

Short communication

Highly efficient and stable palladium/imidazolium salt-phosphine catalysts for Suzuki–Miyaura cross-coupling of aryl bromides

Ji-Cheng Shi^{a,b,*}, Peng-Yu Yang^a, Qingsong Tong^b, Yang Wu^b, Yiru Peng^b

^a State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China

^b College of Chemistry and Materials Science, Fujian Normal University, Fuzhou 350007, China

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Abstract

A robust palladium catalyst system supported by the hybrid ligand *N*-heterocyclic carbene along with a phosphine derived from ferrocene has been discovered for the Suzuki cross-coupling reaction. This novel system effectively catalyzes the cross-coupling of aryl bromides and phenylboronic acid with up to 20,000 TONs and 10,000 h⁻¹ TOFs to produce biaryl products in excellent yields.

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Keywords: Cross-coupling; Palladium; *N*-Heterocyclic carbene; Phosphine; Biaryl

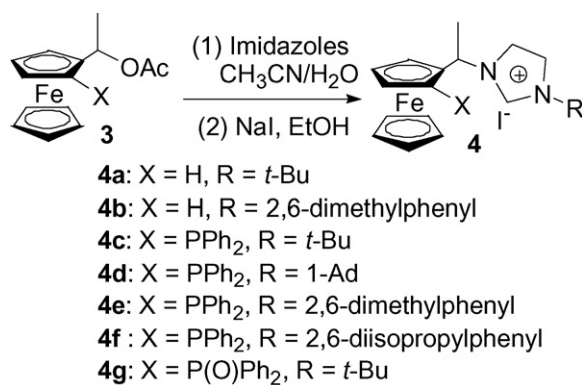
The Suzuki–Miyaura cross-coupling reaction is an efficient method for the preparation of biaryl compounds [1]. It has been applied to the syntheses of polymers, materials, liquid crystals [2], pharmaceutical compounds and natural products [3]. Initially, arylphosphines were used as ligands for palladium-catalyzed reactions [4]. Recently, two classes of compounds have been reported as more efficient ligands: the monodentate, bulky and electron-donating tertiary phosphines [5], and the nucleophilic *N*-heterocyclic carbene (NHC) derivatives [6]. The application of the NHC ligand to the palladium-catalyzed Suzuki–Miyaura cross-coupling was first reported by Herrmann in 1998 [7]. Subsequently, palladium complexes of some NHCs, such as 1,3-bisadamantylimidazol-2-ylidene (**1**) [8a] and 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (**2**) [8b], were found to be highly active catalyst systems for coupling reactions using aryl chlorides at room temperature [9]. However, these NHCs ligands have two major drawbacks: (1) the loading of palladium catalyst is relatively high [8,9]; (2) some of the catalysts were unstable, resulting in the precipitation of palladium black even under mild reaction conditions [8a]. Therefore, it is desirable to develop a new NHC–palladium catalyst system that is both highly active and stable under the reaction conditions.

It is believed that the high catalytic activities of palladium catalysts using the *N*-heterocyclic carbenes **1** and **2** as ligand arise from their strong σ -donating character and their bulkiness. The severe steric demanding of the ligands **1** and **2** makes a 12-electron Pd⁽⁰⁾ species possible. The electron richness and the readily available coordination sites of the 12e species greatly facilitate the oxidative addition of palladium to aromatic chlorides. The high reactivity of 12e Pd⁽⁰⁾ species, however, may be also responsible for the instability of catalysts and the side reactions via β -H elimination. Theoretical calculations indicated that certain bidentate chelating ligands could improve the stability of catalyst, and favor the oxidative-addition process [10]. Hybrid *N*-heterocyclic carbene-phosphines are one type of the bidentate ligands [11]. A few examples using such ligands were applied to the Heck reaction and the Suzuki–Miyaura reaction by Nolan [11e] and Zhou [11f]. Herein we present our preliminary results in developing such a highly active and stable palladium catalysts supported by *N*-heterocyclic carbenes for the Suzuki–Miyaura reaction.

In the palladium-catalyzed cross-coupling, the proper bite angle (around 102°) induced by chelating ligands plays a crucial role on the activity and selectivity [12]. Josiphos derived from the ferrocenyl derivatives [13] **3** (X = PR₂) ligating to palladium with a proper bite angle exhibits excellent performance on the palladium-catalyzed cross-coupling for C–N formation [14]. We envisioned that compound **4** could be a good precursor for the NHC carbene bidentate ligand. The readily available

* Corresponding author. Tel.: +86 591 8346 5225.

E-mail address: jchshi@fjnu.edu.cn (J.-C. Shi).



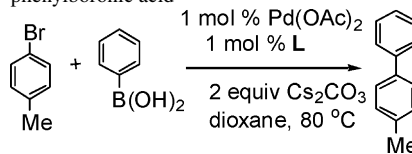
Scheme 1. Phosphine-functionalized imidazolium salts.

racemic ferrocenyl derivative **3** can be easily converted to imidazolium salt **4** in high yield [11d]. Compound **4**, a precursor of carbene, provided us a good module for the development of a stable and highly active catalyst system (Scheme 1). The scaffold of imidazolium **3** should result in a type of hybrid ligands **4c–h** with a proper bite angle of the chelating carbene-phosphine to palladium [15]. In addition, the degree of steric hindrance of the synthesized imidazolium salts can be finely tuned through the size of the substituents on the imidazoles used. For confirming the chelating effect, the imidazolium salts without a side arm (**4a** and **4b**) and with non-coordinated side arm were also synthesized (**4g**).

First, we tested the newly synthesized imidazolium salts as a ligand with Pd(OAc)₂ for the cross-coupling reaction between 4-bromotoluene and phenylboronic acid using dioxane as solvent, Cs₂CO₃ as base, and at 80 °C [16]. Using imidazolium salts **4a** and **4b** without a phosphine side arm, the coupling reaction produced, after 3 h, the desired product in 62–72% of yields as determined by GC (Table 1, entries 1 and 2). No further conversion of 4-bromotoluene with extension of reaction time and appearance of palladium black indicated the decomposition of the catalyst supported by unidentate imidazol-2-ylidene derived from **4a** and **4b** [17]. Employing a reaction protocol based the reported conditions [16], in which the Pd/L ratio is 1:2, did not increase the conversion significantly. To our delight, with phosphine side arm, the imidazolium salts **4c**, **4d**, and **4e** not only significantly increased the stability of the catalyst but also enhanced the rate of the reaction, resulting in complete conversions of 4-bromotoluene with 94–97% of isolated yields (Table 1, entries 3–5). It should be mentioned that the size of the substituent introduced from the imidazole also plays a steric role in the catalytic performance to some extent. For example, with 2,6-diisopropylphenyl substitute (**4f**), the conversion

Table 1

Ligand effect in Suzuki–Miyaura cross-coupling of 4-bromotoluene with phenylboronic acid^a



Entry	Ligand	Time (h)	Conversion ^b (%)	Yield ^c (%)
1	4a	6	62	/
2	4b	6	72	/
3	4c	1	>99	96
4	4d	1.5	>99	94
5	4e	1.5	>99	97
6	4f	3	90	85
7	4g	6	56	/
8	5	1	>99	95

^a Reaction conditions: 1.0 mmol of 4-bromotoluene, 1.5 mmol of phenylboronic acid, 2.0 mmol of Cs₂CO₃, 1.0 mol% Pd(OAc)₂, 1.0 mol% ligand, 2 mL of dioxane, 80 °C.

^b GC yield.

^c Isolated yield.

of 4-bromotoluene was not completed even after 3 h. As the phosphine was oxidized to phosphine oxide, the performance of the imidazolium salt **4g** was similar to that of the imidazolium salts **4a** and **4b** without a side arm, implying the contribution of chelating effect to the stability of the catalyst system. For comparison, the palladium complex **5** (Scheme 2) was also synthesized and tested for the reaction; its catalytic activity (Table 1, entry 8) is comparable to that formed in situ. Since two steps were needed to prepare the complex **5**, most of catalytic studies were carried out using the catalysts formed in situ. It should be noted that, with the prepared catalyst or once the catalyst formed in situ, the coupling reaction can be carried out under air and no visible changes of the performance of the palladium catalyst were observed.

A brief study of the influence of the base indicated that a range of bases are suitable for the catalyst system. In dioxane, potassium carbonate, sodium hydroxide, sodium *tert*-butoxide are as effective as cesium carbonate (Table 2, entries 1, 4, 5 and 6), although 1–3 h of longer reaction time was needed to completely consume 4-bromotoluene. In turn, KF, a very effective additive for *N*-heterocyclic carbenes, proved to be less effective in our case, supporting 70% of conversion (Table 2, entry 9). Other bases such as lithium carbonate, sodium carbonate, sodium acetate, potassium acetate, and potassium phosphate proved to be inefficient for coupling 4-bromotoluene with phenylboronic acid. Various solvents, such as THF, DME, and

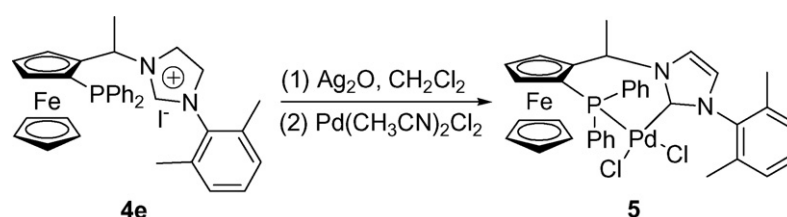
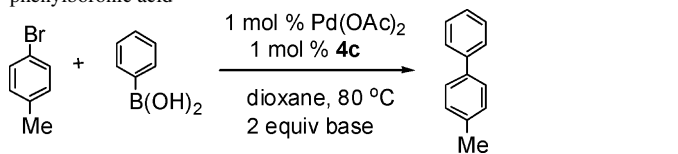
Scheme 2. Synthesis of the palladium complexes **5**.

Table 2

Effect of base on Pd(OAc)₂/**4c**-catalyzed cross-coupling of 4-bromotoluene with phenylboronic acid^a

Entry	Base	Time (h)	Conversion ^b (%)	Yield ^c (%)
1	Cs ₂ CO ₃	1	>99	97
2	Li ₂ CO ₃	20	<2	/
3	Na ₂ CO ₃	24	28	/
4	K ₂ CO ₃	2	>99	96
5	NaOH	3	98	93
6	NaOBu ^t	2	98	95
7	NaOAc	20	<2	/
8	KOAc	20	<5	/
9	KF	4	70	/
10	K ₃ PO ₄	20	11	/
11	Et ₃ N	24	<2	/
12	Hunig's base	24	<2	/

^a Reaction conditions: 1.0 mmol of 4-bromotoluene, 1.5 mmol of phenylboronic acid, 2.0 mmol of base, 1.0 mol% Pd(OAc)₂, 1.0 mol% ligand, 2 mL of dioxane, 80 °C.

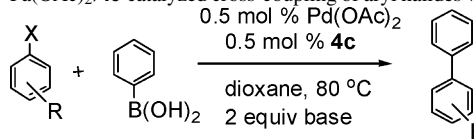
^b GC yield.

^c Isolated yield.

to some extent toluene, are also suitable for the catalyst system. Pd(CH₃CN)₂Cl₂ [(C₃H₅)PdCl]₂ (C₃H₅ = allyl) were all good alternative Pd sources for Pd(OAc)₂. However, no reaction was observed with Pd₂(dba)₃.

As shown in Table 3, the procedure employing the 0.5 mol% of Pd(OAc)₂/**4c** system is extremely effective in coupling of a wide range of aryl bromides with phenylboronic acid. Sterically congested substrates also led to excellent yields (entries 4, 7, 8 and 10). As expected, nitrile and keto functional groups were found to be compatible under these reaction conditions (entries 5, 6 and 8). In fact, good yields could be obtained from the deac-

Table 3

Pd(OAc)₂/**4c**-catalyzed cross-coupling of aryl halides with phenylboronic acid^a

Entry	Aryl halide	Time (h)	Conversion (%) ^b	Yield (%) ^c
1	Bromobenzene (6a)	2	>99	94
2	4-Bromotoluene (6b)	2	>99	96
3	3-Bromotoluene (6c)	2	>99	93
4	2-Bromotoluene (6d)	6	>99	95
5	4-Bromobenzotrifluoride (6e)	2	>99	93
6	4-Bromoacetophenone (6f)	2	>99	97
7	4-Bromo- <i>m</i> -xylene (6g)	2	90	85
8	2-Bromobenzonitrile (6h)	2	>99	95
9	4-Bromoanisole (6i)	2	>99	94
10	2-Bromopyridine (6j)	12	92	85
11 ^d	4-Chlorobenzotrifluoride	24	90	81
12 ^d	4-Chloroacetophenone	24	83	76
13 ^d	2-Chlorobenzonitrile	24	85	77

^a Reaction conditions: 1.0 mmol of aryl halide, 1.5 mmol of phenylboronic acid, 2.0 mmol of K₂CO₃, 0.5 mol% Pd(OAc)₂, 0.5 mol% ligand **4c**, 2 mL of dioxane, 80 °C.

^b Determined by GC.

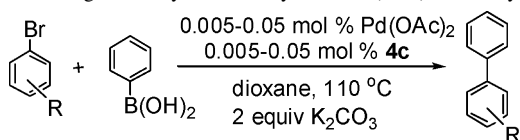
^c Yields for isolated products of >95% purity judged by ¹H NMR.

^d 2.0 mol% of catalyst, 2 equiv. of Cs₂CO₃, 110 °C.

activated 4-bromoanisole as substrate (entry 9) [18]. Furthermore, activated aryl chlorides can also couple with phenylboronic acid in high yields although 2 mol% of the catalyst system was required. In all cases examined, only traces of homocoupling and dehalogenation product were found (<2%).

The efficiency of the Pd(OAc)₂/**4c** catalyst system in the Suzuki–Miyaura reaction was further evaluated and the results are summarized in Table 4. For the coupling of bromobenzene (**6a**), 4-bromotoluene (**6b**), and 3-bromotoluene (**6c**) with phenylboronic acid in dioxane, the catalyst could be decreased

Table 4

Screening the catalytic efficiency of the Pd(OAc)₂/**4c** catalyst system for the Suzuki–Miyaura reaction^a

Entry	ArBr	Pd (mol%)	Time (h)	Conversion (%)	Yield (%) ^b	Tonnes
1	6a	0.005	24	>99	99	20000
2 ^c	6a	0.005	2	>99	99	20000
3	6b	0.005	24	>99	99	20000
4	6c	0.005	24	>99	99	20000
5	6d	0.025	16	>99	99	4000
6	6g	0.025	16	>99	99	4000
7	6i	0.05	24	92	90	1840
8	6j	0.025	24	99	98	3960

^a Reaction conditions: aryl bromide (1.0 equiv.), phenylboronic acid (1.5 equiv.), K₂CO₃ (2.0 equiv.), Pd(OAc)₂ (0.005 mmol), **4c** (0.005 mmol), dioxane/aryl bromides (2 mL/mmol), 110 °C.

^b Yields for isolated products of >95% purity judged by ¹H NMR.

^c In 95% aqueous ethanol, at refluxing.

to 0.005 mol% and almost quantitative yields could be obtained at 110 °C (Table 4, entries 1, 2 and 3), corresponding to 20,000 TONs. However, the efficiencies of the Pd(OAc)₂/4c catalyst system decreased to some extent for the substrates with steric hindrance. For example, 0.025 mol% of the catalyst was required to reach 100% of conversion for the substrates with one *ortho*-methyl substituent (Table 4, entries 5 and 6). High TONs could also be achieved for the deactivated 4-bromoanisole with 92% of conversion (Table 4, entry 7) and for the heterocyclic substrate (Table 4, entry 8).

Gratified by the low loading of the Pd(OAc)₂/4c catalyst, we tested the coupling of 4-bromotoluene with phenylboronic acid in 95% aqueous ethanol, which is a cheaper and environmentally benign solvent for industry, particularly for the pharmaceutical industry. Thus, with a 0.005 mol% loading of Pd(OAc)₂/4c, a complete conversion of 4-bromotoluene with 99% yield was realized within 2 h in refluxing in 95% aqueous ethanol (Table 4, entry 2). The data indicated that the TOFs is as high as ~10,000 h⁻¹ (average) in the condition of complete conversion.

In summary, we have developed a novel and robust palladium catalyst system supported by the hybrid ligand *N*-heterocyclic carbene along with a phosphine derived from ferrocene. In the course of the study, we have applied successfully the chelating effect, the bite angle, and the steric hindrance to the design of the novel bitendate ligand. This type of bidentate ligand is not only very active but also very stable under the reaction conditions with TONs up to 20,000 and TOFs to 10,000 h⁻¹. A wide range of bases and solvents are suitable for the catalyst system. We have found that the chelating effect is a promising tool for developing highly stable palladium/*N*-heterocyclic carbene catalysts for the Suzuki–Miyaura cross-coupling, although the activity of the present catalyst system toward arylchlorides is still low. Investigation of labile coordinating atoms *cis* to *N*-heterocyclic carbene, aiming at increasing the activity toward arylchlorides and retaining the stability, is underway.

1. Experimental

1.1. Suzuki–Miyaura cross-coupling of aryl halides with phenylboronic acid: general procedure

In air, imidazolium salt (0.005 mmol), Pd(OAc)₂ (0.005 mmol) and K₂CO₃ (2.0 mmol) were added to an oven-dried Schlenk tube equipped with a stir bar. The Schlenk tube was fitted with a rubber septum, evacuated, and then refilled with nitrogen. 1,4-Dioxane (1.0 mL) was added via syringe. The mixture was stirred for 30 min at room temperature. Then aryl halide (1.0 mmol), phenylboronic acid (1.5 mmol), undecane (0.5 mmol) and again 1,4-dioxane (1.0 mL) were added. The tube was sealed and immersed in oil bath at 80 °C and the course of the reaction was monitored by GC. After being quenched, and the reaction mixture was diluted with ether, filtered through a pad of silica gel with copious washings, concentrated, and purified by column chromatography.

Acknowledgments

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