



# Palladium complexes of amido-functionalized N-heterocyclic carbenes as effective precatalysts for the Suzuki–Miyaura C–C cross-coupling reactions of aryl bromides and iodides

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## ABSTRACT

A series of air-stable, robust and highly active palladium based precatalysts of amido-functionalized N-heterocyclic carbenes for the Suzuki–Miyaura C–C cross-coupling reaction has been designed. In particular, the [1-R-3-{N-(benzylacetamido)imidazol-2-ylidene}]<sub>2</sub>PdCl<sub>2</sub> [R = *i*-Pr (**1c**) and CH<sub>2</sub>Ph (**2c**)] complexes efficiently carried out the Suzuki–Miyaura coupling of the aryl bromide and iodide substrates with phenyl boronic acid in good to excellent yields in air at 90 °C in 12 h. Quite interestingly, of these palladium precatalysts, the *i*-propyl derivative (**1c**) exhibited superior activity as compared to the benzyl derivative (**2c**). The density functional theory (DFT) studies carried out on the **1c** and **2c** complexes revealed the strong  $\sigma$ -donating nature of the NHC ligand as reflected in their high *d/b* ratio [i.e. forward  $\sigma$ -donation (*d*) to backward  $\pi$ -donation (*b*)] of these complexes and, thus, point towards greater stability of the Pd–NHC interaction in these complexes.

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## 1. Introduction

As a convenient approach to accessing the “biaryl frameworks”, so ubiquitous in many important bioactive molecules as well as in value-added chemical feedstock, the Suzuki–Miyaura C–C cross-coupling reaction, today, has emerged as a major work horse in synthetic organic chemistry [1–7]. In particular, the famed reaction involves highly efficient C–C cross-coupling of aryl halide with aryl boronic acid in a catalytic fashion aided by palladium in presence of a base. The extreme popularity of the Suzuki–Miyaura reaction stems from its regio- and stereoselectivity, functional group tolerance, ready availability of the boron based starting materials, its non-toxic nature and its air and moisture stability. Thus, because of its utility as an important synthetic methodology, a significant amount of research focus had been devoted to designing improved catalysts for the Suzuki–Miyaura cross-coupling reaction. In this regard it is noteworthy that though numerous catalysts of phosphine based systems [8,9] have been reported for the coupling reaction, the use of N-heterocyclic carbenes based ones is a relatively new affair [10,11]. The N-heterocyclic carbene based precatalysts possess distinct advantages that arise from the tight binding of the NHC ligand to the metal, leading to a greater stability of the complex under the catalysis conditions, and which in turn helps suppress

the leaching of the catalysts [12–14]. The tight binding of the NHC ligand to the metal is reflected in the high NHC–metal bond dissociation energy *eg.* 74.8 kcal/mol in *trans*-[1-benzyl-3-(3,3-dimethyl-2-oxobutyl)imidazol-2-ylidene]<sub>2</sub>PdBr<sub>2</sub>, [15] 75.1 kcal/mol in *cis*-[1-benzyl-3-(*N*-*t*-butylacetamido)imidazol-2-ylidene]<sub>2</sub>PdCl<sub>2</sub> [15] and 81.9 kcal/mol in *trans*-[1-(benzyl)-3-(*N*-*t*-butylacetamido)imidazol-2-ylidene]Pd(pyridine)Cl<sub>2</sub> [16] etc. The additional advantages of the N-heterocyclic carbenes arise from their easy tunability and from their behavior as good “spectator” ligands, which while influencing the catalysis, do not get consumed or chemically react in the process.

In continuing with our efforts on designing new precatalysts for a host of C–C bond forming reactions namely, the Hiyama [17], Sonogashira [15,17,18], Suzuki–Miyaura [16,19] and the base-free Michael reactions [20,21], we were in look out for new N-heterocyclic carbene based scaffolds for stabilizing palladium precatalysts for the coupling reactions. More specifically, with regard to the Suzuki–Miyaura coupling, we demonstrated the use of the *trans*-(NHC)<sub>2</sub>PdX<sub>2</sub> (X = halide) and the famed PEPPSI [22–27] themed (NHC)PdX<sub>2</sub>(pyridine) type complexes, of which the former ones showed ultra high activity [16,19]. Thus, the present efforts are directed along the line of developing new *trans*-(NHC)<sub>2</sub>PdX<sub>2</sub> (X = halide) type complexes for application in the Suzuki–Miyaura cross-coupling reaction. In this connection, we additionally emphasized on employing well-defined N-heterocyclic carbene based precatalysts for the said study as opposed to performing it

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under the more common “Ligand Assisted Catalysis” (LAC) conditions is because the use of well-characterized catalysts display shorter reaction times and also significantly reduces the unwanted side reactions.

Here in this contribution, we report a series of robust and highly efficient palladium complexes of amido-functionalized N-heterocyclic carbenes namely, [1-R-3-{*N*-(benzylacetamido)imidazol-2-ylidene]<sub>2</sub>PdCl<sub>2</sub> [R = *i*-Pr (**1c**) and CH<sub>2</sub>Ph (**2c**)], for the Suzuki–Miyaura cross-coupling reactions of aryl bromides and iodides with phenyl boronic acid in air (Fig. 1).

## 2. Results and discussion

Two new amido-functionalized N-heterocyclic carbene ligands were designed with the intent of stabilizing palladium complexes for use as precatalysts for the Suzuki–Miyaura cross-coupling reaction. In this regard the following new N-heterocyclic carbene precursors, 1-R-3-*N*-(benzylacetamido)imidazolium chloride salts [R = *i*-Pr (**1a**) and CH<sub>2</sub>Ph (**2a**)], were synthesized by the direct reaction of the *N*-benzyl-2-chloro-acetamide with the respective 1-R-imidazole (R = *i*-Pr and CH<sub>2</sub>Ph) in 81–84% yield (Scheme 1). The appearance of the downfield shifted peaks at *ca.* 9.97–10.05 ppm in the <sup>1</sup>H NMR and at *ca.* 132.6–135.5 ppm in <sup>13</sup>C{<sup>1</sup>H} NMR, that are characteristics of the NCHN resonances, indicated the clean formation of the imidazolium chloride salts **1a** and **2a**.

The palladium complexes [1-R-3-{*N*-(benzylacetamido)imidazol-2-ylidene]<sub>2</sub>PdCl<sub>2</sub> [R = *i*-Pr (**1c**) and CH<sub>2</sub>Ph (**2c**)] were obtained by following the transmetallation route from the silver complexes {[1-R-3-{*N*-(benzylacetamido)imidazol-2-ylidene]<sub>2</sub>Ag}<sup>+</sup>Cl<sup>−</sup> [R = *i*-Pr (**1b**) and CH<sub>2</sub>Ph (**2b**)] by treatment with (COD)PdCl<sub>2</sub> (COD = *cis*-, *cis*-1,5-cyclooctadiene) in 52–64% yield. The silver complexes **1b** and **2b** were in turn synthesized from the respective imidazolium chloride salt **1a** and **2a** by the reaction with Ag<sub>2</sub>O in 61–67% yield. Of interest, are the diagnostic M–C<sub>carbene</sub> resonances that appeared downfield shifted [M = Ag, 179.8 ppm (**1b**) and 182.2 ppm (**2b**); M = Pd, 169.2 ppm and 169.3 ppm (**1c**) and 159.0 ppm and 156.8 ppm (**2c**)] in the <sup>13</sup>C{<sup>1</sup>H} NMR spectrum.

Quite expectedly, the molecular structure of the **1c** and **2c** complexes revealed monomeric square-planar geometry at the

metal consistent with a *d*<sup>8</sup> palladium(II) metal center (Figs. 2 and 3 and Supplementary material Table S1). The Pd–C<sub>carbene</sub> bond distances [2.029 (3) Å (**1c**) and 2.032 (6) Å (**2c**)] are comparable to the sum of the individual covalent radii of Pd and C (2.055 Å) [28] and also to other related structurally characterized (NHC)<sub>2</sub>PdCl<sub>2</sub> type examples namely, *trans*-[1-benzyl-3-(3,3-dimethyl-2-oxobutyl)imidazol-2-ylidene]<sub>2</sub>PdBr<sub>2</sub> [2.018(9) Å] [15], *cis*-[1-benzyl-3-(*N*-*t*-butylacetamido)imidazol-2-ylidene]<sub>2</sub>PdCl<sub>2</sub> [1.998(2) Å] [15], and *trans*-[1-benzyl-3-*t*-butylimidazol-2-ylidene]<sub>2</sub>PdCl<sub>2</sub> [2.044(4) Å] [29]. The Pd–Cl distances in **1c** and **2c** are 2.3167(8) Å and 2.309(2) Å, respectively. The other notable aspects of the **1c** and **2c** structures are the *trans* disposition of the of the N1 and N3 substituents of the imidazole rings, that make a coplanar arrangement to each other.

Deeper understanding of the nature of the Pd–NHC interaction could be obtained by the density functional theory studies. Specifically, the respective geometry optimized structure of the palladium complexes, **1c** and **2c**, were obtained by computing at the B3LYP/SDD, 6-31G(d) level of theory using the atomic coordinates adopted from the X-ray analysis (Supplementary material Tables S2 and S3). Subsequent, single-point calculation was performed on the geometry optimized structure to obtain insight on the electronic properties of the complexes.

Quite interestingly, the NBO analysis indicated that the Pd–NHC bond is composed of an interaction of a C<sub>carbene</sub> *sp*<sup>2</sup> orbital with a *sd* orbital of the palladium center (Supplementary material Table S9). Indeed, a careful look at the electronic configuration of the palladium center in **1c** and **2c** relative to that in the PdCl<sub>2</sub> species as well as of the C<sub>carbene</sub> center in **1c** and **2c** relative to that in the free NHC ligand fragment reveal that electron donation occur from the free NHC ligand fragment on to the 5s orbital of the palladium center in **1c** and **2c** (Supplementary material Table S6). Corroborating the above mentioned observation, both the Mulliken and Natural Charge analysis showed that as a result of the σ-donation from the free NHC ligand fragment, the electron density at the palladium center increased from that in the PdCl<sub>2</sub> species to that in **1c** and **2c** (Supplementary material Tables S4 and S5). Also, attesting to the good σ-donating ability of the NHC ligand, the *d/b* ratio [1.96 (**1c**) and 2.98 (**2c**)], which is a measure of the relative extent of the NHC to metal σ-donation (*d*) and the metal to NHC π-back donation (*b*) and is computed using the Charge Decomposition Analysis (CDA) method, for the **1c** and **2c** complexes were found to be greater than unity (Supplementary material Table S8).

A closer look at the Pd–NHC interaction could be obtained by constructing the molecular orbital (MO) correlation diagram from the individual fragment molecular orbitals (FMO) of the respective free NHC ligand fragment and the PdCl<sub>2</sub> species (Figs. 4 and 5 and Supplementary material Figs. S1 and S2). Quite interestingly, the molecular orbitals HOMO–39 (**1c**) and HOMO–45 (**2c**) represent the σ-orbital interaction between the palladium center and the free NHC ligand fragment. Specifically, the Pd–NHC σ-bonding orbital, HOMO–39 (25% NHC, 31% PdCl<sub>2</sub>), in **1c** showed an interaction of the carbene lone pair (HOMO–1 of the free NHC fragments) with a metal based vacant LUMO (72% palladium with 28% *s* and 44% *d* character) of the PdCl<sub>2</sub> fragment (Fig. 4). In the **2c** complex, the Pd–NHC σ-bonding orbital, HOMO–45 (21% NHC, 29% PdCl<sub>2</sub>) showed an interaction of the carbene lone pair (HOMO–1 of the free NHC fragments) with a metal based vacant LUMO (72% palladium with 28% *s* and 44% *d* character) of the PdCl<sub>2</sub> fragment (Fig. 5). It is worth noting that these low lying Pd–NHC σ-molecular orbitals signify stable interaction which are less vulnerable to the electrophilic or nucleophilic attacks. In this regard it is noteworthy that carbenes along with its metal complexes, as such, are highly reactive compounds that readily undergo reactions with electrophiles and nucleophiles.

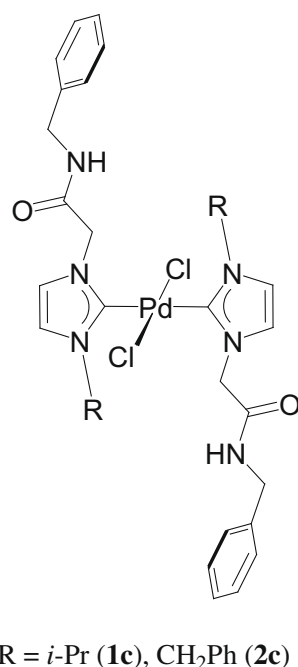


Fig. 1. Palladium complexes of amido-functionalized N-heterocyclic carbenes.

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