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# An efficient protocol for palladium-catalyzed ligand-free Suzuki-Miyaura coupling in water

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An *in situ* generated catalytic system based on PdCl<sub>2</sub> and sodium sulfate exhibited excellent catalytic activity in the Suzuki-Miyaura cross-coupling reactions of aryl halides with arylboronic acids at room temperature in water. Similar catalytic system can be obtained with PdCl<sub>2</sub> and sodium chloride or sodium acetate and is equally effective in Suzuki-Miyaura cross-coupling reactions. This method offers a mild and efficient alternative to the existing protocols since the reaction is preceded in water at room temperature under ligand free conditions.

The palladium catalyzed Suzuki-Miyaura cross-coupling reaction is one of the most powerful and convenient approaches for the synthesis of biaryl and alkene derivatives that are structural components of numerous natural products, agrochemicals, pharmaceuticals, and polymers, such as organic electroluminescence (EL) materials.<sup>1</sup> The first method to prepare biaryls by the Suzuki-Miyaura cross-coupling of aryl boranes with haloarenes was reported<sup>2</sup> in 1981 and since this discovery, various modifications have been made to the reaction conditions. Most of the catalyst systems for these transformations composed of Pd(0) or Pd(II) derivatives associated with appropriate ligands in conventional organic or biphasic media.<sup>3</sup> Current developments into expansion of the Suzuki-Miyaura reaction have been carried out chiefly by using different ligands and noticeable advances have been achieved with phosphine-based ligands such as, simple tertiaryphosphines, hemilabile-type phosphines, sterically crowded biphenyl-type phosphines, other electron rich phosphines and with other ligands that are capable of forming phosphapalladacycles.<sup>3-4</sup> Phosphine-based palladium catalysts are generally employed since they are stable to prolonged heating;<sup>1a</sup> however, extremely high coupling reaction rates can sometimes be achieved by using palladium catalysts with non-phosphine ligand such as *N*-heterocyclic carbenes<sup>5</sup>, amine-based<sup>6</sup>, oxime-based<sup>7</sup> etc. Although, complexes containing such ligands often show excellent activity, however, in majority of cases, the principal drawbacks are the availability, stability, and cost of the palladium complexes and related ligands. Moreover, many of these complexes are sensitive to air and moisture, and thus the reactions are performed in inert atmosphere. In most of the cases these reactions are performed in organic solvents. However from environmental and economic points of view, the use of water as an environmentally benign and economically favorable alternative to organic solvents in organic synthesis has got tremendous interests, because water is a cheap, readily available, non-toxic and non-flammable solvent.<sup>8</sup> In this

respect, the development of catalysis in pure water seems particularly suitable for the Suzuki-Miyaura reaction due to the excellent stability of boronic acids in aqueous media. Moreover the ability to dissolve bases in water for activating arylboronic acid has enhanced the rate of the reaction in an aqueous medium. Accordingly a number of remarkable results have been reported concerning the cross-coupling of boronic compounds with aryl or vinyl iodide, bromide and even demanding chloride substrates under mild conditions in water.<sup>9</sup> However, in most of the cases either an elevated reaction condition or the use of ligand or co-solvent is required even when the aryl bromides were used as substrate.<sup>10</sup> Green Chemistry focuses on the design, manufacture, and use of chemicals and chemical processes that have little or no pollution potential or environmental risk, and are both economically and technologically feasible.<sup>11</sup> Therefore, the concept of Green Chemistry is part of the more general approach of Sustainable Chemistry, which is the maintenance of an ecologically sound development for the chemical industry using non toxic cheap chemical reagents under mild reaction conditions. Thus, the development of new catalytic systems that can promote Suzuki Miyaura reactions in water with improve yield and simplify the reaction protocol is still remain a major challenge. In this communication we wish to report the use of easily accessible, cheap and non toxic sodium sulfate as excellent promoter in palladium catalyzed Suzuki-Miyaura cross-coupling reactions of aryl halides with arylboronic acids at room temperature in water.

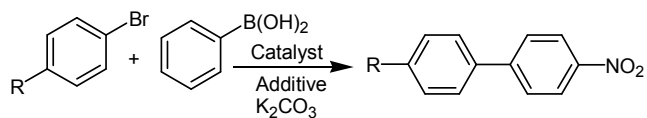
## Result and discussions

It is a well known fact that a suitable amount of water is very important for improving the reactivity of Suzuki Miyaura reactions and many reports have described use of water as co solvent in Suzuki-Miyaura reaction. But only few reports are available where pure water or alcohol has been used as solvent. Therefore we wish to study the use of pure alcohol and pure water as solvent in Suzuki-Miyaura reaction. Recently Fan et al has reported the rate enhancement in Suzuki-Miyaura reaction by Lewis acid in presence of palladium chloride anchored on modified polystyrene at elevated temperature.<sup>12</sup> At the outset, to examine the effectiveness of different Lewis acid in Suzuki-Miyaura reaction, we use 4-nitrobromobenzene (0.5 mmol) and phenylboronic acid (0.55 mmol) as the model substrates and potassium carbonate (1.5 mmol) for reaction development. The results were shown in table 1. In an initial experiment the reaction was carried out in presence of FeCl<sub>3</sub> (8 mol %) and PdCl<sub>2</sub> (5

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mol%) in isopropanol at room temperature and we were able to isolate 88% of cross coupling product (Table 1, entry 1). It has been observed for the Table 1 that different ferric and ferrous salt has similar enhancing effects on reaction rate (Table 1, entries 1-4) and  $\text{Fe}_2(\text{SO}_4)_3 \cdot 10\text{H}_2\text{O}$  gave

**Table 1:** Optimization of reaction conditions for Suzuki-Miyaura reaction



Sl No	Catalyst	Additive	R	Solvent	Time (h)	Yield
1	$\text{PdCl}_2$	$\text{FeCl}_3$	$\text{NO}_2$	<i>i</i> -PrOH	5	88
2	$\text{PdCl}_2$	$\text{Fe}(\text{NO}_3)_3$	$\text{NO}_2$	<i>i</i> -PrOH	6	90
3	$\text{PdCl}_2$	$\text{Fe}_2(\text{SO}_4)_3 \cdot 7\text{H}_2\text{O}$	$\text{NO}_2$	<i>i</i> -PrOH	6	90
4	$\text{PdCl}_2$	$\text{Fe}_2(\text{SO}_4)_3 \cdot 10\text{H}_2\text{O}$	$\text{NO}_2$	<i>i</i> -PrOH	3	98
5	$\text{PdCl}_2$	$\text{CuI}$	$\text{NO}_2$	<i>i</i> -PrOH	8	65
6	$\text{PdCl}_2$	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$	$\text{NO}_2$	<i>i</i> -PrOH	3	90
7	$\text{PdCl}_2$	$\text{ZnCl}_2$	$\text{NO}_2$	<i>i</i> -PrOH	6	45
8	$\text{PdCl}_2$	$\text{MnCl}_2$	$\text{NO}_2$	<i>i</i> -PrOH	4	90
9	$\text{PdCl}_2$	$\text{Na}_2\text{SO}_4$	$\text{NO}_2$	<i>i</i> -PrOH	5	90
10	$\text{Pd}(\text{OAc})_2$	$\text{Na}_2\text{SO}_4$	$\text{NO}_2$	<i>i</i> -PrOH	4	90
11	$\text{Pd}(\text{OAc})_2$	-	$\text{NO}_2$	<i>i</i> -PrOH	10	20
12	$\text{PdCl}_2$	$\text{Na}_2\text{SO}_4$	$\text{CH}_3$	<i>i</i> -PrOH	4	95
13	$\text{PdCl}_2$	$\text{Na}_2\text{SO}_4$	$\text{CH}_3$	<i>i</i> -PrOH	5	99
14	$\text{PdCl}_2$	$\text{Na}_2\text{SO}_4$	$\text{CH}_3$	$\text{H}_2\text{O}$	2	97
15	$\text{PdCl}_2$	$\text{NaCl}$	$\text{CH}_3$	$\text{H}_2\text{O}$	1.5	98
16	$\text{Pd}(\text{OAc})_2$	$\text{NaOAc}$	$\text{CH}_3$	$\text{H}_2\text{O}$	1	96
17	$\text{Pd}(\text{OAc})_2$	$\text{NaCl}$	$\text{CH}_3$	$\text{H}_2\text{O}$	3.5	91
18	$\text{Na}_2\text{PdCl}_4$	-	$\text{CH}_3$	$\text{H}_2\text{O}$	0.5	97
19	$\text{Na}_2\text{Pd}(\text{OAc})_4$	-	$\text{CH}_3$	$\text{H}_2\text{O}$	0.5	92
21	$\text{Pd}(\text{OAc})_2$	-	$\text{CH}_3$	$\text{H}_2\text{O}$	6	80

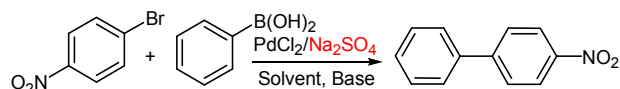
Reaction conditions: Arylbromide (0.5 mmol), phenylboronic acid (0.55 mmol), Palladium source (5 mol % for entries 1-9 and 2 mol% for entries 13-21), Additive (8 mol %) Base (1.5 mmol), Solvent (4 mL), 25 °C, in air. Isolated yields

the best result with 98% cross coupling product (Table 1, entry 4). Next we examine the effect of copper iodide and copper sulfate in Suzuki Miyaura reaction under the same reaction conditions and found that copper sulfate has prominent enhancing effect compared to copper iodide (Table 1, entry 5 vs 6). The use of zinc chloride could not enhance the reaction rate and resulted only 45% isolated yield (Table 1, entry 7). However manganese chloride showed very good enhancing effect (Table 1, entry 8). It is well documented in the literature that in many Pd(II) salt-catalyzed reactions, Pd(II) species are reduced to Pd(0) species at the end of each cycle.<sup>13</sup> Consequently, to make the reaction catalytic with respect to Pd(II), the presence of oxidants such as  $\text{CuCl}_2$ ,  $\text{Cu}(\text{OAc})_2$ , benzoquinone, *tert*-butyl hydroperoxide (TBHP),  $\text{MnO}_2$ , or  $\text{HNO}_3$  is required to allow for the conversion of Pd(0) into Pd(II) *in situ*.<sup>12</sup> Under the present reaction

conditions it is believed that the presence of transition metal salts has played a vital role for the conversion of Pd(0) into Pd(II) *in situ* and significantly enhance the reaction yields (Table 1 entries 1-8). We further wish to investigate the effect of different common salts in Suzuki Miyaura reaction. Initially we use anhydrous sodium sulfate, which is a very common, cheap and non-toxic routinely used laboratory reagent. We observed prominent enhancing effect of sodium sulfate in the coupling reaction and gave higher yields (Table 1, entry 9). It was clear that sodium sulfate with other palladium(II) salts such as  $\text{Pd}(\text{OAc})_2$  also exhibited high catalytic activity (Table 1, entry 10). But in absence of sodium sulfate the yield of the reaction was dramatically decreased (Table 1, entry 11). It is important to mention that, generally, aryl bromides with electron-withdrawing groups at *para* position are much more reactive than aryl bromides bearing electron donating groups. Thus, to investigate the effects of the new catalytic system with an electron-donating substrate, we performed the reaction between 4-bromotoluene and phenylboronic acid under similar conditions. It is surprising to see that 4-bromotoluene gave superior product formation compared to 4-bromonitrobenzene within shorter reaction time (Table 1, entry 12). It is important to mention that the reaction was preceded with 2 mol%  $\text{PdCl}_2$  (Table 1, entry 13). Considering the advantage of water as green solvent, we examine the effectiveness of the  $\text{PdCl}_2/\text{Na}_2\text{SO}_4$  system in water and interestingly excellent yield of the product was obtained in water within shorter reaction time (Table 1, entry 14). Similarly the reaction is also enhanced by the presences of NaCl and NaOAc in water (Table 1, entries 15-17) with comparable yields of the product. It is believed that the addition of additives such as sodium sulfate, sodium chloride and sodium acetate could provide water soluble *ate* complexes of palladium which is the actual catalytic species. For example the complexation of  $\text{PdCl}_2$  and  $\text{Na}_2\text{SO}_4$  could afford *in situ* formation of a water soluble species  $\text{Na}_2\text{PdCl}_2(\text{SO}_4)_2$  which actually catalyzed the Suzuki Miyaura reaction. Interestingly the water soluble *ate* complexes  $\text{Na}_2\text{PdCl}_4$  and  $\text{Na}_2\text{Pd}(\text{OAc})_4$  were also effective as catalyst for the Suzuki Miyaura reaction in water (Table 1, entries 18 and 19) which indirectly support the involvement of a palladium *ate* complex in the reaction. However long reaction time was required for the completion of reaction and yield of the product was decreased in absence of sodium sulfate in water (Table 1, entry 21). As reported in Table 2, we next studied the impacts of different bases and solvents on the cross-couplings of 4-bromonitrobenzene with phenylboronic acid using  $\text{PdCl}_2$  and sodium sulfate (8 mol%) as promoter. Screening of bases using isopropanol as solvent showed that potassium carbonate has worked as most efficient base in our catalytic system (Table 2, entry 1). Besides  $\text{K}_2\text{CO}_3$ , the reaction can tolerate other inorganic bases such as  $\text{Na}_2\text{CO}_3$ , NaOH, KOH,  $\text{Cs}_2\text{CO}_3$ ,  $\text{Na}_3\text{PO}_4 \cdot 12\text{H}_2\text{O}$  and gave almost comparable yields of the cross-coupling product (Table 2: entries 2-5). Moreover the reaction was found to be proceeded in both protic, and aprotic solvents although, significant variations in yields were noticed. The polar protic solvents such as isopropanol and THF:water (1:1) were found to be the most effective solvents and gave excellent result (Table 2,

entry 1 & 11). On the other hand aprotic solvents, both polar and non-polar (Table 2, entries 6-10), gave comparatively less yields. The lowest yield (28%) was obtained with ethylacetate (Table 2, entry 9). However the coupling reactions did not proceed in the absence of base (Table 2, entry 12).

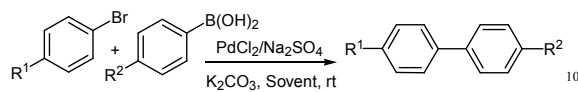
**Table 2** Solvent and Base effect for Suzuki-Miyaura Reaction



Sl No	Solvent	Base	Time (h)	Yield
1	<i>i</i> -PrOH	K <sub>2</sub> CO <sub>3</sub>	5	99
2	<i>i</i> -PrOH	Na <sub>2</sub> CO <sub>3</sub>	6	80
3	<i>i</i> -PrOH	NaOH	6	78
4	<i>i</i> -PrOH	CS <sub>2</sub> CO <sub>3</sub>	6	75
5	<i>i</i> -PrOH	Na <sub>3</sub> PO <sub>4</sub> ·12H <sub>2</sub> O	1	95
6	CH <sub>3</sub> Cl	K <sub>2</sub> CO <sub>3</sub>	6	45
7	THF	K <sub>2</sub> CO <sub>3</sub>	6	51
8	MeCN	K <sub>2</sub> CO <sub>3</sub>	8	49
9	Ethylacetate	K <sub>2</sub> CO <sub>3</sub>	6	28
10	Acetone	K <sub>2</sub> CO <sub>3</sub>	6	45
11	THF: H <sub>2</sub> O (1:1)	K <sub>2</sub> CO <sub>3</sub>	2	97
12	<i>i</i> -PrOH	-	3	-

Reaction conditions: 4-nitrobromobenzene (0.5 mmol), phenylboronic acid (0.55 mmol), PdCl<sub>2</sub> (5 mol %), Additive (8 mol%) Base (1.5 mmol), Solvent (4 mL), 25 °C, in air. Isolated yield

**Table 3:** PdCl<sub>2</sub>/Na<sub>2</sub>SO<sub>4</sub> catalyzed Suzuki-Miyaura reaction



Sl No	R <sup>1</sup>	R <sup>2</sup>	Solvent	Time (h)	Yield (%)
1	NO <sub>2</sub>	H	<i>i</i> PrOH	5	90
2	CHO	H	<i>i</i> PrOH	7	98
3	COCH <sub>3</sub>	H	<i>i</i> PrOH	5	96
4	OCH <sub>3</sub>	H	<i>i</i> PrOH	7	98
5	H	H	<i>i</i> PrOH	3	100
6	CH <sub>3</sub>	OCH <sub>3</sub>	<i>i</i> PrOH	1	90
7	CH <sub>3</sub>	OCH <sub>3</sub>	H <sub>2</sub> O	1	97
8	CHO	OCH <sub>3</sub>	H <sub>2</sub> O	3	95
9	OCH <sub>3</sub>	OCH <sub>3</sub>	H <sub>2</sub> O	2	90
10	H	OCH <sub>3</sub>	H <sub>2</sub> O	6	94
11	CHO	H	H <sub>2</sub> O	5	95
12	H	H	H <sub>2</sub> O	1	98
13	CH <sub>3</sub>	H	H <sub>2</sub> O	2	97
14	OCH <sub>3</sub>	H	H <sub>2</sub> O	5	97
15	NO <sub>2</sub>	H	H <sub>2</sub> O	1	91 <sup>a</sup>

Reaction conditions: Arylbromide (0.5 mmol), arylboronic acid (0.55 mmol), Palladium Chloride (2 mol %), Additive (8 mol%) Base (1.5 mmol), Solvent (4 mL), 25 °C, in air.

<sup>a</sup> *i*PrOH (1 mL) was used as co-solvent. Isolated yields

To evaluate the scope and limitations of the current procedure, reactions of a wide array of electronically diverse aryl bromides with arylboronic acids were examined using the sodium sulfate promoted catalyst system (Table 3). Both water and isopropanol gave almost comparable yields of the product; therefore both the solvent has been used in Suzuki-Miyaura cross coupling reaction.

The aryl bromides with electron withdrawing and electron donating substituents underwent the coupling reactions with phenylboronic acid effectively to afford the desired biaryls in excellent yields (90-100%) in isopropanol (Table 3, entries 1-6) and in water (Table 3, entries 7-14). The catalytic system is equally effective for electronically diversified arylboronic acids (Table 3) in both isopropanol and in water. Thus, our present result is quite significant as the desired biaryls could be achieved at room temperature using water or isopropanol as a solvent and, with relatively low catalyst loading (2 mol%) without using any ligand.

## Experimental

### General procedure for Suzuki-Miyaura Reaction:

A 50 ml round-bottom flask was charged with a mixture of aryl halide (0.5 mmol), aryl boronic acid (0.55 mmol), base (1.5 mmol), PdCl<sub>2</sub> (2 mol %) and additive (8 mol %) and the mixture was stirred in 4 mL of solvent at room temperature for the required time. After completion, the reaction mixture was diluted with water (20 ml) and extracted with ether (3×20 ml). The combined extract was washed with brine (2×20 ml) and dried over Na<sub>2</sub>SO<sub>4</sub>. After evaporation of the solvent under reduced pressure, the residue was chromatographed (silica gel, ethyl acetate-hexane: 1:9) to obtain the desired products. The products were confirmed by comparing the <sup>1</sup>H and <sup>13</sup>C NMR and mass spectral data with authentic samples.

## Conclusions

A convenient methodology has been developed for the palladium catalyzed Suzuki-Miyaura reaction in water. The reaction is catalyzed by an *in situ* generated catalytic system based on PdCl<sub>2</sub> and sodium sulfate. Similar catalytic system can be obtained with PdCl<sub>2</sub> and sodium chloride or sodium acetate and is equally effective in Suzuki-Miyaura cross-coupling reactions. This method offers a mild and efficient alternative to the existing protocols since the reaction is preceded at room temperature under ligand free conditions in water which is a cheap, non-toxic, non-volatile solvent.

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## Notes and references

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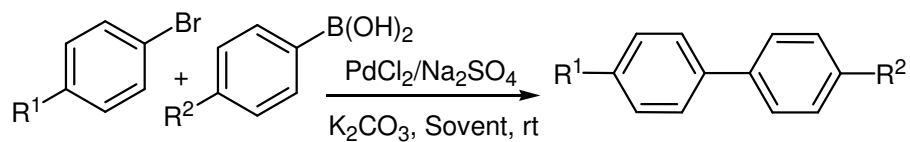


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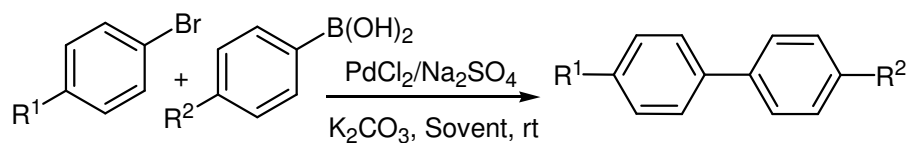
R<sup>1</sup> = H, NO<sub>2</sub>, CHO, COCH<sub>3</sub>, OCH<sub>3</sub>

R<sup>2</sup> = H, OCH<sub>3</sub>

Solvent = H<sub>2</sub>O, or *i*PrOH,

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An *in situ* generated catalytic system based on  $\text{PdCl}_2$  and sodium sulfate exhibit excellent catalytic activity in the Suzuki-Miyaura cross-coupling reactions of aryl halides with arylboronic acids at room temperature in water under ligand free conditions.



$\text{R}^1 = \text{H}, \text{NO}_2, \text{CHO}, \text{COCH}_3, \text{OCH}_3$

$\text{R}^2 = \text{H}, \text{OCH}_3$

Solvent =  $\text{H}_2\text{O}$ , or *i*PrOH,