methoxyphenyl)-2-methylthiopyrimidine (entry 8). This compound was isolated as a white solid (95 % yield) from the reaction of 4-chloro-2-methylthiopyrimidine and 4-methoxyphenylboronic acid using the general procedure. $^1\text{H NMR}$ (CDCl_3): δ 8.45 (d, J = 5.3, 1H, ArH), 8.05 (d, J = 9.0, 2H, ArH), 7.26 (d, J = 5.8, 1H, ArH), 6.97 (d, J = 9.0, 2H, ArH), 3.85 (s, 3H, OCH_3), 2.62 (s, 3H, SCH_3). $^{13}\text{C NMR}$ (CDCl_3): δ 172.5, 163.3, 162.2, 157.4, 128.8, 128.7, 114.3, 111.0, 55.5, 14.2.

4-{2-(Methylthio)pyrimidin-4-yl}benzonitrile (entry 9). This compound was isolated as an off-white solid (94 % yield) from the reaction of 4-chloro-2-methylthiopyrimidine and 4-cyanophenylboronic acid using the general procedure. $^1\text{H NMR}$ (CDCl_3): δ 8.64 (d, J = 5.3, 1H, ArH), 8.20 (d, J = 8.6, 2H, ArH), 7.79 (d, J = 8.4, 2H, ArH), 7.40 (d, J = 5.3, 1H, ArH), 2.65 (s, 3H, SCH_3). $^{13}\text{C NMR}$ (CDCl_3): δ 173.5, 161.8, 158.3, 140.5, 132.7, 127.8, 118.4, 114.5, 112.2, 14.3.

4-(2,6-Dimethylphenyl)-2-(methylthio)pyrimidine (entry 10). This compound was isolated as a colorless oil (99 % yield) from the reaction of 4-chloro-2-methylthiopyrimidine and 2,6-dimethylphenylboronic acid using the general procedure except 0.1 mol % catalyst was used. $^1\text{H NMR}$ (CDCl_3): δ 8.47 (d, J = 4.9, 1H, ArH), 7.12 (t, J = 7.6, 1H, p -ArH), 7.01 (d, J = 7.5, 2H, m -ArH), 6.80 (d, J = 5.0, 1H, ArH), 2.47 (s, 3H, SCH_3), 2.01 (s, 6H, Ar CH_3). $^{13}\text{C NMR}$ (CDCl_3): δ 171.9, 166.8, 156.1, 136.9, 134.2, 127.6, 126.8, 116.1, 19.2, 13.1.

2,4-Dimethoxy-6-(4-methoxyphenyl)pyrimidine (entry 11). This compound was isolated as an off-white solid (98 % yield) from the reaction of 4-chloro-2,6-dimethoxypyrimidine and 4-methoxyphenylboronic acid using the general procedure except 0.1 mol % catalyst was used. $^1\text{H NMR}$ (CDCl_3): δ 8.02 (d, J = 8.6, 2H, ArH),

6.97 (d, $J = 8.6$, 2H, ArH), 6.7 (s, 1H, ArH), 4.07 (s, 3H, OCH₃), 3.99 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃). ¹³C NMR (CDCl₃): δ 172.5, 165.6, 165.4, 161.7, 129.3, 128.6, 114.0, 95.9, 55.4, 54.7, 53.9.

2-(4-Methoxyphenyl)-6-methylpyrimidine-4-carboxylate (entry 12). This compound was isolated as an off-white solid (89 % yield) from the reaction of 2-chloro-6-methylpyrimidine-4-carboxylate and 4-methoxyphenylboronic acid using the general procedure except 0.01 mol % catalyst were used. ¹H NMR (CDCl₃): δ 8.47 (d, $J = 8.8$, 2H, ArH), 7.63 (s, 1H, ArH), 6.98 (d, $J = 8.6$, 2H, ArH), 4.02 (s, 3H, COOCH₃), 3.86 (s, 3H, OCH₃), 2.63 (s, 3H, ArCH₃). ¹³C NMR (CDCl₃): δ 169.5, 165.5, 164.8, 162.1, 154.9, 130.2, 129.8, 127.7, 117.3, 113.9, 55.4, 53.1, 24.6.

3-Methoxy-6-(4-methoxyphenyl)pyridazine (entry 13). This compound was isolated as a white solid (97 % yield) from the reaction of 3-chloro-6-methoxypyridazine and 4-methoxyphenylboronic acid using the general procedure. ¹H NMR (CDCl₃): δ 7.96 (d, $J = 8.8$, 2H, ArH), 7.72 (d, $J = 9.2$, 1H, ArH), 7.27 – 6.99 (m, 3H, ArH), 4.17 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃). ¹³C NMR (CDCl₃): δ 164.0, 160.8, 154.9, 128.8, 127.8, 126.6, 117.7, 114.4, 55.4, 54.8.

2-(*p*-Tolyl)thiophene (entry 14). This compound was isolated as a white solid (96 % yield) from the reaction of 2-chlorothiophene and *p*-tolylboronic acid using the general procedure. ¹H NMR (CDCl₃): δ 7.48 (d, $J = 8.2$, 2H, ArH), 7.24 (d, $J = 3.5$, 1H, ArH), 7.2 (d, $J = 5$, 1H, ArH), 7.15 (d, $J = 7.9$, 2H, ArH), 7.03 (d/d, $J = 5.1/3.6$, 1H, ArH), 2.33 (s, 3H, ArCH₃). ¹³C NMR (CDCl₃): δ 144.6, 137.3, 131.6, 129.5, 127.9, 125.8, 124.2, 122.6, 21.2.

4-(4-methoxyphenyl)-1,3,5-trimethylpyrazole (entry 15). This compound was isolated as a white solid (93 % yield) from the reaction of 4-bromo-1,3,5-trimethylpyrazole and 4-methoxyphenylboronic acid using the general procedure. ¹H NMR (CDCl₃): δ 7.15 (d, $J = 8.6$, 2H, ArH), 6.94 ($J = 8.6$, 2H, ArH), 3.82 (s, 3H, CH₃), 3.76 (s, 3H, CH₃), 2.22 (s,

3H, ArCH₃), 2.20 (s, 3H, ArCH₃). ¹³C NMR (CDCl₃): δ 158.1, 145.0, 136.0, 130.5, 126.6, 118.8, 113.9, 55.3, 36.0, 12.4, 10.2.

4-(4-Fluorophenyl)-1,3,5-trimethylpyrazole (entry 16). This compound was isolated as a white solid (95 % yield) from the reaction of 4-bromo-1,3,5-trimethylpyrazole and 4-fluorophenylboronic acid using the general procedure. ¹H NMR (CDCl₃): δ 7.10 (d/d, J = 8.8, 5.7, 2H, ArH), 6.99 (t, J = 8.8, 2H, ArH), 3.69 (s, 3H, NCH₃), 2.13 (s, 3H, ArCH₃), 2.12 (s, 3H, ArCH₃). ¹³C NMR (CDCl₃): δ 161.7, 159.2, 143.9, 135.1, 130.0, 129.9, 114.27 (d, J_{CF} = 20.7, ArF), 35.0, 11.3, 9.13. ¹⁹F NMR (CDCl₃): δ -116.

2-(*p*-Tolyl)benzonitrile (entry 17). This compound was isolated as white needle crystals (94 % yield) from the reaction of 2-chlorobenzonitrile and *p*-tolylphenylboronic acid using the general procedure, except 0.01 mol % catalyst was used. ¹H NMR (CDCl₃): δ 7.23 (d, J = 7.8, 1H, ArH), 7.58 (t, J = 7.4, 1H, ArH), 7.49 – 7.37 (m, 4H, ArH), 7.28 (d, J = 8.1, 2H, ArH), 2.40 (s, 3H, ArCH₃). ¹³C NMR (CDCl₃): δ 145.6, 138.7, 135.3, 133.8, 132.8, 130.0, 129.5, 128.7, 127.3, 118.9, 111.2, 21.3.

2-(*p*-Tolyl)-5-fluoroanisole (entry 18). This compound was generated by the reaction of 2-chloro-5-fluoroanisole and *p*-tolylboronic acid using the general procedure. GC-MS yield was reported.

$\text{PdCl}_2\{\text{P}^t\text{Bu}_2\text{P}(\text{Ph}-p\text{-CF}_3)_2\}_2$, ^1H NMR (CDCl_3).

$\text{PdCl}_2\{\text{P}^i\text{Bu}_2\text{P}(\text{Ph-}p\text{-CF}_3)_2\}_2$, ^{31}P NMR (CDCl_3).

$\text{PdCl}_2\{\text{P}^i\text{Bu}_2\text{P}(\text{Ph}-p\text{-CF}_3)_2\}$, ^{19}F NMR (CDCl_3).

$\text{PdCl}_2\{\text{P}^t\text{Bu}_2\text{P}(\text{Ph})_2\}$, $^1\text{H NMR}$ (CD_2Cl_2).

$\text{PdCl}_2\{\text{P}^t\text{Bu}_2\text{P}(\text{Ph})_2\}$, ^{31}P NMR (CD_2Cl_2).

$\text{PdCl}_2\{\text{P}^t\text{Bu}_2\text{P}(\text{Ph}-p\text{-NMe}_2)_2\}_2$, ^1H NMR (CDCl_3).

$\text{PdCl}_2\{\text{P}'\text{Bu}_2\text{P}(\text{Ph}-p\text{-NMe}_2)_2\}_2$, ^{31}P NMR (CDCl_3).

Table 1, entry 1, ^1H NMR (CDCl_3).

Table 1, entry 1, ^{13}C NMR (CDCl_3).

Table 1, entry 2, ^1H NMR (CDCl_3).

Table 1, entry 2, ^{13}C NMR (CDCl_3).

Table 1, entry 3, ^1H NMR (CDCl_3).

Table 1, entry 3, ^{13}C NMR (CDCl_3).

Table 1, entry 4, ^1H NMR (CDCl_3).

Table 1, entry 4, ^{13}C NMR (CDCl_3).

Table 1, entry 5, ^1H NMR (CDCl_3).

Table 1, entry 5, ^{13}C NMR (CDCl_3).

Table 1, entry 6, ^1H NMR (CDCl_3).

Table 1, entry 6, ^{13}C NMR (CDCl_3).

Table 1, entry 7, ^1H NMR (CDCl_3).

Table 1, entry 7, ^{13}C NMR (CDCl_3).

Table 1, entry 8, ^1H NMR (CDCl_3).

Table 1, entry 8, ^{13}C NMR (CDCl_3).

Table 1, entry 9, ^1H NMR (CDCl_3).

Table 1, entry 9, ^{13}C NMR (CDCl_3).

Table 1, entry 10, ^1H NMR (CDCl_3).

Table 1, entry 10, ^{13}C NMR (CDCl_3).

Table 1, entry 11, ^1H NMR (CDCl_3).

Table 1, entry 11, ^{13}C NMR (CDCl_3).

Table 1, entry 12, ^1H NMR (CDCl_3).

Table 1, entry 13, ^1H NMR (CDCl_3).

Table 1, entry 13, ^{13}C NMR (CDCl_3).

Table 1, entry 14, ^1H NMR (CDCl_3).

Table 1, entry 14, ^{13}C NMR (CDCl_3).

Table 1, entry 15, ^1H NMR (CDCl_3).

Table 1, entry 15, ^{13}C NMR (CDCl_3).

Table 1, entry 16, ^1H NMR (CDCl_3).

Table 1, entry 16, ^{13}C NMR (CDCl_3).

Table 1, entry 16, ^{19}F NMR (CDCl_3).

Table 1, entry 17, ^1H NMR (CDCl_3).

Table 1, entry 17, ^{13}C NMR (CDCl_3).