

## **SUPPORTING INFORMATION**

# **Two Methods for Direct *ortho*-Arylation of Benzoic Acids**

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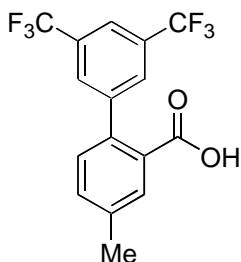
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## Experimental Section

**General considerations:** Reactions were performed in 2-dram vials with PTFE caps. Flash chromatography was performed on 60Å silica gel (Sorbent Technologies). Purification by preparative HPLC was performed on a Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Varian Dynamax (250 mm x 21.4 mm; Microsorb 100 Si packing) column. All preparative HPLC runs were performed using 2% acetic acid in hexanes as an eluent. GC analyses were performed on a Shimadzu CG-2010 chromatograph equipped with a Restek column (Rtx®-5, 15m, 0.25 mm ID). The  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{19}\text{F}$  NMR spectra were recorded on a GE QE-300 spectrometer using residual solvent peak (for  $^1\text{H}$  and  $^{13}\text{C}$ -NMR) and  $\text{C}_6\text{F}_6$  ( $^{19}\text{F}$ ) as reference. Melting points were measured on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab Inc. of Norcross, GA. IR spectra were obtained using ThermoNicolet Avatar 370 FT-IR instrument.

**Materials.** Palladium acetate was obtained from J&J Materials and was used as received. Molecular sieves 3Å (Aldrich) were flame dried under reduced pressure and stored under argon. Powdered  $\text{Cs}_2\text{CO}_3$  (Strem), anhydrous DMF (Fluka or Aldrich) and butyldi-1-adamantylphosphine (Strem) were stored under argon. The following starting materials were obtained from commercial sources and were used without further purification: 4-(trifluoromethyl)benzoic acid, 3-fluorobenzoic acid, 3-(trifluoromethyl)benzoic acid, 4-chlorobenzotrifluoride, 4-chloriodobenzene, 3-iodotoluene, 3,5-dichloriodobenzene, 1-chloro-3-fluorobenzene, biphenyl-3-carboxylic acid and *bis*-3,5-(trifluoromethyl)iodobenzene (Oakwood Products); mono-methyl terephthalate, 5-iodo-*m*-xylene, 2-biphenylcarboxylic acid, and 3-chlorotoluene (Acros); (trimethylsilyl)diazomethane (2.0 M in hexanes), lithium wire in mineral oil, deuterium oxide and 3,4-dimethylbenzoic acid (Aldrich); 2-methylbenzoic acid and 4-methylchlorobenzene (Matheson); 3-nitrobenzoic acid, mono-methyl isophthalate, 2-bromotoluene, 1-iodo-4-isopropylbenzene, and 3,4-dimethoxybenzoic acid (Alfa Aesar); 3-methylbenzoic acid, 2-naphthoic acid, and 3-bromobenzoic acid (Eastman). 3-Isopropoxybenzoic acid is known.<sup>1a</sup> Silver acetate was prepared as described before.<sup>1b</sup>

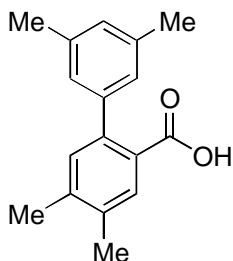
**General procedure for coupling of iodoarenes with benzoic acids.** Without special precautions, a 2-dram vial equipped with a magnetic stir bar was charged with Pd(OAc)<sub>2</sub> (5 mol %), silver acetate (1.3 equiv), ArCO<sub>2</sub>H (1 equiv), iodoarene (3 equiv) and acetic acid (200  $\mu$ L per mmol ArCO<sub>2</sub>H). The sealed vial was placed in a preheated oil bath (100-130  $^{\circ}$ C) and heated until all benzoic acid starting material had been consumed as determined by TLC or GC (4.5 to 7 h). The reaction mixture was allowed to cool to room temperature, diluted with dichloromethane (2 mL) and filtered through a pad of Celite®. The reaction vessel and Celite® pad were rinsed with dichloromethane (2 x 1 mL). The filtrate was concentrated under reduced pressure and the residue suspended in 5% aqueous KOH. The mixture was extracted with dichloromethane (3 x 10 mL), the aqueous layer was acidified with concentrated HCl to pH=2 followed by extraction with dichloromethane (3 x 10 mL). After filtering through a pad of Celite® the dichloromethane layer was concentrated to a volume of about 2 mL. The mixture was adsorbed on silica gel and was subjected to flash chromatography (hexanes then dichloromethane-ethyl acetate 95:5). After the removal of the solvent and trituration with hexanes the residue was dried under reduced pressure (50  $^{\circ}$ C) to give the product.



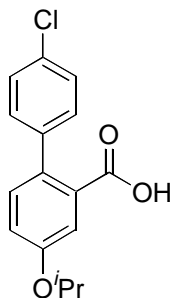
**2-(3,5-Bis(trifluoromethyl)phenyl)-5-methylbenzoic acid (Entry 1, Table 1):**

Palladium acetate (11.4 mg, 0.05 mmol), AgOAc (217 mg, 1.3 mmol), 3-methylbenzoic acid (136 mg, 1.0 mmol), 3,5-bis(trifluoromethyl)iodobenzene (1.02 g, 3.0 mmol) and acetic acid (200  $\mu$ L) were combined and heated at 120 $^{\circ}$ C for 4.5 h. After purification white solid was obtained, 207 mg (59%), mp 217-219  $^{\circ}$ C (isooctane).  $R_f$  = 0.60 (1/9 ethyl acetate-dichloromethane).  $^1\text{H}$  NMR (300 MHz, acetone- $d_6$ ):  $\delta$  2.46 (s, 3H), 7.38-7.51 (m, 2H), 7.87 (s, 1H), 7.94 (s, 2H), 8.00 (s, 1H), 11.3 (br s, 1H).  $^{13}\text{C}$  NMR (75 MHz, acetone- $d_6$ )  $\delta$  20.6, 120.9 (br s), 124.2 (q,  $J$ =271.1 Hz), 129.7 (br s), 130.8, 131.1 (q,  $J$ =33.3 Hz),

131.5, 131.7, 133.1, 137.6, 139.3, 144.9, 168.0. FT-IR (neat,  $\text{cm}^{-1}$ )  $\nu$  1689, 1290, 1121.  
 Anal. calcd for  $\text{C}_{16}\text{H}_{10}\text{F}_6\text{O}_2$  (348.2 g/mol) C, 55.18; H, 2.89; Found: C, 55.07; H, 2.81.

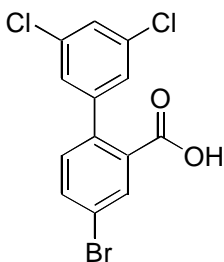


**2-(3,5-Dimethylphenyl)-4,5-dimethylbenzoic acid (Entry 2, Table 1):** Palladium acetate (11.4 mg, 0.05 mmol), AgOAc (217 mg, 1.3 mmol), 3,4-dimethylbenzoic acid (150 mg, 1.0 mmol), 3,5-dimethyliodobenzene (696 mg, 3.0 mmol) and acetic acid (200  $\mu\text{L}$ ) were combined and heated at 110  $^{\circ}\text{C}$  for 5 h. After purification light tan solid was obtained, 136 mg (53 %), mp 189-192  $^{\circ}\text{C}$  (isooctane).  $R_f=0.60$  (1/9 ethyl acetate-dichloromethane).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta$  2.34 (s, 12H), 6.93 (s, 2H), 7.01 (s, 1H), 7.12 (s, 1H), 7.73 (s, 1H), 10.7 (br s, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  19.7, 20.3, 21.9, 126.9, 129.3, 132.4, 133.1, 136.0, 137.9, 141.6, 141.8, 141.9, 173.9. Signal for one aromatic carbon could not be located. FT-IR (neat,  $\text{cm}^{-1}$ )  $\nu$  1695, 1667, 1287. Anal calcd for  $\text{C}_{17}\text{H}_{18}\text{O}_2$  (254.32 g/mol): C, 80.28; H, 7.13; Found: C, 79.44; H, 7.12.

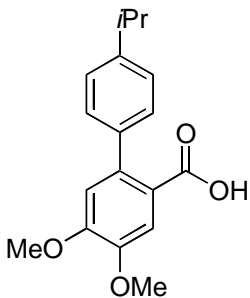


**2-(4-Chlorophenyl)-4-isopropoxybenzoic acid (Entry 3, Table 1):** Palladium acetate (11.4 mg, 0.05 mmol), AgOAc (217 mg, 1.3 mmol), 3-isopropoxybenzoic acid (180 mg, 1.0 mmol), 4-chloriodobenzene (715.5 mg, 3.0 mmol) and acetic acid (200  $\mu\text{L}$ ) were combined and heated at 100  $^{\circ}\text{C}$  for 5.5 h. After purification light yellow solid was obtained, 200 mg (69 %), mp 144-147  $^{\circ}\text{C}$  (isooctane).  $R_f=0.46$  (1/9 ethyl acetate-dichloromethane).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta$  1.37 (d,  $J=6.0$  Hz, 6H), 4.64 (sept,

$J=6.0$  Hz, 1H), 7.09 (dd,  $J=8.0$  Hz, 3.0 Hz, 1H), 7.22-7.26 (m, 3H), 7.32-7.36 (m, 2H), 7.46 (d,  $J=3.0$  Hz, 1H), 10.2 (br s, 1H).  $^{13}\text{C}$  NMR (75 MHz, acetone- $d_6$ )  $\delta$  21.3, 69.9, 116.7, 118.3, 127.8, 130.2, 131.9, 132.1, 132.3, 133.0, 140.1, 157.2, 168.2. FT-IR (neat,  $\text{cm}^{-1}$ )  $\nu$  1690, 1278. Anal calcd for  $\text{C}_{16}\text{H}_{15}\text{ClO}_3$  (290.74 g/mol): C, 66.10; H, 5.20. Found: C, 65.91; H, 5.11.

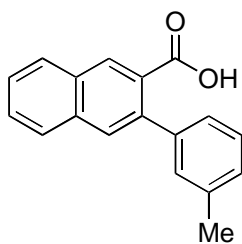


**2-(3,5-Dichlorophenyl)-4-bromobenzoic acid (Entry 4, Table 1):** Palladium acetate (11.4 mg, 0.05 mmol), AgOAc (217 mg, 1.3 mmol), 3-bromobenzoic acid (201 mg, 1.0 mmol), 3,5-dichloriodobenzene (819 mg, 3.0 mmol) and acetic acid (200  $\mu\text{L}$ ) were combined and heated at 120  $^{\circ}\text{C}$  for 5.5 h. After purification light tan solid was obtained, 183 mg (53 %), mp 182-186  $^{\circ}\text{C}$  (isooctane).  $R_f=0.38$  (1/9 ethyl acetate-dichloromethane).  $^1\text{H}$  NMR (300 MHz, acetone- $d_6$ )  $\delta$  7.32 (br s, 2H), 7.36 (d,  $J=8.4$  Hz, 1H), 7.44 (br s, 1H), 7.79 (d,  $J=8.4$  Hz, 1H), 8.05 (br s, 1H). Carboxylate proton signal was not observed.  $^{13}\text{C}$  NMR (75 MHz, acetone- $d_6$ )  $\delta$  122.2, 127.6, 127.7, 133.2, 133.3, 134.6, 135.0, 139.4, 144.5, 166.7. A signal for one aromatic carbon could not be located. FT-IR (neat,  $\text{cm}^{-1}$ )  $\nu$  1699, 1299, 857. Anal. calcd for  $\text{C}_{13}\text{H}_7\text{BrCl}_2\text{O}_2$  (346.00 g/mol): C, 45.13; H, 2.04. Found: C, 45.17; H, 2.04.

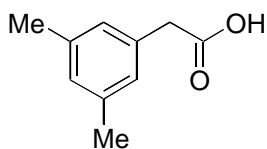


**2-(4-isopropylphenyl)-3,4-dimethoxybenzoic acid (Entry 5, Table 1):** Palladium acetate (11.4 mg, 0.05 mmol), AgOAc (217 mg, 1.3 mmol), 3,4-dimethoxybenzoic acid (182 mg, 1.0 mmol), 1-iodo-4-isopropylbenzene (738 mg, 3.0 mmol) and acetic acid (200

$\mu\text{L}$ ) were combined and heated at 130 °C for 7 h. After column chromatography and preparative HPLC 165 mg (55 %) of a white solid was obtained, mp 125-127 °C (isooctane).  $R_f=0.52$  (1:9 ethyl acetate-dichloromethane).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.28 (d,  $J=6.6$  Hz, 6H), 2.94 (septet,  $J=6.6$  Hz, 1H), 3.90 (s, 3H), 3.93 (s, 3H), 6.77 (s, 1H), 7.23 (s, 4H), 7.51 (s, 1H). Carboxylate proton signal was not observed.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  24.7, 34.6, 56.8, 56.9, 114.6, 115.1, 121.4, 126.8, 129.4, 139.3, 139.5, 148.5, 148.6, 152.7, 172.5. FT-IR (neat,  $\text{cm}^{-1}$ )  $\nu$  1686, 1283, 1208.

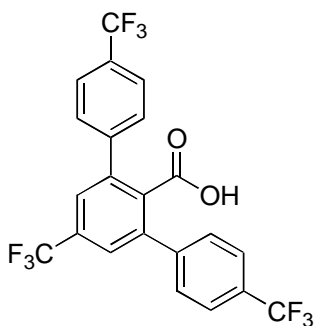


**3-(3-Methyl)-2-naphthoic acid (Entry 6, Table 1):** Palladium acetate (11.4 mg, 0.05 mmol), AgOAc (217 mg, 1.3 mmol), 2-naphthoic acid (172 mg, 1.0 mmol), 3-iodotoluene (654 mg, 3.0 mmol) and acetic acid (200  $\mu\text{L}$ ) were combined and heated at 130 °C for 6 h. After column chromatography and preparative HPLC 176 mg (67 %) of a light yellow solid was obtained, mp 182-184 °C (acetone).  $R_f=0.64$  (1:9 ethyl acetate-dichloromethane).  $^1\text{H}$  NMR (300 MHz, acetone- $d_6$ )  $\delta$  2.37 (s, 3H), 7.13-7.18 (m, 1H), 7.19-7.30 (m, 3H), 7.54-7.64 (m, 2H), 7.86 (s, 1H), 7.95-7.98 (m, 1H), 8.02-8.06 (m, 1H), 8.42 (s, 1H). Carboxylate proton signal was not observed.  $^{13}\text{C}$  NMR (75 MHz, acetone- $d_6$ )  $\delta$  21.3, 126.5, 127.4, 128.3, 128.4, 128.5, 128.8, 129.1, 129.9, 130.2, 130.8, 131.0, 132.3, 135.0, 138.0, 139.5, 142.2, 169.0. FT-IR (neat,  $\text{cm}^{-1}$ )  $\nu$  1675, 1297.



**3,5-Dimethylphenyl acetic acid:** Palladium acetate (11.4 mg, 0.05 mmol), AgOAc (217 mg, 1.3 mmol), 5-iodo-*m*-xylene (696, 3.0 mmol) and acetic acid (200  $\mu\text{L}$ ) were combined and heated at 130 °C for 7 h. After column chromatography and preparative HPLC 112 mg (52 % based on AgOAc) of a white solid was obtained,  $^1\text{H}$  NMR (300 MHz,  $\text{CHCl}_3$ ):  $\delta$  . 2.31 (s, 6H), 3.57 (s, 2H), 6.91 (s, 2H), 6.93 (s, 1H), 10.87 (br s, 1H). This compound is known.<sup>2</sup>

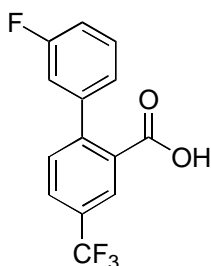
**General procedure for coupling of chloroarenes with benzoic acids.** Outside the glovebox a 2-dram vial equipped with a magnetic stir bar was charged with Pd(OAc)<sub>2</sub> (5 mol %), ArCO<sub>2</sub>H (0.5 mmol) and chloroarene (3-5 equiv). The vial was flushed with argon, capped and placed inside a glovebox. To this mixture was added butyl-di-1-adamantylphosphine (10 mol %), Cs<sub>2</sub>CO<sub>3</sub> (2.2 equiv), molecular sieves 3 Å (155 mg) and anhydrous DMF (2.5 mL). The sealed vial was taken out of the glovebox, stirred at room temperature for 2 h and placed in a preheated oil bath (145 °C) for 24 h. The reaction mixture was allowed to cool to room temperature and quenched with 15% aqueous HCl (4 mL). Resulting suspension was extracted with ethyl acetate (3 x 3 mL) and the organic layer filtered through a pad of Celite®. The filtrate was concentrated under vacuum to a volume of about 2 mL. The mixture was adsorbed on silica gel and subjected to flash chromatography (hexanes then dichloromethane-ethyl acetate 95:5). The DCM-EtOAc fraction was concentrated, the residue triturated with distilled water (3 x 2 mL) and dried under reduced pressure. The residue, after trituration with hexanes (2 x 2 mL) and/or purification by preparative HPLC and drying under reduced pressure (50 °C) yielded the product.



**2,6-Bis(4-trifluoromethylphenyl)-4-trifluoromethylbenzoic acid (Entry 1, Table 3):**

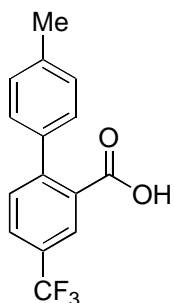
Palladium acetate (5.6 mg, 0.025 mmol), 4-(trifluoromethyl)benzoic acid (95 mg, 0.5 mmol), 4-chlorobenzotrifluoride (271.5 mg, 1.5 mmol), butyl-di-1-adamantylphosphine (19.2 mg, 0.05 mmol), Cs<sub>2</sub>CO<sub>3</sub> (358 mg, 1.1 mmol), molecular sieves 3 Å (155 mg) and anhydrous DMF (2.5 mL). After column chromatography 180 mg (75 %) of a white solid

was obtained, mp 135-136 °C (isooctane).  $R_f=0.66$  (1/9 ethyl acetate-dichloromethane).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.50-7.53 (m, 4H), 7.65-7.68 (m, 6H), 10.2 (br s, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  123.7 (q,  $J=273.0$  Hz), 124.5 (q,  $J=271.7$  Hz), 126.0 (q,  $J=3.5$  Hz), 126.8 (q,  $J=3.7$  Hz), 129.4, 131.4 (q,  $J=33.3$  Hz), 132.9 (q,  $J=34.0$  Hz), 135.1, 140.6, 142.6, 173.1. FT-IR (neat,  $\text{cm}^{-1}$ )  $\nu$  1171, 1324, 1133. Anal. calcd for  $\text{C}_{22}\text{H}_{11}\text{F}_9\text{O}_2$  (478.31 g/mol): C, 55.24; H, 2.32. Found: C, 55.21; H, 2.43.

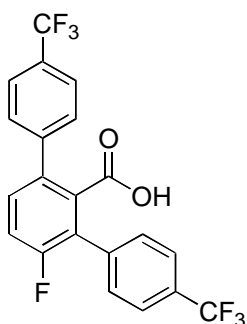


**2-(3-Fluorophenyl)-5-(trifluoromethyl)benzoic acid (Entry 2, Table 3):** Palladium acetate (5.6 mg, 0.025 mmol), 3-(trifluoromethyl)benzoic acid (95 mg, 0.5 mmol), 1-chloro-3-fluorobenzene (131 mg, 1.0 mmol), butyldi-1-adamantylphosphine (19.2 mg, 0.05 mmol),  $\text{Cs}_2\text{CO}_3$  (358 mg, 1.1 mmol), molecular sieves  $3\text{\AA}$  (155 mg) and anhydrous DMF (2.5 mL). After column chromatography and preparative HPLC 102 mg (72 %) of a white solid was obtained, mp 107-110 °C (isooctane).  $R_f=0.36$  (1/9 ethyl acetate-dichloromethane).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.01-7.13 (m, 3H), 7.25-7.41 (m, 1H), 7.46-1.50 (m, 1H), 7.80-7.85 (m, 1H), 8.25 (s, 1H), 10.7 (br s, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ; C-F coupling constants assigned where possible; list of signals where assignment not possible)  $\delta$  115.4, 115.7, 115.8, 116.1, 124.6, 124.7, 128.5 (q,  $J=3.6$  Hz), 129.4 (q,  $J=3.6$  Hz), 130.2, 130.3, 130.4, 130.8 (q,  $J=33.5$  Hz), 132.3, 142.3, 142.2, 146.2, 163.0 (d,  $J=246.6$  Hz), 172.6. FT-IR (neat,  $\text{cm}^{-1}$ )  $\nu$  1689, 1287, 1130. Anal. calcd for  $\text{C}_{14}\text{H}_8\text{F}_4\text{O}_2$  (284.21 g/mol): C, 59.16, H, 2.84. Found: C, 59.33; H, 2.79.





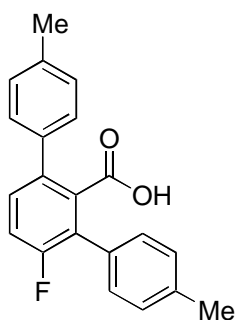
**2-(4-Methylphenyl)-5-(trifluoromethyl)benzoic acid (Entry 3, Table 3):** Palladium acetate (5.6 mg, 0.025 mmol), 3-(trifluoromethyl)benzoic acid (95 mg, 0.5 mmol), 4-chlorotoluene (127 mg, 1.0 mmol), butyl-di-1-adamantylphosphine (19.2 mg, 0.05 mmol),  $\text{Cs}_2\text{CO}_3$  (358 mg, 1.1 mmol), molecular sieves 3 Å (155 mg) and anhydrous DMF (2.5 mL). After column chromatography and preparative HPLC 116 mg (83 %) of a white solid was obtained, mp 128-129 °C (isooctane).  $R_f=0.54$  (1/9 ethyl acetate-dichloromethane).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  2.40 (s, 3H), 7.22 (s, 4H), 7.48-7.51 (m, 1H), 7.76-7.81 (m, 1H), 8.20 (br s, 1H), 10.6 (br s, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  21.8, 124.2 (q,  $J=271.9$  Hz), 128.3 (q,  $J=2.9$  Hz), 128.8, 129.2 (q,  $J=3.4$  Hz), 129.6, 130.0 (q,  $J=33.5$  Hz), 130.4, 132.4, 137.2, 138.6, 147.4, 173.3. FT-IR (neat,  $\text{cm}^{-1}$ )  $\nu$  1699, 1281, 1124. Anal. calcd for  $\text{C}_{15}\text{H}_{11}\text{F}_3\text{O}_2$  (280.24 g/mol): C, 64.29, H, 3.96. Found: C, 64.57; H, 3.90.



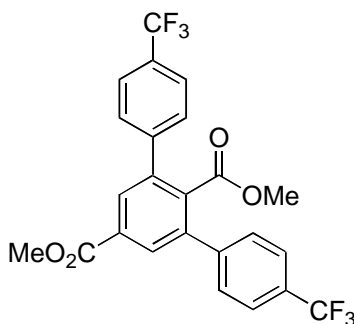
**2,6-Bis(4-(trifluoromethyl)phenyl)-3-fluorobenzoic acid (Entry 4, Table 3):** Palladium acetate (5.6 mg, 0.025 mmol), 3-fluorobenzoic acid (70 mg, 0.5 mmol), 4-chlorobenzotrifluoride (271.5 mg, 1.5 mmol), butyl-di-1-adamantylphosphine (19.2 mg, 0.05 mmol),  $\text{Cs}_2\text{CO}_3$  (358 mg, 1.1 mmol), molecular sieves 3 Å (155 mg) and anhydrous DMF (2.5 mL). After column chromatography 195 mg (91 %) of a white solid was obtained, mp 163-164 °C (isooctane).  $R_f=0.70$  (1/9 ethyl acetate-dichloromethane).  $^1\text{H}$

NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.30-7.41 (m, 2H), 7.43-7.47 (m, 4H), 7.61-7.66 (m, 4H), 9.9 (br s, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>; C-F coupling constants assigned where possible; list of signals where assignment not possible)  $\delta$  118.4, 118.0, 124.5 (q,  $J=272.0$ ), 124.6 (q,  $J=273.0$  Hz), 125.7 (q,  $J=3.7$  Hz), 125.9 (q,  $J=3.7$  Hz), 127.4, 127.2, 129.4, 130.5, 130.8 (q,  $J=31.1$  Hz), 131.2 (q,  $J=33.3$  Hz), 132.0, 131.9, 134.1 (br s), 135.7, 135.6, 137.0, 143.2, 159.4 (d,  $J=250.4$  Hz), 172.8. FT-IR (neat, cm<sup>-1</sup>)  $\nu$  1704, 1324, 1127. Anal. calcd for C<sub>21</sub>H<sub>11</sub>F<sub>7</sub>O<sub>2</sub> (428.30 g/mol): C, 58.89; H, 2.59. Found: C, 58.79; H, 2.56.

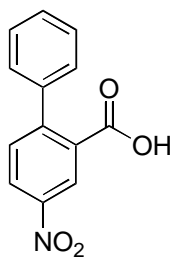
A sample of the acid (10 mg) was suspended in triethylamine (1 mL). The mixture was heated until it became homogeneous. After cooling to room temperature colorless crystals suitable for X-ray structure determination were formed.



**3-Fluoro-2,6-bis(4-methylphenyl)benzoic acid (Entry 5, Table 3)** Palladium acetate (5.6 mg, 0.025 mmol), 3-fluorobenzoic acid (95 mg, 0.5 mmol), 4-chlorotoluene (254 mg, 2 mmol), butyldi-1-adamantylphosphine (19.2 mg, 0.05 mmol), Cs<sub>2</sub>CO<sub>3</sub> (358 mg, 1.1 mmol), molecular sieves 3Å (155 mg) and anhydrous DMF (2.5 mL). After flash chromatography and preparative HPLC 109 mg (68 %) of a white solid was obtained, mp 167-168 °C (isooctane).  $R_f=0.76$  (1/9 ethyl acetate-dichloromethane). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  2.40 (br s, 6H), 7.15-7.34 (m, 10H). Carboxylate proton signal was not observed. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, C-F coupling constants assigned where possible; list of signals where assignment not possible)  $\delta$  21.7, 21.8, 117.3, 117.6, 128.1, 128.4, 128.9, 129.4, 129.6, 130.0, 130.6, 131.0, 131.1, 134.4, 134.5, 136.6, 136.7, 137.2, 138.0, 138.5, 159.3 (d,  $J=246.1$  Hz), 172.7. FT-IR (neat, cm<sup>-1</sup>)  $\nu$  1701, 1469, 1287. Anal. calcd for C<sub>21</sub>H<sub>12</sub>FO<sub>2</sub> (320.36 g/mol): C, 78.73; H, 5.35. Found: C, 78.38; H, 5.44.

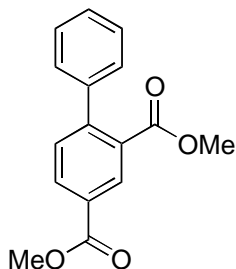


**Dimethyl 2,6-bis(4-trifluoromethylphenyl)-1,4-benzenedicarboxylate (Entry 6, Table 3):** Palladium acetate (5.6 mg, 0.025 mmol), monomethyl terephthalate (90 mg, 0.5 mmol), 4-chlorobenzo-trifluoride (271.5 mg, 1.5 mmol), butyldi-1-adamantylphosphine (19.2 mg, 0.05 mmol),  $\text{Cs}_2\text{CO}_3$  (358 mg, 1.1 mmol), molecular sieves  $3\text{\AA}$  (155 mg) and anhydrous DMF (2.5 mL). After the reaction and workup the residue was dissolved in methanol (10 mL) and cooled to  $0\text{ }^\circ\text{C}$ . (Trimethylsilyl)diazomethane in hexanes (5.0 mL of a 2.0M solution, 1 mmol) was added dropwise, the cooling bath was removed and the mixture stirred for 5 h. The solvent was removed under reduced pressure. Purification by flash chromatography (hexanes then dichloromethane-ethyl acetate 95:5) afforded 190 mg (79 %) of a white solid, mp  $158\text{--}160\text{ }^\circ\text{C}$  (isooctane).  $R_f=0.36$  (1/9 ethyl acetate-hexanes).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$ 3.41 (s, 3H), 3.94 (s, 3H), 7.55–7.57 (m, 4H), 7.71–7.74 (m, 4H), 8.11 (s, 2H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$ 52.7, 53.1, 124.7 (q,  $J=272.95\text{ Hz}$ ), 125.9 (q,  $J=3.9\text{ Hz}$ ), 129.4, 130.5 (q,  $J=32.1\text{ Hz}$ ), 130.8, 132.1, 136.9, 140.0, 143.6, 166.1, 168.9. FT-IR (neat,  $\text{cm}^{-1}$ )  $\nu$  1731, 1326, 1120. Anal. calcd for  $\text{C}_{24}\text{H}_{16}\text{F}_6\text{O}_4$  (482.37 g/mol): C, 59.76; H, 3.34. Found: C, 59.62; H, 3.29.

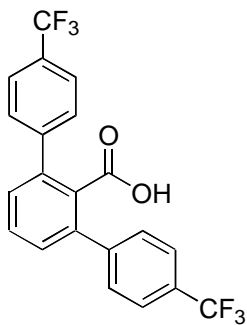


**2-Phenyl-3-nitrobenzoic acid (Entry 7, Table 3):** Palladium acetate (5.6 mg, 0.025 mmol), 3-nitrobenzoic acid (84 mg, 0.5 mmol) and 4-chlorobenzene (283 mg, 2.5 mmol), butyldi-1-adamantylphosphine (19.2 mg, 0.05 mmol),  $\text{Cs}_2\text{CO}_3$  (358 mg, 1.1 mmol), molecular sieves  $3\text{\AA}$  (155 mg) and anhydrous DMF (2.5 mL). After flash chromatography and preparative HPLC 79 mg (65 %) of a white solid was obtained.

Analytical data are consistent with that of previously reported data.<sup>3</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.32-7.37 (m, 2H), 7.42-7.46 (m, 3H), 7.57 (d,  $J$ =8.4 Hz, 1H), 8.40 (dd,  $J$ =8.4 Hz, 2.1 Hz, 1H), 8.80 (d,  $J$ =2.1 Hz, 1H). Carboxylate proton signal was not observed.

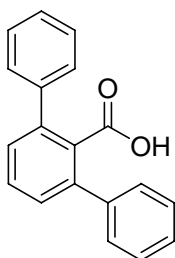


**Dimethyl 4-phenylisophthalate (Entry 8, Table 3):** Palladium acetate (5.6 mg, 0.025 mmol), mono-methyl isophthalate (90 mg, 0.5 mmol) and chlorobenzene (283 mg, 2.5 mmol), butyldi-1-adamantylphosphine (19.2 mg, 0.05 mmol), Cs<sub>2</sub>CO<sub>3</sub> (358 mg, 1.1 mmol), molecular sieves 3Å (155 mg) and anhydrous DMF (2.5 mL). After the reaction and workup the residue was dissolved in methanol (10 mL) and cooled to 0 °C. (Trimethylsilyl)diazomethane in hexanes (5.0 mL of a 2.0M solution, 1 mmol) was added dropwise, the cooling bath was removed and the mixture stirred for 5 h. The solvent was removed under reduced pressure. Purification by preparative HPLC afforded 101 mg (75 %) of a colorless oil. Analytical data are consistent with that of previously reported data.<sup>4</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  3.67 (s, 3H), 3.95 (s, 3H), 7.30-7.47 (m, 6H), 8.15-8.18 (m, 1H), 8.5 (br s, 1H).

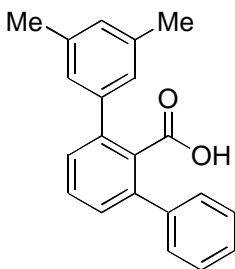


**2,6-Bis(4-trifluoromethylphenyl)benzoic acid (Entry 9, Table 3):** Palladium acetate (5.6 mg, 0.025 mmol), benzoic acid (61 mg, 0.5 mmol) and 4-chlorobenzotrifluoride (271.5 mg, 1.5 mmol), butyldi-1-adamantylphosphine (19.2 mg, 0.05 mmol), Cs<sub>2</sub>CO<sub>3</sub> (358 mg, 1.1 mmol), molecular sieves 3Å (155 mg) and anhydrous DMF (2.5 mL). After

column chromatography 168 mg (82 %) of a white solid was obtained, mp 158-159 °C (isooctane).  $R_f=0.80$  (1/9 ethyl acetate-dichloromethane).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38-7.40 (m, 2H), 7.48-7.50 (m, 4H), 7.55-7.58 (m, 1H), 7.61-7.64 (m, 4H). Carboxylate proton signal was not observed.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  124.1 (q,  $J=271.5$  Hz), 125.3 (q,  $J=2.8$  Hz), 128.8, 129.5, 130.1 (q,  $J=32.1$  Hz), 130.1, 131.9, 139.2, 143.6, 172.8. FT-IR (neat,  $\text{cm}^{-1}$ )  $\nu$  1702, 1325, 1127. Anal. calcd for  $\text{C}_{21}\text{H}_{12}\text{F}_6\text{O}_2$  (410.31 g/mol): C, 61.47; H, 2.95. Found: C, 61.41; H, 2.98.

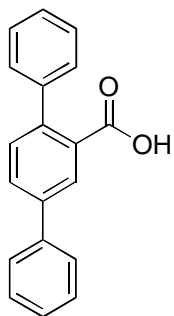


**2,6-Diphenylbenzoic acid (Entry 10, Table 3):** Palladium acetate (5.6 mg, 0.025 mmol), benzoic acid (61 mg, 0.5 mmol) and 4-chlorobenzene (283 mg, 2.5 mmol), butyl-di-1-adamantylphosphine (19.2 mg, 0.05 mmol),  $\text{Cs}_2\text{CO}_3$  (358 mg, 1.1 mmol), molecular sieves 3Å (155 mg) and anhydrous DMF (2.5 mL). After flash chromatography and preparative HPLC 10 mg (10 %) of 2-phenylbenzoic acid and 97 mg (71%) of 2,6-diphenylbenzoic acid was obtained. Analytical data are consistent with that of previously reported data.<sup>5</sup>  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31-7.43 (m, 7H), 7.53-7.61 (m, 1H), 7.91-7.97 (m, 1H), 10.7 (br s, 1H).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35-7.41 (m, 12H), 7.48-7.53 (m, 1H). Carboxylate proton signal was not observed.

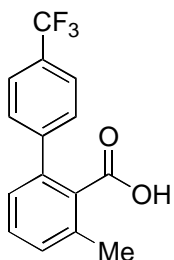


**2-(3,5-Dimethylphenyl)-6-phenylbenzoic acid (Entry 11, Table 3):** Palladium acetate (5.6 mg, 0.025 mmol), 2-phenylbenzoic acid (99 mg, 0.5 mmol) and 3,5-dimethylchlorobenzene (211 mg, 1.5 mmol), butyl-di-1-adamantylphosphine (19.2 mg, 0.05 mmol),  $\text{Cs}_2\text{CO}_3$  (358 mg, 1.1 mmol), molecular sieves 3Å (155 mg) and anhydrous

DMF (2.5 mL). After flash chromatography and preparative HPLC 101 mg (67 %) of a white solid was obtained, mp 198-200 °C (isooctane).  $R_f=0.79$  (1/9 ethyl acetate-dichloromethane).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  2.30 (s, 6H), 7.00 (s, 1H), 7.03 (s, 2H), 7.33-7.38 (m, 7H), 7.46-7.52 (m, 1H), 9.6 (br s, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  21.7, 122.5, 126.9, 128.1, 128.8, 129.0, 129.3, 129.5, 129.8, 130.0, 132.0, 138.3, 140.7, 141.0, 141.2, 174.2. FT-IR (neat,  $\text{cm}^{-1}$ )  $\nu$  1688, 1295. Anal. calcd for  $\text{C}_{21}\text{H}_{18}\text{O}_2$  (302.37 g/mol): C, 83.42; H, 6.00. Found: C, 83.13; H, 6.05.

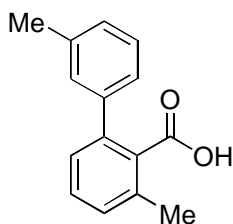


**2,5-Diphenylbenzoic acid (Entry 12, Table 3):** Palladium acetate (5.6 mg, 0.025 mmol), 3-phenylbenzoic acid (99 mg, 0.5 mmol) and 4-chlorobenzene (169 mg, 1.5 mmol), butyl-di-1-adamantylphosphine (19.2 mg, 0.05 mmol),  $\text{Cs}_2\text{CO}_3$  (358 mg, 1.1 mmol), molecular sieves 3 Å (155 mg) and anhydrous DMF (2.5 mL). After flash chromatography and preparative HPLC 97 mg (71 %) of a white solid was obtained. Analytical data are consistent with that of previously reported data.<sup>6</sup>  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36-7.50 (m, 10H), 7.63-7.66 (m, 2H), 7.75-7.78 (m, 1H), 8.15-8.18 (m, 1H). Carboxylate proton signal was not observed.



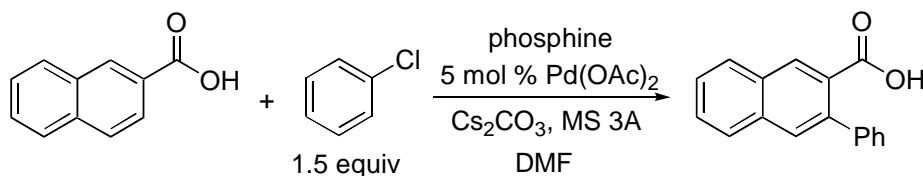
**2-Methyl-6-(4-trifluoromethylphenyl)benzoic acid (Entry 13, Table 3):** Palladium acetate (5.6 mg, 0.025 mmol), 2-methylbenzoic acid (68 mg, 0.5 mmol), 4-chlorobenzotrifluoride (181 mg, 1.0 mmol), butyl-di-1-adamantylphosphine (19.2 mg,

0.05 mmol), Cs<sub>2</sub>CO<sub>3</sub> (358 mg, 1.1 mmol), molecular sieves 3 Å (155 mg) and anhydrous DMF (2.5 mL). After column chromatography 101 mg (72 %) of a white solid was obtained, mp 120-122 °C (isooctane). R<sub>f</sub>=0.56 (1/9 ethyl acetate-dichloromethane). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ2.44 (s, 3H), 7.17-7.20 (m, 1H), 7.25-7.29 (m, 1H), 7.35-7.41 (m, 1H), 7.47-7.51 (m, 2H), 7.60-7.65 (m, 2H), 9.4 (br s, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ20.4, 124.7 (q, *J*=271.7 Hz), 125.8 (q, *J*=4.0 Hz), 127.9, 129.3, 130.3 (q, *J*=31.5 Hz), 130.55, 130.58, 132.4, 136.4, 139.4, 144.8, 175.5. FT-IR (neat, cm<sup>-1</sup>) ν 1697, 1326, 1119. Anal. calcd for C<sub>15</sub>H<sub>11</sub>F<sub>3</sub>O<sub>2</sub> (280.24 g/mol): C, 64.29; H, 3.96. Found: C, 63.69; H, 3.84.



**2-Methyl-6-(3-methylphenyl)benzoic acid (Entry 14, Table 3):** Palladium acetate (5.6 mg, 0.025 mmol), 2-methylbenzoic acid (68 mg, 0.5 mmol), 3-chlorotoluene (127 mg, 1.0 mmol), butyldi-1-adamantylphosphine (19.2 mg, 0.05 mmol), Cs<sub>2</sub>CO<sub>3</sub> (358 mg, 1.1 mmol), molecular sieves 3 Å (155 mg) and anhydrous DMF (2.5 mL). After column chromatography and preparative HPLC 103 mg (91 %) of a white solid was obtained, mp 88-89 °C (isooctane). R<sub>f</sub>=0.22 (1/9 ethyl acetate-hexanes). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ2.36 (s, 3H), 2.44 (s, 3H), 7.17-7.25 (m, 6H), 7.33-7.36 (m, 1H), 9.8 (br s, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ20.5, 22.0, 125.9, 128.0, 128.8, 128.9, 129.7, 130.2, 132.6, 135.9, 138.6, 140.8, 141.1, 176.0. A signal for one aromatic carbon could not be located. FT-IR (neat, cm<sup>-1</sup>) ν 1688, 1282. Anal. calcd for C<sub>15</sub>H<sub>14</sub>O<sub>2</sub> (226.27 g/mol): C, 79.62; H, 6.24. Found: C, 79.91; H, 6.23.

#### A. Procedure for the screening of phosphine ligands.



A 2-dram vial equipped with a magnetic stir bar was charged with Pd(OAc)<sub>2</sub> (5.6 mg; 0.025 mmol), 2-naphthoic acid (86 mg; 0.5 mmol) and chlorobenzene (85 mg; 0.75 mmol). The vial was flushed with argon, capped and placed inside a glovebox. To the above mixture was added a phosphine ligand (10 mol %), Cs<sub>2</sub>CO<sub>3</sub> (358 mg; 1.1 mmol), molecular sieves 3Å (155 mg) and anhydrous DMF (2.5 mL). The sealed vial was taken out of the glovebox, stirred at room temperature for 2 h and placed in a pre-heated oil bath (145 °C) for 24 h. The reaction mixture was allowed to cool to room temperature and quenched with 15% aqueous HCl (4 mL). Hexadecane internal standard (0.1 mL) was added. Resulting suspension was extracted with ethyl acetate (3 x 3 mL) and the organic layer was filtered through a pad of Celite®. An aliquot of the solution was treated with excess (trimethylsilyl)diazomethane (2.0 M in hexanes; until yellow color persisted) and analyzed by GC. Response factors were obtained by separate injection of a known mixture of internal standard, methyl ester of 2-naphthoic acid and methyl ester of 3-phenyl-2-naphthoic acid.

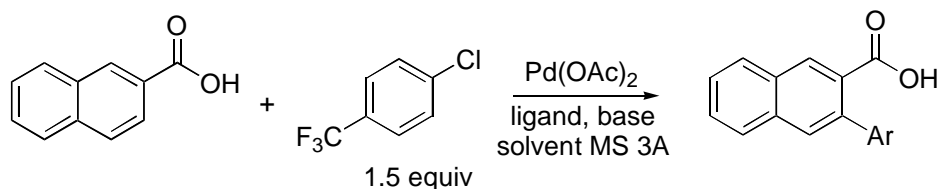
Table S1: Evaluation of phosphine ligands.

Entry	10 mol % L and 5 mol % Pd	%Yield by GC <sup>a</sup>
A1	Cy <sub>3</sub> P and Pd <sub>2</sub> (dba) <sub>3</sub> CHCl <sub>3</sub>	3
A2	( <i>t</i> Bu <sub>3</sub> P) <sub>2</sub> Pd	2
A3	Cy <sub>3</sub> P and Pd(OAc) <sub>2</sub>	46
A4	<i>t</i> Bu <sub>2</sub> MeP-HBF <sub>4</sub> and Pd(OAc) <sub>2</sub>	58
A5	<i>n</i> Octyl <sub>3</sub> P and Pd(OAc) <sub>2</sub>	7
A6	Ph <sub>3</sub> P and Pd(OAc) <sub>2</sub>	1
A7	<i>t</i> Bu(Cy) <sub>2</sub> P and Pd(OAc) <sub>2</sub>	57
A8	<i>n</i> Bu(Ad) <sub>2</sub> P and Pd(OAc) <sub>2</sub>	65
A9	<i>p</i> -Tol <sub>3</sub> P and Pd(OAc) <sub>2</sub>	2
A10	DPPP and Pd(OAc) <sub>2</sub>	7
A11	none	<1

<sup>a</sup> Determined using hexadecane as internal standard.



## B. Procedure for the screening of reagent quality.



A 2-dram vial equipped with a magnetic stir bar was charged with  $\text{Pd}(\text{OAc})_2$  (5.6 mg, 0.025 mmol), 2-naphthoic acid (86 mg, 0.5 mmol) and 4-chlorobenzotrifluoride (136 mg, 0.75 mmol). The vial was flushed with argon, capped and placed inside the glovebox. Depending on the experiment, to each vial was added a combination of these: ligand (10 mol %),  $\text{Cs}_2\text{CO}_3$  (2.2 equiv), molecular sieves 3Å (155 mg) and DMF (2.5 mL) (see Table S2 for exact conditions). The sealed vial was taken out of the glovebox, stirred at room temperature for 2 h and placed in a pre-heated oil bath (145 °C) for 24 h. The reaction mixture was allowed to cool to room temperature, quenched with 15% aqueous HCl (4 mL) and hexadecane (0.1 mL) was added as internal standard. Resulting suspension was extracted with ethyl acetate (3 x 3 mL) and the organic layer filtered through a pad of Celite®. An aliquot was treated with excess (trimethylsilyl)diazomethane (2.0 M in hexanes; until yellow color persisted) and analyzed by GC. Response factors were obtained by separate injection of a known mixture of internal standard, and methyl esters of 2-naphthoic acid and 3-(4-trifluoromethylphenyl)-2-naphthoic acids.

Table S2. Evaluation of reagent quality.

Entry	DMF	MS 3Å <sup>a</sup>	$\text{Cs}_2\text{CO}_3$ <sup>b</sup>	%Yield by GC <sup>c</sup>
B1	Aldrich (anhydrous)	flame-dried	dry	quantitative
B2	Fluka (anhydrous)	flame-dried	dry	quantitative
B3	Aldrich (anhydrous)	none	dry	19
B4	Aldrich (ReagentPlus™)	wet	dry	quantitative
B5	Aldrich (ReagentPlus™)	wet	wet	quantitative
B6	Acros (regular)	flame-dried	dry	quantitative
B7	Acros (regular)	wet	wet	quantitative
B8	Aldrich (anhydrous)	wet	wet	89
B9	Aldrich (anhydrous)	flame-dried, air-flushed <sup>d</sup>	dry	97

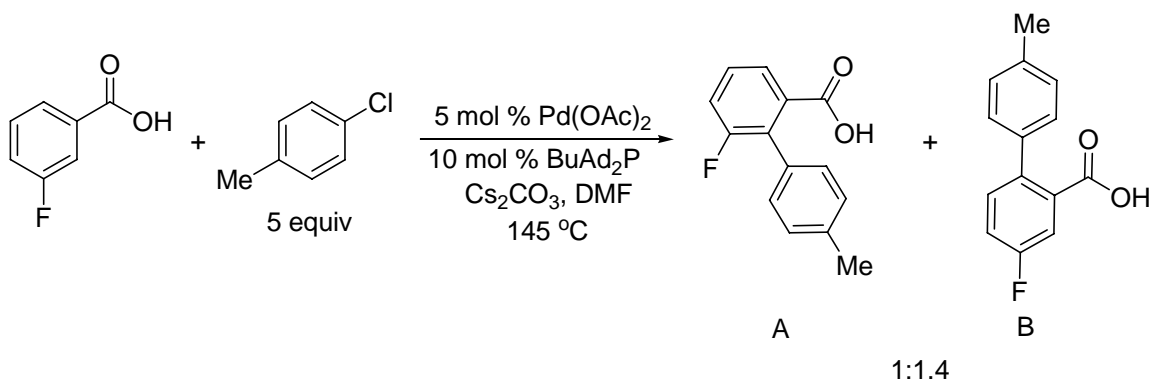
<sup>a</sup>Flame-dried under reduced pressure for at least 2 h. Wet: commercial sieves, not dried, kept without special precautions under air.

<sup>b</sup>Dried at 170 °C under reduced pressure for at least 24 h. Wet: commercial material, stored without special precautions.

<sup>c</sup>Determined using hexadecane as internal standard.

<sup>d</sup>After being taken out of the glovebox, 1 mL of air was injected into reaction mixture and vial was resealed.

### C. Procedure for the determination of regioselectivity of arylation.



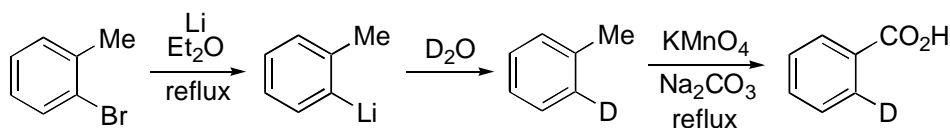
Outside the glovebox a 2-dram vial equipped with a magnetic stir bar was charged with Pd(OAc)<sub>2</sub> (5.6 mg, 5 mol %), 3-fluorobenzoic acid (95 mg, 0.5 mmol) and chlorotoluene (625 mg, 5 mmol). The vial was flushed with argon, capped and placed inside a glovebox. To this mixture was added butyldi-1-adamantylphosphine (19.2 mg, 0.05 mmol), Cs<sub>2</sub>CO<sub>3</sub> (325 mg), molecular sieves 3 Å (155 mg) and anhydrous DMF (2.5 mL). The sealed vial was taken out of the glovebox, stirred at room temperature for 2 h and placed in a preheated oil bath (145 °C) for ~3h (before the onset of biarylation as determined by GC). The reaction mixture was allowed to cool to room temperature and quenched with 15% aqueous HCl (4 mL). Resulting suspension was extracted with ethyl acetate (3 x 3 mL) and the organic layer filtered through a pad of Celite®. The regioisomers were separated by preparative HPLC and dried under reduced pressure (50 °C).

a) 5-Fluoro-2-(4-methylphenyl)benzoic acid (30 mg, 26%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.39 (s, 3H), 7.19-7.35 (m, 6H), 7.62 (dd, *J*=8.6 Hz, 3.0 Hz, 1H). Signal of carboxylate proton could not be located. Analytical data are consistent with that of previously reported data.<sup>7</sup>

b) 3-Fluoro-2-(4-methylphenyl)benzoic acid (21 mg, 18%), mp 154-156 °C (isooctane), *R*<sub>f</sub>=0.50 (1/9 ethyl acetate-dichloromethane). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.40 (s, 3H),

7.17-7.41 (m, 7H), 7.72 (d,  $J=7.2$  Hz). Signal of carboxylate proton could not be located. NMR (75 MHz,  $\text{CDCl}_3$ , C-F coupling constants assigned where possible; list of signals where assignment not possible)  $\delta$  21.8, 120.0, 120.3, 126.8, 126.9, 128.8, 129.0, 129.1, 129.4, 129.7, 130.9, 131.3, 132.3, 138.3, 160.5 (d,  $J=244.5$  Hz), 172.5.  $^{19}\text{F}$  NMR (283 MHz,  $\text{CDCl}_3$ )  $\delta$  -160.9 (dd,  $J=8.6$  Hz, 5.9 Hz). FT-IR (neat,  $\text{cm}^{-1}$ )  $\nu$  1706, 1450, 1295, 1263.

#### D. Procedure for the determination of intramolecular kinetic isotope effect (KIE)

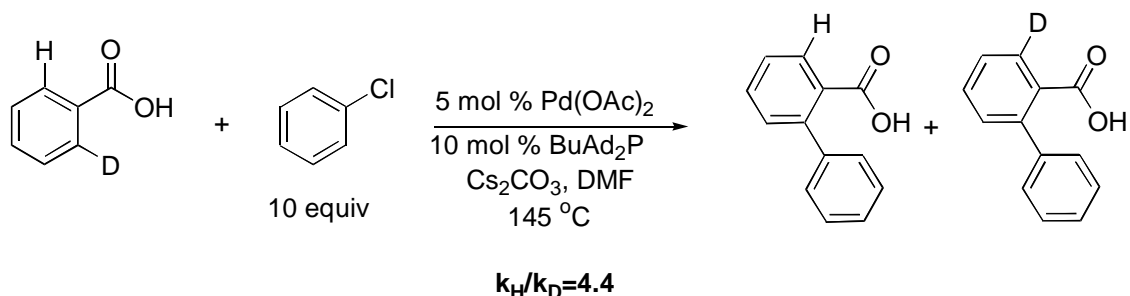


**Synthesis of 2-deuteriobenzoic acid:** a) A 200 mL flame-dried Schlenk flask equipped with a magnetic stir bar was charged with lithium metal in mineral oil (5 g, 720 mmol). The lithium metal was sequentially rinsed with toluene (2 x 30 mL) and ether (2 x 30 mL). The metal was suspended in 100 mL of ether and cooled in an ice bath. Under argon atmosphere, a solution of 2-bromotoluene (25 g, 146 mmol) in ether (40 mL) was added dropwise. The resulting suspension was allowed to warm to room temperature and stirred for an additional 2 hours then refluxed for 12 hours. After cooling to room temperature the mixture was filtered. The reaction vessel and the residue was rinsed with  $\text{Et}_2\text{O}$ . The filtrate was cooled in an ice bath and quenched with  $\text{D}_2\text{O}$  (5 mL) and allowed to warm to room temperature overnight. The mixture was diluted with water (100 mL) and the organic phase was separated. The organic phase was washed with water (3 x 100 mL) followed by drying with  $\text{MgSO}_4$ . The mixture was distilled collecting diethyl ether and then 2-deuteriotoluene (7.6 g, 56%).

b) A round-bottom flask equipped with a stir bar and condenser was charged with 2-deuteriotoluene (2.9 g, 31 mmol),  $\text{KMnO}_4$  (12 g, 76 mmol),  $\text{Na}_2\text{CO}_3$  (1.5 g, 14 mmol) and water (100 mL). The suspension was refluxed for 8 hours then cooled to room temperature. The mixture was filtered through a pad of Celite®, acidified with 12M HCl, and extracted with dichloromethane (3 x 20 mL). The dichloromethane layer was washed with water. The crude product was recrystallized from water to yield 2.3 g (60%) of 2-

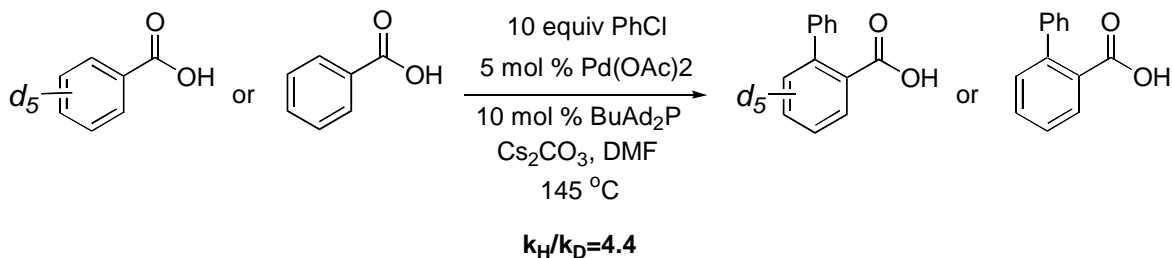
deuteriobenzoic acid as fine white needles. The deuterium content was checked by NMR and EI-MS.

### Determination of intramolecular kinetic isotope effect.



Outside the glovebox a 2-dram vial equipped with a magnetic stir bar was charged with  $\text{Pd}(\text{OAc})_2$  (5.6 mg, 5 mol %), 2-deuteriobenzoic acid (61.5, 0.5 mmol) and chlorobenzene (565 mg, 5 mmol). The vial was flushed with argon, capped and placed inside a glovebox. To this mixture was added butyldi-1-adamantylphosphine (19.2 mg, 0.05 mmol),  $\text{Cs}_2\text{CO}_3$  (325 mg), molecular sieves  $3\text{\AA}$  (155 mg) and anhydrous DMF (2.5 mL). The sealed vial was taken out of the glovebox, stirred at room temperature for 2 h and placed in a preheated oil bath ( $145\text{ }^\circ\text{C}$ ) for 75 min. The reaction mixture was allowed to cool to room temperature and quenched with 15% aqueous HCl (4 mL). Resulting suspension was extracted with ethyl acetate (3 x 3 mL) and the organic layer filtered through a pad of Celite®. The product was purified by preparative HPLC and dried under reduced pressure ( $50\text{ }^\circ\text{C}$ ) for 12 h. The ratio of the deuterated to non-deuterated product was found to be 4.4:1 by  $^1\text{H}$  NMR (integration of the doublet at 7.94 ppm (*o*-H) relative to a triplet at 7.56 ppm (*p*-H)). A similar experiment using 10 mol %  $\text{Pd}(\text{OAc})_2$  and 20 mol % BuAd<sub>2</sub>P gave the same result.

### E. Procedure for the determination of intermolecular kinetic isotope effect (KIE)



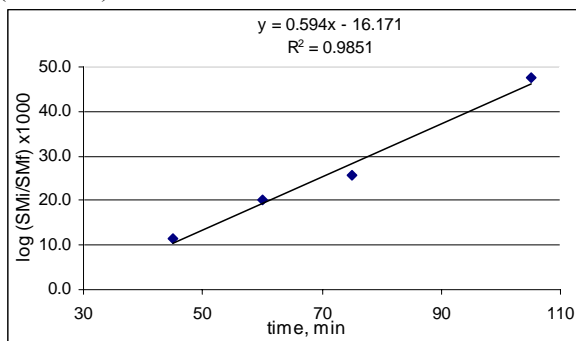
The 1,2,3,4,5-pentadeuteriobenzoic acid was prepared by  $\text{KMnO}_4$  oxidation of the perdeuterated toluene by using a method used in synthesis of 2-deuterobenzoic acid.

Outside the glovebox a 2-dram vial equipped with a magnetic stir bar was charged with  $\text{Pd}(\text{OAc})_2$  (5.6 mg, 5 mol %), benzoic acid (either  $\text{H}_5$ - or  $\text{D}_5$ ) (0.5 mmol) and chlorobenzene (565 mg, 5 mmol). The vial was flushed with argon, capped and placed inside a glovebox. To this mixture was added butyldi-1-adamantylphosphine (19.2 mg, 0.05 mmol),  $\text{Cs}_2\text{CO}_3$  (325 mg), molecular sieves  $3\text{\AA}$  (155 mg) and anhydrous DMF (2.5 mL). The sealed vial was taken out of the glovebox, stirred at room temperature for 2 h and placed in a preheated oil bath ( $145\text{ }^\circ\text{C}$ ) and taken out after the indicated reaction time (see Table S3 and S4). After cooling the reaction mixture to room temperature, a weighed amount of hexadecane internal standard was added ( $\sim 25$  mg) and the mixture was quenched with 15% aqueous HCl (4 mL). Resulting suspension was extracted with ethyl acetate ( $3 \times 3$  mL) and the organic layer was filtered through a pad of Celite® and diluted with ethyl acetate (1 mL). An aliquot was analyzed by GC. The response factors were determined by a separate injection of a known mixture of starting material, product and internal standard.

$\text{SM}_i$	$\text{SM}_f$	time, min	$\log (\text{SM}_i/\text{SM}_f) \times 10^3$
0.5000	0.4881	30	10.5
0.5000	0.4869	45	11.5
0.5000	0.4774	60	20.1
0.5000	0.4714	75	25.6
0.5000	0.4483	105	47.4

Table S3. Reaction of benzoic acid with PhCl under optimum conditions versus time in minutes.

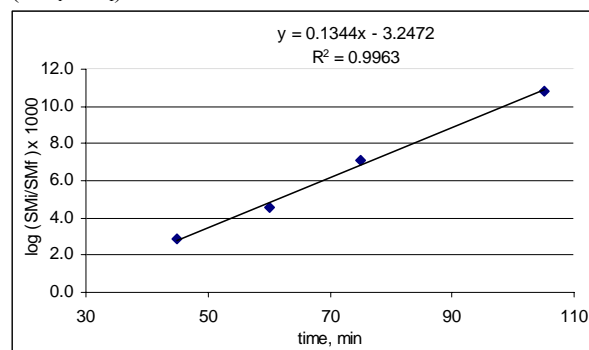
Figure S1. Plot of time in minutes versus  $\log (\text{SM}_i/\text{SM}_f) \times 10^3$ .



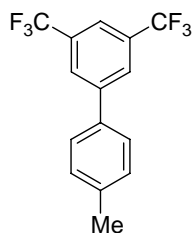
SMi	SMf	time, min	log (SMi/SMf)x10 <sup>3</sup>
0.5000	0.4977	30	2.0
0.5000	0.4967	45	2.9
0.5000	0.4948	60	4.6
0.5000	0.4919	75	7.1
0.5000	0.4877	105	10.8

Table S4. Reaction of 1,2,3,4,5-pentadeuteriobenzoic acid with PhCl under optimum conditions versus time in minutes.

Figure S2. Plot of time in minutes versus log (SM<sub>i</sub>/SM<sub>f</sub>)x10<sup>3</sup>.

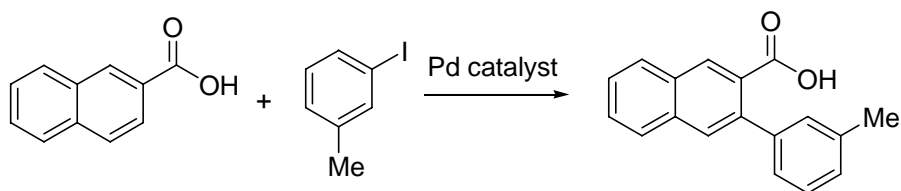


### E. Procedure for the decarboxylation.



**3,5-Bis(trifluoromethyl)-4'-methylbiphenyl:** Outside the glovebox a 2-dram vial equipped with a magnetic stir bar was charged with CuO (12 mg, 0.15 mmol), 1,10-phenanthroline (27 mg, 0.15 mmol), quinoline (19 mg, 0.15 mmol), K<sub>2</sub>CO<sub>3</sub> (21 mg, 0.15 mmol) and 2-(3,5-bis(trifluoromethyl)phenyl)-5-methylbenzoic acid (115 mg, 33 mmol). The vial was flushed with argon, capped and placed inside a glovebox. To this mixture was added anhydrous NMP (3 mL), the vial was sealed and taken out of the glovebox. The mixture was stirred at 160 °C for 24 h. The mixture was allowed to cool to room temperature and quenched with 15% KOH (4 mL). Resulting suspension was extracted with dichloromethane (3 x 3 mL) and the organic layer filtered through a pad of Celite®. The filtrate was concentrated carefully under vacuum (~30 °C) to a volume of about 2 mL. The mixture was adsorbed on silica gel and subjected to flash chromatography (hexanes). After removal of the solvent, the residue was dried under reduced pressure (~30 °C) to yield a colorless oil (86 mg, 86%). Analytical data are consistent with that of previously reported data.<sup>8</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.42 (s, 3H), 7.31 (d, *J*=8.1 Hz, 2H), 7.51 (d, *J*=8.1 Hz, 2H), 7.83 (s, 1H), 8.00 (s, 2H).

**F. Arylation by using either Pd(II) or Pd(0) sources.**



A mixture of a Pd complex (0.2 mmol Pd), 2-naphthoic acid (x g, 1 mmol), 3-iodotoluene (x g, 3 mmol), and AcOH (0.2 mL) was heated at 130 °C for 30 h. GC analysis was performed as in the case of isotope effect determination.

- a) Pd(*t*Bu<sub>3</sub>)<sub>2</sub>, no arylation observed by GC.
- b) Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>, no arylation observed by GC.
- c) Pd(OAc)<sub>2</sub>, 24 % conversion to the arylated product by GC.

It was also determined that under any of the above conditions 1-hydroxy-2-naphthoic, 3-hydroxy-2-naphthoic, 1-acetoxy-2-naphthoic, and 3-acetoxy-2-naphthoic acids were not formed (GC analysis of crude reaction mixtures; comparison with authentic samples).

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### **G. X-Ray Data for Triethylammonium 3-Fluoro-2,6-bis(4-trifluoromethylphenyl)benzoate.**

All measurements were made with a Siemens SMART platform diffractometer equipped with a 4K CCD APEX II detector. A hemisphere of data (1271 frames at 6 cm detector distance) was collected using a narrow-frame algorithm with scan widths of 0.30° in omega and an exposure time of 35 s/frame. The data were integrated using the Bruker-Nonius SAINT program, with the intensities corrected for Lorentz factor, polarization, air absorption, and absorption due to variation in the path length through the detector faceplate. A psi scan absorption correction was applied based on the entire data set. Redundant reflections were averaged. Final cell constants were refined using 2066 reflections having  $I > 10\sigma(I)$ , and these, along with other information pertinent to data collection and refinement, are listed in Table 1. The Laue symmetry was determined to be -1, and the space group was shown to be either P1 or P-1. The asymmetric unit consists of two independent cation/anion pairs which differ mainly in the orientations of the cations. Each of the CF<sub>3</sub> groups was found to be disordered, and this was treated by refinement of two or three ideal rigid body models at each location. Occupancy factors were estimated based on comparison of isotropic displacement parameters.

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#### **Table S5. Crystal Data and Structure Refinement for Triethylammonium 3-Fluoro-2,6-bis(4-trifluoromethylphenyl)benzoate (Table 3, Entry 4).**

Empirical formula C<sub>27</sub>H<sub>26</sub>F<sub>7</sub>NO<sub>2</sub>

Formula weight 529.49

Temperature 223(2) K

Wavelength 0.71073 Å



Crystal system, space group Triclinic, P-1

Unit cell dimensions  $a = 9.748(2)$  Å  $\alpha = 105.117(2)$ .

$b = 12.943(2)$  Å  $\beta = 94.607(3)$  deg.

$c = 20.949(3)$  Å  $\gamma = 94.565(3)$  deg.

Volume  $2529.5(8)$  Å<sup>3</sup>

Z, Calculated density 4, 1.390 Mg/m<sup>3</sup>

Absorption coefficient  $0.122$  mm<sup>-1</sup>

F(000) 1096

Crystal size  $0.35 \times 0.15 \times 0.15$  mm

Theta range for data collection  $1.64$  to  $23.54$  deg.

Limiting indices  $-10 \leq h \leq 10$ ,  $-14 \leq k \leq 14$ ,  $0 \leq l \leq 23$

Reflections collected / unique  $10955 / 7424$  [ $R(\text{int}) = 0.0394$ ]

Completeness to  $\theta = 23.54$  98.9 %

Absorption correction Empirical

Max. and min. transmission  $0.9972$  and  $0.7276$

Refinement method Full-matrix least-squares on  $F^2$

Data / restraints / parameters  $2626 / 11 / 626$

Goodness-of-fit on  $F^2$   $0.912$

Final R indices [ $I > 4\sigma(I)$ ]  $R1 = 0.0591$ ,  $wR2 = 0.1471$

R indices (all data)  $R1 = 0.1606$ ,  $wR2 = 0.1978$

Largest diff. peak and hole  $0.718$  and  $-0.633$  e.Å<sup>-3</sup>

**Figure S3.** View of triethylammonium 3-fluoro-2,6-bis(4-trifluoromethylphenyl)benzoate (Table 3, Entry 4) showing partial atom numbering scheme. Thermal ellipsoids are 40% equiprobability envelopes.

