An Air Stable and Thermally Stable One Component Precatalyst for the Amination of Aryl Chlorides

Danilo Zim and Stephen L. Buchwald*

Contribution from the Department of Chemistry, Massachusetts Institute of Technology,
Cambridge, Massachusetts 02139

Supporting Information

General Considerations. All reactions were carried out under an argon atmosphere, in oven-dried Schlenk flasks. Elemental analyses were performed by Atlantic Microlabs Inc. Anhydrous toluene was purchased from Aldrich Chemical Co. in Sure/Seal[®] bottles and was used without further purification. Aryl halides were purchased from commercial sources and were used without further purification. Amines were purchased from commercial sources and were distilled (if liquid at room temperature) before use. 2-(Di-*t*-butylphosphino)biphenyl was purchased from Strem Chemical Company. Palladium acetate was purchased from Alfa Aesar. Sodium *tert*-butoxide and sodium methoxide were purchased from Aldrich Chemical Co.; the bulk of these materials were stored under nitrogen in a Vacuum Atmospheres glovebox. Small portions (1-2 g) were removed from the glovebox in glass vials, stored in the air in desiccators filled with anhydrous calcium sulfate, and weighed in the air. Potassium hydroxide was purchased from Mallinckrodt Baker Inc. and powdered in the air immediately prior to use. Yields in Table 1 refer to isolated yields (average of two runs) of compounds estimated to be $\geq 95\%$ pure as determined by ¹H NMR and GC analysis. Gas chromatographic analysis was performed on a Hewlett-Packard 6890 Series with an FID detector and 25 m x 0.11 mm i.d. HP-1 capillary column. NMR spectra were recorded on a Varian Mercury 300 or Varian Inova-501 (¹³C NMR of the palladacycle **1**). The chemical shifts (δ) for ¹H and ¹³C are given in ppm relative to residual signals of the solvent and external 85% H₃PO₄ for ³¹P. Mass spectra were obtained on a Hewlett-Packard G 1800B. Compounds described in the literature were characterized by comparing their melting points and ¹H NMR spectra to the previously reported

data. The procedures described here are representative, thus the yields may differ from those given in Table 1.

Synthesis of palladacycle 2: A 25 mL round bottom flask adapted with a Schlenk type fitting was charged with Pd(OAc)₂ (314 mg, 1.4 mmol) and 2-(di-*t*-butylphosphino)biphenyl (418 mg, 1.4 mmol). The flask was evacuated, backfilled with argon and then toluene (10 mL) was added. The mixture was stirred at room temperature for 16 h. The clear yellow solution was filtered through a column of basic alumina (2 g) and then the solvent was removed under vacuum. Pentane (5 mL) was added and completely removed under vacuum (3 x 5 ml) to facilitate the precipitation of the complex (this was repeated a total of three times). The resulting yellow powder was dried under vacuum for 12 hours to afford 608 mg (94% yield) of the complex. ¹H NMR (300 MHz, CDCl₃) δ 7.92 (td, 1H, J = 7.7 Hz, 2.1 Hz), 7.81 (m, 2H), 7.51 (app tt, 1H), 7.25-7.32 (m, 3H), 7.01-7.11 (m, 3H), 2.06 (s, 3H), 1.39 (s, 9H), 1.34 (s, 9H); ¹³C {¹H} NMR (75 MHz, CDCl₃) δ 187.3, 151.2 (d, J_{PC} = 9.6 Hz), 138.7 (d, J_{PC} = 8.3 Hz), 136.8 (d, J_{PC} = 3.5 Hz), 134.2, 131.7 (d, J_{PC} = 1.4 Hz), 130.8 (d, J_{PC} = 1.4 Hz), 128.7 (d, J_{PC} = 5.5 Hz), 127.9, 127.6 (d, J_{PC} = 1 Hz), 126.1, 125.9 (d, J_{PC} = 4.1 Hz), 120.8 (d, J_{PC} = 50.3 Hz), 38.3 (d, J_{PC} = 12.1 Hz), 30.7 (d, J_{PC} = 2.4 Hz), 23.9. Anal. Calcd for C₂₂H₂₉O₂PPd: C, 57.09; H, 6.32. Found: C, 56.80; H, 6.30.

Amination of Aryl Chlorides:

Method A: An oven-dried resealable Schlenk flask was charged with **2** (2.3-9.2 mg, 0.005-0.02 mmol) and NaOt-Bu (134 mg, 1.4 mmol). The flask was evacuated, backfilled with argon and then, to it, were added the aryl chloride (1 mmol), toluene (1 mL) and the amine (1.2 mmol). The flask was sealed with a Teflon screwcap and the mixture was stirred at 80 °C. After all starting material had been consumed, as judged by GC, the mixture was allowed to cool to room temperature and then was diluted with ether (40 mL). The resulting suspension was transferred to a separatory funnel and washed with water (10 mL). The organic layer was separated, dried with MgSO₄ and concentrated under vacuum. The crude material was purified by flash chromatography on silica gel with hexane/ethyl acetate.

Method B: An oven-dried resealable Schlenk flask was charged with **2** (4.6 mg, 0.01 mmol), (di-*t*-butylphosphino)biphenyl (3.0 mg, 0.01 mmol) and KOH (86 mg, 1.5 mmol). The flask was evacuated, backfilled with argon and then, to it, were added the aryl chloride (1 mmol), toluene (1 mL) and the amine (1.2 mmol). The flask was sealed with a Teflon screwcap and the mixture was stirred at 90 °C for 20 hours. After all starting material had been consumed, as judged by GC, the mixture was allowed to cool to room temperature and then was diluted with ether (40 mL). The resulting suspension was transferred to a separatory funnel and washed with water (10 mL). The organic layer was separated, dried with MgSO₄ and concentrated under vacuum. The crude material was purified by flash chromatography on silica gel with hexane/ethyl acetate.

Method C: An oven-dried resealable Schlenk flask was charged with palladium complex **2** (4.6 mg, 1 mmol) and NaOMe (76 mg, 1.4 mmol). The flask was evacuated, backfilled with argon and then, to it, were added the aryl chloride (1 mmol), triethylamine (70 μ L, 0.5 mmol), toluene (1 mL) and the amine (1.2 mmol) (aryl chlorides and amines that were solids at room temperature were weighed and added to the flask following the addition of **2**). The flask was sealed with a Teflon screwcap and the mixture was stirred at 60 °C. After all starting material had been consumed, as judged by GC, the mixture was allowed to cool to room temperature and then was diluted with ether (40 mL). The resulting suspension was transferred to a separatory funnel and washed with water (10 mL). The organic layer was separated, dried with MgSO₄ and concentrated under vacuum. The crude material was purified by flash chromatography on silica gel with hexane/ethyl acetate.

***N*-(4-methylphenyl)morpholine.**¹ (Entry 1) The coupling of morpholine and 4-chlorotoluene was effected using method A to afford 173 mg (98% yield) of the title compound as a white solid (mp 48-49 °C, lit 49.8-50.4 °C). ¹H NMR (300 MHz, CDCl₃) δ 7.08 (d, 2H, J = 8.7 Hz), 6.82 (d, 2H, J = 8.7 Hz), 3.85 (m, 4H), 3.10 (m, 4H), 2.27 (s, 3H).

***N*-(4-methylphenyl)morpholine.**¹ (Entry 2) The coupling of morpholine and 4-chlorotoluene was effected using method B, slightly modified so that Pd(OAc)₂ (2.2 mg, 0.01 mmol) and 2-(di-*t*-butylphosphino)biphenyl (6.0 mg, 0.02 mmol) were used instead **2**, to afford 173 mg (97% yield) of the title compound as a white solid.

***N*-(3-methoxyphenyl)pyrrolidine.**² (Entry 3) The coupling of pyrrolidine and 3-chloroanisole was effected using method A to afford 175 mg (99% yield) of the title compound as a pale yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 7.09 (t, 1H, J = 8.0 Hz), 6.21 (dd, 1H, J = 8.0, 2.0 Hz), 6.16 (dd, 1H, J = 8.0, 2.0 Hz), 6.09 (t, 1H, J = 2.0 Hz), 3.75 (s, 3H), 3.21-3.24 (m, 4H), 1.92-1.96 (m, 4H).

***N*-(2-methoxyphenyl)morpholine.**³ (Entry 4) The coupling of morpholine and 2-chloroanisole was effected using method A to afford 178 mg (92% yield) of the title compound as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.87-7.04 (m, 4H), 3.87 (s, 3H), 3.86-3.91 (m, 4H), 3.07-3.08 (m, 4H).

***N*-methyl-*N*-phenyl-2,5-xylidene.**⁴ (Entry 5) The coupling of *N*-methylaniline and 2-chloro-*p*-xylene was effected using method A to afford 205 mg (97% yield) of the title compound as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.14-7.19 (m, 3H), 6.95-7.01 (m, 2H), 6.67-6.72 (m, 1H), 6.51-6.54 (m, 2H), 3.20 (s, 3H), 2.30 (s, 3H), 2.09 (s, 3H).

***N*-(2,6-dimethylphenyl)-*n*-hexylamine.**⁵ (Entry 6) The coupling of *n*-hexylamine and 2-chloro-*m*-xylene was effected using method A, slightly modified so that the reaction was carried out at 120 °C, to afford 196 mg (96% yield) of the title compound as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 6.98 (d, 2H, J = 7.5 Hz), 6.79 (t, 1H, J = 7.5 Hz), 2.97 (t, 2H, J = 7.2 Hz), 2.94-2.99 (b, 1H), 2.28 (s, 6H), 1.52-1.60 (m, 2H), 1.28-1.41 (m, 6H), 0.89 (t, 3H, J = 6.8 Hz).

***N*-(4-*n*-butylphenyl)aniline.**⁶ (Entry 7) The coupling of aniline and 4-*n*-butylbenzene was effected using method A, slightly modified so that Et₃N (70 μ L, 0.5 mmol) was added into the Schlenk flask following the addition of toluene, to afford 165 mg (93% yield) of the title compound as a pale brown oil. ¹H NMR (300 MHz, CDCl₃) δ 7.18-7.24 (m, 2H), 6.97-7.08 (m, 6H), 6.83-6.88 (m, 1H), 5.54 (b, 1H), 2.54 (t, 2H, J = 7.5 Hz), 1.57 (m, 2H), 1.35 (m, 2H), 0.93 (t, 3H, J = 7.3 Hz).

***N*-(2,6-dimethylphenyl)benzylamine.**⁷ (Entry 8) The coupling of benzylamine and 2-chloro-*m*-xylene was effected using method A, slightly modified so that the reaction was carried out at 120 °C, to afford 208 mg (99% yield) of the title compound as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.26-7.40 (m, 5H), 7.01 (d, 2H, J = 7.3 Hz), 6.85 (t, 1H, J = 7.8 Hz), 4.11 (s, 2H), 3.21 (b, 1H), 2.07 (s, 6H).

***N*-(2-methoxyphenyl)benzylamine.**⁸ (Entry 9) The coupling of benzylamine and 2-chloroanisole was effected using method B to afford 203 mg (95% yield) of the title compound as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.20 (m, 5H), 6.86-6.76 (m, 2H), 6.70-6.57 (m, 2H), 4.66 (b, 1H), 4.35 (s, 2H), 3.84 (s, 3H).

***N*-(4-methoxyphenyl)pyrrolidine.**⁹ (Entry 10) The coupling of pyrrolidine and 4-chloroanisole was effected using method B to afford 165 mg (93% yield) of the title compound as a white solid (mp 41-42 °C, lit 40-41 °C). ¹H NMR (300 MHz, CDCl₃) δ 6.84 (d, 2H, J = 9.1 Hz), 6.53 (d, 2H, J = 9.0 Hz), 3.76 (s, 3H), 3.20-3.28 (m, 4H), 1.9-2.02 (m, 4H).

***N*-isobutyl-4-methylaniline.**¹⁰ (Entry 11) The coupling of isobutylamine and 4-chlorotoluene was effected using method B, slightly modified so that 3 mmol of amine was used, to afford 148 mg (91% yield) of the title compound as a pale yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 7.05 (d, 2H, J = 8.0 Hz), 6.67 (d, 2H, J = 8.0 Hz), 3.63 (b, 1H), 2.97 (d, 2H, J = 6.9 Hz), 2.03 (s, 3H), 1.97 (m, 1H), 1.04 (d, 6H, J = 6.7 Hz).

***N*-(3-carbomethoxyphenyl)morpholine.**¹¹ (Entry 12) The coupling of morpholine and 3-carbomethoxychlorobenzene was effected using method C, slightly modified so that the reaction was carried out at room temperature and Et₃N was not added, to afford 148 mg (81% yield) of the title compound as a pale yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 7.56-7.60 (m, 2H), 7.33 (t, 1H, J = 8.1 Hz), 7.09 (dd, 1H, J = 7.5 Hz, 1.8 Hz), 3.91 (s, 3H), 3.87 (t, 4H, J = 4.5 Hz), 3.21 (t, 4H, J = 5.1 Hz).

***N*-(2-nitrophenyl)morpholine.**¹² (Entry 13) The coupling of morpholine and 3-chloronitrobenzene was effected using method C to afford 158 mg (76% yield) of the title compound as a yellow solid (mp 104-105 °C, lit 106.5 °C). ¹H NMR (300 MHz, CDCl₃) δ 7.65-7.75 (m, 2H), 7.37 (t, 1H, J = 8.0 Hz), 7.10-7.15 (m, 1H), 3.85-3.89 (m, 4H), 3.18-3.25 (m, 4H).

***N*-(3-cyanophenyl)morpholine.**¹³ (Entry 14) The coupling of morpholine and 3-chlorobenzonitrile was effected using method C to afford 152 mg (81% yield) of the title compound as a white solid

(mp 101-102 °C, lit 102-103 °C). ¹H NMR (300 MHz, CDCl₃) δ 7.25-7.35 (m, 1H), 7.08-7.12 (m, 3H), 3.84-3.87 (m, 4H), 3.16-3.19 (m, 4H).

***N*-(3-carbomethoxyphenyl)-4-methylaniline.** (Entry 15) The coupling of 3-carbomethoxyaniline and 4-chlorotoluene was effected using method C to afford 217 mg (90% yield) of the title compound as a white solid (mp 43-44 °C). ¹H NMR (300 MHz, CDCl₃) δ 7.67 (s, 1H), 7.36 (d, 1H, *J* = 7.8 Hz), 7.31 (d, 1H, *J* = 7.5 Hz), 7.17-7.27 (m, 3H), 7.03 (d, 2H, *J* = 8.4 Hz), 5.75 (b, 1H), 3.91 (s, 3H), 2.35 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 167.3, 144.5, 139.6, 131.9, 131.4, 130.2, 129.5, 121.3, 120.7, 119.7, 117.4, 52.5, 21.2; GC-MS (IE, 70 eV) *m/z* (%) 241 (100, M⁺), 167 (29), 240 (20), 180 (20), 91 (18), 91 (15), 182 (17), 242 (14). Anal. Calcd for C₁₅H₁₅NO₂: C, 74.69; H, 6.22; N, 5.81. Found: C, 74.71; H, 6.15; N, 5.72.

¹ Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.

² Desmarets, C.; Schneider, R.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 3029.

³ Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560.

⁴ Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.

⁵ Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.

⁶ Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268.

⁷ Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144.

⁸ Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

⁹ Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264.

¹⁰ Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268.

¹¹ Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144.

¹² Hurst, D. T. *Heterocycles* **1988**, *27*, 371.

¹³ Belfield, A. J.; Brown, G. R.; Foubister, A. J.; Ratcliffe, P. D. *Tetrahedron* **1999**, *55*, 13285.