REGIOSELECTIVE SYNTHESIS OF 1,5-DIARYL-1*H*- IMIDAZOLES BY PALLADIUM-CATALYZED DIRECT ARYLATION OF 1-ARYL-1*H*-IMIDAZOLES

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SUPPORTING INFORMATION

General methods S2

Experimental details S2–S8

Experimental Section

General Methods. Melting points are uncorrected. Precoated Merck 60 F₂₅₄ aluminum silica gel sheets were used for TLC analyses. GLC analyses were performed using two types of capillary columns: an Alltech AT-35 bonded FSOT column (30 m × 0.25 mm i.d.) and an Alltech AT-1 bonded FSOT column (30 m × 0.25 mm i.d.). Purifications by MPLC were performed using silica gel Merck 60 (particle size 0.015–0.040 mm). NMR spectra were recorded at room temperature at 200 or 600 MHz (¹H) and 50.3 or 150 MHz (¹³C). The NMR spectra at 200 and 50.3 MHz were referred to TMS and those at 600 and 150.3 MHz were referred to the central line of the triplet at 77.02 ppm for CDCl₃. The structures of compounds **3a–e**, **3g**, **3i–k**, **3m**, **7f** and **8h** were assigned on the basis of their ¹H and ¹³C NMR spectra recorded at 600 and 150 MHz, respectively, in CDCl₃ solution and by a combination of 2D NMR techniques which included ¹H-¹³C HMBC (Heteronuclear Multiple Bond Correlation) and ¹H-¹³C HSQC (Heteronuclear Single Quantum Coherence). All reactions were performed in flame-dried glassware under argon, by standard syringe, cannula and septa techniques. 1-Phenyl-1*H*-imidazole (**1a**), 4-anisyl iodide (**2a**), 4-anisyl bromide (**2b**), 4-anisyl triflate (**2c**), iodobenzene (**2d**), 4-(trifluoromethyl)phenyl iodide (**2e**), 4-chlorophenyl iodide (**2f**), 3,4,5-trimethoxyphenyl iodide (**2g**), 1-naphthyl iodide (**2h**), 2-thienyl iodide (**2i**), 4-fluorophenyl iodide (**2j**), 3-fluoro-4-methoxyphenyl bromide (**2k**), *trans*-di(μ -acetato)-bis[(di-*o*-tolylphosphino)benzyl]dipalladium(II), copper(I) trifluoromethanesulfonate toluene complex, *trans,trans*-dibenzylideneacetone, 1,10-phenanthroline, imidazole (**13**) and 4-fluorophenyl methylsulfone (**2m**) were commercially available.

Experimental details

1-(4-Methoxyphenyl)-1*H*-imidazole (1b). The crude reaction product obtained from the copper(I)-catalyzed reaction of **13** with **2a** was purified by MPLC on silica gel with a mixture of CH₂Cl₂ and methanol (97 : 3) as eluent to give **1b** (3.34 g, 96 %) as a light brown solid: mp 62–63 °C (lit¹ mp 60–61 °C); ¹H NMR (200 MHz, CDCl₃) δ 7.76 (s, 1H), 7.23 (m, 2H), 7.20 (s, 1H), 7.18 (s, 1H), 6.98 (m, 2H), 3.84 (s, 3H); ¹³C NMR (50.3 MHz, CDCl₃) δ 158.7, 135.7, 129.9, 129.6, 123.0 (2C), 118.6, 114.7 (2C), 55.5; IR (KBr) ν_{max} 3108, 1506, 1303, 1239, 1093, 1058, 830 cm⁻¹; EI-MS: *m/z* (%) 175 (12), 174 (100), 159 (15), 147 (10), 134 (10), 132 (38), 77 (13); Anal. Calcd. For C₁₀H₁₀N₂O: C, 68.95; H, 5.79, Found: C,

68.82; H, 5.68.

1-(3,4,5-Trimethoxyphenyl)-1*H*-imidazole (1c). The crude reaction product obtained from the copper(I)-catalyzed reaction of **13** with **2g** was purified by MPLC on silica gel with a mixture of CH₂Cl₂ and methanol (97 : 3) as eluent. GLC-MS analyses showed that the chromatographic fractions contained **1c** contaminated by 1,10-phenanthroline. Thus, they were collected and concentrated and the residue was dissolved in CH₂Cl₂. The resultant solution was washed thoroughly with a 1 M CuCl₂ aqueous solution and water, dried, filtered over Celite and concentrated under reduced pressure to give chemically pure **1c** (3.28 g, 70 %) as a pale orange solid: mp 73–75 °C; ¹H NMR (200 MHz, CDCl₃) δ 7.81 (br s, 1H), 7.24 (br s, 1H), 7.19 (br s, 1H), 6.59 (s, 2H), 3.91 (s, 6H), 3.88 (s, 3H); ¹³C NMR (50.3 MHz, CDCl₃) δ 153.9 (2C), 137.4, 135.8, 133.3, 130.1, 118.7, 99.7 (2C), 61.0, 56.3 (2C); IR (KBr) ν_{max} 3008, 2960, 1602, 1509, 1126, 996, 810 cm⁻¹; EI-MS, *m/z* (%) 235 (14), 234 (100), 219 (71), 191 (12), 176 (12), 161 (9), 149 (8); Anal. Calcd. For C₁₂H₁₄N₂O₃: C, 61.53; H, 6.02. Found: C, 61.40; H, 5.91. The spectral properties of this compound were in agreement with those previously reported.¹

1-(1-Naphthyl)-1*H*-imidazole (1d). The crude reaction product obtained from the copper(I)-catalyzed reaction of **13** with **2h** was purified by MPLC on silica gel with a mixture of CH₂Cl₂ and methanol (98 : 2) as eluent to give **1d** (3.84 g, 99 %) as a yellow solid: mp 58–59 °C; ¹H NMR (200 MHz, CDCl₃) δ 7.97–7.92 (m, 2H), 7.77 (br s, 1H), 7.59–7.42 (m, 5H), 7.31–7.26 (m, 2H); ¹³C NMR (50.3 MHz, CDCl₃) δ 138.3, 134.0, 129.3 (2C), 129.1 (2C), 128.2, 127.5, 126.8, 125.0, 123.5, 122.2, 121.5; IR (KBr) ν_{max} 3103, 1593, 1499, 1486, 1247, 1033, 774 cm⁻¹; EI-MS: *m/z* (%) 195 (14), 194 (100), 193 (32), 166 (50), 154 (19), 139 (18), 127 (21); Anal. Calcd. for C₁₃H₁₀N₂: C, 80.39; H, 5.19. Found: C, 80.25; H, 5.07. The spectral properties of this compound were in agreement with those previously reported.²

1-(4-Chlorophenyl)-1*H*-imidazole (1e). The crude reaction product obtained from the copper(I)-catalyzed reaction of **13** with **2f** was purified by MPLC on silica gel with a mixture of CH₂Cl₂ and methanol (98 : 2) as eluent to give **1e** (3.43 g, 96 %) as a light brown solid: mp 84–86 °C (lit³ mp 85–87 °C); ¹H NMR (200 MHz, CDCl₃) δ 7.75 (s, 1H), 7.37 (m, 2H), 7.25 (m, 2H), 7.17 (s, 1H), 7.13 (s, 1H); ¹³C NMR (50.3 MHz, CDCl₃) δ 135.8, 135.3, 132.9, 130.5, 129.8 (2C), 122.5 (2C), 118.0; IR (KBr) ν_{max} 3108, 1506, 1303, 1239, 1058, 830, 768 cm⁻¹; EI-MS: *m/z* (%) 180 (32), 179 (11), 178 (100), 151 (57), 124

(26), 111 (24), 75 (23); Anal. Calcd. for $C_9H_7ClN_2$: C, 60.52; H, 3.95. Found: C, 60.39; H, 3.83.

1-(4-Methylthiophenyl)-1H-imidazole (1f). The crude reaction product obtained from the copper(I)-catalyzed reaction of **13** with **2m** was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (98 : 2) as eluent to give **1f** (3.65 g, 96 %) as an orange solid: mp 92–93 °C (lit⁴ 93 °C); ¹H NMR (200 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.32 (m, 4H), 7.25 (br s, 1H), 7.20 (br s, 1H), 2.51 (s, 3H); ¹³C NMR (50.3 MHz, $CDCl_3$) δ 135.8, 135.4, 134.4, 130.2, 127.6 (2C), 121.8 (2C), 118.1, 15.9; IR (KBr) ν_{max} 3107, 1505, 1302, 1245, 1058, 817, 754 cm^{-1} ; EI-MS: m/z (%) 191 (12), 190 (100), 175 (32), 150 (9), 148 (31), 135 (10), 108 (8); Anal. Calcd. for $C_{10}H_{10}N_2S$: C, 63.13; H, 5.30. Found: C, 63.01; H, 5.17.

1,5-Diphenyl-1H-imidazole (3b). The crude reaction product obtained from the palladium-catalyzed reaction of **1a** with **2d** (Table 2, entry 3) was purified by MPLC on silica gel with a mixture of toluene and AcOEt (50 : 50 + 0.1 % Et_3N) as eluent to give **3b** (90 mg, 41 %) as a pale yellow solid: mp 125–126 °C (lit⁵ mp 127–128 °C); ¹H NMR (600 MHz, $CDCl_3$) δ 7.96 (br s, 1H, H-2), 7.43 (m, 3H, H-3'', H-4'' and H-5''), 7.37 (br s, 1H, H-4), 7.28 (m, 3H, H-3', H-4' and H-5'), 7.21 (m, 2H, H-2'' and H-6''), 7.14 (m, 2H, H-2' and H-6'); ¹³C NMR (150 MHz, $CDCl_3$) δ 138.1 (C-2), 136.0 (C-1''), 133.8 (C-5), 129.7 (C-3'' and C-5''), 128.8 (C-4''), 128.6 (C-3' and C-5'), 128.4 (C-1'), 128.3 (C-2' and C-6'), 128.2 (C-4'), 126.4 (C-4), 125.7 (C-2'' and C-6''); IR (KBr) ν_{max} 2922, 1597, 1499, 1114, 916, 817, 760 cm^{-1} ; EI-MS: m/z (%) 221 (17), 220 (100), 193 (35), 165 (17), 117 (20), 90 (16), 77 (15); Anal. Calcd. for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49. Found: C, 81.63; H, 5.42.

1-Phenyl-5-(4-trifluoromethylphenyl)-1H-imidazole (3c). The crude reaction product obtained from the palladium-catalyzed reaction of **1a** with **2l** (Table 2, entry 5) was purified by MPLC on silica gel with a mixture of toluene and AcOEt (50 : 50 + 0.1 % Et_3N) as eluent to give **3c** (0.17 g, 59 %) as a pale yellow solid: mp 58–60 °C; ¹H NMR (600 MHz, $CDCl_3$) δ 7.85 (br s, 1H, H-2), 7.51 (m, 2H, H-3' and H-5'), 7.45 (m, 1H, H-4''), 7.44 (m, 2H, H-3'' and H-5''), 7.39 (br s, 1H, H-4), 7.24 (m, 2H, H-2' and H-6'), 7.20 (m, 2H, H-2'' and H-6''); ¹³C NMR (150 MHz, $CDCl_3$) δ 139.4 (C-2), 136.0 (C-1''), 132.7 (C-1'), 132.6 (C-5), 132.1 (C-4'), 129.9 (C-4), 129.8 (C-3'' and C-5''), 128.8 (C-4''), 128.1 (C-2' and C-6'), 125.7 (C-2'' and C-6''), 125.5 (C-3' and C-5'), 124.0 (CF_3); IR (KBr) ν_{max} 3094, 1618, 1500, 1327, 1122, 1109, 820 cm^{-1} ; EI-MS: m/z (%) 289 (18), 288 (100), 261 (40), 165 (10), 117 (17), 90 (15), 77 (17);

Anal. Calcd. for $C_{16}H_{11}F_3N_2$: C, 66.66; H, 3.85. Found: C, 66.55; H, 3.78.

5-(4-Chlorophenyl)-1-phenyl-1H-imidazole (3d). The crude reaction product obtained from the palladium-catalyzed reaction of **1a** with **2f** (Table 2, entry 6) was purified by MPLC on silica gel with a mixture of toluene and AcOEt (50 : 50 + 0.1 % Et_3N) as eluent to give **3d** (99 mg, 39 %) as a pale yellow solid: mp 144–145°C; 1H NMR (600 MHz, $CDCl_3$) δ 8.17 (br s, 1H, H-2), 7.48 (m, 2H, H-3'' and H-5''), 7.47 (m, 1H, H-4''), 7.42 (br s, 1H, H-4), 7.28 (m, 2H, H-3' and H-5'), 7.22 (m, 2H, H-2'' and H-6''), 7.07 (m, 2H, H-2' and H-6'); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.2 (C-2), 135.0 (C-4' and C-1''), 132.0 (C-5), 129.6 (C-2', C-6' and C-4''), 129.5 (C-3'' and C-5''), 129.1 (C-3' and C-5'), 125.7 (C-2'' and C-6''), 125.0 (C-1'), 124.2 (C-4); IR (KBr) ν_{max} 2923, 1595, 1486, 1260, 1090, 915, 813 cm^{-1} ; EI-MS: m/z (%) 256 (32), 255 (17), 254 (100), 192 (13), 165 (13), 117 (17), 77 (13); Anal. Calcd. for $C_{15}H_{11}ClN_2$: C, 70.73; H, 4.35. Found: C, 70.60; H, 4.23.

1,5-Bis(4-methoxyphenyl)-1H-imidazole (3f). The crude reaction product obtained from the palladium-catalyzed reaction of **1b** with **2a** (Table 2, entry 8) was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (98 : 2) as eluent to give **3f** (0.10, 36 %) as a pale pink solid: mp 115–116 °C; 1H NMR (600 MHz, $CDCl_3$) δ 8.0 (br s, 1H, H-2), 7.5 (s, 1H, H-4), 7.14 (d, J = 8.4 Hz, 2H, H-2'' and H-6''), 7.05 (d, J = 8.4 Hz, 2H, H-2' and H-6'), 6.95 (d, J = 8.4 Hz, 2H, H-3'' and H-5''), 6.84 (d, J = 8.4 Hz, 2H, H-3' and H-5'), 3.85 (s, 3H, OMe_b), 3.80 (s, 3H, OMe_a). ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.5 (C-4''), 159.4 (C-4'), 130.7 (C-1''), 129.7 (C-2' and C-6'), 127.0 (C-2'' and C-6''), 114.7 (C-3'' and C-5''), 114.0 (C-3' and C-5'), 55.2 (OMe_b and OMe_a). In this spectrum the resonances due to C-2, C-

4 and C-5 could not be detected. IR (KBr) $\nu_{\max}$ 2954, 1517, 1500, 1249, 1178, 1024, 831 cm^{-1} ; EI-MS: m/z (%) 281 (19), 280 (100), 265 (30), 253 (13), 238 (29), 140 (6), 77 (6); Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2$: C, 72.84; H, 5.75. Found: C, 72.71; H, 5.74.

5-(3-Fluoro-4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)-1H-imidazole (3j). The crude reaction product obtained from the palladium-catalyzed reaction of **1c** with **2k** (Table 2, entry 14) was purified by MPLC on silica gel with a mixture of CH_2Cl_2 and methanol (97 : 3) as eluent to give **3j** (0.26, 72 %) as a brown viscous liquid. ^1H NMR (600 MHz, CDCl_3) δ 7.75 (br s, 1H, H-2), 7.23 (br s, 1H, H-4), 6.91 (d, $J = 12$ Hz, 1H, H-2'), 6.86 (m, 2H, H-5' and H-6'), 6.39 (s, 2H, H-2'' and H-6''), 3.87 (s, 6H, OMe_a and OMe_c), 3.73 (s, 3H, OMe_b); ^{13}C NMR (150 MHz, CDCl_3) δ 153.7 (C-3'' and C-5''), 152.0 (C-3'), 147.3 (C-4'), 138.6 (C-2), 138.1 (C-4''), 132.1 (C-5), 131.9 (C-1''), 127.9 (C-4), 124.1 (C-6'), 122.2 (C-1'), 115.9 (C-2'), 113.3 (C-5'), 103.4 (C-2'' and C-6''), 61.0 (OMe_c), 56.3 (OMe_b), 56.2 (OMe_a); IR (film) $\nu_{\max}$ 2940, 1598, 1506, 1464, 1271, 1128, 761 cm^{-1} ; EI-MS: m/z (%) 359 (21), 358 (100), 343 (25), 316 (7), 300 (11), 285 (6), 163 (5); Anal. Calcd. For $\text{C}_{19}\text{H}_{19}\text{FN}_2\text{O}_4$: C, 63.08; H, 5.34. Found: C, 63.43; H, 5.19.

1-(4-Chlorophenyl)-5-(4-methoxyphenyl)-1H-imidazole (3l). The crude reaction product obtained from the palladium-catalyzed reaction of **1e** with **2a** (Table 2, entry 16) was purified by MPLC on silica gel with a mixture of toluene and AcOEt (50 : 50 + 0.1 % Et_3N) as eluent to give **3l** (0.10 g, 36 %) as a pale yellow solid: mp 109–111 $^\circ\text{C}$; ^1H NMR (600 MHz, CDCl_3) δ 7.70 (br s, 1H, H-2), 7.36 (d, $J = 8.7$

Hz, 2H, H-3'' and H-5''), 7.20 (br s, 1H, H-4), 7.12 (d, $J = 8.7$ Hz, 2H, H-2'' and H-6''), 7.05 (d, $J = 8.7$ Hz, 2H, H-2' and H-6'), 6.81 (d, $J = 8.7$ Hz, 2H, H-3' and H-5'), 3.79 (s, 3H, OMe); ^{13}C NMR (150 MHz, CDCl_3) δ 159.3 (C-4'), 138.1 (C-2), 135.2 (C-1''), 134.1 (C-4''), 133.0 (C-5), 129.7 (C-2', C-6', C-3'' and C-5''), 128.0 (C-4), 126.8 (C-2'' and C-6''), 121.3 (C-1'), 114.1 (C-3' and C-5'), 55.2 (OMe); IR (KBr) ν_{max} 2923, 1561, 1497, 1467, 1092, 1031, 830 cm^{-1} ; EI-MS: m/z (%) 286 (34), 285 (18), 284 (100), 269 (45), 242 (12), 151 (8), 111 (7); Anal. Calcd. for $\text{C}_{16}\text{H}_{13}\text{ClN}_2\text{O}$: C, 67.49; H, 4.60. Found: C, 67.39; H, 4.51.

5-(4-Fluorophenyl)-1-(4-methylthiophenyl)-1H-imidazole (3m). The crude reaction product obtained from the palladium-catalyzed reaction of **1f** with **2j** (Table 2, entry 17) was purified by MPLC on silica gel with a mixture of toluene and AcOEt (50 : 50 + 0.1 % Et_3N) as eluent to give **3m** (26 mg, 9 %) as a pale yellow solid: mp 190–192°C; ^1H NMR (600 MHz, CDCl_3) δ 7.85 (br s, 1H, H-2), 7.28 (br s, 1H, H-4), 7.25 (m, 2H, H-3'' and H-5''), 7.12 (m, 2H, H-2' and H-6'), 7.09 (m, 2H, H-2'' and H-6''), 6.99 (m, 2H, H-3' and H-5'), 2.51 (s, 3H, SMe); ^{13}C NMR (150 MHz, CDCl_3) δ 162.5 (C-4'), 140.1 (C-4''), 137.9 (C-2), 132.7 (C-1''), 132.4 (C-5), 130.2 (C-2' and C-6'), 127.0 (C-4), 126.9 (C-3'' and C-5''), 125.9 (C-2'' and C-6''), 124.8 (C-1'), 115.8 (C-3' and C-5'), 15.5 (SMe); IR (KBr) ν_{max} 2919, 1552, 1499, 1216, 1095, 822, 812 cm^{-1} ; EI-MS: m/z (%) 285 (19), 284 (100), 269 (19), 268 (10), 242 (13), 210 (720), 135 (29); Anal. Calcd. for $\text{C}_{16}\text{H}_{13}\text{FN}_2\text{S}$: C, 67.58; H, 4.61. Found: C, 67.40; H, 4.47.

^1H and ^{13}C NMR data for 2-(4-methoxyphenyl)-1-phenyl-1H-imidazole (7a).²²

^1H NMR (600 MHz, CDCl_3) δ 7.43 (m, 1H, H-4''), 7.42 (m, 2H, H-3'' and H-5''), 7.37 (m, 2H, H-2'

and H-6'), 7.30 (br s, 1H, H-4), 7.24 (m, 2H, H-2'' and H-6''), 7.14 (br s, 1H, H-5), 6.81 (m, 2H, H-3' and H-5'), 3.79 (s, 3H, OMe); ^{13}C NMR (150 MHz, CDCl_3) δ 160.3 (C-4'), 146.3 (C-2), 138.1 (C-1''), 130.3 (C-2' and C-6'), 129.7 (C-3'' and C-5''), 128.6 (C-4''), 127.0 (C-4), 125.9 (C-2'' and C-6''), 122.5 (C-5), 121.3 (C-1'), 113.6 (C-3' and C-5'), 55.3 (OMe).

^1H and ^{13}C NMR data for 2,5-bis(4-methoxyphenyl)-1-phenyl-1H-imidazole (8a).²²

^1H NMR (600 MHz, CDCl_3) δ 7.42 (m, 1H, H-4''), 7.38 (m, 2H, H-3'' and H-5''), 7.36 (br s, 1H, H-4), 7.35 (d, 2H, H-2''' and H-6''', $J = 8.6$ Hz), 7.11 (m, 2H, H-2'' and H-6''), 6.99 (d, 2H, H-2' and H-6', $J = 8.4$ Hz), 6.79 (d, 2H, H-3''' and H-5''', $J = 8.6$ Hz), 6.77 (d, 2H, H-3' and H-5', $J = 8.4$ Hz), 3.78 (s, 3H, OMe_b), 3.77 (s, 3H, OMe_a); ^{13}C NMR (150 MHz, CDCl_3) δ 160.5 (C-4'''), 159.5 (C-4'), 144.6 (C-2), 136.2 (C-1''), 135.4 (C-5), 130.7 (C-4''), 130.6 (C-2''' and C-6'''), 130.3 (C-3'' and C-5''), 130.2 (C-2' and C-6'), 128.0 (C-2'' and C-6''), 123.6 (C-4), 120.8 (C-1'), 120.1 (C-1'''), 55.3 (OMe_b), 55.2 (OMe_a).

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- (5) The synthesis of 1,2-diaryl-1*H*-imidazoles **7** and 1,2,5-triaryl-1*H*-imidazoles **8** by palladium- and copper-mediated reaction of 1-aryl-1*H*-imidazoles **1** with aryl halides **2** will be described in detail in a forthcoming paper.