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# Palladium-Catalyzed Suzuki Reactions in Water with no Added Ligand: Effects of Reaction Scale, Temperature, pH of Aqueous Phase, and Substrate Structure

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## **TOC FIGURE**



#### ABSTRACT

The heterogeneous palladium-catalyzed Suzuki reactions between model aryl bromides (4bromoanisole, 4-bromoaniline, 4-amino-2-bromopyridine, and 2-bromopyridine) and phenylboronic acid have been successfully conducted in water with no added ligand at the 100-mL scale using 20-40 millimoles of aryl bromide. The product yields associated with these substrates were optimized and key reaction parameters affecting the yields were identified. The results clearly indicate that *the reaction parameters necessary to achieve high yields are substrate dependent*. In addition, it is demonstrated that aqueous Suzuki reactions of substrates containing basic nitrogen centers can produce quantitative yields of desired products in the absence of added ligand.

**KEYWORDS:** palladium catalysis without added ligand, Suzuki reactions in water, heterogeneous catalysis, scale-up, green and sustainable Suzuki reactions.

#### **INTRODUCTION**

The palladium-catalyzed Suzuki-Miyaura coupling reaction has been extensively studied and widely used in both academia<sup>1-7</sup> and industry.<sup>8,9</sup> It is a particularly powerful synthetic strategy for the construction of numerous natural compounds, pharmaceuticals, agrochemicals, and polymers.<sup>3-9</sup> Typical systems for Suzuki coupling consist of an aryl bromide, an arylboronic acid or ester, catalytic quantities of Pd(0) or Pd(II) salts in the presence of a ligand, and the presence of added bases.<sup>10</sup> The reactions are usually conducted in an organic medium or in a biphasic organic-aqueous media. Ligand complexity can vary greatly as a function of the application and reaction system requirement. For example, Suzuki reactions with substrates that contain basic nitrogen centers, such as aromatic amines and pyridines, suffer from the limitations of slow rates and low yields<sup>11-14</sup> due to the competitive interaction between the basic nitrogen center and the palladium catalyst.<sup>14-17</sup> However, the development of customized ligands that strategically incorporate bulky and electron-rich groups enable high yields with reasonable rates.<sup>14,16,18</sup>

The increasing demand of modern chemical industry for green and sustainable processes calls for modifications of the Suzuki coupling conditions.<sup>19</sup> These modifications include the development of *ligand-free* catalytic systems and the use of environmentally benign solvents such as water or ionic liquids.<sup>7</sup> It is necessary to note that the terminologies of "ligand-free" and "ligandless" commonly used in literature specifically referred to a catalytic system with no added ligand. Although commercial or designer ligands have been successfully employed in developing Suzuki coupling processes, the economics associated with these ligands could be cost-prohibitive in large-scale production. As a consequence, methodologies that do not require added custom-designed or commercial ligands are desirable and have been explored.<sup>20-40</sup> In addition, compared to air-sensitive and expensive ligand-palladium complexes, ligand-free palladium catalysts (*e.g.* Pd(OAc)<sub>2</sub> and PdCl<sub>2</sub>) can be safely handled

and easily removed from the reaction mixture. The literature contains many examples of aqueous Suzuki coupling reactions being conducted successfully in both the presence and the absence of added ligand.<sup>25-56</sup> However, the limited solubility of the halogenated substrates and ligands in water often leads to slow rate and low yields. To overcome this limitation, alternative methodologies using water-soluble ligands,<sup>52-56</sup> organic co-solvents,<sup>25-32</sup> phase-transfer catalysts<sup>33,48-51</sup> and inorganic salt promoters,<sup>34,35</sup> and heating with microwave or ultrasound were reported.<sup>36-40</sup>

In 1989, Bumagin *et al.*<sup>57</sup> were the first to report a  $Pd(OAc)_2$  catalyzed Suzuki reaction of phenylboronic acid with aryl iodides containing a –OH or –COOH substituents; Na<sub>2</sub>CO<sub>3</sub> was employed as the base in neat water under an argon atmosphere. Later, a series of academic papers<sup>58-69</sup> reported palladium-catalyzed Suzuki couplings of various aryl and allylic halides (I, Br, Cl) with no added ligand or additives in hot water. Excellent yields (up to 99%) of cross-coupling products were reported. As of today, the ligand-free catalytic systems in water have proven to be successful on milliliter scales (*i.e.* up to 1 mmol of substrates with 1 ~ 5 mL of water). Few practical examples of larger scale Suzuki coupling reactions in water without any added ligand have been reported.<sup>70</sup> Data on scales between small labscale and commercial-scale reactions could have great importance for developing industrial processes. A major reason could be that the Suzuki reactions in water are heterogeneous; the catalyst and substrate have partial to minute solubility in water. Multiphasic systems are inherently difficult to scale-up. Mass transfer between phases and the possibility of interfacial reactions make the extrapolation of the results from small to larger scale difficult.

Although the current literature reports encouraging results for aqueous Suzuki coupling reactions without added ligand, the reported work has been limited to rather small-scale reaction systems which limit the scope and applicability of ligand-free processes.<sup>57-69</sup> In addition, a clear answer has not been provided on whether the current ligand-free/aqueous protocols are effective for the Suzuki couplings of

unprotected basic nitrogen containing substrates at scales greater than a few milliliters. Herein, we report 100-mL scale palladium-catalyzed Suzuki reactions with no added ligand in neat water involving four model substrates, three of which contain basic nitrogen centers. Pertinent reaction variables such as (a) reaction scale, (b) the relative amounts of the substrate, base, and Pd catalyst, and (c) the initial and final pH of the aqueous phase are reported.

#### **RESULTS AND DISCUSSION**

#### (1) Reaction Protocol Development for Model Aryl Bromide Substrates

While Suzuki coupling reactions in water with no added ligand have been reported in the literature, these reactions were conducted on a relatively small scale—usually 1 to 4 mL and sometimes at 10 mL involving only 0.5 - 1 mmol of substrates. It is important to note that all of these reactions were heterogeneous and, from a process point of view, mass transfer can become an issue as the scale of heterogeneous reaction processes is increased. In order to determine the best protocols for aqueous, ligand-free Suzuki reactions on a substantially larger scale (20-40 millimoles aryl bromide in 100 mL water), preliminary experiments were performed on a series of widely different aryl bromides with phenylboronic acid (PhB(OH)<sub>2</sub>). The aryl bromides investigated were 4-bromoanisole, 4-bromoaniline, 4-amino-2-bromopyridine, and 2-bromopyridine. It is important to note that the latter three substrates possess basic nitrogen centers which, in the absence of added ligand, could possibly act as ligands for the Pd catalyst and potentially retard or prevent successful coupling. This concern was an integral component of our protocol development. At the 100 mL scale, 20 or 40 mmol of aryl bromide were reacted with 1.1 equivalents of phenylboronic acid at 100 °C for periods of time varying from 1 to 4 hours (Scheme 1). In order to minimize the number of variables in this investigation dealing with the reaction scale, the pH of the aqueous phase, and the substrate structure, we chose to use an industrially

attractive base: K<sub>3</sub>PO<sub>4</sub>. It is inexpensive and easily separated from the organic product post-reaction. Each of these reactions was conducted under a nitrogen atmosphere. The use of an inert atmosphere was considered especially important for the substrates containing basic nitrogen centers which could be the points of reaction with atmospheric oxygen. The results are summarized in **Table 1**. The yields for all four model substrates are high and the isolated yields are consistent with the yields determined by GC and <sup>1</sup>H NMR. As a consequence, GC and/or <sup>1</sup>H NMR were employed for in-situ determination of the yields for the coupling reactions for a wide variety of aryl substrates presented later in this report.

Scheme 1. Palladium-Catalyzed Suzuki Coupling Reactions in Water with no Added Ligand



 Table 1. Comparison of Reaction Yields Determined by Various Analytic Methods

Entwy	A mul Duomido	Broduct	Time		Yield (%)		
Entry	Ary Aryr Dronnide Troduct		(h)	Isolated <sup>e</sup>	GC	<sup>1</sup> H NMR	
1 <sup>a</sup>	H <sub>3</sub> CO-Br (1)	H <sub>3</sub> CO-() (5)	4	75	74	76	
2 <sup>b</sup>	$H_2N \rightarrow Br$ (2)	$H_2N \longrightarrow (6)$	1	97	100	99	
3°	$H_2N$ $H_2N$ $H_2N$ $H_2$ H	$\overset{H_2N}{\swarrow} {\longrightarrow} {\longrightarrow} (7)$	1	100	100	100	
4 <sup>d</sup>	$\sim$ Br (4)	(8)	4	92	92	95	

<sup>a</sup> Reaction conditions: 4-bromoanisole (40 mmol), PhB(OH)<sub>2</sub> (44 mmol), K<sub>3</sub>PO<sub>4</sub> (84 mmol), Pd(OAc)<sub>2</sub> (5 mol%), H<sub>2</sub>O (100 mL), N<sub>2</sub>, 100 °C.

<sup>b</sup> Reaction conditions: 4-bromoaniline (40 mmol), PhB(OH)<sub>2</sub> (44 mmol), K<sub>3</sub>PO<sub>4</sub> (40 mmol), Pd(OAc)<sub>2</sub> (0.25 mol%), H<sub>2</sub>O (100 mL), N<sub>2</sub>, 100 °C.

<sup>c</sup> Reaction conditions: 4-amino-2-bromopyridine (40 mmol), PhB(OH)<sub>2</sub> (44 mmol), K<sub>3</sub>PO<sub>4</sub> (40 mmol), Pd(OAc)<sub>2</sub> (2 mol%), H<sub>2</sub>O (100 mL), N<sub>2</sub>, 100 °C.

<sup>d</sup> Reaction conditions: 2-bromopyridine (20 mmol), PhB(OH)<sub>2</sub> (22 mmol), K<sub>3</sub>PO<sub>4</sub> (22 mmol), Pd(OAc)<sub>2</sub> (2 mol%),

H<sub>2</sub>O (100 mL), N<sub>2</sub>, 100 °C. <sup>e</sup> by column chromatographic separation.

Several additional experimental observations are pertinent. (1) Visually the four model reactions differed greatly (**Table S1, Supporting Information (SI)**). For the reactions involving solid aryl bromides (4-bromoaniline and 4-amino-2-bromopyridine), two phases were observed—a solid phase composed of catalyst and substrate and an aqueous phase. In the case of the liquid aryl bromides (4-bromoanisole and 2-bromopyridine) an additional organic phase was present. (2) Under the conditions described in **Table 1**, PhB(OH)<sub>2</sub> was completely dissolved in the aqueous phase in the presence of base. (3) In all cases only small amounts (< 5%) of biphenyl were detected by both GC and <sup>1</sup>H NMR which is consistent with the homo-coupling of the excess PhB(OH)<sub>2</sub>. The homo-coupling of aryl bromide substrates was only observed in the reaction of 2-bromopyridine; approximately 10% of the substrate was consumed with the formation of 2,2'-bipyridyl. (4) With the exception of the 4-bromoanisole substrate, the formation of palladium black was not observed. It should be emphasized, however, that in this case 5 mol% Pd catalyst was employed compared to 0.25 mol% for 4-bromoaniline and 2 mol% for 4-amino-2-bromopyridine.

Using the above model reactions and accompanying protocols as points of reference the following variables were investigated in order to determine how certain critical parameters influence the yield of coupled product. These include (a) reaction scale, (b) the relative amounts of the substrate, base, and Pd catalyst employed, and (c) the initial and final pH of the aqueous phase. Each of the model substrates is addressed individually with respect to several of these reaction variables. The results of this study illustrate that the conditions necessary for maximizing yields of product is clearly substrate dependent.

#### (2) Suzuki Coupling Reactions of 4-Bromoanisole in Water with no Added Ligand

The results of the Suzuki cross-coupling of 4-bromoanisole with PhB(OH)<sub>2</sub> in water was conducted at scales ranging from 1-mL to 100-mL. The results are summarized in Table 2. In each of the experiments the ratio of substrate (1) to water was held constant. On 1-mL scale, the product yield obtained was only 37 % (Entry 1, Table 2) which is in agreement with the reported low yield (25%) by Liu *et al*<sup>65</sup> obtained using the identical catalytic system (Pd(OAc)<sub>2</sub>/K<sub>3</sub>PO<sub>4</sub>/H<sub>2</sub>O) conducted on the same reaction scale. The yield, however, increased to 68 - 77% at scales of 10 to 100 mL. It is important to note that the product yields were consistent regardless of the choice of reactor-glass tubes or roundbottom flasks (Entry 2 and 3, Table 2). In order to minimize or eliminate the possible impact of mass transfer on reaction rate and product yield all of these heterogeneous reactions were conducted with magnetic stirring at rates varying from 600 - 800 rpm. The results in **Table 2** suggest that with controlled stirring rates the Suzuki coupling reaction of 4-bromoanisole produces reasonably high yields at scales of 10 mL and greater.

#### Table 2. Scale-Dependent Yields of Suzuki Coupling Reactions of 4-Bromoanisole with PhB(OH)<sub>2</sub> in Water<sup>a</sup>

	$H_{3}CO + H_{3}CO + I$	Pd(OAc) <sub>2</sub> , K <sub>3</sub> PO <sub>4</sub> H <sub>2</sub> O, 100 ℃	H <sub>3</sub> CO 5				
4-Bromoanisole (mmol)/ $H_2O$ (mL) = 0.4							
Entry	4-Bromoanisole (mmol)	H <sub>2</sub> O (mL)	GC Yield (%)				
1 <sup>b</sup>	0.4	1	37				
2 <sup>b</sup>	4.0	10	68				
3°	4.0	10	69				
$4^{\rm c}$	20	50	77				
5 <sup>°</sup>	40	100	74				

<sup>a</sup> Reaction conditions: 4-bromoanisole (0.4 mmol/1 mL H<sub>2</sub>O, 1.0 equiv), PhB(OH)<sub>2</sub> (1.1 equiv), K<sub>3</sub>PO<sub>4</sub> (2.1 equiv), Pd(OAc)<sub>2</sub> (5 mol%), N<sub>2</sub>, 100 °C, 4 h.

<sup>b</sup> Reaction was run in a 20-mL Carousel reaction tube with magnetic stirrer.

<sup>c</sup> Reaction was run in a round-bottom flask with magnetic stirrer.

As indicated in **Table 2** all reactions were conducted under an inert nitrogen atmosphere. The question regarding the necessity for conducting this coupling reaction under an inert atmosphere was also explored. Companion experiments for the reaction of 4-bromoanisole were conducted in the presence of air or under a blanket of nitrogen (Pd(OAc)<sub>2</sub>, PhB(OH)<sub>2</sub>, K<sub>3</sub>PO<sub>4</sub>, 4 hours). The results are summarized in **Table S2**, **SI**. Similar product yields were obtained under both air and nitrogen and at two palladium catalyst loadings.

The effects of several reaction variables (mole% Pd catalyst, equivalents of PhB(OH)<sub>2</sub> and K<sub>3</sub>PO<sub>4</sub>, and reaction time) on the yield of coupled product in the reaction of 40 mmol of 4-bromoanisole with PhB(OH)<sub>2</sub> in 100 mL of water are summarized in **Table 3**. In addition, the measured initial and final pH of the aqueous phase for each entry is also indicated. A 46% yield of 4-methoxybiphenyl (**5**) was observed using 0.5 mol% of Pd(OAc)<sub>2</sub> in the presence of 2.1 equivalents of K<sub>3</sub>PO<sub>4</sub> over a reaction time of 4 hours (**Entry 1, Table 3**). This result is in stark contrast to the results obtained with 4-bromoaniline where only 0.25 mol % Pd was employed to achieve a quantitative yield (**Entry 2, Table 1**). Not surprisingly, the yields increase as the catalyst loading and the reaction time are increased (**Entries 2-5, Table 3**). Indeed, after 24 hours a product yield of 90% is achieved. In each of these cases, the initial and final pH of the aqueous phase varies less than 1 pH unit; the aqueous phase remained highly basic (pH varies from 11.4 to 10.3) throughout the course of reaction.

The effect of varying the equivalents of base is also summarized in **Table 3**. As the equivalents of base increases from 0.5 to 2.1 the yield steadily increases (**Entries 4 and 6-8, Table 3**). It appears, however, to plateau above 2.1 equivalents (**Entries 8 and 9, Table 3**). It is interesting to note that, other things being equal, reduced yields (25% and 49%, respectively) are obtained over the same period of time, when the final pH of the aqueous phase drops to 9 and below (**Entries 6 and 7, Table 3**). In all the other cases in **Table 3** high yields are realized when the initial and final pH of the aqueous phase

remains highly basic (pH above 10). The relationship between pH of aqueous phase and yield was investigated by means of the comparison between a series of aqueous Suzuki reactions carried out with various amounts of PhB(OH)<sub>2</sub>. Theoretically, the cross-couplings could be accelerated by increasing the amount of PhB(OH)<sub>2</sub>; however, the decrease in pH caused by excess PhB(OH)<sub>2</sub> was observed to be detrimental. For instance, when the amount of PhB(OH)<sub>2</sub> was increased from 1.1 to 2.0 equivalents, the resulting initial pH decreased from 11.0 to 10.1. The yield of the corresponding reactions dropped from 74% (Entry 4, Table 3) to 46% (Entry 10, Table 3). By adding an additional equivalent of PhB(OH)<sub>2</sub>, the detrimental effect of a lower pH was somewhat attenuated leading to a yield of 71% (Entry 11, 
**Table 3**). The use of excess of boronic acids is not synthetically attractive.

Table 3. Screening Conditions for 100-mL Scale Pd(OAc)<sub>2</sub> Catalyzed Suzuki Reaction of 4-Bromoanisole (1) and PhB(OH)<sub>2</sub> in H<sub>2</sub>O.<sup>a</sup> / 

	H₃CO			H₂O, 100 ℃	H <sub>3</sub> CO	5	
Entry	Pd(OAc) <sub>2</sub> (mol%)	PhB(OH) <sub>2</sub> (equiv)	K <sub>3</sub> PO <sub>4</sub> (equiv)	Time (h)	Yield <sup>b</sup> (%)	pl initial	H final
1	0.5	1.1	2.1	4	46	11.4	11.0
2	1	1.1	2.1	4	49	11.2	10.9
3	2	1.1	2.1	4	62	11.1	10.6
4	5	1.1	2.1	4	74	11.0	10.4
5	5	1.1	2.1	24	90	11.1	10.3
6	5	1.1	0.5	4	25	9.0	8.1
7	5	1.1	1.0	4	49	9.6	9.0
8	5	1.1	1.5	4	73	10.4	9.6
9	5	1.1	3.0	4	65	11.9	11.5
10	5	2.0	2.1	4	46	10.1	10.0
11	5	3.0	2.1	4	71	9.9	9.2

The effect of the amounts (millimoles) of arvl bromide in 100 mL of water on the yield of product was also investigated. The results are summarized in Table 4. In each of the experiments a

constant ratio of 4-bromoanisole, PhB(OH)<sub>2</sub>, K<sub>3</sub>PO<sub>4</sub> and Pd(OAc)<sub>2</sub> was employed. The results show that as the ratio of moles of aryl bromide to liters of water decreases the product yield increases from 74% to the mid-90's (**Entries 1, 3-6, Table 4**). Further decrease in this ratio resulted in a decrease in the yield to 74% (**Entry 7, Table 4**). No difference in yield was observed by just simply decreasing the scale of the reaction by a factor of two (**Entries 1 and 2, Table 4**); a consistent yield in the mid-70's was observed. In all cases reported in **Table 4** the initial pH of the aqueous phase was essentially constantapproximately 11 to 11.4. The final pH varied slightly from a pH of 10.7 to 9.8.

Table 4. Effect of the Amount of Aryl Bromide on the Heterogeneous Pd(OAc)<sub>2</sub> Catalyzed Suzuki Reaction of 4-Bromoanisole (1) and PhB(OH)<sub>2</sub> in H<sub>2</sub>O.<sup>a</sup>

	H3CO	Br +	$\begin{tabular}{ c c c c c c } \hline Pd(OAc)_2 & (5 \text{ mol}\%) \\ \hline K_3PO_4 & (2.1 \text{ equiv}) \\ \hline H_2O & (100 \text{ mL}) \\ 100 \ ^\circ\text{C}, 4 \text{ h} \end{tabular}$	H <sub>3</sub> CO	5	
	4-Bromoanisole	$H_2O$	4-bromoanisole/H <sub>2</sub> O	Yield <sup>b</sup>	pl	H
Entry	(mmol)	(mL)	(mol/L)	(%)	initial	final
1	40	100	0.4	74	11.0	10.4
2	20	50	0.4	77	11.1	10.7
3	30	100	0.3	92	11.2	10.6
4	20	100	0.2	96	11.4	10.2
5	10	100	0.1	93	11.4	10.1
6	4	100	0.04	95	11.4	9.9
7	1	100	0.01	74	11.4	9.8

<sup>a</sup> Reaction conditions: 4-bromoanisole (1.0 equiv), PhB(OH)<sub>2</sub> (1.1 equiv), K<sub>3</sub>PO<sub>4</sub> (2.1 equiv), Pd(OAc)<sub>2</sub> (5 mol%), H<sub>2</sub>O (100 mL), N<sub>2</sub>, 100 °C, 4 h. <sup>b</sup> GC vield

#### (3) Suzuki Coupling Reactions of 4-Bromoaniline in Water with no Added Ligand

In contrast to 4-bromoanisole, 4-bromoaniline has a relatively basic nitrogen center. The effect of the mol % catalyst loading and the number of equivalents of  $K_3PO_4$  are summarized in **Table 5**. Quantitative yields of product were realized with a catalyst loading of 0.25 mol%. Indeed, a 98% yield was achieved with 0.25 mol% catalyst in 30 minutes of reaction time (**Entry 9, Table 5**). These results are in stark contrast to 4-bromoanisole where 5 mol% catalyst was needed to achieve reasonable results.

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What was surprising was that the Suzuki coupling reaction of 4-bromoaniline appears to be insensitive to the pH of the aqueous phase. Indeed, in several of the experiments the product yield remained high even though the pH dropped to the near neutral range (**Entries 6-9, Table 5**). It is noted that the optimized reaction condition set (**Entry 8, Table 5**) was found to be scalable, which can be readily applied to quantitatively produce the cross-coupling product **6** on 50-gram scale (**Entry 10, Table 5**).

 Table 5. Screening Conditions for 100 to 750 mL-Scale Pd(OAc)<sub>2</sub> Catalyzed Suzuki Reaction of 4 

 Bromoaniline (2) and PhB(OH)<sub>2</sub> in H<sub>2</sub>O.<sup>a</sup>

	$H_2N$ 2	Br + B(	OH) <sub>2</sub> Pd(OAc) <sub>2</sub> , H H <sub>2</sub> O, 100	$4_{3}PO_{4}$ $H_{2}N$	6	
	Pd(OAc) <sub>2</sub>	K <sub>3</sub> PO <sub>4</sub>	Time	Yield <sup>b</sup>	pl	H
Entry	(mol%)	(equiv)	(h)	(%)	initial	final
1	5	2.1	4	100	11.2	9.9
2	2	2.1	4	100	11.3	10.2
3	0.5	2.1	4	100	11.5	10.2
4	0.25	2.1	4	100	11.5	10.2
5	0.10	2.1	4	99	11.8	10.4
6	0.25	1.0	4	100	10.3	7.3
7	0.25	0.5	4	86	9.2	6.5
8	0.25	1.0	1	100	10.3	7.4
9	0.25	1.0	0.5	98	10.1	7.4
$10^{\circ}$	0.25	1.0	1	99	10.3	7.4

<sup>a</sup> Reaction conditions: 4-bromoaniline (40 mmol, 1 equiv), PhB(OH)<sub>2</sub> (44 mmol, 1.1 equiv), H<sub>2</sub>O (100 mL), N<sub>2</sub>, 100 °C.

<sup>b</sup> GC yield

<sup>c</sup> 50-gram scale reaction: 4-bromoaniline (300 mmol), PhB(OH)<sub>2</sub> (330 mmol), H<sub>2</sub>O (750 mL), N<sub>2</sub>, 100 °C.

The coupling reaction of 4-bromoaniline was investigated at five temperatures: 40, 60, 70, 80, and 100°C. The results are tabulated and graphically illustrated in **Table 6** and **Figure 1**. At 40 and 60°C the measured yields after 1 hour were 10% and 52%, respectively. At 70°C and higher, the yields ranged from 97 to 100%. Also note that at the higher temperatures the pH of the aqueous phase changed by

approximately 3 pH units; the final pH was near the neutral range (7.4-7.8).

# Table 6. Temperature Effects on the 100-mL Scale Suzuki Reaction of 4-Bromoaniline (2) with PhB(OH)<sub>2</sub> in H<sub>2</sub>O with no Added Ligand.<sup>a</sup>

	H <sub>2</sub> N 2	H B(OH)	$\frac{Pd(OAc)_2, K_3PO_4}{H_2O, 1 h}$	H <sub>2</sub> N 6	
	Temperature	Yield <sup>b</sup>		pН	
Entry	(°C)	(%)	initial	Final	ΔpH <sup>c</sup>
1	40	10	10.4	9.9	0.5
2	60	52	10.2	9.2	1.0
3	70	97	10.1	7.8	2.3
4	80	98	10.3	7.6	2.7
5	100	100	10.3	7.4	2.9

<sup>a</sup> Reaction conditions: 4-bromoaniline (40 mmol), PhB(OH)<sub>2</sub> (44 mmol), K<sub>3</sub>PO<sub>4</sub> (40 mmol), Pd(OAc)<sub>2</sub> (0.25 mmol%), H<sub>2</sub>O (100 mL), N<sub>2</sub>, 1 h. <sup>b</sup> GC yield

 $^{\circ}\Delta pH = initial pH - final pH$ 



Figure 1. Temperature effects on the Suzuki reaction of 4-bromoaniline with  $PhB(OH)_2$  in  $H_2O$  without added ligand, also reported in **Table 6**.

The high yields associated with the reaction of 4-bromoaniline with phenylboronic acid were maintained when the source of Pd catalyst was varied (**Table 7**). In fact, all of the Pd (II) catalysts (**Entries 1 – 7, Table 7**) exhibited very high catalytic activity in both the absence and the presence of a ligand. Quantitative yields were realized with all the Pd catalysts initially in the +2 oxidation state. In

contrast, Pd/C, a heterogeneous catalyst, did not give a good yield of product (**Entry 8, Table 7**) within the one hour time frame used in this comparative investigation.<sup>65</sup>

#### Table 7. The Effect of Palladium Catalysts on the 100-mL Scale Suzuki Reaction of 4-Bromoaniline (2) and PhB(OH)<sub>2</sub> in H<sub>2</sub>O.<sup>a</sup>

	$H_2N$ $2$ $+$ $H_2N$ $+$ H_2N $+$ $H_2N$	$\begin{array}{c} \underline{Pq}, \kappa_3 PO_4 \\ \hline H_2O, 100 \ ^{\circ}C, 1 \ h \\ H_2 \end{array}$		
		Yield <sup>b</sup>	рН	
Entry	[Pd] Catalyst	(%)	Initial	final
1	$Pd(OAc)_2$	100	10.3	7.4
2	$Pd(CF_3COO)_2$	98	10.3	7.6
3	PdCl <sub>2</sub>	98	10.1	7.5
4	$K_2PdCl_4$	95	10.4	7.7
5	$Pd(acac)_2$	100	10.5	7.6
6	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub>	99	10.4	7.6
7	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	96	10.4	7.8
8	Pd ( $10\%$ wt on C)	25	10.3	9.7

<sup>a</sup> Reaction conditions: 4-bromoaniline (40 mmol), PhB(OH)<sub>2</sub> (44 mmol), K<sub>3</sub>PO<sub>4</sub> (40 mmol), [Pd] (0.25 mol%), H<sub>2</sub>O (100 mL), N<sub>2</sub>, 100 °C, 1 h. <sup>b</sup> GC yield

The excellent results obtained with 4-bromoaniline prompted employing the developed protocol for several bromo anilines with a variety of aryl boronic acids and esters. The reactions were conducted with 0.25 mol% Pd(OAc)<sub>2</sub> and 1.0 equivalents of  $K_3PO_4$  at 100 °C in water for one hour. The results are summarized in **Table 8**. Arylboronic acids with electron-donating and electron-withdrawing groups underwent reactions with 4-bromoaniline efficiently to afford the desired products in good to excellent yields (**Entries 1 – 5, Table 8**). High yields were also observed in the reactions of 3-bromoaniline and 2-methyl-4-bromoaniline (**Entries 6 – 8, Table 8**). The reaction of 2-bromoaniline, in contrast, resulted in a somewhat lower yield (79%). This observation could be presumably due to the steric effects between the amino group and the adjacent bromine atom (**Entry 9, Table 8**).<sup>69</sup> The current protocol was not as effective for the Suzuki couplings of 4-bromobenzylamine (an aliphatic amine substrate), 2amino-5-bromopyridine and 4-amino-2-bromopyridine (Entries 10-12, Table 8). Only a 13% yield was achieved with 4-bromobenzylamine while the yields associated with 2-amino-5-bromopyridine and 4-amino-2-bromopyridine were 37% and 29%, respectively.

Table 8. Pd(OAc)<sub>2</sub> Catalyzed Suzuki Reactions of NH<sub>2</sub>-Containing Aryl Bromide and Aryl Boronic Acids (Esters) in H<sub>2</sub>O.

Entry	Ar-Br	Ar'-BX	Product	Yield (%)
1 <sup>a</sup>	H <sub>2</sub> N-	B(OH) <sub>2</sub>		100 <sup>c</sup>
2 <sup>a</sup>	H <sub>2</sub> N-	B_0 ⊂	H <sub>2</sub> N-	97°
3 <sup>a</sup>	H <sub>2</sub> N-	O= →B(OH) <sub>2</sub>		98 <sup>d</sup>
4 <sup>b</sup>	H <sub>2</sub> N-	H <sub>2</sub> N B(OH) <sub>2</sub>		95°
5 <sup>b</sup>	H <sub>2</sub> N-	H <sub>3</sub> CO-		88°
6 <sup>a</sup>	H <sub>2</sub> N-	B(OH)2	H <sub>2</sub> N	99 <sup>d</sup>
$7^{\mathrm{a}}$	H <sub>2</sub> N-	⟨B_O	H <sub>2</sub> N	100 <sup>c</sup>
8 <sup>a</sup>	H <sub>3</sub> C H <sub>2</sub> N-	B(OH)2	$H_3C$ $H_2N$	97 <sup>d</sup>
9 <sup>a</sup>	Br H <sub>2</sub> N	B(OH) <sub>2</sub>	NH <sub>2</sub>	79°
10 <sup>a</sup>	H <sub>2</sub> N Br	B(OH) <sub>2</sub>	$H_2N$	13 <sup>c</sup>
11 <sup>a</sup>	H <sub>2</sub> N-	B(OH) <sub>2</sub>		37°
12 <sup>a</sup>	H <sub>2</sub> N -Br	B(OH) <sub>2</sub>	H <sub>2</sub> N	29 <sup>c</sup>

<sup>a</sup> 40 mmol/100-mL scale. Reaction conditions: aryl bromide (40 mmol), aryl boronic acid (ester) (44 mmol), K<sub>3</sub>PO<sub>4</sub> (40 mmol), Pd(OAc)<sub>2</sub> (0.25 mol%), H<sub>2</sub>O (100 mL), N<sub>2</sub>, 100 °C, 1 h.
<sup>b</sup> 20 mmol/50-mL scale. Reaction conditions: aryl bromide (20 mmol), aryl boronic acid (22 mmol), K<sub>3</sub>PO<sub>4</sub> (20 mmol), Pd(OAc)<sub>2</sub> (0.25 mol%), H<sub>2</sub>O (50 mL), N<sub>2</sub>, 100 °C, 1 h.

<sup>c</sup>GC yield

<sup>d</sup> Isolated yield

#### (4) Suzuki Coupling Reactions of Bromopyridines in Water with no Added Ligand.

Two typical bromopyridines (4-amino-2-bromopyridine and 2-bromopyridine) were selected as the substrates for the Suzuki cross-couplings with PhB(OH)<sub>2</sub> using Pd(OAc)<sub>2</sub>/K<sub>3</sub>PO<sub>4</sub> in water under a N<sub>2</sub> atmosphere with no added ligand. The results for 4-amino-2-bromopyridine (**3**) are reported in **Table 9**. Increasing the Pd(OAc)<sub>2</sub> loading from 0.25 to 2 mol% resulted in an increase in yield from 29 to 94% (**Entries 1 – 4, Table 9**). Higher catalyst loading did not show significant effect (**Entry 5, Table 9**). The reaction is relatively fast. In a time period of just 1 hour excellent yields were achieved. Longer reaction times lead to marginal increases in yield (**Entries 7 and 8, Table 9**). Recalling **Entry 3, Table 1**, a quantitative yield of product was isolated when 40 mmol of aryl bromide was reaction on a 100 mL scale under the same conditions over a reaction period of one hour. **Table 9** reveals interesting information concerning the relationship of the change in pH during the course of reaction and the product yield. It appears that when the pH is allowed to ultimately reach a value of approximately 8.4 during the course of reaction, the highest yields were achieved (**Entries 4, 5, 7, and 8, Table 9**). These observations are consistent with those reported by Senter *et al.*<sup>71</sup> who showed that in an acetonitrile-water solvent system the best yield for this reaction was realized at an aqueous pH of approximately 8.

	N N	+	H <sub>2</sub> O, 100 <sup>G</sup>		-	
	3	~		~	7	-
Entry	Pd(OAc) <sub>2</sub> (mol%)	Base (equiv)	Time (h)	GC Yield (%)	pl initial	H fina
1 <sup>a</sup>	0.25	1.0	1	29	10.1	10.0
2 <sup>b</sup>	0.5	1.0	1	49	10.4	9.9
3 <sup>b</sup>	1	1.0	1	82	10.4	9.0
4 <sup>b</sup>	2	1.0	1	94	10.3	8.5
5 <sup>b</sup>	5	1.0	1	95	10.4	8.3
6 <sup>b</sup>	1	2.0	1	22	11.9	11.0
7 <sup>b</sup>	2	1.0	2	96	10.0	8.3
8 <sup>b</sup>	2	1.0	4	97	10.1	8.4

Table 9. Suzuki Reaction of 4-Amino-2-bromopyridine (3) and PhB(OH)<sub>2</sub> in H<sub>2</sub>O.

<sup>a</sup> 40 mmol/100-mL scale, Reaction conditions: 4-amino-2-bromopyridine (40 mmol, 1 equiv), PhB(OH)<sub>2</sub> (44 mmol, 1.1 equiv), H<sub>2</sub>O (100 mL), N<sub>2</sub>, 100 °C.
 <sup>b</sup> 20 mmol/50-mL scale, Reaction conditions: 4-amino-2-bromopyridine (20 mmol, 1 equiv), PhB(OH)<sub>2</sub> (22 mmol, 1.1 equiv), H<sub>2</sub>O (50 mL), N<sub>2</sub>, 100 °C.

The results for the reaction of 2-bromopyridine (**4**) with PhB(OH)<sub>2</sub> in water are summarized in **Table 10**. As the number of equivalents of catalyst is changed from 0.5 to 1.1-1.5 the yield of product increases from 50% to 74% (**Entries 1-4, Table 10**). Increasing the amount of catalyst further results in a reduction in the yield (**Entries 5 and 6, Table 10**). For comparison, it is noted that using the optimal protocol for 4-amino-2-bromopyridine which produced a product yield of 96% (**Entry 7, Table 9**) only a 74% yield was obtained in the reaction of 2-bromopyridine accompanied by an 82% conversion (**Entry 3, Table 10**). The difference between the yield and conversion was partially due to the formation of 2,2'-bipyridine formed via the homo-coupling of 2-bromopyridine (**Table S1, SI**). Our previous report indicated that the cross-coupling of 2-bromopyridine (**4**) with PhB(OH)<sub>2</sub> using Pd(TPP)<sub>2</sub>Cl<sub>2</sub>/K<sub>3</sub>PO<sub>4</sub> in acetonitrile-water required a pH of 12 or greater in the aqueous phase to reach the quantitative yield.<sup>71</sup> However, this reaction did not perform as well with the present catalytic system (Pd(OAc)<sub>2</sub>/K<sub>3</sub>PO<sub>4</sub>/H<sub>2</sub>O) when the initial pH was greater than 12 (**Entries 5 and 6, Table 10**). The best yields at 50 mL-scale reactions were observed at the initial pH range of 11 – 12, when 1.1 or 1.5

equivalents of K<sub>3</sub>PO<sub>4</sub> were used. However, it seems that the yield plateaued at about 75% under these conditions (Entries 3 and 8, Table 10). Interestingly, yields increased to 92% when the amount of water increased by a factor of 2 (Compare Entries 3 and 9, Table 10).

Table 10. Suzuki Reaction of 2-Bromopyridine (4) and PhB(OH)<sub>2</sub> in H<sub>2</sub>O.<sup>a</sup>

	ĺ	→Br →N + 4	B(OH	) <sub>2</sub> Pd(OAc) <sub>2</sub> , K <sub>3</sub> PO <sub>4</sub> ► H <sub>2</sub> O, 100 °C			
<b>F</b> 4	H <sub>2</sub> O	$K_3PO_4$	Time	Conversion of (4) <sup>b</sup>	Yield of $(8)^{b}$	<u>pl</u>	<u>H</u>
Entry	(mL)	(equiv)	(n)	(%)	(%)	Initial	linai
1	50	0.5	4	57	50	9.4	6.9
2	50	0.75	4	64	57	10.2	8.2
3	50	1.1	4	82	74	11.0	8.7
4	50	1.5	4	82	74	11.7	9.9
5	50	2.1	4	59	45	12.2	11.4
6	50	3.0	4	42	28	12.2	11.9
7	50	1.1	2	76	69	10.9	9.0
8	50	1.1	24	87	77	10.9	8.5
9	100	1.1	4	100	92	10.6	8.1
10	100	1.1	2	94	87	10.5	8.1

<sup>a</sup> Reaction conditions: 2-bromopyridine (20 mmol, 1 equiv), PhB(OH)<sub>2</sub> (22 mmol, 1.1 equiv), Pd(OAc)<sub>2</sub> (0.4 mmol, 2 mol%), N<sub>2</sub>, 100 °C. <sup>b</sup> Determined by GC

#### (5) Speciation of Palladium in Suzuki Coupling Reactions in Water with no Added Ligand.

Since 2000s, the use of Pd nanoparticles (Pd NPs) in the coupling reactions has attracted more and more interest from both academia and industry.<sup>72-73</sup> These reusable catalysts do not only meet the demand of modern chemical synthesis for sustainability, but can also further decrease the process cost by lowering the loading of expensive Pd, sometimes as low as ppm level.<sup>74</sup> In order to avoid the deactivation by aggregating to low surface-area bulk metal (such as Pd black) during the synthesis and utilization of Pd NPs, two methods have been often employed: (1) using an electrostatic and/or steric stabilizer and (2) immobilization of Pd NPs on a heterogeneous support.<sup>72</sup> At this juncture the question

arises as to whether Pd NPs can form in situ under our ligand-free/water conditions and play an important role therein.

Under the reaction conditions with no added ligand when water and PhB(OH) are present, Pd(OAc)<sub>2</sub> can rapidly generate catalytically active Pd(0) molecules, which undergo aggregation to form nanoclusters, nanoparticles and, eventually, Pd black (**Figure 2**).<sup>75,76</sup> This process was confirmed by our observation of Pd black formation in the reaction of 4-bromoanisole with PhB(OH) using Pd(OAc)<sub>2</sub>/K<sub>3</sub>PO<sub>4</sub>/H<sub>2</sub>O. However, in the other three model reactions, no Pd black formation was visually observed throughout the course of reactions presumably due to the stabilization of Pd(0) by the basic nitrogen atoms in 4-bromoaniline, 2-bromopyridine and 4-amino-2-bromopyridine, as well as their coupled products. In contrast, Pd black formed rapidly at the initial stage of the reaction of 4bromoanisole, since nothing in the reaction system can act as an in-situ ligand to stabilize the active Pd(0) species against aggregation. That is why more Pd(OAc)<sub>2</sub> (5 mol%) was required in this case to maintain a reasonable reaction rate compared to the other three model reactions (0.25 mol% for 4bromoaniline and 2 mol% for 4-amino-2-bromopyridine and 2-bromopyridine).



Figure 2. Process of catalyst activation and deactivation by aggregation.<sup>75</sup>

The interactions between the basic nitrogen centers and Pd(0) can also be verified by the classic mercury test, since the addition of excess of Hg(0) (relative to the Pd catalyst) will lead to the amalgamation of the surface of a Pd particle, thus poisoning it.<sup>77,78</sup> The resulting deactivation effect is

always obvious for a catalytic system containing heterogeneous and unprotected Pd(0) species.<sup>79</sup> When we added 150 - 400 equivalents of Hg (0) (relative to Pd(OAc)<sub>2</sub>) to the four model reactions at t = 0, the catalytic deactivation effect was observed in all of reactions at varying levels (Table 11). Not unexpectedly, the largest impact occurred in reaction of 4-bromoanisole. The reaction yield was greatly decreased from 76% to 22% by adding 200 equivalents of Hg(0) (Entry 1, Table 11). For the cases of 4-bromoaniline and 2-bromopyrinde, the influence of Hg(0) on the coupling reactions was modest, since their basic nitrogen centers can act as an in-situ ligand to protect the catalytically active and watersoluble Pd(0) species. About 30% and 20% lower yields were observed, respectively, compared with the reactions conducted in the absence of Hg(0) (Entries 2 and 3, Table 11). Interestingly, the deactivation effect by adding Hg(0) was not observed in the high-yield reaction of 4-amino-2-bromopyridine (Entry 4, Table 11). It indicated that the two nitrogen atoms act as effective ligands to favor the formation of homogeneous catalytic species which allowed the reaction to complete. If the coupling rate was decreased by lowering the catalyst loading and more Hg(0) was added, the deactivation effect of amalgamation turned to more significant (Entry 5, Table 11).

Table 11. Merce	ury rest for th	e ru(OA	c) <sub>2</sub> Catalyzed Suzuki (	Couplings of M	louel Aryl Brol	maes
with PhB(OH) <sub>2</sub>	in Water					
		Time	without Hg (0)	wit	n Hg(0)	
Arvl-Br		Time	GC Yield	GC Yield	Hg (equiv)	_ Entry

for the Dd(OAs) Catalyzed Symply Couplings of M

	II Water					
		Time	without Hg (0)	wit	h Hg(0)	_
Aryl-Br	(mol%)	(h)	GC Yield (%)	GC Yield (%)	Hg (equiv) relative to Pd	Entry
H <sub>3</sub> CO-	5	4	76	22	200	$1^{a,b}$
H <sub>2</sub> N-	0.25	1	100	67	400	2 <sup>a,c</sup>

3<sup>a,d</sup>

4<sup>a,c</sup>

5<sup>a,c</sup>

<sup>a</sup> Aryl-Br (4.0 mmol), PhB(OH)<sub>2</sub> (4.4 mmol), H<sub>2</sub>O (10 mL), N<sub>2</sub>, 100 °C.

0.25

 $^{b}$  K<sub>3</sub>PO<sub>4</sub> (8.4 mmol)

 $^{c}$  K<sub>3</sub>PO<sub>4</sub> (4.0 mmol)

<sup>d</sup>  $K_3PO_4$  (4.4 mmol)

The catalytic deactivation observed from our mercury test (**Table 11**) confirms that there are several competing catalytic pathways; both heterogeneous and homogeneous catalytic pathways are occurring, as previously reported in literature. The active Pd(0) particles play an important role in the mechanism of Suzuki couplings in water without added ligand. As early studies indicated,<sup>11-17</sup> the coupling process can be retarded by the competitive interactions between the basic nitrogen centers and Pd catalyst, meanwhile, the resulting complexes can also efficiently protect the Pd(0) from deactivation by aggregation (or amalgamation in the mercury test) and stabilize the soluble catalytic species, enabling homogeneous catalysis. The advantage of the latter effect probably overcame the negative influence of the former one under our ligand-free/water conditions. These two competitive effects can also be employed to rationalize the high reactivity of 4-bromoaniline. It is conjectured that the strength of the ligation has to be balanced to favor stabilization of the Pd-species from aggregation over catalytic inhibition

The influence of aromatic  $-NH_2$  on the aqueous Suzuki couplings in the absence of added ligand was further investigated in the reaction of 4-bromoanisole with 3-aminophenylboronic acid, which produced 86% yield of desired coupling product using only 0.25 mol% of Pd(OAc)<sub>2</sub> and over a short time period of 1 h (**Figure 3**). In contrast, a 49% yield (**Entry 7, Table 3**) was obtained from the reaction between 4-bromoanisole and phenylboronic acid using 5 mol% of catalyst and over 4 h. Another important observation of the reaction in **Figure 3** is that Pd black was not formed during the entire reaction course. This has been interpreted to mean that the aromatic  $-NH_2$  in the aryl boronic acid can still play a role in preventing the aggregation of the Pd(0) species, thus promoting the coupling process.

#### **Organic Process Research & Development**



**Figure 3**. Suzuki reaction of 4-bromoanisole with 3-aminophenylboronic acid using  $Pd(OAc)_2/K_3PO_4/H_2O$  in the absence of added ligand.

Lastly, the question still remains regarding the nature of the Pd catalyst under the ligandfree/H<sub>2</sub>O conditions. It is probably a mixture of Pd(0) species with a wide range from molecular to colloidal and fine particles, all possessing different reactivities and different contributions to the coupling process. The basic nitrogen centers in the substrates and products appear to be conductive to prevent the aggregation of catalyst and maintaining the activity of the Pd(0) species. However, for the case with reaction partners without nitrogen coordinating centers, the aggregation of active Pd(0) cannot be avoided; rapid formation of Pd black usually results.

#### **CONCLUSIONS**

In summary, the heterogeneous palladium-catalyzed Suzuki reactions between aryl bromides and phenyl boronic acid in water with no added ligand have been successfully conducted at the 100-mL scale. The reaction of 4-bromoaniline has been successfully scaled up to 50-gram/750-mL scale. The product yields associated with four model substrates were optimized and key reaction parameters affecting the yields were identified. The results clearly indicate that *the reaction parameters necessary to achieve high yields are substrate dependent*. The results in **Tables 5**, **9 and 10** clearly indicated that Suzuki reactions of basic nitrogen containing substrates in water without any added ligand can produce quantitative yields of desired products. The basic nitrogen atoms were presumed to act as in-situ ligands and stabilize the active Pd(0) against deactivation such as aggregation. From a synthetic view point, the

protection of the amino functionality in order to perform Suzuki coupling is not required, thus saving the need for protection-deprotection steps. The scale-up of the heterogeneous aqueous Suzuki reactions in the absence of added ligand presented in this report offers an operational approach to the development of green and sustainable Suzuki reaction processes.

#### EXPERIMENTAL

**General Method.** All solvents and reagents were purchased from Sigma-Aldrich in reagent grade and were used without further purification. 50 to 100-mL scale reactions were carried out in 3-neck round-bottom flasks equipped with a magnetic stirrer and heating mantle. Small scale ( $\leq 10$  mL of solvent) reactions were performed in 20-mL reaction tubes on a Radleys Carousel 12 Plus<sup>TM</sup> Reaction Station. pH values of the aqueous phase were measured by a Cole-Parmer pH 20 meter with "All-in-One" electrode at 25 ± 2 °C. All products were isolated by chromatography on a silica gel (40 – 60 µm) or neutral alumina (32 – 60 µm) column using CH<sub>2</sub>Cl<sub>2</sub> – hexane as eluent.

Melting points were measured on a Mel-Temp capillary melting point apparatus. <sup>1</sup>H (400 MHz) and <sup>13</sup>C (100 MHz) NMR Spectra were recorded on a Varian Mercury Vx 400 spectrometer. Chemical shifts ( $\delta$ ) are reported in ppm relative to TMS and coupling constants (*J*) are in Hz. GC analyses were carried out on a Shimazu GCMS-QP2010S Gas Chromatograph (qualitative) and a Shimazu GC-2010 w/FID Gas Chromatograph (quantitative).

General Procedure for the 50 and 100-mL Scale Suzuki Reactions. A mixture of aryl bromide, arylboronic acid, base, Pd catalyst and solvent in a 3-neck round-bottom flask was well stirred under reflux for the requisite time. The initial and final pH values of the aqueous phase were measured before and after the heating was enabled when the temperature was stabilized at 25 - 27 °C. The cooled reaction mixture was thoroughly extracted with CH<sub>2</sub>Cl<sub>2</sub> or ethyl acetate. The combined organic phase

was dried over anhydrous MgSO<sub>4</sub>, filtered, and then concentrated in *vacuo*. The crude product was analyzed by GC and <sup>1</sup>H NMR following the published methods.<sup>71</sup> The pure product was isolated from a chromatography column packed with silica gel (for the reaction of 4-bromoanisole) or neutral alumina (for reactions containing  $-NH_2$  group) using CH<sub>2</sub>Cl<sub>2</sub> – hexane as eluent. The isolated yields were determined by mass.

General Procedure for the 1 and 10-mL Scale Suzuki Reactions. This study was carried out in a Radleys Carousel 12  $Plus^{TM}$  Reaction Station under N<sub>2</sub> with a reflux head connecting to Lauda E200 refrigerating circulator. The temperature of recirculating coolant is set at 10 °C. In each 20-mL Carousel's reaction tube, a mixture of aryl bromide, phenylboronic acid, Pd(OAc)<sub>2</sub>, K<sub>3</sub>PO<sub>4</sub> and water was stirred at the desired temperature for the indicated reaction time. The same methods as large labscale reactions were used in the subsequent procedures of work-up and evaluation of reaction performance.

**Procedure for 50-Gram Scale Suzuki Reactions.** In a 2-L 3-neck round-bottom Morton flask equipped with a condenser, a mechanical stirrer, and a thermometer, and maintained under nitrogen atmosphere was charged with 4-bromoaniline (51.61 g, 300 mmol), PhB(OH)<sub>2</sub> (40.24 g, 330 mmol),  $K_3PO_4$  (63.68 g, 300 mmol), Pd(OAc)<sub>2</sub> (0.168 g, 0.25 mol%) and H<sub>2</sub>O (750 mL). The reaction mixture was well stirred (500 rpm) under reflux at 100 °C for one hour. The initial and final pH values of the aqueous phase were measured before and after the heating was enabled when the temperature was stabilized at room temperature. The cooled reaction mixture was thoroughly extracted with  $CH_2Cl_2$  (3 × 100 mL). The combined organic phase was washed with brine (200 mL) and water (2 × 200 mL), dried over anhydrous MgSO<sub>4</sub>, filtered, and then concentrated in *vacuo*. An almost quantitative yield of crude product (dark brown solid) was obtained, which included more than 99% of target product analyzed by GC.

**Procedure for Mercury Test.** A mixture of aryl bromide (4 mmol, 1.0 equiv), PhB(OH)<sub>2</sub> (4.4 mmol, 1.1 equiv),  $K_3PO_4$ , Pd(OAc)<sub>2</sub>, mercury (99.9+%) and water (10 mL) in a 50-mL 3-neck roundbottom flask was well stirred under reflux at 100 °C in N<sub>2</sub> for requisite time. The cooled reaction mixture was thoroughly extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL). The combined organic phase was dissolved in methanol and measured in a 100 mL volumetric flask. An aliquot of the organic solution was taken for GC analysis. A reference reaction in the absence of mercury was always conducted under the same reaction conditions for the sake of comparison.

#### ASSOCIATED CONTENT

#### **Supporting Information**

Experimental details and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra of synthesized compounds.

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#### Note

The authors declare no competing financial interest

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### REFERENCE

(1) Miyaura, N.; Suzuki, A. Stereoselective Synthesis of Arylated (E)-Alkenes by the Reaction of Alk-1-Enylboranes with Aryl Halides in the Presence of Palladium Catalyst. *J. Chem. Soc. Chem. Comm.* **1979**, 866-867.

(2) Miyaura, N.; Yamada, K.; Suzuki, A. New Stereospecific Cross-Coupling by the Palladium-Catalyzed Reaction of 1-Alkenylboranes with 1-Alkenyl or 1-Alkynyl Halides. *Tetrahedron Lett.* **1979**, *20*, 3437-3440.

(3) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457-2483.

(4) Suzuki, A. Recent Advances in the Cross-Coupling Reactions of Organoboron Derivatives with Organic Electrophiles, 1995-1998. *J. Organomet. Chem.* **1999**, *576*, 147-168.

(5) Kotha, S.; Lahiri, K.; Kashinath, D. Recent Applications of the Suzuki-Miyaura Cross-Coupling Reaction in Organic Synthesis. *Tetrahedron* **2002**, *58*, 9633-9695.

(6) Bellina, F.; Carpita, A.; Rossi, R. Palladium Catalysts for the Suzuki Cross-Coupling Reaction: An Overview of Recent Advances. *Synthesis-Stuttgart* **2004**, 2419-2440.

(7) Alonso, F.; Beletskaya, I. P.; Yus, M. Non-Conventional Methodologies for Transition-Metal Catalysed Carbon-Carbon Coupling: a Critical Overview. Part 2: The Suzuki Reaction. *Tetrahedron* **2008**, *64*, 3047-3101.

(8) Magano, J.; Dunetz, J. R. Large-Scale Applications of Transition Metal-Catalyzed Couplings for the Synthesis of Pharmaceuticals. *Chem. Rev.* **2011**, *111*, 2177-2250.

(9) Jiao, J.; Nishihara, Y.: Pharmaceuticals. In *Applied Cross-Coupling Reactions*; Nishihara, Y., Ed.; Springer-Verlag: Berlin Heidelberg, 2013; pp 85-109.

(10) Amatore, C.; Le Duc, G.; Jutand, A. Mechanism of Palladium-Catalyzed Suzuki-Miyaura Reactions: Multiple and Antagonistic Roles of Anionic "Bases" and Their Countercations. *Chem.Eur. J.* **2013**, *19*, 10082-10093.

(11) Thompson, A. E.; Hughes, G.; Batsanov, A. S.; Bryce, M. R.; Parry, P. R.; Tarbit, B. Palladium-Catalyzed Cross-Coupling Reactions of Pyridylboronic Acids with Heteroaryl Halides Bearing a Primary Amine Group: Synthesis of Highly Substituted Bipyridines and Pyrazinopyridines. *J. Org. Chem.* **2005**, *70*, 388-90.

(12) Vagnini, M. T.; Smeigh, A. L.; Blakemore, J. D.; Eaton, S. W.; Schley, N. D.; D'Souza, F.; Crabtree, R. H.; Brudvig, G. W.; Co, D. T.; Wasielewski, M. R. Ultrafast Photodriven Intramolecular Electron Transfer from an Iridium-Based Water-Oxidation Catalyst to Perylene Diimide Derivatives. *PNAS* **2012**, *109*, 15651-15656.

(13) Wang, K.; Fu, Q.; Zhou, R.; Zheng, X. L.; Fu, H. Y.; Chen, H.; Li, R. X. Tetraphosphine/Palladium-Catalyzed Suzuki-Miyaura Coupling of Heteroaryl Halides with 3-Pyridineand 3-Thiopheneboronic Acid: an Efficient Catalyst for the Formation of Biheteroaryls. *Appl. Organomet. Chem.* **2013**, *27*, 232-238.

(14) Itoh, T.; Mase, T. Direct Synthesis of Hetero-Biaryl Compounds Containing an Unprotected NH<sub>2</sub> Group via Suzuki-Miyaura Reaction. *Tetrahedron Lett.* **2005**, *46*, 3573-3577.

(15) Hamann, B. C.; Hartwig, J. F. Sterically Hindered Chelating Alkyl Phosphines Provide Large Rate Accelerations in Palladium-Catalyzed Amination of Aryl Iodides, Bromides, and Chlorides, and the First Amination of Aryl Tosylates. *J. Am. Chem. Soc.* **1998**, *120*, 7369-7370.

(16) Lee, D. H.; Choi, M.; Yu, B. W.; Ryoo, R.; Taher, A.; Hossain, S.; Jin, M. J. Expanded Heterogeneous Suzuki-Miyaura Coupling Reactions of Aryl and Heteroaryl Chlorides under Mild Conditions. *Adv. Synth. Catal.* **2009**, *351*, 2912-2920.

(17) Wagaw, S.; Buchwald, S. L. The Synthesis of Aminopyridines: A Method Employing Palladium-Catalyzed Carbon-Nitrogen Bond Formation. J. Org. Chem. **1996**, *61*, 7240-7241.

(18) Caron, S.; Massett, S. S.; Bogle, D. E.; Castaldi, M. J.; Braish, T. F. An Efficient and Cost-Effective Synthesis of 2-Phenyl-3-aminopyridine. *Org. Process Res. Dev.* **2001**, *5*, 254-256.

(19) Bai, L.; Wang, J. X. Environmentally Friendly Suzuki Aryl-Aryl Cross-Coupling Reaction. *Curr. Org. Chem.* **2005**, *9*, 535-553.

(20) Darses, S.; Jeffery, T.; Genet, J. P.; Brayer, J. L.; Demoute, J. P. Cross-Coupling of Arenediazonium Tetrafluoroborates with Arylboronic Acids Catalysed by Palladium. *Tetrahedron Lett.* **1996**, *37*, 3857-3860.

(21) Chi, S. M.; Choi, J. K.; Yum, E. K.; Chi, D. Y. Palladium-Catalyzed Functionalization of 5-and 7-Azaindoles. *Tetrahedron Lett.* **2000**, *41*, 919-922.

(22) Yin, L.; Zhang, Z. H.; Wang, Y. M. PEG (300)-PdCl<sub>2</sub> Promoted Efficient and Convenient Suzuki-Miyaura Coupling of Aryl Chlorides with Arylboronic Acids. *Tetrahedron* **2006**, *62*, 9359-9364.

(23) Liu, C.; Wu, Y. H.; Han, N.; Qiu, J. S. Efficient Synthesis of 4-Heteroaryl-Substituted Triphenylamine Derivatives via a Ligand-Free Suzuki Reaction. *Appl. Organomet. Chem.* **2011**, *25*, 862-866.

(24) Ding, G. D.; Wang, W. T.; Jiang, T.; Han, B. X. An Efficient Palladium Catalyst on Bentonite for Suzuki-Miyaura Reaction at Room Temperature. *Green Chem.* **2013**, *15*, 3396-3403.

(25) Wallow, T. I.; Novak, B. M. Highly Efficient and Accelerated Suzuki Aryl Couplings Mediated by Phosphine-Free Palladium Sources. *J. Org. Chem.* **1994**, *59*, 5034-5037.

(26) Liu, L. F.; Zhang, Y. H.; Xin, B. W. Synthesis of Biaryls and Polyaryls by Ligand-Free Suzuki Reaction in Aqueous Phase. *J. Org. Chem.* **2006**, *71*, 3994-3997.

1	
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30	(27) Kitamura, Y.; Sako, S.; Udzu, T.; Tsutsui, A.; Maegawa, T.; Monguchi, Y.; Sajiki, H. Ligand-Free Pd/C-Catalyzed Suzuki-Miyaura Coupling Reaction for the Synthesis of Heterobiaryl Derivatives. <i>Chem. Commun.</i> <b>2007</b> , 5069-5071.
	(28) Shi, S. Y.; Zhang, Y. H. Silica-Assisted Suzuki-Miyaura Reactions of Heteroaryl Bromides in Aqueous Media. <i>Green Chem.</i> <b>2008</b> , <i>10</i> , 868-872.
	(29) Liu, C.; Ni, Q. J.; Hu, P. P.; Qiu, J. S.: Oxygen-Promoted PdCl <sub>2</sub> -Catalyzed Ligand-Free Suzuki Reaction in Aqueous Media. <i>Org. Biomol. Chem.</i> <b>2011</b> , <i>9</i> , 1054-1060.
	(30) Qiu, J.; Wang, L. M.; Liu, M. T.; Shen, Q.; Tang, J. An Efficient and Simple Protocol for a PdCl <sub>2</sub> - Ligandless and Additive-Free Suzuki Coupling Reaction of Aryl Bromides. <i>Tetrahedron Lett.</i> <b>2011</b> , <i>52</i> , 6489-6491.
	(31) Wan, J. P.; Wang, C. P.; Zhou, R. H.; Liu, Y. Y. Sustainable H <sub>2</sub> O/Ethyl Lactate System for Ligand- Free Suzuki-Miyaura Reaction. <i>RSC Adv.</i> <b>2012</b> , <i>2</i> , 8789-8792.
	(32) Liu, C.; Ni, Q. J.; Bao, F. Y.; Qiu, J. S.: A Simple and Efficient Protocol for a Palladium-Catalyzed Ligand-Free Suzuki Reaction at Room Temperature in Aqueous DMF. <i>Green Chem.</i> <b>2011</b> , <i>13</i> , 1260-1266.
	(33) Rohlich, C.; Wirth, A. S.; Kohler, K. Suzuki Coupling Reactions in Neat Water as the Solvent: Where in the Biphasic Reaction Mixture Do the Catalytic Reaction Steps Occur? <i>Chem. Eur. J.</i> <b>2012</b> , <i>18</i> , 15485-15494 and the references cited therein.
31 32 33	(34) Peng, Y. Y.; Liu, J. B.; Lei, X. L.; Yin, Z. L.: Room-Temperature Highly Efficient Suzuki-Miyaura Reactions in Water in the Presence of Stilbazo. <i>Green Chem.</i> <b>2010</b> , <i>12</i> , 1072-1075.
34 35 36 37	(35) Mondal, M.; Bora, U.: An Efficient Protocol for Palladium-Catalyzed Ligand-Free Suzuki-Miyaura Coupling in Water. <i>Green Chem.</i> <b>2012</b> , <i>14</i> , 1873-1876.
38 39 40	(36) Polackova, V.; Hut'ka, M.; Toma, T. Ultrasound Effect on Suzuki Reactions. 1. Synthesis of Unsymmetrical Biaryls. <i>Ultrason. Sonochem.</i> <b>2005</b> , <i>12</i> , 99-102.
41 42 43	(37) Dallinger, D.; Kappe, C. O.: Microwave-Assisted Synthesis in Water as Solvent. <i>Chem. Rev.</i> <b>2007</b> , <i>107</i> , 2563-2591 and the references cited therein.
44 45 46 47	(38) Kappe, C. O.: Microwave Dielectric Heating in Synthetic Organic Chemistry. <i>Chem. Soc. Rev.</i> <b>2008</b> , <i>37</i> , 1127-1139 and the references cited therein.
48 49 50 51 52	(39) Zhang, J. L.; Yang, F.; Ren, G. R.; Mak, T. C. W.; Song, M. P.; Wu, Y. J. Ultrasonic Irradiation Accelerated Cyclopalladated Ferrocenylimines Catalyzed Suzuki Reaction in Neat Water. <i>Ultrason. Sonochem.</i> <b>2008</b> , <i>15</i> , 115-118.
52 53 54 55 56	(40) Schmidt, B.; Riemer, M. Suzuki-Miyaura Coupling of Halophenols and Phenol Boronic Acids: Systematic Investigation of Positional Isomer Effects and Conclusions for the Synthesis of Phytoalexins from Pyrinae. <i>J. Org.c Chem.</i> <b>2014</b> , <i>79</i> , 4104-4118.
57 58	
59 60	29

(41) Franzen, R.; Xu, Y. J. Review on Green Chemistry - Suzuki Cross Coupling in Aqueous Media. *Can. J. Chem.* **2005**, *83*, 266-272.

(42) Shaughnessy, K. H.; DeVasher, R. B. Palladium-Catalyzed Cross-Coupling in Aqueous Media: Recent Progress and Current Applications. *Curr. Org. Chem.* **2005**, *9*, 585-604.

(43) Lamblin, M.; Nassar-Hardy, L.; Hierso, J. C.; Fouquet, E.; Felpin, F. X. Recyclable Heterogeneous Palladium Catalysts in Pure Water: Sustainable Developments in Suzuki, Heck, Sonogashira and Tsuji-Trost Reactions. *Adv. Synth. Catal.* **2010**, *352*, 33-79.

(44) Polshettiwar, V.; Decottignies, A.; Len, C.; Fihri, A. Suzuki-Miyaura Cross-Coupling Reactions in Aqueous Media: Green and Sustainable Syntheses of Biaryls. *Chemsuschem* **2010**, *3*, 502-522.

(45) Liu, N.; Liu, C.; Jin, Z. L. Green synthesis of fluorinated biaryl derivatives via thermoregulated ligand/palladium-catalyzed Suzuki reaction. *J. Organomet. Chem.* **2011**, *696*, 2641-2647.

(46) Marziale, A. N.; Jantke, D.; Faul, S. H.; Reiner, T.; Herdtweck, E.; Eppinger, J. An Efficient Protocol for the Palladium-Catalysed Suzuki-Miyaura Cross-Coupling. *Green Chem.* **2011**, *13*, 169-177.

(47) Wang, F.; Mielby, J.; Richter, F. H.; Wang, G. H.; Prieto, G.; Kasama, T.; Weidenthaler, C.; Bongard, H. J.; Kegnaes, S.; Furstner, A.; Schuth, F. A Polyphenylene Support for Pd Catalysts with Exceptional Catalytic Activity. *Angew. Chem. Int. Ed.* **2014**, *53*, 8645-8648.

(48) Botella, L.; Najera, C. A Convenient Oxime-Carbapalladacycle-Aatalyzed Suzuki Cross-Coupling of Aryl Chlorides in Water. *Angew. Chem. Int. Ed.* **2002**, *41*, 179-181.

(49) Uozumi, Y.; Matsuura, Y.; Arakawa, T.; Yamada, Y. M. A. Asymmetric Suzuki-Miyaura Coupling in Water with a Chiral Palladium Catalyst Supported on an Amphiphilic Resin. *Angew. Chem. Int. Ed.* **2009**, *48*, 2708-2710.

(50) Jin, M. J.; Lee, D. H. A Practical Heterogeneous Catalyst for the Suzuki, Sonogashira, and Stille Coupling Reactions of Unreactive Aryl Chlorides. *Angew. Chem. Int. Ed.* **2010**, *49*, 1119-1122.

(51) Mao, S. L.; Sun, Y.; Yu, G. A.; Zhao, C.; Han, Z. J.; Yuan, J.; Zhu, X. L.; Yang, Q. H.; Liu, S. H. A Highly Active Catalytic System for Suzuki-Miyaura Cross-Coupling Reactions of Aryl and Heteroaryl Chlorides in Water. *Org. Biomol. Chem.* **2012**, *10*, 9410-9417.

(52) Shaughnessy, K. H. Hydrophilic Ligands and Their Application in Aqueous-Phase Metal-Catalyzed Reactions. *Chem. Rev.* **2009**, *109*, 643-710.

(53) Fleckenstein, C. A.; Plenio, H. Sterically Demanding Trialkylphosphines for Palladium-Catalyzed Cross Coupling Reactions-Alternatives to PtBu<sub>3</sub>. *Chem. Soc. Rev.* **2010**, *39*, 694-711.

(54) Li, L. Y.; Wang, J. Y.; Zhou, C. S.; Wang, R. H.; Hong, M. C. pH-Responsive Chelating *N*-Heterocyclic Dicarbene palladium(II) Complexes: Recoverable Precatalysts for Suzuki-Miyaura Reaction in Pure Water. *Green Chem.* **2011**, *13*, 2071-2077.

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(55) Zhou, C. S.; Wang, J. Y.; Li, L. Y.; Wang, R. H.; Hong, M. C. A Palladium Chelating Complex of Ionic Water-Soluble Nitrogen-Containing Ligand: the Efficient Precatalyst for Suzuki-Miyaura Reaction in Water. Green Chem. 2011, 13, 2100-2106. (56) Kinzhalov, M. A.; Luzyanin, K. V.; Boyarskiy, V. P.; Haukka, M.; Kukushkin, V. Y. ADC-Based Palladium Catalysts for Aqueous Suzuki Miyaura Cross-Coupling Exhibit Greater Activity than the Most Advantageous Catalytic Systems. Organomet. 2013, 32, 5212-5223. (57) Bumagin, N. A.; Bykov, V. V.; Beletskaya, I. P. Synthesis of Diaryls from Phenylboric Acid and Aryl Iodides in an Aqueous-Medium. B. Acad. Sci. USSR Ch+ 1989, 38, 2206-2206. (58) Bumagin, N. A.; Bykov, V. V.; Beletskaya, I. P. Palladium-Catalyzed Phenylation and Vinylation of Aryl Halides in Aqueous-Media. B. Acad. Sci. USSR Ch+ 1990, 39, 2426-2426. (59) Bumagin, N. A.; Bykov, V. V.; Beletskaya, I. P. Palladium-Catalyzed Cross-Coupling of Arylboric Acids and Sodium Tetraphenylborate with Arylhalides in Water Solutions. Dokl. Akad. Nauk SSSR 1990, 315, 1133-1136. (60) Bumagin, N. A.; Bykov, V. V. Ligandless Palladium Catalyzed Reactions of Arylboronic Acids and Sodium Tetraphenylborate with Aryl halides in Aqueous Media. Tetrahedron 1997, 53, 14437-14450. (61) Bykov, V. V.; Bumagin, N. A. Effective Heterogeneous Palladium Catalysis of the Reactions of Organoboron Compounds with Aryl halides. Russ. Chem. B+ 1997, 46, 1344-1346. (62) Sakurai, H.; Tsukuda, T.; Hirao, T. Pd/C as a Reusable Catalyst for the Coupling Reaction of Halophenols and Arylboronic Acids in Aqueous Media. J. Org. Chem. 2002, 67, 2721-2722. (63) Venkatraman, S.; Huang, T.; Li, C. J. Carbon-Carbon Bond Formation via Palladium-Catalyzed Reductive Coupling of Aryl Halides in Air and Water. Adv. Synth. Catal. 2002, 344, 399-405. (64) Molander, G. A.; Biolatto, B. Palladium-Catalyzed Suzuki-Miyaura Cross-Coupling Reactions of Potassium Aryl- and Heteroaryltrifluoroborates. J. Org. Chem. 2003, 68, 4302-4314. (65) Liu, C.; Zhang, Y. X.; Liu, N.; Qiu, J. S. A Simple and Efficient Approach for the Palladium-Catalyzed Ligand-Free Suzuki Reaction in Water. Green Chem. 2012, 14, 2999-3003. (66) Dong, C. N.; Zhang, L. J.; Xue, X.; Li, H. R.; Yu, Z. Y.; Tang, W. J.; Xu, L. J. Pd-Catalyzed Ligand-Free Suzuki Reaction of Beta-Substituted Allylic Halides with Arylboronic Acids in Water. RSC Adv. 2014, 4, 11152-11158. (67) Liang, Q.; Xing, P.; Huang, Z.; Dong, J.; Sharpless, K. B.; Li, X.; Jiang, B. Palladium-Catalyzed, Ligand-Free Suzuki Reaction in Water Using Aryl Fluorosulfates. Org. Lett. 2015, 17, 1942-1945. (68) Liu, C.; Li, X. M.; Liu, C.; Wang, X. N.; Qiu, J. S. Palladium-Catalyzed Ligand-Free and Efficient Suzuki-Miyaura Reaction of Heteroaryl Halides with MIDA Boronates in Water. RSC Adv. 2015, 5, 54312-54315.

(69) Hoffmann, I.; Blumenroder, B.; Thumann, S. O. N.; Dommer, S.; Schatz, J. Suzuki Cross-Coupling in Aqueous Media. *Green Chem.* **2015**, *17*, 3844-3857.

(70) Schlama, T.; Bigouraux, J.-C. Process for Preparing a Polyaromatic Compound. *US Patent 6,800,784 B1, Oct. 5. 2004*. Some of reaction examples therein cannot be reproduced in our lab.

(71) Senter, C.; Rumple, A.; Medina-Ramos, W.; Houle, D.; Cheng, Z.; Gelbaum, C.; Fisk, J.; Holden, B.; Pollet, P.; Eckert, C. A.; Liotta, C. L. The Effects of CO<sub>2</sub> Pressure and pH on the Suzuki Coupling of Basic Nitrogen Containing Substrates. *Org. Biomol. Chem.* **2014**, *12*, 7598-602.

(72) Balanta, A.; Godard, C.; Claver, C. Pd Nanoparticles for C-C Coupling Reactions. *Chem. Soc. Rev.* **2011**, *40*, 4973-4985.

(73) Fihri, A.; Bouhrara, M.; Nekoueishahraki, B.; Basset, J. M.; Polshettiwar, V. Nanocatalysts for Suzuki Cross-Coupling Reactions. *Chem. Soc. Rev.* **2011**, *40*, 5181-5203.

(74) Handa, S.; Wang, Y.; Gallou, F.; Lipshutz, B. H. Sustainable Fe-ppm Pd Nanoparticle Catalysis of Suzuki-Miyaura Cross-Couplings in Water. *Science* **2015**, *349*, 1087-1091.

(75) Adrio, L. A.; Nguyen, B. N.; Guilera, G.; Livingston, A. G.; Hii, K. K. Speciation of Pd(OAc)<sub>2</sub> in Ligandless Suzuki-Miyaura Reactions. *Catal. Sci. Technol.* **2012**, *2*, 316-323.

(76) Bedford, R. B.; Bowen, J. G.; Davidson, R. B.; Haddow, M. F.; Seymour-Julen, A. E.; Sparkes, H. A.; Webster, R. L. Facile Hydrolysis and Alcoholysis of Palladium Acetate. *Angew. Chem. Int. Ed.* **2015**, *54*, 6591-6594.

(77) Foley, P.; Dicosimo, R.; Whitesides, G. M. Mechanism of Thermal-Decomposition of Dineopentylbis(Triethylphosphine)Platinum(II) - Formation of Bis(Triethylphosphine)-3,3-Dimethylplatinacyclobutane. *J. Am. Chem. Soc.* **1980**, *102*, 6713-6725.

(78) Anton, D. R.; Crabtree, R. H. Dibenzo[a,E]Cyclooctatetraene in a Proposed Test for Heterogeneity in Catalysts Formed from Soluble Platinum Group Metal-Complexes. *Organometallics* **1983**, *2*, 855-859.

(79) Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. On the Nature of the Active Species in Palladium Catalyzed Mizoroki-Heck and Suzuki-Miyaura Couplings - Homogeneous or Heterogeneous Catalysis, a Critical Review. *Adv. Synth. Catal.* **2006**, *348*, 609-679.

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