

Supporting Information for

Copper-Catalyzed Aerobic Oxidative Functionalization of an Arene C–H

Bond: Evidence for an Aryl-Copper(III) Intermediate

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Experimental Procedures and Characterization Data

General Considerations

Substrate **1** was synthesized using previously published procedures, and complex **2** was identified by comparison with previously reported characterization data.¹ X-band CW EPR data were collected using a Bruker ESP 300E spectrometer equipped with a Varian EIP model 625A CW frequency counter; the temperature was controlled at 77 K using a liquid-N₂ Dewar. A solution of known CuBr₂ concentration (3.8 mM) was used as an external standard. All spectra were acquired under non-saturating conditions (0.64 mW, 9.34 MHz) with a field modulation of 10.54 G and a frequency of 100 kHz. A computer-interfaced manometry apparatus was used to measure O₂ consumption and the rates of reactions. Electronic absorption spectra were acquired using an Ocean Optics USB4000 photodiode array spectrometer equipped with a USB-ISS-VIS direct attach accessory. Full characterization of **3** has been previously reported by us.²

Aerobic synthesis of 2.

A representative procedure for the synthesis of aryl copper(III) species **2** is as follows. A DMF solution of Cu(ClO₄)₂·6H₂O (50 mM, 1.5 mL, 75 μmol) was added to 1 mL of a solution of **1** (75 mM, 75 μmol) and trimethoxybenzene (20.2 mM, 20.2 μmol) in DMF under an atmosphere of O₂. The reaction was allowed to proceed for 2.5 hours, and the DMF was removed via rotary evaporation. The residue was redissolved in CD₃CN with a minimal amount of DMSO-d₆ to ensure that all solids were dissolved. The amount of **2** formed under different conditions was determined by ¹H NMR spectroscopy (Table 1).

(1) Ribas, X.; Jackson, D. A.; Donnadieu, B.; Mahía, J.; Parella, T.; Xifra, R.; Hedman, B.; Hodgson, K. O.; Llobet, A.; Stack, T. D. P. *Angew. Chem. Int. Ed.* **2002**, *41*, 2991-2994.

(2) Casitas, A.; King, A. E.; Parella, T.; Costas, M.; Stahl, S. S.; Ribas, X. *Chem. Sci.* DOI:10.1039/C0SC00245C.

Stoichiometric synthesis of 4

In a dry flask under an N₂ atmosphere, the arylcopper(III) complex **2** (100 mg, 0.19 mmol) was dissolved in dry methanol (5 mL). The solution was stirred at room temperature for approximately 1 h, during which time the orange solution became colorless. The solvent was removed and the residue was dissolved in a mixture of CH₂Cl₂:CH₃OH:NH₄OH_{aq} (98:1:1 mL) and filtered through a silica plug to remove the copper. Removal of the solvent from the filtrate afforded the pure C–O coupling product **4** in 80% yield (40 mg, 0.15 mmol).

¹H NMR: (499.9 MHz, CD₃CN) δ 7.09 (d, J = 7.2 Hz, 2H), 6.99 (t, J = 7.2, 7.5 Hz, 1H), 4.27 (d, J = 14.3 Hz, 2H), 3.79 (s, 3H), 3.32 (d, J = 14.3 Hz, 2H), 2.48 (br s, 2H), 2.34 (m, 2H), 2.17 (br m, 2H), 1.94 (m, 2H), 1.83 (s, 3H), 1.47 (m, 4H), 2.30 (br s, 2H). ¹³C NMR: (125.7 MHz, CD₃CN) δ 160.97, 137.19, 132.71, 125.82, 63.05, 57.84, 52.53, 46.04, 42.05, 29.45. [ESI-HRMS] (*m/z*): [M+H]⁺ calculated for C₁₆H₂₈N₃O⁺: 278.2227, found: 278.2237.

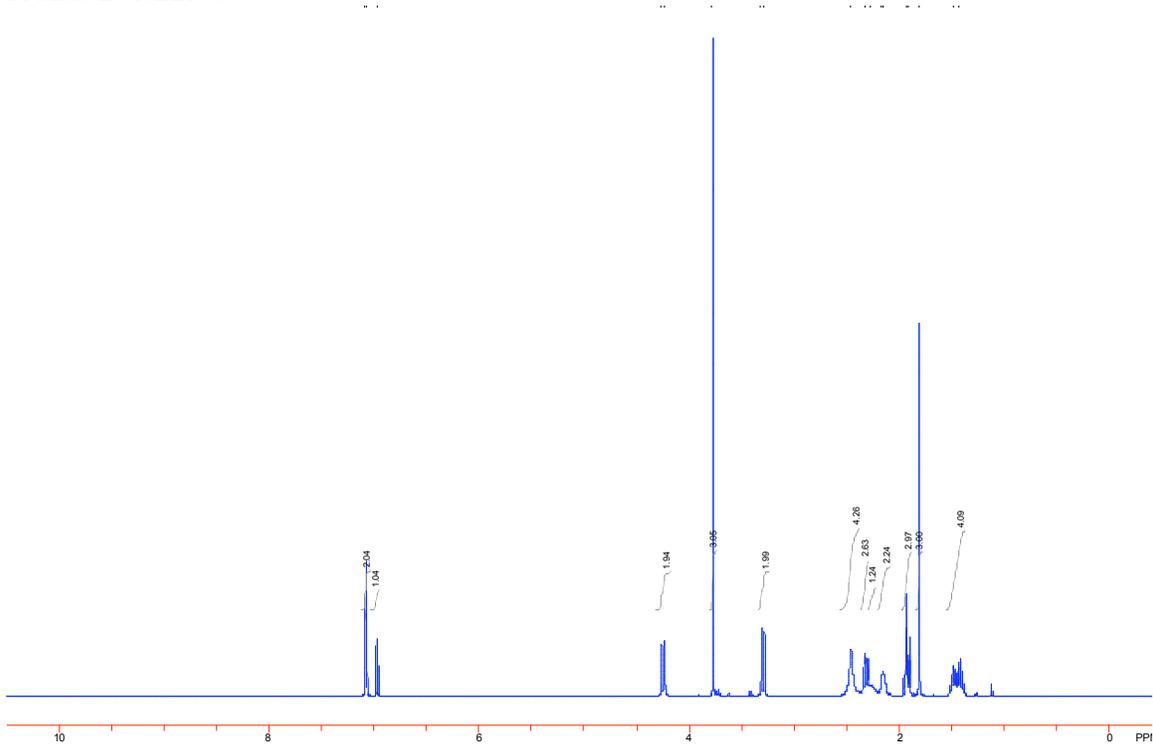


Figure S1: ¹H NMR spectrum of the arene methoxylation product **4**.

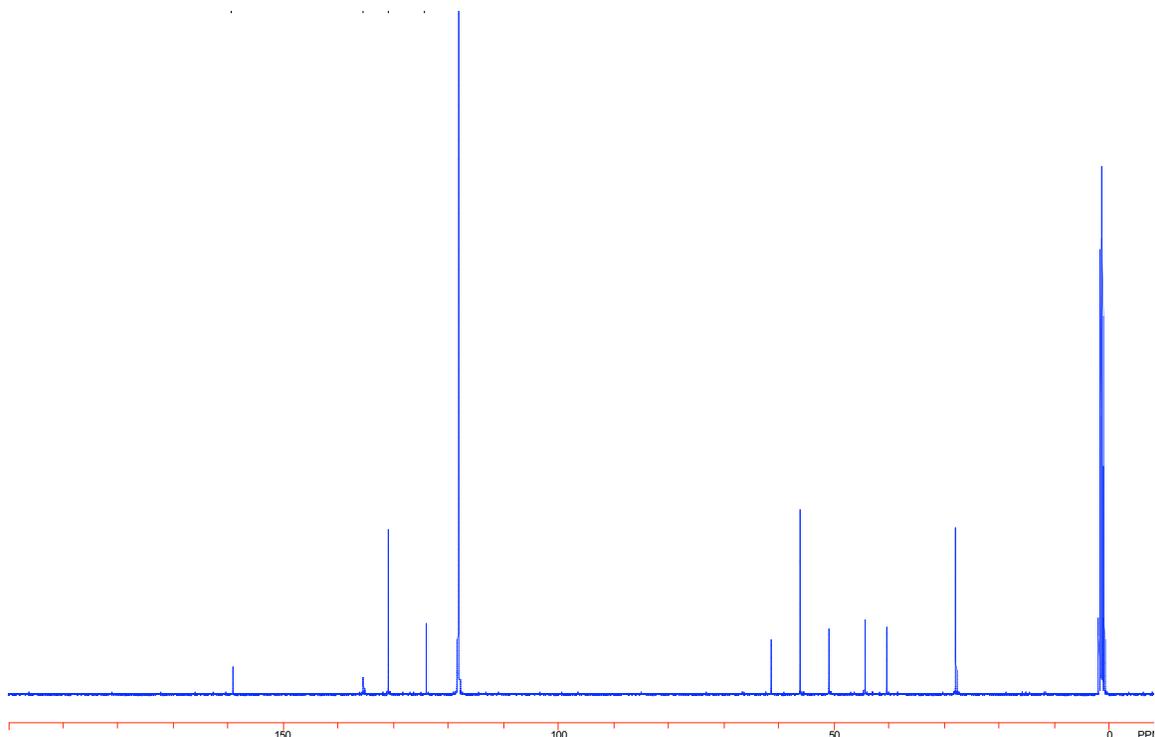


Figure S2: ^{13}C NMR spectrum of the methoxylated product **4**.

Gas-Uptake Kinetic studies

A typical kinetic run was conducted as follows. A volume-calibrated round-bottom flask equipped with a stirbar was attached to the gas-uptake apparatus. The flask was evacuated to 50 torr and filled with O_2 to 900 torr; this cycle was repeated 10 times, and the final pressure prior to substrate addition was set to 500 torr. A solution of the arene **1** in methanol (56 mM, 4.5 mL, 0.250 mmol) was added to the reaction vessel via syringe through a septum, and the pressure was allowed to equilibrate at 25 °C. Subsequently, the reaction was initiated by adding the $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ solution in methanol (25 mM, 0.5 mL, 0.013 mmol) via syringe through a septum (final solution molarity: $[\mathbf{1}] = 50$ mM, $[\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}] = 2.5$ mM). Data were acquired using a custom LabVIEW (National Instruments) software program. Rates were obtained by using the method of initial rates, and data fitting was performed by using Microsoft Excel.

Combined UV-Visible spectroscopy/manometry experiments

A typical kinetic run was conducted as follows. A Schlenk-modified UV-Vis cuvette was equipped with a stirbar and attached to the gas-uptake apparatus. The flask was evacuated to 50 torr and filled with O_2 to 900 torr; this cycle was repeated 10 times, and the final pressure prior to substrate addition was set to 500 Torr. The stock solution of **1** in methanol (12.5 mM, 2.4 mL, 0.030 mmol) was added to the cuvette via syringe through a septum, and the pressure was allowed to equilibrate at 25 °C. Subsequently, the reaction was initiated by adding the CuBr_2 solution in methanol (5.0 mM, 0.6 mL, 0.003 mmol) via syringe through a septum. Final solution molarity: $[\mathbf{1}] = 10$ mM, $[\text{CuBr}_2] = 1$ mM. Manometry data were acquired using a custom LabVIEW (National Instruments)

software program. Rates were obtained by using the method of initial rates. Electronic absorption data were acquired using an Ocean Optics USB4000 photodiode array spectrometer equipped with a USB-ISS-VIS direct attach accessory.

Catalytic synthesis of 5

A solution of 2-hydroxypyridine in CH₃OH (1 mL, [2-hydroxypyridine] = 750 mM) was added to a solution of ligand **1** in CH₃OH (1 mL, [**1**] = 150 mM). The resultant solution was stirred vigorously under O₂ atmosphere (1 atm) and the catalytic reaction was started by dropwise addition of a solution of Cu(ClO₄)₂·6H₂O in CH₃OH (1mL, [Cu(ClO₄)₂·6H₂O]= 15 mM). Final concentrations were as follows: [2-hydroxypyridine] = 250 mM, [**1**] = 50 mM, [Cu(ClO₄)₂·6H₂O] = 5 mM. After completion of the reaction, the solvent was removed under vacuum and 2 mL of CDCl₃ with an internal standard ([trimethoxybenzene] = 5mM) was added. Then, drops of NH₄OH were added to the mixture crude, dried with MgSO₄ and filtered in order to obtain a CDCl₃ solution ready for NMR. (¹H NMR yield: 77%; Note: a 99% yield of **5** was obtained when 20 mol % Cu(ClO₄)₂·6H₂O was used). The same procedure was done using CuBr₂ as a copper source in the catalytic reaction. (¹H NMR yield: 84%). Full characterization of the coupling product **5** was described previously.³

(3) Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196-9197.