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Palladium complexes catalyzed regioselective arylation of 2-oxindole *via in situ* C(sp^2)–OH activation mediated by PyBroP

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ABSTRACT

Pd(II) complexes appended with ONO pincer type ligand were synthesized, structurally characterized and successfully applied as catalysts for regieoselective C–2 arylation of 2-oxindole *via in situ* C (sp^2)–OH activation in aqueous-organic media under an open atmosphere at room-temperature. This catalyst was reused up to four cycles. Favourably, the present protocol doesn't require the addition of any external oxidant, additives or phase transfer agents.

1. Introduction

Tautomerizable heterocycles are most suitable synthons in molecular engineering [1] and have been used as substrates for Pd-catalyzed cross-couplings *via in situ* C–OH activation in the presence of phosphonium salts. In this context, Kang et al. [2] reported direct arylation of tautomerizable heterocycles utilizing boronic acids as coupling accomplice. Herein, we demonstrate bromo-tris-pyrrolidino-phosphonium hexafluorophpsphate (PyBroP) mediated C–OH activation methodology [3] for arylation of 2-oxindole in the presence of palladium pincer type complex. Indole and its derivatives present as one of the main constituents of many natural and synthetic compounds exhibit medicinal [4] as well as material properties applicable to organic photovoltaics [5], OLED [6], sensors [7], nanomaterials [8], and forming useful coordination complexes [9].

Known synthetic routes so far developed to synthesize, for example, C-2 arylated indole derivatives exclude C–OH activation [10]. In addition, those methods require high catalyst loading, elevated temperature, prolonged reaction time, additives, oxidants, and usually require to work in a nitrogen atmosphere. It should be noticed that aromatic Csp^2–OH activation is profoundly difficult when compared to activating Csp^3–OH bonds because of a higher energy barrier and aromatic ring stability [11]. This C–OH activation methodology creates C–O electrophiles are considered a suitable alternative to aryl halides in C–C bond formation reactions [12].

For this reason, a series of aryl C–O electrophiles like acetates [13], carbamates [14], esters [15], ethers [16], pivalates [17], phosphoramides [18], phosphonates [19], triflates [19], sulfamates [20], carbonates [21], and tosylates [22] were introduced as coupling partners in metal-catalyzed cross-coupling reactions. Very recently, PyBroP mediated C–OH activation in the presence of metal catalysts has attracted the attention of several researchers. So far, PyBroP mediated C–OH activation was reported for urea [11], phenol [23], 1-naphthol [24], 2-quinoxalinone [2], 2-methyl-1H-pyridazine-3,6-dione [25], 2-hydroxypyridine [26], 2-oxoquninoline [27], and 2(1H)-pyrazinones [28] in the literature. Palladium based pincer complexes are widely utilized as catalysts for various organic reactions including C–H activation and they undoubtedly play a vital role in the continuous search for the development of new and efficient protocols to form C–C bonds [29]. Some of these complexes are workable in aqueous or aqueous-organic media [30]. We already examined palladium pincer type complexes as catalysts for organic reactions [31]. We herein report the synthesis and spectral characterization of three new palladium (II) complexes (**1**–**3**) bearing ONO pincer type ligands including X-

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ray structures, and studies of their catalytic activity towards C-2 arylation of 2-oxindole using substituted aryl boronic acids in H_2O/EtOH media under open-flask conditions.

2. Experimental procedure

2.1. General information

Elemental analyses (C, H, and N) were performed on a Vario EL III Elemental analyzer instrument. IR spectra (4000–400 cm^{-1}) were recorded on a Nicolet Avatar Model FT-IR spectrophotometer. Melting points were determined with a Lab India instrument. ^1H and ^{13}C NMR spectra were recorded in deuterated $CHCl_3$ as solvent on BRUKER 400 and 100 MHZ instruments, respectively. All reagent grade chemicals were used without further purification unless otherwise specifically mentioned. Solvents were purified and dried according to standard procedures [32].

2.2. Synthesis of ligands H_2L1– H_2L3

The pincer type ligands H_2L1–H_2L3 were synthesized from equimolar quantity of *o*-hydroxynaphthaldehyde with appropriate hydrazides such as benzhydrazide (H_2L1), *p*-chlorobenzhydrazide (H_2L2), and *p*-nitrobenzhydrazide (H_2L3) in ethanol according to a literature method [33]. The reaction mixture was then refluxed on a water-bath for 6 h and poured into crushed ice. The corresponding pincer type hydrazones formed as colorless solid were filtered, washed repeatedly with distilled water and recrystallized from ethanol with 80–90% yield. The purity of the ligands were checked by various analytical techniques and is in accordance with literature report [33].

2.3. General method for the synthesis of the palladium complexes

To a warm methanolic solution (20–30 mL) of appropriate ligands (H_2L1–H_2L3) (1 equiv.) was added a chloroform solution of [$PdCl_2(PPh_3)_2$] (1 equiv.) followed by two drops of triethylamine. Then the reaction mixture was refluxed for 8–10 h and kept at room temperature for crystallization. Needle like reddish brown crystals suitable for X-ray studies were obtained on slow evaporation over 45–60 days.

[Pd(L1) (PPh_3)] (complex **1**) Yield: 85% (112 mg). M. p. 232–234 °C. Elemental analysis (%) calculated for $C_{36}H_{27}N_2O_2PPd$; C, 65.81; H, 4.14; N, 4.26. Found (%) C, 65.82; H, 4.15; N, 4.27. UV–visible (solvent: DMSO, nm): 303, 325, 341, 354. Selected IR bands (KBr, ν in cm^{-1}): 1581 (C–N=N–C), 1528 (C=N), 1433 (PPh_3), 1260 (imidolate –N=C–O), 1185 (naphtholate C–O). ^1H NMR ($CDCl_3$, δ ppm) 9.86 (s, 1H), 9.30 (d, J = 8 Hz, 4H), 7.81 (s, 2H), 7.55 (d, J = 7.6 Hz, 2H), 7.23–7.36 (m, 10H), 7.15 (t, J = 5.8 Hz, 6H), 6.44 (d, J = 15.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, δ ppm) 183.5, 167.5, 145.2, 142.2, 138.5, 134.7, 129.4, 128.3, 127.0, 124.4, 123.9, 120.7, 119.3, 118.4, 112.0.

[Pd(L2) (PPh_3)] (complex **2**) Yield: 80% (111 mg). M. p. 239–242 °C. Elemental analysis (%) calculated for $C_{36}H_{26}ClN_2O_2PPd$; C, 62.53; H, 3.79; N, 4.05. Found (%) C, 62.52; H, 3.78; N, 4.05. UV–visible (solvent: DMSO, nm): 306, 329, 342, 353. Selected IR bands (KBr, ν in cm^{-1}): 1591(C–N=N–C), 1526 (C=N), 1429 (PPh_3), 1267 (imidolate –N=C–O), 1184 (naphtholate C–O), 745 (C–Cl). ^1H NMR ($CDCl_3$, δ ppm): H^1 NMR: 9.86 (s, 1H), 9.16 (d, J = 12.0 Hz, 2), 7.73 (s, 2H), 7.65 (s, 2H), 7.48 (s, 2H), 7.38 (t, J = 6.0 Hz, 9H), 7.18 (t, J = 3.8 Hz, 6H), 6.43 (d, J = 16.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, δ ppm) 183.2, 167.0, 143.7, 142.2, 139.5, 134.2, 131.1, 129.4, 128.7, 127.3, 123.9, 123.3, 120.1, 119.7, 117.7, 114.6.

[Pd(L3) (PPh_3)] (complex **3**) Yield: 88% (124 mg). M. p. 246–248 °C. Elemental analysis (%) calculated for $C_{36}H_{26}N_3O_4PPd$; C, 61.59; H, 3.73; N, 5.99. Found (%) C, 61.58; H, 3.74; N, 5.98. UV–visible (solvent: DMSO, nm): 302, 323, 344, 369. Selected IR bands (KBr, ν in cm^{-1}): 1590 (C–N=N–C), 1526 (C=N), 1477 (NO_2), 1433 (PPh_3), 1249 (imidolate –N=C–O), 1186 (naphtholate C–O). ^1H NMR ($CDCl_3$, δ ppm): H^1 NMR: 9.65 (s, 1H), 9.55 (d, J = 16.0 Hz, 2H), 7.62 (d, J = 6.4 Hz, 3H), 7.52 (t, J = 7.4 Hz, 3H), 7.46 (t, J = 7.4 Hz, 5H), 7.40 (d, J = 6.8 Hz, 2H), 7.25–7.30 (m, 5H), 6.94 (t, J = 3.8 Hz, 2H), 6.44 (d, J = 16 Hz, 3H). ^{13}C NMR ($CDCl_3$, δ ppm) 185.6, 155.8, 154.7, 138.1, 135.6, 130.7, 130.3, 129.2, 128.9, 128.8, 128.7, 127.8, 125.7, 124.5, 124.4, 121.8, 117.1, 113.3.

2.4. Single-crystal X-ray diffraction studies

Suitable crystals of complexes **1**–**3** with approximate dimensions of 0.24 × 0.15 x 0.10, 0.30 × 0.10 x 0.03 and 0.17 × 0.15 × 0.05 mm^3 were mounted on a loop with oil. The data collection were performed by using Bruker APEX II single crystal X-ray diffractometer. All the data were collected using graphite monochromated Mo Kα radiation (λ = 0.71073 Å) from a fine focus sealed tube X-ray source. The collected data were integrated and scaled using hkl-SCALEPACK [34] (for complex **1**) and SAINT, SADABS within the APEX2 software package by Bruker [35] (for complex **2**, and **3**). While using hkl-SCALEPACK program applies a multiplicative correction factor (S) to the observed intensities (I) and has the following form:

$$S = \left(e^{-2B(\sin^2\theta)/\lambda^2}\right)/\text{scale}$$

S is calculated from the scale and the B factor determined for each frame and is then applied to I to give the corrected intensity (I_{corr}). Solution by direct methods (SHELXS, SIR97) [36] produced a complete heavy atom phasing models consistent with the proposed structures. The structure was completed by difference Fourier synthesis with SHELXL97 [37,38]. The scattering factors are from Waasmair and Kirfel [39] Hydrogen atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms with C–H distances in the range 0.95–1.00 Å. Isotropic thermal parameters Ueq were fixed such that they were 1.2 Ueq of their parent atom Ueq for CH's and 1.5 Ueq of their parent atom Ueq in case of methyl groups. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares.

2.5. General procedure for catalytic reaction and reusability

To a mixture of H_2O–EtOH (70:30%), 2-oxindole (3.0 mmol), NEt_3 (6.0 equiv) and PyBroP (1.2 equiv.) were added and stirred for 10 min. To this reaction mixture, complex 3 (0.01 mol) was added and stirred for 30 min at room-temperature followed by the addition of KOH (5 mmol) and phenylboronic acid (4.0 mmol). The progress of the reaction was monitored by thin layer chromatography (TLC). After the completion of the reaction the product mixture was cooled to room temperature; the catalyst was precipitated by the addition of ethyl acetate separated by centrifugation and washed thoroughly with water (to remove inorganic salts). The identity of the products was confirmed by ^1H and ^{13}C NMR techniques. The recovered catalyst was dried and utilized for next cycle under same reaction conditions. The stability of recovered catalyst was identified by ^1H, ^{31}P NMR spectra, melting point data and R_f value of TLC.

3. Results and discussion

Palladium complexes of the composition [Pd (L1–L3) (PPh_3)] were synthesized by reacting equimolar quantity of [$PdCl_2(PPh_3)_2$]