

Supporting information to:

Aqueous-Phase, Palladium-Catalyzed Cross-Coupling of Aryl Bromides Under Mild Conditions Using Water-Soluble, Sterically Demanding Alkylphosphines

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General Information. *t*-Bu-Amphos,¹ *t*-Bu-Pip-phos,¹ Cy-Pip-phos,² and DCPES² were prepared as previously described. BOC protection of *rac*-(4-bromophenyl)alanine using standard conditions gave **1f**.³ Toluene was distilled from sodium under nitrogen prior to use. Water (deionized), acetonitrile, and mixtures thereof were sparged with nitrogen for 15 minutes prior to use. All other reagents were used as received from commercial sources. GC yields were determined by comparison to an internal standard using calibration data determined with authentic samples of the substrates and products.

Spectroscopic data for compounds **3a-e**, **3g-h**, **3m**, and **7a-f** have previously been reported by us.^{1,4} Products produced in this work were spectroscopically identical to our previously reported data.

Representative procedure for the Suzuki coupling in water acetonitrile (Table 1). The compounds in Table 1 were prepared using our previously reported method.¹

2-*tert*-Butoxycarbonylamino-3-(4'-methoxy-4-biphenyl)propionic acid (3f). Using the general procedure, *N*-(*t*-butoxycarbonyl)-(4-bromophenyl)alanine (**1f**) (343 mg, 1.00 mmol) and 4-methoxyphenylboronic acid (**1d**) (181 mg, 1.19 mmol) were coupled at room temperature for 2 hours. After acidification of the reaction mixture with KHSO₄ (pH = 1-2), the product was extracted with ether. The crude product was chromatographed on SiO₂ eluting with 5% methanol in methylene chloride to give a tan solid (357 mg, 97%). The product was contaminated with approximately 3% 4,4'-dimethoxybiphenyl by weight. ¹H NMR (360 MHz, CDCl₃, 323 K): δ 9.1 (vbrs, 1H), 7.45-7.50 (m, 4 H), 7.21 (d, *J* = 8.53 Hz, 2H), 6.94 (d, *J* = 8.53 Hz), 5.1 (vbrs, 1H), 4.58 (brs, 2H), 3.82 (s, 3H), 3.21 (dd, *J* = 5.55, 14.18 Hz, 1H), 3.02-3.15 (brm, 1H), 1.41 (s, 9H). Spectra taken at room temperature gave broad peaks for a mixture of the two carbamate rotomers. ¹³C NMR (90.6 MHz, CDCl₃, 323 K): δ 175.7, 159.4, 155.6,

139.8, 134.4, 133.5, 129.8, 128.0, 126.9, 114.4, 80.5 (br), 55.4, 54.6 (br), 37.7 (br), 28.3. mp: 148-150 °C (decomposed with gas evolution).

Representative procedure for the Suzuki coupling of hydrophobic aryl bromides in neat water (Table 3). In a dry box, a round bottom flask was charged with Na₂PdCl₄ (0.02 mmol), *t*-Bu-Amphos (0.02 mmol), sodium carbonate (2.0 mmol), aryl halide (1.0 mmol), and aryl boronic acid (1.2 mmol). The flask was sealed with a septum and removed from the drybox. Degassed water (5 mL) was added and the reaction stirred at room temperature for 6-8 hours. The reaction was extracted with ethyl acetate (3 × 25 mL). The crude material was flash chromatographed on a short silica gel column eluting with a mixture of ethyl acetate and hexanes.

Representative procedure for preparative-scale Suzuki coupling of hydrophilic aryl halides in neat water. Reactions were assembled as described for water-insoluble aryl bromides. After 6 hours, the reaction mixture was filtered. The product was precipitated from the filtrate by the addition of 25 mL of 10% HCl. The crude product was filtered, and recrystallized from water and a minimal amount of methanol.

Biphenyl-4-carboxylic acid (3i).⁵ 4-Bromobenzoic acid (205.1 mg, 1.03 mmol) and phenylboronic acid (146.9 mg, 1.21 mmol) were coupled by the above procedure. The crude material was recrystallized from water to give a colorless crystalline solid (194.2 mg, 98%). Spectral data were consistent with the commercially available material. ¹H NMR (360 MHz, CD₃OD): δ 8.09 (d, *J* = 7.77 Hz, 2H), 7.69 (m, 4H), 7.47 (t, *J* = 7.77 Hz, 2H), 7.39 (d, *J* = 7.27, 1H). ¹³C NMR (90.6 MHz, CDCl₃): δ 171.3, 146.7, 139.8, 133.6, 130.9, 129.1, 128.5, 127.5, 127.4. mp 226-227 °C (lit. mp 227-229 °C).

Biphenyl-4,4'-dicarboxylic acid (3j).⁶ 4-Bromobenzoic acid (202.9 mg, 1.02 mmol) and 4-carboxyboronic acid (203.1 mg, 1.22 mmol) were coupled by the above procedure. The crude material was recrystallized from water to give a colorless crystalline solid (227.7 mg, 94%). Spectral data were consistent with that previously reported. ¹H NMR (360 MHz, DMSO-*d*₆): □ 8.05 (d, *J* = 8.05 Hz, 4H), 7.86 (d, *J* = 8.05 Hz). ¹³C NMR (90.6 MHz, CDCl₃): □ 165.7, 142.6, 129.5, 126.1, 107.3. mp: 309-310 °C (lit. mp: > 300 °C)

2',4'-Difluoro-4-hydroxybiphenyl-3-carboxylic acid (Diflunisal, 3k).⁷ 5-Bromosalicylic acid (157.3 mg, 1.00 mmol) and 2,4-difluorophenylboronic acid (195.5 mg, 1.23 mmol) were coupled by the above procedure. The crude material was recrystallized from water and a minimal amount of methanol to give a colorless crystalline solid (237.7 mg, 95%). Spectral data were consistent with that previously reported. ¹H NMR (360 MHz, DMSO-*d*₆): □ 7.91 (s, 1H), 7.66 (d, *J* = 8.09 Hz, 1H), 7.56 (dd, *J* = 8.82, 15.44 Hz, 1H), 7.33 (ddd, 2.20, 9.93, 9.93 Hz, 1H), 7.16 (ddd, 2.20, 8.09, 8.09 Hz, 1H), 7.06 (d, 8.82 Hz, 1H). ¹³C NMR (90.6 MHz, DMSO-*d*₆): □ 171.6, 161.8 (dd, *J*_{C-F} = 12.48, 224.72 Hz), 160.7, 158.9 (dd, *J*_{C-F} = 12.48, 226.10 Hz), 135.8 (d, *J*_{C-F} = 2.77 Hz), 131.5 (dd, *J*_{C-F} = 4.16, 9.71 Hz), 130.3 (d, *J*_{C-F} = 2.77 Hz) 125.1, 123.7 (dd, *J*_{C-F} = 4.16, 12.48 Hz), 117.6, 113.2, 112.1 (dd, *J*_{C-F} = 2.77, 20.81 Hz), 105.1 (dd, *J* = 26.35, 26.35 Hz). mp: 210-211°C (lit. mp⁸ 210-211°C)

2',4'-Difluorobiphenyl-3-carboxylic acid (3l).⁹ 3-Bromobenzoic acid (203.1 mg, 1.01 mmol) and 2,4-difluoroboronic acid (193.1 mg, 1.21 mmol) were coupled by the above procedure. The crude material was recrystallized from water and a minimal amount of methanol to give a pale yellow solid (224.8 mg, 96%). Spectral data is consistent with that previously reported. ¹H NMR (360 MHz, DMSO-*d*₆): □ 8.04 (s, 1H), 7.96 (d, *J* = 7.21 Hz, 1H), 7.75 (d, *J* = 7.21 Hz, 1H), 7.57-7.63 (m, 2H), 7.34 (ddd, *J* = 2.22, 9.98, 10.45, 1H), 7.19 (dd, 6.94, 8.88 Hz,

1H). ^{13}C NMR (90.6 MHz, DMSO- d_6): δ 1637.3, 162.1 (dd, $J_{\text{C-F}} = 12.48, 246.92$ Hz), 159.3 (dd, $J_{\text{C-F}} = 12.49, 248.30$ Hz), 134.7, 133.3, 132.2 (dd, $J_{\text{C-F}} = 4.17, 9.71$ Hz), 131.4, 129.6 (d, $J_{\text{C-F}} = 2.77$ Hz), 129.4, 129.0, 124.1 (dd $J_{\text{C-F}} = 4.16, 13.87$ Hz), 112.4 (dd, $J = 2.77, 20.80$ Hz), 104.8 (dd, 26.35, 26.35 Hz). mp: 223-224 °C.

Representative procedure for the Suzuki coupling in water/toluene (Table 5). In a dry box, a round bottom flask was charged with Na_2PdCl_4 (5.8 mg, 0.02 mmol), *t*-Bu-Amphos (5.4 mg, 0.02 mmol), sodium carbonate (166 mg, 2.00 mmol), aryl halide (1.0 mmol), and arylboronic acid (1.2 mmol). The flask was sealed with a septum and removed from the dry box. Degassed toluene (2.5 mL) and water (2.5 mL) were added and the reaction stirred at room temperature until GC analysis showed no residual aryl bromide (6-8 hours). The reaction was taken up in water and the product extracted with ethyl acetate (3 \times 25 mL). The crude material was flash chromatographed on a short silica gel column eluting with a mixture of ethyl acetate and hexanes.

Procedure for catalyst recycling experiment (Table 6). Using the general procedure above, 4-bromotoluene (0.2 mmol) and phenylboronic acid (0.22 mmol) were coupled in the presence of Na_2PdCl_4 (0.004 mmol), *t*-Bu-Amphos (0.004 mmol), sodium carbonate (0.4 mmol) in 0.5 mL water and 0.5 mL toluene. After stirring for 8 hours at room temperature, the organic product was extracted with toluene and analyzed by GC to determine the product yield using mesitylene (10 μL) as internal standard. To the remaining water solution containing the catalyst, 0.5 mL degassed toluene, phenylboronic acid (0.22 mmol), sodium carbonate (0.28 mmol), 4-bromo-toluene (0.2 mmol), and mesitylene (10 μL) were added. The reaction was allowed to stir as before and analyzed by GC. This cycle was repeated for each subsequent cycle. After the fourth cycle, the reaction could no longer be stirred due to precipitation of a large amount of salt.

After toluene extraction, the salts were extracted with acetonitrile:water 1:1. The solvent was then removed under vacuum and the residue was taken back up in neat water. This catalyst solution was then used as above in cycle 5.

Representative procedure for the Sonogashira cross-coupling reactions (Table 8).

Pd(OAc)₂ (8.8 mg, 0.03 mmol), *t*-Bu-Amphos (8.0 mg, 0.03 mmol), and copper iodide (1.9 mg, 0.01 mmol) were added to a 50 mL round bottom equipped with a stir bar and rubber septum while in the dry box. Upon removing from dry box, the aryl bromide (1.00 mmol), diisopropylamine (122 mg, 1.20 mmol), degassed 1:1 CH₃CN:H₂O (10 mL), and alkyne (1.20 mmol), were added via syringe. For the best conversion the alkyne should be added last. The reaction was placed in a pre-heated oil bath and allowed to stir until determined to be complete by GC. The reaction was poured into saturated sodium carbonate (50 mL), extracted with ethyl acetate (3 × 30 mL), and dried with MgSO₄. Products were purified by flash chromatography (SiO₂).

4-(Phenylethynyl)acetophenone (5b).¹⁰ Using the general procedure, 4-bromoacetophenone (201.0 mg, 1.00 mmol) was coupled with phenylacetylene. The crude product was chromatographed eluting with hexane:EtOAc. The crude product was then recrystallized from hexane:toluene to give **5b** (188.7 mg, 85 % yield) as a tan solid. Spectral data were consistent with that previously reported. ¹H NMR (360 MHz, CDCl₃): δ 7.94 (d, *J*=8.02 Hz, 2H), 7.56 (m, 4H), 7.37 (m, 3H), 2.61 (s, 3H). ¹³C NMR (90.6 MHz, CDCl₃): δ 197.6, 136.5, 132.1, 132.0, 129.1, 128.7, 128.5, 122.9, 93.0, 88.8, 26.8. mp 94-96 °C (lit. mp 95-97 °C).

4-(4-Methylphenyl)-3-butyn-1-ol (5c).¹¹ Using the general procedure, 4-bromotoluene (171.0 mg, 1.00 mmol) was coupled with 3-butyn-1-ol. The crude product was chromatographed eluting with a 3:1 ratio of hexane:acetone to give **5c** (146.8 mg, 94%) as a yellow oil. Spectral

data were consistent with that previously reported. ^1H NMR (360 MHz, CDCl_3): δ 7.30 (d, $J=8.02$ Hz, 2H), 7.07 (d, $J=8.02$ Hz, 2H), 3.78 (t, $J=6.16$ Hz, 2H), 3.65 (t, $J=6.16$ Hz, 2H), 2.47 (brs, 1H), 2.31 (s, 3H). ^{13}C NMR (90.6 MHz, CDCl_3): δ 138.1, 131.8, 129.2, 120.6, 85.9, 82.6, 61.4, 24.0, 21.6.

4-(Phenylethynyl)anisole (5d)¹² Using the general procedure, 4-bromoanisole (186.8 mg, 1.00 mmol) was coupled with phenylacetylene. The crude product was chromatographed eluting with hexane followed by hexane: MeCl_2 :EtOAc (75:20:5) to give **5d** (162.1 mg, 78%). Spectral data were consistent with that previously reported. ^1H NMR (360 MHz, CDCl_3): δ 7.50 (m, 4H), 7.33 (m, 3H), 6.88 (m, 2H), 3.82 (s, 3H). ^{13}C NMR (90.6 MHz, CDCl_3): δ 159.9, 133.3, 131.7, 128.5, 128.2, 123.8, 115.6, 114.2, 89.6, 88.3, 55.5.

4-(1-Hexynyl)benzoic acid (5e)¹³ Using the general procedure, 4-bromobenzoic acid (203 mg, 1.01 mmol) and phenyl boronic acid were coupled. The crude product was recrystallized from hot methanol to give **5e** (186.1 mg, 92 %) as a pale yellow solid. ^1H NMR (360 MHz, CDCl_3): δ 7.86 (d, $J=8.2$ Hz, 2H), 7.34 (d, $J=8.3$ Hz, 2H), 2.40 (t, $J=6.8$ Hz, 2H), 1.63 (m, 2H), 1.50 (m, 2H), 0.89 (t, $J=6.80$ Hz, 3H). ^{13}C NMR (90.6 MHz, CDCl_3): δ 170.2, 130.3, 129.6, 128.7, 127.2, 93.3, 78.9, 29.4, 21.0, 18.8, 12.1. mp: 143-145 °C.

4-(Phenylethynyl)benzoic acid (5f)¹⁴ 4-Bromobenzoic acid (202.9 mg, 1.02 mmol) and phenylacetylene (132 μL , 1.20 mmol) were coupled by the above procedure. The crude material was recrystallized from water and a minimal amount of methanol to give **5f** (204.5 mg, 92%) as a colorless solid. ^1H NMR (360 MHz, $\text{DMSO}-d_6$): δ 8.05 (m, 7H), 7.87 (m, 2H). ^{13}C NMR (90.6 MHz, CD_3CN): δ 167.2, 143.1, 131.7, 131.3, 130.4, 130.0, 129.5, 127.1, 81.3, 79.9. One aromatic carbon was masked by solvent. mp: 218-219 °C (lit. mp: 221-222 °C).

2-(Phenylethynyl)toluene (5g).¹² Using the general procedure, 2-bromotoluene (170.6 mg, 1.00 mmol) was coupled with phenylacetylene. The crude product was chromatographed eluting with hexane to give **5g** (172.4 mg, 90%) as a light yellow oil. Spectral data were consistent with that previously reported. ¹H NMR (360 MHz, CDCl₃): δ 7.39 (m, 3H), 7.18 (m, 3H), 7.07 (d, $J=3.70$ Hz, 2H), 7.08 (m, 1H), 2.38 (s, 3H). ¹³C NMR (90.6 MHz, CDCl₃): δ 140.5, 132.1, 131.8, 129.8, 128.7, 128.6, 128.5, 125.9, 123.9, 123.4, 93.7, 88.7, 21.03.

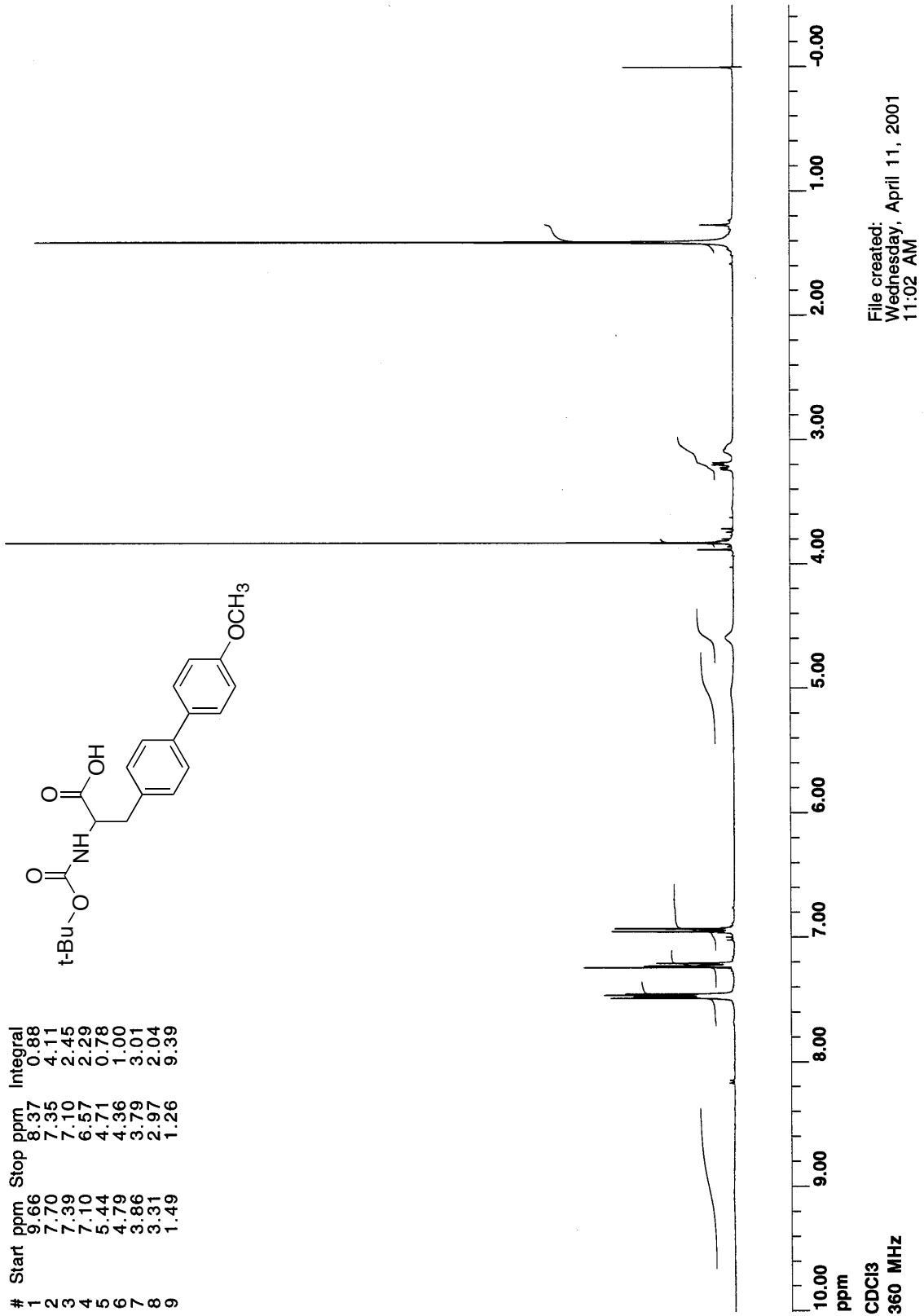
3-Methyl-4-(phenylethynyl)anisole (5h). Using the general procedure, 4-bromo-3-methylanisole (186.8 mg, 1.00 mmol) was coupled with phenylacetylene. The crude product was chromatographed eluting with hexane to give **5h** (159.7 mg, 73%) as an off white solid. ¹H NMR (360 MHz, CDCl₃): δ 7.51 (dd, $J=1.66, 7.77$ Hz, 2H), 7.42 (d, $J=8.32$ Hz, 1H), 7.32 (m, 3H), 6.77 (d, $J=2.78$ Hz, 1H), 6.73 (dd, $J=2.22, 8.32$ Hz, 1H), 3.81 (s, 3H), 2.50 (s, 3H). ¹³C NMR (90.6 MHz, CDCl₃): δ 159.8, 142.2, 133.4, 131.6, 128.5, 128.1, 124.1, 115.6, 115.4, 111.5, 92.2, 88.6, 55.5, 21.3. mp: 77-79 °C.

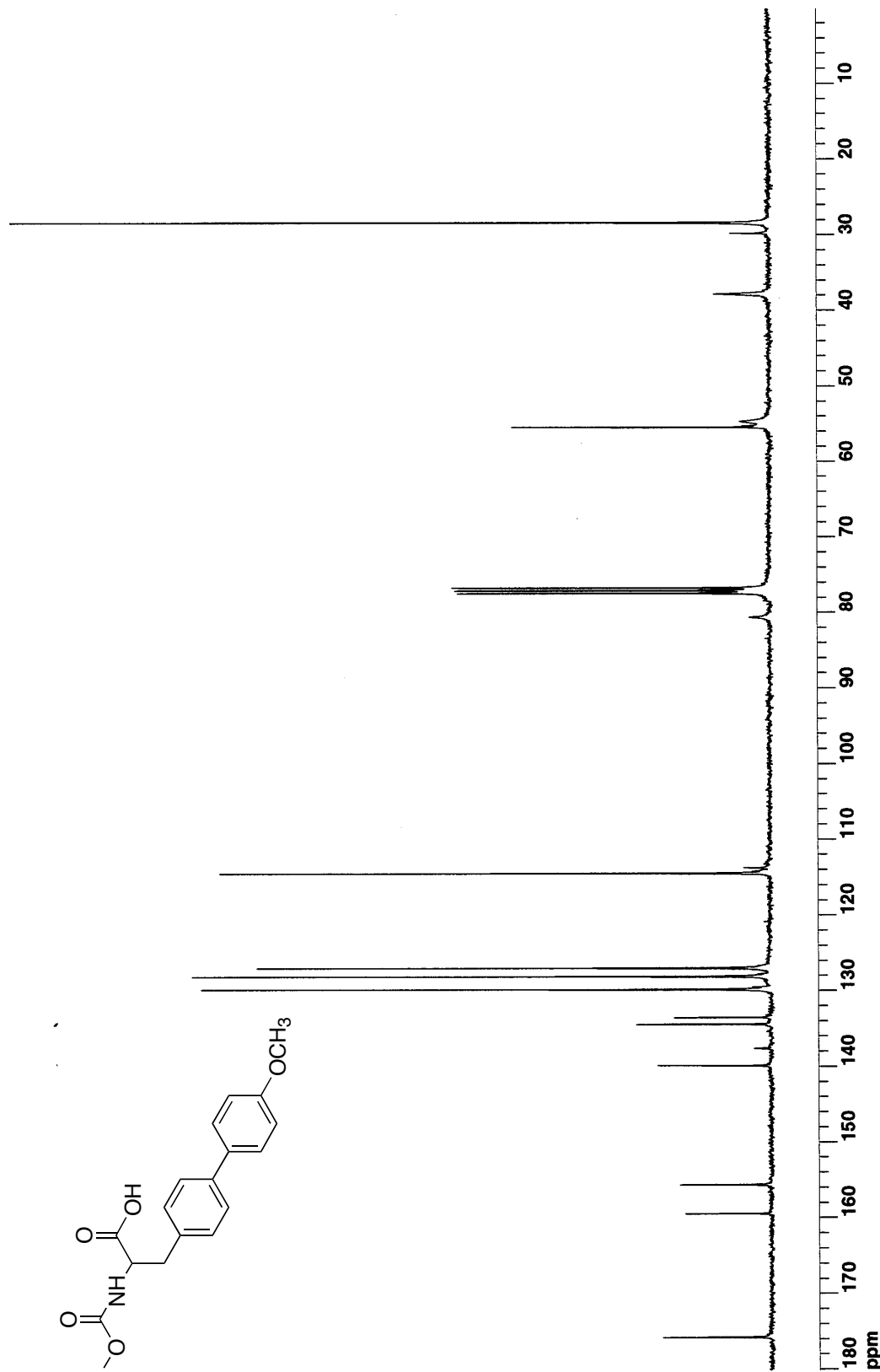
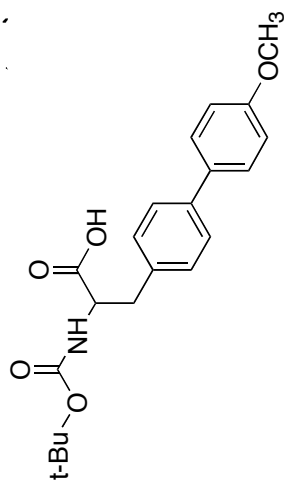
2,6-Dimethyl-1-(phenylethynyl)benzene (5i).¹⁵ 2-Bromo-*m*-xylene (135 μ L, 1.01 mmol) and phenylacetylene (132 μ L, 1.20 mmol) were coupled by the above procedure. The crude material was purified by flash chromatography to give **5i** (61.9 mg, 30%) as a colorless oil. Spectral data were consistent with that previously reported. ¹H NMR (360 MHz, CDCl₃): δ 7.50 (d, $J=7.22$ Hz, 2H), 7.25 (m, 8H), 2.31 (s, 6H). ¹³C NMR (90.6 MHz, CDCl₃): δ 136.4, 134.2, 128.8, 128.0, 127.7, 127.1, 126.9, 126.4, 78.9, 76.5, 21.2.

Representative procedure for the Heck coupling reactions (Table 10). Pd(OAc)₂ (5.6 mg, 0.025 mmol), *t*-Bu-Amphos (6.7 mg, 0.025 mmol) were added to a 50mL round bottom equipped with a stir bar and rubber septum while in the dry box. The appropriate alkene (1.50 mmol) was added either in the dry box (sodium acrylate) or via syringe after removal from the

dry box (styrene). Upon removing from dry box, the aryl bromide (1.00 mmol), diisopropylamine (107.4 mg, 1.05 mmol), and degassed 1:1 CH₃CN:H₂O (10 mL) were added via syringe. The round bottom was placed in an oil bath at 80 °C and allowed to stir for several hours. The reaction mixture was added to saturated sodium carbonate (50mL). Coupled products derived from styrene were extracted with ethyl acetate (3 × 30 mL). The solvent was removed and the crude product purified by column chromatography. When sodium acrylate was used, the crude reaction was extracted with ethyl acetate (3 × 30 mL) and the extracts discarded. The pH of the aqueous phase was then brought to ca. 1 using concentrated H₂SO₄. The cinnamic acid product was extracted with CH₂Cl₂ (3 × 30 mL) and the combined organic extracts were dried over MgSO₄. Removal of solvent under reduced pressure gave the crude product, which was recrystallized from H₂O/Ethanol.

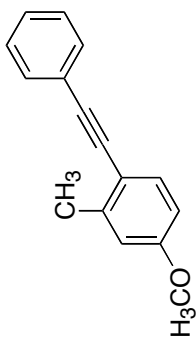
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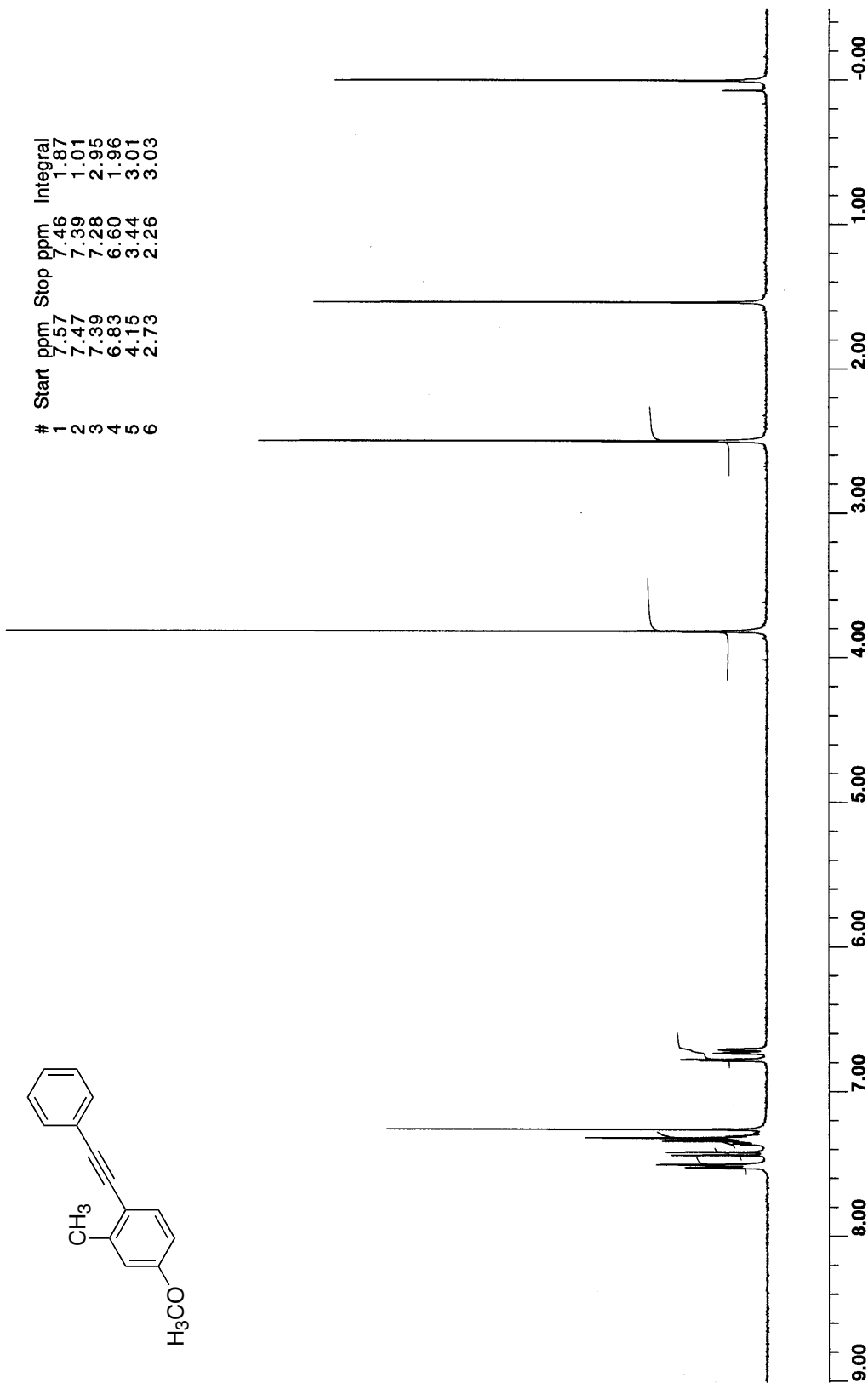


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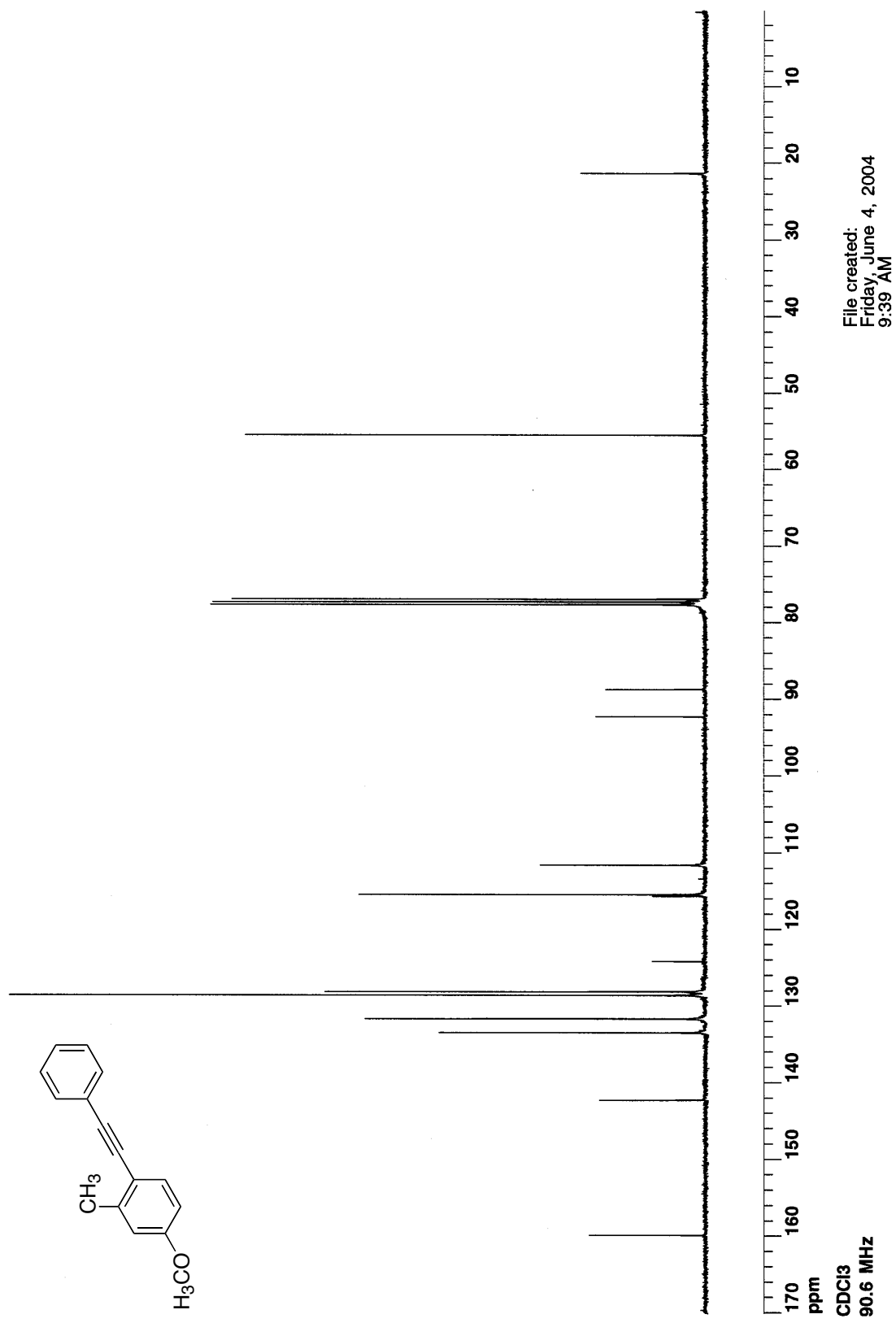


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5	4.15	3.44	3.01
6	2.73	2.26	3.03



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CDCI3
360 MHz



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