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Aqueous Suzuki Coupling Reactions of Basic Nitrogen-Containing Substrates in the Absence of Added Base and Ligand: Observation of High Yields under Acidic Conditions

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ABSTRACT



A series of aqueous heterogeneous Suzuki coupling reactions of substrates containing basic nitrogen centers with phenylboronic acid in the absence of added base and ligand is presented. High yields of products were obtained employing aryl bromides containing aliphatic 1°, 2°, and 3° amine substituents and good to high yields were obtained employing a variety of substituted bromopyridines. In the former series, the pH of the aqueous phase changed from basic to acidic during the course of reaction while in the latter series the aqueous phase was on the acidic side of the pH scale throughout the entire course of reaction. A mechanistic interpretation for these observations, which generally preserves the oxo palladium catalytic cycle widely accepted in the literature, is presented.

INTRODUCTION

Heterocyclic biaryl compounds, particularly those containing nitrogen, are components in many pharmaceutical and biologically active molecules.¹ While many synthetic methods have been employed for coupling aromatic reaction partners to form biaryl products, the Suzuki coupling reaction has emerged as the most versatile of the synthetic protocols.²⁻¹¹ These Pd-

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catalyzed reactions are usually conducted in an organic-aqueous co-solvent in the presence of a suitable ligand.^{12,13} In addition, the presence of base (e.g., K_3PO_4) is considered to be crucial for the success of the reaction.^{2-4,14} Indeed, in his Nobel address, Professor Suzuki emphasized that no coupling reaction occurs without base.⁴ While there has been great success in a wide range of Suzuki coupling processes, reaction partners containing basic nitrogen centers often react more slowly and/or produce the desired coupled products in lower yields compared to the neutral substrates under the same reaction conditions.¹⁵⁻¹⁸ In these cases, the basic nitrogen centers are postulated to coordinate with the palladium catalyst, reducing or poisoning its catalytic activity.¹⁸⁻²¹ As a consequence, the use of additional protection/deprotection steps or expensive designer ligands is often necessary to achieve reasonable reaction rates and high yields.^{18,21,22} Herein, we report the surprising observation that aqueous heterogeneous Suzuki coupling reactions of a wide variety of aryl bromides containing aliphatic 1°, 2°, and 3° amine substituents and substituted bromopyridines produce excellent yields in the absence of added base and *ligand*. In the former cases, it will be shown that the 1°, 2°, and 3° amines are basic enough to produce hydroxide ions in the aqueous phase such that at least the initial stages of the reaction take place in the presence of a basic aqueous phase. In contrast, it will also be shown that the less basic substituted bromopyridines undergo the coupling process under acidic aqueous conditions throughout the entire course of reaction. The observed changes in pH of the aqueous phase at the beginning and at the end of each reaction and, in several cases, throughout the course of reaction are presented. A mechanistic interpretation for these results, which generally preserves the literature accepted catalytic cycle, is presented.

Previously, we reported that the outcome of Suzuki coupling reactions of 4-amino-2halopyridines with phenylboronic acid using PdCl₂ and triphenylphosphine ligand in

acetonitrile/water medium (60/40, v/v) is highly dependent on the buffered pH of the aqueous phase of the reaction mixture.²³ For example, buffering the reaction mixture at pH 8 provided the desired product in near quantitative yield, whereas conducting the same reaction at a buffered pH of 13 resulted in only a 30% yield (Figure 1a). In contrast, however, the opposite effect of pH was observed with 2-halopyridines. The highest yields were obtained at a pH buffered at 11 while the yields fell precipitously at a buffered pH of 8 (Figure 1b). These results strongly suggested that the pH of the acetonitrile-water phase is an important parameter in developing a successful Suzuki cross-coupling process for substrates containing basic nitrogen centers—at least in mixed solvent systems in the presence of a ligand. In addition, these results suggest that the optimum pH of the aqueous phase may be substrate dependent.²³



Figure 1. Effect of aqueous buffered pH on the Suzuki coupling of substrates containing basic nitrogen centers.²³

The literature contains a number of reports describing Suzuki reactions of heterocyclic molecules in the absence of added ligand (so called "ligand-free") using only water as a solvent.²⁴⁻³⁷ In general, good to high yields of coupled products are reported. Based upon our observations that the buffered pH of the acetonitrile-water phase appears to be playing an

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important role in the success of the Suzuki coupling process,²³ we elected to investigate this by simplifying the reaction system still further. The co-solvent and the ligand were removed, and the reactions were conducted in pure water in *the absence of added base*. In order to ascertain the effects of the "no added base" Suzuki reactions, additional experiments were performed in which varying quantities of base (K₃PO₄) were added to the reaction mixture. Two different nitrogencontaining substrates were used in this study: 4-bromobenzylamine and 4-amino-2bromopyridine. Each of these substrates was reacted with phenylboronic acid using 2 and 4 mol% Pd(OAc)₂. In addition to the yields of the coupled products, specific attention was paid to the phase behavior of the reaction system and the initial and final pH of the aqueous phase. Finally, the results described for 4-bromobenzylamine and 4-amino-2-bromopyridine were extended to a series of aryl bromides containing aliphatic 1°, 2°, and 3° amine substituents and substituted bromopyridines.

RESULTS AND DISCUSSION





Table 1 summarizes reaction conversions and product yields as a function of time and catalyst loading for the ligand-free reaction of 4-bromobenzylamine with phenylboronic acid (PhB(OH)₂) in water in the absence of added base (eq 1). With a catalyst loading of 2 mol%, a 78% yield of product was obtained after 4 hours of reaction (Entry 4, Table 1). Increasing the

reaction time to 24 hours produced a 94% yield (Entry 5, Table 1). Doubling the amount of catalyst to 4 mol% produced a 93 % yield in just 4 hours (Entry 9, Table 1). In all the experiments listed in Table 1 the initial pH of the aqueous phase ranged from 9.1 to 9.5. The final pH, however, was highly acidic for the high conversion cases (Entries 5, 9 and 10, Table 1). Table 2 summarizes the yields of products as a function of amounts of added base. Employing 2 mol% catalyst loading, the yields appear to be largely independent of the amount of added base. Within a reaction period of 4 hours, the yield varies from 73 to 83% (Entries 1 – 3, and 7 – 9, Table 2) and the final pH ranges from neutral to highly basic—especially when large quantities of added base are employed (Entries 8 and 9, Table 2). The 2 mol% catalyst data summarized in Tables 1 and 2 are graphically displayed in Figure 2. The yield of coupled product appears to be largely independent of the absence or presence of base added to the system.

Table 1. Reaction of 4-Bromobenzylamine with PhB(OH)₂ in Water in the Absence of Added Base Following the Reaction Conditions in Eq 1

Enter	Pd(OAc) ₂	Time	GC Yield	pł	ł
Entry	(equiv)	(h)	(%)	initial	final
1	2.0%	0.5	38	9.2	7.4
2	2.0%	1	55	9.4	7.1
3	2.0%	2	68	9.3	7.2
4	2.0%	4	78	9.1	6.8
5	2.0%	24	94	9.5	3.2
6	4.0%	0.5	53	9.4	7.7
7	4.0%	1	65	9.5	7.7
8	4.0%	2	83	9.4	6.1
9	4.0%	4	93	9.4	2.1
10	4.0%	6	92	9.5	2.8

Table 2. Reaction of 4-Bromobenzylamine with $PhB(OH)_2$ in Water in the Presence of Varying Amounts of Added K₃PO₄ Following the Reaction Conditions in Eq 1

F == 4++++	Pd(OAc) ₂	K ₃ PO ₄	Time	GC Yield	pł	I
Entry	(equiv)	(equiv)	(h)	(%)	initial	final
1	2.0%	0.10	4	78	9.9	7.1
2	2.0%	0.25	4	72	10.6	7.5
3	2.0%	0.50	4	74	10.7	8.7
4	2.0%	1.0	0.5	42	11.3	10.4
5	2.0%	1.0	1	59	11.3	9.2
6	2.0%	1.0	2	73	11.3	9.5
7	2.0%	1.0	4	83	11.5	9.9
8	2.0%	1.5	4	82	11.6	10.2
9	2.0%	2.0	4	77	11.8	10.8
10	4.0%	0.10	4	90	10.1	5.4
11	4.0%	1.0	0.5	74	11.7	9.8
12	4.0%	1.0	1	81	11.8	9.8
13	4.0%	1.0	2	86	11.8	9.8
14	4.0%	1.0	4	90	11.8	9.8



Figure 2. The effect of initial pH on product yield in the ligand-free Suzuki reactions of 4bromobenzylamine in H₂O; reaction conditions: 4-bromobenzylamine (10 mmol), PhB(OH)₂ (11 mmol), Pd(OAc)₂ (2 mol%), H₂O (25 mL), N₂, 100 °C, 4 h.





Table 3 summarizes the product yields as a function of time and catalyst loading for the ligand-free reaction of 4-amino-2-bromopyridine with $PhB(OH)_2$ in water in the absence of added base (eq 2). With a catalyst loading of 2 mol% a near quantitative yield was obtained in one hour. An increased catalyst loading of 4 mol% did very little in improving the rate of reaction; a quantitative yield was obtained in one hour. In all the experiments listed in Table 3, the initial pH of the aqueous phase ranged from 6.2 to 6.5. The final pH was even more acidic, reaching as low as 2.2. These results clearly demonstrate a Suzuki coupling process taking place entirely on the acidic side of the pH scale.

Table 3. Reaction of 4-Amino-2-bromopyridine with $PhB(OH)_2$ in Water in the Absence ofAdded Base Following the Reaction Conditions in Eq 2

Entwy	Pd(OAc) ₂	Time	GC Yield	рН			
Entry	(equiv)	(h)	(%)	initial	final		
1	2.0%	0.5	82	6.4	4.8		
2	2.0%	0.75	89	6.5	4.6		
3	2.0%	1	96	6.6	4.2		
4	2.0%	2	95	6.4	4.2		
5	2.0%	4	100	6.2	2.2		
6	4.0%	0.5	93	6.4	4.1		
7 ^a	4.0%	1	100	6.5	2.3		
8	4.0%	4	100	6.5	2.6		
^a GC yield is independent of stirring rate, 100% for 60, 100, 150, 200, 400, 600 rpm or greater.							

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Table 4 summarizes the results for the same reaction conducted in the presence of varying quantities of added base as a function of time. As the amount of added base increases, the yield of product remains relatively constant (Entries 1-7, Table 4). However, when 1.5 to 2.0 equivalents of added base were employed, the yield decreases significantly (Entries 8 and 9, Table 4). It is also interesting to note that the final pH for these latter entries remained highly basic in contrast to the reactions conducted with 0.25 to 1.0 equivalents of added base. The 2 mol% catalyst results are graphically summarized in Figure 3. It was quite surprising to observe that a 95% yield of coupled product was achieved in the absence of added base and where the reaction proceeded entirely on the acidic side of the pH scale.

Table 4. Reaction of 4-Amino-2-bromobenzylamine with $PhB(OH)_2$ in Water in the Presence of Varying Amounts of Added K₃PO₄ Following the Reaction Conditions in Eq (2) (2.0 mol% $Pd(OAc)_2$)

Entry	K ₃ PO ₄	Time	GC Yield	рН	
	(equiv)	(h)	(%)	initial	final
1	0.25	2	90	9.1	7.1
2	0.50	2	91	9.5	7.6
3	0.75	2	92	9.9	8.1
4	1.0	0.5	78	10.8	8.9
5	1.0	1	94	10.3	8.5
6	1.0	2	96	10.0	8.3
7	1.0	4	97	10.1	8.4
8	1.5	2	83	11.8	9.9
9	2.0	2	49	12.4	11.4



Figure 3. The effect of initial pH on product yield in the ligand-free Suzuki reactions of 4amino-2-bromopyridine in H₂O; reaction conditions: 4-amino-2-bromopyridine (10 mmol), PhB(OH)₂ (11 mmol), Pd(OAc)₂ (2 mol%), H₂O (25 mL), N₂, 100 $^{\circ}$ C, 2 h

Reaction of Aryl Bromides Containing 1°, 2°, and 3° Amine Substituents with

Phenylboronic Acid

 In order to explore the scope of the aqueous, base-free and ligand-free conditions for conducting Suzuki reactions, a variety of aryl bromides containing 1°, 2°, and 3° aliphatic amine substituents in pure water was investigated. The results are shown in Table 5. The substrate conversions, the yields of coupled products, and the pH values of the aqueous phase before and after reaction are indicated. All of these aryl bromides (Table 5, Entries 1-11) underwent smooth cross-coupling in the absence of added base to afford the products in excellent yields. It is interesting to note that the reactions with the primary and secondary amine substrates (Table 5, Entries 1-7) had initial pH values of approximate 9.0 and a final pH of 1.5-3.6. In contrast, for the tertiary amines (Table 5, Entries 8-11), the initial pH was approximately 7.0 and decreased to

a final pH which ranged from 2.0 to 2.7. These results indicate that at least a portion of the reactions took place on the acidic side of the pH scale.

Table 5. $Pd(OAc)_2$ Catalyzed Suzuki Reactions of Aryl Bromides Containing 1°, 2°, and 3° Aliphatic Amine Substituents with PhB(OH)₂ in Water in the Absence of Added Base and Ligand^a

		Time	Conversion	Yield of	pl	H
Entry	Ar-Br	(h)	of Ar-Br (%) ^c	Product (%)	Initial	Final
1 ^b	$4-BrC_6H_4CH_2NH_2$	4	93	93°	9.5	2.8
2 ^b	$3-BrC_6H_4CH_2NH_2$	4	92	92 ^c	9.2	3.1
3 ^b	4-BrC ₆ H ₄ CH(CH ₃)NH ₂	4	94	94 ^c	9.3	1.5
4	$4-BrC_6H_4CH_2CH_2NH_2$	6	99	99°	9.6	3.1
5	4-BrC ₆ H ₄ CH ₂ NHCH ₃	4	94	96 ^d	9.0	3.4
6	3-BrC ₆ H ₄ CH ₂ NHCH ₃	4	94	98 ^d	9.0	3.0
7	4-BrC ₆ H ₄ CH ₂ NH <i>i</i> -Pr	4	97	92 ^d	8.7	3.6
8	$4-BrC_6H_4CH_2N(CH_3)_2$	4	95	92 ^d	7.2	2.6
9	$4-BrC_6H_4CH_2NEt_2$	4	95	98 ^d	7.5	2.3
10	$4-BrC_6H_4CH_2NPr_2$	4	96	96 ^d	6.9	2.7
11	$4-BrC_6H_4CH_2N(i-Pr)_2$	4	86	87^{d}	6.6	2.0
^a Reaction co	onditions: Ar-Br (10 mmol), PhB	(OH) ₂ (15	mmol), Pd(O	$Ac)_2$ (4 mc	ol%), H ₂	2O (25
mL), N ₂ , 100	°C.					
^b PhB(OH) ₂ (11 mmol)					
^c Determined	by GC					

Reaction of Pyridyl Bromides with Phenylboronic Acid

^d Determined by ¹H NMR

A study similar to that involving the amine-containing aryl bromides was conducted with a variety of pyridyl bromides. The results are summarized in Table 6. The substrate conversions, the yields of coupled products, and pH values of the aqueous phase before and after reaction are shown; 4 mol% $Pd(OAc)_2$ was employed. For this series of reactions the initial pH varied from 6.5 to 3.2 and the final pH from 1.1 to 4.4. Each of the reactions appears to have taken place entirely on the acid side of the pH scale. Excellent yields were obtained for the first six substrates (Table 6, Entries 1-8) while good to modest yields were realized for the remaining five substrates (Table 6, Entries 9-15). It is interesting to note that in the latter cases the yields of coupled products and the corresponding conversions were within a few percent of each other.

Table 6. Pd(OAc)₂ Catalyzed Suzuki Reactions of Substituted Pyridyl Bromides with PhB(OH)₂ in Water in the Absence of Added Base and Ligand^a

An Bn	Entwy	Time	Conversion	Yield of Product	pl	рH	
AI-DI	Entry	(h)	of Ar-Br (%) ^c	(%)	Initial	Final	
NH ₂	1^{b}	1	100	100 ^c	6.5	2.3	
Br	2	4	81	83 ^d	5.7	4.4	
N NH₂	3	24	97	97^{d}	5.6	2.1	
Br	4	4	96	96 ^c	5.2	2.0	
NH ₂	5	4	94	91 ^d	4.8	2.6	
Br N NH ₂	6	4	94	93 ^d	4.6	2.7	
CH ₃	7	4	89	75 [°]	4.0	1.4	
N Br	8	24	97	82 ^c	3.9	1.5	
	9	4	64	59 ^c	3.8	1.9	
NBr	10	24	73	69 ^c	3.7	1.9	
H ₃ C	11	4	41	34 ^c	3.6	1.7	
N Br	12	24	50	43 ^c	3.7	1.8	
	13	4	39	35 ^d	3.5	1.3	
H ₃ CO N Br	14	4	35	29 ^d	3.3	1.3	
	15	4	34	29 ^d	3.2	1.1	

 a Reaction conditions: Ar-Br (10 mmol), PhB(OH)_2 (15 mmol), Pd(OAc)_2 (4 mol%), H_2O (25 mL), N_2, 100 $^o\mathrm{C}.$

^b PhB(OH)₂ (11 mmol)

^c Determined by GC

 ^d Determined by ¹H NMR

pH Changes During the Course of Reaction of 4-Bromobenzylamine and 4-Amino-2-Bromopyridine with Phenylboronic Acid.

The issue regarding the pH change during the course of reaction was also investigated. The results for 4-bromobenzylamine and 4-amino-2-bromopyridine are summarized in Figure 4. Figure 4a shows the product yield and the pH of the aqueous phase vs. time for the $Pd(OAc)_2$ catalyzed reaction of 4-bromobenzylamine with PhB(OH)₂ in water in the absence of base and in the presence of 1.0 equivalent of K₃PO₄. During the first 1.5 hours both reactions proceeded smoothly in a system in which the aqueous phase was in the basic pH region. At this point in time the yields of products were approximately 85% and 75% in the presence and absence of added base, respectively. After 1.5 hours of reaction, the pH of the base-free system dropped below 7. Nevertheless, the reaction proceeded to produce an identical yield as that obtained in the presence of K_3PO_4 . Figure 4b shows the corresponding product yield and the pH of the aqueous phase vs. time for the reaction of 4-amino-2-bromopyridine in the absence and presence of 1.0 equivalent of K_3PO_4 . In this case, the rate profiles are almost identical for the two reaction conditions. Quantitative yields are obtained under both sets of conditions. The major difference is the pH profiles. In the presence of base, the entire reaction experiences a basic aqueous phase. while in the absence of base the entire reaction takes place within a pH range substantially below

7.



Figure 4. Reaction yield and pH as functions of time for the ligand-free Suzuki reactions of (a) 4-bromobenzylamine and (b) 4-amino-2-bromopyridine with $PhB(OH)_2$ in water in the presence of 1.0 equivalent of K_3PO_4 or without added bases. Reaction conditions: aryl bromide (10 mmol), $PhB(OH)_2$ (11 mmol), $Pd(OAc)_2$ [(a) 4 mol%, (b) 2 mol%], H_2O (25 mL), N_2 .

4-Amino-2-bromopyridine is a weaker base than 4-bromobenzylamine due to delocalization of its nitrogen lone pairs. The initial pH of the Suzuki reaction of 4-amino-2-bromopyridine is lower due to its lower basicity. Reaction mixtures with 4-amino-2-bromopyridine were, in fact, acidic, presumably due to the known hydrolysis equilibrium between PhB(OH)₂ and trihydroxyphenylborate (PhB(OH)₃⁻, eq 3). In the absence of added K_3PO_4 , the pH of both reaction mixtures decreased with increasing conversion due to generation of B(OH)₃ and HBr (buffered by the basic nitrogen centers of products) by the Suzuki coupling.¹⁴

Mechanistic Interpretation of Aqueous Suzuki Coupling in the Absence of Added Base and Ligand

At this juncture the question arises as to whether the generally accepted Suzuki mechanism (Scheme 1) 14,38,39 is operating in the absence of added base and ligand when dealing with substrates containing basic nitrogen centers-especially in situations where the entire reaction readily takes place within an acidic pH range as is the case for the 4-amino-2bromopyridine substrate. The Suzuki coupling of aryl bromides is widely accepted to proceed via a mechanism which involves oxidative addition of Pd(0) species, transmetallation and reductive elimination of the biaryl product to regenerate the catalytically active Pd(0) (Scheme 1).¹⁴ Following oxidative addition, the resulting L_nPd(Ar)Br intermediate can undergo substitution of the bromide ligand by hydroxide ion (use as is or generated by ionization of water) to form oxo palladium intermediate, L_pPd(Ar)OH. The transmetallation step is less understood and has been proposed to occur via reaction with either PhB(OH)₃ (boronate pathway) or PhB(OH)₂ (oxo palladium mechanism).⁴⁰ Hartwig⁴¹ has demonstrated that in the absence of added base, the stoichiometric reaction of L_nPd(Ar)OH with ArB(OH)₂ is orders of magnitude faster than reaction of $L_n Pd(Ar)Br$ with $ArB(OH)_3$. At high pH, the equilibrium between boronic acid and trihydroxyborate strongly favors $ArB(OH)_3^{-14}$ However, the acidic pH would be expected to decelerate either potential pathways for transmetallation by decreasing the concentration of $ArB(OH)_3$ or $L_nPd(Ar)OH$, and leads to low catalytic activity.





Our observation of high-yielding Suzuki couplings at acidic pH is unusual in light of the vast literature which typically demonstrates the requirement of base for catalytic activity. The observation that the nitrogen-containing substrates in Figure 4 undergo Suzuki coupling at rates which are essentially insensitive to added base suggests that the pH of the aqueous phase may not be a critical parameter in these reaction processes.

Under the reaction conditions in the presence of water and PhB(OH)₂, but in the absence of added ligand, Pd(OAc)₂ can rapidly generate catalytically active Pd(0) molecules, which undergo aggregation to form clusters, nanoparticles and, eventually, Pd black.^{42,43} We observed the formation of Pd black in these reaction mixtures, and the mercury drop test^{44,45} showed an partial catalytic deactivation caused by adding an excess of Hg(0) (Supporting Information (SI), Section 1). These observations are consistent with literature and support that there are competitive catalytic pathways operating including active Pd(0) particles (highly likely a mixture

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of Pd(0) clusters and nanoparticles) and water-soluble oxo-Pd catalytic species.⁴⁶ The contribution of each pathway most likely changes from reaction to reaction based upon conditions such as the ability of substrate to be an effective ligand and the pH of aqueous phase.

The limited solubility of the substrates in Figure 4 in water leads to the presence of two or more phases at the reaction temperature. In both cases there is an aqueous liquid phase. In the case of 4-bromobenzylamine there is an additional liquid organic phase, and in the case of 4-amino-2-bromopyridine there is an additional solid organic phase. Due to the heterogeneity of these reaction mixtures, it is uncertain in which phase the catalytic steps occur. It is important to note, however, that the basic nitrogen centers can act as both ligands for Pd(0) (Figure 5b) and effective hydrogen bonding centers with water to create incipient hydroxide ions (Figure 5a). Thus, it is conjectured that both the oxidative addition of Pd(0) and the metathesis step to generate the oxo palladium intermediate take place primarily at the organic-aqueous interface where the substrate behaves as both the ligand and the source of incipient hydroxide.



Figure 5. Basic nitrogen-containing substrates acting as (a) the source of incipient hydroxide ions and (b) Pd(0) ligands.

In order to test our hypothesis, we compared the Suzuki reactivity of 4bromobenzylamine with analogues which did not contain a nitrogen lone pair (Table 7). Experiments with 4-bromoanisole confirmed that essentially no Suzuki coupled product was

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observed at acidic pH (3.3 - 2.5) with PhB(OH)₂ (Entry 11, Table 7). In the absence of added base, there is apparently insufficient concentration of hydroxide ion to convert the L_nPd(Ar)Br species to L_nPd(Ar)OH. Under these same reaction conditions, 4-bromobenzylamine (Entry 1, Table 7) gave 90% yield of coupled product with no added base. Protonation of the benzylamine in 4-bromo-benzylammonium bromide (Entry 9, Table 7) sequestered this internal basic nitrogen atom and drastically decreased conversion. Similarly, the quaterized amine substituent in 4bromobenzyltriethyl-ammonium bromide lacks a basic nitrogen atom and was essentially unreactive in the absence of added base (Entry 10, Table 7). In the case of 4-amino-2bromopyridine, the quantitative yields (Entries 7 and 8, Table 3) can be attributed to the cooperation of the aromatic amino and pyridyl nitrogen atoms (Figure 5), although both of them are less basic than the benzylic amines, and neither of which can produce a high yield of crosscoupling product alone (Entries 12 and 13, Table 7) under the same reaction conditions accompanied by the excellent yield when they work together (Entries 7 and 8, Table 3).

In addition, the importance of the presence of substantial quantities of water in the reaction system was addressed. 4-Bromobenzylamine was reacted with $PhB(OH)_2$ in water and a variety of mixed and pure organic solvent systems using 4 mol% $Pd(OAc)_2$ for 4 hours in the absence of added base at reflux temperatures (Entries 1-8, Table 7). While the reflux temperature varied approximately 24 degrees over the solvent systems investigated, the general conclusion from this series of reactions is still qualitatively instructive. All of the reaction systems were heterogeneous. The observed yield in water was greater than 90%. The corresponding yields in ethanol, acetonitrile and *tert*-butanol were extremely poor (approximately 21%). In the mixed solvent systems, it is clear that as the quantity of water increases, the corresponding yields

increase. Water, the source of hydroxide ion for the metathesis step in the catalytic cycle, is essential for successful coupling.

 Table 7 Control Reactions for the Pd(OAc)₂ Catalyzed Suzuki Reactions in Water in the

 Absence of Added Base and Ligand^a

Substrate	Entry	Solvent	Temperature (°C)	GC Yield (%)
	1	$\begin{array}{c} H_2O\\ (pH: 9.4 \rightarrow 2.1) \end{array}$	100	93
	2	EtOH	76	21
	3	CH ₃ CN	82	21
Br — CH ₂ NH ₂	4	<i>t</i> BuOH	82	22
	5	EtOH (20% H ₂ O)	80	38
	6	EtOH (40% H ₂ O)	80	69
	7	EtOH (60% H ₂ O)	86	86
	8	CH ₃ CN (40% H ₂ O)	79	50
Br-CH ₂ NH ₂ HBr	9	$\begin{array}{c} \text{H}_2\text{O}\\ \text{(pH: 4.7} \rightarrow 1.5) \end{array}$	100	14
Br — H ₂ CN — Br	10	$\begin{array}{c} H_2O\\ (pH: 4.0 \rightarrow 1.3) \end{array}$	100	11 ^b
Br	11	$\begin{array}{c} H_2O\\ (pH: 3.3 \rightarrow 2.5) \end{array}$	100	1
N Br	12	$\begin{array}{c} \mathrm{H_2O} \\ \mathrm{(pH: 3.8} \rightarrow 2.0) \end{array}$	100	39
NH ₂ Br	13	H ₂ O (pH: 4.4 \rightarrow 2.6)	100	21

^a Reaction conditions: Ar-Br (10 mmol), PhB(OH)₂ (11 mmol), Pd(OAc)₂ (4 mol%), solvent (25 mL), N₂, reflux, 4 h. ^b Determined by ¹H NMR

Lastly, the question still remains as to the mechanism by which the oxo palladium intermediate is presumably generated at the organic-aqueous interface. Differences in the initial pH of the Suzuki reaction mixtures are likely due to differences in the p K_b of the amine moiety in the aryl bromide. In the absence of added base, reaction mixtures of 4-bromobenzylamine had an initial pH of 9.1 – 9.5 (Table 1). We hypothesized that 4-bromobenzylamine is, therefore,

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sufficiently basic to cause ionization of water to generate hydroxide ion required for producing the oxo palladium intermediate. This mechanism is conceptually similar to the existing "base-free" approaches using boronate reagents that can liberate in-situ base species.⁴⁷⁻⁵²

Conversely, bromopyridine substrates are less mechanistically straightforward due to their lower basicity. Suzuki coupling reaction mixtures of 4-amino-2-bromopyridine had a much lower initial pH (6.2 - 6.5, Table 3) due to the lower basicity of the aromatic amino and pyridyl nitrogen atoms in comparison to benzylic amines. For the less basic bromopyridine substrates, we hypothesize that the oxo palladium species may be generated via the deprotonation of a cationic aqua palladium intermediate (Figure 6). Following oxidative addition, the resulting $L_nPd(Ar)Br$ intermediate may be solvated by the aqueous media, resulting in the formation of a cationic aqua palladium complex, $L_nPd(Ar)(OH_2)^{+.53}$ Deprotonation of the cationic aqua ligand complex by the weakly basic pyridine and amino substituent of 4-amino-2-bromopyridine would ultimately afford the desired oxo palladium intermediate, $L_nPd(ArH)^+(OH)$, required for the catalytic cycle (Figure 6).



Figure 6. Generation of oxo palladium species via cationic aqua palladium complexes

Structurally characterized palladacyclic aqua complexes have been found to be highly active Suzuki catalyst precursors at basic pH ranges below the pK_a (10.9) of the Pd hydroxide species.⁵⁴ However, it is likely that the aqua ligands in this reported example serve primarily as weakly bound ligands which easily dissociate and facilitate entry into the catalytic cycle.

Consequently, the aqua complex does not seem to be responsible for the surprising reactivity of our Suzuki coupling catalyst system under acidic pH conditions since aryl bromides which lack nitrogen lone pairs should also be expected to undergo cross coupling under acidic conditions. One possible explanation for the unusual reactivity of bromopyridines at low pH is that the weakly basic amine moiety stabilizes the oxo palladium intermediate (Figure 6). It has been reported that the cationic aqua palladium complexes are quite acidic even with aliphatic amine ligands.⁵⁵ Although the relative basicities of the pyridyl nitrogen atoms and Pd-OH groups are not exactly known, we propose that protonation of the pyridines would increase the acidity of the aqua ligand and favor $L_nPd(ArH)^+(OH)$, thereby allowing the oxo palladium mechanism to proceed under acidic conditions. The mechanistic details of ligand-free and aqueous Suzuki couplings under acidic conditions will be addressed in future investigations.

CONCLUSIONS

It is concluded that these pH-independent Suzuki couplings of basic nitrogen containing substrates proceed by the widely accepted oxo palladium and Pd(0) catalysis mechanisms. The reactions are heterogeneous and results are consistent with the reaction taking place primarily at the organic-aqueous interface where the substrate behaves as both the ligand and the source of incipient hydroxide for generating the oxo palladium intermediate. In the case of relatively basic benzylic amines, the amino substituent is able to generate hydroxide ion for oxo palladium intermediate that undergoes transmetallation. For less basic bromopyridines, the deprotonation of a cationic aqua intermediate is proposed to allow the oxo palladium intermediate to form under acidic conditions.

General Method

The commercially available solvents, reagents and standard products for GC analysis were purchased from commercial providers in reagent grade and were used without further purification. Some aryl bromides substrates, such as some of *N*-substituted 4-bromobenzylamines⁵⁶ and *N*-(4-bromobenzyl)-*N*,*N*,*N*-triethylammonium bromide⁵⁷ were synthesized following the published methods.

pH values of the aqueous phase were measured by a portable pH meter at 25 ± 2 °C. Melting points were measured on a capillary melting point apparatus. ¹H (400 MHz) and ¹³C (100 MHz) NMR spectra were recorded on a 400 MHz NMR spectrometer. Chemical shifts (δ) are reported in ppm relative to TMS and coupling constants (*J*) are in Hz. GC analyses were carried out on a GC-MS (qualitative) and a GC-FID (quantitative) fitted with a capillary column (30 m × 0.32 mm × 1.00 µm, length × inside diameter × film thickness).

General Experimental Procedure for Suzuki Reactions

A mixture of aryl bromide, arylboronic acid, base (*if used*), Pd(OAc)₂ and solvent in a 3neck round-bottom flask was stirred (600 - 800 rpm) under reflux for the requisite time. The initial and final pH values of the aqueous phase were measured pre and post- reaction, once the temperature had stabilized at 25 - 27 °C. The initial reaction time (t = 0) was taken when the reaction mixture began to reflux; the time to reach this temperature was approximately 20 - 30minutes. The cooled reaction mixture was extracted with organic solvents (chloroform for benzylamines, ethyl acetate for aminopyridines, and dichloromethane for the rest). The combined organic phase was dried over anhydrous MgSO₄ and filtered. The solvent was removed under

vacuum and the crude product was analyzed by GC and ¹H NMR following the published methods (SI, Section 2).²³

Procedure for the Reactions of 4-Bromobenzylamine with Phenylboronic Acid in Water in the Absence of Added Base (Table 1)

A mixture of 4-bromobenzylamine (1.861 g, 10 mmol, 1.0 equiv), PhB(OH)₂ (1.341 g, 1.1 equiv), Pd(OAc)₂ (0.0449 g, 2 mol%; or 0.0898 g, 4 mol%) and H₂O (25 mL) in a 3-neck round-bottom flask (100-mL) was stirred under reflux at 100 °C in N₂. The reactions were triphasic: an aqueous phase, an organic phase and a solid phase (catalyst). Palladium black gradually formed when 100 °C was reached. Once the reaction time was reached, the reaction mixture was cooled, basified to pH \geq 12 using 30% NaOH aqueous solution, and then was thoroughly extracted with chloroform. The combined organic phase was dried over anhydrous MgSO₄ and filtered. The solvent was removed under vacuum. The crude product was analyzed by GC and ¹H NMR.

Procedure for the Reactions of 4-Bromobenzylamine with Phenylboronic Acid in Water in the Presence of Varying Amount s of Added Base (Table 2)

A mixture of 4- bromobenzylamine (1.861 g, 10 mmol, 1.0 equiv), $PhB(OH)_2$ (1.341 g, 1.1 equiv), K_3PO_4 , $Pd(OAc)_2$ (0.0449 g, 2 mol%; or 0.0898 g, 4 mol%) and H_2O (25 mL) in a 3neck round-bottom flask (100-mL) was stirred under reflux at 100 °C in N₂. The reactions were triphasic: an aqueous phase, an organic phase and a solid phase (catalyst). Formation of palladium black was not observed. After cooling to room temperature, the reaction was thoroughly extracted with chloroform. The combined organic phase was dried over anhydrous MgSO₄ and filtered. The solvent was removed under vacuum. The crude product was analyzed by GC and ¹H NMR.

Procedure for the Reactions of 4-Amino-2-bromopyridine with Phenylboronic Acid in Water in the Absence of Added Base (Table 3)

A mixture of 4-amino-2-bromopyridine (1.730 g, 10 mmol, 1.0 equiv), phenylboronic acid (PhB(OH)₂,1.341 g, 1.1 equiv), Pd(OAc)₂ (0.0449 g, 2 mol%; or 0.0898 g, 4 mol%) and H₂O (25 mL) in a 3-neck round-bottom flask (100-mL) was stirred under reflux at 100 °C in N₂. The reactions were biphasic: an aqueous phase and a solid phase (catalyst and substrate). Palladium black gradually formed when 100 °C was reached. After cooling to room temperature, the reaction mixture was basified to pH \geq 12 using 30% NaOH aqueous solution, and then was thoroughly extracted with ethyl acetate. The combined organic phase was dried over anhydrous MgSO₄ and filtered. The solvent was removed under vacuum. The crude product was analyzed by GC and ¹H NMR.

Procedure for the Reactions of 4-Amino-2-bromopyridine with Phenylboronic Acid in Water in the Presence of Varying Amounts of Added Base (Table 4)

A mixture of 4-amino-2-bromopyridine (1.730 g, 10 mmol, 1.0 equiv), PhB(OH)₂ (1.341 g, 1.1 equiv), K_3PO_4 , Pd(OAc)₂ (0.0449 g, 2 mol%) and H₂O (25 mL) in a 3-neck round-bottom flask (100-mL) was stirred under reflux at 100 °C in N₂. The reactions were biphasic: an aqueous phase and a solid phase (catalyst and substrate). The formation of palladium black was not observed. The cooled reaction mixture was thoroughly extracted with ethyl acetate. The

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combined organic phase was dried over anhydrous MgSO₄, and filtered. The solvent was removed under vacuum. The crude product was analyzed by GC and ¹H NMR.

Procedure for the Reactions of Aryl Bromides Containing 1°, 2°, and 3° Amine Substituents with Phenylboronic Acid in Water in the Absence of Added Base (Table 5)

A mixture of aryl bromides (10 mmol, 1.0 equiv), phenylboronic acid (1.829 g, 1.5 equiv), $Pd(OAc)_2$ (0.0899 g, 4 mol%) and H_2O (25 mL) in a 3-neck round-bottom flask (100-mL) was stirred under reflux at 100 °C in N₂. The reactions were tri-phasic: an aqueous phase, an organic phase (substrate) and a solid phase (catalyst). Palladium black gradually formed when 100 °C was reached. After cooling to room temperature, the reaction mixture was basified to pH \geq 12 using 30% NaOH aqueous solution, and then was thoroughly extracted with chloroform. The combined organic phase was dried over anhydrous MgSO₄ and filtered. The solvent was removed under vacuum. The crude product was analyzed by GC and ¹H NMR.

Procedure for the Reactions of Pyridyl Bromides with Phenylboronic Acid in Water in the Absence of Added Base (Table 6)

A mixture of bromopyridine substrate (10 mmol, 1.0 equiv), PhB(OH)₂ (1.829 g, 1.5 equiv), Pd(OAc)₂ (0.0898 g, 4 mol%) and H₂O (25 mL) in a 3-neck round-bottom flask (100-mL) was well stirred under reflux at 100 °C in N₂. The reactions with solid substrates were biphasic: an aqueous phase and a solid phase (catalyst and substrate). If the substrate was a liquid, there was an additional liquid organic phase. The gradual formation of palladium black was observed when the reaction temperature reached 100 °C. After cooling to room temperature, the reaction mixture was basified to pH \geq 12 using 30% NaOH aqueous solution, and then was

thoroughly extracted with ethyl acetate (for aminopyridines) or dichloromethane (for the rest). The combined organic phase was dried over anhydrous MgSO₄ and filtered. The solvent was removed under vacuum. The crude product was analyzed by GC and ¹H NMR.

Procedure for the Reaction of 4-Bromoanisole with Phenylboronic Acid in Water in the Absence of Added Base (Entry 11, Table 7)

A mixture of 4- bromoanisole (1.870 g, 10 mmol, 1.0 equiv), PhB(OH)₂ (1.341 g, 1.1 equiv), Pd(OAc)₂ (0.0898 g, 4 mol%) and H₂O (25 mL) in a 3-neck round-bottom flask (100-mL)was well stirred under reflux at 100 °C in N₂ for 4 h. The reactions were tri-phasic: an aqueous phase, an organic phase and a solid phase (catalyst). Palladium black formed immediately upon addition of Pd(OAc)₂ to the reaction mixture. After cooling to room temperature, the reaction mixture was thoroughly extracted with dichloromethane. The combined organic phase was dried over anhydrous MgSO₄ and filtered. The solvent was removed under vacuum. The crude product was analyzed by GC and ¹H NMR.

Procedure for the Control Reactions of 4-Bromobenzylamine with Phenylboronic Acid in Varying Solvents in the Absence of Added Base (Entries 2 – 8, Table 7)

A mixture of 4-bromobenzylamine (1.861 g, 10 mmol, 1.0 equiv), PhB(OH)₂ (1.341 g, 1.1 equiv), Pd(OAc)₂ (0.0898 g, 4 mol%) and solvent (25 mL) in a 3-neck round-bottom flask (100-mL) was stirred under reflux in N₂ for 4 h. The reactions were tri-phasic: an aqueous phase, an organic phase and a solid phase (catalyst). After cooling to room temperature, the reaction mixture was basified to pH \geq 12 using 30% NaOH aqueous solution, and was thoroughly extracted with chloroform. The combined organic phase was dried over anhydrous MgSO₄,

filtered. The solvent was removed under vacuum. The crude product was analyzed by GC and ¹H NMR.

Procedure for the Control Reactions of Varing Aryl Bromides with Phenylboronic Acid in Water in the Absence of Added Base (Entries 9, 10, 12, 13, Table 7)

A mixture of aryl bromide (10 mmol, 1.0 equiv), PhB(OH)₂ (1.341 g, 1.1 equiv), Pd(OAc)₂ (0.0898 g, 4 mol%) and H₂O (25 mL) in a 3-neck round-bottom flask (100-mL) was stirred under reflux at 100 °C in N₂. After cooling to room temperature, the reaction mixture was basified to pH \geq 12 using 30% NaOH aqueous solution, and then was thoroughly extracted with dichloromethane. The combined organic phase was dried over anhydrous MgSO₄, filtered. The solvent was removed under vacuum. The crude product was analyzed by GC and ¹H NMR.

Procedure for Mercury Test

A mixture of aryl bromide (4 mmol, 1.0 equiv), $PhB(OH)_2$ (4.4 mmol, 1.1 equiv), $Pd(OAc)_2$ (2 mol% for 4-amino-2-bromopyridine, 4 mol% for 4-bromobenzylamine), mercury (99.9+%) and water (10 mL) in a 3-neck round-bottom flask (50-mL) was stirred under reflux at 100 °C in N₂. After cooling to room temperature, the reaction mixture was basified using 30% NaOH aqueous solution (2 mL). The resulting reaction mixture was diluted with methanol and measured in a 100 mL volumetric flask. An aliquot of the organic solution was taken for GC analysis. In parallel, a control reaction in the absence of mercury was carried out under the identical reaction conditions for comparison.







A mixture of 4-bromombenzyl bromide (7.498 g, 30 mmol), amine (35 mmol), K_2CO_3 (6.346 g, 35 mmol) and THF (50.0 mL) was stirred under a N_2 atmosphere at room temperature overnight. When reaction completed (monitored by GC-FID), the white solid was removed by filtration, while the filtrate was concentrated as much as possible and then dissolved in dichloromethane (~50.0 mL). The resulting organic solution was thoroughly washed with cold water, dried over MgSO₄ and filtered. The solvent was removed under vacuum to afford slightly yellow to yellow oil.

4-Bromo-*N***-isopropylbenzylamine** (substrate for Entry 7, Table 5), 90%, yellow oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.37 – 7.40 (m, 2H), 7.14 – 7.18 (m, 2H), 3.69 (s, 2H), 2.79 (heptet, *J* = 6.2 Hz, 1H), 1.05 (d, *J* = 6.2 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 139.8, 131.4, 129.8, 120.5, 50.9, 48.1, 22.9.

4-Bromo-*N*,*N***-dimethylbenzylamine** (substrate for Entry 8, Table 5), 97%, yellow oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.37 – 7.40 (m, 2H), 7.11 – 7.16 (m, 2H), 3.31 (s, 2H), 2.17 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 137.9, 131.1, 130.7, 120.8, 63.6, 45.3.

4-Bromo-*N*,*N***-diethylbenzylamine** (substrate for Entry 9, Table 5), 96%, yellow oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.40 – 7.43 (m, 2H), 7.20 – 7.23 (m, 2H), 3.50 (s, 2H), 2.50 (q, *J* = 7.1 Hz, 4H), 1.03 (t, *J* = 7.1 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 139.1, 131.2, 130.5, 56.9, 46.7, 11.8.

4-Bromo-*N*,*N***-dipropylbenzylamine** (substrate for Entry 10, Table 5), 92%, yellow oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.41 – 7.45 (m, 2H), 7.22 – 7.26 (m, 2H), 3.50 (s, 2H), 2.38

(t, *J* = 7.4 Hz, 4H), 2.79 (sextet, *J* = 7.3 Hz, 4H), 0.89 (t, *J* = 7.4 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 139.6, 131.1, 130.4, 120.2, 58.1, 55.9, 20.2, 11.9.

4-Bromo-*N*,*N***-diisopropylbenzylamine** (substrate for Entry 11, Table 5), 93%, slightly yellow oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.41 – 7.44 (m, 2H), 7.27 – 7.31 (m, 2H), 3.60 (s, 2H), 2.79 (heptet, *J* = 6.6 Hz, 2H), 1.04 (d, *J* = 6.6 Hz, 12H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 142.4, 131.0, 129.6, 119.6, 48.4, 48.0, 20.8.

Synthesis of *N*-(4-Bromobenzyl)-*N*,*N*,*N*-triethylammonium Bromide (Substrate for Entry 10, Table 7)⁵⁷



A mixture of 4-bromombenzyl bromide (12.497 g, 50 mmol), triethylamine (7.589 g, 75 mmol), dry Et₂O (100 mL) was stirred under a N₂ atmosphere at room temperature overnight, while a white solid gradually precipitated. The precipitated solid was collected by filtration, washed with dry Et₂O, and dried in a vacuum overnight to afford *N*-(4-Bromobenzyl)-*N*,*N*,*N*-triethylammonium bromide (8.778 g, yield: 50%) as white fluffy solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.36 – 7.50 (m, 4H), 4.76 (s, 2H), 3.32 (q, *J* = 6.8 Hz, 6H), 1.34 (t, *J* = 6.8 Hz, 9H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 134.3, 132.4, 126.2, 125.2, 60.6, 53.2, 8.7.

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ASSOCIATED CONTENT

Supporting Information: results of mercury test, analytical methods, NMR spectra. This material is available free of charge via the Internet at <u>http://pubs.acs.org</u>

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