**The Palladium Catalyzed Multicomponent Coupling of Alkynes, Imines and
Acid Chlorides: A Direct and Modular Approach to Pyrroles**

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I. General

Unless otherwise noted, all manipulations were performed under an inert atmosphere in a Vacuum Atmospheres 553-2 dry box or by using standard Schlenk or vacuum line techniques. The catalysts, $[\text{Pd}(\text{Cl})[\eta^2\text{-CH}(\text{R}^1)\text{NR}^2(\text{COR}^5)]_2$, were prepared according to previous literature procedures.¹ Carbon monoxide (99.99%) was purchased from Matheson and used as received. Imines were prepared using standard literature procedures.² **5a**³ and dibenzoylacetylene⁴ were prepared using literature procedures. All other reagents were purchased from Aldrich[®] and used as received. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under nitrogen. Acetonitrile was distilled from CaH_2 under nitrogen. Deuterated solvents were dried as their protonated analogues, but were transferred under vacuum from the drying agent, and stored over 3 Å molecular sieves.

^1H and ^{13}C were recorded on JEOL 270, Varian Mercury 300 MHz, Mercury 400 MHz, and Unity 500 MHz spectrometers. Mass spectra were obtained from the McGill University Mass Spectral Facility.

II. General Procedure for Pyrrole formation⁵

Imine (0.272 mmol) and acid chloride (0.381 mmol) were dissolved in 4.5 mL of acetonitrile. This solution was added to $[\text{Pd}(\text{Cl})[\eta^2\text{-CH}(\text{R}^1)\text{NR}^2(\text{COR}^5)]_2$ (5 mol%) and $\text{P}(\text{o-tolyl})_3$ (15 mol%) in 4.5 mL of acetonitrile. The reaction mixture was transferred to a 50 mL reaction bomb, and alkyne (0.54 mmol) (in 4.5 mL of THF) and EtN^iPr_2 (0.44 mmol) (in 4.5 mL of THF) were added. The solution was evacuated, carbon monoxide (60 psi) added, and the solution stirred at 65°C for 18 hours. In the case of dimethoxyacetylenedicarboxylate (DMAD)

and acetylene, the alkyne was added to the pre-formed Münchnone solution after catalysis. Products were purified by silica gel chromatography using hexanes/ethyl acetate as eluent.

1-(4-Methoxy-phenyl)-2,5-di-p-tolyl-4-(4-trifluoromethyl-phenyl)-1H-pyrrole-3-carboxylic acid ethyl ester (2a) Yield: 81% ¹H NMR (300 MHz, CDCl₃): δ 7.46 (d, 2H, 8.80 Hz), 7.35 (d, 2H, 8.80 Hz), 7.12-7.00 (m, 4H), 6.88-6.74 (m, 6H), 6.66-6.59 (m, 2H), 4.00 (q, 2H), 3.70 (s, 3H), 2.31 (s, 3H); 2.22 (s, 3H); 0.89 (t, 3H). ¹³C NMR (75 MHz, CD₃CN): δ 165.4, 158.6, 139.8, 138.9, 137.5, 137.0, 133.4, 131.3, 131.1, 131.0, 130.8, 130.2, 129.0, 128.7, 128.4, 128.2, 127.9, 127.4 (q), 124.5 (q), 122.5, 113.8, 113.7, 60.0, 55.5, 21.7, 21.5, 14.0 HRMS. Calculated for C₃₅H₃₀F₃NO₃: 569.21778; found: 569.21829.

1-Ethyl-2-phenyl-5-[1-(toluene-4-sulfonyl)-1H-indol-3-yl]-1H-pyrrole-3,4-dicarboxylic acid dimethyl ester (2b) Yield: 71%. ¹H NMR (400 MHz, CDCl₃): δ 8.02 (d, 1H), 7.84-7.74 (m, 3H), 7.50-7.40 (m, 5H), 7.40-7.30 (m, 2H), 7.28-7.20 (m, 3H), 3.80-3.60 (2H, m), 3.66 (s, 3H), 3.47 (s, 3H), 2.34 (s, 3H), 0.78 (t, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 165.4, 165.0, 145.4, 137.6, 135.2, 134.8, 130.9, 130.7, 130.5, 130.1, 129.1, 128.6, 127.7, 127.1, 126.9, 125.4, 124.1, 120.5, 116.7, 115.3, 114.0, 112.9, 52.0, 51.8, 40.5, 22.0, 16.8. HRMS. Calculated for C₃₁H₂₈N₂O₆S: 556.16681; found: 556.16671.

1-Benzyl-5-tert-butyl-2,4-diphenyl-1H-pyrrole-3-carboxylic acid methyl ester (2c): (major isomer: 67%) ¹H NMR (400 MHz, CDCl₃): δ 7.60-7.10 (m, 13H), 6.72 (d, 2H, 8.22 Hz), 5.36 (s, 2H), 3.27 (s, 3H), 1.26 (s, 9H). ¹³C NMR (100 MHz, CDCl₃): δ 165.7, 139.6, 139.6, 139.5, 137.5, 133.0, 131.5, 130.8, 128.5, 128.1, 127.8, 127.2, 127.1, 126.5, 125.7, 123.8, 115.3, 50.7, 50.7, 34.7, 33.2. HRMS. Calculated for C₂₉H₂₉NO₂: 423.21983; found: 423.21868. 1-Benzyl-2-tert-butyl-4,5-diphenyl-1H-pyrrole-3-carboxylic acid methyl ester) (minor isomer: 13%) ¹H NMR (400 MHz, CDCl₃): δ 7.19-7.03 (m, 11H), 6.96 (d, 2H, 8.22 Hz), 6.65 (d, 2H, 6.45 Hz), 5.30 (s, 2H), 3.64 (s, 3H), 1.44 (s, 9H). ¹³C NMR (100 MHz, CDCl₃): δ 170.8, 139.4, 138.3, 135.0, 132.9, 132.2, 131.7, 129.4, 128.4, 128.2, 127.9, 127.6, 126.9, 125.8, 125.7, 122.0, 115.3, 77.5, 52.3, 50.2, 34.2, 31.6. HRMS. Calculated for C₂₉H₂₉NO₂: 423.21983; found: 423.21944.

[4-Benzoyl-5-(4-bromo-phenyl)-2-cyclohexyl-1-ethyl-1H-pyrrol-3-yl]-phenyl-methanone

(2d): Yield: 63%. ^1H NMR (400 MHz, CDCl_3): δ 7.42-7.39 (m, 4H), 7.33-7.10 (m, 8H), 7.04 (m, 2H), 3.93 (q, 2H), 2.83 (m, 1H), 2.00-1.60 (m, 7H), 1.40-1.24 (m, 3H), 1.24 (t, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 194.9, 192.0, 141.2, 140.5, 139.7, 134.7, 132.8, 132.1, 131.7, 131.5, 130.4, 129.0, 128.9, 128.1, 127.8, 124.3, 123.1, 122.0, 39.9, 37.8, 32.6, 27.6, 26.0, 17.4. HRMS. Calculated for $\text{C}_{32}\text{H}_{30}\text{NO}_2\text{Br}$: 539.14559; found: 539.14541.

[4-Benzoyl-1-ethyl-2-furan-2-yl-5-(4-methylsulfanyl-phenyl)-1H-pyrrol-3-yl]-phenyl-

methanone (2e): Yield: 73%. ^1H NMR (400 MHz, CDCl_3): δ 7.52-7.38 (m, 5H), 7.34-7.23 (m, 4H), 7.21-7.06 (m, 6H), 6.66 (m, 1H), 6.35 (m, 1H), 4.04 (q, 2H, 7.04 Hz), 2.45 (s, 3H), 1.12 (t, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 192.0, 191.8, 143.6, 143.4, 139.9, 139.5, 139.3, 137.8, 132.1, 132.0, 131.3, 129.1, 129.1, 128.0, 128.0, 126.8, 126.0, 125.8, 125.3, 124.0, 113.8, 111.5, 41.4, 16.6, 15.8. HRMS. Calculated for $\text{C}_{31}\text{H}_{25}\text{NO}_3\text{S}$: 491.15551; found: 491.15630.

1-Ethyl-2-phenyl-5-p-tolyl-1H-pyrrole (2f):⁶ Yield: 77%. ^1H NMR (400 MHz, CDCl_3): δ 7.56-7.26 (m, 9H), 6.33 (d, 1H), 6.31 (d, 1H), 4.17 (q, 1H), 2.47 (s, 3H), 0.93 (t, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 137.0, 136.2, 135.8, 134.4, 131.4, 129.4, 129.3, 128.7, 127.2, 109.7, 109.5, 40.4, 21.8, 16.7. HRMS. Calculated for $\text{C}_{19}\text{H}_{19}\text{N}$: 261.15175; found: 261.15123.

1-Benzyl-3-phenyl-2,5-di-p-tolyl-1H-pyrrole (2g). Yield: 56%. ^1H NMR (500 MHz, CDCl_3): δ 7.36 (d, 2H), 7.31 (d, 2H), 7.26-7.08 (m, 12H), 6.76 (d, 2H), 6.62 (s, 1H), 5.15 (s, 2H), 2.40 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 139.6, 137.5, 137.1, 136.6, 135.6, 132.3, 131.4, 130.8, 130.4, 129.4, 129.4, 129.2, 128.4, 128.3, 127.8, 126.9, 126.2, 125.3, 123.2, 109.4, 48.7, 21.8, 21.7. Calculated for $\text{C}_{31}\text{H}_{27}\text{N}$: 413.21435; found: 413.21484.

1-Methoxycarbonylmethyl-2-methyl-5-p-tolyl-4-(4-trifluoromethyl-phenyl)-1H-pyrrole-3-

carboxylic acid ethyl ester (2h). Yield: 65%. ^1H NMR (300 MHz, CDCl_3): δ 7.43 (d, 2H), 7.38-7.30 (m, 4H), 7.24 (d, 2H), 7.12-7.04 (m, 4H), 4.34 (s, 2H), 3.93 (q, 2H), 3.61 (s, 3H), 2.42 (3H, s), 2.34 (s, 3H), 0.83 (t, 3H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 169.2, 164.9, 139.5, 139.5, 138.8, 138.5, 133.2, 131.2, 131.1, 130.7, 129.5, 129.1, 128.9, 127.9, 127.4 (q), 126.5,

124.3 (q), 123.0, 113.3, 59.7, 52.6, 47.1, 21.8, 21.6, 13.9. HRMS. Calculated for $C_{31}H_{28}F_3NO_4$: 535.19704; found: 535.19775.

Acetic acid 1-(3,4-dibenzoyl-1-benzyl-5-phenyl-1H-pyrrol-2-yl)-1-methyl-ethyl ester (2i):

56%. 1H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, 2H), 7.41 (t, 1H), 7.38-7.24 (m, 3H), 7.22-7.08 (m, 4H), 7.00-6.90 (m, 7H), 6.65 (d, 2H), 5.43 (s, 2H), 4.21 (s, 2H), 1.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1, 192.1, 170.8, 140.4, 139.6, 138.8, 138.1, 135.9, 132.7, 131.3, 131.2, 130.7, 129.4, 129.3, 128.7, 128.4, 128.3, 127.9, 127.4, 127.4, 125.5, 125.4, 124.3, 71.6, 50.7, 38.4, 24.5, 21.1. HRMS. Calculated for $C_{37}H_{33}NO_4$: 555.24096; found: 555.24053.

1-Benzyl-4-phenyl-2,5-di-p-tolyl-1H-pyrrole-3-carboxylic acid methyl ester (2j): Yield:

95%. 1H NMR (400 MHz, $CDCl_3$): δ 7.40-7.05 (m, 9H), 7.05-6.95 (m, 7H), 6.70 (m, 2H), 5.03 (s, 2H), 3.51 (s, 3H), 2.42 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 139.1, 138.5, 138.2, 137.6, 135.7, 133.0, 131.5, 130.9, 130.9, 129.4, 129.1, 128.9, 128.9, 128.5, 127.5, 127.2, 126.3, 126.1, 124.5, 113.3, 51.1, 48.8, 21.9, 21.7. HRMS. Calculated for $C_{33}H_{29}NO_2$: 471.21983; found: 471.22052.

1-Benzyl-3-phenyl-4-(toluene-4-sulfonyl)-2,5-di-p-tolyl-1H-pyrrole (2k): NMR Yield: 74%.

1H NMR (300 MHz, $CDCl_3$): δ 7.22 (d, 2H), 7.20-7.08 (d, 12H), 6.98 (d, 2H), 6.91 (m, 5H), 6.58-6.52 (m, 2H), 4.88 (s, 2H), 2.40 (s, 3H), 2.32 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, CD_3CN): δ 142.4, 141.0, 138.9, 137.7, 137.7, 137.6, 133.7, 132.1, 131.5, 131.1, 129.0, 128.9, 128.7, 128.4, 128.0, 127.9, 127.9, 127.4, 127.3, 127.3, 126.8, 126.3, 123.5, 121.4, 49.0, 22.0, 21.9, 21.7. HRMS. Calculated for $C_{38}H_{33}NO_2S$: 567.22320; found: 567.22409.

{4-Benzoyl-1-ethyl-5-phenyl-2-[1-(toluene-4-sulfonyl)-1H-indol-3-yl]-1H-pyrrol-3-yl}-

phenyl-methanone (2l) Yield: 66%. ^1H NMR (300 MHz, CDCl_3): δ 7.95 (m, 2H); 7.75 (d, 2H), 7.50-7.38 (m, 7H), 7.38-7.24 (m, 5H), 7.24-7.06 (m, 6H), 7.04-6.96 (m, 2H), 3.95 (t, 2H), 2.22 (s, 3H), 0.85 (t, 3H). ^{13}C NMR (75.5 MHz, CDCl_3): δ 192.2, 191.8, 145.3, 136.9, 139.4, 138.2, 135.0, 134.7, 132.0, 131.9, 130.9, 130.8, 130.6, 130.1, 130.1, 129.1, 128.9, 128.8, 128.6, 128.0, 127.8, 127.5, 127.1, 125.8, 125.3, 124.4, 124.1, 120.3, 114.0, 112.2, 41.1, 22.0, 16.7. Calculated for $\text{C}_{41}\text{H}_{32}\text{N}_2\text{O}_4\text{S}$: 648.20828; found: 648.20933

2-Benzo[1,3]dioxol-5-yl-1-ethyl-5-phenyl-1H-pyrrole-3,4-dicarboxylic acid dimethyl ester

(2m) Yield: 81%. ^1H NMR (400 MHz, CDCl_3): δ 7.43-7.35 (m, 5H), 6.87 (m, 3H), 6.01 (s, 2H), 3.69 (s, 3H), 3.32 (q, 2H), 3.68 (s, 3H), 3.63 (s, 3H), 0.84 (t, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 165.6, 165.5, 148.2, 147.6, 136.3, 135.9, 131.1, 130.6, 128.9, 128.5, 124.7, 124.4, 114.6, 114.5, 111.0, 108.5, 101.6, 52.0, 51.9, 40.2, 16.6. HRMS. Calculated for $\text{C}_{23}\text{H}_{21}\text{NO}_6$: 407.13689; found: 407.13644.

1-Ethyl-2-naphthalen-2-yl-5-phenyl-1H-pyrrole-3,4-dicarboxylic acid dimethyl ester (2n)

Yield: 88%. ^1H NMR (400 MHz, CDCl_3): δ 7.97-7.86 (m, 4H), 7.58-7.42 (m, 8H), 3.81 (q, 2H), 3.69 (s, 3H), 3.64 (s, 3H), 0.84 (t, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 165.6, 165.6, 136.7, 136.4, 133.4, 133.1, 131.2, 130.7, 130.2, 129.0, 128.6, 128.6, 128.5, 128.2, 128.0, 128.0, 127.0, 126.7, 115.0, 114.9, 52.0, 51.9, 40.4, 16.6. HRMS. Calculated for $\text{C}_{26}\text{H}_{23}\text{NO}_4$: 413.16271; found: 413.16317.

1-Ethyl-3-methyl-2-phenyl-1,4-dihydro-5-oxa-1-aza-cyclopenta[a]naphthalene (12)

Imine **13**⁷ (188 mg, 0.93 mmol) and benzoyl chloride (184 mg, 1.30 mmol) were dissolved in 6 mL of acetonitrile. This solution was added to Pd₂(dba)₃CHCl₃ (2.5 mol%) and P(o-tolyl)₃ (10 mol%) in 6 mL of acetonitrile. The reaction mixture was transferred to a 100 mL reaction bomb and EtNⁱPr₂ (184 mg, 1.43 mmol) (in 12 mL of THF) was added. The solution was evacuated, carbon monoxide (60 psi) added, and stirred at 55°C for 18 hours. The product was purified by silica gel chromatography using hexanes/ethyl acetate as eluent.

Yield: 73%. ¹H NMR (400 MHz, CDCl₃): δ 7.60-7.40 (m, 6H), 7.15-7.00 (m, 3H), 5.29 (s, 2H), 4.16 (q, 2H), 2.01 (s, 3H), 1.30 (t, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 153.4, 134.2, 132.6, 131.1, 128.7, 127.8, 126.5, 122.6, 121.9, 120.6, 120.2, 117.6, 116.6, 112.6, 65.3, 40.8, 17.2, 10.0. HRMS. Calculated for C₂₀H₁₉NO₃: 289.14666; found: 289.14589.

III. Kinetic Studies on Münchnone Formation

p-tolyl(H)C=NBn (114 mg, 0.54 mmol) was combined with benzoyl chloride (107 mg, 0.76 mmol) in 8 mL of acetonitrile. To this solution was added $[\text{Pd}(\text{Cl})[\eta^2\text{-CH}(\text{p-tolyl})\text{NBn}(\text{COPh})]_2$ (5 mol%, 24.6 mg) in 8 mL of acetonitrile, Bu_4NBr (176 mg, 0.54 mmol) in 8 mL of THF and EtN^iPr_2 (0.86 mmol, 111 mg) in 8 mL of THF. The solution was divided into 8 portions and added to 50 mL reaction bombs, followed by the addition of carbon monoxide (60 psi). The solutions were warmed to 55°C, and the reactions were stopped at intervals of 0, 1, 2, 3, 5, 7, 12, and 24 hours. The yield of Münchnone generated was determined by ^1H NMR (utilizing benzyl benzoate as an internal standard). See plot below.

IV. Conditions for Ligand Scanning (Table 1)

p-tolyl(H)C=NBn (156 mg, 0.75 mmol) was combined with benzoyl chloride (147 mg, 1.04 mmol) in 16 mL of acetonitrile. To 1/8 of this solution was added [Pd(Cl)[η^2 -CH(p-tolyl)NBn(COPh)]₂ (4.3 mg, 0.0047 mmol) and the ligand (0.012 mmol, 15 mol%) in 3 mL of acetonitrile, followed by EtNⁱPr₂ (19 mg, 0.11 mmol) in 4.5 mL of THF. The solution was evacuated, carbon monoxide (60 psi) added, and stirred at 65°C for 3.5 hours. The yields of Münchnone were determined by ¹H NMR (utilizing benzyl benzoate as an internal standard)

V. References

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4. Zhang, J.-J.; Schuster, G. B. *J. Am. Chem. Soc.* **1989**, *111*, 7149.
5. Reactions of C-alkyl substituted imines (**2c**, **2i**) were performed at 75°C with 1 eq. of LiOTf, and [Pd(Cl)[η^2 -CH(Tol)NEt(COPh)]₂ catalyst, in CH₃CN.
6. 60 psi of acetylene is added to the solution of Münchnone and stirred at 50°C for 8 hours.
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VI. ^1H NMR Spectra of 2 and 12

2c (major isomer)

2c (minor isomer)

2d

2e

2f

2g

2h

2i

2i

2k

2l

2m

2n

12