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Abnormal NHC supported palladacycles: Regioselective arylation of heteroarenes *via* decarboxylation

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We report synthesis of two new palladium(II) complexes of abnormal *N*-heterocyclic carbene ligands. The catalytic activity of these palladium(II) complexes was examined for the decarboxylative arylation of *N*-methylindole-carboxylic acids. An exclusive regioselectivity and very good yields were obtained with a variety of aryl halide partners.

1. Introduction

Heteroaromatic biaryls form an important class of organic compounds owing to their widespread applications in materials and biological sciences [1,2]. In medicinal chemistry for example; substituted indole nucleus has broad applications as biologically active natural and unnatural products [3]. In addition, indole derivatives can exhibit several photophysical properties [4,5]. Thus developing efficient methods for synthesis of compounds with indole nucleus is of great interest. Conventionally, biaryl motifs are synthesized by transition-metal catalyzed cross-coupling reactions or direct arylation *via* C-H bond activation [6,7]. An alternative approach is decarboxylative cross-coupling of aromatic carboxylic acid with aryl halides [8–10]. Over the past decade, carboxylic acids gained particular interest as coupling partners owing to their wide availability with variations in nature, ease of handling compared to highly sensitive organometallic reagents and high selectivity at carboxylic acid position compared to that of direct C-H functionalization [8–10].

Pioneering work in decarboxylation reaction was done in 1930 by Shepard [11] who reported that benzoic acid undergoes photodecarboxylation in the presence of stoichiometric amount of copper salts when heated at high temperature. Later Nilsson and co-workers [12–14] studied the decarboxylative coupling of nitrobenzoic acid derivatives with aryl halides as well as kinetics of decarboxylation in presence of stoichiometric amount of copper or silver salts at elevated temperatures. Further Cohen and co-workers [15,16] also studied the decarboxylation of aromatic carboxylic acids mediated by copper salts. The first catalytic decarboxylative coupling to form biaryls was reported by Forgione and co-workers in 2006 [17]. They have employed carboxylic acid functional group as a protecting group to functionalize or remove later during reaction. But arylation was observed at the carbon bearing carboxylic acid functional group after extrusion of carbon dioxide rather than C-H arylated product. Reports on decarboxylative C-C coupling of indole-carboxylic acid moieties are very scarce in literature. First report appeared in 2009, when Miura and co-workers [18] have reported decarboxylative cross-coupling of indole-carboxylic acid with aryl-bromide using $Pd(OAc)_2$ and phosphine ligand. However, it led to biarylated product and inaccessibility of mono-arylated product was the major drawback of Miura's reaction protocol (Scheme 1) and it works only with aryl bromide coupling partners. In 2012, Lee and co-workers [19] have reported synthesis of mono-arylated indoles at C2 position from 3-carboxyindoles and aryl bromides using a palladium(0)NHC based catalyst.

In several cases upon using 2-carboxyindole as indole partner C2-arylated product was obtained along with C3-arylated product

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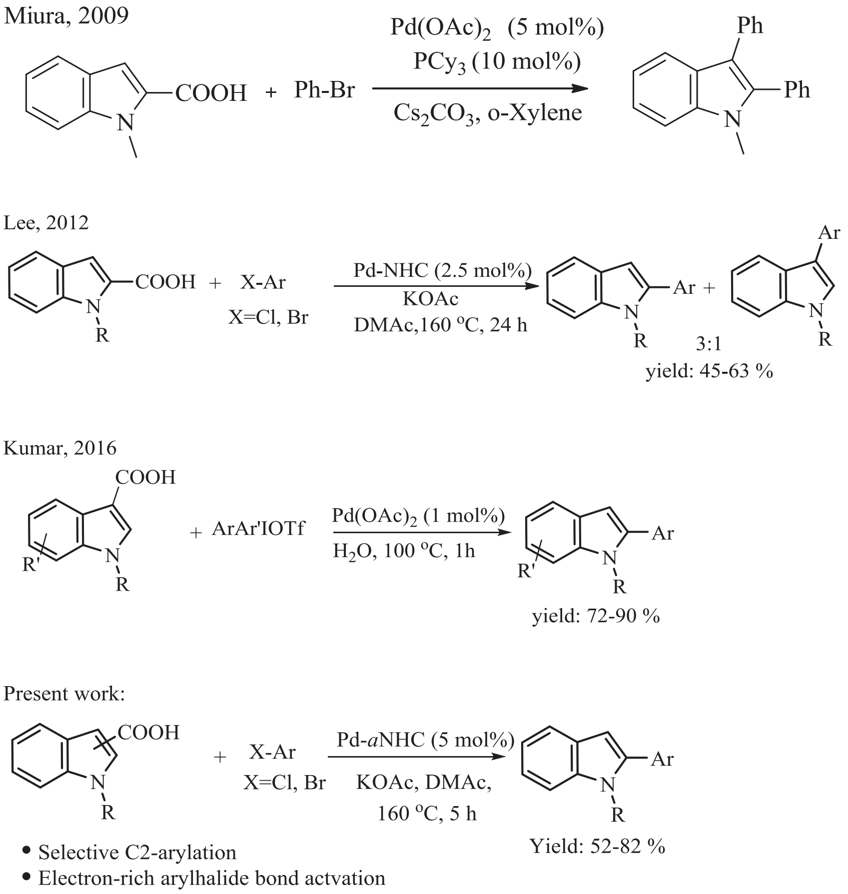

Scheme 1. Previous reports on decarboxylative C-C cross coupling of indole-carboxylic acid with different aryl partners and the present work.

with nearly 3:1 ratio (Scheme 1). In addition to this regioselectivity issue, Lee and co-workers failed to obtain higher yields. Later in 2016, Kumar and co-workers reported synthesis of 2-arylindoles *via* Pd-catalyzed decarboxylative strategy in water without base, oxidant and ligand (Scheme 1) [20]. Though a wide range of 2-arylindoles were synthesized in good yields, they have utilized diaryliodonium salts as aryl coupling partners instead of economically attractive aryl halide partners.

Thus, from the previous reports on decarboxylative coupling of *N*-methylindole-carboxylic acids with aryl halides, it clearly indicates important limitations such as lack of regioselective C2-arylation, poor yields using more abundant aryl halide coupling partners [18–20]. It may be noted that phosphine ligands used in the work of Miura was later replaced by NHC ligands [18,19], with anticipation that a stronger σ-donor ligand might improve the activity of the catalyst. As a part of our interest in developing abnormal NHC (*a*NHC) based catalysts [21–30], we herein report an efficient decarboxylative coupling protocol for arylation of indoles using *a*NHC bearing palladium catalysts. In this study, we report synthesis of two new *a*NHC ligand based palladium(II) complexes and their efficacy in catalytic decarboxylative coupling reaction of indole-carboxylic acids was tested. These *a*NHC supported palladium complexes afforded exclusive regioselectivity in C2 arylation with good yield even for unactivated aryl halide partners.

2. Results and discussion

Herein we report syntheses of two palladacycles, complex **1** and complex **2** using corresponding *a*NHC salts, 1-(2,6-diisopropylphenyl)-2,3,5-triphenyl-imidazolium chloride (ligand **A)** and 3-methyl-2,4-diphenyl-1-(pyridin-2-yl)-1H-imidazol-3-ium chloride (ligand **B)**, respectively (Scheme 2). Ligand **A** was synthesized according to the literature procedure [31], and ligand **B** was synthesized by *N*-arylation of 2,4-diphenyl-1H-imidazole (**I**) through C-N coupling reaction with 2-bromopyridine using $CuSO_4 \cdot 5H_2O$ as catalyst followed by *N*-methylation using iodomethane to give 3-methyl-2,4-diphenyl-1-(pyridin-2-yl)-1H-imidazol-3-ium iodide salt (**III**) (Scheme 2B). Corresponding chloro salt was obtained by using DOWEX chloride ion-exchange resin. A change in colour from brown to yellow was observed after the ion-exchange from iodide to chloride. Complexes **1** and **2** were synthesized using ligand **A** and ligand **B** by charging with palladium acetate in dioxane and heating at 80 °C for 8 h. It resulted in the formation of yellow coloured chloro-bridged, C-H activated palladium dimer **1** and monomeric complex **2**, respectively (Scheme 2). Complex **1** was characterized by spectroscopic methods (^{1}H and ^{13}C NMR spectroscopy) and elemental analysis. The C-5 resonance upon Pd(II) coordination resonates at δ 147.1 ppm, as observed in the ^{13}C NMR spectrum of complex **1**, which may be assigned to carbene-Pd resonance as also noted for similar palladium-*a*NHC complexes [27–29]. The NMR spectrum for complex **2** could not be recorded as the complex **2** is insoluble in common deuterated solvents ($CDCl_3$, Toluene-d_8, DMSO-d_6, THF-d_8, D_2O). Later, complexes **1** and **2** were characterized by single crystal X-ray crystallography. Analytically pure **1** and **2** were obtained by crystallization from DCM/hexane mixture and single crystal X-ray studies clearly established the molecular structures of **1** and **2**. The ORTEP diagrams of complexes **1** and **2** are displayed in Fig. 1. The crystal

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