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Carbene adduct of cyclopalladated ferrocenylimine: Efficient catalyst for the Suzuki coupling of sterically hindered aryl chlorides with a weaker base and low catalyst loading

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ABSTRACT

One-pot synthesis of the *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) adduct of cyclopalladated ferrocenylimine complex **1** has been described. This complex has been successfully applied to Suzuki coupling reaction. Various aryl chlorides and boronic acids can be coupled efficiently with a mild base $K_3PO_4 \cdot 7H_2O$ and low catalyst loadings. This system has been proven to be compatible with the sterically hindered aryl chlorides and some boronic acids leading to form di- and tri-*ortho*-substituted biaryls in high yields.

1. Introduction

The use of *N*-heterocyclic carbenes (NHCs) as ligands has led to an array of exciting developments in Pd-catalyzed cross-coupling reactions [1–4]. Compared to the traditional phosphine ligands, the NHCs not only have the same σ-donor and exhibit low π-acceptor ability as phosphine in terms of their metal coordination chemistry [5,6] but also have unique virtues, such as ready preparation, air and moisture stability, nontoxicity, low loading and high efficiency [7,8]. Therefore, the transition-metal carbene complexes have been applied in a variety of catalytic reactions [9–16].

The Suzuki–Miyaura reaction offers a powerful and general methodology for the construction of C–C bonds and is perhaps the most widely used transition-metal-mediated cross-coupling reaction today. It has been applied to the syntheses of polymers, materials, liquid crystals, pharmaceutical compounds and natural products [17–20]. However, some of the challenges associated with cross-coupling reactions have focused on the use of "unreactive" aryl chlorides as coupling partners in view of their attractive cost and readily available diversity [21]. Another challenge is to achieve cross-coupling under optimum conditions for highly hindered biaryl junctures such as poly-*ortho*-substituted biaryls [22].

With the renaissance and flourishing of the nucleophilic carbenes, a number of palladium *N*-heterocyclic carbene systems have been employed for the Suzuki–Miyaura reaction with great success. It is worth noting that recently the groups of Herrmann [23,24], Nolan [25–30], Beller [31], Sigman [32] and Organ [33,34] have published an array of highly active *N*-heterocyclic carbene catalysts for this reaction. However, most of the NHCs ligands reported so far usually have had at least one of the following limitations: (1) strong or expensive bases, such as ^{t}BuOK, ^{t}BuONa, Cs_2CO_3 and CsF, were generally used in the case of aryl chlorides as substrate; (2) only a few reports on the coupling of sterically hindered aryl chlorides with arylboronic acids to generate di- or tri-*ortho* substituted biaryls have been published [22,26,30]; (3) higher loading of catalyst (1–3 mol% was used).

Over the past decade, part of our research effort has focused on the synthesis and application of cyclopalladated ferrocenylimines [35]. Very recently, we have reported that catalyst **1** was an effective catalyst for the Buchwald–Hartwig amination of aryl chlorides [36]. To circumvent the above-mentioned limitations in carbene complex catalyzed Suzuki reaction, we investigated the efficiency of catalyst **1** for the Suzuki reaction. To our delight, catalyst **1** was able to catalyze Suzuki reaction with a weaker base and low catalyst loading within a short reaction time, and even the sterically hindered aryl chlorides was also successfully coupled.

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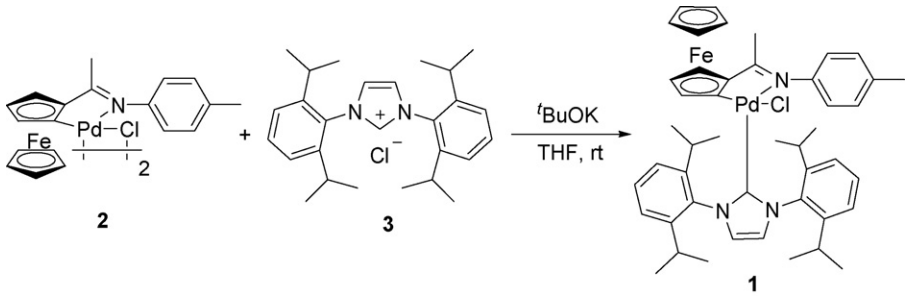


Scheme 1. Synthesis of compound **1**.

2. Experimental

2.1. General comments

Melting points were measured on a WC-1 microscopic apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer in $CDCl_3$ with TMS as an internal standard. Elemental analyses were conducted with a Carlo Erba 1160 elemental analyzer.

All the solvents were purified by the standard methods [37]. The chloride-bridged palladacyclic dimer [38] and imidazolium salt [39] were prepared according to the published procedures. The phenylboronic acid and 1-naphthylboronic acid were prepared according to the literature procedure [40]. The other arylboronic acids and aryl chlorides were obtained from commercial sources and used without purification.

2.2. Preparation of catalyst *1*

A mixture of **2** (0.5 mmol, 463 mg), **3** (1.2 mmol, 507 mg) and ^{t}BuOK (1.2 mmol, 135 mg) was charged in a Schlenk tube, after vacuuming, 10 mL THF was syringed to the flask and a red clear solution was obtained after the mixture was stirred at room temperature for 1 h. Upon completion, water was added to the reaction mixture and the mixture was extracted with dichloromethane. The solvent was removed by rotary evaporation and the crude material was purified by silica gel chromatography using ethyl acetate/petroleum ether. The complex was isolated as a red power (722 mg, yield 85%) and the characterizing data was consistence with those reported before [36].

2.3. General procedure for the Suzuki coupling reaction

In a typical reaction, a vial charged with aryl chloride (0.5 mmol), arylboronic acid (0.6 mmol), base $K_3PO_4{\cdot}7H_2O$ (1.5 mmol), catalyst **1** (0.1–0.5 mol%) and dioxane (1.5 mL) was put into a preheated oil bath for an appropriate period of time (2–3 h) under nitrogen. The reaction mixture was allowed to cool to room temperature and was quenched by filtering through a short silica column (eluent: ethyl acetate) and then concentrated under reduced pressure. After purification by flash chromatography (eluent: ethyl acetate/petroleum ether), the products were determined by ^{1}H NMR and ^{13}C NMR spectroscopy.

3. Results and discussion

3.1. Synthesis of catalyst *1*

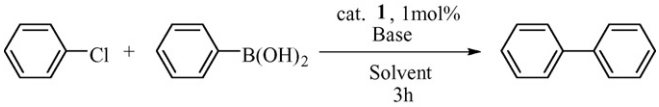
In our previous procedure for the preparation of catalyst **1** [36], the unstable carbene ligand was prepared first, which made the preparation of catalyst **1** inconvenient. Here we prepared catalyst **1** by a one-pot method by treatment imidazolium salt **3** with cyclopalladated ferrocenylimine **2** in THF at ambient temperature, and complex **1** was directly obtained in 85% yield after purification by column chromatography (Scheme 1).

3.2. Suzuki cross-coupling reactions

We initially investigated the effect of base and solvent on Suzuki reaction using chlorobenzene and phenylboronic acid as standard substrates (Table 1). As shown in Table 1, dioxane was the most effective solvent. Among bases, $K_3PO_4{\cdot}7H_2O$ was found to be the most effective in terms of conversion and price. The strong bases ^{t}BuOK and ^{t}BuONa, which were usually used in carbene complex catalyzed Suzuki reaction, just offered moderate yields. The probable reason is that the strong base resulted in the dehalogenation reaction [27].

Once the optimized base and solvent were selected, a survey of catalytic cross-coupling of various aryl chlorides with phenylboronic acid with lower catalyst loadings and short reaction time was conducted (Table 2). As shown in Table 2, both unactivated (Table 2, entries 2–4) and activated (Table 2, entries 7–10) aryl chlorides coupled smoothly with phenylboronic acid in short reaction time using 0.1–0.5 mol% catalyst **1**, which was lower compared to the common usage 1–3 mol% carbene complexes for aryl chlorides [22–24,33,34]. The low catalyst loading is important in the preparation of fine chemicals and pharmaceuticals which reduces the palladium residues in the products. Although Nolan's group [28] used 50 parts-per-million (ppm) (NHC)Pd(allyl)Cl catalyst in this reaction, a strong base ^{t}BuOK which can promote cleavage of some base-sensitive substrate was employed. Aryl chlorides with *ortho*-substituents have no deleterious effect in this reaction. Fur-

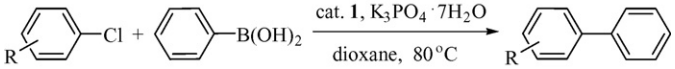
Table 1
Effect of the base and solvent on Suzuki–Miyaura cross-coupling reaction

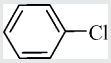
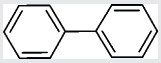
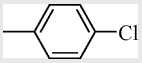
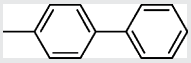
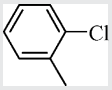
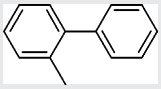
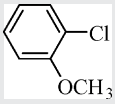
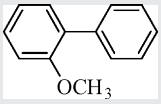
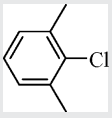
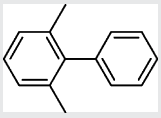
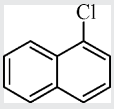
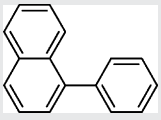
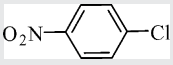
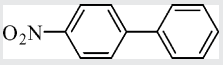
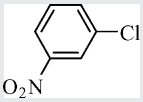
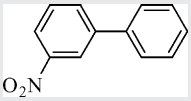
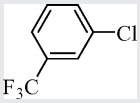
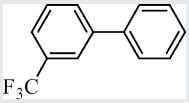
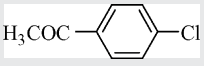
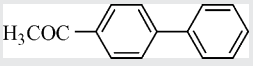


Entry[a]	Base	Solvent	Temperature (°C)	Yield (%)[b]
1	^{t}BuOK	Toluene	110	65
2	^{t}BuOK	THF	70	42
3	^{t}BuOK	Dioxane	80	75
4	^{t}BuOK	Methanol	70	47
5	^{t}BuONa	Dioxane	80	17
6	Cs_2CO_3	Dioxane	80	43
7	$KF{\cdot}2H_2O$	Dioxane	80	8
8	$K_3PO_4{\cdot}7H_2O$	Dioxane	80	98
9	KOH	Dioxane	80	55

[a] Reaction conditions: chlorobenzene, 0.5 mmol; phenylboronic acid, 0.6 mmol; base, 1.5 mmol; solvent, 1.5 mL.
[b] Isolated yields based on chlorobenzene.

Table 2
Suzuki–Miyaura cross-coupling of aryl chlorides with phenylboronic acid



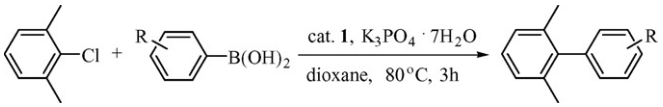
Entry[a]	Aryl Chloride	Product	mol% Pd	Time (h)	Yield (%)[b]
1			0.5	2	98
2			0.5	2	94
3			0.5	2	100
4			0.5	2	99
5			0.5	2	100
6			0.5	3	96
7			0.1	2	91
8			0.1	2	98
9			0.1	2	99
10			0.1	2	85

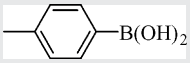
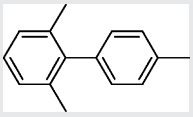
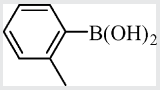
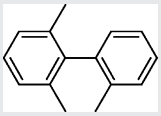
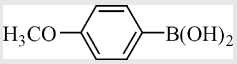
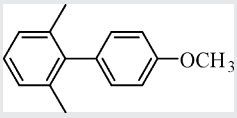
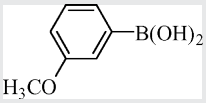
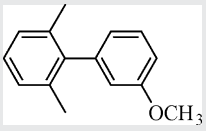
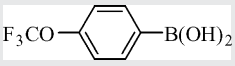
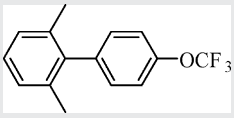
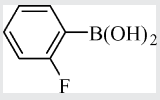
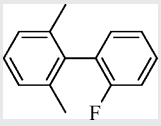
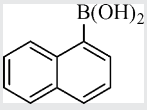
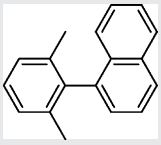
[a] Reaction conditions: aryl chloride, 0.5 mmol; phenylboronic acid, 0.6 mmol; $K_3PO_4 \cdot 7H_2O$, 1.5 mmol; dioxane, 1.5 mL.
[b] Isolated yields based on aryl chloride of two runs.

thermore, it should be pointed out that sterically encumbering *ortho*-substituents on the aryl chlorides afforded slightly higher isolated yields (Table 2, entries 3–6).

Ortho-substituted biaryls are important substructures of biologically active compounds and organic functional materials [41–43]. Only a few groups reported the coupling of sterically hindered aryl chlorides with boronic acids to form *ortho*-substituted biaryls by using phosphine [44,45] or carbene ligands [28,46]. Encouraged by the results of *ortho*-substituted aryl chlorides that offered higher yields in this reaction (Table 2, entries 3–6), we carried out reactions of much sterically hindered substrate 2-chloro-*m*-xylene with various arylboronic acids (Table 3). Gratifyingly, complex **1** was proved to be an excellent catalyst for the synthesis of sterically hindered biaryls in good to excellent yields. Even 1-naphthylboronic acid coupled with 2-chloro-*m*-xylene to afford 80% isolated yield (Table 3, entry 7). Many different substituents on the arylboronic acid, including methyl, methoxy, trifluromethoxy, fluoro and naphthyl can be accommodated.

Table 3
Suzuki cross-coupling of 2-chloro-*m*-xylene with various arylboronic acids



Entry[a]	Arylboronic acid	Product	Yield (%)[b]
1			99
2			82
3			99
4			83
5			99
6			95
7			80

[a] Reaction conditions: 2-chloro-*m*-xylene, 0.5 mmol; arylboronic acid, 0.6 mmol; catalyst **1**, 0.5 mol%; $K_3PO_4{\cdot}7H_2O$, 1.5 mmol; dioxane, 1.5 mL.
[b] Isolated yields based on aryl chloride of two runs.

4. Conclusions

In summary, the conveniently synthesized complex **1** was an efficient mediator for Suzuki couplings of various aryl chlorides and boronic acids with mild base $K_3PO_4{\cdot}7H_2O$ and low catalyst loadings. Sterically hindered unactivated aryl chlorides coupled with various arylboronic acids under these conditions leading to form di- and tri-*ortho*-substituted biaryls in high yields.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcata.2008.05.001.

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