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C–H Arylation of Nitroimidazoles and Nitropyrazoles Guided by the Electronic Effect of the Nitro Group

Haeun Jung, Seri Bae, Ha-Lim Jang, and Jung Min Joo*

*Department of Chemistry, Pusan National University, Busan 609-735, Korea. *E-mail: jmjoo@pusan.ac.kr*
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A palladium-catalyzed C–H arylation reaction of nitroimidazoles and nitropyrazoles was developed using aryl bromides as arene donors. The electron-withdrawing effect of the nitro group allows for direct C–H arylation reactions of the nitro diazoles with high regioselectivity under mild conditions. The new C–H arylation approach is thus complementary to nucleophilic substitution reactions, enabling the preparation of complex nitroazole compounds.

Key Words : C–H arylation, Nitroimidazole, Nitropyrazole, Palladium

Introduction

Nitroazoles constitute an important heterocyclic class in medicinal chemistry and materials science.[1] Activated by reduction in hypoxic cells, nitroazole drugs and drug candidates have been developed to treat cancer and anaerobic bacterial infection, such as metronidazole, tinidazole, and nimorazole.[2] Also, the nitro group, readily introduced by various nitration methods, is one of the most straightforward ways to provide a nitrogen atom source to heteroarenes, transformed to the amino group by reduction and nitrogen-containing heterocycles by reductive cyclization.[3,4] Despite the importance of the nitroaromatic compounds, the C–H arylation of nitro compounds has been limited to nitrobenzene, pyridine, and pyrazole substrates.[5-8] Particularly, these studies found that the arylation of nitroheteroarenes required a stoichiometric amount of coinage metal salts, such as Ag_2CO_3 and CuI, thus complicating the isolation of products and limiting the scope of substrates.

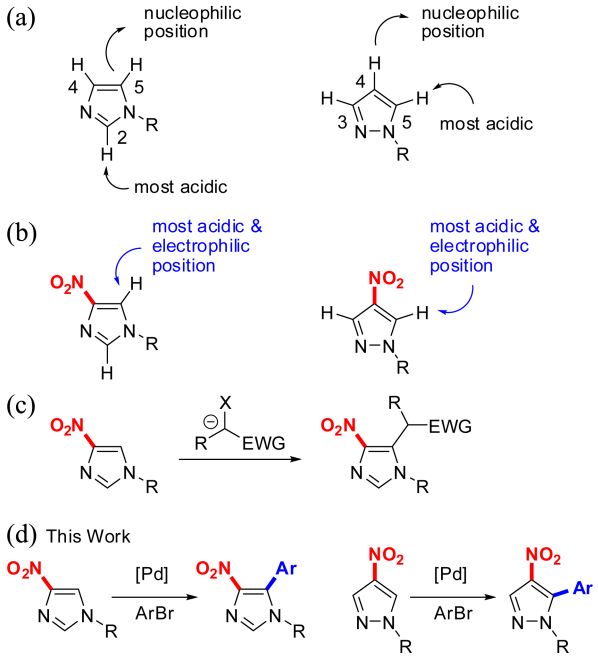


Figure 1. (a) General reactivity of imidazoles and pyrazoles. (b) General reactivity of nitroimidazoles and nitropyrazoles. The presence of the nitro group renders the C5 positions of the diazoles to be the most acidic, electrophilic, and thus highly reactive for direct C–H functionalization. (c) Nitroimidazoles as electrophiles for the vicarious nucleophilic substitution reaction. (d) Regioselective C–H arylation of nitroimidazoles and nitropyrazoles.

The general reactivity of simple diazoles suggest that the C5 position of imidazoles and C4 of pyrazoles are susceptible to electrophilic substitution, whereas the C–H bonds at the C2 of imidazoles and C5 of pyrazoles are the most acidic (Figure 1(a) and 1(b)).[9] In contrast, the nitro derivatives of diazoles have been studied mostly in the context of the vicarious nucleophilic substitution reaction by taking advantage of the electron-withdrawing nitro group (Figure 1(c)).[10] However, the high electrophilicity prevented from the use of strong bases for deprotonation of nitroazoles, thus limiting the synthetic utility of nitroazoles as nucleophiles. We envisioned that the presence of the nitro group should enable both the C5 positions of imidazoles and pyrazoles to be not only electrophilic but also the most acidic, allowing for efficient C–H functionalization reactions (Figure 1(d)). Guided by the electronic effect of the nitro group, we have developed a regioselective C–H arylation reaction of nitroimidazoles and nitropyrazoles.[11]

Experimental

General. All solvents were purchased from Sigma-Aldrich (anhydrous, Sure/Seal). All reagents were used as received unless otherwise noted. $[PCy_3H]BF_4$ was purchased from Alfa Aesar and stored in a dessicator. 4-Nitroimidazole, 4-nitropyrazole, dimetridazole (**8**), and 1-butylimidazole (**10**) were purchased from TCI.

Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm, 60 Å pore-size) impregnated with a fluorescent indicator (254

nm). TLC plates were visualized by exposure to ultraviolet light and then were stained by submersion in potassium permanganate solution followed by brief heating on a hot plate. Flash column chromatography was performed on silica gel (40-63 μm) using the indicated solvent system. Nuclear Magnetic Resonance spectra were recorded at 300 K on a 300 Fourier transform NMR spectrometer in $CDCl_3$. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CDCl_3$, δ 7.26). Data for ^{1}H NMR are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br = broad), coupling constant (*J*) in Hertz, and integration. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$, δ 77.16). Infrared (IR) spectra were reported in frequency of the absorption (cm^{-1}).

General Procedures for the Preparation of 1-Alkyl-4-nitroazoles. To a stirred solution of 4-nitroimidazole or 4-nitropyrazole (1.00 g, 8.84 mmol) in DMF (6.00 mL) at 25 °C were added K_2CO_3 (1.47 g, 10.6 mmol) and alkyl iodide (10.6 mmol). After stirring for 16 h at 25 °C, the reaction mixture was treated with water (15 mL) and EtOAc (20 mL) and transferred to a 125 mL separatory funnel. The organic layer was collected and the aqueous layer was extracted with EtOAc (25 mL × 2). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate and filtered. The filtrate was concentrated, and the residue was purified by flash column chromatography to provide the corresponding alkyl azole.

1-Butyl-4-nitro-1*H*-imidazole (1). Purification by flash column chromatography (EtOAc/hexanes = 2:1) provided butyl imidazole **1** as a white solid (1.27 g, 85% yield). mp 38−40 °C; IR (film) 3118, 2958, 2931, 2872, 1544, 1464, 1413 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.42 (s, 1H), 4.02 (t, *J* = 7.2 Hz, 2H), 1.90-1.80 (m, 2H), 1.44-1.31 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 135.9, 119.5, 47.7, 32.2, 19.1, 12.9; HRMS (ESI) calcd for $C_7H_{12}N_3O_2$ $[M+H]^+$ 170.0930, found 170.0919.

1-Benzyl-4-nitro-1*H*-imidazole (6).[12] Purification by crystallization (EtOAc/hexanes) provided imidazole **6** as a white solid (1.40 g, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.50 (s, 1H), 7.45-7.39 (m, 2H), 7.28-7.21 (m, 3H), 5.18 (s, 2H).

1-Benzyl-4-nitro-1*H*-pyrazole. Purification by flash column chromatography (EtOAc/hexanes = 1:1) provided 1-benzyl-4-nitro-1*H*-pyrazole as a white solid (1.76 g, 98% yield). Alternatively, the crude product can be crystallized using hexanes and EtOAc. mp 51−53 °C; IR (film) 3128, 1455, 1437, 1425, 1363, 1335 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 8.05 (s, 1H), 7.45-7.25 (m, 3H), 7.35-7.27 (m, 2H), 5.32 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 134.0, 129.3, 129.1, 128.5, 128.4, 57.4; HRMS (FAB) calcd for $C_{10}H_{10}N_3O_2$ $[M+H]^+$ 204.0773, found 204.0775.

1-Methyl-4-nitro-1*H*-pyrazole.[8] Purification by flash column chromatography (EtOAc/hexanes = 2:1) provided 1-methyl-4-nitro-1*H*-pyrazole as a white solid (980 mg, 87% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 1H), 8.06 (s, 1H), 3.97 (s, 3H).

General Procedures for the C–H Arylation of Nitroazoles. To a 8 mL glass vial equipped with a magnetic stir bar were sequentially added K_2CO_3 (207 mg, 1.5 mmol), the nitroazole substrate (0.50 mmol), aryl halide (0.50 mmol or as indicated), toluene (0.50 M or 1.0 M), $Pd(OAc)_2$ (5.60 mg, 0.025 mmol) and $[PCy_3H]BF_4$ (18.4 mg, 0.050 mmol). The reaction mixture was purged with nitrogen through a Teflon-lined cap. Then the cap was replaced with a new Teflon-lined solid cap. The reaction vial was moved to a pre-heated reaction block. After stirring for 18 h at the indicated temperature, the reaction mixture was cooled to 25 °C and concentrated. The residue was purified by flash column chromatography to provide the desired arylated product.

1-Butyl-5-(4-butylphenyl)-4-nitro-1*H*-imidazole (2). Purification by flash column chromatography (EtOAc/hexanes = 2:1) provided arylimidazole **2** as a white solid (103 mg, 68% yield): mp 65−67 °C; IR (film) 2932, 2873, 1574, 1516, 1464, 1340 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.37-7.26 (m, 4H), 3.81 (t, *J* = 7.5 Hz, 2H), 2.70 (t, *J* = 7.7 Hz, 2H), 1.75-1.65 (m, 4H), 1.45-1.35 (m, 2H), 1.27-1.17 (m, 2H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.82 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 144.3, 134.8, 132.5, 129.8, 128.8, 123.8, 45.8, 35.5, 33.2, 32.3, 22.3, 19.4, 13.9, 13.3; HRMS (ESI) calcd for $C_{17}H_{24}N_3O_2$ $[M+H]^+$ 302.1869, found 302.1859.

1-Butyl-2,5-bis(4-butylphenyl)-4-nitro-1*H*-imidazole (3). Purification by flash column chromatography (EtOAc/hexanes = 1:2) provided diarylimidazole **3** as a yellow solid (164 mg, 75% yield): mp 110−113 °C; IR (film) 3028, 2927, 2858, 1616, 1575, 1541, 1512, 1349 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.34 (br s, 4 H), 7.30 (d, *J* = 8.1 Hz, 2H), 3.95-3.85 (m, 2H), 2.80-2.65 (m, 4H), 1.75-1.60 (m, 4H), 1.45-1.25 (m, 6H), 1.05-0.90 (m, 8H), 0.60 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.2, 144.9, 144.8, 143.9, 133.3, 129.8, 129.0, 128.7, 126.4, 124.6, 45.3, 35.4, 35.3, 33.2, 31.7, 29.6, 22.2, 22.1, 19.1, 13.8, 12.9; HRMS (FAB) calcd for $C_{27}H_{36}N_3O_2$ $[M+H]^+$ 434.2808, found 434.2806.

1-Butyl-4-nitro-5-phenyl-1*H*-imidazole (4). Purification by flash column chromatography (EtOAc/hexanes = 2:1) provided arylimidazole **4** as a white solid (64 mg, 52% yield): mp 42−44 °C; IR (film) 3115, 2959, 2931, 2873, 1565, 1509, 1460 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.50 (m, 4H), 7.40-7.32 (m, 2H), 3.82 (t, *J* = 7.3 Hz, 2H), 1.65-1.57 (m, 2H), 1.28-1.15 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.9, 132.3, 130.1, 130.0, 128.9, 126.8, 45.9, 32.4, 19.5, 13.4; HRMS (FAB) calcd for $C_{13}H_{16}N_3O_2$ $[M+H]^+$ 246.1243, found 246.1245.

3-(1-Butyl-4-nitro-1*H*-imidazol-5-yl)pyridine (5). Purification by flash column chromatography (EtOAc only) provided arylimidazole **5** as a yellow solid (70 mg, 57% yield): mp 92−94 °C; IR (film) 3113, 3057, 2959, 2872, 1571, 1501, 1468 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (d, *J* = 4.7 Hz, 1H), 8.63 (br s, 1 H), 7.78 (dt, *J* = 7.7, 1.7 Hz,

1H), 7.57 (s, 1H), 7.50 (dd, J = 7.8, 4.9 Hz, 1H), 3.84 (t, J = 7.4 Hz, 2H), 1.67-1.57 (m, 2H), 1.30-1.18 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.0, 150.2 138.0, 135.6, 128.6, 123.6, 123.5, 46.1, 32.4, 19.5, 13.3; HRMS (ESI) calcd for $C_{12}H_{15}N_4O_2$ $[M+H]^+$ 247.1195, found 247.1194.

1-Benzyl-5-(4-butylphenyl)-4-nitro-1*H*-imidazole (7). Purification by flash column chromatography (EtOAc/hexanes = 2:1) provided arylimidazole **7** as a white solid (117 mg, 70% yield): mp 101−103 °C; IR (film) 2956, 2930, 1515, 1498, 1342, 837 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.37-7.26 (m, 5H), 7.23-7.16 (m, 2H), 7.02-6.92 (m, 2H), 4.97 (s, 2H), 2.67 (t, J = 7.6 Hz, 2H), 1.72-1.62 (m, 2H), 1.45-1.35 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2, 144.4, 135.2, 134.5, 132.8, 130.0, 129.1, 128.8, 127.3, 123.6, 49.8, 35.5, 33.3, 22.4, 14.0; HRMS (FAB) calcd for $C_{20}H_{22}N_3O_2$ $[M+H]^+$ 336.1712, found 336.1708.

1,2-Dimethyl-5-nitro-4-phenyl-1*H*-imidazole (9).[13] Purification by flash column chromatography (EtOAc/hexanes = 2:1) provided arylimidazole **10** as a light yellow solid (47 mg, 44% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77-7.67 (m, 2H), 7.47-7.37 (m, 3H), 3.88 (s, 3H), 2.49 (s, 3H).

1-Benzyl-5-(4-butylphenyl)-4-nitro-1*H*-pyrazole (12). Purification by flash column chromatography (EtOAc/hexanes = 1:1) provided mono-arylated pyrazole **12** as a yellow oil (143 mg, 85% yield) along with di-arylation product **13** (17 mg, 7% yield): IR (film) 2956, 2929, 2857, 1615, 1560, 1509, 1444, 1356 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.32-7.24 (m, 5H), 7.24-7.17 (m, 2H), 7.06-7.00 (m, 2H), 5.16 (s, 2H), 2.75-2.65 (m, 2H), 1.72-1.60 (m, 2H), 1.46-1.36 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 142.0, 136.8, 135.4, 133.2, 129.7, 128.9, 128.8, 128.3, 127.5, 123.6, 54.1, 35.6, 33.3, 22.4, 14.0; HRMS (ESI) calcd for $C_{20}H_{22}N_3O_2$ $[M+H]^+$ 336.1712, found 336.1708.

1-Benzyl-3,5-bis(4-butylphenyl)-4-nitro-1*H*-pyrazole (13). Purification by flash column chromatography (EtOAc/hexanes = 1:3) provided di-arylation product **13** as a yellow oil (59 mg, 25% yield) along with mono-arylation product **12** (104 mg, 62% yield): IR (film) 3033, 2930, 2859, 1616, 1561, 1496, 1321 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 7.9 Hz, 2H), 7.35-7.20 (m, 9H), 7.10-0.02 (m, 2H), 5.18 (s, 2H), 2.75-2.60 (m, 4H), 1.70-1.58 (m, 4H), 1.45-1.32 (m, 4H), 1.00-0.90 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 145.4, 144.2, 143.4, 135.6, 129.7, 129.1, 128.9, 128.8, 128.4, 128.2, 127.9, 127.6, 124.3, 54.2, 35.7, 33.6, 33.4, 22.5, 14.1; HRMS (FAB) calcd for $C_{30}H_{34}N_3O_2$ $[M+H]^+$ 468.2651, found 468.2649.

5-(4-Butylphenyl)-1-methyl-4-nitro-1*H*-pyrazole (14). Purification by flash column chromatography (EtOAc/hexanes = 1:1) provided arylpyrazole **14** as a yellow oil (100 mg, 77% yield): IR (film) 2957, 2929, 2859, 1466, 1436 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 3.74 (s, 3H), 2.70 (t, J = 7.8 Hz, 2H), 1.72-1.60 (m, 2H), 1.46-1.34 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.5, 141.7, 136.4, 132.9, 129.6, 128.8, 123.6, 38.0, 35.6, 33.3, 22.4, 14.0; HRMS (FAB) calcd for $C_{14}H_{18}N_3O_2$ $[M+H]^+$ 260.1399, found 260.1396.

5-(4-Fluorophenyl)-1-methyl-4-nitro-1*H*-pyrazole (15). Purification by flash column chromatography (EtOAc/hexanes = 2:1) provided arylpyrazole **15** as a yellow solid (93 mg, 84% yield): mp 109−111 °C; IR (film) 1607, 1511, 1472, 1393, 1326 1239, 1161 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.45-7.35 (m, 2H), 7.30-7.25 (m, 2H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8 (d, $^1J_{C\text{-}F}$ = 251.4 Hz), 140.5, 136.4, 132.0 (d, $^3J_{C\text{-}F}$ = 8.9 Hz), 122.5 (d, $^4J_{C\text{-}F}$ = 3.6 Hz), 116.3 (d, $^2J_{C\text{-}F}$ = 22.1 Hz), 38.1; HRMS (ESI) calcd for $C_{10}H_9FN_3O_2$ $[M+H]^+$ 222.0679, found 222.0678.

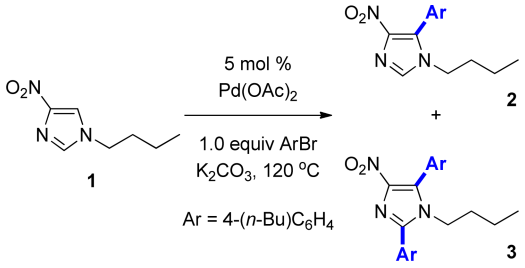
3-(1-Methyl-4-nitro-1*H*-pyrazol-5-yl)pyridine (16). Purification by flash column chromatography (EtOAc only) provided arylpyrazole **16** as a yellow solid (72 mg, 71% yield): mp 141−143 °C; IR (film) 1602, 1572, 1505 1411, 1324, 1247 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.67 (s, 1H), 8.27-8.20 (m, 1H), 7.85-7.75 (m, 1H), 7.58-7.48 (m, 1H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3, 149.9, 138.2, 137.7, 136.4, 123.5, 123.1, 38.2; HRMS (FAB) calcd for $C_9H_9N_4O_2$ $[M+H]^+$ 205.0726, found 205.0728.

5-(4-Methoxyphenyl)-1-methyl-4-nitro-1*H*-pyrazole (17).[8] Purification by flash column chromatography (EtOAc:hexanes = 1:1) provided arylpyrazole **17** as a yellow solid (93 mg, 79% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 3.75 (s, 3H).

Results and Discussion

Many transition metal-catalyzed C–H arylation reactions of diazoles are affected by the strength of the base, requiring strong alkoxide bases or highly soluble carboxylates in polar aprotic solvents.[14,15] Naturally, base-sensitive functional groups do not tolerate these conditions, including nitroazole compounds. However, we considered that carbonate bases and nonpolar solvents should be sufficient to lead to arylated nitroazoles as nitroazoles are highly reactive due to the presence of the nitro group.[16] In fact, we observed that the C–H arylation reaction of nitroimidazole **1** in nonpolar toluene produced 5-arylated imidazole **2** more selectively than the one in polar DMA, presumably due to the more effective coordination of the palladium complex with the nitro group in the nonpolar medium (Table 1, entries 1 and 2). In lieu of K_2CO_3, Cs_2CO_3 can be used for the arylation of nitroimidazoles (Table 1, entry 3). These results showed that the base-sensitive nitroazole compounds were tolerant of the carbonate bases at the high temperature. The air-stable, commercially available electron-rich phosphonium salt $[PCy_3H]BF_4$ was used on the benchtop for the arylation of nitroazole compounds. In the absence of the ligand, the desired arylation product was not formed (Table 1, entry 4). Neither phenanthroline nor PPh_3 was as efficient as the electron-rich phosphine ligand (Table 1, entries 5 and 6).[17] However, the conversion was significantly decreased when the reaction was carried out at 100 °C instead of 120 °C

Table 1. Arylation of 4-nitroimidazole **1**: Optimization



Entry	Ligand (10 mol %)	K_2CO_3 (equiv)	Solvent	Yield[a] (%, 1:2:3)
1	$[PCy_3H]BF_4$	2.5	DMA	22:55:21
2	**$[PCy_3H]BF_4$**	**2.5**	**toluene**	**13:72:15**
3[b]	$[PCy_3H]BF_4$	2.5	toluene	7:73:15
4	no ligand	2.5	toluene	95: < 2: < 2
5[c]	phenanthroline	2.5	toluene	95: < 2: < 2
6	PPh_3	2.5	toluene	63:37:0
7[d]	$[PCy_3H]BF_4$	2.5	toluene	75:20:0
8[e]	$[PCy_3H]BF_4$	3.0	toluene	15:42:21

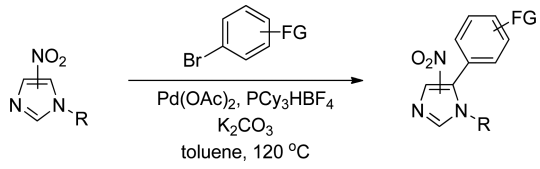
[a] ^{1}H NMR yield. [b]Cs_2CO_3 was used instead of K_2CO_3. [c]5 mol % of the ligand was used. [d]The reaction was carried out at 100 °C. [e]0.30 equiv of PivOH was added.

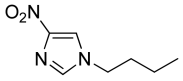
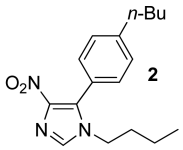
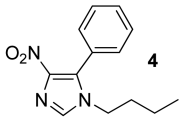
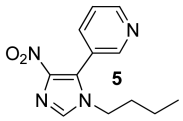
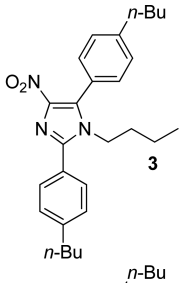
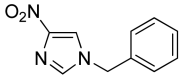
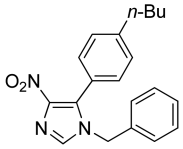
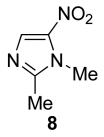
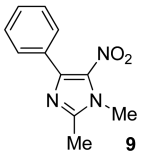
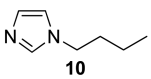
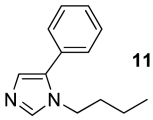
(Table 1, entry 7). The addition of pivalic acid that in situ generates the soluble pivalate base only deteriorated the regioselectivity of the arylation reaction (Table 1, entry 8).

With the optimized conditions in hand, we demonstrated that 1-butyl-4-nitroimidazole **1** gave rise to C5-arylimidazole **2** and **4** in 68% and 52% yields, respectively (Table 2, entries 1 and 2). Functionalized arene donors, such as 3-bromopyridine, can also be coupled with the nitroimidazole (Table 2, entry 3).[18] Furthermore, the enhanced reactivity resulted from the nitro substituent allowed for a di-arylation reaction when an excess of the aryl bromide and a catalytic amount of pivalic acid were used; diarylimidzole **3** was obtained in 75% yield (Table 2, entry 4). In addition, 1-benzyl nitroimidazole **6** can be used for the C–H arylation, affording the corresponding product **7** in 70% yield (Table 2, entry 5). The X-ray analysis of product **7** unambiguously confirmed the regioselectivity of the arylation reaction of 4-nitroimidazoles (Figure 2). These results consistently indicate that the C5 position of 4-nitroimidazoles is preferred to the C2 position for the C–H arylation. Not only 4-nitroimidazoles but also 5-nitroimidazole, dimetridazole **8** was arylated (Table 2, entry 6); the result that the arylation took place at the C4 position that is generally the least reactive in the palladium-catalyzed arylation of imidazoles is another example of the strong activating effect of the nitro group.[19] More importantly, the observed reactivity is in stark contrast to that of simple imidazole like **10** that resulted in only a trace amount of the arylation products under the standard toluene conditions (Table 2, entry 7).[20]

The protocol developed for nitroimidazoles can also be applied for the regioselective arylation of nitropyrazoles. Similar to nitroimidazoles, the C5 position of 4-nitropyrazoles was the most reactive, giving 5-arylated pyrazoles in

Table 2. C–H arylation of nitroimidazoles[a]



Entry	Imidazole	Product	% Yield[b]
1	 **1**	 **2**	68%
2	**1**	 **4**	52% (74%)[c]
3	**1**	 **5**	57%
4	**1**	 **3**	75%[d]
5	 **6**	 **7**	70%
6	 **8**	 **9**	44%
7	 **10**	 **11**	<5%

[a]Conditions: 0.50 mmol of the imidazole, 1.0 equiv of Ar-Br, 5.0 mol % of $Pd(OAc)_2$, 10 mol % of $[PCy_3H]BF_4$, 2.5 equiv of K_2CO_3, toluene (0.50 M), 120 °C. [b]Isolated yield. [c] ^{1}H NMR yield. [d]0.30 equiv of PivOH, 2.5 equiv of the bromide, and 4.0 equiv of K_2CO_3 were used.

high yields (Table 3). The di-arylation of 4-nitropyrazoles was not as efficient as that of 4-nitroimidazoles; when 2.5 equiv of the aryl bromide in conjunction with 0.30 equiv of pivalic acid was used, the di-arylation product **13** was obtained in 25% yield along with the mono-arylation product **12** in 62% yield. Not only the *N*-benzylpyrazole but also the *N*-methyl counterpart reacted with a variety of aryl bromides to provide 5-arylated pyrazoles. Both electron-rich

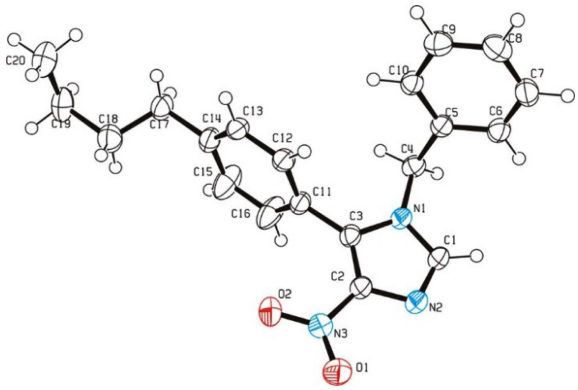
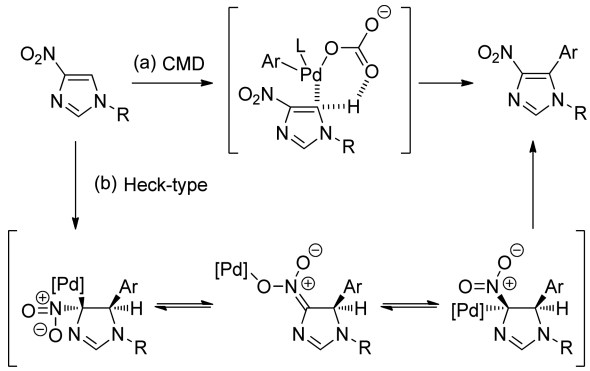


Figure 2. ORTEP diagram of C5-arylated imidazole **7**.

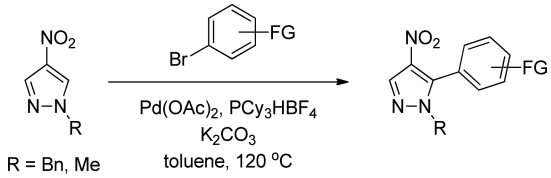


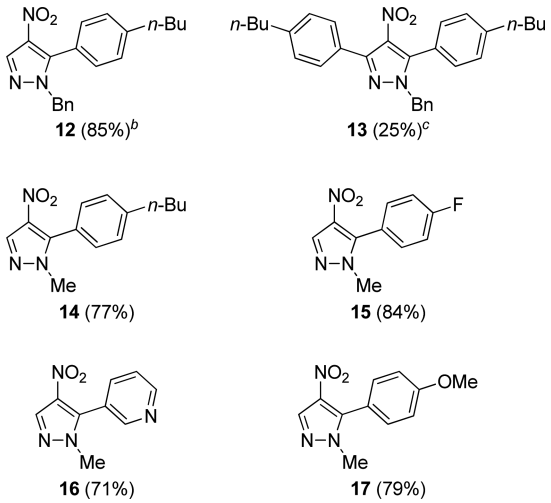
Scheme 1. Proposed mechanism. (a) Concerted metalation/deprotonation (CMD). (b) Heck-type addition/elimination.

and electron-deficient bromoarene donors can be employed for the process. Notably, it was not necessary to include an excess of transition metal additives to prevent the cleavage of the N–N bond of the nitropyrazole ring;[8] the nitropyrazoles were compatible with the mild toluene conditions.

We propose that the C−H arylation of nitroazoles occur *via* concerted metalation/deprotonation (CMD) where the carbonate base is involved in the intramolecular deprotonation (Scheme 1, path a). Given to the highly electrophilic nature of the nitroazole ring, however, we cannot exclude a Heck-type addition/elimination mechanism (Scheme 1, path b).[21,22] Similar to vicarious nucleophilic substitution reactions, the aryl palladium species could undergo an addition to the heterocyclic ring. Subsequent epimerization through the nitro group followed by β−H elimination would restore the aromaticity, giving the arylated azole product.

Table 3. C–H arylation of 4-nitropyrazoles[a]





[a]Conditions: 0.50 mmol of the nitropyrazole, 1.0 equiv of Ar-Br, 5.0 mol % of $Pd(OAc)_2$, 10 mol % of $[PCy_3H]BF_4$, 3.0 equiv of K_2CO_3, toluene (1.0 M), 120 °C. [b]The reaction was carried out at 100 °C. [c]0.30 equiv of PivOH, 2.5 equiv of the bromide, and 4.0 equiv of K_2CO_3 were used.

Conclusion

In conclusion, we have developed a direct C−H arylation reaction of nitroimidazoles and nitropyrazoles using aryl bromides as arene donors. Guided by the electronic character of the nitroazole ring, we have found that a catalytic amount of the palladium complex derived from air-stable $[PCy_3H]BF_4$ and a stoichiometric amount of weak base K_2CO_3 resulted in high yields of arylated nitroimidazoles and nitropyrazoles. Under these practical conditions, the base-sensitive nitroazole heterocycles were well tolerated. Combined with vicarious nucleophilic substitution reactions, the direct C−H arylation strategy will allow for rapid functionalization of synthetically important nitroazole compounds.

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Supporting Information. Copies of ^1H and ^{13}C NMR spectra and X-ray crystallographic data of compound **7**. Crystallographic data for arylimidazole **7** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 995468. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/conts/retrieving.html or from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, E-mail: deposit@ccdc.cam.ac.uk (or FIZ, D-76344, Eggenstein-Leopoldshafen, Germany, E-mail: crysdata@fiz-karlsruhe.de).

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