Amination Reactions of Aryl Halides with Nitrogen-Containing Reagents Mediated by Palladium/Imidazolium Salt Systems

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Supporting Information

- **General Considerations.** All aryl halides (Aldrich), amines and indoles were used as received. 1,4-Dioxane and toluene (anhydrous, Aldrich) were distilled under argon from sodium benzenophene ketyl. Potassium t-butoxide, potassium phosphate and sodium hydroxyde (Aldrich) were stored under argon in a MBraun glovebox or in desiccators over anhydrous calcium carbonate. (Tris-(dibenzylideneacetone) dipalladium(0), bis-(dibenzylideneacetone)palladium(0) and palladium acetate were purchased from Strem Chemical Company. Flash chromatography was performed on silica gel 60 (230-400 mesh) (Natland International corporation) using hexanes or hexanes:ethyl acetate=15:1.

- The imidazolium salts: IPrHCl (1, 1,3-Bis(2,6-diisopropylphenyl)imidazolium chloride, IMesHCl (2, 1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride), IXyHCl (3, 1,3-Bis(2, 6-dimethylphenyl)imidazolium, ITolHCl (4, 1,3-Bis(tolyl)imidazolium chloride) were prepared according to reported procedures: (a) Arduengo, A. J. III. US patent 5,077,414, 1991; (b) Arduengo, A. J. III., Dias, H. V. R.; Harlow, R. L. and Kline, M. J. Am. Chem. Soc. 1992, 114, 5530-5534. (c) Huang, J. Nolan, S. P. J. Am. Chem. Soc, 1999, 120, 9889-9890.

- $^1$H and $^{13}$C nuclear magnetic resonance spectra were recorded on a Varian-300 or Varian-400 MHz spectrometer at ambient temperature in CDCl$_3$ (Cambridge Isotope
Laboratories, Inc.). Elemental analyses were performed by Desert Analysis, Tucson, AZ.

- All reactions were carried out under an atmosphere of argon in oven-dried-glassware or in screw cap vials with magnetic stirring, unless otherwise indicated.
- All yields reported in Tables 1-10 are isolated yields and are the average of two runs.

**Synthesis of Dihydroimidazolium Chlorides.** Anilines (mesitylamine 0.4 mol 5.4 g) (Aldrich) were reacted in methanol with glyoxal (0.2 mol, 40 percent aqueous solution, Aldrich) at room temperature in the presence of a few drops of formic acid. After stirring for 3 hours, the precipitated yellow product, a diazabutadiene, was filtered and washed with methanol and dried in vacuum (yield 92%). Hydrogenation of diazabutadiene (0.01mol 3.92g) was performed in MeOH/THF (40/60) mixture in the presence of NaBH₄ (0.1 mol, 3.78g). After 1.5 hour the solution turned white. A saturated aqueous solution of NH₂Cl was used to quench the reaction. The diamine was extracted 3 times with ether and washed with deionized water. Ether extracts were dried over MgSO₄ and evaporated under reduced pressure to afford the substituted diamine (97%, 3.6g). One equivalent of diamine, 1.1 equivalent of NH₂Cl and 2.5 equivalent of triethyl orthoformate were stirred together at 110°C under argon flow (to drive EtOH from the reaction). After 1.5 hour the reaction mixture turns to a solid. The solid was dissolved in a minimum amount of CHCl₃ and reprecipitated with ether. The 'H NMR of the product was comparable with previously reported spectroscopic data for the desired product. The desired product was obtained in > 85% yield in this manner. Similar experimental methods were used for SIPr·HCl.

**Aminations of Aryl Halides with Amines. General procedure:** Under an atmosphere of argon 1,4-dioxane (3 mL), KO'Bu (168 mg, 1.5 mmol), aryl halide (1.0 mmol), amine (1.2 mmol) were added in turn to a Schlenk tube charged with Pd₃(dba)₃ (10 mg, 0.01 mmol), 1 (17 mg, 0.04 mmol or 8mg, 0.02 mmol), and a magnetic stirring bar. The Schlenk tube was placed in a 100 °C oil bath and stirred for 3-30 h. The mixture was then allowed to cool to room temperature. The mixture was diluted with water then extracted with diethyl ether. The extracts were combined, washed with saturated saline
solution, and then dried over MgSO₄. The solvent was removed under vacuum and residue was purified by flash chromatography (hexane or hexane/ethyl acetate).

**Workup Method B.** The reaction mixture was allowed to cool to room temperature and absorbed directly on silicagel column.

**N-Methyl-N-phenyl-p-toluidine (Table 2, entry 1).** The general procedure using 1.0 mol % Pd₂(dba)₃ and 4.0 mol % of 1 afforded 195 mg (99 %) of the title compound.

**1-(4-methylphenyl)piperidine (Table 2, entry 2).** The general procedure using 1.0 mol % Pd₂(dba)₃ and 4.0 mol % of 1 afforded 168 mg (96 %) of the title compound.

**1-(4-tolylphenyl)piperidine (Table 2, entry 3).** The general procedure using 1.0 mol % Pd₂(dba)₃ and 4.0 mol % of 1 afforded 152 mg (86 %) of the title compound.

**1-(4-methylphenyl)morpholine (Table 2, entry 4).** The general procedure using 1.0 mol % Pd₂(dba)₃ and 4.0 mol % of 1 afforded 145 mg (82 %) of the title compound.

**N,N-Dibutyl-p-toluidine (Table 2, entry 5).** The general procedure using 1.0 mol % Pd₂(dba)₃ and 4.0 mol % of 1 afforded 208 mg (95 %) of the title compound.

**N-Hexyl-p-toluidine (Table 2, entry 6)** The general procedure using 1.0 mol % Pd₂(dba)₃ and 4.0 mol % of 1 afforded 155 mg (86 %) of the title compound.

**N-Phenyl-p-toluidine (Table 2, entry 7).** The general procedure using 1.0 mol % Pd₂(dba)₃ and 4.0 mol % of 1 afforded 176 mg (96 %) of the title compound.

**2,4,6-trimethyl-N-(4-Methylphenyl)-benzenamine (Table 2, entry 8).** The general procedure using 1.0 mol % Pd₂(dba)₃ and 4.0 mol % of 1 afforded 154 mg (59 %) of the title compound.

**2,6-diisopropyl-N-(4-Methylphenyl)-benzenamine (Table 2, entry 9).** The general procedure using 1.0 mol % Pd₂(dba)₃ and 2.0 mol % of 1 afforded 239 mg (90 %) of the title compound.

**N-Phenyl-N-methyl-p-anisidine (Table 2, entry 10).** The general procedure using 1.0 mol % Pd₂(dba)₃ and 4.0 mol % of 1 afforded 194 mg (91 %) of the title compound.

**N-Phenyl-p-anisidine (Table 2, entry 11).** The general procedure using 1.0 mol % Pd₂(dba)₃ and 4.0 mol % of 1 afforded 181 mg (91 %) of the title compound.

**4-Methoxyphenylmorpholine (Table 2, entry 12).** The general procedure using 1.0 mol % Pd₂(dba)₃ and 4.0 mol % of 1 afforded 154 mg (80 %) of the title compound.
N,N-Dibutyl-\(p\)-anisidine (Table 2, entry 13).\(^7\) The general procedure using 1.0 mol % Pd\(_2\)(dba)\(_3\) and 4.0 mol % of \(1\) afforded 230 mg (98%) of the title compound.

N-Methyl-N-phenyl-2,5-dimethylbenzenamine (Table 2, entry 14).\(^7\) The general procedure using 1.0 mol % Pd\(_2\)(dba)\(_3\) and 4.0 mol % of \(1\) afforded 198 mg (94%) of the title compound.

N-Methyl-N-phenyl-\(p\)-toluidine (Table 4, entry 2).\(^1\) The general procedure using 1.0 mol % Pd\(_2\)(dba)\(_3\) and 2.0 mol % of \(1\) afforded 189 mg (96%) of the title compound.

N-Phenyl-\(p\)-toluidine (Table 4, entry 4).\(^2\) The general procedure using 1.0 mol % Pd\(_2\)(dba)\(_3\) and 2.0 mol % of \(1\) afforded 167 mg (92%) of the title compound.

N,N-Dibutyl-\(p\)-toluidine (Table 4, entry 6).\(^4\) The general procedure using 1.0 mol % Pd\(_2\)(dba)\(_3\) and 4.0 mol % of \(1\) afforded 197 mg (90%) of the title compound.

Amination of Aryl Bromides with Various Amines. General procedure: Under an atmosphere of argon 1,4-dioxane (3 mL), KO\(\text{\textprime}Bu\) (168 mg, 1.5 mmol), aryl halide (1.0 mmol), amine (1.2 mmol) were added in turn to a Schlenk tube charged with Pd\(_2\)(dba)\(_3\) (10 mg, 0.01 mmol), \(1\) (17 mg, 0.04 mmol or 8 mg, 0.02 mmol), and a magnetic stirring bar. The reaction mixture was stirred at room temperature for 3-30 h. The mixture was diluted with water then extracted with diethyl ether. The extracts were combined, washed with saturated saline solution, and then dried over MgSO\(_4\). The solvent was removed under vacuum and residue was purified by flash chromatography (hexane or hexane/ethyl acetate).

N-Methyl-N-phenyl-\(p\)-toluidine (Table 3, entry 1).\(^1\) The general procedure using 1.0 mol % Pd\(_2\)(dba)\(_3\) and 4.0 mol % of \(1\) afforded 175 mg (89%) of the title compound.

1-(4-methylphenyl)piperidine (Table 3, entry 2).\(^2\) The general procedure using 1.0 mol % Pd\(_2\)(dba)\(_3\) and 4.0 mol % of \(1\) afforded 145 mg (83%) of the title compound.

1-(4-Chlorophenyl)piperidine (Table 3, entry 3).\(^3\) The general procedure using 1.0 mol % Pd\(_2\)(dba)\(_3\) and 4.0 mol % of \(1\) afforded 183 mg (94%) of the title compound.

1-(4-Chlorophenyl)piperidine (Table 3, entry 4).\(^3\) The general procedure using 1.0 mol % Pd\(_2\)(dba)\(_3\) and 4.0 mol % of \(1\) afforded 189 mg (97%) of the title compound.
Aminations of Chloropyridines and Bromopyridines with Amines. General procedure: 1,4-dioxane (3 mL), KO'Bu (168 mg, 1.5 mmol), Pd(dba)$_2$ (10.9 mg, 0.02 mmol), 1 (8mg, 0.02 mmol) (1L/Pd) were loaded in the dry box in a screw cap vial with liner. The halopyridine (1.0 mmol) and amine (1.1 mmol) were added in turn to the vial via micro syringe. The vial was placed in a 100 °C oil bath and stirred for 3 h. The mixture was then allowed to cool to room temperature. The mixture was diluted with water then extracted with diethyl ether. The extracts were combined, washed with saturated saline solution, and then dried over MgSO$_4$. The solvent was removed under vacuum and residue was purified by flash chromatography (hexane or hexane/ethyl acetate).

Workup Method B. The reaction mixture was allowed to cool to room temperature and absorbed directly on silicagel column.

N-(2-Pyridyl)morpholine (Table 5, entry 1). The general procedure using 2.0 mol % Pd(dba)$_2$ and 2.0 mol % of 1 afforded 162 mg (99 %) of the title compound.

N-Methyl-N-(2-Pyridyl)aniline (Table 5, entry 2). The general procedure using 2.0 mol % Pd(dba)$_2$ and 2.0 mol % of 1 afforded 178 mg (97 %) of the title compound.

N-(2-Pyridyl)aniline (Table 5, entry 3). The general procedure using 2.0 mol % Pd(dba)$_2$ and 2.0 mol % of 1 afforded 144 mg (88 %) of the title compound.

N-(3-Pyridyl)morpholine (Table 5, entry 4). The general procedure using 2.0 mol % Pd(dba)$_2$ and 2.0 mol % of 1 afforded 158 mg (97 %) of the title compound.

N-Methyl-N-(3-Pyridyl)aniline (Table 5, entry 5). The general procedure using 2.0 mol % Pd(dba)$_2$ and 2.0 mol % of 1 afforded 167 mg (91 %) of the title compound.

N-(3-Pyridyl)aniline (Table 5, entry 6). The general procedure using 2.0 mol % Pd(dba)$_2$ and 2.0 mol % of 1 afforded 168 mg (98 %) of the title compound.

N-(4-Pyridyl)morpholine (Table 5, entry 7). The general procedure using 2.0 mol % Pd(dba)$_2$ and 2.0 mol % of 1 afforded 150 mg (88 %) of the title compound.

N-Methyl-N-(4-Pyridyl)aniline (Table 5, entry 8). The general procedure using 2.0 mol % Pd(dba)$_2$ and 2.0 mol % of 1 afforded 130 mg (70 %) of the title compound.

N-(4-Pyridyl)aniline (Table 5, entry 9). The general procedure using 2.0 mol % Pd(dba)$_2$ and 2.0 mol % of 1 afforded 143 mg (73 %) of the title compound.
N-(2-Pyridyl)morpholine (Table 5, entry 10). The general procedure using 2.0 mol % Pd(dba)$_2$ and 2.0 mol % of 1 afforded 156 mg (95%) of the title compound.

N-Methyl-N-(2-Pyridyl)aniline (Table 5, entry 11). The general procedure using 2.0 mol % Pd(dba)$_2$ and 2.0 mol % of 1 afforded 182 mg (99%) of the title compound.

N-(2-Pyridyl)aniline (Table 5, entry 12). The general procedure using 2.0 mol % Pd(dba)$_2$ and 2.0 mol % of 1 afforded 158 mg (96%) of the title compound.

Aminations of Aryl Halides with Benzophenone Imine. General procedure: Under an atmosphere of argon 1,4-dioxane (3 mL), KO'Bu (168 mg, 1.5 mmol), aryl halide (1.0 mmol), benzophenone imine (1.05 mmol) were added in turn to a screw-capped vial equipped with a teflon septum and magnetic stirring bar charged with Pd(dba)$_2$ (10.9 mg, 0.01 mmol), and 1 (8 mg, 0.02 mmol). The vial was placed in an oil bath at the indicated temperature and stirred for the indicated time. The reaction was monitored by GC. In some cases the yields were determined by GC using biphenyl as internal standard. The mixture was then allowed to cool to room temperature. The mixture was directly absorbed onto silicagel column and eluted with hexane or hexane/ethyl acetate.

N-(Diphenyl methylene)-2,5-dimethylaniline (Table 6, entry 3). The general procedure using 2.0 mol % Pd(dba)$_2$ and 2.0 mol % of 1 afforded 283 mg (99%) of the title compound. $^1$H NMR: (400 MHz, CDCl$_3$) δ 2.12 (s, 3H), 2.13 (s, 3H), 6.90 — 7.0 (m, 2H), 7.30 (s, 1H), 7.36 — 7.52 (m, 5H), 7.74 — 7.84 (m, 5H); IR: 1600 cm$^{-1}$. $^{13}$C NMR: (400 MHz, CDCl$_3$) δ 167.19 (C=N), 149.97 (C), 139.67 (C), 136.55 (C), 135.36 (C), 132.56 (CH), 129.79 (CH), 129.31 (CH), 128.94 (CH), 128.61 (CH), 128.19 (CH), 127.84 (CH), 124.77 (C), 123.82 (CH), 120.28 (CH), 20.98 (CH$_3$), 17.80 (CH$_3$). Anal. Calcd. for C$_{21}$H$_{19}$N: C, 88.38; H, 6.71; N, 4.91. Found: C, 88.00; H, 6.98; N, 4.93.

N-(Diphenyl methylene)-3,5-dimethylaniline (Table 7, entry 2). The general procedure using 2.0 mol % Pd(dba)$_2$ and 2.0 mol % of 1 afforded 283 mg (99%) of the title compound. $^1$H NMR: (CDCl$_3$) δ 2.16 (s, 6H), 6.35 (s, 2H), 6.57 (s, 1H), 7.38 — 7.46 (m, 6H), 7.50 — 7.73 (d, J = 92 Hz, 4H); IR: 1601, 1590 cm$^{-1}$. $^{13}$C NMR: δ 167.74 (C=N), 151.15 (C), 139.91 (C), 137.95 (C), 136.42 (C), 129.25 (CH), 128.17 (CH), 127.97 (CH),
129.15 (CH), 126.84 (CH), 126.52 (CH), 123.54 (CH), 117.39 (CH), 19.87 (CH₃); Anal. Calcd. for C₁₂H₁₉N: C, 88.38; H, 6.71; N, 4.91. Found: C, 88.39; H, 6.61; N, 5.02.

N-(Diphenyl methylene)-3,5-bis(trifluoromethyl)aniline (Table 7, entry 3). The general procedure using 2.0 mol % Pd(dba)₂ and 2.0 mol % of 1 afforded 236 mg (60%) of the title compound. ¹H NMR: (CDCl₃) δ 7.14 (s, 2H), 7.33 (s, 1H), 7.43 — 7.47 (t, J = 8Hz, 4H), 7.52 — 7.56 (t, J = 8Hz, 2H), 7.78 — 7.80 (d, J = 8Hz, 4H); IR: 1601, 1590 cm⁻¹; ¹⁹F NMR: δ 104.88(s, 6F); ¹³C NMR: (400 MHz, CDCl₃) δ 171.55 (C=N), 152.48 (C), 138.46 (C), 134.95 (C), 131.93 (CH), 131.66 (CH), 129.61 (CH), 129.35 (CH), 129.12 (CH), 128.41 (CH), 124.55 (C), 121.85 (CH), 121.43 (CH), 116.62 (CF₃); Anal. Calcd. for C₁₂H₁₃F₂N: C, 64.13; H, 3.33; N, 3.56. Found: C, 63.75; H, 3.45; N, 3.73.

N-(Diphenyl methylene)-6-methoxy-2-naphtylamine (Table 7, entry 6). The general procedure using 2.0 mol % Pd(dba)₂ and 2.0 mol % of 1 afforded 330 mg (98%) of the title compound. ¹H NMR: (CDCl₃) δ 3.88 (s, 3H), 6.88 — 6.91 (m, 2H), 7.05 — 7.08 (m, 2H), 7.43 (s, 1H), 7.45 (s, 1H), 7.47 — 7.55 (m, 5H), 7.77 — 7.83 (m, 5H); IR: 1600 cm⁻¹. ¹³C NMR: 168.40 (C=N), 156.80 (C), 147.00 (C), 139.92 (C), 136.37 (C), 132.46 (C), 131.27 (CH), 130.73 (CH), 130.11 (CH), 129.64 (CH), 129.37, (CH), 128.97 (CH), 128.63 (CH), 128.25 (CH), 128.04 (CH), 126.94 (C), 122.36 (CH), 118.75 (CH), 117.99 (CH), 55.28 (CH₃); Anal. Calcd. for C₂₆H₂₆NO: C, 85.43; H, 5.68; N, 4.15. Found: C, 85.35; H, 5.88; N, 3.50.

N-(Diphenyl methylene)-4-methylaniline (Table 6, entry 1).¹¹ The general procedure using 2.0 mol % Pd(dba)₂ and 2.0 mol % of 1 afforded 268 mg (99%) of the title compound.

N-(Diphenyl methylene)-aniline (Table 6, entry 2).¹² The general procedure using 2.0 mol % Pd(dba)₂ and 2.0 mol % of 1 afforded 247 mg (96%) of the title compound.

N-(Diphenyl methylene)-2,6-dimethylaniline (Table 6, entry 4).¹³ The general procedure using 2.0 mol % Pd(dba)₂ and 2.0 mol % of 1 afforded 279 mg (98%) of the title compound.

N-(Diphenyl methylene)-4-methoxyaniline (Table 6, entry 5).¹⁴ The general procedure using 2.0 mol % Pd(dba)₂ and 2.0 mol % of 1 afforded 284 mg (99%) of the title compound.
N-(Diphenyl methylene)-4-pyridinamine (Table 6, entry 6). The general procedure using 2.0 mol % Pd(dba)$_2$ and 2.0 mol % of 1 afforded 155 mg (60 %) of the title compound.

N-(Diphenyl methylene)-4-methylaniline (Table 7, entry 1). The general procedure using 2.0 mol % Pd(dba)$_2$ and 2.0 mol % of 1 afforded 266 mg (98 %) of the title compound.

N-(Diphenyl methylene)-2,4,6-trimethylaniline (Table 7, entry 4). The general procedure using 2.0 mol % Pd(dba)$_2$ and 2.0 mol % of 1 afforded 296 mg (99 %) of the title compound.

N-(Diphenyl methylene)-4-methoxyaniline (Table 7, entry 5). The general procedure using 2.0 mol % Pd(dba)$_2$ and 2.0 mol % of 1 afforded 284 mg (99 %) of the title compound.

Acidic Cleavage of Benzophenone Imine Aducts

Benzophenone imine adducts were converted to the corresponding N-unsubstituted anilines according to the reported procedure: Wolfe, J.P.; Ahman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. Tetrahedron Lett. 1997, 38, 6367-6370.

N-Arylation of Indoles with Aryl Bromides. General Procedure: Under an atmosphere of argon 1,4-dioxane (3 mL), NaOH (80 mg, 2 mmol), aryl halide (1.0 mmol), indole (1.1 mmol) were added in turn to a screw-capped vial equipped with a teflon septum and magnetic stirring bar charged with Pd(dba)$_2$ (10.9 mg, 0.0 mmol), and 5 (8 mg, 0.02 mmol). The vial was placed in an oil bath at the indicated temperature and stirred for the indicated time. The reaction was monitored by GC. In some cases the yields were determined by GC using biphenyl as internal standard. The mixture was then allowed to cool to room temperature. The mixture was directly absorbed onto silicagel column and eluted with hexane or hexane/ethyl acetate.

N-(4-methylphenyl)indole (Table 10, entry 1). The general procedure using 2.0 mol % Pd(OAc)$_2$ and 2.0 mol % of 5 afforded 201 mg (97 %) of the title compound.
N-phenyl-indole (Table 10, entry 2). The general procedure using 2.0 mol % Pd(OAc)$_2$ and 2.0 mol % of 5 afforded 193 mg (100 %) of the title compound.

N-(4-methoxyphenyl)indole (Table 10, entry 3). The general procedure using 2.0 mol % Pd(OAc)$_2$ and 2.0 mol % of 5 afforded 196 mg (88 %) of the title compound.

N-(2,4,6-trimethylphenyl)indole (Table 10, entry 4). The general procedure using 2.0 mol % Pd(OAc)$_2$ and 2.0 mol % of 5 afforded 160 mg (68 %) of the title compound.

N-(4-methylphenyl)-2-phenylindole (Table 10, entry 5). The general procedure using 2.0 mol % Pd(OAc)$_2$ and 2.0 mol % of 5 afforded 283 mg (100 %) of the title compound.

N-phenyl-2-phenylindole (Table 10, entry 6). The general procedure using 2.0 mol % Pd(OAc)$_2$ and 2.0 mol % of 5 afforded 269 mg (100 %) of the title compound.

N-(4-methylphenyl)-2-phenylindole (Table 10, entry 7). The general procedure using 2.0 mol % Pd(OAc)$_2$ and 2.0 mol % of 5 afforded 183 mg (61 %) of the title compound.

N-(4-methylphenyl)-2-(2-fluorophenyl)indole (Table 10, entry 8). The general procedure using 2.0 mol % Pd(OAc)$_2$ and 2.0 mol % of 5 afforded 292 mg (97 %) of the title compound.

N-phenyl-2-(2-fluorophenyl)indole (Table 10, entry 9). The general procedure using 2.0 mol % Pd(OAc)$_2$ and 2.0 mol % of 5 afforded 238 mg (83 %) of the title compound.

References to known compounds