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An efficient and simple protocol for a $PdCl_2$-ligandless and additive-free Suzuki coupling reaction of aryl bromides

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ABSTRACT

A highly efficient, convenient, and environmentally friendly protocol was developed for the $PdCl_2$-catalyzed ligandless and additive-free Suzuki reaction of aryl bromides with arylboronic acids in water/ethanol.

Introduction

The Pd-catalyzed Suzuki cross-coupling reaction of aryl halides with arylboronic acids is one of the most powerful and versatile methods for C–C bond formation.[1] Traditionally, Suzuki coupling reactions have been catalyzed by palladium complexes with phosphine ligands in organic solvents. In most cases, the reactions are oxygen and moisture sensitive.[2] Although some reactions could work in water and air, complicated ligands were used.[3] Recently, much attention has been paid to developing ligand-free catalytic systems for the Suzuki reaction,[4] however, in most systems additives were added.[5] In order to stabilize the Pd species, much work has been involved in immobilizing Pd to polymers,[6] carbon nanotubes,[7] magnetite,[8] and functional ionic liquid.[3c]

Recently, some mild and efficient protocols were reported for the $Pd(OAc)_2$-ligandless Suzuki reaction of aryl bromides with arylboronic acids in toluene,[1c] aqueous acetone,[9] and PEG 300.[6b] Sajiki and co-workers described a Pd/C-catalyzed ligand-free system for the Suzuki reaction in aqueous ethanol at room temperature.[10] However, they suffered from either high temperature or long reaction time. Very recently, Ni and co-workers developed a fast protocol for the Suzuki reaction in aqueous DMF.[11] It has the advantages of being highly efficient, ligand-free, and having mild reaction conditions, but was not environment-friendly, because of the toxic and hard-to-handle DMF. Aqueous ethanol has been widely used as a solvent due to its correspondence with the concept of green chemistry.[3c,7]

Herein, we would like to report an efficient, convenient, and environmentally friendly protocol for $PdCl_2$-ligandless Suzuki reaction of aryl bromides with arylboronic acids in mild conditions.

Results and discussion

To optimize the reaction conditions, the model coupling reaction of *p*-bromoacetophenone with phenylboronic acid was carried out at room temperature in air. Initially, the effect of the palladium species for this reaction was investigated. The results indicated that the cross-coupling reaction was completed quantitatively within 5 min in the presence of 0.5 mol % of $PdCl_2$ or $Pd(OAc)_2$ (Table 1, entries 1 and 5), while the zero-valent pre-catalysts Pd/C and $Pd_2(dba)_3$ (Table 1, entries 3 and 4) showed poor catalytic activity.[1c,11] Notably, the amount of $PdCl_2$ could be decreased even to 0.1 mol %, giving the product in 92% yield (Table 1, entry 2). Further studies found that the base had dramatic effect on this ligand-free Suzuki reaction (Table 1). Among the tested bases, K_2CO_3 gave the best result (99% yield).

Then the effect of solvent was examined for the same model reaction (Table 2). As reported, the volume ratio of water–organic was very important for the reactivity of Suzuki reactions.[11] In our investigations, alcoholic and alcoholic/aqueous solvents, especially when the alcoholic content of more than 50% gave satisfactory results (Table 2, entries 2–5), whereas the use of pure H_2O gave quite a poor result (Table 2, entry 8). Considering the factors of economy

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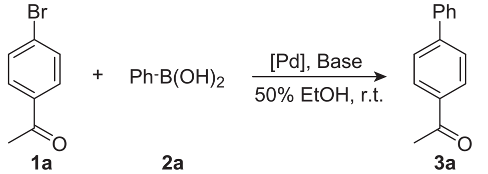
Table 1

Optimization of the reaction conditions for the Suzuki reaction of 4-bromoanisole with phenylboronic acid[a]



Entry	[Pd]	Base	Yield[b] (%)
1	$PdCl_2$	K_2CO_3	99
2	$PdCl_2$	K_2CO_3	92[c]
3	$Pd_2(dba)_3$	K_2CO_3	11
4	Pd/C	K_2CO_3	Trace
5	$Pd(OAc)_2$	K_2CO_3	96
6	$PdCl_2$	Na_2CO_3	98
7	$PdCl_2$	Cs_2CO_3	97
8	$PdCl_2$	NaOH	20
9	$PdCl_2$	$K_3PO_4 \cdot 3H_2O$	25
10	$PdCl_2$	KBr	Trace
11	$PdCl_2$	CH_3COONa	10

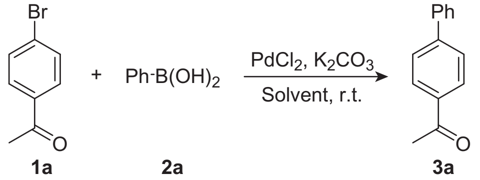
[a] Reaction conditions: *p*-bromoacetophenone (0.5 mmol), phenylboronic acid (0.75 mmol), [Pd] (0.5 mol %), base (1 mmol), 50% EtOH (4 mL), room temperature, in air.

[b] Isolated yield.

[c] 0.1 mol % of $PdCl_2$ was used.

Table 2

Effect of solvents on the Suzuki coupling reaction[a]



Entry	Solvent	Time/min	Yield[b] (%)
1	EtOH	5	99
2	50% MeOH	5	99
3	50% EtOH	5	99
4	50% *i*-PrOH	5	99
5	50% *t*-BuOH	5	99
6	35% EtOH	60	95
7	25% EtOH	120	81
8	H_2O	120	27

[a] Reaction conditions: *p*-bromoacetophenone (0.5 mmol), phenylboronic acid (0.75 mmol), $PdCl_2$ (0.5 mol %), K_2CO_3 (1 mmol), solvent (4 mL), room temperature, in air.

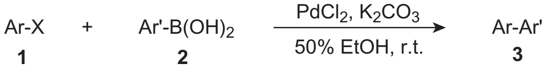
[b] Isolated yield.

and environment, the reaction was performed in EtOH/H_2O (1:1) for further investigations.

The substrate scope was then investigated under the optimized conditions. In general, all the reactions gave biaryl derivatives in excellent yields as shown in Table 3. Most of these reactions were completed within 5 min, monitored by TLC. It was obvious that various 4-substituted aryl bromides bearing either electron-donating or electron-withdrawing groups, such as methoxy, cyano, chloro, and formyl, coupled with phenylboronic acid in high yields (Table 3, entries 10–12). As reported,[12] electron-withdrawing substituted arylboronic acids showed a slightly lower reactivity, and longer reaction time was needed (Table 3, entry 14). The coupling reaction of *ortho*-substituted bromobenzene with phenylboronic acid gave the desired product in lower yield due to its bulky steric hindrance (Table 3, entry 17). Representative heteroaromatic substrates were also tolerated for this protocol (Table 3, entries 18 and 19). Disappointedly, phenyl chloride was a poor substrate for this reaction (Table 3, entry 20).

Table 3

Suzuki reactions of aryl bromides with arylboronic acids[a]



$$\underset{\mathbf{1}}{Ar\text{-}X} + \underset{\mathbf{2}}{Ar'\text{-}B(OH)_2} \xrightarrow[\text{50\% EtOH, r.t.}]{PdCl_2,\ K_2CO_3} \underset{\mathbf{3}}{Ar\text{-}Ar'}$$

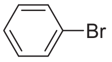
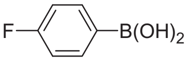
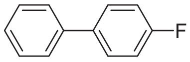
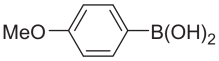
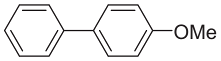
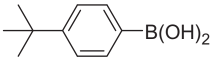
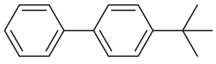
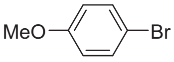
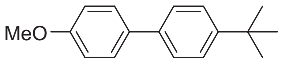
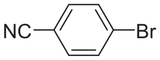
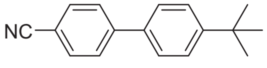
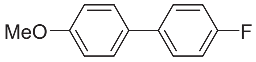
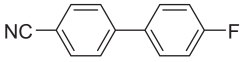
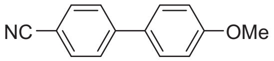
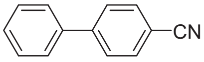
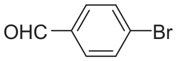
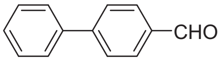
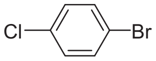
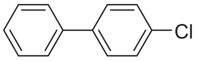
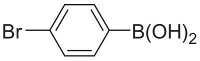
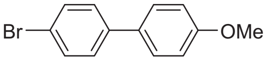
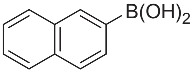
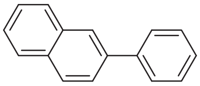
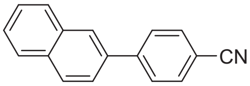
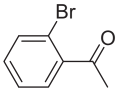
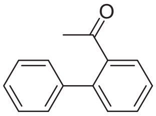
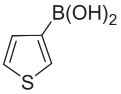
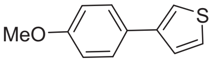
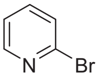
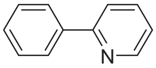
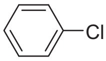
Entry	RX (**1**)	R′B(OH)$_2$ (**2**)	Time (min)	Product (**3**)	Yield[b] (%)
1	**1a**	**2a**	5	**3a**	99
2	 (1b)	 (2b)	5	 (3b)	98
3	**1b**	 (2c)	5	 (3c)	99
4	**1b**	 (2d)	5	 (3d)	99
5	 (1c)	**2d**	5	 (3e)	99
6	 (1d)	**2d**	5	 (3f)	99
7	**1c**	**2b**	5	 (3g)	99
8	**1d**	**2b**	5	 (3h)	99
9	**1d**	**2c**	5	 (3i)	99

Table 3 (*continued*)

Entry	RX (**1**)	R′B(OH)$_2$ (**2**)	Time (min)	Product (**3**)	Yield[b] (%)
10	**1c**	**2a**	3	**3c**	99
11	**1d**	**2a**	3	 **(3j)**	99
12	 **(1f)**	**2a**	5	 **(3k)**	97
13	 **(1e)**	**2a**	5	 **(3l)**	99
14	**1c**	 **(2e)**	30	 **(3m)**	97
15	**1b**	 **(2f)**	30	 **(3n)**	91
16	**1d**	**2f**	5	 **(3o)**	98
17	 **(1g)**	**2a**	60	 **(3p)**	87
18	**1c**	 **(2g)**	120	 **(3q)**	85
19	 **(1h)**	**2a**	120	 **(3r)**	70
20	 **(1j)**	**2c**	120	**3c**	10[c]

[a] Reaction conditions: aryl bromides (0.5 mmol), arylboronic acids (0.75 mmol), $PdCl_2$ (0. 5 mol %), K_2CO_3 (1 mmol), 50% EtOH (4 mL), room temperature, in air. The reaction was monitored by TLC.

[b] Isolated yield.

[c] Reaction was performed at 60 °C.

Conclusions

In summary, we have successfully developed a simple and efficient protocol for the $PdCl_2$-ligandless Suzuki coupling of aryl bromides with arylboronic acids. The advantages of this procedure are simple operation, good to excellent yields, short reaction time, absence of ligands, and mild and environmentally friendly conditions. A great diversity of substrates were tolerated for this method.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.115.

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