Supporting Information

for

Carbonylative Cross-Coupling of *ortho*-Disubstituted Aryl Iodides. Convenient Synthesis of Sterically Hindered Aryl Ketones.

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Experimental Procedures:

General. Unless otherwise noted, solvents and reagents were used without further purification. Tetrahydrofuran was dried by filtration through two columns of activated, neutral alumina according to the procedure described by Grubbs.¹ Dioxane was distilled from sodium metal and benzophenone prior to use. *N*-methylpyrrolidinone was dried over 4 Å MS before use. Dimethylformamide was dried by filtration through two columns of activated molecular sieves. ZnBr₂ was sublimed under reduced pressure before use and stored in a desiccator. *Cs*₂*CO*₃ *powder was purchased from Alfa Aesar (Stock # 12887) and stored in a desiccator. The source of Cs*₂*CO*₃ *(and particle size) may be critical for the success of the reaction.* CO_(g) (99.9%) was obtained from Praxair. All reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen or argon in glassware that was flame dried.

Carbonylative Suzuki Cross-Coupling of *ortho*-Disubstituted Aryl Iodides (60 psi, Method A):

The aryl iodide (1.0 mmol), boronic acid (2.0 mmol), PEPPSI-*i*Pr (0.03 mmol) and Cs_2CO_3 (2.5 mmol) were placed into a 10 ml glass sleeve fitted with a rubber septum. The sleeve was then evacuated and backfilled with $CO_{(g)}$ three times. Dioxane (5.0 mL) was added, and the mixture sparged with $CO_{(g)}$ for 2 min, whereupon the rubber septum was removed, and the glass sleeve was quickly sealed in a stainless steel pressure reactor. The reactor was evacuated and backfilled with $CO_{(g)}$ (3 cycles, 60 psi). The reactor was heated at 140 °C (oil bath) with stirring for 24 h at 60 psi of $CO_{(g)}$. The reaction mixture was filtered through a pad of Celite, eluting with EtOAc. The filtrate was washed with H₂O (20 mL), brine (20 mL), dried (MgSO₄), filtered and the organics were concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with the indicated solvent to afford the desired benzophenone.

⁽¹⁾ Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. Organometallics 1996, 15, 1518.

Carbonylative Suzuki Cross-Coupling of *ortho*-Disubstituted Aryl Iodides (balloon pressure, Method B):

The aryl iodide (1.0 mmol), boronic acid (2.0 mmol), PEPPSI-*i*Pr (0.03 mmol) and Cs_2CO_3 (3.0 mmol) were placed into a 25 mL round bottomed flask that was fitted with a reflux condenser. Chlorobenzene (5 mL) was added, and the flask was evacuated and backfilled with $CO_{(g)}$ (3 cycles). The mixture was heated to 80 °C (oil bath) with stirring for 24 h under a balloon of $CO_{(g)}$. The reaction mixture was filtered through a pad of Celite, eluting with EtOAc, and the filtrate was washed with H₂O (20 mL), brine (20 mL), dried (MgSO₄), filtered and the organics were concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with the indicated solvent to afford the desired benzophenone.

Carbonylative Negishi Coupling of *ortho*-Disubstituted Aryl Iodides with Alkynylzinc Reagents (Method C):

n-BuLi (0.63 mmol, 2.12 M solution in hexanes) was added dropwise to a solution of the alkyne (0.60 mmol) in THF (1.0 mL) at -78 °C. The resultant solution was stirred for 30 min, whereupon a solution of ZnBr₂ (0.63 mmol) in THF (0.65 mL) was added. The cooling bath was removed, and the solution was warmed to ambient temperature. The aryl iodide (0.30 mmol), PEPPSI-*i*Pr (0.009 mmol) and LiBr (0.90 mmol) were placed into a dry, 10 mL glass sleeve. The sleeve was placed into the metal jacket of the stainless steel pressure reactor, fitted with a rubber septum, and placed under nitrogen. NMP (2 mL) was added, and the mixture was cooled to -78 °C, whereupon the previously prepared zinc acetylide solution (2 mL, 0.3 M) was added dropwise. The jacket was removed from the bath, and the pressure reactor was sealed. The reactor was evacuated and backfilled with $CO_{(g)}$ (3 cycles, 60 psi). The reactor was heated to 80 °C (oil bath) with stirring for 24 h at 60 psi of $CO_{(g)}$. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and brine (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organics were dried (MgSO₄), filtered and were concentrated under reduced pressure. The crude residue was purified

by flash column chromatography, eluting with the indicated solvent to deliver the desired ketone.



2,6-Dimethylbenzophenone (2). Method A: 82%. Method B: 95% of **2** as an off-white solid (98:2 hexanes/EtOAc); mp = 64 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, *J* = 7.2 Hz, 2 H), 7.57 (comp, 1 H), 7.43 (t, *J* = 7.9 Hz, 2 H), 7.22 (t, *J* = 7.0 Hz, 1 H), 7.06 (d, *J* = 7.0 Hz, 2 H), 2.10 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 200.5, 139.6, 136.9, 134.1, 133.7, 129.4, 128.8, 128.7, 127.5, 19.4; IR (neat) 3061, 1673 cm⁻¹; mass spectrum (CI) *m/z* 211.1123 [C₁₅H₁₅O (M + 1) requires 211.1123], 421, 212, 211.



2,2',6-Trimethylbenzophenone (6a). Method A: 93%. Method B: 99% of **6a** as a white solid (98:2 hexanes/EtOAc): mp = 68-69 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.42-7.36 (m, 2 H), 7.31 (d, *J* = 7.2 Hz, 1 H), 7.24-7.20 (m, 1 H), 7.16 (t, *J* = 7.5 Hz, 1 H), 7.06 (d, *J* = 7.5 Hz, 2 H), 2.73 (s, 3 H), 2.14 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 202.3, 141.1, 140.1, 136.4, 134.1, 132.3, 132.2, 131.9, 128.6, 127.6, 125.9, 21.8, 19.3; IR (neat) 2922, 1665, 1454 cm⁻¹; mass spectrum (CI) *m/z* 225.1280 [C₁₆H₁₇O (M + 1) requires 225.1279], 253, 226, 225.



2,6-Dimethyl-4'-methoxybenzopheone (6b). Method A: >99%. Method B: 75% of **6b** as a yellow oil that solidified on standing (9:1 hexanes/EtOAc): mp = 37-38 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.75 (comp, 2 H), 7.19 (t, *J* = 7.7 Hz, 1 H), 7.03 (d,

J = 7.7 Hz, 2 H), 6.89 (d, J = 8.9 Hz, 2 H), 3.82 (s, 3 H), 2.10 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 198.8, 163.9, 139.8, 133.9, 131.6, 130.0, 128.4, 127.4, 113.9, 55.3, 19.2; IR (neat) 2954, 1665 cm⁻¹; mass spectrum (CI) *m/z* 241.1228 [C₁₆H₁₇O₂ (M + 1) requires 241.1229], 481, 242, 241.



4'-Cyano-2,6-dimethylbenzophenone (6c). Method A: 43%. Method B:13% of **6c** as an off-white solid (9:1 hexanes/EtOAc): mp = 90-91 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, *J* = 8.4 Hz, 2 H), 7.74 (d, *J* = 8.4 Hz, 2 H), 7.25 (t, *J* = 7.5 Hz, 1 H), 7.07 (d, *J* = 7.5 Hz, 2 H), 2.07 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 198.9, 139.7, 138.2, 134.1 (2C), 132.7 (2C), 129.5 (2C), 129.3, 127.8 (2C), 117.8, 116.8, 19.3 (2C); IR (neat) 2922, 2231, 1676 cm⁻¹; mass spectrum (CI) *m/z* 236.1079 [C₁₆H₁₃NO (M + 1) requires 236.1075], 268, 264, 236.



2,6-Dimethyl-2',6'-dimethoxybenzophenone (6d). Method A: 62%. Method B: 95% of **6d** as an off-white solid (9:1→ 0:1 hexanes/EtOAc): mp = 139-140 ° C; ¹H NMR (400 MHz, CDCl₃) δ 7.28 (t, *J* = 8.4 Hz, 1 H), 7.09 (t, *J* = 7.6 Hz, 1 H), 6.94 (d, *J* = 7.6 Hz, 2 H), 6.52 (d, *J* = 8.4 Hz, 2 H), 3.63 (s, 6 H), 2.20 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 199.1, 158.5, 142.2, 135.1, 132.0, 128.4, 127.6, 120.4, 104.4, 55.8, 19.5; IR (neat) 2951, 1666 cm⁻¹; mass spectrum (CI) *m/z* 271.1337 [C₁₇H₁₉O₃ (M + 1) requires 271.1334], 272, 271, 239, 165.



3-(2',6'-Dimethylbenzoyl)thiophene (6e). Method B: 50% of **6e** as a pale orange/pink solid (9:1 hexanes/EtOAc): mp = 65-66 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.71 (dd, *J* = 2.9, 1.2 Hz, 1 H), 7.53 (dd, *J* = 5.1, 1.2 Hz, 1 H), 7.32 (dd, *J* = 5.1, 2.9 Hz, 1 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 7.04 (d, *J* = 7.6 Hz, 2 H), 2.14 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 194.1, 143.0, 140.4, 135.1, 133.9, 128.7, 127.5, 127.0, 126.9, 19.3; IR (neat) 2921, 1659 cm⁻¹; mass spectrum (CI) *m/z* 217.0692 [C₁₃H₁₂OS (M + 1) requires 217.0687], 433, 327, 245, 218, 217.



2,4,4',6-Tetramethoxybenzophenone (6f) Method B: 52% of 6f as a white solid (9:1 → 4:1 hexanes/EtOAc): mp = 144 °C (EtOH); ¹H NMR (400 MHz, CDCl₃) δ 7.81-7.77 (comp, 2 H), 6.88-6.84 (comp, 2 H), 6.14 (s, 2 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.65 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 193.6, 163.4, 162.1, 158.4, 131.7, 131.3, 113.4, 111.1, 90.6, 55.7, 55.37, 55.33; IR (neat) 2940, 1661 cm⁻¹; mass spectrum (ESI) *m/z* 303.12270 [C₁₇H₁₉O₅ (M + 1) requires 303.1231], 331, 304, 303.



2,2',4,6,6'-Pentamethoxybenzophenone (6g). Method B: 33% of 6g as a tan solid (9:1 → 0:1 hexanes/EtOAc): mp = 142-143 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.18 (t, *J* = 8.3 Hz, 1 H), 6.49 (d, *J* = 8.3 Hz, 2 H), 6.04 (s, 2 H), 3.79 (s, 3 H), 3.67 (s, 6 H), 3.64 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 192.8, 162.6, 160.3, 157.91, 130.1, 122.9, 115.0, 104.4, 91.0, 56.25, 56.28, 55.3; IR (neat) 2939, 1673 cm⁻¹; mass spectrum (ESI) *m/z* 333.13327 [C₁₈H₂₁O₆ (M + 1) requires 333.1338], 361, 334, 333.



2-Hydroxy-4,6-dimethylbenzophenone (6h). Method B (K₂CO₃ was used as the base): 51% of **6h** as an off-white solid (9:1 hexanes/EtOAc): mp = 138-139 °C; ¹H NMR (400 MHz, CDCl₃) δ 9.41 (s, 1 H), 7.66-7.63 (comp, 2 H), 7.56-7.52 (comp, 1 H), 7.45-7.41 (comp, 2 H), 6.69 (s, 1 H), 6.55 (s, 1 H), 2.30 (s, 3 H), 1.91 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 201.4, 159.4, 144.6, 140.4, 138.8, 132.6, 128.8, 128.6, 124.0, 120.2, 115.4, 22.6, 21.6; IR (neat) 3352 (br), 2922, 1651 cm⁻¹; mass spectrum (ESI) *m/z* 249.08860 [C₁₅H₁₄O₂Na (M + Na) requires 249.0891], 255, 228, 227.



2-Chloro-6-methylbenzophenone (6i). Method B: 89% of **6i** as a colorless oil that solidified upon standing (9:1 hexanes/EtOAc): mp = 54-55 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.81-7.79 (comp, 2 H), 7.59-7.54 (comp, 1 H), 7.46-7.41 (comp, 2 H), 7.26-7.23 (comp, 2 H), 7.15-7.13 (comp, 1 H), 2.15 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 196.3, 138.4, 136.8, 136.1, 133.9, 130.2, 129.8, 129.4, 128.8, 128.6, 126.7, 19.2; IR (neat) 3061, 1674 cm⁻¹; mass spectrum (CI) *m/z* 231.0579 [C₁₄H₁₂ClO (M + 1) requires 231.0577], 233, 232, 231.



(*E*)-1-(2',6'-dimethylphenyl)-4-methylhex-4-en-2-yn-1-one (8a). Method A: 49% of 8a as a yellow oil (9:1 hexanes/EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 7.16 (t, *J* = 7.7 Hz, 1 H), 7.01 (d, *J* = 7.7 Hz, 2 H), 6.27 (qq, *J* = 7.2, 1.7 Hz, 1 H), 2.35 (s, 6 H), 1.82 (comp, 3 H), 1.75 (comp, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 184.6, 141.1, 140.5, 134.6, 129.3, 128.1, 117.1, 97.6, 86.8, 19.6, 16.1, 14.7; IR (neat) 2924, 2180, 1646 cm⁻¹; mass spectrum (CI) m/z 213.1276 [C₁₅H₁₇O (M + 1) requires 213.1279], 213, 213.



1-(2',6'-Dimethylphenyl)-3-phenylprop-2-yn-1-one (8b). Method C: 80% of **8b** as a light yellow oil (9:1 hexanes/EtOAc): ¹H NMR (400 MHz, CDCl₃) δ 7.58-7.55 (comp, 2 H), 7.47-7.42 (comp, 1 H), 7.39-7.34 (comp, 2 H), 7.21 (t, *J* = 7.7 Hz, 1 H), 7.06 (d, *J* = 7.7 Hz, 2 H), 2.42 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 184.4, 140.1, 134.8, 133.2, 130.9, 129.6, 128.6, 128.2, 119.9, 93.6, 89.3, 19.6; IR (neat) 2959, 2191, 1645 cm⁻¹; mass spectrum (CI) *m/z* 235.1126 [C₁₇H₁₄O (M + 1) requires 235.1123], 470, 469, 236, 235, 133.



1-(2',6'-Dimethylphenyl)-3-(4''-methoxyphenyl)prop-2-yn-1-one (8c). Method C: 75% of 8c as a yellow oil (9:1 hexanes/EtOAc): ¹H NMR (400 MHz, CDCl₃) δ 7.53-7.50 (comp, 2 H), 7.20 (t, J = 7.7 Hz, 1 H), 7.05 (d, J = 7.7 Hz, 2 H), 6.89-6.85 (comp, 2 H), 3.82 (s, 3 H), 2.40 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 184.5, 161.8, 140.4, 135.3, 134.7, 129.4, 128.1, 114.3, 111.7, 95.0, 89.4, 55.4, 19.6; IR (neat) 2961, 2183, 1643 cm⁻¹; mass spectrum (CI) *m/z* 265.1229 [C₁₈H₁₇O₂ (M + 1) requires 265.1229], 529, 266, 265.



1-(2'-Methoxy-4',6'-dimethylphenyl)-3-phenylprop-2-yn-1-one (8d). Method C (3 mol % PPh₃ was added to the reaction mixture and the pressure was increased to 170

psi of CO): 67% of **8d** as a yellow oil (9:1 hexanes/EtOAc): ¹H NMR (400 MHz, CDCl₃) δ 7.55-7.53 (comp, 2 H), 7.43-7.39 (comp, 1 H), 7.36-7.32 (comp, 2 H), 6.64 (s, 1 H), 6.62 (s, 1 H), 3.85 (s, 3 H), 2.35 (s, 3 H), 2.33 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 181.0, 158.0, 141.9, 137.5, 133.0, 130.4, 128.5, 126.7, 124.0, 120.6, 110.0, 90.9, 90.1, 55.8, 21.7, 19.5; IR (neat) 2925, 2193, 1644 cm⁻¹; mass spectrum (ESI) *m/z* 265.12231 [C₁₈H₁₇O₂ (M + 1) requires 265.1228], 288, 265, 163.



2-Iodo-1-methoxy-3,5-dimethylbenzene (7). Sodium hydride (0.32 g, 8.1 mmol) was added in one portion to a solution of 2-iodo-3,5-dimethylphenol (1.0 g, 4.0 mmol) and methyl iodide (1.3 mL, 20.2 mmol) in DMF (20 mL) at 0 °C. After gas evolution had subsided, the cooling bath was removed, and the mixture was stirred at ambient temperature for 30 min. The mixture was recooled to 0 °C, whereupon saturated NH₄Cl (10 mL) was slowly added. The mixture was diluted with EtOAc (50 mL), and the layers were separated. The organic layer was washed with H₂O (4 x 50 mL) and brine (50 mL), dried (MgSO₄), filtered, and was concentrated. The crude residue was purified by flash column chromatography, eluting with hexanes/ethyl acetate (9:1), to afford 0.95 g (90%) of 7 as a white solid: mp = 43-44 °C; ¹H NMR (400 MHz, CDCl₃) δ 6.72 (s, 1 H), 6.46 (s, 1 H), 3.85 (s, 3 H), 2.43 (s, 3 H), 2.30 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 157.8, 142.7, 138.7, 123.2, 109.0, 88.8, 56.2, 28.4, 21.1; IR (neat) 2936, 1572, 1457 cm⁻¹; mass spectrum (ESI) *m/z* 262.99273 [C₉H₁₂IO (M + 1) requires 262.9927], 263, 262.



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