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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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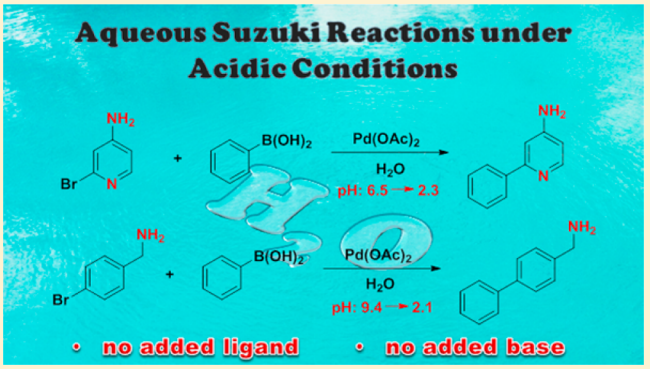
Supporting Information

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 by employing aryl bromides containing aliphatic 1°, 2°, and 3° amine substituents, and good to high yields were obtained by 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 the 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-catalyzed reactions are usually conducted in an organic−aqueous cosolvent 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-2-halopyridines with phenylboronic acid using $PdCl_2$ 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

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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

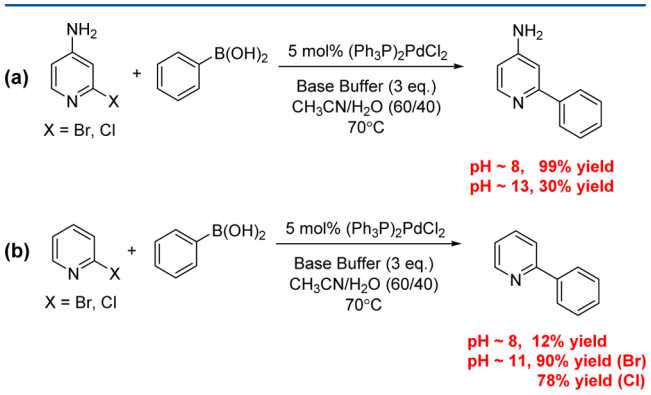


Figure 1. Effect of aqueous buffered pH on the Suzuki coupling of substrates containing basic nitrogen centers.[23]

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]

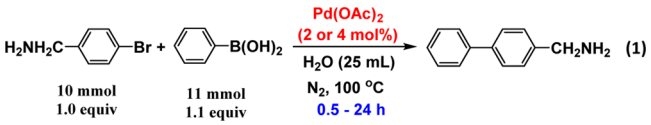
The literature contains a number of reports describing Suzuki reactions of heterocyclic molecules in the absence of added ligand (so-called "ligand-free") using only water as a solvent.[24−37] In general, good to high yields of coupled products are reported. Based upon our observations that the buffered pH of the acetonitrile–water phase appears to be playing an important role in the success of the Suzuki coupling process,[23] we elected to investigate this by simplifying the reaction system still further. The cosolvent 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 (K_3PO_4) were added to the reaction mixture. Two different nitrogen-containing substrates were used in this study: 4-bromobenzylamine and 4-amino-2-bromopyridine. Each of these substrates was reacted with phenylboronic acid using 2 and 4 mol % of $Pd(OAc)_2$. 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

Reaction of 4-Bromobenzylamine with Phenylboronic Acid. 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 h of reaction (entry 4, Table 1). Increasing the

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

				pH	
entry	$Pd(OAc)_2$ (equiv)	time (h)	GC yield (%)	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



reaction time to 24 h produced a 94% yield (entry 5, Table 1). Doubling the amount of catalyst to 4 mol % produced a 93% yield in just 4 h (entry 9, Table 1). In all of 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. When 2 mol % of catalyst loading was employed, the yields appear to be largely independent of the amount of added base. Within a reaction period of 4 h, 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 2. Reaction of 4-Bromobenzylamine with $PhB(OH)_2$ in Water in the Presence of Varying Amounts of Added K_3PO_4 Following the Reaction Conditions in eq 1

					pH	
entry	$Pd(OAc)_2$ (equiv)	K_3PO_4 (equiv)	time (h)	GC yield (%)	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

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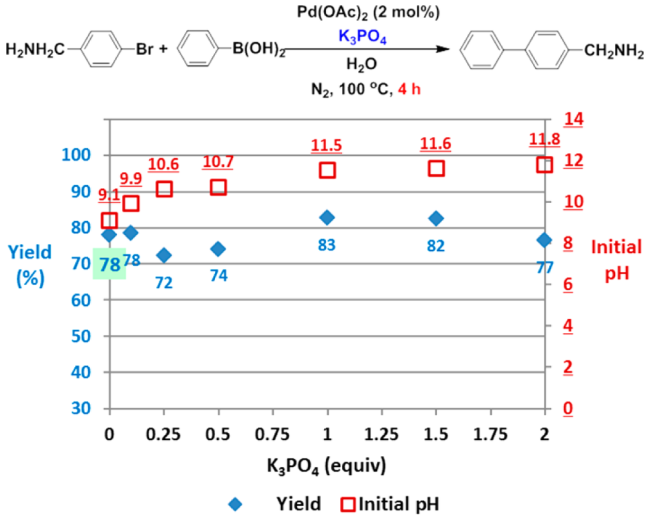

Figure 2. Effect of initial pH on product yield in the ligand-free Suzuki reactions of 4-bromobenzylamine in H_2O. Reaction conditions: 4-bromobenzylamine (10 mmol), $PhB(OH)_2$ (11 mmol), $Pd(OAc)_2$ (2 mol %), H_2O (25 mL), N_2, 100 °C, 4 h.

Reaction of 4-Amino-2-bromopyridine with Phenylboronic Acid. 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 1 h (entry 3, Table 3). An increased catalyst loading of 4 mol % did very little to improve the rate of reaction; a quantitative yield was obtained in 1 h (entry 7, Table 3). 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 of Added Base Following the Reaction Conditions in eq 2

				pH	
entry	$Pd(OAc)_2$ (equiv)	time (h)	GC yield (%)	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.

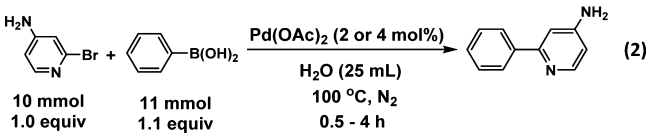

Table 4 summarizes the results for the same reaction conducted in the presence of varying quantities of added base as a function of time. As the amount of added base increases, the yield of product remains relatively constant (entries 1–7, Table 4). However, when 1.5–2.0 equiv of added base was employed, the yield decreased 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 0.25–1.0 equiv 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 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 K_3PO_4 Following the Reaction Conditions in eq 2 (2.0 mol % of $Pd(OAc)_2$)

				pH	
entry	K_3PO_4 (equiv)	time (h)	GC yield (%)	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

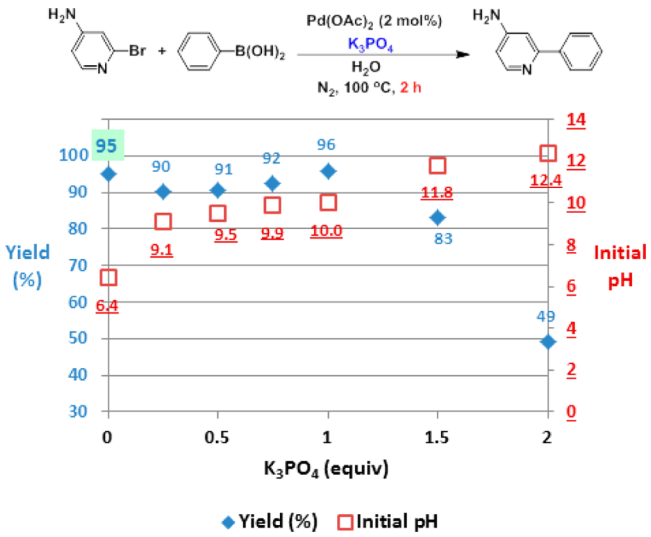

Figure 3. Effect of initial pH on product yield in the ligand-free Suzuki reactions of 4-amino-2-bromopyridine in H_2O. Reaction conditions: 4-amino-2-bromopyridine (10 mmol), $PhB(OH)_2$ (11 mmol), $Pd(OAc)_2$ (2 mol %), H_2O (25 mL), N_2, 100 °C, 2 h.

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

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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]

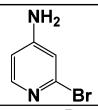
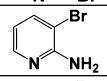
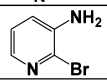
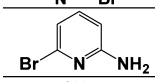
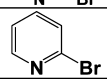
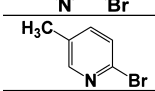
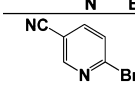
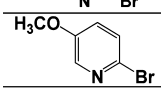
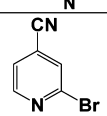
entry	ArBr	time (h)	conv of ArBr[c] (%)	yield of product (%)	pH initial	pH final
1[b]	4-$BrC_6H_4CH_2NH_2$	4	93	93[c]	9.5	2.8
2[b]	3-$BrC_6H_4CH_2NH_2$	4	92	92[c]	9.2	3.1
3[b]	4-$BrC_6H_4CH(CH_3)NH_2$	4	94	94[c]	9.3	1.5
4	4-$BrC_6H_4CH_2CH_2NH_2$	6	99	99[c]	9.6	3.1
5	4-$BrC_6H_4CH_2NHCH_3$	4	94	96[d]	9.0	3.4
6	3-$BrC_6H_4CH_2NHCH_3$	4	94	98[d]	9.0	3.0
7	4-$BrC_6H_4CH_2NHi$-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 conditions: ArBr (10 mmol), $PhB(OH)_2$ (15 mmol), $Pd(OAc)_2$ (4 mol %), H_2O (25 mL), N_2, 100 °C. [b]$PhB(OH)_2$ (11 mmol). [c]Determined by GC. [d]Determined by ^1H NMR.

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.

Reaction of Pyridyl Bromides with Phenylboronic Acid. 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 % of $Pd(OAc)_2$ 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]

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

[a]Reaction conditions: ArBr (10 mmol), $PhB(OH)_2$ (15 mmol), $Pd(OAc)_2$ (4 mol %), H_2O (25 mL), N_2, 100 °C. [b]$PhB(OH)_2$ (11 mmol). [c]Determined by GC. [d]Determined by ^1H NMR.

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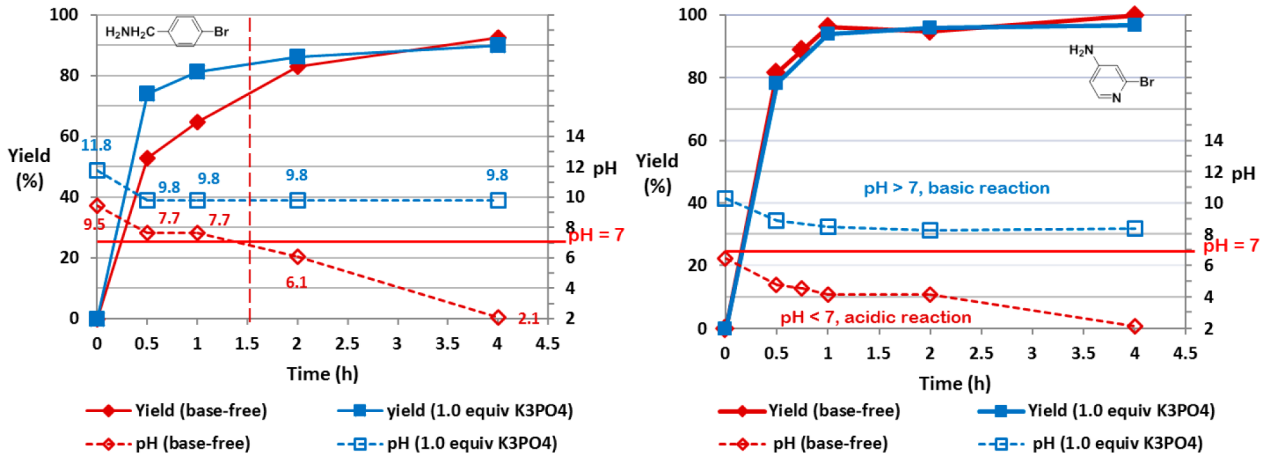
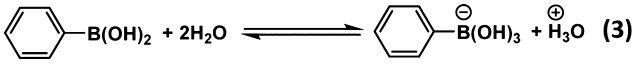


Figure 4. Reaction yield and pH as functions of time for the ligand-free Suzuki reactions of (a) 4-bromobenzylamine and (b) 4-amino-2-bromopyridine with $PhB(OH)_2$ in water in the presence of 1.0 equiv of K_3PO_4 or without added bases. Reaction conditions: aryl bromide (10 mmol), $PhB(OH)_2$ (11 mmol),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

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 equiv of K_3PO_4. During the first 1.5 h, 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 h of reaction, the pH of the base-free system dropped below 7. Nevertheless, the reaction proceeded to produce a yield identical to 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 equiv 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.

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

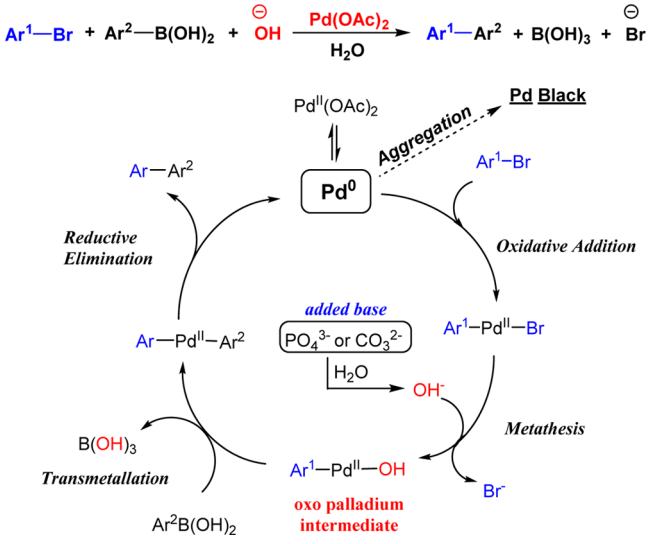


(3)

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-2-bromopyridine substrate. The Suzuki coupling of aryl bromides is widely accepted to proceed via a mechanism which involves oxidative addition of Pd(0) species, transmetalation, 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 $L_nPd(Ar)OH$. The transmetalation 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] Hartwig[41] has demonstrated that in the absence of added base the stoichiometric reaction of

Scheme 1. Mechanism of Ligand-Free Palladium-Catalyzed Suzuki Coupling Reactions in H_2O (Oxo Palladium Intermediate Pathway)[14]



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J. Org. Chem. 2016, 81, 8520−8529

$L_nPd(Ar)OH$ with $ArB(OH)_2$ is orders of magnitude faster than reaction of $L_nPd(Ar)Br$ 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 transmetalation 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 a partial catalytic deactivation caused by addition of an excess of Hg(0) (Supporting Information). These observations are consistent with the literature and support that there are competitive catalytic pathways operating, including active Pd(0) particles (highly likely a mixture 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

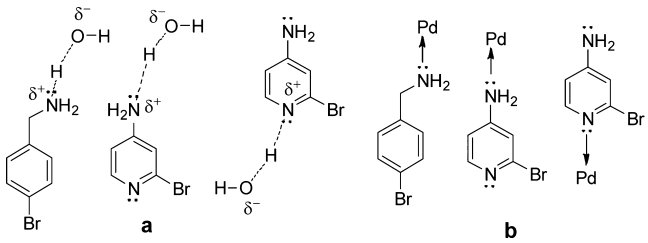

Figure 5. Basic nitrogen-containing substrates acting as the source of (a) incipient hydroxide ions and (b) Pd(0) ligands.

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.

In order to test our hypothesis, we compared the Suzuki reactivity of 4-bromobenzylamine with analogues which did not contain a nitrogen lone pair (Table 7). Experiments with 4-bromoanisole confirmed that essentially no Suzuki-coupled product was 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-bromobenzylammonium bromide (entry 9, Table 7) sequestered this internal basic nitrogen atom and drastically decreased conversion. Similarly, the quaterized amine substituent in 4-bromobenzyltriethylammonium 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-2-bromopyridine, 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 cross-coupling product alone (entries 12 and 13, Table 7) under the same reaction conditions accompanied by 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 % of $Pd(OAc)_2$ for 4 h in the absence of added base at reflux temperatures (entries 1−8, Table 7). While the reflux temperature varied approximately 24 °C 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*-butyl alcohol 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.

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 pK_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, sufficiently basic to cause ionization of water to generate the 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

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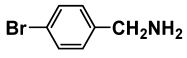
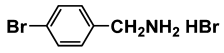
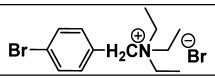
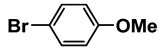
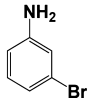
Table 7. Control Reactions for the $Pd(OAc)_2$-Catalyzed Suzuki Reactions in Water in the Absence of Added Base and Ligand[a]

Substrate	Entry	Solvent	Temperature (°C)	GC Yield (%)
	1	H_2O (pH: 9.4 → 2.1)	100	93
	2	EtOH	76	21
	3	CH_3CN	82	21
	4	*t*BuOH	82	22
	5	EtOH (20% H_2O)	80	38
	6	EtOH (40% H_2O)	80	69
	7	EtOH (60% H_2O)	86	86
	8	CH_3CN (40% H_2O)	79	50
	9	H_2O (pH: 4.7 → 1.5)	100	14
	10	H_2O (pH: 4.0 → 1.3)	100	11[b]
	11	H_2O (pH: 3.3 → 2.5)	100	1
	12	H_2O (pH: 3.8 → 2.0)	100	39
	13	H_2O (pH: 4.4 → 2.6)	100	21

[a]Reaction conditions: ArBr (10 mmol), $PhB(OH)_2$ (11 mmol), $Pd(OAc)_2$ (4 mol %), solvent (25 mL), N_2, reflux, 4 h. [b]Determined by ^1H NMR.

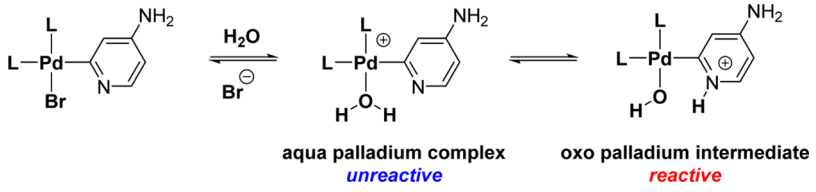


Figure 6. Generation of oxo palladium species via cationic aqua palladium complexes.

palladium intermediate, $L_nPd(ArH)^+(OH)$, required for the catalytic cycle (Figure 6).

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 transmetalation. For less basic bromopyridines, the deprotonation of a cationic aqua intermediate is proposed to allow the oxo palladium intermediate to form under acidic conditions.

EXPERIMENTAL SECTION

General Methods. 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 bromide substrates, such as some of the *N*-substituted 4-bromobenzylamines[56] and *N*-(4-bromobenzyl)-*N*,*N*,*N*-triethylammonium bromide,[57] were synthesized following 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 ^{13}C (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

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J. Org. Chem. 2016, 81, 8520−8529

(J) are reported in hertz. 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 three-neck, 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 20−30 min. 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 $MgSO_4$ and filtered. The solvent was removed under vacuum, and the crude product was analyzed by GC and ^{1}H NMR following the published methods (SI).[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 H_2O (25 mL) in a three-neck, round-bottom flask (100 mL) was stirred under reflux at 100 °C in N_2. 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 ≥ 12 using 30% NaOH aqueous solution, and then thoroughly extracted with chloroform. The combined organic phase was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under vacuum. The crude product was analyzed by GC and ^{1}H NMR.

Procedure for the Reactions of 4-Bromobenzylamine with Phenylboronic Acid in Water in the Presence of Varying Amounts 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 three-neck, round-bottom flask (100 mL) was stirred under reflux at 100 °C in N_2. The reactions were triphasic: an aqueous phase, an organic phase, and a solid phase (catalyst). Formation of palladium black was not observed. After being cooled to room temperature, the reaction was thoroughly extracted with chloroform. The combined organic phase was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under vacuum. The crude product was analyzed by GC and ^{1}H 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 H_2O (25 mL) in a three-neck, round-bottom flask (100 mL) was stirred under reflux at 100 °C in N_2. The reactions were biphasic: an aqueous phase and a solid phase (catalyst and substrate). Palladium black gradually formed when 100 °C was reached. After being cooled to room temperature, the reaction mixture was basified to pH ≥ 12 using 30% NaOH aqueous solution and then was thoroughly extracted with ethyl acetate. The combined organic phase was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under vacuum. The crude product was analyzed by GC and ^{1}H 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 H_2O (25 mL) in a three-neck, round-bottom flask (100 mL) was stirred under reflux at 100 °C in N_2. 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 combined organic phase was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under vacuum. The crude product was analyzed by GC and ^{1}H 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 three-neck, round-bottom flask (100 mL) was stirred under reflux at 100 °C in N_2. The reactions were triphasic: an aqueous phase, an organic phase (substrate), and a solid phase (catalyst). Palladium black gradually formed when 100 °C was reached. After being cooled to room temperature, the reaction mixture was basified to pH ≥ 12 using 30% NaOH aqueous solution and then was thoroughly extracted with chloroform. The combined organic phase was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under vacuum. The crude product was analyzed by GC and ^{1}H 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 H_2O (25 mL) in a three-neck, round-bottom flask (100 mL) was well stirred under reflux at 100 °C in N_2. 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 being cooled to room temperature, the reaction mixture was basified to pH ≥ 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 $MgSO_4$ and filtered. The solvent was removed under vacuum. The crude product was analyzed by GC and ^{1}H 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 H_2O (25 mL) in a three-neck, round-bottom flask (100 mL) was well stirred under reflux at 100 °C in N_2 for 4 h. The reactions were triphasic: 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 being cooled to room temperature, the reaction mixture was thoroughly extracted with dichloromethane. The combined organic phase was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under vacuum. The crude product was analyzed by GC and ^{1}H 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 three-neck, round-bottom flask (100 mL) was stirred under reflux in N_2 for 4 h. The reactions were triphasic: an aqueous phase, an organic phase, and a solid phase (catalyst). After being cooled to room temperature, the reaction mixture was basified to pH ≥ 12 using 30% NaOH aqueous solution and was thoroughly extracted with chloroform. The combined organic phase was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under vacuum. The crude product was analyzed by GC and ^{1}H 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, and 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 H_2O (25 mL) in a three-neck, round-bottom flask (100 mL) was stirred under reflux at 100 °C in N_2. After being cooled to room temperature, the reaction mixture was basified to pH ≥ 12 using 30% NaOH aqueous solution and then was thoroughly extracted with dichloromethane. The combined organic phase was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under vacuum. The crude product was analyzed by GC and ^{1}H 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),

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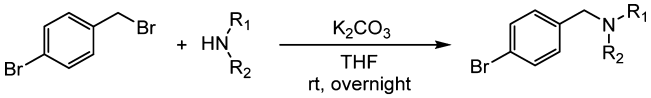
mercury (99.9+%), and water (10 mL) in a three-neck, round-bottom flask (50 mL) was stirred under reflux at 100 °C in N_2. After being cooled to room temperature, the reaction mixture was basified using 30% NaOH aqueous solution (2 mL). The resulting reaction mixture was diluted with methanol and measured 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 identical reaction conditions for comparison.

Synthesis of *N*-Substituted 4-Bromobenzylamines.[56]



R_1, R_2 = H, or Alkyl

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 the reaction was complete (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 $MgSO_4$, 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. ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.8, 131.4, 129.8, 120.5, 50.9, 48.1, 22.9.

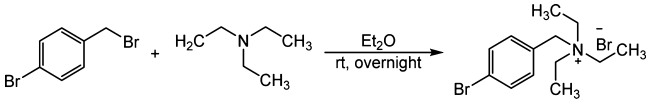
4-Bromo-N,N-dimethylbenzylamine. Substrate for entry 8, Table 5: 97%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37−7.40 (m, 2H), 7.11−7.16 (m, 2H), 3.31 (s, 2H), 2.17 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 137.9, 131.1, 130.7, 120.8, 63.6, 45.3.

4-Bromo-N,N-diethylbenzylamine. Substrate for entry 9, Table 5: 96%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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. ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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. ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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-bromobenzyl bromide (12.497 g, 50 mmol), triethylamine (7.589 g, 75 mmol), and dry Et_2O (100 mL) was stirred under a N_2 atmosphere at room temperature overnight, while a white solid gradually precipitated. The precipitated solid was collected by filtration, washed with dry Et_2O, and dried in a vacuum overnight to afford *N*-(4-bromobenzyl)-*N*,*N*,*N*-triethylammonium bromide (8.778 g, yield 50%) as a white fluffy solid. ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 134.3, 132.4, 126.2, 125.2, 60.6, 53.2, 8.7.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01683.

Results of mercury test, analytical methods, NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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