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Carboxyamido/carbene ligated palladium (II) complex: A versatile catalyst for the synthesis of aryl-substituted heteroarenes

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ABSTRACT

Carboxy amido/carbene ligated Pd-complex catalyzed Suzuki-Miyaura cross-coupling of aryl-boronic acids with heteroaryl bromides is described. The protocol has a broad substrate scope that includes electron-rich, electron-deficient and sterically hindered arylboronic acids and heteroaryl bromides. The catalytic activity of the catalyst has been further investigated in the coupling of 2,6-dibromopyridine with arylboronic acids.

1. Introduction

Biaryls are prevalent structural constituents in natural products [1–4], pharmaceuticals [5–7], agrochemicals and advanced functional materials [8–11]. They are traditionally synthesized by transition metal catalyzed C–C coupling reaction like Suzuki-Miyaura cross coupling reactions [12–18]. In particular, the Suzuki reaction of heteroaryl halides has received considerable attention due to the growing significance of these products as biologically active compounds [19–21]. However, their catalytic synthesis is challenging due to the high affinity of active palladium species toward heteroatom resulting into deactivation of the catalyst. In order to avoid catalyst deactivation, palladium is coordinated with bulky phosphine based ligands and this has been very well reported in literature [22–36]. Subsequently, the ligand-free catalyst for the Suzuki cross-coupling reaction of arylboronic acids with heteroaryl halides has also been developed. However, these are less reactive or have limited scope toward heteroaryl halides [37–41]. Recently, Nechave et al. reported the Suzuki-Miyaura cross-coupling reaction of heteroaryl halides with simple arylboronic acids using diamino carbene palladium complex [42]. These processes are important advancements made in the field of transition metal catalysis which aid the synthesis of aryl substituted heteroarenes; however, it is desirable to develop catalytic protocols that have broad substrate scope and efficiency.

In recent years, attention has been laid on the synthesis of air-stable palladium complexes that are an alternative to toxic and air-sensitive phosphine ligands or palladium phosphine catalysts. In this direction, various palladium complexes comprising S-, N-, O-and N-heterocyclic carbene donor-centered ligands have been developed. With the remarkable catalytic activity, N-heterocyclic carbene-palladium complexes have become a paradigmatically new generation of strong sigma donor ligands in palladium-catalyzed cross coupling reactions [43–51]. Among the class of N-heterocyclic carbene ligands, carbocyclic carbene ligands are less known and recently used in cross-coupling reactions [52]. Earlier, we have reported the synthesis and application of palladium complex of carboxyamido/carbocylic carbene ligand for decarboxylative cross-coupling of alkynyl carboxylic acids with aryl and heteroaryl halides [53]. In continuation to these studies, herein, we report the Suzuki-Miyaura cross-coupling reaction of aryl boronic acids with different heteroaryl bromides using carboxyamido/carbocylic carbene ligated palladium complex (II) (catalyst 1) in aqueous ethanol.

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2. Experimental

2.1. Materials and instrumentations

All reagents were commercial grade materials and were used without further purification. All solvents were dried and distilled by standard methods. Purification of products was carried out by column chromatography using commercial column chromatography grade silica gel (60–120 mesh) purchased from s. d. fine-chemicals Ltd. using mixture of ethyl acetate and hexane as eluting solvent. All synthesized compounds were characterized and compared with the literature reports. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker-Avance (300 MHz), and Varian-Inova (500 MHz) spectrophotometer using $CDCl_3$ solvent, and TMS as the internal standard.

2.2. Experimental procedure for the Suzuki cross coupling reaction of heteroaryl bromides

The reaction vessel was charged with heteroaryl bromides (1.0 mmol), arylboronic acid (1.2 mmol), $K_3PO_4{\cdot}7H_2O$ (1.5 mmol), and the catalyst **1** (0.5 mol%) in EtOH/H_2O (1:2, v/v 3 mL). The reaction mixture was heated at 60 °C in air and the progress of the reaction was monitored by TLC. At the end of the reaction, the reaction mixture was diluted with water (20 mL) and then extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL) and then dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by flash chromatography over silica gel using ethyl acetate/hexane as an eluent to afford the pure product.

3. Results and discussion

In the initial screening of Suzuki cross-coupling reactions, phenylboronic acid (1.0 mmol) and 3-bromopyridine (1.5 mmol) were selected to examine the catalytic activity of carboxy amido/carbene ligated palladium complex (II) (Fig 1). The optimization studies were conducted using various base and solvents at 60 °C, and the results are tabulated in Table 1. Remarkably, the reaction did not proceed in polar aprotic solvents like DMF, DMSO and DMA (Table 1, entries 1–3). However, the use of polar protic solvents like MeOH and EtOH afforded good yields of the desired product, namely, 3-phenylpyridine (Table 1, entries 4 & 5). Further improvement in the product yield was observed using 1:2, v/v EtOH/H_2O mixture (Table 1, entry 6).

In the screening study of bases, it was observed that K_3PO_4 is the best suitable base (Table 1, entry 6) although, carbonate bases like K_2CO_3, Na_2CO_3 and Cs_2CO_3 also gave good results (Table 1, entries 8–10). Lowering the catalyst loading (0.3 mol%, Table 1, entry 11) or lowering the temperature (40 °C, Table 1, entry 12) resulted in poor yield of the coupling product. Thus, the optimized conditions for the coupling reaction are 0.5 mol% of palladium complex, (2.0 equiv) K_3PO_4 in 3 mL of EtOH/H_2O (1:2, v/v) at 60 °C for 4 h (96%, Table 1, entry 6).

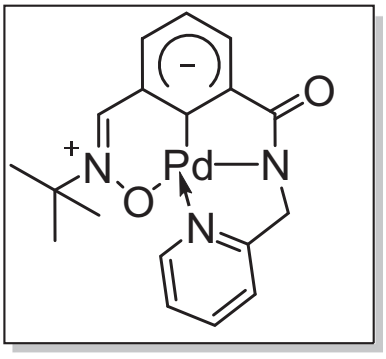
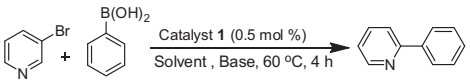


Fig. 1. Structure of carboxyamido/carbene palladium complex (II).

Table 1
Optimization of reaction conditions.[a]

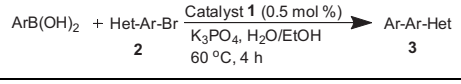


Entry	Solvent	Base	Yield (%)[b]
1	DMF	K_3PO_4	0
2	DMA	K_3PO_4	0
3	DMSO	K_3PO_4	0
4	MeoH	K_3PO_4	70
5	EtOH	K_3PO_4	86
6	**EtOH/H_2O (1:2)**	**K_3PO_4**	**96**[e]
7	MeOH/H_2O (1:2)	K_3PO_4	80
8	EtOH/H_2O (1:2)	K_2CO_3	84
9	EtOH/H_2O (1:2)	Na_2CO_3	80
10	EtOH/H_2O (1:2)	Cs_2CO_3	79
11[c]	EtOH/H_2O (1:2)	K_3PO_4	77
12[d]	EtOH/H_2O (1:2)	K_3PO_4	70

[a] The reactions were carried out with 3-bromopyridine (1 mmol), phenylboronic acid (1.5 mmol), base (2 eq) and catalyst (0.5 mol%) in 3 mL of solvent at 60 °C for 4 h.
[b] Isolated yields.
[c] Catalyst loading 0.3 mol%.
[d] Reaction at 40 °C.
[e] Optimized condition: 1:2, v/v EtOH/H_2O; 3 mL K_3PO_4.

The scope of the reaction was extended to various structurally diverse heteroaryl bromides using the optimized reaction conditions and the results are summarized in Table 2. The reaction of the phenylboronic acid with electron-deficient heteroaryl bromides such as 3-bromopyridine, 2-bromopyridine, 3-bromoquinoline, 4-bromoisoquinoline, 5-bromopyrimidine and 2-bromopyrazine (Table 2, **3a**-**3f**) proceeded smoothly to afford the corresponding coupling products in excellent yields. Similarly, the reaction carried out with electron-rich heteroaryl bromide like 2-bromothiophene (Table 2, 3g) produced the desired product in 88% yield. Furthermore, electron donating and electron withdrawing heteroaryl bromides such as 2-bromo-6-methylpyridine and 5-bromo-2-nitropyridine (Table 2, **3h**, and 2i) also reacted well with phenylboronic acid and the corresponding products were obtained in 96% and 85% yield, respectively.

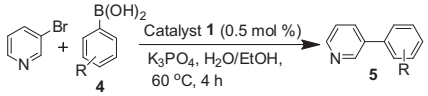
Table 2
Suzuki coupling reaction of phenylboronic acid with heteroarylbromides.[a]



Entry	Heteroarylbromides (2)	Product	Yield (%)[b]
1	3-bromopyridine	**3a**	96
2	2-bromopyridine	**3b**	91
3	3-bromoquinoline	**3c**	89
4	4-bromoisoquinoline	**3d**	87
5	5-bromopyrimidine	**3e**	95
6	2-bromopyrazole	**3f**	86
7	3-bromothiphene	**3g**	88
8	2-metyl-6-bromopyridine	**3h**	86
9	3-bromo5-nitropyridine	**3i**	96

[a] The reactions were carried out with hetroaryl bromides (1 mmol), phenylboronic acid (1.5 mmol), K_3PO_4 (2 eq) and catalyst (0.5 mol%) in 3 mL of EtOH/H_2O at 60 °C for 4 h.
[b] Isolated yields.

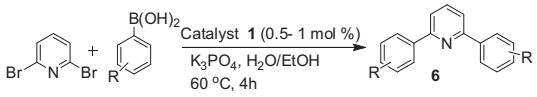
Table 3
Suzuki coupling reaction of aryl and heteroarylboronic acids with 3-bromopyridine.[a]



Entry	Arylboronic acid (4)	Product	Yield (%)[b]
1	p-tolylboronic acid	**5a**	97
2	(4-methoxyphenyl)boronic acid	**5b**	95
3	(2-methoxyphenyl)boronic acid	**5c**	93
4	(3-methoxy-4-methylphenyl)boronic acid	**5d**	89
5	(2,3,4-trimethoxyphenyl)boronic acid	**5e**	87
6	Naphthalen-2-ylboronic acid	**5f**	88
7	(E)-styrylboronic acid	**5g**	89
8	(4-fluorophenyl)boronic acid	**5h**	86
9	(4-chlorophenyl)boronic acid	**5i**	88
10	(3-nitrophenyl)boronic acid	**5j**	90
11	(4-formylphenyl)boronic acid	**5k**	87
12	Pyridin-3-ylboronic acid	**5l**	89

[a] The reactions were carried out with 3-bromopyridine (1 mmol), arylboronic acids (1.5 mmol), K_3PO_4 (2 eq) and catalyst (0.5 mol%) in 3 ml of EtOH/H_2O 60 °C for 4 h.
[b] Isolated yields.

Table 4
Suzuki coupling reaction of 2,6-dibromopyridine with arylboronic acids.[a]



Entry	Arylboronic acid	Product	Yield (%)[b]
1	Phenylboronic acid	**6a**	90
2	(4-methoxyphenyl)boronic acid	**6b**	92
3	(4-formylphenyl)boronic acid	**6c**	76

[a] The reactions were carried out with 2,6-dibromopyridine (1 mmol), arylboronic acid (2 mmol), K_3PO_4 (2 eq) and catalyst (0.5–1 mol%) in 3 mL of EtOH/H_2O at 60 °C for 4 h.
[b] Isolated yields.

Next, the scope of the reaction was explored in the reaction of 3-bromopyridine with various arylboronic acids and the results are given in Table 3. Arylboronic acids containing the electron-donating substituents such as methoxy and methyl at para position reacted well with 3-bromopyridine furnishing excellent yields of the corresponding coupled products (Table 3, **5a**, **5b**, and **5d**). Similarly, the reaction of sterically hindered substrates, such as 2-methoxyphenylboronic acid, and 2,3,4-trimethoxyphenylboronic acids also proceeded smoothly to afford the respective products in good yields (Table 3, **5c** and **5e**). The reaction of the 2-napthylboronic acid and (*E*)-styrylboronic acid also afforded the corresponding products in 88% and 89% yields, respectively (Table 3, **5f** and **5g**). Arylboronic acids containing electron withdrawing substituents such as chloro, fluoro, formyl, and nitro also reacted well with 3-bromopyridine producing the respective products in good yields (Table 3, **5h**–**5k**). Also, heterocyclic boronic acid like 3-pyridylboronic acid gave the desired product in 89% yield (Table 3, entry **5l**).

Finally, we investigated the scope of the Suzuki coupling in the reaction of 2,6-dibromopyridine with substituted phenylboronic acids, and the results are presented in Table 4. The reaction of 2,6-dibromopyridine with phenylboronic acid, and electronically rich 4-methoxyphenylboronic acid afforded 90% and 92% yield of the corresponding products, respectively (Table 4, entries **6a** and **6b**). However, the reaction of electron deficient 4-formylphenylboronic acid furnished only 75% yield of the desired product (Table 4, 6c).

4. Conclusions

In summary, the carboxyamido/carbene ligated Pd-complex has been synthesized and characterized fully by various analytical tools. The catalytic activity of the Pd catalyst was then investigated in the Suzuki-Miyaura cross-coupling reaction of heteroaryl bromides with aryl-boronic acids in an ethanol–water medium under the phosphine-free condition. Pd catalyst showed excellent activity toward a wide variety of heteroaryl bromides and arylboronic acids including electron-donating, electron-withdrawing and sterically hindered substrates.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.poly.2016.07.038.

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