Palladium-Catalyzed Direct C(sp3)-H Arylation of Indole-3-ones with Aryl Halides: A Novel and Efficient Method for the Synthesis of Nucleophilic 2-Monoarylated Indole-3-ones

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1. General Information
Chemicals and solvents were either purchased from commercial suppliers or purified by standard procedures as specified in Purification of Laboratory Chemicals, 4th Ed (Armarego, W. L. F.; Perrin, D. D. Butterworth Heinemann: 1997). Analytical thin-layer chromatography (TLC) was performed on silica gel plates with F-254 indicator and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating. Flash chromatography was carried out utilizing silica gel (200-300 mesh). $^1$H NMR, $^{13}$C NMR spectra were recorded on a Varian Mercury 400 spectrometer (400 MHz $^1$H, 100 MHz $^{13}$C). The spectra were recorded in CDCl$_3$ as the solvent at room temperature, $^1$H and $^{13}$C NMR chemical shifts are reported in ppm relative to either the residual solvent peak ($^{13}$C) ($\delta = 77.00$ ppm) or TMS ($^1$H) ($\delta = 0$ ppm) as an internal standard. Data for $^1$H NMR are reported as follows: chemical shift ($\delta$ ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet), integration, coupling constant (Hz) and assignment. Data for $^{13}$C NMR are reported as chemical shift. HRMS were performed on a Thermofisher (Vanquish (UPLC) — Q-Exactive Plus) mass instrument (ESI).

2. Preparation of Substrates
Substrates 1 were prepared by following the publish procedures $^{[1-3]}$

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\begin{align*}
\text{R}^1 \quad \text{COOH} & \quad \text{NH}_2 & + & \text{Br} \quad \text{COOH} & \quad \stackrel{1)}{\text{NaOH}} & \quad \text{R}^1 \quad \text{COOH} & \quad \stackrel{2)}{\text{HCl}} & \quad \text{R}^1 \quad \text{COOH} \\
\text{R}^1 & \quad \text{N} & + & \text{Br} & \quad \text{COOH} & \quad \stackrel{1)}{\text{NaOH}} & \quad \text{R}^1 \quad \text{COOH} & \quad \stackrel{2)}{\text{HCl}} & \quad \text{R}^1 \quad \text{COOH} \\
\text{R}^1 & \quad \text{N} & & & & & & & \\
\end{align*}
\]

3. General procedure for the Direct C(sp3)-H Arylation of Indole-3-ones with Aryl Halides

Indole-3-ones 1 (0.25 mmol), Pd(dba)$_2$ (0.005 mmol, 4.6 mg), K$_2$CO$_3$ (0.275 mmol, 38 mg, 1.1 equiv.) and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl L3 (0.07 mmol, 3.3 mg) were added to a Schlenk tube equipped with a stir bar. Then sealed with a rubber septum and vacuum purged five times with high pure nitrogen to remove air. To these solids, aryl halides 2 (0.275 mmol, 1.1 equiv.) and fresh distilled degassed THF (2 ml) or Toluene (1 ml) was added consecutively under a positive
flow of high pure nitrogen. The reaction mixture was stirred at 70 °C or 110 °C. After the required period of time, the reaction was complete (as judged by TLC analysis). The reaction mixture was directly purified by flash column chromatography (eluted with petroleum ether/EtOAc = 15:1 to 10:1) to afford the C-2 aryl indole-3-ones 3.

4. Analytical data of 3a–p

![Chemical structure of 3a](image)

**1-Acetyl-2-phenylindolin-3-one (3a).** White solid; Reaction time: 14 h; Yield: 87%; m. p.: 125-126 °C; \(^1\)HNMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.62 (d, \(J = 8.8\) Hz, 1H), 7.90 – 7.50 (m, 2H), 7.30 – 7.25 (m, 3H), 7.23 – 7.10 (m, 3H), 5.12 (s, 1H), 1.99 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 195.2, 169.6, 154.1, 137.9, 134.7, 129.8, 129.0, 126.0, 125.0, 123.0, 118.8, 69.8, 24.9; HRMS (ESI): calculated [M+H]\(^+\) for C\(_{16}\)H\(_{14}\)NO\(_2\): 252.10191, found [M+H]\(^+\): 252.10171.

![Chemical structure of 3b](image)

**1-Acetyl-2-(4-methoxyphenyl)indolin-3-one (3b).** White solid; Reaction time: 14 h; Yield: 95%; m. p.: 138-139 °C; \(^1\)HNMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.68 (d, \(J = 8.8\) Hz, 1H), 7.80 – 7.60 (m, 2H), 7.35 – 7.20 (m, 2H), 6.90 – 6.78 (m, 3H), 5.16 (s, 1H), 3.78 (s, 3H), 2.08 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 195.0, 169.6, 154.0, 137.8, 136.1, 130.8, 124.9, 123.0, 118.7, 118.0, 114.0, 111.9, 69.7, 55.5, 24.8; HRMS (ESI): calculated [M+H]\(^+\) for C\(_{17}\)H\(_{16}\)NO\(_3\): 282.11247, found [M+H]\(^+\): 282.11228.

![Chemical structure of 3c](image)

**1-Acetyl-2-(3-methoxyphenyl)indolin-3-one (3c).** Pale yellow solid; Reaction time: 14 h; Yield: 49%; m. p.: 135-136 °C; \(^1\)HNMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.61 (d, \(J = 8.4\) Hz, 1H), 7.70 – 7.60 (m, 2H), 7.25 – 7.14 (m, 2H), 6.88 – 6.68 (m, 3H), 5.09 (s, 1H), 3.71 (s, 3H), 2.01 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 195.0, 169.6, 160.6, 154.0, 137.8, 133.2, 130.8, 125.0, 118.7, 118.1, 114.1, 112.0, 69.8, 55.5, 24.8; HRMS (ESI): calculated [M+H]\(^+\) for C\(_{17}\)H\(_{16}\)NO\(_3\): 282.11247, found [M+H]\(^+\): 282.11224.

![Chemical structure of 3d](image)

**1-Acetyl-2-(2-methoxyphenyl)indolin-3-one (3d).** White solid;
Reaction time: 14 h; Yield: 50%; m. p.: 152-153 °C; \(^1\)HNMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.66 (d, \(J = 6.8\) Hz, 1H), 7.85 – 7.65 (m, 2H), 7.35 – 7.18 (m, 2H), 7.08 – 6.77 (m, 3H), 5.72 (s, 1H), 3.83 (s, 3H), 2.03 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 196.5, 169.6, 157.4, 154.2, 137.4, 130.2, 127.3, 124.6, 124.5, 124.0, 121.5, 118.6, 112.1, 64.5, 56.2, 24.5; HRMS (ESI): calculated [M+H]\(^+\) for C\(_{17}\)H\(_{16}\)NO\(_3\): 282.11247, found [M+H]\(^+\): 282.11225.

**1-Acetyl-2-mesitylindolin-3-one (3e).** Yellow solid; Reaction time: 14 h; Yield: 26%; m. p.: 120-121 °C; \(^1\)HNMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.59 (s, 1H), 7.74 – 7.60 (m, 2H), 7.24 – 7.15 (m, 1H), 6.90 (s, 1H), 6.69 (s, 1H), 5.59 (s, 1H), 2.47 (s, 3H), 2.19 (s, 3H), 1.89 (s, 3H), 1.72 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 196.3, 169.7, 153.7, 153.6, 137.6, 131.4, 130.1, 129.4, 124.5, 124.3, 123.7, 66.6, 24.3, 21.2, 21.0, 20.0; HRMS (ESI): calculated [M+H]\(^+\) for C\(_{19}\)H\(_{20}\)NO\(_2\): 294.14886, found [M+H]\(^+\): 294.14877.

**1-Acetyl-2-(2-fluorophenyl)indolin-3-one (3f).** White solid; Reaction time: 14 h; Yield: 43%; m. p.: 140-141 °C; \(^1\)HNMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.60 (d, \(J = 8.0\) Hz, 1H), 7.82 – 7.53 (m, 2H), 7.32 – 7.23 (m, 1H), 7.23 – 7.17 (m, 1H), 7.16 – 7.07 (m, 1H), 7.06 – 7.00 (m, 1H), 6.99-6.89 (m, 1H), 5.53 (s, 1H), 1.99 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 194.9, 169.2, 161.9, 159.4, 154.2, 147.7, 147.2, 137.8, 125.2, 124.9, 124.8, 124.6, 122.7, 122.5, 118.7, 116.8, 116.6, 63.5, 24.4; HRMS (ESI): calculated [M+H]\(^+\) for C\(_{15}\)H\(_{13}\)FNO\(_2\): 270.09248, found [M+H]\(^+\): 270.09270.

**Methyl 4-(1-acetyl-3-oxoindolin-2-yl)benzoate (3g).** White solid; Reaction time: 14 h; Yield: 88%; m. p.: 147-148 °C; \(^1\)HNMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.67 (d, \(J = 7.6\) Hz, 1H), 8.04 (d, \(J = 8.2\) Hz, 2H), 7.73 (t, \(J = 8.2\) Hz, 2H), 7.35 (d, \(J = 8.3\) Hz, 2H), 7.29 – 7.24 (m, 1H), 5.24 (s, 1H), 3.89 (s, 3H), 2.02 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 194.3, 169.4, 166.6, 154.0, 139.5, 138.1, 131.0, 126.1, 125.3, 125.2, 125.1, 122.8, 118.9, 69.5, 52.6, 24.8; HRMS (ESI): calculated [M+H]\(^+\) for C\(_{18}\)H\(_{16}\)NO\(_4\): 310.10738, found [M+H]\(^+\): 310.10714.
4-(1-Acetyl-3-oxoindolin-2-yl)benzaldehyde (3h). White solid; Reaction time: 14 h; Yield: 63%; m. p.: 157-158 °C; ¹H NMR (400 MHz, CDCl₃): δ 10.01 (s, 1H), 8.70 (d, J = 7.6 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H), 7.80-7.70 (m, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.40 – 7.17 (m, 1H), 5.33 (s, 1H), 2.06 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 194.0, 191.6, 169.2, 154.0, 141.1, 138.2, 136.7, 131.0, 130.6, 126.7, 125.3, 125.1, 122.7, 118.8, 69.4, 24.8; HRMS (ESI): calculated [M+H]⁺ for C₁₇H₁₄NO₃: 280.09682, found [M+H]⁺: 280.09641.

1-Acetyl-2-(4-chloro-3-fluorophenyl)indolin-3-one (3i). White solid; Reaction time: 14 h; Yield: 42%; m. p.: 141-142 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.68 (s, 1H), 7.80 – 7.60 (m, 2H), 7.38 – 7.24 (m, 2H), 7.24 – 7.08 (m, 2H), 5.15 (s, 1H), 2.09 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 194.4, 169.2, 159.8, 157.3, 138.2, 131.9, 128.3, 128.0, 125.9, 125.3, 118.1, 117.9, 68.5, 24.9; HRMS (ESI): calculated [M+H]⁺ for C₁₆H₁₂ClFNO₂: 304.05351, found [M+H]⁺: 304.05351.

1-Acetyl-2-(3,4-dichlorophenyl)indolin-3-one (3j). White solid; Reaction time: 14 h; Yield: 28%; m. p.: 112-113 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.61 (s, 1H), 7.75 – 7.60 (m, 2H), 7.50-7.35 (m, 1H), 7.23 – 7.16 (m, 1H), 7.13 – 6.98 (m, 1H), 5.08 (s, 1H), 2.02 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 194.1, 169.2, 159.8, 157.3, 138.2, 131.9, 128.3, 128.0, 125.9, 125.3, 118.1, 117.9, 68.5, 24.9; HRMS (ESI): calculated [M+H]⁺ for C₁₆H₁₂Cl₂NO₂: 320.02396, found [M+H]⁺: 320.02396.

2-(1,1'-biphenyl-3-yl)-1-acetylindolin-3-one (3k). White solid; Reaction time: 14 h; Yield: 72%; m. p.: 160-161 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.55 (d, J = 6.8 Hz, 1H), 7.91 – 7.47 (m, 4H), 7.47 – 7.26 (m, 5H), 7.25 – 7.15 (m, 2H), 6.86 (d, J = 6.8 Hz, 1H), 5.36 (s, 1H), 1.60 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 196.7, 169.6, 154.4, 142.9, 140.0, 137.8, 133.0, 128.7, 128.4, 127.9, 124.8, 124.5, 123.4, 118.6, 65.7, 24.6; HRMS (ESI): calculated [M+H]⁺ for C₂₂H₁₈NO₂:
328.13321, found [M+H]+: 328.13318.

1-Acetyl-2-(naphthalen-2-yl)indolin-3-one (3l). White solid; Reaction time: 14 h; Yield: 53%; m. p.: 130-131 ºC; 1H NMR (400 MHz, CDCl3): δ 8.72 (d, J = 8.4 Hz, 1H), 7.87 – 7.73 (m, 5H), 7.52 – 7.45 (m, 2H), 7.40 – 7.25 (m, 2H), 5.34 (s, 1H), 2.07 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 195.2, 169.8, 154.0, 137.9, 133.6, 133.5, 132.0, 130.0, 128.6, 128.2, 128.1, 128.0, 127.0, 126.8, 125.5, 125.1, 124.9, 118.8, 69.9, 24.9; HRMS (ESI): calculated [M+H]+ for C20H16NO2: 302.11756, found [M+H]+: 302.11730.

1-Acetyl-2-(benzo[b]thiophen-5-yl)indolin-3-one (3m). Yellow solid; Reaction time: 14 h; Yield: 41%; m. p.: 160-161 ºC; 1H NMR (400 MHz, CDCl3): δ 8.66 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.75 – 7.60 (m, 3H), 7.41 (d, J = 5.2 Hz, 1H), 7.28 – 7.13 (m, 3H), 5.24 (s, 1H), 2.00 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 196.3, 169.7, 154.1, 140.4, 140.3, 137.9, 130.9, 129.0, 128.2, 125.1, 124.0, 123.9, 121.8, 121.1, 118.8, 69.8, 24.9; HRMS (ESI): calculated [M+H]+ for C18H14NO2S: 308.07398, found [M+H]+: 308.07397.

1-Acetyl-5-methyl-2-phenylindolin-3-one (3n). White solid; Reaction time: 14 h; Yield: 32%; m. p.: 155-156 ºC; 1H NMR (400 MHz, CDCl3): δ 8.50 (d, J = 8.4 Hz, 1H), 7.51 – 7.42 (m, 2H), 7.33 – 7.25 (m, 3H), 7.21 – 7.14 (m, 2H), 5.11 (s, 1H), 2.32 (s, 3H), 1.97 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 195.2, 169.3, 152.3, 147.3, 139.0, 135.0, 134.9, 129.7, 129.0, 126.0, 124.2, 123.2, 119.3, 118.5, 70.1, 24.7, 21.0; HRMS (ESI): calculated [M+H]+ for C17H16NO2: 266.11756, found [M+H]+: 266.11743.

1-Acetyl-5-chloro-2-phenylindolin-3-one (3o). White solid; Reaction time: 14 h; Yield: 91%; m. p.: 155-156 ºC; 1H NMR (400 MHz, CDCl3): δ 8.59 (d, J = 8.4 Hz, 1H), 7.69 – 7.53 (m, 2H), 7.39 – 7.24 (m, 3H), 7.24 – 7.15 (m, 2H), 5.16 (s, 1H), 1.98 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 194.0, 169.5, 152.4, 147.3, 139.0, 135.0, 134.9, 129.7, 129.0, 126.0, 124.2, 123.2, 119.3, 118.5, 70.1, 24.7, 21.0; HRMS (ESI): calculated [M+H]+ for C16H13ClNO2: 286.06293, found [M+H]+: 286.06286.
1-Acetyl-5-bromo-2-phenylindolin-3-one (3p). White solid; Reaction time: 14 h; Yield: 53%; m. p.: 155-156 °C; \(^1\)HNMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.61 (d, \(J = 8.0\) Hz, 1H), 7.90 – 7.75 (m, 2H), 7.45 – 7.30 (m, 3H), 7.28 – 7.15 (d, \(J = 6.9\) Hz, 2H), 5.22 (s, 1H), 2.06 (s, 3H); \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 193.8, 169.5, 147.3, 140.4, 134.2, 130.3, 129.9, 129.6, 127.6, 126.0, 124.2, 120.4, 118.0, 70.1, 24.8; HRMS (ESI): calculated [M+H]\(^+\) for C\(_{16}\)H\(_{13}\)BrNO\(_2\): 330.01242, found [M+H]\(^+\): 330.01256.

1-Acetyl-2-(4-chlorophenyl)indolin-3-one (3q). White solid; Reaction time: 14 h; Yield: 40%; m. p.: 120-121 °C; \(^1\)HNMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.68 (d, \(J = 5.4\) Hz, 1H), 7.77 – 7.60 (m, 2H), 7.36 (d, \(J = 8.4\) Hz, 2H), 7.28 – 7.20 (m, 3H), 5.17 (s, 1H), 2.07 (s, 3H); \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 194.7, 169.3, 154.0, 138.0, 135.1, 133.3, 130.0, 127.4, 125.2, 122.9, 118.9, 69.2, 24.8; HRMS (ESI): calculated [M+H]\(^+\) for C\(_{16}\)H\(_{13}\)ClNO\(_2\): 286.06293, found [M+H]\(^+\): 286.06286.

References

NMR spectrogram