A Novel and Efficient Iron-Copper Co-Catalyzed Arylation of Nitrogen Nucleophiles

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General Experimental Procedures

All reactions were carried out in 35 mL Schlenk tubes or in Carousel “reaction stations RR98030” Radley tubes, under a pure and dry nitrogen atmosphere. DMF was distilled from CaH₂ and was stored on 4 Å activated molecular sieves under a nitrogen atmosphere. Cesium carbonate (Acros), CuO (Acros) and Fe(acac)₃ (Acros) and all other solid materials were stored in the presence of P₄O₁₀ in a bench-top desiccator under vacuum at room temperature and weighed in the air. Aryl iodide and aryl bromides were purchased from commercial sources (Aldrich, Acros, Avocado, Fluka, Lancaster). If solids, they were recrystallized in an appropriate solvent.[1] If liquids, they were distilled under vacuum and stored under an atmosphere of nitrogen. Special care was taken with liquid iodobenzene which was regularly distilled and stored protected from light. Column chromatography was performed with SDS 60 A C.C silica gel (35-70 µm). Thin layer chromatography was carried out using Merck silica gel 60 F₂₅₄ plates. All products were characterized by their NMR, GC/MS and IR spectra. NMR spectra were recorded at 20°C on a Bruker AC 400 MHz or on a DRX-250 spectrometer working respectively at 400 MHz for ¹H, at 100 MHz for ¹³C. Chemical shifts are reported in ppm/TMS for ¹H and ¹³C δ 77.00 for CDCl₃ signal. The first-order peak patterns are indicated as s (singulet), d (doublet), t (triplet), q (quadruplet). Complex non-first-order signals are indicated as m (multiplet). Gas chromatography - mass spectra (GC/MS) were recorded on an Agilent Technologies 6890 N instrument with an Agilent 5973 N mass detector (EI) and a HP5-MS 30 m x 0.25 mm capillary apolar column (Stationary phase: 5 % diphenyldimethylpolysiloxane film, 0.25 µm). GC/MS method: Initial temperature: 45°C; Initial time: 2 min; Ramp: 2°C/min until 50°C then 10 °C/min; Final temperature: 250°C; Final time: 10 min. IR spectra were recorded on a Nicolet 210 FT-IR instrument (neat, thin film for liquid products and KBr pellet or in carbon tetrachloride solution for solid products). FAB+ mass spectra and HRMS were recorded on a JEOL JMS-DX300 spectrometer (3 keV, xenon) in a m-nitrobenzylalcohol matrix. Melting points were determined using a Büchi B-540 apparatus and are uncorrected.

General Procedure for Copper-Iron Co-catalyzed Coupling Reaction (1 mmol and 2 mmol scale)

After standard cycles of evacuation and back-filling with dry and pure nitrogen, an oven-dried Radley tube (Carousel “reaction stations RR98030”) equipped with a magnetic stirring bar was charged with CuO (0.1 eq.), Fe(acac)₃ (0.3 eq.), the nucleophile (1.5 eq.), Cs₂CO₃ (2 eq.) and the aryl halide (1 eq.), if a solid. The tube was evacuated, back-filled with nitrogen. If a liquid, aryl bromide was added under a stream of nitrogen by syringe at room temperature, followed by anhydrous and degassed DMF (1.0 mL). The tube was sealed under a positive pressure of nitrogen, stirred and heated to 90 or 125 °C or 140°C for the required time period. After cooling to room temperature, the mixture was diluted with dichloromethane (~ 20 mL) and filtered through a plug of celite.® If liquids, the filter cake was further washed with dichloromethane (~ 5 mL). The filtrate was washed twice with water (~ 10 mL x 2). Gathered aqueous phases were twice extracted with dichloromethane (~ 10 mL). Organic layers were gathered, dried over Na₂SO₄, filtered and concentrated in vacuum to yield the crude product obtained was purified by silica gel chromatography with an eluent of hexanes and dichloromethane. The products were characterized by NMR, IR and mass spectra with those of authentic samples.
General Procedure for Reactivity Comparison of Different Catalyst System (0.5 mmol scale)

After standard cycles of evacuation and back-filling with dry and pure nitrogen, an oven-dried Radley tube (Carousel “reaction stations RR98030”) equipped with a magnetic stirring bar was charged with indicated catalysts, the pyrazole (51 mg, 1.5 eq.), Cs$_2$CO$_3$ (325 mg, 2 eq.). The tube was evacuated, back-filled with nitrogen. Iodobenzene (56 µL, 0.5 mmol, 1 eq.) or bromobenzene (53 µL, 0.5 mmol, 1 eq.) was added under a stream of nitrogen by syringe at room temperature, followed by anhydrous and degassed DMF (0.5 mL). The tube was sealed under a positive pressure of nitrogen, stirred and heated to 100 °C for 15 hours. After cooling to room temperature, the mixture was diluted with dichloromethane (~ 20 mL) and filtered through a plug of celite®, the filter cake being further washed with dichloromethane (~ 5 mL). 65 µL of 1,3-dimethoxybenzene (internal standard) were added. A small sample of the reaction mixture was taken and filtered through a plug of celite®, the filter cake being further washed with dichloromethane. The filtrate was washed three times with water and analyzed by gas chromatography. The GC yields were determined by obtaining the correction factors using authentic samples of the expected products.

Experimental procedures and characterization data

1-Phenyl-1H-pyrazole$^2$

**Experimental procedure**

Following the general procedure (90°C, 30 hours), 1H-pyrazole (205 mg, 3.0 mmol) was coupled with bromobenzene (212 µL, 2.0 mmol). The crude brown oil was purified by flash chromatography on silica gel (eluent: dichloromethane/hexanes=50/50) to provide 270 mg (94 % yield) of the desired product as a light yellow oil.

**Identification**

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.95-7.96 (dd, 1H, H$_7$), 7.71-7.75 (m, 3H, H$_2,6,9$), 7.47-7.50 (m, 2H, H$_3,5$), 6.49-6.50 (dd, 1H, H$_8$).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 141.09 (C$_9$), 140.22 (C$_1$), 129.45 (C$_3,5$), 126.75 (C$_7$), 126.46 (C$_4$), 119.23 (C$_2,6$), 107.61 (C$_8$).

IR (KBr): ν (cm$^{-1}$) = 3142, 3050, 2924, 1600, 1520, 1500, 1393, 1332, 1198, 1120, 1046, 936, 914, 755, 689, 654, 610, 515.

GC/MS: rt = 14.53 min, M/Z = 144.

HRMS: 145.0766 (M+H). Theoretical: 145.0766

1-Phenyl-1H-imidazole$^3$

**Experimental procedure**

Following the general procedure (90°C, 30 hours), 1H-imidazole (102 mg, 1.5 mmol) was coupled with iodo-benzene (112 µL, 1.0 mmol). The crude brown oil was purified by flash chromatography on silica gel (eluent: hexane/ethylacetate=20/80) to provide 130 mg (90 % yield) of the desired product as a light yellow oil.

**Identification**

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.81 (s, 1H, H$_9$), 7.40-7.43 (m, 2H, H$_3,5$), 7.28-7.34 (m, 3H, H$_2,4,6$), 7.22 (s, 1H, H$_7$), 7.15 (s, 1H, H$_8$).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 141.09 (C$_4$), 135.59 (C$_9$), 130.32 (C$_8$), 129.92 (C$_3,5$), 127.56 (C$_7$), 121.53 (C$_2,6$), 118.32 (C$_1$).

IR (KBr): ν (cm$^{-1}$) = 3115, 3067, 1600, 1509, 1304, 1247, 1112, 1057, 962, 905, 815, 759, 692, 658, 582.

GC/MS: rt = 16.14 min, M/Z = 144.

HRMS: 145.0768 (M+H). Theoretical: 145.0766

4-Pyrazol-1-yl-benzoic acid ethylester$^4$

**Experimental procedure**

Following the general procedure (90°C, 30 hours), 1H-pyrazole (205 mg, 3.0 mmol) was coupled with ethyl 4-bromobenzoate (336 µL, 2.0 mmol). The crude brown oil was purified by flash chromatography on silica gel (eluent: dichloromethane/hexanes=80/20) to provide 400 mg (93 % yield) of the desired product as a white solid.

**Identification**

Mp: 66°C.
Identification
1-(4-Pyrazol-1-yl-phenyl)-ethanone

Experimental procedure
Following the general procedure (90°C, 30 hours), 1H-pyrazole (205 mg, 3.0 mmol) was coupled with 4-bromo-1,1'-biphenyl (446 mg, 2.0 mmol). The crude brown oil was purified by flash chromatography on silica gel (eluent: dichloromethane/hexanes=50/50) to provide 330 mg (98 % yield) of the desired product as a white solid.

Identification
1-Biphenyl-4-yl-1H-pyrazole
Experimential procedure
Following the general procedure (90°C, 30 hours), 1H-pyrazole (205 mg, 3.0 mmol) was coupled with 4-methoxybenzene (468 mg, 2.mmol). The crude brown oil was purified by flash chromatography on silica gel (eluent: dichloromethane/hexanes=50/50) to provide 340 mg (98 % yield) of the desired product as a white solid.

Identification
4-Pyrazol-1-yl-benzonitrile
Experimental procedure
Following the general procedure (90°C, 30 hours), 1H-pyrazole (205 mg, 3.0 mmol) was coupled with 4-bromo-1,1'-biphenyl (446 mg, 2.0 mmol). The crude brown oil was purified by flash chromatography on silica gel (eluent: dichloromethane/hexanes=50/50) to provide 410 mg (93 % yield) of the desired product as a white crystal.

Identification
1-(4-Methoxy-phenyl)-1H-pyrazole

Experimental procedure
Following the general procedure (90°C, 30 hours), 1H-pyrazole (205 mg, 3.0 mmol) was coupled with 1-iodo-4-methoxybenzene (468 mg, 2.mmol). The crude brown oil was purified by flash chromatography on silica gel (eluent: dichloromethane/hexanes=50/50) to provide 340 mg (98 % yield) of the desired product as a white solid.

Identification
1-Biphenyl-4-yl-1H-pyrazole

Experimental procedure
Following the general procedure (90°C, 30 hours), 1H-pyrazole (205 mg, 3.0 mmol) was coupled with 4-bromo-1,1'-biphenyl (446 mg, 2.0 mmol). The crude brown oil was purified by flash chromatography on silica gel (eluent: dichloromethane/hexanes=50/50) to provide 410 mg (93 % yield) of the desired product as a white crystal.

Identification
4-Pyrazol-1-yl-benzonitrile

Experimental procedure
Following the general procedure (90°C, 30 hours), 1H-pyrazole (205 mg, 3.0 mmol) was coupled with 4-bromo-1,1'-biphenyl (446 mg, 2.0 mmol). The crude brown oil was purified by flash chromatography on silica gel (eluent: dichloromethane/hexanes=50/50) to provide 410 mg (93 % yield) of the desired product as a white crystal.

Identification
1-(4-Pyrazol-1-yl-phenyl)-ethanone

Experimental procedure
Following the general procedure (90°C, 30 hours), 1H-pyrazole (205 mg, 3.0 mmol) was coupled with 4-bromo-1,1'-biphenyl (446 mg, 2.0 mmol). The crude brown oil was purified by flash chromatography on silica gel (eluent: dichloromethane/hexanes=50/50) to provide 410 mg (93 % yield) of the desired product as a white crystal.
Experimental procedure
Following the general procedure (90°C, 30 hours), 1H-pyrazole (205 mg, 3.0 mmol) was coupled with 1-(4-bromophenyl)ethanone (398 mg, 2.0 mmol). The crude brown oil was purified by flash chromatography on silica gel (eluent: dichloromethane/hexanes=50/50) to provide 300 mg (81% yield) of the desired product as a white solid.

Identification
Mp: 108°C (Litt. [2]: 110°C).
1H NMR (400 MHz, CDCl3): δ 7.98-8.00 (m, 3H, H3,5,7), 7.70-7.76 (m, 3H, H2,6,9), 6.46 (s, 1H, H8), 2.56 (s, 3H, H11).
13C NMR (100 MHz, CDCl3): δ 196.84 (C10), 143.33 (C1), 142.09 (C9), 134.80 (C4), 130.01 (C3,5), 126.91 (C7), 118.39 (C2,6), 108.62 (C8).
IR (KBr): ν (cm⁻¹) = 3135, 3114, 3101, 1673 (C=O), 1605, 1528, 1395, 1264, 1210, 935, 838, 762, 611, 589, 518.
GC/MS: rt = 19.96 min, M/Z = 186.

1-(4-Nitro-phenyl)-1H-pyrazole

Experimental procedure
Following the general procedure (90°C, 30 hours), 1H-pyrazole (205 mg, 3.0 mmol) was coupled with 1-bromo-4-nitrobenzene (404 mg, 2.0 mmol). The crude brown oil was purified by flash chromatography on silica gel (eluent: dichloromethane/hexanes=50/50) to provide 340 mg (90% yield) of the desired product as a yellow solid.

Identification
1H NMR (400 MHz, CDCl3): δ 8.26-8.29 (m, 2H, H3,5), 7.97 (d, 1H, H7), 7.81-7.84 (m, 2H, H2,6), 7.73-7.74 (d, 1H, H9), 6.49-6.50 (dd, 1H, H8).
13C NMR (100 MHz, CDCl3): δ 144.42 (C4), 142.81 (C9), 133.52 (C1), 134.80 (C4), 127.08 (C7), 125.42 (C3,5), 118.62 (C2,6), 109.38 (C8).
IR (KBr): ν (cm⁻¹) = 3152, 3119, 3085, 1596, 1532, 1517, 1392, 1334 (NO2), 1206, 1112, 1050, 1030, 929, 852, 764, 749, 685, 497.
GC/MS: rt = 20.30 min, M/Z = 189.
HRMS: 190.0615 (M+H). Theoretical: 190.0617

1-(4-Tolyl)-1H-pyrazole

Experimental procedure
Following the general procedure (125°C, 24 hours), 1H-pyrazole (102 mg, 1.5 mmol) was coupled with 1-bromo-4-methylbenzene (122 µL, 1.0 mmol). The crude brown oil was purified by flash chromatography on silica gel (eluent: dichloromethane/hexanes=70/30) to provide 90 mg (57% yield) of the desired product as an uncolored oil.

Identification
1H NMR (400 MHz, CDCl3): δ 7.78-7.79 (m, 1H, H7), 7.62 (d, 1H, H9), 7.47-7.49 (d, 2H, H2,6), 7.14-7.17 (t, 2H, H3,5), 6.35-6.36 (dd, 1H, H8), 2.29 (s, 3H, H10).
13C NMR (100 MHz, CDCl3): δ 139.72 (C9), 136.95 (C1), 135.18 (C4), 128.88 (C3,5), 125.63 (C7), 118.13 (C2,6), 106.27 (C8), 19.87 (C10).
IR (KBr): ν (cm⁻¹) = 3123, 3040, 2922, 2863, 1610, 1525, 1394, 1331, 1196, 1123, 1046, 1031, 929, 852, 764, 749, 685, 497.
GC/MS: rt = 16.08 min, M/Z = 158.
HRMS: 159.0913 (M+H). Theoretical: 159.0922

1-(4-Trifluoromethyl-phenyl)-1H-pyrazole

Experimental procedure
Following the general procedure (140°C, 24 hours), 1H-pyrazole (102 mg, 1.5 mmol) was coupled with 1-chloro-4-(trifluoromethyl)benzene (134 µL, 1.0 mmol). The crude brown oil was purified by flash chromatography on silica gel (eluent: dichloromethane/hexanes=50/50) to provide 80 mg (38% yield) of the desired product as a white solid.

Identification
Mp: 93°C (Litt. [2]: 94-95°C).
1H NMR (400 MHz, CDCl3): δ 7.92-7.93 (d, 1H, H7), 7.76-7.78 (d, 2H, H3,5), 7.70 (d, 1H, H9), 7.64-7.66 (d, 2H, H2,6),
Experimental procedure

Following the general procedure (125°C, 24 hours), 1H-pyrazole (102 mg, 1.5 mmol) was coupled with 4-iodoaniline (220 mg, 1.0 mmol). The crude brown oil was purified by flash chromatography on silica gel (eluent: dichloromethane/hexanes=50/50) to provide 90 mg (57% yield) of the desired product as an orange solid.

Identification

HRMS: \( m/z = 213.0659 \) (M+H). Theoretical: 213.0640

**1-(3-Methoxy-phenyl)-1H-pyrazole**

Experimental procedure

Following the general procedure (125°C, 24 hours), 1H-pyrazole (102 mg, 1.5 mmol) was coupled with 4-iodoaniline (220 mg, 1.0 mmol). The crude brown oil was purified by flash chromatography on silica gel (eluent: dichloromethane/hexanes=50/50) to provide 90 mg (57% yield) of the desired product as a orange solid.

Identification

HRMS: \( m/z = 213.0659 \) (M+H). Theoretical: 213.0640
Following the general procedure (90°C, 30 hours), 1H-[1,2,4]triazole (104 mg, 1.5 mmol) was coupled with iodo-benzene (112 μL, 1.0 mmol). The crude brown oil was purified by flash chromatography on silica gel (eluent: dichloromethane/hexanes=50/50) to provide 120 mg (83% yield) of the desired product as a light yellow solid.

**Identification**

Mp: 46°C (Lit.[3], 46°C).

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.49 (s, 1H, H$_8$), 8.03 (s, 1H, H$_7$), 7.58-7.61 (m, 2H, H$_{2,6}$), 7.40-7.44 (t, 2H, H$_{3,5}$), 7.31-7.35 (m, 1H, H$_9$).  

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 152.62 (C$_7$), 140.91 (C$_6$), 136.99 (C$_4$), 129.77 (C$_{3,5}$), 128.21 (C$_2$), 120.04 (C$_{2,6}$).  

IR (KBr): ν$_{max}$ (cm$^{-1}$) = 3105, 2924, 2852, 1600, 1514, 1416, 1359, 1278, 1223, 1152, 1055, 981, 876, 754, 681, 671, 503.  

HRMS: 146.0721 (M+H). Theoretical: 146.0718

2-Phenyl-2H-[1,2,3]triazole$^{[7]}$ and 1-Phenyl-1H-[1,2,3]triazole$^{[8]}$

**Experimental procedure**

Following the general procedure (90°C, 30 hours), 1H-[1,2,3]triazole (87μL, 1.5 mmol) was coupled with iodo-benzene (112 μL, 1.0 mmol). The crude uncolored oil was purified by flash chromatography on silica gel (eluent: dichloromethane/hexanes=50/50) to provide 70 mg of 1-Phenyl-1H-[1,2,3]triazole (48% yield) as a light yellow solid.

**Identification**

Mp: 56°C (Lit.$^{[8]}$, 53-55°C).

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.99-8.02 (m, 2H, H$_{2,6}$), 7.72 (s, 2H, H$_{3,5}$), 7.38-7.42 (m, 2H, H$_{3,5}$), 7.24-7.28 (m, 1H, H$_8$).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 139.90 (C$_4$), 135.51 (C$_7$), 129.30 (C$_{3,5}$), 127.56 (C$_{2,6}$), 118.97 (C$_{2,6}$).  

IR (KBr): ν$_{max}$ (cm$^{-1}$) = 3125, 3060, 2926, 2854, 1598, 1500, 1410, 1376, 1260, 1215, 1149, 1069, 950, 821, 756, 695, 640.

HRMS: 145.0653 (M). Theoretical: 145.0640

1-Phenyl-1H-pyrrole$^{[3]}$

**Experimental procedure**

Following the general procedure (90°C, 30 hours), 1H-pyrazole (104 μL, 1.5 mmol) was coupled with iodo-benzene (112 μL, 1.0 mmol). The crude brown oil was purified by flash chromatography on silica gel (eluent: hexanes) to provide 130 mg (91% yield) of the desired product as a white solid.

**Identification**

Mp: 60°C (Lit.$^{[3]}$, 62°C).

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.28-7.34 (m, 4H, H$_{2,3,5,6}$), 7.14-7.15 (t, 1H, H$_8$), 6.99-7.00 (t, 2H, H$_{2,6}$), 6.26-6.27 (t, 1H, H$_7$).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 140.82 (C$_4$), 129.60 (C$_{3,5}$), 125.66 (C$_4$), 120.57 (C$_2$), 119.37 (C$_{7,8}$), 110.46 (C$_{2,6}$).  

IR (KBr): ν$_{max}$ (cm$^{-1}$) = 3142, 3102, 2924, 1603, 1556, 1511, 1459, 1400, 1326, 1255, 1189, 1083, 1014, 919, 895, 758, 684, 640.  

HRMS: 143.0740 (M). Theoretical: 143.0735

1-Phenyl-1H-indole$^{[3]}$

**Experimental procedure**

Following the general procedure (90°C, 30 hours), 1H-indole (104 μg, 1.5 mmol) was coupled with iodo-benzene (112 μL, 1.0 mmol). The crude white solid was purified by flash chromatography on silica gel (eluent: dichloromethane/hexanes=50/50) to provide 120 mg (83% yield) of the desired product as a light yellow solid.
Following the general procedure (90°C, 30 hours), 1H-indole (176 mg, 1.5 mmol) was coupled with iodo-benzene (112 µL, 1.0 mmol). The crude brown oil was purified by flash chromatography on silica gel (eluent: hexanes) to provide 180 mg (93% yield) of the desired product as a light green oil.

**Identification**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.57-7.59 (m, 1H, H$_{11}$), 7.44-7.47 (m, 1H, H$_8$), 7.36-7.37 (d, 4H, H$_{2,3,5,6}$), 7.20-7.23 (m, 2H, H$_{10,16}$), 6.56-6.57 (m, 1H, H$_{13}$).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 139.93 (C$_1$), 135.95 (C$_7$), 129.72 (C$_{2,6}$), 129.45 (C$_{12}$), 128.06 (C$_{14}$), 126.54 (C$_4$), 124.46 (C$_{3,5}$), 122.48 (C$_9$), 121.26 (C$_{11}$), 120.49 (C$_{10}$), 110.64 (C$_8$), 103.70 (C$_{13}$).

IR (KBr): $\nu$ (cm$^{-1}$) = 3104, 3055, 3032, 2924, 1597, 1515, 1497, 1456, 1331, 1233, 1213, 1135, 1014, 908, 773, 741, 695, 577, 426.

GC/MS: rt = 20.44 min, M/Z = 193.

HRMS: 193.0924 (M+H). Theoretical: 193.0891

**References**


1-Phenyl-1H-pyrazole

1-Phenyl-1H-imidazole
4-Pyrazol-1-yl-benzoic acid ethylester
1-(4-Methoxy-phenyl)-1H-pyrazole
4-Pyrazol-1-yl-benzonitrile
1-(4-Pyrazol-1-yl-phenyl)-ethanone
1-(4-Nitro-phenyl)-1H-pyrazole
1-(4-Tolyl)-1H-pyrazole
1-(4-Trifluoromethyl-phenyl)-1H-pyrazole
1-(3-Methoxy-phenyl)-1H-pyrazole
1-Phenyl-pyrrolidin-2-one
1-Phenyl-1H-[1,2,4]triazole
2-Phenyl-2H-[1,2,3]triazole
1-Phenyl-1H-[1,2,3]triazole
1-Phenyl-1H-pyrrole
1-Phenyl-1H-indole