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# COMMUNICATION

# Suzuki–Miyaura cross-coupling coupling reactions with low catalyst loading: a green and sustainable protocol in pure water

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The Suzuki–Miyaura coupling reaction represents one of the most important synthetic transformations developed in the 20th century. However, the use of toxic organic solvents remains a scientific challenge and an aspect of economical and ecological relevance, and benign water as a reaction medium was found to be highly effective to overcome some of these issues. In the present manuscript, we described Suzuki– Miyaura coupling reactions in neat water, without using any phase transfer reagent. Notably, this protocol also works with ultra-low loading of catalyst with high turnover numbers and also able to couple challenging substrates like aryl chlorides.

# Introduction

Reaction solvents are one of the most important constituents in any chemical process including Suzuki-Miyaura coupling reactions<sup>1-3</sup> and play a key role in deciding its environmental impact as well as its cost, safety, and health issues. The majority of these solvents are volatile and highly inflammable organic liquids, which is the main cause of ecological contamination. However, it is quite difficult to avoid the use of solvents as they are crucial in various stages from reactant mixing to product isolation. The ideal solution is to use a "green solvent" which does not pollute the environment.<sup>4-6</sup> Biphasic solvent systems such as the combination of fluorous and ionic liquids along with aqueous systems and supercritical carbon dioxide have created the central drive of this movement. However, the cost and toxicity of these systems are core issues in using them as a solvent. Thus, naturally abundant water appears to be a superior choice as a 'green solvent' because of its non-toxic, non-corrosive and non-flammable nature. It possesses several unique characteristic such as polarity, elevated surface tension, and strong hydrogen bonding potential. Also, water can be easily contained because of its comparatively high vapor pressure with respect to organic solvents, rendering it as a sustainable alternative. Importantly, 'water' is the primary solvent

in various natural processes taking place inside and around us and is responsible for our sustainable life, this encouraged researchers to use water as a reaction medium in various challenging chemical processes.

In general, water has not been considered to be an appropriate solvent for synthetic chemistry because of several issues such as substrate molecules themselves reacting with water molecules. Insolubility of most of the organic reactants in water, making the reaction mixture heterogeneous, was another worry. Even though reactants and/or reagents are not homogenized in aqueous medium, water was still found to speed up the rate of several reactions.7-8 The rationale behind this is that water molecules avoid high energy polar-non-polar mixing with the reactant molecules for which it has to go through structural organization modification, which in turn will decreases the entropy of the reaction mixture. Thus to avoid this thermodynamically unfavorable system, water molecules direct the organic molecules towards each other, resulting in an isolated organic phase (from the water phase) where the actual reaction takes place.9-11 Also, the isolation of products from aqueous media is another concern. For this, evaporation of water from the reaction mixture may be an option, but it is not an energy-efficient process.

During the past decade, numerous reactions that were conventionally carried out in organic solvents have been now developed using water as a solvent.<sup>12-13</sup> Among the various reactions studied, in our recent review on Suzuki–Miyaura reaction in an aqueous medium,<sup>14</sup> we observed that although the Suzuki–Miyaura coupling protocol is an excellent example of this development and this process was exponentially benefited by aqueous chemistry, however, despite the impressive progress, a number of challenges remain unresolved; importantly the coupling of the readily available and low-cost aryl chlorides continues to pose difficulties and the difference between their activity in homogeneous and heterogeneous phases is very high.<sup>15</sup>

Another difficulty is to design and prepare ligands that are suitable for aqueous phase reactions. The development of greener and sustainable pathways for organic transformations<sup>16–19</sup> and the necessity to provide catalytic systems minimizing the consumption of expensive transition-metals can be fulfilled through the synthesis of accessible, efficient and inexpensive ligands. Ligand **1** reported herein was developed following these objectives and pertains to a family of highly efficient catalytic auxiliaries.

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#### Table 1 Optimization of the reaction conditions



# **Results and discussion**

Mannich-type reactions of various phosphines, formaldehyde and amines were demonstrated to be a powerful method of constructing aminomethylphosphines, which are promising ligands for the design of homogeneous catalysts.<sup>20,21</sup> Starting from the work of Markl *et al.*<sup>22,23</sup> and Tzschach and coworkers <sup>24,25</sup> a wide variety of chelate complexes of this type has been obtained, including phosphines with cyclodextrin,<sup>26</sup> dendrimer,<sup>27,28</sup> amino acid and peptide<sup>29</sup> moieties. Herein, we report the synthesis and catalytic activity of 1,5-diphenyl-3,7dicyclohexyl-1,5-diaza-3,7-diphosphacyclooctane **1** which is obtained from bis(hydroxymethyl)cyclohexylphosphine by addition of aniline (Scheme 1). The palladium complex was synthesized by treatment of **1** with palladium acetate at room temperature for two hours, this ligands is not soluble in water at room temperature but is soluble in refluxing water. Pd(II) complex 2 was purified and stored under nitrogen. It was isolated with 85% yield and characterized by <sup>1</sup>H, <sup>31</sup>P NMR and MS.

We initially investigated the reaction of 4-bromoacetophenone with phenylboronic acid to establish the feasibility of our strategy and to optimize the reaction conditions (Table 1). First the reaction was conducted without any base and no reaction (NR) was observed. Then several bases were tested and a good to excellent yield of the coupling product was observed in all cases. Interestingly, under the same conditions catalyst **2** gave the product in 81% yield. Considering the economical and environmental advantages, we chose  $K_2CO_3$  as the base.

To further define the scope of this protocol and following our catalysis objective, the coupling of various aryl halides by palladium complexes stabilized by **1** was investigated and representative results are summarized in Table 2.



Scheme 1 Synthesis of 1 and 2.

	0.1 mol% Pd(OAc) <sub>2</sub>					
			0.1 mol% 1	$\sum_{n=2}^{\infty}$		
		B(OH)2	H <sub>2</sub> O, 100 °C	// <sup></sup>		
			K <sub>2</sub> CO <sub>3</sub> , 2h			
Entry	R <sup>1</sup>	$\mathbf{R}^2$	Product	Yield (%)		
1	OMe	Н	MeO	90		
2	CN	Н		93		
3	$NO_2$	Н		92		
4	MeCO	Н	MeOC	95		
5	OMe	OMe	MeO	92		
6	CN	OMe		93		
7	$NO_2$	OMe	O <sub>2</sub> N-OMe	92		
8	MeCO	OMe	MeOC	91		
9	Br			26		
10	,			83ª		
11				95		
11	⟨N_Br			85		
12	K S Br			0		

Table 2	Suzuki-Miyaura	coupling reaction	ns of aryl bromides	in neat water
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" 0.4 mole% of  $Pd(OAc)_{\scriptscriptstyle 2}$  and 1

Aryl bromides with various functional groups efficiently reacted with boronic acids (entries 1–10), to yield Suzuki–Miyaura products in good to excellent yields. 2-Bromopyridine underwent smooth reaction with phenylboronic acid (entry 11), providing a useful way for the synthesis of aryl-substituted nitrogen heterocycles; however no product was observed in the case of 2bromothiophene, which may be due to its instability in water. These results indicate that with these  $\alpha$ -substituted heteroaryl bromides, a possible interaction between the hetero-element and the palladium complex has a deactivation effect on the rate of the reaction.

In order to test the feasibility of this protocol for challenging substrates, we conducted two reactions with aryl chloride (Scheme 2) and observed good product yield. Importantly, no phase transfer catalyst (which is generally used by most of the reports) was used during these reactions.

We also studied the effect of catalyst amount on the reaction rate and product yield (Scheme 3). Interestingly, these reactions could also be conducted with ultra-low loading of catalyst as low as 0.0001 mol%, with high turnover numbers.

For practical applications of any catalyst systems, the lifetime of the catalyst and its level of reusability are very important factors. Although recycling of homogeneous catalysts is difficult and generally not preferred, since we were using water as the reaction medium, we studied the possibility of recycling and reusing the catalyst. We established a set of experiments using the recycled catalyst for the Suzuki–Miyaura reaction of 4-bromoactephenone and phenylboronic acid and the reactions were carried out under similar conditions in water. After completion of the reaction, the 4-acetobiphenyl was extracted from the reaction mixture with *n*pentane and the catalyst was reused for another run by adding fresh 4-bromoactephenone, phenylboronic acid and potassium carbonate to the reaction media. The first reaction afforded the corresponding coupling product in 95% yield, the product yield for the 2nd cycle was nearly the same (85%), however in the 3rd cycle it was reduced to 57%. Thus, this catalyst system could be used for at least 3 times, which is fairly good for a homogenous system.

## Conclusions

In conclusion, we have developed efficient Suzuki–Miyaura coupling reactions in neat water, which does not use any phase transfer reagent and was also able to couple challenging substrates like aryl chloride. Reactions also work with ultralow loading of catalyst with high turnover numbers. Our current investigations are focused on the feasibility of electronic modification around phosphine-palladium catalysts, through phosphorus substituents, with the view to increasing their activity.



Scheme 2 Suzuki-Miyaura coupling reactions using challenging substrates.

leCO Br +	B(OH) <sub>2</sub> 7.5 mmol	Pd(OAc)₂/1 H₂O, 100°C K₂CO₃, 2h	MeCO
Entry	mol % Pd	Yield (%)	TON
1	10-1	95	950
2	10-2	93	9300
3	10-3	92	92000
4	10 <sup>-4</sup>	77	770 000
5	10 <sup>-5</sup>	0	0

Scheme 3 Suzuki–Miyaura coupling reactions using ultra-low loading of catalyst.

N

## Experimental

All reactions and workup procedures were performed under an inert atmosphere of argon using conventional vacuum-line and glasswork techniques. Solvents were dried and freshly distilled under argon. All other materials were obtained from commercial suppliers and used as received. Water (deionized) was degassed by sparging with nitrogen. Chromatography was performed on neutral silica gel. NMR spectra were recorded on a Bruker instrument operating at 400.13 MHz for proton, 100.62 MHz for carbon, and 161.96 MHz for phosphorus.

### Synthesis of 1,5-diphenyl-3,7-dicyclohexyl-1,5-diaza-3,7diphosphacyclooctane 1

A Schlenk flask was charged with cyclohexylphosphine (10% in hexane, 14.6 mL, 8.3 mmol) and degassed aqueous formaldehyde (37%, 1.92 mL, 25.8 mmol) in degassed CH<sub>3</sub>CN (20 mL). After stirring for 30 min at room temperature, the solvent was removed under vacuum and the resulting oil was combined with aniline (773 mg, 8.3 mmol) in degassed EtOH (20 mL) and the solution was refluxed overnight. The solution was allowed to cool down to room temperature. A white precipitate was filtered and washed with EtOH and dried under vacuum to give a white powder (3.28 g, 7.1 mmol, 85%). <sup>31</sup>P{<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 161.96 MHz,  $\delta$  in ppm): - 40.9 ppm (s). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400.13 MHz): 7.18-7.27 (m, 10H, NC<sub>6</sub>H<sub>5</sub>), 4.47 (d, 2H,  ${}^{2}J_{HH}$  = 12.8 Hz, NCH<sub>2</sub>P), 4.50 (d, 2H,  ${}^{2}J_{HH}$  = 12.8 Hz, NCH<sub>2</sub>P), 4.83 (d, 2H,  ${}^{2}J_{HH}$  = 12.8 Hz, NCH<sub>2</sub>P), 4.86 (d, 2H,  ${}^{2}J_{HH} = 12.8$  Hz, NCH<sub>2</sub>P), 1.82–0.88 (m) (22H total,  $C_6H_{11}$ ). <sup>31</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 100.62 MHz): 15.21 (d, <sup>4</sup>J<sub>CP</sub> = 1.2 Hz, CCy), 25.41 (d,  ${}^{2}J_{CP} = 10.7$  Hz, CCy), 28.07 (d,  ${}^{1}J_{CP} = 14.5$ Hz, CCy), 29.66 (d,  ${}^{3}J_{CP} = 9.4$  Hz, CCy),45.4 (d,  ${}^{1}J_{CP} = 19.8$  Hz, NCP), 115.8 (s, C<sub>6</sub>H<sub>5</sub>), 118.8 (s, C<sub>6</sub>H<sub>5</sub>), 128.3 (s, C<sub>6</sub>H<sub>5</sub>), 149.6 (s,  $C_6H_5$ ).

#### Synthesis of 1,5-diphenyl-3,7-dicyclohexyl-1,5-diaza-3,7diphosphacyclooctane palladium complex 2

To a 20 mL dichloromethane solution of 0.1 g (0.22 mmol) of 1,5diphenyl-3,7-dicyclohexyl-1,5-diaza-3,7-diphosphacyclooctane was dropwise added a solution of 0.05 g (0.22 mmol) of Pd(OAc)<sub>2</sub> in 10 mL of the same solvent. After stirring 2 h at room temperature, the solvent was removed under vacuum to give a solid that was washed with cold pentane and dried under vacuum to yield complex **2** as a brown solid (129 mg, 85%). <sup>31</sup>P{<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 161.96 MHz,  $\delta$  in ppm): 31.9 ppm (s).<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400.13 MHz): 1.5 (s, 6H, CH<sub>3</sub>), 2.1–0.9 (22 H total, C<sub>6</sub>H<sub>11</sub>), 4.13 (d, <sup>2</sup>J<sub>HH</sub> = 13.2 Hz, PCH<sub>2</sub>N), 4.42 (dd, <sup>2</sup>J<sub>HH</sub> = 14.2 Hz, <sup>2</sup>J<sub>PH</sub> = 5.7 Hz, PCH<sub>2</sub>N), 4.18 (d, <sup>2</sup>J<sub>HH</sub> = 12.8 Hz, PCH<sub>2</sub>N), MS (ES): *m*/*z* (%): 707.37 (100) [M – NH<sub>4</sub>]<sup>+</sup>.

A general procedure for the cross-coupling reaction is as follows: to a solution of 4-methoxyphenylboronic acid (1.14 g, 7.5 mmol), 4'-bromoacetophenone (995.25 mg, 5 mmol), K<sub>2</sub>CO<sub>3</sub> (1.38 g, 10 mmol), 1,5-diphenyl-3,7-dicyclohexyl-1,5-diaza-3,7-diphosphacyclooctane (2.34 mg, 5  $10^{-3}$  mmol, 0.1 mol%) and Pd(OAc)<sub>2</sub> (1.2 mg, 5  $10^{-3}$  mmol, 0.1 mol%) in 5 mL water was flushed with nitrogen and capped. The reaction mixture was heated and stirred in the oil bath at reflux for 2 h and the reaction mixture was extracted with dichloromethane (3 × 5 mL). The combined dichloromethane phase was dried with anhydrous MgSO<sub>4</sub>. The

organic layers were combined, dried over MgSO<sub>4</sub>, filtered and evaporated under reduced pressure. Purification of the crude product by flash chromatography on silica gel afforded 1070 mg of 4-acetyl-4'-methoxybiphenyl (91%) as white solid. <sup>1</sup>H NMR (400.13 MHz, CDCl<sub>3</sub>):  $\delta$  7.95 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H), 2.56 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  197.7, 159.9, 145.3, 135.3, 132.2, 128.9, 128.3, 126.6, 114.4, 55.4, 26.6.

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