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Copper-Catalyzed Free-Radical C-H Arylation of Pyrroles

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General remarks. All commercial solvents and reagents were used as received from the Aldrich Chemical Company, Fischer Scientific Ltd, Alfa Aesar Company or TCI Europe companies and were degased with argon before use. Silica gel (40-63 μ m) used in flash column chromatography was obtained from Merck. Analytical thin-layer chromatography (TLC) was performed on silica gel plates (TLC silica gel 60 F254 purchased from Merck), visualized with a Spectroline UV₂₅₄ lamp, and stained with a basic solution of KMnO₄. Solvent systems associated with R_f values and flash column chromatography are reported as percent by volume values. ¹H and ¹³C, recorded at 400 MHz or 300 MHz, 100 MHz or 75 MHz, respectively, were performed Bruker Advance 400 and Bruker Advance 300 spectrometers. Proton chemical shifts were internally referenced to the residual proton resonance in CDCl₃ (δ 7.26 ppm). Carbon chemical shifts were internally referenced to the deuterated solvent signals in CDCl₃ (δ 77.0 ppm). FT-IR spectra were recorded on a Bruker Tensor 27 spectrometer with samples loaded as KBr plates. HRMS in ESI mode were recorded on a LTQ-Orbitrap (ThermoFisher Scientific) at the ENV of Nantes.

General procedure for the C-H arylation of N-Boc pyrrole. To a mixture of aniline and MeSO₃H (65 μ L, 1.0 mmol) in H₂O (1 mL) at 25 °C was added *t*BuONO (180 μ L, 1.35 mmol, 90% purity). The reaction mixture was stirred for 30 minutes at 25 °C. Then, CaCO₃

(100 mg, 1.0 mmol), N-Boc pyrrole **2** (0.67 mL, 4.0 mmol), $Cu(OAc)_2.H_2O$ (20.0 mg, 10 mol%) and acetone (2.5 mL) were successively added. After being stirred for the required time (see Table 2), the mixture was diluted with EtOAc (10 mL) and H₂O (5 mL). The aqueous phase was extracted with EtOAc (3x). The collected organic extracts were dried on Na₂SO₄, filtered and evaporated to dryness. The crude was purified by flash chromatography on silica gel to give the pure product.

N-tert-butoxycarbonyl-2-(4-nitrophenyl)-1*H*-pyrrole 3a. The crude was purified by flash chromatography on silica gel (5% EtOAc-petroleum ether) to give 3a as a yellow solid (239 mg, 83%). mp 122-123 °C [lit.¹ 120-121 °C]; ¹H NMR (400 MHz, CDCl₃,) δ 8.21 (d, 2H, J = 8.9 Hz), 7.51 (d, 2H, J = 8.9 Hz), 7.40 (dd, 1H, J = 3.3 Hz, J = 1.7 Hz), 6.32 (dd, 1H, J = 3.3 Hz, J = 1.7 Hz), 6.27 (app t, 1H, J = 3.3 Hz), 1.43 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 149.1, 146.8, 140.9, 132.9, 129.7 (2C), 124.4, 123.1 (2C), 116.6, 111.3, 84.7, 27.9 (3C); IR (KBr) v 3147, 2982, 1742, 1596, 1506, 1331, 1304, 1142 cm⁻¹; HRMS (ESI) calcd for C₁₅H₁₆O₄ N₂ Na [M+Na⁺]: 311.1002 , found: 311.0996.

N-tert-butoxycarbonyl-2-(4-benzoyl)-1*H*-pyrrole 3d. The crude product was purified by flash chromatography on silica gel (5% EtOAc-petroleum ether) to give the product as a brown orange oil (260 mg, 75%). ¹H NMR (300 MHz, CDCl₃,) δ 7.84-7.80 (m, 4H), 7.62-7.56 (m, 1H), 7.52-7.46 (m, 4H), 7.40 (dd, 1H, *J* = 1.8, 3.2 Hz), 6.31-6.25 (m, 2H), 1.42 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 196.4, 149.3, 138.6, 137.9, 136.0, 134.1, 132.4, 130.1 (2C), 129.7 (2C), 128.9 (2C), 128.4 (2C), 123.7, 115.8, 111.1, 84.2, 27.8 (3C); IR (neat) *v* 1740, 11658, 1313, 1276, 1143, 733, 701 cm⁻¹; HRMS (ESI) calcd for C₂₂H₂₂NO₃ [M+H⁺]: 348.11594 , found: 348.1592.

N-tert-butoxycarbonyl-2-(4-acetyl)-1*H*-pyrrole 3e. The crude was purified by flash chromatography on silica gel (7.5% EtOAc-petroleum ether) to give 3e as a yellow oil (187 mg, 66%). ¹H NMR (400 MHz, CDCl₃,) δ 7.94 (d, 2H, J = 8.4 Hz), 7.44 (d, 2H, J = 8.4 Hz), 7.38-7.37 (m, 1H), 6.27-6.24 (m, 2H), 2.61 (s, 3H), 1.39 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 197.6, 149.0, 138.9, 135.5, 133.9, 129.0 (2C), 127.7 (2C), 123.5, 115.5, 110.9, 84.0,

¹ Groenendaal, L.; Bruining, M. J.; Hendrickx, E. H. J.; Persoons, A.; Vekemans, J. A. J. M.; Havinga, E. E.; Meijer, E. W. *Chem. Mat.* 1998, *10*, 226.

27.6 (3C), 26.6. IR (neat) ν 2981, 2934, 1734, 1684, 1148 cm⁻¹. HRMS (ESI) calcd for C₁₇H₂₀NO₃ [M+H⁺]: 286.1438, found: 286.1438.

N-tert-butoxycarbonyl-2-(4-cyanophenyl)-1*H*-pyrrole 3f. The crude was purified by flash chromatography on silica gel (7.5% EtOAc-petroleum ether) to give 3f as a yellow solid (188 mg, 70%). mp 109 °C [Lit.² 110-112 °C]. ¹H NMR (300 MHz, CDCl₃,) δ 7.63 (d, 2H, *J* = 8.6 Hz), 7.45 (d, 2H, *J* = 8.6 Hz), 7.39 (dd, 1H, *J* = 2.0, 3.3 Hz), 6.28-6.24 (m, 2H), 1.42 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 148.8, 138.7, 133.0 (2C), 131.3 (2C), 129.4, 123.8, 118.9, 116.0, 110.9, 110.4, 84.2, 27.6 (3C); IR (KBr) *v* 2971, 2227, 1735, 1610, 1342, 1318 cm⁻¹. HRMS (ESI) calcd for C₁₆H₁₇N₂O₂ [M+H⁺]: 269.1285, found: 269.1276.

N-tert-butoxycarbonyl-2-(4-bromophenyl)-1*H*-pyrrole 3g. The crude was purified by flash chromatography on silica gel (5% EtOAc-petroleum ether) to give 3g as a yellow solid (244 mg, 76%). mp 98 °C. ¹H NMR (300 MHz, CDCl₃,) δ 7.46 (dm, 2H, J = 8.7 Hz), 7.34 (dd, 1H, J = 1.8, 3.3 Hz), 7.21 (dm, 2H, J = 8.7 Hz), 6.22-6.16 (m, 2H), 1.39 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 149.1, 133.7, 133.2, 130.7 (2C), 130.7 (2C), 122.8, 121.2, 114.7, 110.7, 83.8, 27.6 (3C); IR (KBr) ν 3146, 2980, 1730, 1315 cm⁻¹. HRMS (ESI) calcd for C₁₅H₁₇BrNO₂ [M+H⁺]: 322.0437, found: 322.0439.

N-tert-butoxycarbonyl-2-(4-chlorophenyl)-1*H*-pyrrole 3h. The crude was purified by flash chromatography on silica gel (5% EtOAc-petroleum ether) to give 3h as an orange solid (183 mg, 66%). mp 66-68 °C. ¹H NMR (300 MHz, CDCl₃,) δ 7.35-7.24 (m, 5H), 6.23-6.16 (m, 2H), 1.39 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 149.1, 133.7, 133.1, 132.8, 130.4 (2C), 127.7 (2C), 122.8, 114.7, 110.6, 83.8, 27.6 (3C). IR (KBr) ν 3146, 2980, 1730, 1315, 1142, 1069, 974, 845, 743 cm⁻¹. HRMS (ESI) calcd for C₁₅H₁₆ClNNaO₂ [M+Na⁺]: 300.0762, found: 300.0767.

N-tert-butoxycarbonyl-2-(4-methoxycarbonylphenyl)-1*H*-pyrrole 3i. The crude was purified by flash chromatography on silica gel (7.5% EtOAc-petroleum ether) to give 3i as a pale yellow oil (207 mg, 69%). ¹H NMR (300 MHz, CDCl₃,) δ 8.03 (d, 2H, J = 8.7 Hz), 7.42 (d, 2H, J = 8.7 Hz), 7.38 (dd, 1H, J = 1.8, 3.3 Hz), 6.27-6.23 (m, 2H), 3.92 (s, 3H), 1.37 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 166.9, 149.1, 138.8, 133.8, 128.8 (4C), 128.5, 123.4,

² Molander, G. A.; Canturk, B.; Kennedy, L. E. J. Org. Chem. 2008, 74, 973.

115.4, 110.8, 84.0, 52.0, 27.5 (3C). IR (neat) ν 2962, 1750, 1718, 1609, 1306, 1274 cm⁻¹. HRMS (ESI) calcd for C₁₇H₂₀NO₄ [M+H⁺]: 302.1387, found: 302.1384.

N-tert-butoxycarbonyl-2-(2-methoxycarbonylphenyl)-1*H*-pyrrole **3j**. The crude was purified by flash chromatography on silica gel (7.5% EtOAc-petroleum ether) to give **3j** as a yellow oil (177 mg, 59%). ¹H NMR (400 MHz, CDCl₃,) δ 8.01 (d, 1H, *J* = 7.6 Hz), 7.59 (app t, 1H, *J* = 8.8 Hz), 7.54-7.31 (m, 3H), 6.26-6.24 (m, 1H), 6.11-6.09 (m, 1H), 3.72 (s, 3H), 1.28 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 167.1, 149.2, 135.8, 133.1, 131.5, 131.5, 130.6, 129.9, 127.6, 121.4, 113.6, 110.4, 83.1, 52.0, 27.4 (3C). IR (neat) *v* 2981, 2951, 1734, 1150 cm⁻¹. HRMS (ESI) calcd for C₁₇H₂₀O₄N [M+H⁺]: 302.1387, found: 302.1394.

N-tert-butoxycarbonyl-2-(2-methoxy-4-nitrophenyl)-1*H*-pyrrole 3k. The crude was purified by flash chromatography on silica gel (5% EtOAc-petroleum ether, then 10% EtOAc-petroleum ether) to give 3k as a yellow oil (232 mg, 73%). ¹H NMR (300 MHz, CDCl₃,) δ 7.88 (dd, 1H, J = 2.1, 8.4 Hz), 7.72 (d, 1H, J = 2.1 Hz), 7.42 (d, 1H, J = 8.4 Hz), 7.38 (dd, 1H, J = 1.8, 3.3 Hz), 6.29-6.23 (m, 2H), 3.86 (s, 3H), 1.40 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 157.5, 148.9, 148.1, 131.0, 129.9, 128.9, 123.0, 115.8, 115.3, 110.7, 104.9, 83.6, 55.8, 27.6 (3C). IR (neat) v 2977, 1740, 1526, 1320, 1148 cm⁻¹. HRMS (ESI) calcd for C₁₆H₁₉O₅N₂ [M+H⁺]: 319.1288, found: 319.1285.

N-tert-butoxycarbonyl-2-(2-anthraquinone)-1*H*-pyrrole 3l. The crude was purified by flash chromatography on silica gel (5% EtOAc-petroleum ether) to give 3l as an orange solid (216 mg, 58%). mp 166°C. ¹H NMR (100 MHz, CDCl₃) δ 8.38 (d, 1H, *J* = 3.8 Hz), 8.29-8.26 (m, 1H), 8.17-8.14 (m, 1H), 7.79-7.67 (m, 4H), 7.49 (br s, 1H), 6.33 (t, 1H, *J* = 3.1 Hz), 6.15 (br s, 1H), 1.21 (s, 9H). ¹³C NMR (75 MHz, CDCl3) δ 183.3, 183.2, 148.9, 137.4, 135.4, 134.2, 134.0, 133.6, 133.0, 132.9, 132.7, 132.2, 127.3, 127.1, 126.7, 121.7, 113.0, 110.8, 83.0, 27.5 (3C). IR (KBr) *v* 2984, 1734, 1676, 1314, 1272 cm⁻¹. HRMS (ESI) calcd for C₂₃H₂₀O₄N [M+H⁺]: 374.1387, found: 374.1378.

N-tert-butoxycarbonyl-2-[3-(2-methoxycarbonyl)thienyl]-1*H*-pyrrole 3m. The crude was purified by flash chromatography on silica gel (7.5% EtOAc-petroleum ether) to give 3m as a yellow solid (200 mg, 65%). mp 116 °C. ¹H NMR (300 MHz, CDCl₃,) δ 7.46 (d, 1H, J = 5.0 Hz), 7.42 (dd, 1H, J = 2.0, 3.2 Hz), 7.06 (d, 1H, J = 5.0 Hz), 6.26-6.19 (m, 2H), 3.75 (s, 3H),

1.36 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 162.1, 149.0, 139.8, 131.3, 129.4, 128.5, 127.0, 122.3, 114.5, 110.2, 83.0, 51.8, 27.4 (3C). IR (KBr) *v* 3157, 2997, 2980, 2949,1741, 1714, 1333 cm⁻¹. HRMS (ESI) calcd for C₁₅H₁₈NO₄S [M+H⁺]: 308.0951, found: 308.0953.

N-tert-butoxycarbonyl-2,5-(4-nitrophenyl)pyrrole 4a. The crude was purified by flash chromatography on silica gel (50% CH₂Cl₂-petroleum ether) to give 4a as a yellow solid. mp 188-189 °C; ¹H NMR (300 MHz, CDCl₃,) δ 8.27 (d, 4H, J = 9.0 Hz), 7.57 (d, 4H, J = 9.0 Hz), 6.42 (s, 2H), 1.20 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 149.0, 147.0 (2C), 140.1 (2C), 136.0 (2C), 129.3 (4C), 123.2 (4C), 115.0 (2C), 85.7, 27.2 (3C); IR (KBr) *v* 2975, 2927, 1745, 1594, 1514, 1338, 1307, 1141, 1102 cm⁻¹. HRMS (ESI) calcd for C₂₁H₁₉O₆N₃Na [M+Na⁺]: 432.1166, found: 432.1162.

N-tert-butoxycarbonyl-2-(4-nitrophenyl)-5-(2-methoxy-4-nitrophenyl)pyrrole 4b. The crude was purified by flash chromatography on silica gel (20% AcOEt-petroleum ether) to give 4b as a yellow oil. ¹H NMR (400 MHz, CDCl₃,) δ 8.25 (d, 2H, *J* = 8.8 Hz), 7.94 (dd, 1H, *J* = 2.0, 8.4 Hz), 7.75 (d, 1H, J = 2 Hz), 7.54 (d, 2H, J = 8.8 Hz), 7.50 (d, 2H, J = 8.4 Hz), 6.39 (d, 1H, J = 3.2 Hz), 6.30 (d, 1H, J = 3.6 Hz), 3.87 (s, 3H), 1.18 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 149.0, 147.0 (2C), 140.1 (2C), 136.0 (2C), 129.3 (4C), 123.2 (4C), 115.0 (2C), 85.7, 27.2 (3C). IR (neat) *v* 2979, 1751, 1700, 1517, 1343, 1307, 1145 cm⁻¹. HRMS (ESI) calcd for C₂₂H₂₁O₇N₃Na [M+Na⁺]: 462.1272, found: 462.1267.

Arylation of N-methylpyrrole – C2-azo adduct. To a mixture of aniline and MeSO₃H (65 μ L, 1.0 mmol) in H₂O (1 mL) at 25 °C was added *t*BuONO (180 μ L, 1.35 mmol, 90% purity). The reaction mixture was stirred for 30 minutes at 25 °C. Then, CaCO₃ (100 mg, 1.0 mmol), *N*-methylpyrrole (4.0 mmol), Cu(OAc)₂.H₂O (20.0 mg, 10 mol%) and acetone (2.5 mL) were successively added. After being stirred for the required time (see Table 2), the mixture was diluted with EtOAc (10 mL) and H₂O (5 mL). The aqueous phase was extracted with EtOAc (3 x). The collected organic extracts were dried on Na₂SO₄, filtered and evaporated to dryness. The crude was purified by flash chromatography on silica gel (5% AcOEt-petroleum ether) to give the product as a red solid. mp 134 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.30 (dm, 2H, *J* = 6.7 Hz), 7.88 (dm, 2H, *J* = 6.7 Hz), 7.08 (br s, 1H), 6.83 (dd, 1H, *J* = 2.1, 5.8 Hz), 6.36 (dd, 1H, *J* = 3.4, 5.8 Hz), 3.99 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 157.3, 147.1,

146.9, 129.6, 124.6, 122.2, 111.5, 102.5, 33.6. IR δ 1510, 1320 cm⁻¹. HRMS (ESI) calcd for C₁₁H₁₁N₄O₂ [M+H⁺] : 231.0877, found : 231.0867.

Studies of the kinetic isotope effect. To a mixture of aniline and MeSO₃H (65 µL, 1.0 mmol) in H₂O (1 mL) at 25 °C was added *t*BuONO (180 µL, 1.35 mmol, 90% purity). The reaction mixture was stirred for 30 minutes at 25 °C. Then, CaCO₃ (100 mg, 1.0 mmol), *N*-Boc pyrrole **2** (4.0 mmol) and *N*-Boc Pyrrole d_4 -**2** (4.0 mmol), Cu(OAc)₂.H₂O (20.0 mg, 10 mol%) and acetone (2.5 mL) were successively added. After being stirred for 3 hours, the mixture was diluted with EtOAc (10 mL) and H₂O (5 mL). The aqueous phase was extracted with EtOAc (3 x). The collected organic extracts were dried on Na₂SO₄, filtered and evaporated to dryness. The crude showed a mixture of **3d** and d_3 -**3d** giving a k_H/k_D = 3.16 and was purified by flash chromatography on silica gel (5% AcOEt-petroleum ether) to give **3d** / d_3 -**3d** in 73% yield.

DFT Calculations. Quantum mechanical simulations have been performed with the Gaussian 09 program.³ They consisted in geometry optimization and calculations of the vibrational spectrum in order to confirm the nature of the stationery points (minimum of transition state). Calculations have been performed using Truhlar's M06-2X functional that is known to accurately predict both transition state energies and weak interactions.⁴ A triple- ζ basis set, containing two sets of polarization orbitals, namely 6-311G(2d,2p), was applied throughout.

³ Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, revision A.02; Gaussian Inc.: Wallingford CT, 2009.
⁴ Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* 2008, *120*, 215–241.

The *ultrafine* pruned (99,590) integration grid was applied, as it is known that the M06-2X results are sensitive to the grid.⁵ Likewise tighten SCF (10^{-10} a.u) and force minimizations (10^{-5} a.u.) have been applied throughout in order to reach numerically accurate values.

⁵ Wheeler, S. E.; Houk, K. N. J. Chem. Theory Comput. 2010, **6**,395–404.

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3a

146.62	140.68	132.75	122.89		84.49	$\overbrace{76.68}^{77.31}$		27.69	O ₂ N

Boc

3a









N 1 Boc





N

Boc

3f





N

Boc

3g





	×133.712 133.070 132.756 130.415 127.711 122.791	 $ = 83.816 \\ 77.422 \\ 76.999 \\ 76.575 \\ 76.575 $	27.629

N

Boc

3h

С









Boc

3j







-3.864



N

3k

Boc



31







27.5







3m



	162.05	 139.75	129.38	122.31			51.827	
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Boc

MeO₂C

3m









