



N-Heterocyclic carbene-palladacyclic complexes: synthesis, characterization and their applications in the C-N coupling and α -arylation of ketones using aryl chlorides

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ARTICLE INFO

Article history:

Received 28 June 2018

Received in revised form

26 July 2018

Accepted 27 July 2018

Available online 4 August 2018

Keywords:

N-heterocyclic carbene-palladacyclic complex

Aryl chlorides

C-N coupling

α -arylation

Synthetic methods

ABSTRACT

N-Heterocyclic carbene-palladacyclic complexes **3** were successfully achieved in a one-pot procedure under mild conditions. The structure of **3a** was unambiguously confirmed by X-ray single crystal diffraction and it was an active catalyst in the Buchwald-Hartwig amination and α -arylation of ketones even at very low catalyst loadings (0.01 mol%).

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1. Introduction

Palladium-catalyzed cross-coupling reactions are the most important methods in the modern organic synthesis for the formation of carbon-carbon and carbon-heteroatom bonds [1]. Among the organic electrophiles involved, aryl chlorides seem to be the most important but challenging ones because they are more available and cheaper but less active than aryl bromides and iodides, which thus attract much attention [2]. Consequently, a series of tertiary phosphine ligands with high activity but air- and moisture-sensitive has been developed for the efficient coupling of aryl chlorides [3]. In order to overcome the disadvantages of phosphine ligands, lots of well-defined N-heterocyclic carbene (NHC)-palladium complexes, which usually are air- and thermal-stable, mainly developed by Nolan [4], Organ [5], Lavigne [6], Tu [7] and others [8], have shown efficiently catalytic activity in the cross-coupling reactions of aryl chlorides. Among these NHC-Pd(II) complexes, besides the bulky and strong donating NHC skeleton, the ancillary ligands also play important role in the catalytic activities. We were therefore interested in the development of easily

synthesized and highly reactive NHC-Pd(II) complexes by trying different ancillary ligands. As a consequence, we also have successfully developed a series of NHC-Pd(II) complexes and found them to be efficient catalysts in the cross-coupling reactions of aryl chlorides [9]. To continue investigating the influence of ancillary ligands, N-heterocyclic carbene-palladacyclic complexes **3** were synthesized by using imidazolium salts **1**, PdCl₂ and benzo[h]quinoline **2** in a one-pot procedure [10]. In addition, one of the complexes, complex **3a**, was found to be an active catalyst in the Buchwald-Hartwig amination and α -arylation of ketones using aryl chlorides even at very low catalyst loadings. Herein, we report these results in detail.

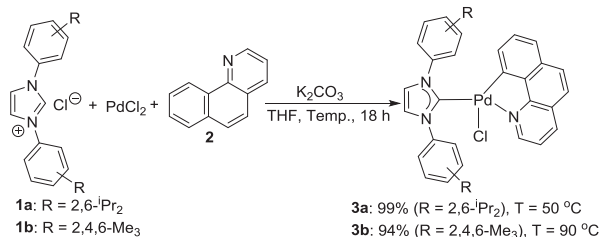
2. Results and discussion

2.1. Synthesis of NHC-Pd(II) complexes **3**

First, by a slightly modified method according to our previously reported procedure [9b], N-heterocyclic carbene-palladacyclic complexes **3** were easily obtained in 99% and 94% yields from commercially available imidazolium salts **1**, PdCl₂ and benzo[h]quinoline **2** in a one-step process (Scheme 1). Crystals of **3a** were grown in the mixture of ethyl acetate and dichloromethane, and its

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Scheme 1. Synthesis of complexes **3**.

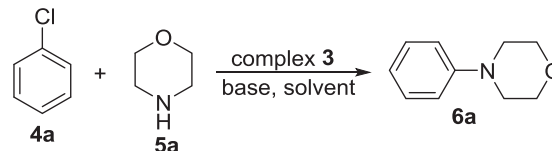
structure was unambiguously determined by X-ray single crystal diffraction (Fig. 1) [11].

2.2. Buchwald-Hartwig amination of aryl chlorides

To evaluate the catalytic properties of *N*-heterocyclic carbene-palladacyclic complexes **3**, the amination of chlorobenzene **4a** with morpholine **5a** was selected as the model reaction (Table 1). Using **3a** (0.1 mol%) as the catalyst, KO^tBu (1.3 equiv) as the base, the reaction of chlorobenzene **4a** (0.5 mmol) with morpholine **5a** (0.6 mmol) gave the corresponding aminated product **6a** in 94% yield in toluene at 90 °C for 3 h (entry 1). When NaO^tBu was used as the base, very low yield of the desired aminated product **6a** was observed (entry 2). In the presence of other bases such as LiO^tBu and K₂CO₃, no reaction occurred (entries 3 and 4). Using KO^tBu as the base, a variety of solvents was then tested. For instance, when THF and dioxane were chosen as the solvents, **6a** can be obtained in 85 and 56% yields, respectively (entries 5 and 6). When polar solvent such as DMF was used, only 5% yield was observed (entry 7). Catalytic activity of **3b** was also tested and only 9% yield of product **6a** was found (entry 8). The catalytic property of complex **3a** at lower catalyst loadings was then further investigated. When the catalyst loading was lowered to 0.05 mol%, **6a** can be achieved in 79% yield within a prolonged reaction time (entry 9). The reaction can proceed smoothly and afford satisfactory yield in the presence of 0.04 mol% **3a** at 110 °C for 24 h (entry 10). When the catalyst loading was further lowered to 0.03 mol%, **6a** was obtained in moderate yield even the reaction was carried out at 110 °C for 24 h (entry 11).

Using complex **3a** as the catalyst, a series of aryl chlorides and amines were used as the substrates to test the generality and limitation of the reactions. As shown in Table 2, all reactions proceeded smoothly to give the corresponding coupling products **6** in good to

Table 1
Optimization for the complex **3**-catalyzed coupling of chlorobenzene **4a** with morpholine **5a**.



Entry ^a	3	Base	Solvent	Yield (%) ^b
1	3a	KO ^t Bu	toluene	94
2	3a	NaO ^t Bu	toluene	<5
3	3a	LiO ^t Bu	toluene	NR
4	3a	K ₂ CO ₃	toluene	NR
5	3a	KO ^t Bu	THF	85
6	3a	KO ^t Bu	dioxane	56
7	3a	KO ^t Bu	DMF	5
8	3b	KO ^t Bu	toluene	9
9 ^c	3a	KO ^t Bu	toluene	79
10 ^d	3a	KO ^t Bu	toluene	96
11 ^e	3a	KO ^t Bu	toluene	55

^a Otherwise specified, all reactions were carried out using chlorobenzene **4a** (0.5 mmol), morpholine **5a** (0.6 mmol), base (1.3 equiv) and **3** (0.1 mol%) in solvent (1.0 mL) at 90 °C for 3 h.

^b Isolated yields.

^c **3a** (0.05 mol%), 90 °C, 24 h.

^d **3a** (0.04 mol%), 110 °C, 24 h.

^e **3a** (0.03 mol%), 110 °C, 24 h.

excellent yields. The relative position of the same substituents on the phenyl ring of aryl chlorides has some effect on the coupling reactions. For example, when 2-chlorotoluene **4f** was used as the substrate, more catalyst loading (0.05 mol%) was necessary to achieve similarly high yields (**6h**, **6l**, **6o** and **6p**) (entries 7, 11, 14 and 15). For 3-chlorotoluene **4c**, only 0.015 mol% **3a** was necessary and the aminated product **6e** was formed in 89% yield (entry 4). For electron-deficient substrates such as 3-chlorofluorobenzene **4d** and 4-chlorofluorobenzene **4e**, the reactions took place smoothly to give the desired products **6f**, **6g**, **6j**, **6k** and **6n** in good to high yields in the presence of 0.025 mol% **3a** (entries 5, 6, 9, 10 and 13). The reaction of sterically hindered substrates 2-chloro-1,3-diisopropylbenzene **4h** with 2,4,6-trimethylaniline **5h** gave almost quantitative yield with 0.05 mol% **3a** (entry 20).

2.3. α -Arylation of ketones with aryl chlorides

Then we investigated the use of *N*-heterocyclic carbene-palladacyclic complex **3a** as the catalyst in the α -arylation of ketones with aryl chlorides (Table 3). Using **3a** as the catalyst, the reaction of 4-chloroanisole **4i** with propiophenone **7a** was carried out in toluene at 80 °C for 3 h. A lot of bases were tested and NaO^tBu gave the best outcome, giving the corresponding α -arylated product **8a** in 93% yield (entry 2). Almost no reaction was observed when other solvents such as THF, dioxane and DMF were used (entries 7–9).

Under the optimal reaction conditions, a series of aryl chlorides and propiophenone derivatives were examined (Table 4). Most reactions performed well enough in the presence of 1.0 or 2.0 mol% **3a** at 80 °C. It seems that the relative position of the same substituents on the phenyl rings of aryl chlorides affected the reactions to some extent. For example, *para*-substituted aryl chlorides are better than *ortho*- and *meta*-substituted ones, giving higher yields under the same reaction conditions (entries 4, 6, 7–9 and 12). When 2-chloroanisole and 3-chloroanisole were used, the amount of complex **3a** should be increased to 2.0 mol% to achieve

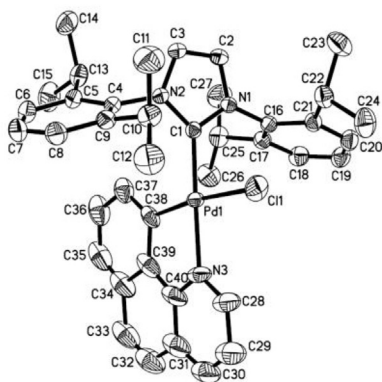


Fig. 1. Molecular structure of **3a**. Hydrogens have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)–C(1) = 1.990(3); Pd(1)–C(38) = 1.988(5); Pd(1)–N(3) = 2.086(4); Pd(1)–Cl(1) = 2.3864(12); C(1)–Pd(1)–N(3) = 176.36(15); C(1)–Pd(1)–Cl(1) = 90.70(10); N(3)–Pd(1)–Cl(1) = 90.89(16); C(38)–Pd(1)–C(1) = 96.25(18); C(38)–Pd(1)–N(3) = 82.1 (2).

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