One-pot Synthesis of Carbazoles by Palladium-catalyzed N-Arylation and Oxidative Coupling

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Table 1: Investigation of the reaction conditions in oxidative coupling.

<table>
<thead>
<tr>
<th>Entry</th>
<th>cat. (mol %)</th>
<th>Oxidant (equiv)</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Yield (%) (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>—</td>
<td>80</td>
<td>3</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>O(_2)</td>
<td>80</td>
<td>11</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>O(_2)</td>
<td>80</td>
<td>24</td>
<td>85, trace</td>
</tr>
</tbody>
</table>

\(^a\) HPLC yield (absolute calibration curve method).\(^7\)

After the completion of the reaction, the oxide of the phosphine ligand 3 was observed. Dicyclohexyl(2′,4′,6′-triisopropylbiphenyl-2-yl)phosphine oxide: \(^{31}\)P NMR (202 MHz, CDCl\(_3\)) \(\delta\) 46.8 (the chart shown in p S39). \(^{31}\)P NMR for the ligand 3: \(-11.5\) (see: X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 6653).
Experimental Section

Typical Procedure for the One-Pot Reaction by Palladium-catalyzed N-Arylation and Oxidative Coupling (Table 3, entry 6): Toluene (0.4 mL) was added to a flask containing 4-methylphenyl triflate 1b (48.0 mg, 0.20 mmol), 4-methoxycarbonyl aniline 2d (33.3 mg, 1.1 equiv), Pd(OAc)$_2$ (10 mol%), ligand 3 (15 mol%) and Cs$_2$CO$_3$ (1.2 equiv) under argon atmosphere. The mixture was stirred at 100 °C for 1.5 h, then stirred at room temperature for 5 min. AcOH (1.6 mL) was added to the mixture and an oxygen balloon was connected to the reaction vessel, then the reaction mixture was stirred at 80 °C for 22.5 h. After cooling, the reaction mixture was diluted with ethyl acetate, washed with saturated NaHCO$_3$, dried over MgSO$_4$, and concentrated in vacuo. The crude material was purified by flash chromatography with hexane/ethyl acetate (15:1) to afford the desired carbazole 10 (37.4 mg, 78 % yield).

Materials: $^1$H NMR and $^{13}$C NMR spectral data of diphenylamine 4a$^1$ and carbazoles 5a$^2$, 5b$^3$, 5c$^3$, 5d$^4$, 5f$^5$, 5g$^3$, 6$^6$, 7$^7$ were in agreement with those previously reported.

1 Commercially available – CAS# 122-39-4
2 Commercially available – CAS# 86-74-8
4 Li, W.-S.; McChesney, J. D.; El-Feraly, F. S. Phytochemistry 1991, 30, 133.

Characterization Data for Carbazoles (New Compounds)

Benzyl 9H-Carbazole-3-carboxylate (5e): White solid; IR cm$^{-1}$: 3289 (NH), 1693 (CO); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.43 (s, 2H, CH$_2$), 7.27 (m, 1H, Ar), 7.35-7.44 (m, 6H, Ar), 7.51 (d, $J$ = 7.1 Hz, 2H, Ar), 8.10 (d, $J$ = 7.8 Hz, 1H, Ar), 8.16 (dd, $J$ = 7.8, 1.5 Hz, 1H, Ar), 8.35 (s, 1H, NH), 8.84 (s, 1H, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 66.5, 110.1, 110.9, 120.3, 120.7, 121.3, 123.0, 123.1, 123.3, 126.6, 127.6, 128.1, 128.2 (2C), 128.6 (2C), 136.5, 139.9, 142.4, 167.2; m.p. = 154-155°C; HRMS (EI): $m/z$ calcd for C$_{20}$H$_{15}$NO$_2$ (M$^+$) 301.1103; found: 301.1100.
Methyl 7-Methyl-9\textit{H}-carbazole-3-carboxylate (8): Yellow white solid; IR cm\textsuperscript{-1}: 3336 (NH), 2949 (CH), 1697 (CO); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 2.52 (s, 3H, CH\textsubscript{3}), 3.97 (s, 3H, CO\textsubscript{2}Me), 7.12 (d, J = 8.0 Hz, 1H, Ar), 7.22 (s, 1H, Ar), 7.37 (d, J = 8.5 Hz, 1H, Ar), 7.98 (d, J = 8.0 Hz, 1H, Ar), 8.10 (dd, J = 8.5, 1.5 Hz, 1H, Ar), 8.24 (s, 1H, NH), 8.76 (s, 1H, Ar); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 22.0, 51.9, 110.0, 111.0, 120.3, 121.0, 121.3, 121.9, 122.5, 123.2, 127.0, 136.9, 140.4, 142.3, 168.0; m.p. = 210-212\textdegree C; HRMS (EI): m/z calcd for C\textsubscript{15}H\textsubscript{13}NO\textsubscript{2} (M\textsuperscript{+}) 239.0946; found: 239.0942.

3-Trifluoromethyl-7-methyl-9\textit{H}-carbazole (9): Brown solid; IR cm\textsuperscript{-1}: 3392 (NH), 2928 (CH); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 2.52 (s, 3H, CH\textsubscript{3}), 7.10 (d, J = 8.0 Hz, 1H, Ar), 7.20 (s, 1H, Ar), 7.39 (d, J = 8.5 Hz, 1H, Ar), 7.60 (d, J = 8.5 Hz, 1H, Ar), 7.94 (d, J = 8.0 Hz, 1H, Ar), 8.03 (s, 1H, NH), 8.27 (s, 1H, Ar); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 22.0, 110.5, 111.0, 117.5 (q), 120.2, 120.5, 121.9, 122.0 (q), 122.1, (d) 123.1, 125.3 (q), 137.2, 140.4, 140.9; m.p. = 202-203\textdegree C; HRMS (FAB): m/z calcd for C\textsubscript{14}H\textsubscript{10}F\textsubscript{3}N (M\textsuperscript{+}) 249.0765; found: 249.0768.

Methyl 6-methyl-9\textit{H}-carbazole-3-carboxylate (10): Yellow white solid; IR cm\textsuperscript{-1}: 3295 (NH), 2948-2851 (CH), 1684 (CO); \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}): δ 2.49 (s, 3H, CH\textsubscript{3}), 3.90 (s, 3H, CO\textsubscript{2}Me), 7.29 (d, J = 8.3 Hz, 1H, Ar), 7.44 (d, J = 8.3 Hz, 1H, Ar), 7.53 (d, J = 8.5 Hz, 1H, Ar), 7.99 (d, J = 8.5 Hz, 1H, Ar), 8.75 (s, 1H, Ar), 8.75 (s, 1H, Ar), 11.58 (s, 1H, NH); \textsuperscript{13}C NMR (100 MHz, DMSO-d\textsubscript{6}): δ 21.0, 51.7, 110.7, 111.1, 119.5, 120.3, 122.0, 122.2, 122.5, 126.4, 127.7, 128.3, 138.5, 142.7, 166.9; m.p. = 233-235\textdegree C; HRMS (FAB): m/z calcd for C\textsubscript{15}H\textsubscript{13}NO\textsubscript{2} (M\textsuperscript{+}) 239.0946; found: 239.0945.

Methyl 7-tert-Butyl-9\textit{H}-carbazole-3-carboxylate (11): White solid; IR cm\textsuperscript{-1}: 3282 (NH), 2968 (CH\textsubscript{3}), 1695 (CO); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 1.43 (s, 9H, t-Bu), 3.97 (s, 3H, CO\textsubscript{2}Me), 7.37 (dd, J = 8.3, 1.7 Hz, 1H, Ar), 7.41 (d, J = 8.5 Hz, 1H, Ar), 7.46 (d, J = 1.7 Hz, 1H, Ar), 8.03 (d, J = 8.3
Hz, 1H, Ar), 8.10 (dd, J = 8.5, 1.7 Hz, 1H, Ar), 8.19 (s, 1H, NH), 8.77 (s, 1H, Ar); 13C NMR (100 MHz, CDCl3): δ 31.7 (3C), 35.2, 51.9, 107.4, 110.0, 118.5, 120.1, 121.0, 121.3, 122.7, 123.2, 127.0, 140.2, 142.5, 150.5, 168.0; m.p. = 224-228°C; HRMS (FAB): m/z calcd for C18H19NO2 (M+) 281.1416; found: 281.1414.

Methyl 6-tert-Butyl-9H-carbazole-3-carboxylate (12): White solid; IR cm⁻¹: 3331 (NH), 2955 (CH), 1694 (CO); ^1H NMR (400 MHz, CDCl3): δ 1.45 (s, 9H, t-Bu), 3.98 (s, 3H, CO₂Me), 7.39 (d, J = 8.5 Hz, 1H, Ar), 7.40 (d, J = 8.5 Hz, 1H, Ar), 7.54 (dd, J = 8.5, 2.0 Hz, 1H, Ar), 8.11 (dd, J = 8.5, 1.7 Hz, 1H, Ar), 8.14 (s, 1H, Ar), 8.22 (s, 1H, NH), 8.83 (s, 1H, Ar); 13C NMR (100 MHz, CDCl3): δ 31.9 (3C), 34.8, 51.9, 110.1, 110.4, 116.8, 121.2, 122.7, 123.1, 123.4, 124.6, 127.2, 138.0, 142.7, 143.5, 167.9; m.p. = 216-217°C; HRMS (FAB): m/z calcd for C18H19NO2 (M+) 281.1416; found: 281.1414.

Methyl 7-Methyl-9H-carbazole-4-carboxylate (13) and Methyl 7-Methyl-9H-carbazole-2-carboxylate (14). By a procedure identical with that described for the synthesis of 10, triflate 1c (48.0 mg, 0.20 mmol) and aniline 2e (33.3 mg, 1.1 equiv) were converted into a regioisomeric mixture of 13 and 14 (28.5 mg, 60% yield; 13/14 = 86:14), which was separated by HPLC.

Compound 13: white solid; IR cm⁻¹: 3402 (NH), 2950-2860 (CH), 1702 (CO); ^1H NMR (400 MHz, CDCl3): δ 2.49 (s, 3H, CH₃), 4.05 (s, 3H, CO₂Me), 7.07 (d, J = 8.3 Hz, 1H, Ar), 7.12 (s, 1H, Ar), 7.36 (dd, J = 8.1, 7.6 Hz, 1H, Ar), 7.49 (d, J = 8.1 Hz, 1H, Ar), 7.84 Hz (d, J = 7.6 Hz, 1H, Ar), 8.12 (s, 1H, NH), 8.71 (d, J = 8.3 Hz, 1H, Ar); 13C NMR (100 Hz, CDCl3): δ 21.9, 52.1, 110.4, 114.8, 119.6, 121.4, 122.0, 122.6, 124.1, 124.7, 125.2, 137.2, 140.3, 140.8, 168.6; m.p. = 220-221°C; HRMS (FAB): m/z calcd for C₁₅H₁₃NO₂ (M⁺) 239.0946; found: 239.0942.

Compound 14: white solid; IR: ν = 3402 (NH), 2952 (CH), 1713 (CO); ^1H NMR (400 MHz, CDCl3): δ 2.54 (s, 3H, CH₃), 3.97 (s, 3H, CO₂Me), 7.10 (d, J = 8.1 Hz, 1H, Ar), 7.26 (s, 1H, Ar), 7.92 (d, J = 8.1 Hz, 1H, Ar), 7.98 (d, J = 8.1 Hz, 1H, Ar), 8.05 Hz (d, J = 8.1 Hz, 1H, Ar), 8.12 (s, 1H, NH), 8.13 (s, 1H, Ar); ^13C NMR (100 Hz, CDCl3): δ 22.2, 52.1, 111.0, 112.3, 119.6, 120.3, 120.7, 120.8, 121.7, 126.8, 127.3, 137.7, 138.8, 141.3, 167.8; m.p. = 215-216°C; HRMS (FAB): m/z calcd for C₁₅H₁₃NO₂ (M⁺) 239.0946; found: 239.0948.
Supplementary Material (ESI) for Chemical Communications
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