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REGULAR ARTICLE

Pd-catalyzed C–H bond activation of Indoles for Suzuki reaction

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Abstract. We present a practical method for Suzuki coupling by which unprotected or *N*-protected indoles may be selectively arylated in the C2-position through direct C–H bond activation by electrophilic $Pd(TFA)_2$ catalyst. The protocol is operationally simple as it is carried out in dioxane/water mixture, and air as the sole oxidant at room temperature. Various 2-arylated indoles were obtained in good yields. The protocol works for benzofuran, pyrrole and thiophene also.

Keywords. C–H arylation of indole; boronic acid; Pd catalysis; air.

1. Introduction

Pd-catalyzed C–C bond formation has become a powerful tool for the construction of complex molecules.[1] In such reactions, aryl iodides, bromides and triflates are commonly used as one of the reaction components. As aryl halides or triflates are not either easily available or need to be made from corresponding hydrocarbon or phenol, direct C–H bond activation[2] has become an alternative method of choice.

In this direction, Ru-,[3] Rh-,[4] Ir-[5] and Pd-[6]catalyzed cross-coupling reactions have been reported through the activation of C–H bond. Among these metals, Pd is comparatively cheap, easily available and its reactivity can particularly be tuned using a suitable ligand and conditions, and this chemistry has been studied well. Recently, a few reports have been published to increase the electrophilicity of Pd-catalyst for the activation of C–H bond of indoles[7] and heteroarenes.[8] A pioneering work on direct arylation of 1-tosylindole with chloropyrazines has been reported by Ohta *et al.*[2e] Broad applications and detailed mechanistic study on C-2 and C-3 arylation of indoles with aryl halides have been reported by Sames and co-workers.[7a,b,c] Shortly after, Sanford *et al.,* reported arylation with $[Ar–I–Ar]BF_4$ on indole using electrophilic Pd(II) catalyst.[7d] Larrosa *et al.,* reported the arylation of indoles from aryl iodide by *in situ* generation of highly active electrophilic Pd-catalyst in the presence of Silver(I) carboxylates.[7e] Bellina and co-workers also developed an excellent method for selective palladium- and copper-mediated C-2 arylations of indoles with aryl iodides in absence of base and ligands.[8a,b] All these arylation reactions have been reported using aryl iodide as a coupling partner. Aryl boronic acids have several advantages over aryl halides including easy availability, non-toxicity, high stability and environmental tolerance. Shi and co-workers made a significant contribution by $Pd(OAc)_2$ catalyzed direct C-2 arylation with aryl boronic acids as an arylating agent.[7f] Zhang *et al.,* has reported the C-arylation of indoles using aryltrifluoroborate salts.[7g] Pd-catalyzed indole-aryl bond formation was reported by Fagnou *et al.,*[7h] where unfunctionalized arene was involved in direct cross-coupling reaction in the presence of an oxidant. In all these cases Pd(II) salts have been used as catalyst and arylation at the C-2 position of indole was the major product.

Gaunt and co-workers[7i] have explored the use of Cu(II) catalyst in selectively C-2 or C-3 arylation of indoles. In the reaction, medium Cu-catalyst is oxidized in the presence of diaryl-iodine(III) reagents to form a highly electrophilic aryl-Cu(III) intermediate that is participated in the arylation process. Pd-catalyzed C-3 arylation of indoles was achieved by He and co-workers.[7j]

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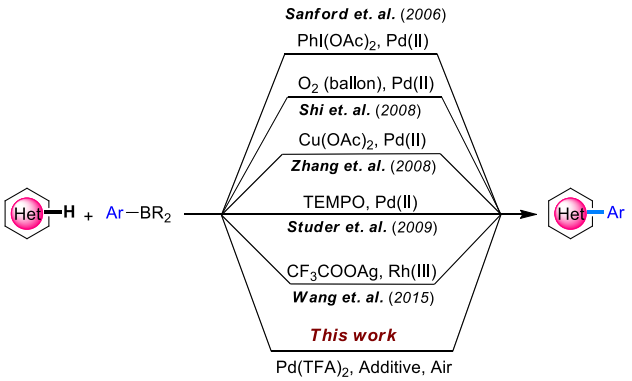


Scheme 1. Pd catalyzed direct C–H arylation of indoles.

Successful coupling was observed in the case of aromatic sodium sulfonates,[9a] arylsulfinic acids,[9b] arylsulfonyl hydrazides[9c] and (hetero)arenesulfonyl chlorides[9d] also. Recently, heterogeneous Pd-catalyzed direct C-2 arylation of indoles using diaryliodonium salts under mild conditions was reported by Olofsson[10] and Wan's group.[11] Very recently, Markandeya's group reported the same transformation using phosphine free tetradentate Pd catalyst.[12]

Since indoles[13] are present in many biologically and pharmacologically active compounds and our lab is involved in the synthesis of indole-based natural products and various indole derivatives[14] for biological screening, we are looking for a suitable methodology for the derivatization of indole moiety.

During the course of our work, we wanted to synthesis 2-arylated indole using Shi's protocal[7f] (Scheme 1). Though we obtained the clean product with clean conversion, the reaction had to be set up in Schlenk line without which the reaction went incomplete and poor yield was obtained. Moreover, it requires acetic acid as a solvent and $Cu(OAc)_2$ as co-oxidant in case of electron-withdrawing heterocycles. Herein, we explored Pd(II) catalyzed selective C-2 arylation of indoles with aryl boronic acids under mild reaction conditions and extended to benzofuran, pyrrole and thiophene also.

2. Experimental

2.1 *Materials and physical measurements*

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All reagent-grade solvents were purchased from commercial sources and used after distillation for reaction, work-up and purification. Reactions monitoring and determination of R_f values for all compounds were performed by thin-layer chromatography (TLC) on silica gel 60 F_{254} (Merck; layer thickness 0.25 mm) and visualization was accomplished by irradiation with UV light at 254 nm or vanillin stain. Column chromatography was performed on Merck silica gel (100–200 mesh) with eluent as mentioned, unless otherwise reported. Proton and carbon NMR spectra were recorded on BRUKER AVANCE III 500 MHz, BRUKER AVANCE III HD 400 MHz and BRUKER AVANCE III HD 300 MHz spectrometers in deuterated solvents at ambient probe temperature (300 K). Proton chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$ δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = double doublet), coupling constants (Hz) and integration. ^{13}C chemical shifts are reported in ppm (δ) from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$ δ 77.0 ppm). High-resolution mass spectra were taken using micromass Q-Tof microsystem by electron spray ionization (ESI) technique. IR spectra were taken using a Perkin-Elmer FT Infrared Spectrometer Model Spectrochem Two, the wavenumbers (n) of recorded IR-signals are reported in cm^{-1}.

2.2 *General procedure for the C–H arylation reaction*

To an oven-dried 25 mL RB containing a magnetic stir bar, heterocycle (0.6 mmol, 1.0 equiv), $Pd(TFA)_2$ (0.06 mmol, 5 mol%), arylboronic acid (1.2 mmol, 2.0 equiv), TFA (1.2 mmol, 2.0 equiv) and 1,4-Dioxane:H_2O (1.0 M, 3:1 ratio) was added and allowed to stir in the presence of air (open atmosphere) at 25 °C for 4–12 h. After completion of the reaction, the mixture was filtered through celite and concentrated. The resulting mixture was diluted with EtOAc (25 mL), washed with aqueous $NaHCO_3$ (2 × 15 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by column chromatography (SiO_2, *n*-Hexane/EtOAc) to give the desired arylated product.

2.3 *Synthesis and characterization of the arylindole derivatives*

2-Phenyl-1*H*-indole (3a)[9a]: White solid; yield: 58 mg, 47%; M.p.: 186–188 °C; R_f = 0.5 (12% EtOAc/*n*-hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.66–7.57 (m, 3H), 7.46–7.26 (m, 4H), 7.22–7.08 (m, 2H), 6.81 (d, J = 2.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.8, 136.8, 132.3, 129.2, 128.9, 127.7, 125.1, 122.3, 120.6, 120.2, 110.9, 99.9 ppm. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{12}N$: 194.0964; found 194.0966.

2-(*o*-Tolyl)-1*H*-indole (3b)[9a]: White solid; yield: 58 mg, 47%; M.p.: 92–94 °C; R_f = 0.5 (12% EtOAc/n-hexane). ^1H NMR (500 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.63 (dd, J = 7.8, 0.4 Hz, 1H), 7.46–7.40 (m, 1H), 7.35 (dd, J = 8.0, 0.7 Hz, 1H), 7.31–7.22 (m, 3H), 7.21–7.16 (m, 1H),

7.14–7.10 (m, 1H), 6.59 (dd, J = 2.1, 0.8 Hz, 1H), 2.47 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.4, 136.1, 136.0, 132.6, 131.0, 128.9, 128.8, 127.9, 126.0, 122.0, 120.5, 120.0, 110.7, 102.9, 21.0 ppm. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{14}N$: 208.1121; found 208.1123.

2-(4-(*tert*-Butyl)phenyl)-1*H*-indole (3c)[9a]: White solid; yield: 64 mg, 43%; M.p.: 186–188 °C; R_f = 0.5 (15% EtOAc/*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 7.69–7.57 (m, 3H), 7.48 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.0 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 6.81 (d, J = 1.2 Hz, 1H), 1.38 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.9, 137.9, 136.7, 129.5, 129.3, 125.9, 124.9, 122.1, 120.5, 120.1, 110.8, 99.5, 34.6, 31.2 ppm. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{20}N$: 250.1590; found 250.1592.

2-(Naphthalen-2-yl)-1*H*-indole (3d)[9a]: White solid; yield: 106 mg, 73%; M.p.: 200–202 °C; R_f = 0.5 (10% EtOAc/n-hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (br. s, 1H), 8.05 (s, 1H), 7.94–7.79 (m, 4H), 7.68 (d, J = 7.7 Hz, 1H), 7.57–7.41 (m, 3H), 7.26–7.11 (m, 2H), 6.97 (dd, J = 2.1, 0.7 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.8, 137.0, 133.6, 132.8, 129.7, 129.3, 128.7, 127.9, 127.8, 126.7, 126.1, 123.8, 123.0, 122.5, 120.7, 120.3, 110.9, 100.7 ppm. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{14}N$: 244.1121; found 244.1127.

2-(3-(Trifluoromethyl)phenyl)-1*H*-indole (3e)[16]: White solid; yield: 80 mg, 51%; M.p.: 145–147 °C; R_f = 0.5 (13% EtOAc/n-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (br. s, 1H), 7.86 (s, 1H), 7.78 (d, J = 6.6 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.58–7.47 (m, 2H), 7.39 (d, J = 8.0 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 6.87 (d, J = 1.5 Hz, 1H) ppm. (75 MHz, $CDCl_3$): δ 137.0, 136.2, 133.1, 131.6, 131.2, 129.5, 129.0, 128.2 (d, J =0.9 Hz, 1C), 124.10 (q, J = 3.8 Hz, 1C), 123.0, 121.8-121.6 (m, 1C), 120.9, 120.6, 111.1, 101.2 ppm. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{11}F_3N$: 262.0838; found 262.0846.

2-(3-Fluorophenyl)-1*H*-indole (3f)[8g]: White solid; yield: 70 mg, 55%; M.p.: 128–130 °C; R_f = 0.5 (15% EtOAc/*n*-hexane). ^{1}H NMR (300 MHz, CD_3OD): δ 7.58 (d, J = 8.2 Hz, 1H), 7.55–7.47 (m, 2H), 7.43–7.34 (m, 2H), 7.11 (m, 1H), 7.04–6.93 (m, 2H), 6.83 (s, 1H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ 164.8 (d, J = 243.5 Hz, 1C), 139.0, 137.9, 136.6 (d, J = 8.3 Hz, 1C), 131.6 (d, J = 8.5 Hz, 1C), 130.4, 123.2, 121.9 (d, J = 2.8 Hz, 1C), 121.4, 120.7, 114.7 (d, J = 21.6 Hz, 1C), 112.6 (d, J = 23.1 Hz, 1C), 112.2, 100.8 ppm. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{11}FN$: 212.0870; found 212.0872.

2-(2-Chlorophenyl)-1*H*-indole (3g)[9a]: White solid; yield: 61 mg, 45%; M.p.: 85–87 °C; R_f = 0.5 (15% EtOAc/*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.73 (br. s, 1H), 7.65 (dd, J = 7.6, 1.8 Hz, 2H), 7.47 (dd, J = 7.9, 1.4 Hz, 1H), 7.41 (dd, J = 8.1, 0.9 Hz, 1H), 7.36–7.18 (m, 3H), 7.17–7.09 (m, 1H), 6.86 (dd, J = 2.1, 0.8 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.4, 135.1, 131.3, 131.2, 130.8, 130.7, 128.8, 128.1, 127.2, 122.6, 120.8, 120.2, 111.0, 103.5 ppm. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{11}ClN$: 228.0575; found 228.0576.

2-(2-Bromophenyl)-1*H*-indole (3h)[17,18]: White plates; yield: 65 mg, 40%; M.p.: 75–77 °C; R_f = 0.5 (10% EtOAc/*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.64 (s, 1H), 7.69 (t, J = 7.5 Hz, 2H), 7.62 (dd, J = 7.7, 1.7 Hz, 1H), 7.47–7.34 (m, 2H), 7.27–7.20 (m, 2H), 7.20–7.11 (m, 1H), 6.83 (dd, J = 2.18, 0.91 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2, 133.9, 133.5, 131.4, 129.2, 128.2, 127.7, 122.6, 121.3, 120.8, 120.2, 111.0, 103.6 ppm. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{11}NBr$: 272.0069; found 272.0068.

2-(4-Bromophenyl)-1*H*-indole (3i)[9a, 18]: White solid; yield: 101 mg, 62%; M.p.: 210–212 °C; R_f = 0.5 (10% EtOAc/*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 8.0 Hz, 1H), 7.22 (t, J = 7.4 Hz, 1H), 7.14 (t, J = 7.4 Hz, 1H), 6.82 (s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 137.1, 136.2, 131.7, 131.4, 128.4, 128.3, 126.8, 121.8, 120.2, 120.1, 119.5, 111.3 ppm. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{11}NBr$: 272.0069; found 272.0066.

2-(4-Methoxyphenyl)-1*H*-indole (3j)[9a]: White solid; Yield: 104 mg, 78%; M.p.: 228–230 °C; R_f = 0.5 (20% EtOAc/*n*-hexane). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.40 (br. s, 1H), 7.79 (d, J = 8.6 Hz, 2H), 7.49 (d, J = 7.7 Hz, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.11–6.92 (m, 4H), 6.75 (s, 1H), 3.80 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.7, 137.7, 136.8, 128.7, 126.3, 124.8, 120.9, 119.6, 119.1, 114.2, 110.9, 97.2, 55.1 ppm. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{14}NO$: 224.1070; found 224.1071.

4-(1*H*-Indol-2-yl)benzonitrile (3k)[18]: Yellow solid; yield: 38 mg, 29%; M.p.: 190–192 °C; R_f = 0.5 (20% EtOAc/*n*-hexane). IR (Neat) = 3350, 2224, 1605, 1446, 1429, 1301, 1177 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (s, 1H), 7.82–7.60 (m, 5H), 7.43 (d, J = 8.1 Hz, 1H), 7.30–7.22 (m, 1H), 7.16 (t, J = 7.5 Hz, 1H), 6.96 (d, J = 1.2Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.4, 136.5, 135.5, 132.8, 128.9, 127.9, 125.2, 123.6, 121.2, 120.8, 118.8, 111.2, 102.6 ppm. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{11}N_2$: 219.0917; found 219.0918.

4-(1*H*-Indol-3-yl)benzonitrile (4k)[19]: Yellow solid; yield: 30 mg, 23%; M.p.: 165–167 °C; R_f = 0.5 (5% EtOAc/*n*-hexane). IR (Neat): 3339, 2226, 1602, 1537, 1458, 1431, 1334, 1178 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.47 (s, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H), 7.51–7.45 (m, 2H), 7.30 (t, J = 7.2 Hz, 1H), 7.27–7.23 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.6, 136.8, 132.6, 127.4, 125.1, 123.1, 123.0, 121.1, 119.5, 119.4, 116.7, 111.7, 108.9 ppm. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{11}N_2$: 219.0917; found 219.0916.

3-(1*H*-Indol-2-yl)benzonitrile (3l): Yellow solid; yield: 82 mg, 63%; M.p.: 165–167 °C; R_f = 0.5 (15% EtOAc/*n*-hexane). IR (Neat): 3347, 3055, 2236, 1603, 1485, 1431,

1364, 1306, 1233 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.49 (br. s, 1H), 7.94 (s, 1H), 7.89 (td, J = 7.3, 1.7 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.62–7.51 (m, 2H), 7.44 (d, J = 8.1 Hz, 1H), 7.30–7.21 (m, 1H), 7.19–7.12 (m, 1H), 6.89 (d, J = 1.3 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.2, 135.2, 133.7, 130.7, 129.8, 129.2, 128.9, 128.4, 123.3, 121.0, 120.7, 118.6, 113.2, 111.2, 101.6 ppm. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{11}N_2$: 219.0917; found 219.0924.

2-(4-Methoxyphenyl)-1-methyl-1*H*-indole (3m)[20]: White solid; yield: 107 mg, 75%; M.p.: 118–120 °C; R_f = 0.5 (10% EtOAc/*n*-hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 7.8 Hz, 1H), 7.44 (d, J = 8.6 Hz, 2H), 7.36 (d, J = 8.2 Hz, 1H), 7.27–7.20 (m, 1H), 7.14 (t, J = 7.4 Hz, 1H), 7.01 (d, J = 8.6 Hz, 2H), 6.51 (s, 1H), 3.88 (s, 3H), 3.73 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4, 141.4, 138.1, 130.6, 127.9, 125.2, 121.4, 120.2, 119.7, 113.9, 109.5, 100.9, 55.3, 31.0 ppm. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{16}NO$: 238.1226; found 238.1228.

1-Butyl-2-(4-methoxyphenyl)-1*H*-indole (3n): Colourless oil: yield: 117 mg, 70%; R_f = 0.5 (12% EtOAc/*n*-hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 7.8 Hz, 1H), 7.53–7.41 (m, 3H), 7.30 (t, J = 7.5 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.06 (d, J = 8.7 Hz, 2H), 6.55 (s, 1H), 4.20 (t, J = 7.5 Hz, 2H), 3.93 (s, 3H), 1.81–1.69 (m, 2H), 1.35–1.20 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3, 141.1, 137.1, 130.6, 128.2, 125.6, 121.1, 120.3, 119.6, 113.8, 109.9, 101.4, 55.2, 43.6, 32.0, 19.9, 13.6 ppm. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{22}NO$: 280.1696; found 280.1698.

5-Bromo-2-(4-methoxyphenyl)-1H-indole (3o): White solid; Yield: 67 mg, 37%; M.p.: 178–180 °C; R_f = 0.5 (22% EtOAc/*n*-hexane). ^1H NMR (300 MHz, DMSO-d_6): δ 11.64 (s, 1H), 7.79 (d, J = 8.7 Hz, 2H), 7.66 (d, J = 1.7 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.16 (dd, J = 8.5, 1.8 Hz, 1H), 7.04 (d, J = 8.7 Hz, 2H), 6.75 (d, J = 1.5 Hz, 1H), 3.80 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.0, 139.3, 135.5, 130.7, 126.5, 124.2, 123.3, 121.6, 114.3, 112.9, 111.6, 96.8, 55.1 ppm. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{13}BrNO$: 302.0175; found 302.0174.

2-(4-Methoxyphenyl)-1H-indol-5-ol (3p): White solid; yield: 103 mg, 72%; M.p.: 237–239 °C; R_f = 0.5 (25% EtOAc/*n*-hexane). ^1H NMR (400 MHz, CD_3OD): δ 7.67 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.6 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 2.1 Hz, 1H), 6.63 (dd, J = 8.6, 2.3 Hz, 1H), 6.52 (s, 1H), 3.83 (s, 3H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ 160.6, 151.7, 140.2, 133.8, 131.6, 127.4, 127.2, 115.3, 112.3, 112.2, 105.1, 98.0, 55.8 ppm. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{14}NO_2$: 240.1019; found 240.1026.

2-(4-Methoxyphenyl)-1*H*-indole-5-carbonitrile (3q): Yellow solid; yield: 37 mg, 25%; M.p.: 122–124 °C; R_f = 0.5 (32% EtOAc/*n*-hexane). IR (Neat): 3338, 2219, 1614, 1470, 1421, 1347, 1323, 1221 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 12.04 (s, 1H), 8.00 (s, 1H), 7.81 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.4 Hz, 1H), 7.41 (dd, J = 8.4, 1.5 Hz, 1H), 7.05 (d, J = 8.8 Hz, 2H), 6.89 (s, 1H), 3.80 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.4, 140.5, 138.8, 128.7, 126.9, 125.0, 123.9, 120.9, 115.7, 114.5, 112.3, 101.3, 97.9, 55.3 ppm. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{13}N_2O$: 249.1028; found 249.1027.

3-(4-Methoxyphenyl)-1*H*-indole-5-carbonitrile (4q): Yellow solid; yield: 43 mg, 29%; M.p.: 165–167 °C; R_f = 0.5 (32% EtOAc/*n*-hexane). IR (Neat): 3337, 2961, 2841, 2221, 1608, 1503, 1276, 1250, 1181 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.74 (s, 1H), 8.22 (s, 1H), 7.52 (d, J = 8.7 Hz, 2H), 7.50–7.43 (m, 2H), 7.40 (d, J = 2.4 Hz, 1H), 7.03 (d, J = 8.7 Hz, 2H), 3.88 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6, 138.1, 128.7, 126.4, 125.8, 125.6, 125.0, 123.1, 120.8, 118.8, 114.5, 112.3, 102.9, 55.3 ppm. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{13}N_2O$: 249.1022; found 249.1026.

3-(4-Methoxyphenyl)-2-methyl-1H-indole (3r)[21]: Yellow solid; yield: 44 mg, 31%; M.p.: 127–129 °C; R_f = 0.5 (5% EtOAc/*n*-hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 7.92 (br. s, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 8.2 Hz, 1H), 7.21–7.06 (m, 2H), 7.05–6.99 (m, 2H), 3.88 (s, 3H), 2.49 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8, 135.1, 130.9, 130.4, 128.0, 127.7, 121.4, 119.8, 118.7, 114.1, 113.9, 110.2, 55.3, 12.4 ppm. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{16}NO$: 238.1226; found 238.1230.

2-(4-Methoxyphenyl)benzofuran (3s)[22]: Colourless flakes; yield: 51 mg, 38%; M.p.: 149–151 °C; R_f = 0.5 (5% EtOAc/*n*-hexane). ^1H NMR (300 MHz, DMSO-d_6): δ 11.40 (br. s, 1H), 7.79 (d, J = 8.6 Hz, 2H), 7.49 (d, J = 7.7 Hz, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.11–6.92 (m, 4H), 6.75 (s, 1H), 3.80 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.9, 149.9, 149.6, 146.5, 130.9, 129.9, 127.7, 116.6, 116.1, 115.6, 114.3, 113.3, 54.9 ppm. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{13}O_2$: 225.0916; found 225.0918.

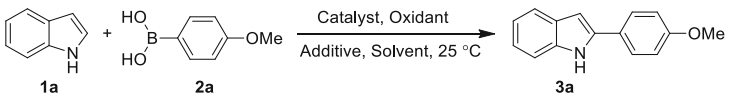
2-(4-Methoxyphenyl)-1*H*-pyrrole (3t): White solid; yield: 46 mg, 44%; M.p.: 143–145 °C; R_f = 0.5 (15% EtOAc/*n*-hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.41 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 1.3 Hz, 1H), 6.50–6.24 (m, 2H), 3.84 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.2, 132.1, 125.8, 125.2, 118.1, 114.3, 109.8, 104.8, 55.3 ppm. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_{11}NO$: 174.0913; found 174.09.

2-(4-Methoxyphenyl)thiophene (3u)[23]: White solid; yield: 26 mg, 38%; M.p.: 107–109 °C; R_f = 0.5 (5% EtOAc/*n*-hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, J = 8.8 Hz, 2H), 7.39–7.32 (m, 3H), 6.94 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.9, 142.0, 128.7, 127.5, 126.2, 126.0, 118.9, 114.2, 55.3 ppm.

Mechanistic Investigation:

Catalyst Poisoning Test[24]: To investigate the reaction mechanism, Hg(0) poisoning test was performed using Hg(0) (1.0 mmol, 1 equiv) with indole (0.6 mmol, 1.0 equiv)

Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst	Oxidant	Additive (Equiv)	Solvent	Time (h)	Yield (%)
1	$Pd(MeCN)_2Cl_2$	BQ	H_2SO_4 (2)	Toluene	12	N.R.
2	$Pd(OAc)_2$	BQ	H_2SO_4 (2)	MeCN	12	Trace
3	$Pd(OAc)_2$	BQ	H_3PO_4 (2)	MeCN	12	Trace
4	$Pd(OAc)_2$	BQ	AcOH (2)	MeCN	12	11
5	$Pd(OAc)_2$	BQ	AcOH (2)	EtOAc	12	17
6	$Pd(TFA)_2$	BQ	TFA (2)	EtOAc	12	18
7	$Pd(TFA)_2$	$Cu(OAc)_2$	TFA (2)	EtOAc	12	32
8	$Pd(TFA)_2$	$K_2S_2O_8$	TFA (2)	EtOAc	12	N.R.
9	$Pd(TFA)_2$	Ag_2O	TFA (2)	EtOAc	12	5
10	$Pd(TFA)_2$	Air	TFA (2)	EtOAc	12	38
11	**$Pd(TFA)_2$**	**Air**	**TFA (2)**	**Dioxane : H_2O(3 : 1)**	**4**	**78**
12	$Pd(TFA)_2$	Air	TFA (3)	Dioxane:H_2O (3:1)	4	76
13	$Pd(TFA)_2$	Air	TFA (1)	Dioxane:H_2O (3:1)	4	54
14[b]	$Pd(TFA)_2$	Air	TFA (2)	Dioxane:H_2O (3:1)	4	46
15[c]	$Pd(TFA)_2$	Air	TFA (2)	Dioxane:H_2O (3:1)	4	74

[a]Unless otherwise stated, all the reactions were carried out using **1a** (0.2 mmol, 1.0 equiv), **2a** (0.4 mmol, 2.0 equiv), catalyst (5 mol%), oxidant (0.34 mmol, 1.7 equiv), additive (0.4 mmol, 2.0 equiv) for 4–12 h at 25 °C in open atmosphere. [b]With 2 mol% $Pd(TFA)_2$. [c]With 10 mol% $Pd(TFA)_2$. N.R. = no reaction.

and 4-methoxyphenylboronic acid (1.2 mmol, 2.0 equiv) as coupling partners, $Pd(TFA)_2$ (0.06 mmol, 5 mol%), TFA (1.2 mmol, 2.0 equiv) following general procedure. The reaction afforded the desired product (**3j**) in comparable yield (76%) suggesting that the reaction goes through homogeneous catalysis.

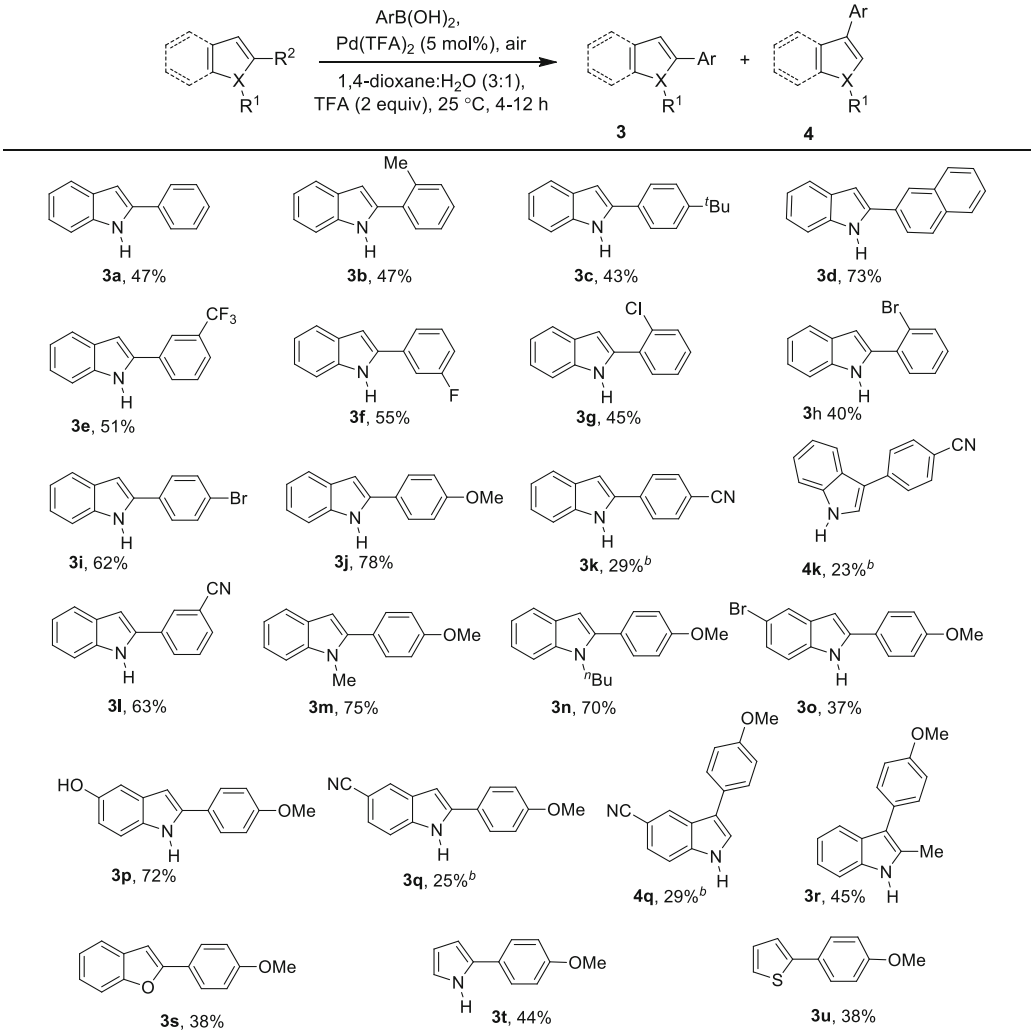
3. Results and Discussion

Initially, the reaction was studied using indole as a substrate and 4-methoxyphenylboronic acid as an arylating agent to screen the optimal conditions, and the results are summarized in Table 1. $Pd(OAc)_2$ and $Pd(MeCN)_2Cl_2$ turned out to be less efficient catalysts for this coupling reaction (Table 1, entries 1 to 5) whereas the use of $Pd(TFA)_2$ gave better yields (entries 6 to 10). When the reaction was carried out in Toluene, MeCN, **1a** was almost completely recovered (Table 1, entries 1–4). Pleasingly, when EtOAc was used as a solvent with TFA as an additive under an aerobic condition, the 2-arylindole was obtained in 38% yield (Table 1, entry 10). More surprisingly, 78% yield was obtained when a mixture of 1,4-dioxane and water (3:1) was used as a solvent (Table 1, entry 11).

Subsequently, different acids such as H_2SO_4, H_3PO_4, AcOH were tested, but none of them could give comparable results as with TFA. Screening of oxidant revealed that air was the most effective for the promotion of reaction (Table 1, entries 10, 11). Other organic and inorganic oxidants gave inferior results under these reaction conditions. In order to drive the reaction to completion, the reaction mixture was allowed to heat at 70 °C for a long time but no improvement was observed. The homocoupling product from boronic acid was obtained as a minor product which could be separated by column chromatography. Reducing the amount of catalyst from 5 to 2 mol% affected the yield significantly (Table 1, entry 14). However, increasing the catalyst loading did not affect the yield to a great extent (Table 1, entry 15).

With the optimized reaction conditions in hand $Pd(TFA)_2$ (5 mol%), air, TFA (2 equiv), 1,4-dioxane/water (3:1) at RT, direct C-2 arylation of indoles was extended to various boronic acids as summarized in Table 2. Both electron-donating and electron-withdrawing substituents on the phenyl ring of the boronic acids underwent the transformation in moderate to good yields. However, phenylboronic acids bearing electron-withdrawing groups were shown to be less compatible under these reaction conditions. In addition, boronic acids with an ortho substituent delivered the desired products in lower yields indicating that steric hindrance could play a role in this reaction (Table 2, compound **3b**, **3g**). 2-Napthylboronic acid also underwent coupling and provided the desired product **3d** in 73% yield within 4 h. Moreover, halogen atom (F,

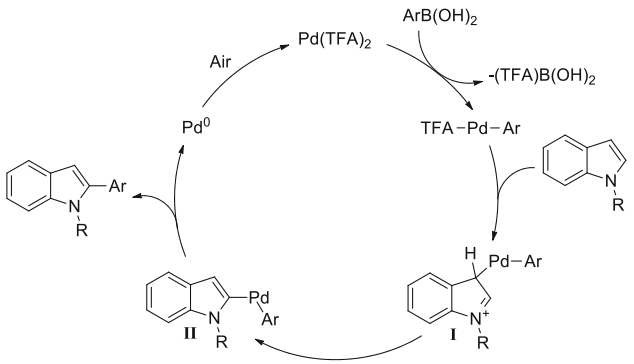
Table 2. Direct Arylation of Indoles, Benzofuran, Pyrrole and Thiophene with various Arylboronic acids.[a]



[a]Reaction conditions;, all the reactions were carried out with heterocycle (0.6 mmol, 1.0 equiv), boronic acid (2.0 equiv), $Pd(TFA)_2$ (5 mol%), 1,4-dioxane/H_2O (3:1 2.0 mL), 0.5 M) in presence of air (open atmosphere) for 4–12 h; yield refers to isolated materials. [b]Both the products were isolated.

Cl, Br) substituted aryl rings in indole derivatives can be used as a precursor for elaboration by transition metal-catalyzed coupling reactions. Unfortunately, no product was obtained when cyclohexylboronic acid was used in the current reaction system, and the starting material was completely recovered. With the positive results above, various structurally diverse indole derivatives were explored to further expand their substrate scope. *N*-alkyl indoles were well-tolerated under this protocol (Table 2, compound **3m**, **3n**). Irrespective of the electronic nature of substituents on the 5- position of the indole ring, the coupling reaction could be performed affording the desired products in moderate yields (Table 2, compound **3o**, **3p**, **3q**, **4q**). Surprisingly, in case of 5-cyano indole and 4-cyanophenylboronic acid C-3 arylated products **4k**, **4q** were obtained along with C-2 arylated indole derivatives. 2-Methyl indole exhibited lower yield to arylation affording the corresponding 3-arylindole derivative (Table 2, compound **3r**). We were pleased that benzofuran, pyrrole and thiophene were also compatible with the current protocol (Table 2, compounds **3s**, **3t**, **3u**). However, when imidazole and 7-azaindole were subjected to these conditions, no desired products were obtained.

On the basis of the above experimental results, a plausible mechanism for this reaction is proposed in Scheme 2. Initially, the reaction of Pd(II) with arylboronic acid afforded the palladium intermediate. Following this step, indole coordination occurs at the metallic centre through C-3 position and then C3–C2



Scheme 2. Proposed mechanism for direct C-H arylation of indole with boronic acid.

migration of the Pd centre afforded the complex leading to the C-2 regioisomer. Furthermore, blocking the C2–H position by a –Me group showed low conversion towards the C-3 regioisomer supporting the fact that the presence of –Me group at C-2 position inhibits the C3–C2 migration. Additionally, in substrates containing electron-withdrawing group (e.g.- cyano) the migration from C3–C2 becomes slow as expected (which provides extra stability to the palladium intermediate leading to the formation of a mixture of C-3 and C-2 aryl indole derivatives). Though the exact role of TFA is not known, it might be said that deprotonation of Pd intermediate formed through electrophilic substitution is favoured in acidic conditions allowing C3–C2 migration.[15] In order to know the homogeneity of the catalyst, we performed the reaction in the presence of an excess of Hg(0) w.r.t $Pd(TFA)_2$ in catalyst poisoning experiment,[24] where no inhibitory activity of the catalyst was noticed (see the Experimental Section).

4. Conclusions

In summary, we have standardized the Suzuki reaction for the conversion of indole to C-2 arylated indole derivatives using air as the sole oxidant and Pd(II) as a catalyst. Particularly, free –NH indoles are well-tolerated for this transformation, thus expected to show great potentiality in the formation of complex molecules used in many pharmaceutical chemistries.

Supplementary Information (SI)

^{1}H, ^{13}C NMR spectra for the characterization of compounds are given in the supporting information. Supplementary Information is available at www.ias.ac.in/chemsci.

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