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

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MS received 14 February 2019; revised 10 May 2019; accepted 24 May 2019

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 activation² has become an alternative method of choice.

In this direction, Ru-,³ Rh-,⁴ Ir-⁵ and Pd-⁶catalyzed 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 indoles⁷ 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]BF₄ 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-workers⁷ⁱ 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 Olofsson¹⁰ and Wan's group.¹¹ Very recently, Markandeya's group reported the same transformation using phosphine free tetradentate Pd catalyst.¹²

Since indoles¹³ 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 derivatives¹⁴ 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 synthesize 2-arylated indole using Shi's protocol^{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 F₂₅₄ (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 (CDCl₃ 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. ¹³C chemical shifts are reported in ppm (δ) from tetramethylsilane (TMS) with the solvent resonance as the internal standard (CDCl₃ 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 (ν) 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:H₂O (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 NaHCO₃ (2 × 15 mL). The organic layers were combined, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude material was purified by column chromatography (SiO₂, *n*-Hexane/EtOAc) to give the desired arylated product.

2.3 Synthesis and characterization of the arylindole derivatives

2-Phenyl-1H-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, CDCl₃): 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. ¹³C NMR (75 MHz, CDCl₃): 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 C₁₄H₁₂N: 194.0964; found 194.0966.

2-(*o*-Tolyl)-1H-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, CDCl₃): 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) $\delta = 137.4, 136.1, 136.0, 132.6, 131.0, 128.9, 128.8, 127.9, 126.0, 122.0, 120.5, 120.0, 110.7, 102.9, 21.0$ ppm. HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{14}\text{N}$: 208.1121; found 208.1123.

2-(4-(*tert*-Butyl)phenyl)-1H-indole (3c)^{9a}: White solid; yield: 64 mg, 43%; M.p.: 186–188 °C; $R_f = 0.5$ (15% EtOAc/*n*-hexane). ^1H 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 $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{20}\text{N}$: 250.1590; found 250.1592.

2-(Naphthalen-2-yl)-1H-indole (3d)^{9a}: White solid; yield: 106 mg, 73%; M.p.: 200–202 °C; $R_f = 0.5$ (10% EtOAc/*n*-hexane). ^1H 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) $\delta = 137.8, 137.0, 133.6, 132.8, 129.7, 129.3, 128.7, 127.9, 127.8, 126.7, 126.1, 123.8, 123.0, 122.5, 120.7, 120.3, 110.9, 100.7$ ppm. HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{14}\text{N}$: 244.1121; found 244.1127.

2-(3-(Trifluoromethyl)phenyl)-1H-indole (3e)¹⁶: White solid; yield: 80 mg, 51%; M.p.: 145–147 °C; $R_f = 0.5$ (13% EtOAc/*n*-hexane). ^1H 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 $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{11}\text{F}_3\text{N}$: 262.0838; found 262.0846.

2-(3-Fluorophenyl)-1H-indole (3f)^{8g}: White solid; yield: 70 mg, 55%; M.p.: 128–130 °C; $R_f = 0.5$ (15% EtOAc/*n*-hexane). ^1H 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 $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{11}\text{FN}$: 212.0870; found 212.0872.

2-(2-Chlorophenyl)-1H-indole (3g)^{9a}: White solid; yield: 61 mg, 45%; M.p.: 85–87 °C; $R_f = 0.5$ (15% EtOAc/*n*-hexane). ^1H 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 $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{11}\text{ClN}$: 228.0575; found 228.0576.

2-(2-Bromophenyl)-1H-indole (3h)^{17,18}: White plates; yield: 65 mg, 40%; M.p.: 75–77 °C; $R_f = 0.5$ (10% EtOAc/*n*-hexane). ^1H 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 $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{11}\text{NBr}$: 272.0069; found 272.0068.

2-(4-Bromophenyl)-1H-indole (3i)^{9a, 18}: White solid; yield: 101 mg, 62%; M.p.: 210–212 °C; $R_f = 0.5$ (10% EtOAc/*n*-hexane). ^1H 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, $\text{DMSO}-d_6$): $\delta = 137.1, 136.2, 131.7, 131.4, 128.4, 128.3, 126.8, 121.8, 120.2, 120.1, 119.5, 111.3$ ppm. HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{11}\text{NBr}$: 272.0069; found 272.0066.

2-(4-Methoxyphenyl)-1H-indole (3j)^{9a}: White solid; Yield: 104 mg, 78%; M.p.: 228–230 °C; $R_f = 0.5$ (20% EtOAc/*n*-hexane). ^1H NMR (300 MHz, $\text{DMSO}-d_6$): 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, $\text{DMSO}-d_6$): 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 $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{14}\text{NO}$: 224.1070; found 224.1071.

4-(1H-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} . ^1H 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, $J = 1.2$ Hz, 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 $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{11}\text{N}_2$: 219.0917; found 219.0918.

4-(1H-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} . ^1H 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 $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{11}\text{N}_2$: 219.0917; found 219.0916.

3-(1H-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 $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{11}\text{N}_2$: 219.0917; found 219.0924.

2-(4-Methoxyphenyl)-1-methyl-1H-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 $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{16}\text{NO}$: 238.1226; found 238.1228.

1-Butyl-2-(4-methoxyphenyl)-1H-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 $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{22}\text{NO}$: 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, $\text{DMSO}-d_6$): 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, $\text{DMSO}-d_6$): 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 $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{13}\text{BrNO}$: 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 $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{14}\text{NO}_2$: 240.1019; found 240.1026.

2-(4-Methoxyphenyl)-1H-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, $\text{DMSO}-d_6$): 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, $\text{DMSO}-d_6$): 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 $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{13}\text{N}_2\text{O}$: 249.1028; found 249.1027.

3-(4-Methoxyphenyl)-1H-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 $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{13}\text{N}_2\text{O}$: 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 $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{16}\text{NO}$: 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, $\text{DMSO}-d_6$): 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, $\text{DMSO}-d_6$): 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 $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{13}\text{O}_2$: 225.0916; found 225.0918.

2-(4-Methoxyphenyl)-1H-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 $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{11}\text{NO}$: 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 Test²⁴: 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) ₂ Cl ₂	BQ	H ₂ SO ₄ (2)	Toluene	12	N.R.
2	Pd(OAc) ₂	BQ	H ₂ SO ₄ (2)	MeCN	12	Trace
3	Pd(OAc) ₂	BQ	H ₃ PO 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 ₂ S ₂ O ₈	TFA (2)	EtOAc	12	N.R.
9	Pd(TFA) ₂	Ag ₂ O	TFA (2)	EtOAc	12	5
10	Pd(TFA) ₂	Air	TFA (2)	EtOAc	12	38
11	Pd(TFA)₂	Air	TFA (2)	Dioxane : H₂O (3 : 1)	4	78
12	Pd(TFA) ₂	Air	TFA (3)	Dioxane:H ₂ O (3:1)	4	76
13	Pd(TFA) ₂	Air	TFA (1)	Dioxane:H ₂ O (3:1)	4	54
14 ^b	Pd(TFA) ₂	Air	TFA (2)	Dioxane:H ₂ O (3:1)	4	46
15 ^c	Pd(TFA) ₂	Air	TFA (2)	Dioxane:H ₂ O (3:1)	4	74

^aUnless 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. ^bWith 2 mol% Pd(TFA)₂. ^cWith 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)₂Cl₂ 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 H₂SO₄, H₃PO₄, 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-Naphthylboronic 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

^aReaction 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/H₂O (3:1 2.0 mL), 0.5 M in presence of air (open atmosphere) for 4–12 h; yield refers to isolated materials. ^bBoth 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)

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

Acknowledgements

Financial support from the Science and Engineering Research Board, Department of Science and Technology, Government of India (Grant No. (SR/S1/OC/0087/2012) is gratefully acknowledged. I. B. and K.C.G are thankful to Council for Scientific and Industrial Research (CSIR) New Delhi for the fellowship.

References

- (a) Corbet J-P and Mignani G 2006 Selected Patented Cross-Coupling Reaction Technologies *Chem. Rev.* **106** 2651; (b) Hassan J, Sevignon M, Gozzi C and Shulz M 2002 Aryl-Aryl Bond Formation One Century after the Discovery of the Ullmann Reaction *Chem. Rev.* **102** 1359; (c) Anastasia L and Negishi E 2002 In *Handbook of Organopalladium Chemistry for Organic Synthesis* E Negishi (Ed.) (New York: J. Wiley & Sons) p. 311; (d) Roy D and Uozumi Y 2018 Recent Advances in Palladium-Catalyzed Cross-Coupling Reactions at ppm to ppb Molar Catalyst Loadings *Adv. Synth. Catal.* **360** 602; (e) Nicolaou K C, Bulger P G and Sarlah D 2005 Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis *Angew. Chem. Int. Ed.* **44** 4442
- (a) Yu J-Q and Shi Z (Eds.) 2010 *C–H Activation*. Topics in Current Chemistry (Berlin: Springer) p. 380; (b) Bheeter C B, Chen L, Soulé J-F and Doucet H 2016 Regioselectivity in palladium-catalysed direct arylation of 5-membered ring heteroaromatics *Catal. Sci. Technol.* **6** 2005; (c) Joucla L, Batail N and Djakovitch L 2010 “On Water” Direct and Site- Selective Pd-Catalysed C-H Arylation of (NH)-Indoles *Adv. Synth. Catal.* **352** 2929; (d) Lebrasseur N and Larrosa I 2012 Recent Advances in the C2 and C3 Regioselective Direct Arylation of Indoles *Adv. Heterocycl. Chem.* **105** 309; (e) Akita Y, Itagaki Y, Takizawa S and Ohta A 1989 Cross-coupling reactions of chloropyrazines with 1-substituted indoles *Chem. Pharm. Bull.* **37** 1477; (f) Basu D, Kumar S, Sudhir V S and Bandichhor R 2018 Transition metal catalyzed C-H activation for the synthesis of medicinally relevant molecules: A Review *J. Chem. Sci.* **130** 1
- (a) Kakiuchi F and Murai S 2002 Catalytic C-H/Olefin Coupling *Acc. Chem. Res.* **35** 826; (b) Ackermann L 2014 Carboxylate-Assisted Ruthenium-Catalyzed Alkyne Annulations by C-H/Het-H Bond Functionalizations *Acc. Chem. Res.* **47** 281
- (a) Manan R S and Zhao P 2016 Merging rhodium-catalysed C–H activation and hydroamination in a highly selective [4 + 2] imine/alkyne annulation *Nat. Commun.* **7** 1; (b) Colby D A, Bergman R G and Ellman J A 2010 Rhodium-Catalyzed C-C Bond Formation via Heteroatom-Directed C-H Bond Activation *Chem. Rev.* **110** 624; (c) Song G, Wang F and Li X 2012 C–C, C–O and C–N bond formation via rhodium(III)-catalyzed oxidative C–H activation *Chem. Soc. Rev.* **41** 3651
- (a) Mkhali I A I, Barnard J H, Marder T B, Murphy J M and Hartwig J F 2010 C-H Activation for the Construction of C-B Bonds *Chem. Rev.* **110** 890; (b) Li L, Brennessel W W and Jones W D 2008 Rhodium(III) Catalyzed Arylation of Boc-Imines via

- C–H Bond Functionalization *J. Am. Chem. Soc.* **130** 12414; (c) Schultz D M and Wolfe J P 2012 Disguise gets a reaction *Nature* **483** 42; (d) Larsen M A and Hartwig J F 2014 Iridium-Catalyzed C–H Borylation of Heteroarenes: Scope, Regioselectivity, Application to Late-Stage Functionalization, and Mechanism *J. Am. Chem. Soc.* **136** 4287
6. (a) Alberico D, Scott M E and Lautens M 2007 Aryl–Aryl Bond Formation by Transition-Metal-Catalyzed Direct Arylation *Chem. Rev.* **107** 174; (b) Campeau L-C, Stuart D R and Fagnou K 2007 Palladium-Catalyzed Domino Heck/C–H Activation/Intermolecular Direct Arylation Reactions *Aldrichim. Acta* **20** 35; (c) Satoh T and Miura M 2007 Catalytic Direct Arylation of Heteroaromatic Compounds *Chem. Lett.* **36** 200; (d) Seregin I V and Gevorgyan V 2007 Direct transition metal-catalyzed functionalization of heteroaromatic compounds *Chem. Soc. Rev.* **36** 1173; (e) Godula K and Sames D 2006 C–H Bond Functionalization in Complex Organic Synthesis *Science* **312** 67; (f) Kakiuchi F and Chatani N 2003 Catalytic Methods for C–H Bond Functionalization: Application in Organic Synthesis *Adv. Synth. Catal.* **345** 1077; (g) Lyons T W and Sanford M S 2010 Palladium-Catalyzed Ligand-Directed C–H Functionalization Reactions *Chem. Rev.* **110** 1147; (h) Wencel-Delord J, Dröge T, Liu F and Glorius F 2011 Towards mild metal-catalyzed C–H bond activation *Chem. Soc. Rev.* **40** 4740; (i) Jia C, Kitamura T and Fujiwara Y 2001 Catalytic Functionalization of Arenes and Alkanes via C–H Bond Activation *Acc. Chem. Res.* **34** 633; (j) Motoyama T, Shimazaki Y, Yajima T, Nakabayashi Y, Naruta Y and Yamauchi O 2004 Reactivity of the Indole Ring in Palladium(II) Complexes of 2N1O-Donor Ligands: Cyclopalladation and π -Cation Radical Formation *J. Am. Chem. Soc.* **126** 7378; (k) Tollari S, Demartin F, Cenini S, Palmisano G and Raimondi P 1997 Cyclometallation of indole derivatives: cyclopalladation of gramine and 1-methyl gramine and CO insertion *J. Organomet. Chem.* **527** 93; (l) Sehnal P, Taylor R J K and Fairlamb I J S 2010 Emergence of Palladium (IV) Chemistry in Synthesis and Catalysis *Chem. Rev.* **110** 824; (m) Jiao L, Herdtweck E and Bach T 2012 Pd (II) -Catalyzed Regioselective 2–Alkylation of Indoles via a Norbornene-Mediated C–H Activation: Mechanism and Applications *J. Am. Chem. Soc.* **134** 14563
 7. C–H activation of indoles: (a) Lane B S, Brown M A and Sames D 2005 Direct Palladium-Catalyzed C-2 and C-3 Arylation of Indoles: A Mechanistic Rationale for Regioselectivity *J. Am. Chem. Soc.* **127** 8050; (b) Lane B S and Sames D 2004 Direct C–H Bond Arylation: Selective Palladium-Catalyzed C-2 Arylation of *N*-Substituted Indoles *Org. Lett.* **6** 2897; (c) Sezen B and Sames D 2003 Selective C-Arylation of Free (NH)-Heteroarenes via Catalytic C–H Bond Functionalization *J. Am. Chem. Soc.* **125** 5274; (d) Deprez N R, Kalyani D, Krause A and Sanford M S 2006 Room Temperature Palladium-Catalyzed 2-Arylation of Indoles *J. Am. Chem. Soc.* **128** 4972; (e) Lebrasseur N and Larrosa I 2008 Room Temperature and Phosphine Free Palladium Catalyzed Direct C-2 Arylation of Indoles *J. Am. Chem. Soc.* **130** 2926; (f) Yang S-D, Sun C-L, Fang Z, Li B-J, Li Y-Z and Shi Z-J 2008 Palladium-Catalyzed Direct Arylation of (Hetero) Arenes with Aryl Boronic Acids *Angew. Chem. Int. Ed.* **47** 1473; (g) Zhao J, Zhang Y and Cheng K 2008 Palladium-Catalyzed Direct C-2 Arylation of Indoles with Potassium Aryltrifluoroborate Salts *J. Org. Chem.* **73** 7428; (h) Stuart D R, Ville-mure E and Fagnou K 2007 Elements of Regiocontrol in Palladium-Catalyzed Oxidative Arene Cross-Coupling *J. Am. Chem. Soc.* **129** 12072; (i) Phipps R J, Grimster N P and Gaunt M J 2008 Cu(II)-Catalyzed Direct and Site-Selective Arylation of Indoles Under Mild Conditions *J. Am. Chem. Soc.* **130** 8172; (j) Zhang Z, Hu Z, Yu Z, Lei P, Chi H, Wang Y and He R 2007 Direct palladium-catalyzed C-3 arylation of indoles *Tetrahedron Lett.* **48** 2415
 8. (a) Bellina F, Calandri C, Cauteruccio S and Rossi R 2007 Efficient and highly regioselective direct C-2 arylation of azoles, including free (NH)-imidazole, -benzimidazole and -indole, with aryl halides *Tetrahedron* **63** 1970; (b) Bellina F, Cauteruccio S and Rossi R 2006 Palladium- and Copper-Mediated Direct C-2 Arylation of Azoles - Including Free (NH)-Imidazole, -Benzimidazole and -Indole - Under Base-Free and Ligand-less Conditions *Eur. J. Org. Chem.* 1379; (c) Toure' B B, Lane B S and Sames D 2006 Catalytic C–H Arylation of SEM-Protected Azoles with Palladium Complexes of NHCs and Phosphines *Org. Lett.* **8** 1979; (d) Beck E M, Grimster N P, Hatley R and Gaunt M J 2006 Mild Aerobic Oxidative Palladium (II) Catalyzed C–H Bond Functionalization: Regioselective and Switchable C–H Alkenylation and Annulation of Pyrroles *J. Am. Chem. Soc.* **128** 2528; (e) Dwight T A, Rue N R, Charyk D, Josselyn R and DeBoef B 2007 C–C Bond Formation via Double C–H Functionalization: Aerobic Oxidative Coupling as a Method for Synthesizing Heterocoupled Biaryls *Org. Lett.* **9** 3137
 9. (a) Wu M, Luo J, Xiao F, Zhang S, Deng G-J and Luo H-A 2012 Palladium-Catalyzed Direct and Site-Selective Desulfative Arylation of Indoles with Sodium Sulfonates *Adv. Synth. Catal.* **354** 335; (b) Miao T, Li P, Wang G-W and Wang L 2013 Microwave-Accelerated Pd-Catalyzed Desulfative Direct C-2 Arylation of Free (NH)-Indoles with Arylsulfinic Acids *Chem. Asian J.* **8** 3185; (c) Liu C, Ding L, Guo G, Liu W and Yang F-L 2016 Palladium-catalyzed direct arylation of indoles with arylsulfonyl hydrazides *Org. Biomol. Chem.* **14** 2824; (d) Hfaiedh A, Ammar H B, Soulé J-F and Doucet H 2016 Palladium-catalyzed direct desulfative C-2 arylations of 3-halo-*N*-protected indoles using (hetero) arenesulfonyl chlorides *Org. Biomol. Chem.* **14** 4947
 10. Malmgren J, Nagendiran A, Tai C-W, Bäckvall J-E and Olofsson B 2014 C-2 Selective Arylation of Indoles with Heterogeneous Nanopalladium and Diaryliodonium Salts *Chem. Eur. J.* **20** 13531
 11. Duan L, Fu R, Zhang B, Shi W, Chen S and Wan Y 2016 An Efficient Reusable Mesoporous Solid-Based Pd Catalyst for Selective C2 Arylation of Indoles in Water *ACS Catal.* **6** 1062
 12. Markandeya S V, Renuka C, Lakshmi P K, Rajesh A, Sridhar C and Babu K R 2018 Design and applications of new phosphine-free tetradentate Pd-catalyst: Regioselective C–H activation on 1-substituted 1,2,3-triazoles and indoles(NH-Free) *Synth. Commun.* **48** 135

13. (a) Sundberg R J *The Chemistry of Indoles* 1970 (London: Academic Press); (b) Sundberg R J 1996 *Indoles* (London: Academic Press); (c) Humphrey G R and Kuethe J T 2006 Practical Methodologies for the Synthesis of Indoles *Chem. Rev.* **106** 2875; (d) Brancale A and Silvestri R 2007 Indole, a Core Nucleus for Potent Inhibitors of Tubulin Polymerization *Med. Res. Rev.* **27** 209; (e) Harper S, Avolio S, Pacin B, Di Filippo M, Altamura S, Tomei L, Paonessa G, Di Marco S, Carfi A, Giuliano C, Padron J, Bonelli F, Migliaccio G, De Francesco R, Laufer R, Rowley M and Narjes F 2005 Potent Inhibitors of Subgenomic Hepatitis C Virus RNA Replication through Optimization of Indole-*N*-Acetamide Allosteric Inhibitors of the Viral NS5B Polymerase *J. Med. Chem.* **48** 4547; (f) Soto S, Vaz E, Dell'Aversana C, Alvarez R, Altucci L and de Lera A R 2012 New synthetic approach to paullones and characterization of their SIRT1 inhibitory activity *Org. Biomol. Chem.* **10** 2101
14. (a) Jana G K, Paul S and Sinha S 2011 Progress in the Synthesis of Iboga-alkaloids and their Congeners *Org. Prep. Proc. Int.* **43** 541; (b) Jana G K and Sinha S 2012 Total synthesis of ibogaine, epiibogaine and their analogues *Tetrahedron* **68** 7155; (c) Chakraborty A and Sinha S 2011 Synthesis of 3-[2-(1,3-butadienyl)]-1*H*-indoles en route to murrapanine analogue *Tetrahedron Lett.* **52** 6635; (d) Chakraborty A, Jyothi K and Sinha S 2014 Palladium-catalyzed synthesis of 2-allylindole and 2-allylbenzofuran derivatives from 2-((trimethylsilyl)ethynyl)arenes *Tetrahedron Lett.* **55** 6795; (e) Banerjee T S, Paul S, Sinha S and Das S 2014 Synthesis of iboga-like isoquinuclidines: Dual opioid receptors agonists having antinociceptive properties *Bioorg. Med. Chem.* **22** 6062
15. Grimse N P, Gaunlett C, Godfrey C R A and Gaunt M J 2005 Palladium-Catalyzed Intermolecular Alkenylation of Indoles by Solvent-Controlled Regioselective CH Functionalization *Angew. Chem. Int. Ed.* **44** 3125
16. Chan Sik C, Jun Ho K, Kim T-J and Sang Chul S 2004 Palladium-catalysed synthesis of 2-substituted indole *J. Chem. Res.* 630
17. Dalton L, Humphrey G L, Cooper M M and Joule J A 1983 Indole β -Nucleophilic Substitution. Part 7.¹ β -Halogenation of Indoles. Attempted Intramolecular β -Nucleophilic Substitution of α -Aryl indoles *J. Chem. Soc., Perkin Trans. 1* 2417
18. Moncea O, Poinsoot, D, Fokin A A, Schreiner P R and Hierso J-C 2018 Palladium-Catalyzed C2-H Arylation of Unprotected (NH)-Indoles "On Water" Using Primary Diamantyl Phosphine Oxides as a Class of Primary Phosphine Oxide Ligands *ChemCatChem* **10** 2915
19. Zhang Z, Hu Z, Yu Z, Lei P, Chi H, Wang Y and He R 2007 Direct palladium-catalyzed C-3 arylation of indoles *Tetrahedron Lett.* **48** 2415
20. Denmark S E and Baird J D 2004 Palladium-Catalyzed Cross-Coupling Reactions of 2-Indolyldimethylsilanols with Substituted Aryl Halides *Org. Lett.* **6** 3649
21. Bellina F, Benelli F and Rossi R 2008 Efficient and Practical Synthesis of 4(5)-Aryl-1*H*-imidazoles and 2,4(5)-Diaryl-1*H*-imidazoles via Highly Selective Palladium-Catalyzed Arylation Reactions *J. Org. Chem.* **73** 5529
22. Denmark S E, Smith R C, Chang W-T T and Muhu J M 2009 Cross-Coupling Reactions of Aromatic and Heteroaromatic Silanols with Aromatic and Heteroaromatic Halides *J. Am. Chem. Soc.* **131** 3104
23. Sudo Y, Yamaguchi E and Itoh A 2017 Photo-oxidative Cross-Dehydrogenative Coupling-Type Reaction of Thiophenes with α -Position of Carbonyls Using a Catalytic Amount of Molecular Iodine *Org. Lett.* **19** 1610
24. Chatterjee A and Jensen V R 2017 A Heterogeneous Catalyst for the Transformation of Fatty Acids to α -Olefins *ACS Catal.* **7** 2543