SUPPORTING INFORMATION

Anilide ortho-Arylation Using C-H Activation Methodology
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Materials. Trifluoroacetic acid (Acros), silver acetate purified (Fisher), palladium acetate (J&J Materials), iodobenzene and 4-iodotoluene (Acros), 4-methoxyiodobenzene and 3-bromiodobenzene (Aldrich), 2-methylacetanilide (Lancaster Synthesis), pivalic anhydride, pivaloyl chloride, 3-iodobenzoic acid (Acros), pyridine (EMD), 2-methyl-1-naphthylamine (TCI America) and diphenyliodonium hexafluorophosphate (Aldrich) were used as obtained. Methyl 4-iodobenzoate is available from Acros. The following starting materials were prepared according to literature procedures: pivalanilide, 4-methylpivalanilide, 4-iodopivalanilide, 3-iodopivalanilide, 1-pivaloylaminonaphthalene, methyl 3-iodobenzoate.

General procedure for the coupling of iodoarenes with anilides. The solution of iodoarene (2.2 mmol), anilide (1.0 mmol), palladium acetate (3.3 mg, 0.015 mmol), silver acetate (340 mg, 2.0 mmol) in TFA (2 mL) in a 2-dram screw-cap vial was heated at 90-120 °C for 1-12 hrs (for exact conditions, see below). The reaction was generally stopped when no more precipitate was formed. The reaction mixture was diluted with toluene (5 mL), solution was decanted and the precipitate was washed with toluene (2x5 mL). Combined organic solutions were evaporated under reduced pressure. Product was isolated by flash chromatography on silica gel or alumina.

2,6-Diphenylpivalanilide. General procedure: iodobenzene (250 µL, 2.2 mmol) and pivalanilide (177 mg, 1.0 mmol). Conditions: 3 hr at 120 °C. Flash chromatography (toluene, then dichloromethane) afforded 298 mg (91%) of a white solid; mp 241 – 242 °C (small needles, from toluene); Rf = 0.2 (2:1 dichloromethane/pentane); 1H NMR (CDCl3) δ 0.90 (s, 9H), 6.80 (br s, 1H); 7.35 - 7.50 (m, 13H); 13C NMR (CDCl3) δ 27.0, 38.7, 121.2; 127.3; 128.0; 128.9; 129.6; 131.5; 139.6; 140.9; 176.6. FT-IR (ν, cm⁻¹) 1643 (C=O), 3270 (N-H). Found: %C 83.65, %H 6.97, %N 4.20. C23H23NO. Calculated: %C 83.85, %H 7.04, %N 4.25.

2,6-Di(4′-methylphenyl)-4-iodopivalanilide. General procedure: 4-iodotoluene (1.1 g, 5.0 mmol), 4-iodopivanilide (300 mg, 1.0 mmol) in the presence of palladium acetate (11 mg, 0.049 mmol) and silver acetate (370 mg, 2.2 mmol) in TFA (1 mL). Conditions: 12 h at 120 °C. Purification by flash
chromatography (hexane, then dichloromethane) afforded 443 mg (92%) of a white solid; m.p. 195-197 °C (pentane); R = 0.40 (1:1 dichloromethane/pentane); ^1H NMR (CDCl$_3$) $d$ 0.86 (s, 9H), 2.38 (s, 6H), 6.75 (br s, 1H), 7.20 (m, 8H), 7.66 (s, 2H); ^13C NMR (CDCl$_3$) $d$ 21.1, 27.0, 38.7, 92.2, 128.5, 128.8, 131.8, 135.3, 137.3, 138.0, 142.6, 176.3. FT-IR ($\nu$, cm$^{-1}$) 1639 (C=O), 3270 (N -H). Found: %C 62.28, %H 5.41, %N 2.72. C$_{25}$H$_{26}$INO. Calculated: %C 62.12, %H 5.42, %N 2.90.

2,6-Di(3'-bromophenyl)pivalanilide. General procedure: 3-bromooiodobenzene (380 µL, 3.0 mmol), pivalanilide (177 mg, 1.0 mmol) in the presence of palladium acetate (2 mg, 0.009 mmol) and silver acetate (370 mg, 2.2 mmol) in TFA (1 mL). Conditions: 12 h at 120 °C. Purification by flash chromatography (toluene, then dichloromethane) afforded 267 mg (55%) of a white solid; m.p. 228-229 °C (pentane); $R_f$ = 0.25 (1:1 dichloromethane/pentane); ^1H NMR (CDCl$_3$) $d$ 0.92 (s, 9H), 6.72 (br s, 1H), 7.25-7.50 (m, 11H). ^13C NMR (CDCl$_3$) $d$ 27.1, 38.8, 121.9, 127.5, 129.7, 129.8, 129.9, 130.3, 131.6, 131.7, 139.5, 141.5, 176.6. FT-IR ($\nu$, cm$^{-1}$) 1636 (C=O), 3265 (N -H). Found: %C 56.80, %H 4.30, %N 2.75. C$_{23}$H$_{21}$Br$_2$NO. Calculated: %C 56.70, %H 4.34, %N 2.87.

2,6-Di(4'-methoxyphenyl)pivalanilide. General procedure: 4-methoxyiodobenzene (705 mg, 3.0 mmol) and pivalanilide (177 mg, 1.0 mmol) in the presence of palladium acetate (2.2 mg, 0.01 mmol) and silver acetate (370 mg, 2.2 mmol) in TFA (2 mL). Conditions: 12 h at 120 °C. Purification by flash chromatography (toluene, then dichloromethane/ethyl acetate) afforded 260 mg (67%) of a white solid; mp 229 – 230 °C (ethanol); $R_f$ = 0.15 (dichloromethane); ^1H NMR (CDCl$_3$) $d$ 0.87 (s, 9H), 3.81 (s, 6H), 6.73 (br s, 1H), 6.92 (d, $J$ = 8.4 Hz, 4H), 7.29 (d, $J$ = 8.4 Hz, 4H), 7.25-7.40 (m, 3H); ^13C NMR (CDCl$_3$) $d$ 27.2, 38.7, 55.2, 113.4, 127.1, 129.4, 129.9, 131.8, 132.1, 140.4, 158.7, 176.5. FT-IR ($\nu$, cm$^{-1}$) 1638 (C=O), 3260 (N -H). Found: %C 56.70, %H 4.34, %N 2.87.

2,6-Di(3'-carbomethoxyphenyl)-4-methylpivalanilide. General procedure: methyl 3-iodobenzoate (390 mg, 1.5 mmol) and 4-methylpivalanilide (87 mg, 0.46 mmol) in the presence of palladium acetate (8 mg, 0.036 mmol) and silver acetate (170 mg, 1.0 mmol) in TFA (1 mL). Conditions: 12 h at 100 °C. Flash chromatography (toluene, then 20:1 dichloromethane/ethyl acetate), concentration of the main fraction and purification of the material by extracting into hexanes (3x20 mL) afforded after evaporation of the solvent 180 mg (85%) of a white solid; m.p. 85-86 °C (pentane); $R_f$ = 0.50 (20:1 dichloromethane/ethyl acetate); ^1H NMR (CDCl$_3$) $d$ 0.82 (s, 9H), 2.39 (s, 3H), 3.85 (s,
6H), 6.94 (s, 1H), 7.16 (s, 2H), 7.41 (t, $J = 7.5$ Hz, 2H), 7.55 (dd, $J = 0.9$ and 7.5 Hz, 2H), 7.95 (m, 4H); $^{13}$C NMR (CDCl$_3$) d 20.9, 26.9, 38.6, 52.0, 128.1, 128.3, 128.9, 129.7, 129.8, 130.6, 133.5, 137.3, 139.8, 139.9, 166.8, 176.7. FT-IR ($\nu$, cm$^{-1}$) 1650 (C=O), 1722 (ester C=O), 3370 (N-H).

2,6-Di(4’-carbomethoxyphenyl)-4-methylpivalanilide. General procedure: methyl 4-iodobenzoate (390 mg, 1.5 mmol) and 4-methylpivalanilide (87 mg, 0.46 mmol) in the presence of palladium acetate (8 mg, 0.036 mmol) and silver acetate (170 mg, 1.0 mmol) in TFA (1 mL). Conditions: 12 h at 100 °C. Purification by flash chromatography (toluene, then 10:1 dichloromethane/ethyl acetate) afforded 198 mg (96%) of a white solid; m.p. 233-234 °C (toluene); $R_f$ = 0.37 (20:1 dichloromethane/ethyl acetate); $^1$H NMR (CDCl$_3$) d 0.81 (s, 9H), 2.41 (s, 3H), 3.91 (s, 6H), 6.80 (s, 1H), 7.18 (s, 2H), 7.41 (d, $J = 7.2$ Hz, 4H), 8.01 (d, $J = 7.2$ Hz, 4H); $^{13}$C NMR (CDCl$_3$) d 21.0, 27.1, 38.7, 52.1, 128.7, 128.9, 129.3, 130.6, 137.4, 139.9, 144.4, 166.9, 176.8. FT-IR ($\nu$, cm$^{-1}$) 1640 (C=O), 1720 (ester C=O), 3260 (N-H).

2-phenyl-5-iodopivalanilide. General procedure: iodobenzene (1 mL, 8.9 mmol), 3-iodopivanilide (300 mg, 1.0 mmol) in the presence of palladium acetate (10 mg, 0.045 mmol) and silver acetate (170 mg, 1.0 mmol) in TFA (1 mL). Conditions: 30 min at 130 °C. Purification by flash chromatography (hexane, then dichloromethane) afforded 315 mg (83%) of a white solid; m.p. 133-135 °C (pentane); $R_f$ = 0.35 (1:2 dichloromethane - pentane); $^1$H NMR (CDCl$_3$) d 1.06 (s, 9H), 6.92 (d, $J = 7.8$ Hz, 1H), 7.25-7.55 (m, 6H), 8.80 (d, $J = 1.8$ Hz, 1H); $^{13}$C NMR (CDCl$_3$) d 27.2, 39.8, 93.6, 128.4, 129.0, 129.1, 129.2, 131.0, 131.3, 132.8, 136.1, 137.0, 176.3. FT-IR ($\nu$, cm$^{-1}$) 1645 (C=O), 3255 (N-H). Found: %C 53.89, %H 4.59, %N 3.71. C$_{17}$H$_{18}$INO. Calculated: %C 53.84, %H 4.78, %N 3.69.

1-Pivaloylamino-2-(4’-methylphenyl)naphthalene. General procedure: 4-iodotoluene (2.3 g, 10 mmol) and 1-pivaloylaminonaphthalene (230 mg, 1.0 mmol) in the presence of palladium acetate (3 mg, 0.013 mmol) and silver acetate (340 mg, 2.0 mmol) in TFA solvent (1 mL). Conditions: 4 hr at 130 °C. Purification by flash chromatography (hexane, then dichloromethane) afforded 195 mg (62%) of a white solid; mp 184-185 °C (pentane); $R_f$ = 0.35 (1:1 dichloromethane/pentane); $^1$H NMR (CDCl$_3$) d 1.17 (s, 9H), 2.40 (s, 3H), 7.17-7.30 (m, 5H), 7.40-7.55 (m, 3H), 7.75-7.90 (m, 2H); $^{13}$C NMR (CDCl$_3$) d 21.2, 27.5, 39.1, 123.5, 125.8, 126.6, 127.5, 127.7, 128.0, 128.8, 128.9, 129.8, 130.7, 133.4,
136.6, 136.8, 137.0, 177.7. FT-IR (\(\nu\), cm\(^{-1}\)) 1650 (C=O), 3250 (N-H). Found: %C 82.68, %H 7.29, %N 4.28. \(\text{C}_{22}\text{H}_{23}\text{NO}\). Calculated: %C 83.24, %H 7.30, %N 4.41.

**1-Pivaloylamino-2-methylnaphthalene.** This experiment was carried out to verify the regiochemistry of C-C bond formation. General procedure: iodomethane (120 \(\mu\)L, 1 mmol) and 1-pivaloylaminonaphthalene (112 mg, 0.5 mmol) in the presence of palladium acetate (3 mg, 0.013 mmol) and silver acetate (95 mg, 0.57 mmol) in TFA solvent (2 mL). Conditions: 1 hr at 50 °C. Dilution of the reaction mixture with toluene (50 mL) and filtration through a short pad of alumina afforded 115 mg (95%) of a solid, m.p. 159-160 °C (colorless crystals, from toluene-hexanes) that was found to have identical \(^1\)H NMR with a sample prepared from 2-methyl-1-naphthylamine. \(^1\)H NMR (CDCl\(_3\)) \(d\) 1.45 (s, 9H), 2.37 (s, 3H), 7.20-7.30 (br s, 1H), 7.33 (d, \(J = 8.1\) Hz, 1H), 7.38-7.52 (m, 2H), 7.70 (d, \(J = 8.1\) Hz, 1H), 7.75 (br d, \(J = 8.7\) Hz, 1H), 7.81 (br d, \(J = 8.1\) Hz, 1H).

**6-Methyl-2-phenylacetamide.** General procedure: 4-iodobenzene (0.30 mL, 2.68 mmol) and 2-methylacetanilide (149 mg, 1.0 mmol) in the presence of palladium acetate (2.2 mg, 0.01 mmol) and silver acetate (186 mg, 1.1 mmol) in TFA solvent (1 mL). Conditions: 12 hr at 100 °C. Purification by flash chromatography on alumina (toluene, then dichloromethane) afforded 170 mg (76%) of a white solid; \(R_f = 0.25\) (20:1 dichloromethane/ethyl acetate); mp 132-133 °C (dichloromethane-pentane), (Lit.\(^{[7]}\) 139-140 °C); \(^1\)H NMR (CDCl\(_3\), 60 °C) \(d\) 1.98 (s, 3H), 2.31 (s, 3H), 6.52 (br s, 1H), 7.15-7.45 (m, 8H); FT-IR (\(\nu\), cm\(^{-1}\)) 1655 (C=O), 3230 (N-H).

**2,6-Diphenyl-4-methylpivalanilide.** A solution of 4-methylpivalanilide (96 mg, 0.5 mmol), diphenyliodonium hexafluorophosphate (850 mg, 2 mmol) and Pd(OAc)$_2$ (5.6 mg, 0.0025 mmol) in acetic acid (2 mL) was heated at 70 °C for 23 hr. The solution was evaporated followed by flash chromatography on silica gel in dichloromethane followed by 9:1 dichloromethane/ethyl acetate. After concentration of the major fraction product (135 mg, 79%) was obtained as a white solid. \(R_f = 0.27\) (dichloromethane). M.p. 215-216 °C (hexanes). \(^1\)H NMR (CDCl\(_3\)) \(d\) 0.90 (s, 9H), 2.42 (s, 3H), 6.80 (br s, 1H); 7.22 (s, 2H), 7.35-7.50 (m, 10H); \(^{13}\)C NMR (CDCl\(_3\)) \(d\) 21.1, 27.1, 38.7, 127.1, 127.9, 128.9, 130.3, 137.0, 139.8, 140.7, 140.8, 176.6. FT-IR (\(\nu\), cm\(^{-1}\)) 1643 (C=O), 3280 (N-H). Found: %C 83.83, %H 7.38, %N 4.00. \(\text{C}_{24}\text{H}_{25}\text{NO}\). Calculated: %C 83.93, %H 7.34, %N 4.08. A minor amount of a byproduct, presumably the monophenylated material, was also isolated (\(R_f = 0.37\), dichloromethane).
References


