



NHC–Pd(II)–Im (NHC = *N*-heterocyclic carbene; Im = 1-methylimidazole) complexes as efficient catalysts for Suzuki–Miyaura coupling reactions of aryl chlorides

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ABSTRACT

A new type of well-defined *N*-heterocyclic carbene (NHC)–palladium chloride–imidazole complexes derived from IPr^*HCl or IMes^*HCl , PdCl_2 and 1-methylimidazole exhibits high catalytic activity in the room-temperature Suzuki–Miyaura coupling reactions of aryl or heteroaryl chlorides. Moreover, the large-scale (20.0 mmol) couplings in the presence of 0.01 mol% catalyst loading can also give the corresponding coupling products in high yields.

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1. Introduction

Transition metal-catalyzed cross-coupling reactions are versatile methods for the formation of C–C bonds [1,2]. Among them, the Suzuki–Miyaura reactions play important roles in modern synthetic chemistry [3–11]. A great number of catalytic systems have been developed for the coupling of aryl bromides and iodides with arylboronic acids as well as aryl chlorides, which are attractive substrates because of their low cost and wide availability, though they are relatively unreactive compared to bromides and iodides [12,13]. Introduction of sterically bulky, electron-rich ligands in the transition metal center will enhance the catalyst performance in both of the oxidative addition and reductive elimination steps [11,14–19]. It is reported that *N*-heterocyclic carbenes (NHCs) are a very important class of ligands because of their strong σ -donor and poor π -acceptor abilities [20–27]. By far, several air-stable and well-defined monocoordinated NHC–Pd(II) complexes derived from IPr , and IMes , etc., have been developed and been established to be highly efficient catalysts in various cross-coupling reactions, mainly contributed from Beller [28–30], Nolan [21], Cloke [31–33]

and Organ [16,18], et al. [34–37]. Recently, we reported the synthesis of a novel type of NHC–palladium chloride–imidazole [NHC–Pd(II)–Im] complexes **1** derived from PdCl_2 , IPr^*HCl or IMes^*HCl and 1-methylimidazole. In addition, we found that these complexes showed efficient catalytic activity toward amination reactions between secondary amines and aryl chlorides (Scheme 1) [38]. These results prompted us to further investigate other applications of these complexes in organic synthesis. In continuing investigations, we found that the NHC–Pd(II)–Im complexes **1** showed high activity in the Suzuki–Miyaura coupling of aryl chlorides at room temperature [39–49]. Herein, we wish to report these results in detail.

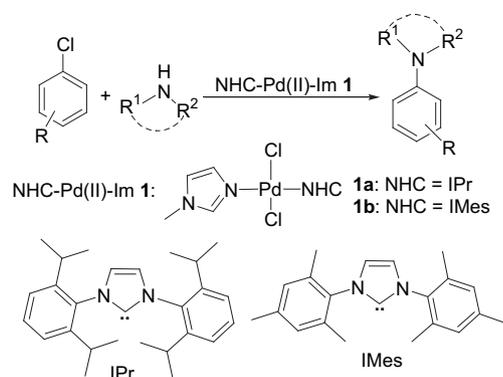
2. Experimental

2.1. General remarks

^1H and ^{13}C NMR spectra were recorded on Bruker AV-II 300 MHz and Bruker AV-III 500 MHz spectrometer for solution in CDCl_3 with tetramethylsilane (TMS) as an internal standard; *J*-values are in Hz. THF, DME and toluene were distilled from sodium (Na) under nitrogen (N_2) atmosphere. Commercially obtained reagents were used without further purification. Flash column chromatography was carried out using Huanghai 300–400 mesh silica gel at increased pressure.

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Scheme 1. NHC–Pd(II)–Im complexes catalyzed aminations of aryl chlorides.

2.2. General procedure for the complex **1a**-catalyzed Suzuki–Miyaura coupling reaction

(If aryl chloride is liquid) under N_2 atmosphere, arylboronic acid **3** (0.6 mmol), **1a** (1.0 mol%), $K_3PO_4 \cdot 3H_2O$ (2.0 equiv), H_2O (2.0 mL), and THF (1.0 mL) were added into a Schlenk reaction tube, then aryl chloride **2** (0.5 mmol) was added. The mixture was stirred at room temperature for 24 h. Then the mixture was extracted with EtOAc, dried over anhydrous Na_2SO_4 , filtered and purified by flash column chromatography to give the pure products.

(If aryl chloride is solid) under N_2 atmosphere, aryl chloride **2** (0.5 mmol), arylboronic acid **3** (0.6 mmol), **1a** (1.0 mol%), $K_3PO_4 \cdot 3H_2O$ (2.0 equiv), H_2O (2.0 mL), and THF (1.0 mL) were added into a Schlenk reaction tube. The mixture was stirred at room temperature for 24 h. Then the mixture was extracted with EtOAc, dried over anhydrous Na_2SO_4 , filtered and purified by flash column chromatography to give the pure products.

3. Results and discussion

Initial examinations were carried out using chlorobenzene **2a** (0.5 mmol) and 4-methoxyphenylboronic acid **3a** (1.2 equiv) as the substrates in the presence of complex **1a** (1.0 mol%) at room

Table 1
Optimization for the reaction of **2a** with **3a** catalyzed by complexes **1**.

Entry ^a	Cat.	Base	Solvent (mL)	Yield (%) ^b
1	1a	$K_3PO_4 \cdot 3H_2O$	H_2O (2)	—
2	1a	$K_3PO_4 \cdot 3H_2O$	THF (2)	<5
3	1a	$K_3PO_4 \cdot 3H_2O$	H_2O/THF (2/1)	95
4	1a	KO ^t Bu	H_2O/THF (2/1)	16
5	1a	K_2CO_3	H_2O/THF (2/1)	54
6	1a	KOH	H_2O/THF (2/1)	81
7	1a	$KHCO_3$	H_2O/THF (2/1)	33
8	1a	$K_3PO_4 \cdot 3H_2O$	H_2O/DME (2/1)	31
9	1a	$K_3PO_4 \cdot 3H_2O$	$H_2O/Toluene$ (2/1)	—
10	1a	$K_3PO_4 \cdot 3H_2O$	$H_2O/EtOH$ (2/1)	36
11	1a	$K_3PO_4 \cdot 3H_2O$	$H_2O/iPrOH$ (2/1)	74
12	1b	$K_3PO_4 \cdot 3H_2O$	H_2O/THF (2/1)	74

^a All reactions were carried out using **2a** (0.5 mmol), **3a** (1.2 equiv), base (2.0 equiv), **1** (1.0 mol%) in the listed solvent at room temperature for 24 h.

^b Isolated yields.

temperature for 24 h. Preliminary results showed that the solvents used dramatically affect the reaction. For example, with $K_3PO_4 \cdot 3H_2O$ (2.0 equiv) as the base, almost no reaction occurred when H_2O or THF alone was used as the solvent, respectively (Table 1, entries 1 and 2). To our pleasure, when the combination of H_2O and THF (2.0/1.0 mL) was used, high yield of the corresponding coupling product **4a** was obtained (Table 1, entry 3). Further screening of bases showed that $K_3PO_4 \cdot 3H_2O$ was the best one (Table 1, entries 4–7). With other solvents screened, all did not give the yields as good as that of H_2O/THF (Table 1, entries 8–11). Complex **1b** gave inferior result for the same reaction (Table 1, entry 12).

The scope of this reaction was then investigated under the optimal conditions (Table 1, entry 3) and the results are summarized in Table 2. We were delighted to find out that a range of chlorides **2** and boronic acids **3** can be coupled to give the products **4** in good to high yields at room temperature. The functional groups in both of the substrates of aryl chlorides and arylboronic acids almost have no effect on the generality of this reaction. For example, functional groups as formyl group, acetyl group and nitro group can be tolerant in these reactions (Table 2, entries 11–13).

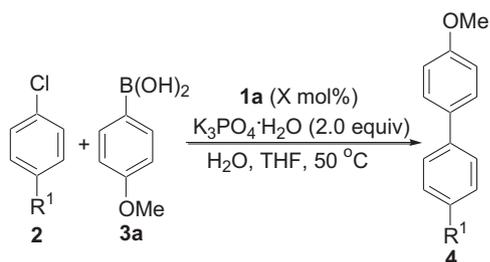
Table 2
Complex **1a** catalyzed coupling reactions of aryl chlorides **2** with boronic acids **3** under the optimized conditions.

Entry ^a	2 (R ¹)	3 (R ²)	Yield (%) ^b
1	2b (4-OMe)	3b (H)	4a , 90
2	2b	3c (4-Me)	4b , 86
3	2b	3d (2-Me)	4c , 99
4	2b	3e (3-Me)	4d , 87
5	2b	3f (3,5-Me ₂)	4e , 80
6	2b	3g (4-F)	4f , 99
7	2c (4-Me)	3a (4-MeO)	4b , 92
8	2d (3-Me)	3a	4d , 99
9	2e (2-Me)	3a	4c , 99
10	2f (3-OMe)	3b	4g , 96
11	2g (4-CHO)	3b	4h , 99
12	2h (4-Ac)	3b	4i , 99
13	2i (4-NO ₂)	3b	4j , 99
14	2j (2,6-Me ₂)	3d	4k , 99
15	2j	3h	4l , 96
16	2b	3i	4m , 85
17	2b	3h	4n , 99
18	2e	3h	4o , 95
19	2b	3j	4p , 97
20	2k	3a	4q , 99

^a All reactions were carried out using **2** (0.5 mmol), **3** (1.2 equiv), **1a** (1.0 mol%), $K_3PO_4 \cdot 3H_2O$ (2.0 equiv), H_2O (2.0 mL), THF (1.0 mL) at room temperature for 24 h.

^b Isolated yields.

Table 3
Varied loading of NHC–Pd(II)–Im **1a** for the Suzuki–Miyaura reactions.



Entry	2 (R ¹)	[X]	Time (h)	Yield (%) ^c
1 ^a	2a (H)	0.1	12	4a , 99
2 ^b	2a	0.01	24	4a , 96
3 ^a	2c (Me)	0.1	12	4b , 88
4 ^b	2c	0.01	24	4b , 84

^a Reaction conditions: **2** (5.0 mmol), **3a** (1.2 equiv), **1a** (0.1 mol%), K₃PO₄·3H₂O (2.0 equiv), N₂, 50 °C, 12 h.

^b Reaction conditions: **2** (20.0 mmol), **3a** (1.2 equiv), **1a** (0.01 mol%), K₃PO₄·3H₂O (2.0 equiv), N₂, 50 °C, 24 h.

^c Isolated yields.

Sterically hindered substrate such as 2,6-dimethylchlorobenzene **2j** was also found to be a suitable substrate and very high yields of the corresponding products **4k** and **4l** were obtained, respectively (Table 2, entries 14 and 15). 1-Naphthylboronic acid **3h**, as well as 2-naphthylboronic acid **3i**, was also found to be a suitable substrate for the coupling with 2,6-dimethylchlorobenzene **2j**, 4-methoxyphenyl chloride **2b** and 2-methylphenyl chloride **2e** (Table 2, entries 15–18). Reactions involving heteroaryl boronic acid such as 3-furylboronic acid **3j** (Table 2, entry 19) and heteroaryl chloride such as 2-chloro-pyridine **2k** (Table 2, entry 20) also gave very high yields.

Once the catalytic activities of the NHC–Pd(II)–Im complex **1a** in the Suzuki–Miyaura coupling reactions of aryl chlorides with arylboronic acids was ascertained, we then investigated the influence of the mol% on the activity. Using K₃PO₄·3H₂O as the base, 0.1 mol% and 0.01 mol% NHC–Pd(II)–Im complex **1a** were used for the reactions of chlorobenzene **2a** and 4-methylphenyl chloride **2c** with 4-methoxyphenylboronic acid **3a** at 50 °C, respectively (Table 3). Almost no effect on the yields was observed when the mol% of Pd catalyst was decreased from 1.0 to 0.1 to 0.01 mol% for the reaction of chlorobenzene **2a** with 4-methoxyphenylboronic acid **3a** (Table 3, entries 1 and 2 vs Table 1, entry 3). Comparable yields were obtained when the mol% of Pd catalyst was decreased from 1.0 to 0.1 to 0.01 mol% for the reaction of 4-methylphenyl chloride **2c** with 4-methoxyphenylboronic acid **3a** at 50 °C (Table 3, entries 3 and 4 vs Table 2, entry 7). It should also be noted here that large-scale couplings (20.0 mmol) were achieved with 0.01 mol% catalyst loading in comparable yields (Table 3, entries 2 and 4), which make the reactions suitable toward an industrial level.

4. Conclusion

In conclusion, well-defined NHC–Pd(II)–Im complexes derived from readily available starting materials as IPr⁺HCl or IMes⁺HCl, PdCl₂ and 1-methylimidazole showed high catalytic activity in the Suzuki–Miyaura coupling reactions of aryl chlorides at room temperature. Under optimal conditions, the corresponding coupling products can be achieved in good to high yields. Furthermore, the reactions with the catalyst loading down to 0.01 mol% were also successfully achieved in comparable yields.

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Appendix. Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2011.08.042. These data include MOL files and InChIKeys of the most important compounds described in this article.

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