Highly Efficient Suzuki Cross-Coupling Catalyzed by Palladium/Phosphine-Imidazolium Carbene System

Ai-E Wang, Jun Zhong, Jian-Hua Xie, Kai Li, Qi-Lin Zhou*

Sate Key Laboratory and Institute of Elemento-organic Chemistry, Nankai University, Tianjin 300071, P. R. China
Fax: (+86)-22-2350-6177, e-mail: qlzhou@nankai.edu.cn

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Abstract: Novel phosphine-imidazolium salts **2** have been synthesized and successfully used in palladium-catalyzed Suzuki cross-coupling. A combination of 0.05 mol % of $[Pd(\eta\text{-}C_3H_5)Cl]_2$ and 0.1 mol % of **2b** in the presence of 2 equivs. of K_3PO_4 as base provided coupling products in excellent yields in the reaction of aryl bromides and chlorides with aryl boronic acids.

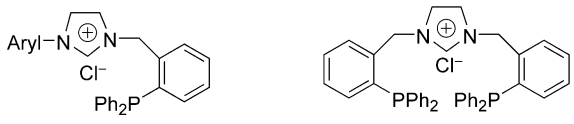
Keywords: carbene ligands; functionalized phosphane ligands; imidazolium salts; *N*-heterocyclic carbenes; palladium; Suzuki cross-coupling

Since the first isolation and X-ray characterization of a stable imidazol-2-ylidene in 1991,[1] nucleophilic *N*-heterocyclic carbenes (NHC's) and their transition metal complexes have attracted much attention.[2] With the pronounced σ-donating but very weak π-accepting properties,[3] NHC's resemble conventional phosphine ligands.[4] Owing to the high stability of the metal complexes of NHC's toward heat, moisture and oxygen, significant improvements have been achieved by replacing phosphine ligands with nucleophilic carbenes in various catalytic reactions, such as amination of aryl chlorides,[5] olefin metathesis,[6] and hydrogenations.[7]

The palladium-mediated cross-coupling of arylboronic acid with aryl halides, the Suzuki reaction, is a versatile and highly useful method for the synthesis of biaryl-containing molecules.[8] With the renaissance and flourishing of the nucleophilic carbenes, a number of palladium/*N*-heterocyclic carbene systems have been employed in this process with great success.[9] Most of them used pre-prepared palladium-imidazol-2-ylidene complexes as catalysts. There were only a few examples using *in situ* formed palladium-NHC species from imidazolium salts and palladium sources in the presence of bases,[9c,e,f,k,l] and the carbenes used were usually monodentate NHC's with bulky groups at the imidazole ring. In addition, most reported functionalized NHC's had a nitrogen-donor such as pyridine, imine or oxazoline as a pendant group.[9,10] Phosphine-functionalized NHC's were rather rare,[11] with only one successful application in the Heck reaction reported by Nolan.[11c] We describe herein the synthesis of novel phosphine-functionalized imidazolium salts and their application in palladium-catalyzed Suzuki couplings of aryl bromides and activated chlorides.

Starting with benzaldehyde, *o*-(diphenylphosphino)-benzyl chloride (**1**) was prepared according to the reported method,[12] and reacted with various 1-substituted imidazoles in refluxing ethanol, giving the bidentate phosphine-imidazolium salts **2**. Using K_2CO_3 as the base, the tridentate phosphine-imidazolium salt **3** was obtained from 1*H*-imidazole and **1** (Scheme 1).

Preliminary studies with 4-bromotoluene and phenylboronic acid as the coupling partners revealed that the palladium complexes generated from $[Pd(\eta\text{-}C_3H_5)Cl]_2$ (0.25 mol %) and phosphine-imidazolium salts **2** (0.5 mol %) in the presence of Cs_2CO_3 were efficient catalysts in Suzuki coupling (Table 1, entries 1–3). The best result was obtained with **2b**, while the reaction with tridentate phosphine-imidazolium **3** required a longer time for completion. A control experiment without the imidazolium salt was carried out in order to confirm whether a nucleophilic carbene generated *in situ* operates as a ligand in the reaction. As expected, a remarkable decrease in activity was observed (entry 5) and precipitation of palladium black occurred within a few hours. This result indicated that the addition of the imidazolium salt is necessary in the reaction and that a nucleophilic carbene formed from **2** or **3** plays an important role as a ligand to afford the product in good yield. A range of palladium compounds was screened for use



2a: Aryl = 2,4,6-trimethylphenyl
2b: Aryl = 2,6-diisopropylphenyl
2c: Aryl = phenyl

3

Scheme 1.

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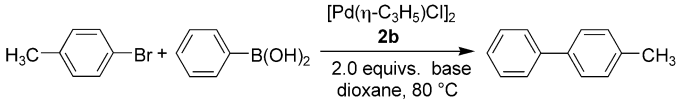
as catalyst precursor and the best result was obtained with $[Pd(\eta\text{-}C_3H_5)Cl]_2$. The Suzuki coupling reaction was prevented when the ratio of imidazolium salt to palladium (**2b**/Pd) was increased from 1:1 to 2:1 (entry 9), which revealed, from one side, that the phosphine-imidazoliums **2** are bidentate ligands. Two ligands **2** occupied all of four coordination sites of palladium to form a stable complex, which was inert in the oxidative-addition step.

Investigations into the optimal base showed that the rate of reaction and the activity of catalyst were significantly influenced by the base used (Table 2). A number of inorganic bases, such as Cs_2CO_3, K_2CO_3, KOH, NaOH, KF and K_3PO_4, could provide cross-coupling products in excellent yield. But when organic bases such as triethylamine and diisopropylethylamine were used, the reactions ceased within minutes and palladium black was observed. Considering its high activity, K_3PO_4 was ultimately chosen as the base for the system. Various solvents were tested in the coupling reaction with K_3PO_4 as the base (Table 3). Dioxane proved to be a suitable solvent, giving the fastest reaction. An attempt to conduct the reaction at a lower temperature led to a dramatic decrease in the conversion of aryl bromide (50 °C/24 h, 61% conversion). Using 0.05 mol % $[Pd(\eta\text{-}C_3H_5)Cl]_2$ and 0.1 mol % **2b** also gave the coupling product in 100% yield after 12 h (entry 2).

Under the optimized reaction conditions, a wide array of aryl bromides can react with phenylboronic acid providing cross-coupling products in excellent yields (Table 4). The palladium/phosphine-imidazolium carbene system was indeed very efficient toward Suzuki coupling and displayed remarkable tolerance towards both "deactivating" electron-donating substituents and sterically encumbering *otho*-substituents on the aryl bromide. We were delighted to find that activated aryl chlorides can also couple with phenylboronic acid efficiently under the same conditions in high yields (Table 4, entries 16–21).

Table 2. Effect of base on the Pd/**2b**-catalyzed Suzuki coupling reaction.[a]



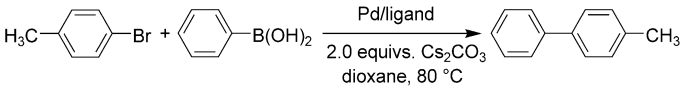
Entry	Base	Time [h]	Conversion [%][b]	Yield [%][c]
1	Cs_2CO_3	10	99	97
2	K_2CO_3	24	99	95
3	KF	6	99	94
4	KOBu-*t*	24	51	31
5	KOAc	24	4	–
6	K_3PO_4	4	100	100
7	KOH	4	99	94
8	NaOH	4	100	95
9	NEt_3	24	2	–
10	$EtN(i\text{-}Pr)_2$	24	6	–

[a] Performed at 0.5 mol % Pd/L (1:1) and 0.33 M.
[b] Determined by GC.
[c] GC yield.

A variety of arylboronic acid (with electron-donating and electron-withdrawing substituents) reacted smoothly with 4-bromotoluene and the cross-coupling products were obtained in excellent yields (Table 5).

In summary, we have developed a highly efficient, convenient to handle palladium/phosphine imidazolium salt system for the cross-coupling reaction of arylboronic acids and aryl bromides and activated chlorides to produce biaryl compounds in excellent yields. The phosphine-functionalized heterocyclic carbenes generated *in*

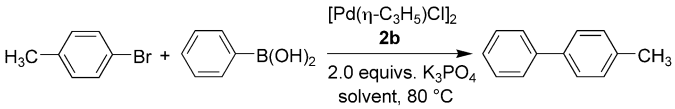
Table 1. Effect of imidazolium salts and palladium resource on the Suzuki coupling of 4-bromotoluene and phenylboronic acid.[a]



Entry	Pd complex	Ligand	Time [h]	Conversion [%]	Yield [%][b]
1	$[Pd(\eta\text{-}C_3H_5)Cl]_2$	**2a**	14	99	92
2	$[Pd(\eta\text{-}C_3H_5)Cl]_2$	**2b**	10	99	97
3	$[Pd(\eta\text{-}C_3H_5)Cl]_2$	**2c**	13	100	89
4	$[Pd(\eta\text{-}C_3H_5)Cl]_2$	**3**	24	93	82
5	$[Pd(\eta\text{-}C_3H_5)Cl]_2$	none	24	23	–
6	$Pd(dba)_2$	**2b**	17	97	90
7	$Pd_2(dba)_3CHCl_3$	**2b**	18	99	99
8	$Pd(OAc)_2$	**2b**	12	99	96
9[c]	$[Pd(\eta\text{-}C_3H_5)Cl]_2$	**2b**	24	5	–

[a] Performed at 0.5 mol % Pd/L (1:1) and 0.33 M.
[b] GC yield.
[c] Pd/L = 1:2.

Table 3. Effect of solvent.[a]

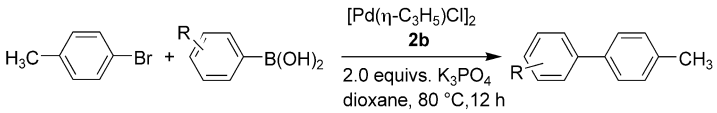


Entry	Solvent	Time [h]	Conversion [%]	Yield [%]
1	Dioxane	4	100	100
2[b]	Dioxane	12	100	100
3	THF	6	100	97
4	Toluene	6	99	94
5	EtOH	6	100	93
6	DMF	6	93	89
7	DMAc	6	87	83
8	DME	6	60	38
9	DMSO	4	61	43
10	CH_3CN	4	70	54

[a] Performed at 0.5 mol % Pd/L (1 : 1) and 0.33 M.
[b] Using 0.05 mol % $[Pd(\eta\text{-}C_3H_5)Cl]_2$.

situ from imidazolium salt were for the first time introduced to the palladium catalyzed Suzuki coupling. Applications involving this new family of phosphine imidazolium salts in other metal-promoted reactions are currently under investigation.

Table 5. Suzuki cross-coupling of 4-bromotoluene with various arylboronic acids.[a]



Entry	R	Conversion [%]	Yield [%][b]
1	H	100	100
2	*m*-OCH_3	100	99
3	*p*-OCH_3	100	97
4	*p*-CH_3	100	100
5	*o*-CH_3	98	93
6	*p*-$COCH_3$	99	96

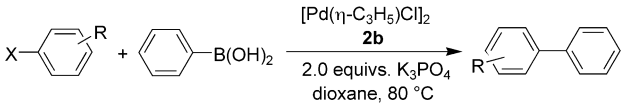
[a] Performed at 0.1 mol% Pd/L (1 : 1) and 0.33 M.
[b] Average of isolated yields based on two runs.

Experimental Section

Cross-Coupling Reactions of Aryl Halides with Arylboronic Acids; General Procedure

Under an atmosphere of argon, 3.0 mL dioxane were injected to a Schlenk tube charged with $[Pd(\eta\text{-}C_3H_5)Cl]_2$ (0.0025 mmol), imidazolium salt (0.005 mmol), and K_3PO_4 (2.0 mmol) (performed at 0.5 mol % cat.), or 3.0 mL dioxane

Table 4. Suzuki cross-coupling of bromides and activated chlorides with phenylboronic acid.[a]



Entry	X	R	Time [h]	Conversion [%]	Yield [%][b]
1	Br	*p*-CH_3	12	100	100
2	Br	*o*-CH_3	12	100	98
3	Br	*m*-CH_3	12	100	100
4	Br	*m*-OCH_3	12	100	100
5	Br	*p*-OCH_3	12	100	100
6	Br	3,5-diCH_3	12	100	100
7	Br	*p*-CN	6	100	100
8	Br	*m*-$COCH_3$	6	100	100
9	Br	*p*-$COCH_3$	6	100	100
10	Br	*p*-CF_3	6	100	98
11	Br	3,5-diCF_3	6	100	93
12	Br	*m*-CHO	6	100	97
13	Br	*p*-NO_2	6	100	100
14	Br	H	6	96	93
15	Br	1-Br-2-Me-Naph	12	100	100
16	Cl	*p*-NO_2	6	100	100
17	Cl	*p*-$COCH_3$	12	96	92
18	Cl	*p*-CN	12	99	99
19	Cl	*o*-CHO	24	97	85
20	Cl	*p*-CHO	12	89	80
21[c]	Cl	*o*-NO_2	36	98	97

[a] Performed at 0.1 mol % Pd/L (1 : 1) and 0.33 M.
[b] Average of isolated yields based at two runs.
[c] Using 0.5 mol % Pd.

solution of $[Pd(\eta\text{-}C_3H_5)Cl]_2$ (0.0005 mmol) and imidazolium salt (0.001 mmol) was injected to a Schlenk tube charged with K_3PO_4 (2.0 mmol) (performed at 0.1 mol % cat.). The mixture was stirred for 30 min at room temperature. Then 1.0 mmol of aryl halide, 1.5 mmol of arylboronic acid (and 0.5 mmol of tridecane as internal standard, if the yield was determined by GC) were added. The reaction mixture was placed in a 80 °C oil bath and the course of the reaction was monitored by GC. After the reaction was complete, the mixture was loaded on a small plug of silica gel and washed with a copious amount of Et_2O. The washings were concentrated and purified by flash chromatography on silica gel column and the products were identified by ^1H NMR.

Acknowledgements

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