NJC

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

rsc.li/njc

View Article Online
DOI: 10.1039/C7NJ03567E

NJC

ARTICLE

Pd-Catalyzed Suzuki Coupling Reactions of Aryl Halides Containing Basic Nitrogen Centers with Arylboronic Acids in Water in the Absence of Added Base

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Zhao Li,[a] Carol Gelbaum,[a] Zachary S. Campbell,[b] Paul C Gould,[a] Jason S. Fisk,[c] Bruce Holden,[c] Arvind Jaganathan,[d] Gregory T. Whiteker,[d] Pamela Pollet,[a] and Charles L. Liotta*[,a,b]

The Pd-catalyzed Suzuki coupling reactions of a series of aryl chlorides and aryl bromides containing basic nitrogen centers with arylboronic acids in water in the absence of added base are reported. The reactions proceed either partially or entirely under acidic conditions. After surveying twenty-two phosphorus ligands, high yields of products were obtained with aryl chlorides only when a bulky ligand, 2-(di-*tert*-butyl-phosphino)-1-phenyl-1*H*-pyrrole (cataCXium®PtB) was used. In contrast, aryl bromides produced high yields of products in the absence of both added base and added ligand. In order to explore the Suzuki coupling process entirely under acidic conditions, a series of reactions were conducted in buffered acidic media using several model substrates. 4-Chlorobenzylamine, in the presence of cataCXium®PtB, produced high yields of product at buffered pH 6.0; the yields dropped off precipitously at buffered pH 5.0 and lower. The fall-off in yield was attributed to the decomposition of the Pd-ligand complex due to the protonation of the ligand in the more acidic aqueous media. In contrast, in the absence of an added ligand, 4-amino-2-chloropyridine produced quantitative yields at buffered pH 3.5 and 4.5 while 4-amino-2-bromopyridine produced quantitative yields in a series of buffered media ranging from pH 4.5 to 1.5. These substrates are only partially protonated in acidic media and can behave as active Pd ligands in the Suzuki catalytic cycle.

Introduction

The palladium-catalyzed Suzuki coupling reaction[1,2] provides a versatile synthetic strategy for the construction of biaryl compounds.[3-9] This is particularly important for those substrates containing basic nitrogen centers,[10-13] which are present in many pharmaceutical and biologically active molecules.[14] However, the Suzuki reactions with substrates containing basic nitrogen centers, such as amino groups and pyridines, often suffer from the limitations of slow rates and low yields of desired coupling products compared to the non-basic neutral substrates under the same reaction conditions.[15-18] It has been suggested that the origin of the slow rates and low yields is the decreased activity of palladium catalyst due to the coordination of the catalyst with the basic nitrogen center of the substrates.[18-21] We have, however, recently demonstrated that this ligation effect of the basic nitrogen atoms of aromatic amines and pyridines could play a positive role under the aqueous, ligand-free conditions by stabilizing the active Pd(0) species against deactivation, i.e. preventing formation of insoluble Pd black.[22] In these cases, quantitative yields of desired products could be obtained without protection of the basic nitrogen centers.[22] This synthetic protocol was further simplified; ligand-free/aqueous Suzuki coupling reactions of phenylboronic acid with a series of aryl bromides containing aliphatic amines and pyridines were successfully coupled in the absence of added base.[23] It should be emphasized that these base-free Suzuki reactions were found to be partially or entirely taking place under acidic conditions.[23]

Encouraged by the success in the development of the synthetic protocols for Suzuki couplings of aryl bromides,[22,23] we expanded the scope of substrates for the aqueous, base-free catalytic systems to aryl chlorides which are lower cost substrates compared to bromide counterparts. However, it is well-known that aryl chlorides exhibit much lower reactivity than the corresponding aryl bromides and iodides.[24] Reports in the literature indicate that an effective way to enable the Pd catalyzed Suzuki reactions of the less reactive aryl chlorides is the use of bulky, electron-rich phosphorus ligands (P-ligands).[25,26] In addition to the commonly used triphenylphosphine, the literature has reported several other efficient P-ligands; these include the PCy_3 and $P(t\text{-}Bu)_3$ ligands developed by the Fu group,[27] the Buchwald ligands and pre-

[a] School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, Georgia 30332, USA. Email: charles.liotta@chemistry.gatech.edu.
[b] School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, Atlanta, Georgia 30332, USA
[c] The Dow Chemical Company, Midland, Michigan 48674, USA.
[d] Dow AgroSciences, Indianapolis, Indiana 46268, USA.

† Electronic Supplementary Information (ESI) available: analytic methods; NMR yields for Tables 1, 3 and 5; data tables for Fig. 4-6; characterization spectra of synthesized compounds and isolated products; NMR spectroscopic data for the unsuccessfully isolated products. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C7NJ03567E

catalysts,[28-30] and the cataCXium® ligand family.[31,32] Recently, the *N*-heterocyclic carbenes (NHC) and their transition metal complexes have been demonstrated to have efficient catalytic activity toward the Suzuki couplings of aryl chlorides,[33-35] and the investigations in neat water were also reported during the past few years.[36-38]

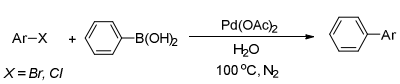
Although the current literature contains a number of reports describing Suzuki reactions of aryl chloride in water in the presence of added ligand and base,[9,26,36-42] to our knowledge *no successful reactions between aryl chlorides and arylboronic acids have been reported in the absence of added base*. Herein, we report (1) a comparison between the reactions of aryl bromides and chlorides containing basic nitrogen centers in the absence of added ligand and added base, (2) the screening of twenty-two phosphorus ligands to optimize the cross-coupling of the aryl chlorides with a variety of arylboronic acids in the absence of added base, (3) the phase behavior of the reaction systems and the pH change of the aqueous phase at the beginning and end of the coupling process, (4) a yield comparison between the base-free reactions of aryl bromides in the absence of added ligand with the aryl chloride counterparts in the presence of an added ligand, and (5) finally, using buffered aqueous media, the demonstration that model substrates (4-chlorobenzylamine, 4-amino-2-chloropyridine, and 4-amino-2-bromopyridine) can undergo the coupling process entirely on the acidic side of the pH scale.

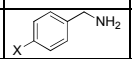
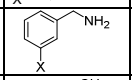
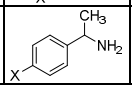
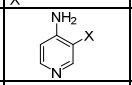
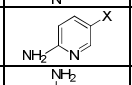
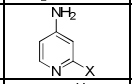
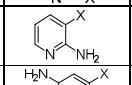
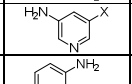
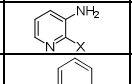
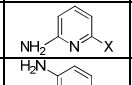
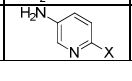
Results and Discussion

(1) Comparison Between Suzuki Reactions of Aryl Bromides and Chlorides in the Absence of Added Ligand and Added Base

Table 1 summarizes the results of the reaction of a variety of aryl bromides and chlorides containing basic nitrogen centers with phenylboronic acid ($PhB(OH)_2$) using 4 mol% $Pd(OAc)_2$ in water at 100°C in the absence of both added ligand and added base for a reaction period of 4 h. In addition, the initial and final pH of the aqueous phase are also indicated. The aryl halides listed in Table 1 include both aliphatic primary amine substituents (Table 1, Entries 1-3) and aromatic basic nitrogen centers (Table 1, Entries 4-11). It is clear that the yields associated with the aryl bromides are, for the most part, good to excellent while those of the aryl chloride counterparts are extremely poor. These results are not unexpected. The literature contains many examples reflecting the greater reactivity of aryl bromides compared with their chloro counterparts. There is, however, one notable exception. 4-Amino-2-bromopyridine and 4-amino-2-chloropyridine (Table 1, Entry 6) both produce quantitative yields of coupled products under the above conditions. This observation is consistent with our previous report in which we observed that these same two substrates produced quantitative yields of coupled products with phenylboronic acid catalyzed by 4 mol% $Pd(PPh_3)_2Cl_2$ in acetonitrile/water (60/40, v/v) in the presence of phosphate base.[43] The only difference is the use of a mixed solvent system and the presence of an added base. Keeping the reaction conditions in Table 1 constant but reducing the amount of Pd catalyst to 2 mol% and reducing the time of reaction to 30 minutes resulted in yields of 100% for 4-amino-2-bromopyridine and only a 62% yield for the chloro counterpart (Table 1, Entry 6). Under these modified conditions, where

Table 1. Suzuki Coupling Reactions of Aryl Bromides and Chlorides Containing Basic Nitrogen Centers with PhB(OH)2 in the Absence of Added Base and Added Ligand.[a]



Entry	Ar-X	Time (h)	X = Br			X = Cl		
			Yield (%)[b]	Initial pH	Final pH	Yield (%)[b]	Initial pH	Final pH
1		4	92	9.2	2.5	15	9.3	7.6
2		4	92	9.2	3.1	12	9.4	7.4
3		4	94	9.3	1.5	28	9.0	7.2
4		4	40	7.9	6.0	13	7.8	6.4
5		4	70	7.4	4.1	3	7.0	4.7
6		1	100 (100)[c]	6.5	2.3	100 (62)[c]	6.3	2.5
7		4	81	5.6	4.4	4	6.6	5.4
8		4	56	5.8	3.1	5	5.5	4.7
9		4	82	4.8	2.6	25	5.3	2.5
10		4	94	4.6	2.7	27	5.1	3.1
11		4	44	4.6	2.7	5	5.1	3.5

[a] Reaction conditions: Ar-X (10 mmol), $PhB(OH)_2$ (15 mmol), $Pd(OAc)_2$ (4 mol%), H_2O (25 mL), N_2, 100 °C. Yields were determined by both GC and ^1H NMR (Supplemental Information S1-S5), GC yields were shown, and NMR yields were summarized in Supplemental Information S6. [b] GC yield, average of 2-3 repetitions with an error < 5%. [c] 2 mol% $Pd(OAc)_2$, 30 minutes.

turnover rates are reduced, the intrinsically higher reactivity of 4-amino-2-bromopyridine over 4-amino-2-chloropyridine is observed. Finally, it is worth noting that Table 1, Entries 4-11 indicates that the pyridyl bromides undergo Suzuki coupling either near neutral pH or completely on the acidic side of the pH scale.

(2) Screening of Phosphorus Ligands

The poor reactivity of aryl chlorides prompted us to investigate the effect of ligand structure on enhancing their reactivity under aqueous conditions in the absence of added base. A total of twenty-two phosphorus ligands and pre-catalysts were surveyed. The base-free Suzuki coupling of 4-chlorobenzylamine (4ClBnAm, **1a**) and $PhB(OH)_2$ (**2**) in water at 100 °C under N_2 catalyzed by 4 mol% of $Pd(OAc)_2$ over a 4 hour

View Article Online
DOI: 10.1039/C7NJ03567E

reaction period was selected as the model reaction for ligand screening. The ligands and the accompanying mol% used in these screening experiments are summarized in Fig. 1. In addition, the yield of coupled product **3a** in the model reaction is also indicated (in red). A 15% yield of product **3a** was obtained without any added ligand. This yield is used as a reference point for evaluating the effectiveness of the added ligands. It has been

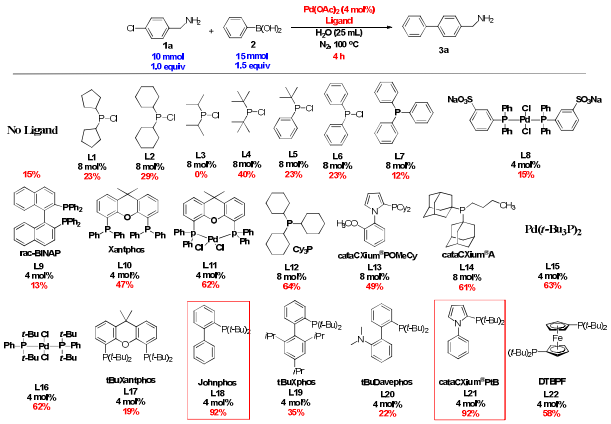


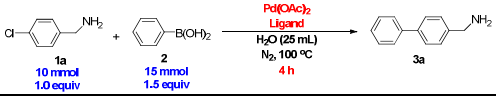
Fig. 1. Screening results of P-ligands for the model reaction between 4ClBnAm (**1a**) and $PhB(OH)_2$ (**2**). Reaction conditions: 4ClBnAm (10 mmol), $PhB(OH)_2$ (15 mmol), $Pd(OAc)_2$ (4 mol%), H_2O (25 mL), N_2, 100 °C, 4 h. Yields of product **3a** were determined by GC.

reported that the hydrolysis of diorganophosphorus chlorides (**L1-L6**) generates phosphine oxides and their less-stable phosphinous acid tautomers which could act as suitable ligands for Pd catalyzed coupling processes.[44] As shown in Fig. 1, marginally improved yields were realized with these ligands. A possible exception is di-*tert*-butylchlorophosphine (**L4**) which resulted in a modest yield of 40%. This, however, is still an unacceptably low yield. The addition of PPh_3 (**L7**) or *rac*-BINAP (**L9**) showed no increase in yield compared to $Pd(OAc)_2$ alone. A somewhat significant increase in yields (approximately 50-60%) was realized with ligands **L10-L16** and **L22.** It should be noted that the pre-catalyst complexes, $Pd(t\text{-}Bu_3P)_2$ (**L15**) and $Pd(t\text{-}Bu_2PhP)_2Cl_2$ (**L16**) were directly used instead of the pyrophoric ligands $P(t\text{-}Bu)_3$[27,45] and $PPh(t\text{-}Bu)_2$[46]. By far, the best results in the ligand screening experiments were obtained with Johnphos (2-(di-*tert*-butylphosphino)biphenyl, **L18**) and cataCXium® PtB (PtB, 2-(di-*tert*-butyl-phosphino)-1-phenyl-1*H*-pyrrole, **L21**); yields greater than of 90% were obtained.

(3) Comparison and Optimization of Johnphos and PtB Ligands

Further comparison of the two most effective ligands, Johnphos (**L18**) and cataCXium® PtB (**L21)** in the first round of screening indicated that the latter is more effective in the base-free Suzuki couplings of 4ClBnAm with $PhB(OH)_2$ in water. The results are shown in Table 2. When the 1:1 loading of the catalyst/ligand pair $Pd(OAc)_2$/JohnPhos is decreased from 4 to 2 mol% the yield of product decrease from 91% to 72% over a four-hour reaction period (Table 2, Entry 2). In contrast, a yield of approximately 90% could be maintained with cataCXiumPtB (**L21**) even when the 1:1 catalyst/ligand loading was decreased to 1 mol% (Table 2, Entries 4 and 5) and reaction time reduced to 1 h (Table 2, Entry 6). In addition, if the catalyst/ligand ratio was changed to 1:2, quantitative yield was obtained in 4 h in the presence of 0.5 mol% of $Pd(OAc)_2$ and 1 mol% of PtB ligand (Table 2, Entry 7). In all the experiments listed in Table 2 the initial pH of the aqueous phase ranged from 8.8 to 9.1; the final pH ranged from 2.9 to 5.8. These results suggest that the Johnphos and PtB ligands might be active under both basic and acidic conditions.

Table 2. Optimization of Coupling Conditions for the Model Reaction Using JohnPhos or PtB as Ligand[a]



Entry	Ligand		$Pd(OAc)_2$ (mol%)	Time (h)	Yield[b] (%)	pH	
	Name	mol%				initial	Final
1	JohnPhos	4	4	4	91	8.8	3.0
2	JohnPhos	2	2	4	72	8.8	4.6
3	PtB	4	4	4	92	9.1	3.2
4	PtB	2	2	4	91	9.0	3.6
5	PtB	1	1	4	91	8.8	3.8
6	PtB	1	1	1	90	8.9	3.3
7	PtB	1	0.5	4	100	9.1	2.9
8	PtB	1	0.5	2	92	8.8	3.2
9	PtB	1	0.5	1	65	8.8	5.6
10	PtB	1	0.5	0.5	54	8.9	5.8
11	PtB	0.5	0.5	4	72	8.8	4.5

[a] Reaction conditions: 4ClBnAm (10 mmol), $PhB(OH)_2$ (15 mmol), H_2O (25 mL), N_2, 100 °C. [b] GC yield, average of 2-3 repetitions with an error < 5%.

(4) Substrate Scope

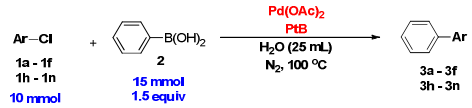
In order to explore the scope of the Suzuki reactions of basic nitrogen-containing aryl chlorides with $PhB(OH)_2$ in water catalyzed by $Pd(OAc)_2$/PtB without added base, a variety of aryl chlorides containing aliphatic amine substituents (**1b-1f**) and aminopyridyl chlorides (**1h-1n**) were investigated. The results are summarized in Table 3. Both the yields of coupled products and the pH of the aqueous phase before and after reaction are shown. Excellent yields were obtained for the first nine substrates (**1b-1f**, **1h-1k**, Table 3, Entries 1-17) while good to modest yields were realized for 3-amino-2-chloropyridine (**1l**) and 2-amino-6-chloropyidine (**1m**) (Table 3, Entries 18-22). Only a 25% yield was obtained for the reaction of 3-amino-6-chloropyridine (**1n**, Table 3, Entries 23-24). While the result for this substrate is only slightly better than the 5% yield obtained without addition of PtB (Table 1, Entry 11), it is still much too low to be of significant synthetic value. The results shown in Table 3 also indicate that the effectiveness of PtB is substrate dependent.

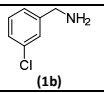
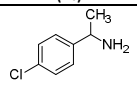
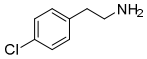
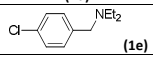
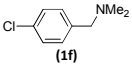
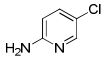
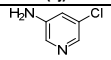
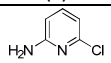
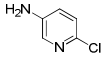
It should be noted that in the reactions with the aliphatic amine substrates (**1b-1f**, Table 3, Entries 1-7) and 4-amino-3-chloropyridine (**1h**, Table 3, Entries 8-9) the pH of the aqueous phase changes from basic to acidic suggesting that at least a portion of these reactions may have taken place in an acidic aqueous environment. In contrast, each of the remaining reactions involving aminopyridyl chlorides (**1i-1n**, Table 3, Entries 10-24) appear to have taken place entirely under acidic aqueous conditions. The initial pH of the reaction solutions

View Article Online
DOI: 10.1039/C7NJ03567E

appear to be simply functions of the pK_a of the amine-substituted aryl chloride substrates calculated using the web-based acidity-basicity calculator available from the University of Kentucky.[47] The pK_a values are listed in Table 3, Column 3. Fig. 2 shows the relationship between the calculated pK_a of the conjugate acids of amine-substituted aryl chlorides (pK_a (Cl-ArH$^+$)) and the initial pH of the aqueous phase for the reactions

Table 3. $Pd(OAc)_2$–PtB Catalyzed Suzuki Reactions of Basic Nitrogen-Containing Aryl Chlorides with $PhB(OH)_2$ in Water in the Absence of Added Base[a]



Entry	Ar-Cl	pK_a (Cl-ArH$^+$)[47]	$Pd(OAc)_2$ (mol%)	PtB (mol%)	Time (h)	Yield (%)[b]	pH initial	pH final
1	 (1b)	9.2	1	1	4	95	9.6	3.5
2	 (1c)	9.5	1	1	4	95	9.3	2.4
3	 (1d)	9.8	1	1	4	95	9.1	2.4
4	 (1e)	9.2	2	2	4	97	8.1	2.5
5	 (1f)	8.7	1	1	2	46	8.1	6.0
6			2	2	4	83	8.1	5.3
7			4	4	4	79	8.2	5.5
8	 (1h)	7.2	2	2	4	74	7.8	5.4
9			4	4	4	95	7.8	4.1
10	 (1i)	4.8	1	2	4	90	6.0	3.7
11			2	2	4	75	6.1	3.8
12			4	4	4	88	6.0	3.8
13	 (1j)	5.1	1	2	4	70	6.6	3.9
14			2	2	4	64	6.6	4.2
15			4	4	4	92	6.5	2.8
16	 (1k)	3.8	2	2	4	65	5.4	3.2
17			4	4	4	90	5.3	2.1
18	 (1l)	1.6	2	2	4	28	5.3	1.9
19			2	2	24	44	5.3	1.8
20			4	4	4	38	5.3	2.1
21	 (1m)	2.9	2	2	4	41	4.8	2.8
22			4	4	4	62	4.8	2.4
23	 (1n)	1.5	2	2	4	17	5.1	3.0
24			4	4	4	25	5.1	3.1

[a] Reaction conditions: Ar-Cl (10 mmol), $PhB(OH)_2$ (15 mmol), H_2O (25 mL), N_2, 100 °C. Yields were determined by both GC and ^1H NMR (Supplemental Information S1-S5), GC Yields were shown, and NMR yields were summarized in Supplemental Information S7. [b] GC Yield, average of 2-3 repetitions with an error < 5%.

in Table 3. It is not surprising that the more basic amine substrates result in a higher pH of the starting solution. Amine basicity was also found to correlate with the yield of product. Fig. 3 shows the relationship between the calculated pK_a values and the observed yield for reactions in Table 3 that were conducted using ≤ 2 mol% Pd.

At this juncture, the correlations clearly indicate that the aliphatic amino substrates (**1a-1f**) are completely protonated below pH 7. As a consequence, the amino functionality in these substrates would not be readily available to act as Pd ligands. However, the presence of the ammonium substituent would increase the solubility of these substrates in the aqueous phase

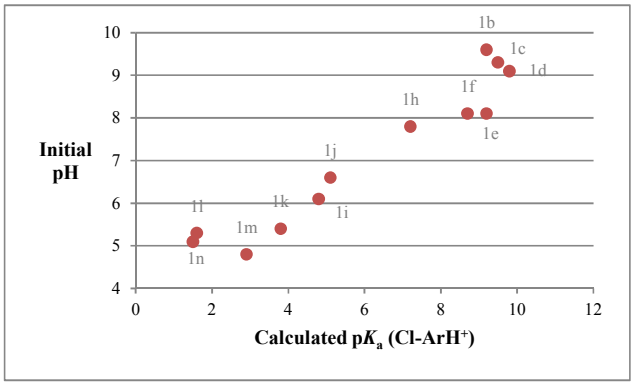


Fig. 2. Relationship between initial pH and calculated pK_a of the conjugate acids of amine-substituted aryl chlorides (pK_a(Cl-ArH$^+$)) based on the data in Table 3. Reaction conditions: Ar-Cl (10 mmol), $PhB(OH)_2$ (15 mmol), H_2O (25 mL), $Pd(OAc)_2$ (0.1 mmol for **1b-1d**; 0.2 mmol for **1e**,**1f**, **1h-1n**), PtB (0.1 mmol for **1b-1d**; 0.2 mmol for **1e**,**1f**, **1h-1n**), N_2, 100 °C, 4 h.

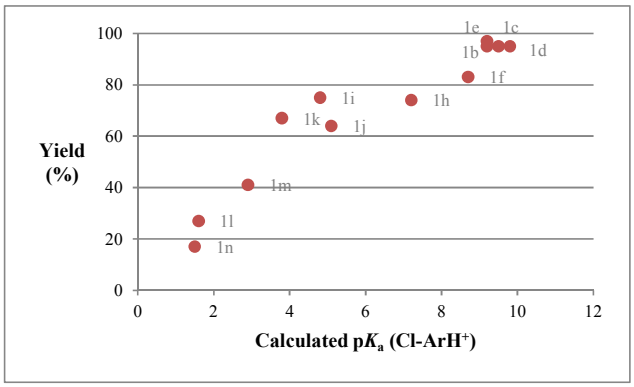


Fig. 3. Relationship between Suzuki coupling yield and calculated pK_a of the conjugate acids amine-substituted aryl chlorides (pK_a(Cl-ArH$^+$)) based on the data in Table 3. Reaction conditions: Ar-Cl (10 mmol), $PhB(OH)_2$ (15 mmol), H_2O (25 mL), $Pd(OAc)_2$ (0.1 mmol for **1b-1d**; 0.2 mmol for **1e**,**1f**, **1h-1n**), PtB (0.1 mmol for **1b-1d**; 0.2 mmol for **1e**,**1f**, **1h-1n**), N_2, 100 °C, 4 h.

and also increase the electrophilic character, inductively and/or electrostatically, of the *ipso* carbon facilitating the oxidative insertion step in the catalytic cycle. In contrast, the pyridyl

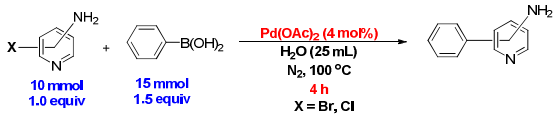
substrates (**1h-1n)** would only be partially protonated. This, of course, would also increase their aqueous solubility, enhance the electrophilic character of the substrate's *ipso* carbon, and would allow them, in principle, to act as Pd ligands.

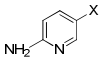
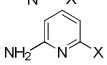
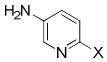
View Article Online
DOI: 10.1039/C7NJ03567E

(5) Yield Comparisons in the Base-Free Reactions of Aryl Bromides in the Absence of Added Ligand and Aryl Chlorides in the Presence of the PtB Ligand

Table 4 represents a comparison of (a) the *ligand-free/base-free* Suzuki coupling reactions of a series of aryl bromides with (b) the *base-free* coupling reactions of the chloro counterparts in the absence and in the presence of the *PtB ligand*. Each reaction in these series used 4 mol% $Pd(OAc)_2$ in water at 100°C for 4 h. As previously mentioned, the H_2O/base-free/ligand-free protocol in Suzuki couplings of aminopyridyl bromides produces poor yields when applied to the chloro counterparts (except for the 4-amino-2-halopyridines, Table 4, Entry 3). However, the

Table 4. Comparison of (a) the Ligand-Free/Base-Free Suzuki Coupling Reactions of a Series of Aryl Bromides with (b) the Base-Free Coupling Reactions of the Chloro Counterparts in the Absence and in the Presence of the PtB Ligand[a]



Entry	Substrate	X = Br		X = Cl		
		Yield (%) ligand-free	Initial pH	Yield (%) ligand-free	Yield (%) 4 mol% PtB	Initial pH
1		40	7.9	13	95	7.8
2		70	7.4	3	88	6.0
3		100	6.5	100	-	6.4
4		81	5.6	4	92	6.6
5		56	5.8	5	90	5.3
6		82	4.8	23	38	5.3
7		93	4.7	27	62	4.8
8		44	4.6	4	25	5.1

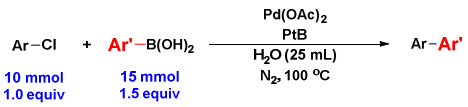
[a] Basing on the Data in Tables 1 and 3, GC yields were shown. Reaction conditions: aminopyridyl halides (10 mmol), $PhB(OH)_2$ (15 mmol), $Pd(OAc)_2$ (4 mmol%), H_2O (25 mL), N_2, 100 °C, 4 h.

use of 4 mol% PtB ligand provides coupled products with the aryl chlorides in excellent yields for several of these substrates (Table 4, Entries 1, 2, 4 and 5). The yields for the aryl chlorides compare favorably to the yields obtained for most of the ligand-free/base free reactions used for aryl bromides.

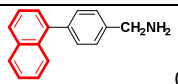
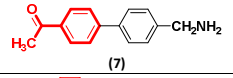
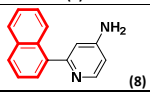
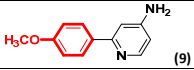
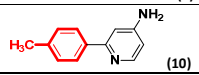
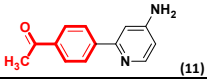
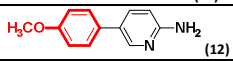
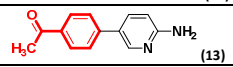
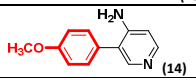
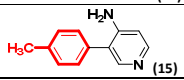
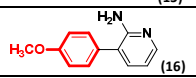
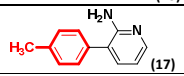
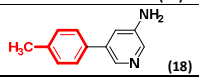
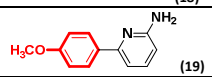
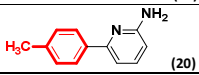
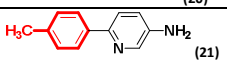
(6) Survey of Arylboronic Acids in Base-Free Suzuki Coupling Reactions of Aryl Chlorides Using the PtB Ligand.

Table 5 summarizes the yields and the reaction conditions for the base-free Suzuki coupling reactions of 4-chlorobenzylamine and aminopyridyl chlorides with a variety of electronically and structurally diverse arylboronic acids in water at 100°C using the $Pd(OAc)_2$/PtB catalyst/ligand system. The initial and final pH of the aqueous phase are also indicated. 1-Naphthylboronic acid, 4-methoxyphenylboronic acid, 4-methylphenylboronic acid and 4-acetylphenylboronic acid were the arylboronic acids employed in this study. All of the coupling reactions proceeded smoothly regardless of the electronic character of arylboronic acids and afforded excellent yields for most of cases (Table 5, Entries 1-15). Interestingly, all of the arylboronic acids successfully reacted with 4-amino-2-chloropyridine under base-free conditions in water without added ligand (Table 5, Entries 5-8). Moderate to good yields were obtained in the reactions of 2-amino-6-chloropyridine with 4-methoxy- and 4-methyl-phenylboronic acids (Table 5, Entries 16 and 17). These results are similar to those obtained with phenylboronic acid (Table 4, Entry 6). Although only 41% yield was observed for the reaction

Table 5. $Pd(OAc)_2$–PtB Catalyzed Suzuki Reactions of Basic Nitrogen-Containing Aryl Chlorides with Arylboronic Acids in Water in the Absence of Added Base[a]

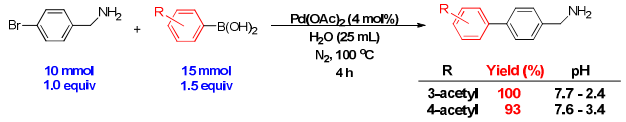


View Article Online
DOI: 10.1039/C7NJ03567E

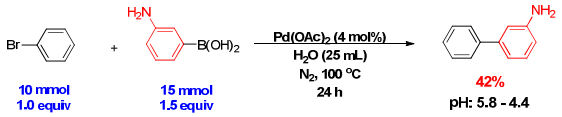
Entry	Product	$Pd(OAc)_2$ (mol%)	PtB (mol%)	Time (h)	Yield[b] (%)	pH initial	pH Final
1	 (4)	1	1	4	99	8.3	2.5
2	 (5)	1	1	4	90[c]	8.5	2.5
3	 (6)	1	1	4	88[c]	8.6	4.1
4	 (7)	1	1	4	96[c]	7.8	2.1
5	 (8)	4	0	2	100	7.1	3.3
6	 (9)	4	0	4	84	7.4	4.7
7	 (10)	4	0	2	100	6.7	2.7
8	 (11)	4	0	2	100	6.6	2.3
9	 (12)	2	2	4	86	6.5	4.0
10	 (13)	4	4	4	85	6.2	3.4
11	 (14)	4	4	4	88[c]	7.9	3.6
12	 (15)	4	4	4	88	7.9	4.1
13	 (16)	4	4	4	92	6.6	3.3
14	 (17)	4	4	4	82	6.3	3.5
15	 (18)	4	4	4	90	5.5	2.2
16	 (19)	4	4	4	65	5.6	2.5
17	 (20)	4	4	4	67	5.4	2.1
18	 (21)	4	4	4	41	5.4	2.9

[a] Reaction conditions: Ar-Cl (10 mmol), **Ar'**$B(OH)_2$ (15 mmol), H_2O (25 mL), N_2, 100 °C. Yields were determined by both GC and ^1H NMR (Supplemental Information S1-S5), GC yields were shown, and NMR yields were summarized in Supplemental Information S8. [b] GC yields, average of 2-3 repetitions with an error < 5%. [c] NMR yield.

of 3-amino-6-chloropyridine with 4-methylphenylboronic acid (Table 5, Entry 18), it is slightly better than the 25% yield of its reaction with $PhB(OH)_2$ (Table 4, Entry 8).



Scheme 1. Ligand-free and base-free Suzuki coupling reactions of 4-bromobenzylamine with 3- and 4-acetylphenylbornic acids in water.



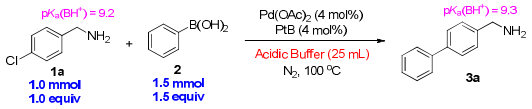
Scheme 2. Ligand-free and base-free Suzuki coupling reaction between bromobenzene and 3-aminophenylbornic acid in water.

It is interesting to note that the ligand-free and base-free Suzuki reactions of 4-bromobenzylamine with 3- and 4-acetylphenylboronic acids produced excellent yields in 4 hours (Scheme 1). It is also of interest to consider the question of whether the base-free protocol reported here can be applied to the Suzuki couplings between neutral aryl halides and the arylboronic acids containing basic nitrogen center(s). In a single preliminary experiment bromobenzene was reacted with 3-aminophenylboronic acid in the absence of added base and added ligand (Scheme 2). Although the reaction conditions were not optimized, a modest 42% isolated yield of coupled product was obtained after 24 hours.

(7) Suzuki Reactions of Aryl Chlorides with $PhB(OH)_2$ in Buffered Acidic Solutions

At this juncture, it appears that the experimentally observed initial and final pH of the aqueous phase suggest that the aryl chlorides in the presence of PtB ligand (Tables 2-5) and aryl bromides in the absence of added ligand (Tables 1 and 4, previous work[23]), both in the absence of added base, undergo the Suzuki coupling process either partially or entirely under aqueous acidic conditions. A notable exception is 4-amino-2-chloropyridine which produces a quantitative yield of coupled product in the absence of added ligand and in the absence of base (Table 1, Entry 6). The question was posed: "what happens to the rate and yield of the reaction in buffered solutions at fixed pH?" In order to address this question, we conducted a series of coupling reactions in buffered aqueous acidic media. In the first set of experiments 4-chlorobenzylamine was chosen as a model substrate for PtB ligand-promoted reactions and in second and third sets of experiments 4-amino-2-chloropyridine and 4-amino-2-bromopyridine, respectively, were chosen as the models for the corresponding ligand-free reactions.

Fig. 4 summarizes results for the reaction of 4-chlorobenzylamine with phenylboronic acid at buffered pH 5.0 and 6.0 as a function of time employing 4 mol% PtB catalyst. Maximum yields of approximately 82% are achieved at pH 6.0 in about two hours. In contrast, adjusting the pH to 5.0 results in a much slower reaction; only a 30% yield is obtained after 4 hours of reaction. Under even more acidic condition the rates of this reaction became extremely slow indicating that, for this particular substrate, a strongly acidic aqueous phase retards the coupling process. It is interesting to note that the same reaction using an unbuffered aqueous phase (see Table 2, Entry 3) produced a 92% yield in four hours. In this case, however, the



View Article Online
DOI: 10.1039/C7NJ03567E
NJC ARTICLE

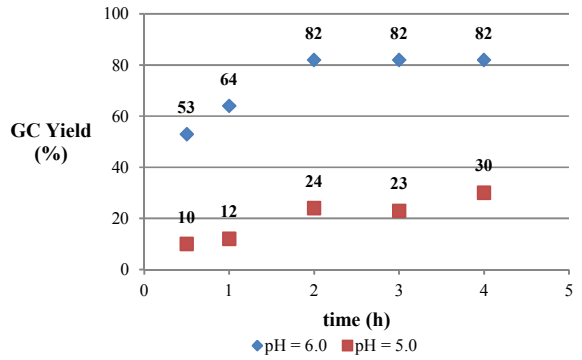
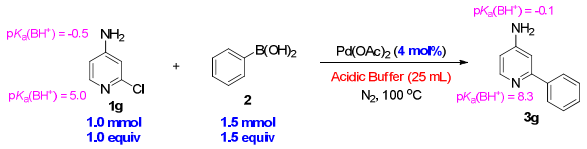


Fig. 4. Reaction yield as functions of time for the $Pd(OAc)_2$/PtB catalyzed Suzuki reaction of 4-chlorobenzyl amine (**1a**) with $PhB(OH)_2$ (**2**) in buffered acidic solutions, basing on the data in Supplemental Information S9. Reaction conditions: **1a** (1.0 mmol), **2** (1.5 mmol), $Pd(OAc)_2$ (0.04 mmol), PtB (0.04 mmol), acidic buffer (25 mL), N_2, 100 °C.



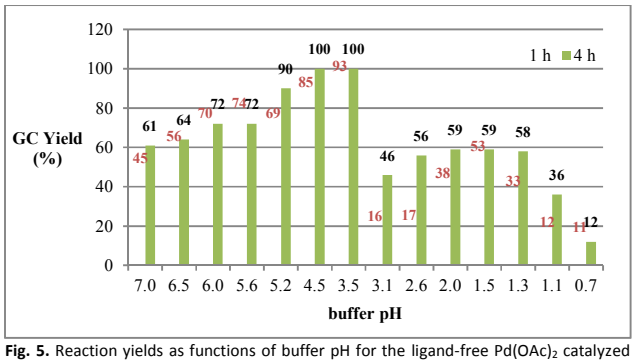


Fig. 5. Reaction yields as functions of buffer pH for the ligand-free $Pd(OAc)_2$ catalyzed Suzuki reaction of 4-amino-2-chloropyridine (**1g**) with $PhB(OH)_2$ (**2**) in buffered acidic solutions, basing on the data in Supplemental Information S10. Reaction conditions: **1g** (1.0 mmol), **2a** (1.5 mmol), $Pd(OAc)_2$ (0.04 mmol), acidic buffer (25 mL), N_2, 100 °C.

initial pH was 9.1 and the final pH 3.2. The results in the buffered media strongly suggest that at least a portion of the unbuffered reaction proceeds on the acidic side of the pH scale.

Fig. 5 summarizes the reaction of 4-amino-2-chloropyridine with phenylboronic acid using 4 mol% catalyst at buffered pH's ranging from 7.0 to 0.7 for reaction periods of one and four hours; the two sets of reactions were conducted *in the absence of added ligand*. Fig. 5 indicates that as reaction proceeds from pH 7.0 to 3.5 the yields steadily increase from 61% to 100% over a period of four hours. Lowering the pH of the buffered aqueous phase below 3.5, however, results in a substantial decrease in yield. The trends in the yield profiles for the one-hour and four-hour reaction times are quite similar.

Fig. 6 summarizes the reaction of the bromo counterpart over the same pH range using 2 mol% catalysts for reaction

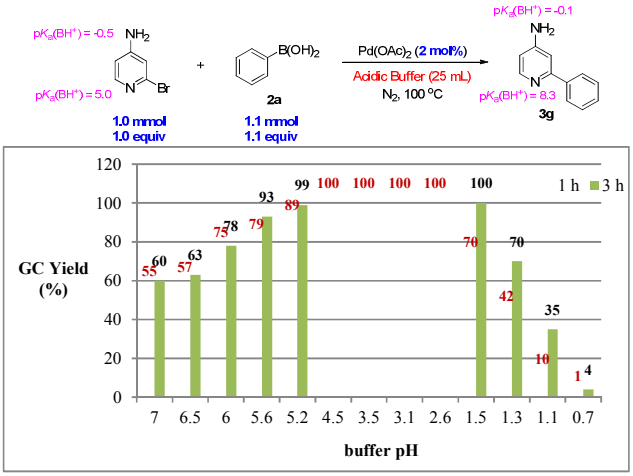


Fig. 6. Reaction yields as a function of pH for the ligand-free $Pd(OAc)_2$ catalyzed Suzuki reaction of 4-amino-2-bromopyridine with $PhB(OH)_2$ (**2**) in buffered acidic solutions, basing on the data in Supplemental Information S11. Reaction conditions: 4-amino-2-bromopyridine (1.0 mmol), **2** (1.1 mmol), $Pd(OAc)_2$ (0.02 mmol), acidic buffer (25 mL), N_2, 100 °C.

periods of one and three hours *in the absence of added ligand*. A very similar trend is observed. The yield of product steadily increases as the pH of the aqueous phase decreases from 7.0 and becomes quantitative at pH 5.2 and remained quantitative down to a pH of 1.5. The trends in yield were the same for both the one-hour and three-hour experiments.

(8) Mechanistic Comments Concerning Suzuki Coupling Reactions Conducted Under Acidic Aqueous Conditions

The palladium-catalyzed Suzuki cross-coupling reactions presented in this report were conducted in water in the absence of added base. The reactions were heterogeneous and were experimentally observed to proceed partially or entirely under acidic aqueous conditions. It was observed that aryl bromides gave excellent yields of products in the absence of added ligand. In contrast, aryl chlorides required the bulky ligand PtB; the only exception was 4-amino-2-chloropyridine which did not require a ligand to achieve a quantitative yield of product. In order to unequivocally demonstrate that the coupling process can take place under acidic aqueous condition, a series of reactions were successfully conducted with model substrates under buffered acidic conditions. Excellent yields of coupled products were obtained when the reactions were conducted entirely on the acidic side of the pH scale (Fig. 4-6). Given these observations it is important to address the relationship between the classical catalytic cycle describing the Suzuki process (Fig. 7) conducted under basic conditions and the catalytic cycle described here conducted in the absence of added base.

The generally accepted mechanistic pathway for the Suzuki cross-coupling reaction is illustrated in Fig. 7.[48-51] It has been stated many times in the literature that the presence of base is essential to achieve a successful reaction.[48] For reactions conducted in aqueous media (water-organic solvent systems), the bases normally employed include K_3PO_4, K_2CO_3, KOH, or KF. The initial step in the catalytic cycle is the oxidative

View Article Online
DOI: 10.1039/C7NJ03567E

addition of the organohalide to the Pd(0) to form a Pd(II) complex. A

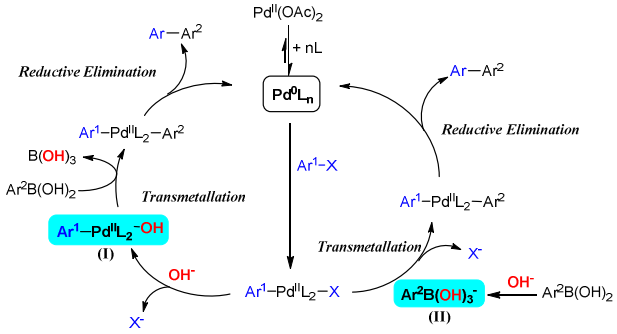


Fig. 7. Mechanism of palladium-catalyzed Suzuki coupling reactions in aqueous media

molecule of the hydroxide (used as is or generated in water) then replaces the halide on the palladium complex to form an oxo-palladium intermediate (Ar^1-$Pd^{II}L_2$-OH, Intermediate **I**).[52-53] It has also been suggested that another hydroxide adds to the organoborane to form the more nucleophilic boronate intermediate ($Ar^2B(OH)_3^-$, Intermediate **II**).[54-57] Transmetalation with the aryl boronic acid/boronate then follows where the Ar^2 group replaces the hydroxide/halide anion on the palladium complexes. Reductive elimination then gives the final coupled product. The palladium catalyst is thus regenerates and the catalytic cycle continues.

It is clear that in this classical representation of the catalytic cycle hydroxide ion is critical for the formation of two intermediates. However, for Suzuki coupling reactions conducted in acidic aqueous media, the amount of hydroxide ion is negligible- especially for those reactions conducted below pH 6.0. We have shown that 4-chlorobenzylamine in the presence of the PtB ligand produces very good yields (82%; Fig. 4) at pH 6.0 and poor yields (30%; Fig. 4) at pH 5.0 and below. It has also been demonstrated that, in the absence of this ligand, an extremely low yield (15%; Table 1, Entry 1) of coupled product is produced; the presence of the ligand is essential. At this juncture, it is conjectured that at pH 5.0 or less, the Pd-ligand complex is not stable thus resulting in the observed poor yield. We suggest that the origin of this instability is the basicity of the phosphine ligand in acidic media. The aqueous pK_a values of a wide variety of tertiary phosphines have been reported in the literature.[58-60] Although the pK_a of PtB has not been determined, the pK_a of diethylphenyl phosphine, a structure somewhat similar to PtB, has been reported to be 6.25.[58] It is conjectured, therefore, reasonable that in acidic aqueous media the complexation of the ligand with Pd competes with the protonation of the ligand. This would explain the decrease in yield from an aqueous pH of 6.0 to 5.0 and below. In contrast, 4-amino-2-chloropyridine and 4-amino-2-bromopyridine, the substrates which do not require an added ligand, produce quantitative yields of coupled product even under highly acidic conditions. Since the calculated pK_a values for these substrates indicate that they are only partially protonated in acidic media, it is suggested that the substrates themselves behave as the active Pd ligands in the Suzuki catalytic cycle- consistent with our previously published work.[22] Further research is necessary to establish the pertinent species involved under acidic conditions as well as the phase location for each of the steps in the overall process.

Conclusions

(1) The heterogeneous $Pd(OAc)_2$ catalyzed aqueous Suzuki couplings of relatively unreactive aryl chlorides containing basic nitrogen centers with arylboronic acids in the absence of added base produce excellent yields of coupled product by the addition of bulky triorganophosphine ligands, such as cataCXium® PtB. For the aryl chlorides containing aliphatic amine substituents, the initial pH of the aqueous phase is basic and the final pH is highly acidic. The pyridyl chloride substrates undergo the coupling process almost entirely on the acidic side of the pH scale.

(2) The couplings of the corresponding aryl bromides produce excellent yields in the absence of both added ligand and added base. The initial and final aqueous phase pH are similar to the chloride counterparts.

(3) At buffered pH 6.0 the reaction of 4-chlorobenzylamine in the presence of the PtB ligand produces an excellent yield of coupled product. At buffered pH 5.0 and below, very poor yields are obtained. These observations are attributed to the protonation of the phosphine ligand in the acidic aqueous phase which disrupts the Pd-ligand interaction.

(4) The reactions of 4-amino-2-chloropyridine and 4-amino-2-bromopyridine, in the absence of added ligand, produce quantitative yields of product entirely under buffered acidic conditions. Since these substrates are only partially protonated in acidic aqueous media, it is suggested that they can act as Pd ligands thus facilitating the Suzuki process.

Experimental

General Method

The commercially available solvents and reagents were purchased from commercial providers in reagent grade and were used without further purification. *N,N*-Dimethyl- and *N,N*-diethyl 4-chlorobenzylamines (**1f** and **1e**) were synthesized following the published methods.[61] The pure products (except **5-7**) used as standards for GC analysis were isolated from the Suzuki reactions via column chromatography. Pure compounds **5-7** have not been successfully isolated due to the degradation during the drying process after column chromatographic separation. Spectroscopic data, however, are presented in the Supplemental Information S14 consistent with the structure of the products.

Reaction yields were determined by both GC and ^{1}H NMR following the reported method[23,43] and are further discussed in Supplemental Information S1-S5. The GC yields are reported in the main text and NMR yields are summarized in Supplemental Information S6-S8. For each reaction, 2 to 3 repetitions were

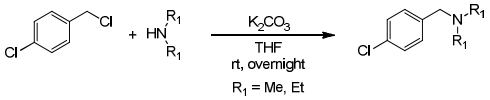
View Article Online
DOI: 10.1039/C7NJ03567E

usually conducted for consistent results with errors less than 5%.

A new compound, 4-amino-2-(4-acetophenyl)pyridine (**11**), was characterized by ^{1}H NMR, ^{13}C NMR, m.p. and HRMS. Known compounds were characterized by ^{1}H NMR, ^{13}C NMR, m.p. (for solids) and MS (EI), and compared with the literature value when available. Some of the m.p. values, and NMR/MS data for "known" compounds have not been previously reported. The "missing" analytical data are now documented in the Experimental Section and in the Supplemental Information.

pH values of the aqueous phase were measured by a Cole-Parmer pH 20 m portable pH meter with an "all-in-one" electrode at 25 ± 2 °C. GC analyses were carried out on a Shimazu GCMS-QP2010S (qualitative) and a Shimazu GC-2010/FID (quantitative) gas chromatographs fitted with Supelco PTA-5 capillary columns (30 m × 0.32 mm × 1.00 µm, length × inside diameter × film thickness). Melting points were measured on a Mel-Temp capillary melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury Vx 400 and a Bruker Avance IIIHD 500 NMR spectrometers. Chemical shifts (δ) are reported in ppm and coupling constants (J) are in Hz. MS analyses (EI-MS and an EI-HRMS) were performed on a MicroMass AutoSpec M mass spectrometer.

Synthesis of *N*,*N*-Dimethyl- and *N*,*N*-Diethyl-4-Chlorobenzylamines[61]



A mixture of 4-chlorobenzyl chloride (4.831 g, 30 mmol), dimethylamine solution (40 wt.% in H_2O) or diethylamine (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), the white solid was removed by filtration, the filtrate concentrated as much as possible and residue 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 oil as product.

4-Chloro-N,N-dimethylbenzylamine (**1f**). CAS: 15184-98-2. 85%, slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.14 (m, 1H), 3.36 (s, 1H), 2.21 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.58, 132.80, 130.42, 128.46, 63.70, 45.40. Agreed with literature data.[62]

4-Chloro-N,N-diethylbenzylamine (**1e**). CAS: 24619-87-2. 90%, slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 1H), 3.52 (s, 1H), 2.50 (q, J = 7.1 Hz, 1H), 1.03 (t, J = 7.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.80, 132.38, 130.20, 128.34, 57.02, 46.87, 11.90. Agreed with literature data.[63]

General Experimental Procedure for $Pd(OAc)_2$ Catalyzed Suzuki Reactions of Basic Nitrogen-Containing Aryl Halides with Arylboronic Acids in H_2O without Added Base

A mixture of aryl halides (10 mmol), arylboronic acid (15 mmol), $Pd(OAc)_2$, ligand (*if used*), and H_2O (25 mL) in a 100-mL 3-neck round-bottom flask was stirred (600 – 800 rpm) under reflux at 100 °C in N_2 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 15- 20 minutes. For the reactions involving solid aryl halides, two phases were observed—an aqueous phase and a solid phase composed of catalyst and substrate. In the case of the liquid aryl halides, an additional liquid organic phase was present. Once the reaction time was reached, the reaction mixture was cooled, the pH was adjusted to pH ≥ 12 using 30% NaOH aqueous solution, and then was thoroughly extracted with organic solvents (chloroform for aliphatic amine-containing substrates, ethyl acetate or CH_2Cl_2 for aminopyridyl halides). 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 (Supplemental Information S1-S5).[23,43] The pure products used as standard for GC analysis were isolated from chromatography columns packed with neutral alumina (for aliphatic amine-containing substrates) or silica gel (for aminopyridyl halides) using CH_2Cl_2-methanol as eluent.

4-Phenylbenzylamine (**3a**). CAS: 712-76-5. White solid, m.p.: 51-53 °C. (lit.[64]: 53-54 °C) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 – 7.50 (m, 4H), 7.45 (t, J = 7.7 Hz, 2H), 7.42 – 7.37 (m, 2H), 7.37 – 7.30 (m, 1H), 3.93 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.52, 141.07, 139.90, 128.87, 127.64, 127.42, 127.30, 127.17, 46.33. Agreed with literature data.[65] MS (EI) m/z: Calcd for [M] $C_{13}H_{13}N$ 183.1; Found 183.1.

3-Phenylbenzylamine (**3b**). CAS: 177976-49-7. White solid, m.p.: 157-159 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 7.74 (s, 1H), 7.73 – 7.60 (m, 3H), 7.54 (t, J = 7.7 Hz, 1H), 7.51 – 7.41 (m, 3H), 7.39 (dd, J = 4.7, 3.5 Hz, 1H), 4.20 (s, 2H). ^{13}C NMR (126 MHz, DMSO) δ 140.32, 139.71, 134.82, 129.15, 129.01, 128.10, 127.72, 127.60, 126.75, 126.53, 42.17. MS (EI) m/z: Calcd for [M] $C_{13}H_{13}N$ 183.1; Found 183.1.

1-Biphenyl-4-yl-ethylamine (**3c**). CAS: 86217-82-5. White solid, m.p.: 218-219 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 7.77 – 7.67 (m, 2H), 7.63 (dd, J = 8.4, 1.3 Hz, 2H), 7.57 – 7.49 (m, 2H), 7.49 – 7.41 (m, 2H), 7.37 (dt, J = 9.4, 4.3 Hz, 1H), 4.51 (q, J = 6.9 Hz, 1H), 1.67 (d, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, DMSO) δ 140.11, 139.59, 138.78, 129.01, 127.66, 127.56, 126.89, 126.73, 49.76, 20.89. MS (EI) m/z: Calcd for [M] $C_{13}H_{13}N$ 197.1; Found 197.2.

2-Biphenyl-4-yl-ethylamine (**3d**). CAS: 17027-51-9. Yellow solid, m.p.: > 300 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 7.71 – 7.56 (m, 4H), 7.50 – 7.40 (m, 2H), 7.40 – 7.29 (m, 3H), 3.21 (t, J = 7.7 Hz, 2H), 3.06 – 2.93 (t, J = 7.7 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 139.89, 138.58, 136.84, 129.30, 128.96, 127.36, 126.87, 126.55, 39.95, 32.80. MS (EI) m/z: Calcd for [M] $C_{13}H_{13}N$ 197.1; Found 197.2.

4-Phenyl-N,N-diethylbenzylamine (**3e**). CAS: 294885-82-8. Colorless oil. ^{1}H NMR (500 MHz, DMSO) δ 7.65 (dd, J = 8.2, 1.0 Hz, 2H), 7.60 (d, J = 8.1 Hz, 2H), 7.46 (dd, J = 10.7, 4.8 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 7.36 – 7.31 (m, 1H), 3.55 (s, 2H), 2.47 (q, J = 7.1 Hz, 4H), 0.99 (t, J = 7.1 Hz, 6H). ^{13}C NMR (126 MHz,

View Article Online
DOI: 10.1039/C7NJ03567E

DMSO) δ 140.08, 139.33, 138.51, 129.03, 128.89, 127.22, 126.54, 126.39, 56.53, 46.14, 11.70. MS (EI) m/z: Calcd for [M] $C_{17}H_{21}N$ 239.2; Found 239.1.

4-Phenyl-N,N-dimethylbenzylamine (**3f**). CAS: 127292-60-8. Colorless oil. ^{1}H NMR (500 MHz, MeOD) δ 7.64 – 7.52 (m, 4H), 7.46 – 7.38 (m, 2H), 7.38 – 7.34 (m, 2H), 7.34 – 7.27 (m, 1H), 3.48 (s, 2H), 2.24 (s, 6H). ^{13}C NMR (126 MHz, MeOD) δ 142.01, 141.69, 137.72, 131.19, 129.85, 128.34, 127.92, 127.90, 64.52, 45.20. Agreed with literature data.[66] MS (EI) m/z: Calcd for [M] $C_{15}H_{17}N$ 211.1; Found 211.1.

4-Amino-2-phenylpyridine (**3g**). CAS: 21203-86-1. Slightly yellow solid, m.p.: 127-128 °C. (lit.[67]: 129-130 °C) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 5.6 Hz, 1H), 7.95 – 7.82 (m, 2H), 7.50 – 7.31 (m, 3H), 6.90 (d, *J* = 1.9 Hz, 1H), 6.45 (dd, *J* = 5.6, 2.3 Hz, 1H), 4.34 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.30, 153.60, 150.14, 139.86, 128.76, 128.63, 126.92, 108.47, 106.60. Agreed with literature data.[18] MS (EI) m/z: Calcd for [M] $C_{11}H_{10}N_2$ 170.1; Found 170.1.

4-Amino-3-phenylpyridine (**3h**). CAS: 1211524-38-7. Yellow wax. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.10 (m, 2H), 7.62 – 7.31 (m, 5H), 6.60 (dd, *J* = 5.6, 0.4 Hz, 1H), 4.27 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.15, 150.11, 149.13, 135.82, 129.25, 129.11, 128.00, 122.80, 109.70. MS (EI) m/z: Calcd for [M] $C_{11}H_{10}N_2$ 170.1; Found 170.1.

2-Amino-5-phenylpyridine (**3i**). CAS: 33421-40-8. Slight yellow solid, m.p.: 132-133 °C (lit.[68]: 130-132 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (dd, *J* = 2.4, 0.7 Hz, 1H), 7.67 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.60 – 7.48 (m, 2H), 7.48 – 7.37 (m, 2H), 7.37 – 7.28 (m, 1H), 6.58 (dd, *J* = 8.5, 0.8 Hz, 1H), 4.53 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.72, 146.54, 138.42, 136.68, 129.02, 127.50, 127.01, 126.40, 108.63 Agreed with literature data.[18] MS (EI) m/z: Calcd for [M] $C_{11}H_{10}N_2$ 170.1; Found 170.1.

2-Amino-3-phenylpyridine (**3j**). CAS: 87109-10-2. Yellow solid. m.p.: 107-108 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 5.0, 1.8 Hz, 1H), 7.59 – 7.41 (m, 4H), 7.41 – 7.31 (m, 2H), 6.73 (dd, *J* = 7.3, 5.0 Hz, 1H), 4.85 – 4.40 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.04, 147.37, 138.22, 137.88, 129.15, 128.76, 127.83, 121.90, 114.49. MS (EI) m/z: Calcd for [M] $C_{11}H_{10}N_2$ 170.1; Found 170.1.

3-Amino-5-phenylpyridine (**3k**). CAS: 31676-54-7. Brown solid. m.p.: 136-137 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 1.9 Hz, 1H), 8.07 (d, *J* = 2.6 Hz, 1H), 7.71 – 7.48 (m, 2H), 7.48 – 7.40 (m, 2H), 7.40 – 7.28 (m, 1H), 7.18 – 7.06 (m, 1H), 3.85 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.54, 138.90, 138.21, 137.07, 136.43, 129.05, 128.09, 127.25, 120.02. MS (EI) m/z: Calcd for [M] $C_{11}H_{10}N_2$ 170.1; Found 170.1.

3-Amino-2-phenylpyridine (**3l**). CAS: 101601-80-3. Yellow solid. m.p.: 53-54 °C. ^{1}H NMR (500 MHz, DMSO) δ 7.92 (ddd, *J* = 4.5, 1.3, 0.7 Hz, 1H), 7.67 (dd, *J* = 7.3, 0.8 Hz, 2H), 7.46 (dd, *J* = 10.4, 4.8 Hz, 2H), 7.42 – 7.33 (m, 1H), 7.27 – 7.11 (m, 1H), 7.06 (dd, *J* = 8.1, 4.5 Hz, 1H), 5.06 (s, 2H). ^{13}C NMR (126 MHz, DMSO) δ 142.91, 141.68, 139.17, 137.85, 128.39, 128.24, 127.59, 123.02, 122.24. Agreed with literature data.[18] MS (EI) m/z: Calcd for [M] $C_{11}H_{10}N_2$ 170.1; Found 170.1.

2-Amino-6-phenylpyridine (**3m**). CAS: 39774-25-9. Yellow solid. m.p.: 69-71 °C (lit.[68]: 70-72 °C). ^{1}H NMR (500 MHz, DMSO) δ 7.99 – 7.89 (m, 1H), 7.54 – 7.39 (m, 2H), 7.36 (dt, *J* = 9.4, 4.3 Hz, 1H), 7.04 (dd, *J* = 7.4, 0.7 Hz, 1H), 6.42 (dd, *J* = 8.2, 0.6 Hz, 1H), 5.97 (s, 1H). ^{13}C NMR (126 MHz, DMSO) δ 159.50, 154.27, 139.39, 137.91, 128.37, 128.33, 126.25, 108.22, 107.00. Agreed with literature data.[18] MS (EI) m/z: Calcd for [M] $C_{11}H_{10}N_2$ 170.1; Found 170.1.

3-Amino-6-phenylpyridine (**3n**). CAS: 126370-67-0. Red solid. m.p.: 102-103 °C (lit.[69]: 105-106 °C). ^{1}H NMR (500 MHz, DMSO) δ 8.03 (d, *J* = 2.7 Hz, 1H), 7.91 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.39 (dd, *J* = 10.9, 4.6 Hz, 2H), 7.33 – 7.20 (m, 1H), 7.00 (dd, *J* = 8.5, 2.8 Hz, 1H), 5.47 (s, 2H). ^{13}C NMR (126 MHz, DMSO) δ 144.11, 143.63, 139.38, 135.97, 128.48, 126.94, 124.97, 120.52, 120.21. Agreed with literature data.[18] MS (EI) m/z: Calcd for [M] $C_{11}H_{10}N_2$ 170.1; Found 170.1.

4-(1-Naphthalenyl)benzylamine (**4**). CAS: 1182977-17-8. Brown oil. ^{1}H NMR (500 MHz, MeOD) δ 7.89 (dd, *J* = 8.2, 0.5 Hz, 1H), 7.87 – 7.74 (m, 2H), 7.54 – 7.30 (m, 8H), 3.87 (s, 2H). ^{13}C NMR (126 MHz, MeOD) δ 142.74, 141.31, 140.74, 135.38, 132.92, 131.19, 129.36, 128.65, 128.45, 127.86, 126.98, 126.79, 126.74, 126.40, 46.47. MS (EI) m/z: Calcd for [M] $C_{17}H_{15}N$ 233.1; Found 233.1.

4-Amino-2-(1-naphthalenyl)pyridine (**8**). CAS: 937378-38-6. Pink solid, m.p.: 120-121 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 5.6 Hz, 1H), 8.18 – 7.97 (m, 1H), 7.86 (ddd, *J* = 6.6, 5.2, 1.8 Hz, 2H), 7.58 – 7.33 (m, 4H), 6.66 (d, *J* = 2.3 Hz, 1H), 6.46 (dd, *J* = 5.6, 2.3 Hz, 1H), 4.31 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.74, 153.25, 149.82, 139.07, 133.84, 131.31, 128.56, 128.24, 126.93, 126.25, 125.98, 125.80, 125.27, 110.79, 108.24. Agreed with literature data.[70] MS (EI) m/z: Calcd for [M] $C_{15}H_{15}N_2$ 220.1; Found 220.1.

4-Amino-2-(4-methoxyphenyl)pyridine (**9**). CAS: 1215072-60-8. White solid, m.p.: 139 °C. ^{1}H NMR (500 MHz, DMSO) δ 8.04 (d, *J* = 5.5 Hz, 1H), 7.96 – 7.78 (m, 2H), 7.05 – 6.96 (m, 2H), 6.93 (d, *J* = 1.9 Hz, 1H), 6.40 (dd, *J* = 5.5, 2.1 Hz, 1H), 6.00 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 159.62, 155.92, 155.03, 149.37, 132.24, 127.43, 113.81, 107.37, 104.09, 55.13. MS (EI) m/z: Calcd for [M] $C_{12}H_{12}N_2O$ 200.1; Found 200.1.

4-Amino-2-(4-methylphenyl)pyridine (**10**). CAS: 1010075-63-4. White solid, m.p.: 118-119 °C. ^{1}H NMR (500 MHz, DMSO) δ 8.06 (d, *J* = 5.5 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 1.9 Hz, 1H), 6.42 (dd, *J* = 5.5, 2.1 Hz, 1H), 6.02 (s, 2H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 156.16, 155.07, 149.43, 137.73, 137.00, 129.07, 126.07, 107.67, 104.59, 20.79. Agreed with literature data.[70] MS (EI) m/z: Calcd for [M] $C_{12}H_{12}N_2$ 184.1; Found 184.1.

4-Amino-2-(4-acetophenyl)pyridine (**11**): **New Compound**. White solid, m.p.: 207-209 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 5.5 Hz, 1H), 8.07 – 7.97 (m, 4H), 7.01 (dd, *J* = 2.2, 0.4 Hz, 1H), 6.54 (dd, *J* = 5.5, 2.3 Hz, 1H), 4.23 (s, 2H), 2.64 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 197.67, 155.31, 154.97, 149.75, 144.00, 136.46, 128.58, 126.38, 108.44, 105.80, 26.84. HRMS (EI) m/z: Calcd for $C_{13}H_{12}N_2O$, 212.0950; Found 212.0951.

2-Amino-5-(4-methoxyphenyl)pyridine (**12**). CAS: 503536-75-2. Yellow solid, m.p.: 172-173 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.17 (d, *J* = 2.4 Hz, 1H), 7.62 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.56 – 7.38 (m, 2H), 7.08 – 6.89 (m, 2H), 6.51 (d, *J* = 8.6 Hz, 1H), 5.98 (s, 2H), 3.76 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 158.74, 158.06, 145.18, 135.03, 130.67, 126.51, 123.76, 114.34,

View Article Online
DOI: 10.1039/C7NJ03567E

107.94, 55.12. Agreed with literature data.[71] MS (EI) m/z: Calcd for [M] $C_{12}H_{12}N_2O$ 200.1; Found 200.1.

2-Amino-5-(4-acetophenyl)pyridine (**13**): CAS: 953420-73-0. Yellow solid, m.p.: 172-174 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.37 (d, *J* = 2.1 Hz, 1H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.79 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 6.55 (dd, *J* = 8.7, 0.8 Hz, 1H), 6.28 (s, 2H), 2.57 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 197.24, 159.82, 146.43, 142.65, 135.49, 134.47, 128.97, 125.03, 122.34, 108.04, 26.66. HRMS (EI) m/z: Calcd for $C_{13}H_{12}N_2O$, 212.1; Found 212.1.

4-Amino-3-(4-methoxyphenyl)pyridine (**14**). CAS: 1258632-56-2. slightly yellow wax. ^{1}H NMR (400 MHz, CD_3OD) δ 7.95 (d, *J* = 5.9 Hz, 1H), 7.90 (s, 1H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.05 (d, *J* = 8.6 Hz, 2H), 6.72 (d, *J* = 5.9 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 160.94, 154.33, 148.70, 147.45, 131.15, 128.71, 123.61, 115.63, 110.45, 55.75. MS (EI) m/z: Calcd for [M] $C_{12}H_{12}N_2O$ 200.1; Found 200.1.

4-Amino-3-(4-methylphenyl)pyridine (**15**). CAS: 1341149-33-4. Yellow solid, m.p.: 90-93 °C. ^{1}H NMR (500 MHz, DMSO) δ 8.18 – 7.70 (m, 2H), 7.52 – 7.03 (m, 4H), 6.65 (d, *J* = 5.5 Hz, 1H), 5.72 (s, 2H), 3.47 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 151.14, 149.43, 148.15, 136.58, 133.25, 129.58, 128.62, 121.26, 109.40, 20.81. MS (EI) m/z: Calcd for [M] $C_{12}H_{12}N_2$ 184.1; Found 184.1.

2-Amino-3-(4-methoxyphenyl)pyridine (**16**).CAS: 1258618-76-6. Yellow solid, m.p.: 109-110 °C. ^{1}H NMR (500 MHz, DMSO) δ 7.92 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.47 – 7.32 (m, 2H), 7.27 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.11 – 6.92 (m, 2H), 6.63 (dd, *J* = 7.3, 4.9 Hz, 1H), 5.52 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 158.53, 156.64, 146.60, 137.26, 130.35, 129.62, 120.32, 114.36, 113.12, 55.13. MS (EI) m/z: Calcd for [M] $C_{12}H_{12}N_2O$ 200.1; Found 200.1.

2-Amino-3-(4-methylphenyl)pyridine (**17**). CAS: 1340103-90-3. Yellow solid, m.p.: 127-128 °C. ^{1}H NMR (500 MHz, DMSO) δ 7.93 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.48 – 7.15 (m, 5H), 6.64 (dd, *J* = 7.3, 4.9 Hz, 1H), 5.52 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 156.51, 146.81, 137.32, 136.54, 135.27, 129.51, 128.29, 120.45, 113.10, 20.78. MS (EI) m/z: Calcd for [M] $C_{12}H_{12}N_2$ 184.1; Found 184.1.

3-Amino-5-(4-methylphenyl)pyridine (**18**). CAS: 1226158-35-5. Slightly yellow solid, m.p.: 141-143 °C. ^{1}H NMR (500 MHz, DMSO) δ 8.01 (d, *J* = 1.4 Hz, 1H), 7.91 (d, *J* = 1.5 Hz, 1H), 7.61 – 7.40 (m, 2H), 7.27 (d, *J* = 7.8 Hz, 2H), 7.12 (t, *J* = 2.0 Hz, 1H), 5.39 (s, 2H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 144.86, 137.13, 135.57, 135.25, 135.10, 129.60, 126.46, 117.36, 20.70. MS (EI) m/z: Calcd for [M] $C_{12}H_{12}N_2$ 184.1; Found 184.1.

2-Amino-6-(4-methoxyphenyl)pyridine (**19**). CAS: 154479-27-3. Slightly brown solid, m.p.: 87-88 °C. ^{1}H NMR (500 MHz, DMSO) δ 8.10 – 7.66 (m, 2H), 7.66 – 7.25 (m, 1H), 7.25 – 6.77 (m, 3H), 6.36 (dd, *J* = 8.1, 0.6 Hz, 1H), 5.92 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 159.60, 159.38, 154.07, 137.84, 131.90, 127.54, 113.73, 107.41, 106.15, 55.13. MS (EI) m/z: Calcd for [M] $C_{12}H_{12}N_2O$ 200.1; Found 200.1.

2-Amino-6-(4-methylphenyl)pyridine (**20**). CAS: 154479-28-4. Yellow solid, m.p.: 79 °C. ^{1}H NMR (400 MHz, DMSO) δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.35 – 7.12 (m, 2H), 7.01 (dd, *J* = 7.5, 0.7 Hz, 1H), 6.38 (d, *J* = 8.1 Hz, 1H), 5.95 (s, 2H), 2.33 (s, 3H).^{13}C NMR (101 MHz, DMSO) δ 159.49, 154.35, 137.90, 137.73, 136.67, 129.04, 126.21, 107.96, 106.74, 20.83. MS (EI) m/z: Calcd for [M] $C_{12}H_{12}N_2$ 184.1; Found 184.1.

3-Amino-6-(4-methylphenyl)pyridine (**21**). CAS: 170850-45-0. Red solid, m.p.: 104-105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 2.9, 0.7 Hz, 1H), 7.85 – 7.65 (m, 2H), 7.51 (dd, *J* = 8.5, 0.7 Hz, 1H), 7.25 – 7.17 (m, 2H), 7.04 (dd, *J* = 8.5, 2.9 Hz, 1H), 3.71 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.75, 141.40, 137.40, 136.87, 136.70, 129.32, 125.77, 122.30, 120.44, 21.13. MS (EI) m/z: Calcd for [M] $C_{12}H_{12}N_2$ 184.1; Found 184.1.

Preparation of Phosphate-Buffered Acidic Solutions

The phosphate-buffered acidic solutions were prepared by adding varied amount of concentrated HCl or 10.0 M of KOH solution to the pH ~ 4.5 stock buffered solution (1.0 M, KH_2PO_4) and adjusting the pH to the requisite values.

Procedure for $Pd(OAc)_2$ Catalyzed Suzuki Reactions of Basic Nitrogen-Containing Aryl Halides with Arylboronic Acids in Phosphate-Buffered Acidic Solutions

A mixture of aryl halides (1.0 mmol), arylboronic acid (1.5 mmol), $Pd(OAc)_2$, ligand (*if used*), and acidic buffer (25 mL, 1.0 M) in a 100-mL 3-neck round-bottom flask was stirred (600 – 800 rpm) at 100 °C in N_2 for the requisite time. After being cooled to room temperature, the pH of the reaction mixture was adjusted to pH ≥ 12 using 30% NaOH aqueous solution, and then was thoroughly extracted with organic solvents (chloroform for aliphatic 4-chlorobenzylamine, ethyl acetate for 4-amino-2-chloropyridine and 4-amino-2-bromopyridine). 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.

Conflicts of interest

There are no conflicts to declare

Acknowledgements

We thank The Dow Chemical Company for their collaboration and financial support. We also thank Merranda Schmid (Ripon College, WI, USA) for the help in product characterization

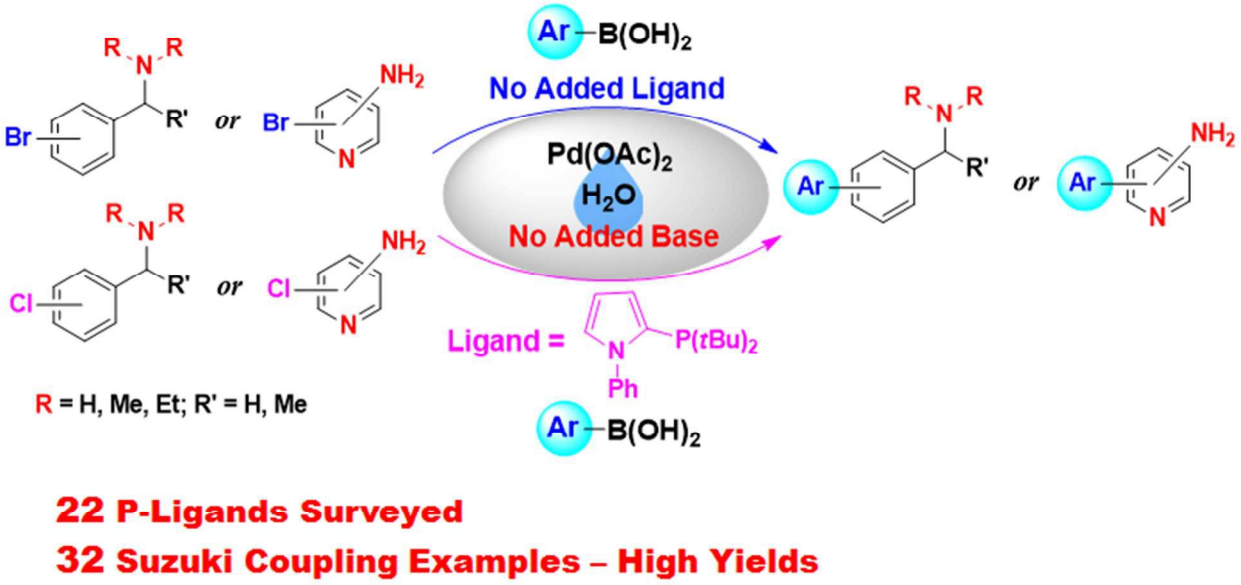
Notes and references

1 N. Miyaura and A. Suzuki, *J. Chem. Soc.Chem. Commun*., 1979, 866-867.
2 N. Miyaura, K. Yamada and A. Suzuki, *Tetrahedron Lett.* 1979, **20**, 3437-3440.
3 N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457-2483.
4 A. Suzuki, *J. Organomet. Chem.*, 1999, **576**, 147-168.
5 S. Kotha, K. Lahiri and D. Kashinath, *Tetrahedron*, 2002, **58**, 9633-9695.
6 F. Bellina, A. Carpita and R.Rossi, *Synthesis Stuttgart*, 2004, 2419-2440.
7 F. Alonso, I. P. Beletskaya and M. Yus, *Tetrahedron*, 2008, **64**, 3047-3101.

View Article Online
DOI: 10.1039/C7NJ03567E

8 R. Rossi, F. Bellina and M. Lessi, *Tetrahedron*, 2011, **67**, 6969-7025.
9 I. Maluenda and O. Navarro, *Molecules*, 2015, **20**, 7528-7557.
10 N. Miyaura, *Top Curr. Chem.*, 2002, **219**, 11-59.
11 J. Magano and J. R. Dunetz, *Chem. Rev.*, 2011, **111**, 2177-2250.
12 M. Beller and H. U. Blaser, *Organometallics as Catalysts in the Fine Chemical Industry*, Springer, Berlin, New York, 2012.
13 Y. Nishihara, *Applied Cross-Coupling Reactions*, Springer, New York, 2013.
14 J. J. Li, *Heterocyclic chemistry in drug discovery*, John Wiley & Sons, Hoboken, N.J., 2013.
15 A. E. Thompson, G. Hughes, A. S. Batsanov, M. R. Bryce, P. R. Parry and B. Tarbit, *J. Org. Chem*., 2005, **70**, 388-390.
16 M. T. Vagnini, A. L. Smeigh, J. D. Blakemore, S. W. Eaton, N. D. Schley, F. D'Souza, R. H. Crabtree, G. W. Brudvig, D. T. Co and M. R. Wasielewski, *Proc. Natl. Acad. of Sci. U. S. A*., 2012, **109**, 15651-15656.
17 K. Wang, Q. Fu, R. Zhou, X. L. Zheng, H. Y. Fu, H. Chen and R. X. Li, *Appl. Organomet. Chem*., 2013, **27**, 232-238.
18 T. Itoh and T. Mase, *Tetrahedron Lett*., 2005, **46**, 3573-3577.
19 B. C. Hamann and J. F. Hartwig, *J. Am. Chem. Soc*., 1998, **120**, 7369-7370.
20 D. H. Lee, M. Choi, B. W. Yu, R. Ryoo, A. Taher, S. Hossain and M. J. Jin, *Adv Synth. Catal*., 2009, **351**, 2912-2920.
21 S. Wagaw and S. L. Buchwald, *J. Org. Chem*., 1996, **61**, 7240-7241.
22 Z. Li, C. Gelbaum, W. L. Heaner, J. Fisk, A. Jaganathan, B. Holden, P. Pollet and C. L. Liotta, *Org. Process Res. Dev*., 2016, **20**, 1489-1499.
23 Z. Li, C. Gelbaum, J. Fisk, B. Holden, A. Jaganathan, G. T. Whiteker, P. Pollet and C. L. Liotta, *J. Org. Chem.*, 2016, **81**, 8520-8529.
24 P. Fitton and E. A. Rick, *J. Organomet. Chem*., 1971, **28**, 287-291.
25 R. Sturmer, *Angew. Chem. Int. Ed*., 1999, **38**, 3307-3308.
26 A. F. Littke and G. C. Fu, *Angew. Chem. Int. Ed*., 2002, **41**, 4176-4211.
27 G. C. Fu, *Acc. Chem. Res*., 2008, **41**, 1555-1564.
28 R. Martin and S. L. Buchwald, *Acc. Chem. Res*., 2008, **41**, 1461-1473.
29 M. A. Dufert, K. L. Billingsley and S. L. Buchwald, *J. Am. Chem. Soc.*, 2013, **135**, 12877-12885.
30 P. Ruiz-Castillo and S. L. Buchwald, *Chem. Rev*., 2016, **116**, 12564-12649.
31 A. Zapf and M. Beller, *Chem. Commun.*, 2005, 431-440.
32 C. A. Fleckenstein and H. Plenio, *Chem. Soc. Rev*., 2010, **39**, 694-711.
33 E. Jiménez-Núñez and M. Alcarazo, *N-Heterocyclic Carbene Complexes in Cross-Coupling Reactions*. In *N-Heterocyclic Carbenes in Transition Metal Catalysis and Organocatalysis*, ed. C. S. J. Cazin, Springer, New York, 2011; Chapter 6, 157-189.
34 C. Valente, S. Çalimsiz, K. H. Hoi, D. Mallik, M. Sayah and M. G. Organ, *Angew. Chem. Int. Ed*., 2012, **51**, 3314-3332.
35 S. Budagumpi, R. A. Haque and A. W. Salman, *Coord. Chem. Rev*., 2012, **256**, 1787-1830.
36 H. D. Velazquezd and F. Verpoort, *Chem. Soc. Rev*., 2012, **41**, 7032–7060.
37 L. A. Schaper, S. J. Hock, W. A. Herrmann and F. E. Kuhn, *Angew. Chem. Int. Ed*., 2013, **52**, 270–289.
38 W. Zhao, V. Ferro and M. V. Baker, *Coord. Chem. Rev*., 2017, **339**, 1-16.
39 R. Franzen and Y. J. Xu, *Can J. Chem*., 2005, **83**, 266-272.
40 V. Polshettiwar, A. Decottignies, C. Len and A. Fihri, *ChemSusChem*, 2010, **3**, 502-522.
41 A. Bruneau, M. Roche, M. Alami and S. Messaoudi, *ACS Catal.*, 2015, **5**, 1386-1396.
42 D. Wang, H. G. Chen, X. C. Tian, X. X. Liang, F. Z. Chen and F. Gao, *RSC Adv*., 2015, **5**, 107119-107122.
43 C. Senter, A. Rumple, W. Medina-Ramos, D. Houle, Z. Cheng, C. Gelbaum, J. Fisk, B. Holden, P. Pollet, C. A. Eckert and C. L. Liotta, *Org. Biomol. Chem*., 2014, **12**, 7598-7602.
44 G. Y. Li, *Angew. Chem. Int. Ed.*, 2001, **40**, 1513-1516.
45 A. F. Littke and G. C. Fu, *Angew. Chem. Int. Ed*., 1998, **37**, 3387-3388.
46 S. D. Dreher, P. G. Dormer, D. L. Sandrock and G. A. Molander, *J. Am. Chem. Soc*., 2008, **130**, 9257-9259.
47 https://epoch.uky.edu/ace/public/pKa.jsp.
48 A. Suzuki, *Angew. Chem. Int. Ed*., 2011, **50**, 6722.
49 K. Matos and J. A. Soderquist, *J. Org. Chem*., 1998, **63**, 461-470.
50 A. J. J. Lennox and G. C. Lloyd-Jones, *Angew. Chem. Int. Ed*., 2013, **52**, 7362-7370
51 A. A. Thomas and S. E. Denmark, *Science*, 2016, **352**, 329-332.
52 C. Amatore, G. Le Duc and A. Jutand, *Chem. Eur. J*., 2013, **19**, 10082-10093.
53 B. P. Carrow and J. F. Hartwig, *J. Am. Chem. Soc*., 2011, **133**, 2116–2119.
54 G. B. Smith, G. C. Dezeny, D. L. Hughes, A. O. King and T. R. *J.* Verhoeven, *Org. Chem*., 1994, **59**, 8151-8156.
55 A. F. Schmidt, A. A. Kurokhtina and E. V. Larina, *Russ. J. Gen. Chem*., 2011, **81**, 1573-1574.
56 A. F. Schmidt and A. A. Kurokhtina, *Kinet. Catal*., 2012, **53**, 714-730.
57 C. F. R. A. C. Lima, A. S. M. C. Rodrigues, V. L. M. Silva, A. M. S. Silva and L. M. B. F. Santos, *ChemCatChem*, 2014, **6**, 1291-1302.
58 C. A. Streuli, *Anal. Chem*., 1960, **32**, 985-987.
59 R. C. Bush and R. J. Angelici, *Inorg. Chem*., 1988, **27**, 681-686.
60 T. Allman and R. G. Goel, *Can. J. Chem*., 1982, **60**, 716-722.
61 K. Moriyama and H. Togo, *Tetrahedron*, 2013, **69**, 3971-3977.
62 G. Cai, Y. Fu, Y. Li, X. Wan and Z. Shi, *J. Am. Chem. Soc*., 2007, **129**, 7666-7673.
63 A. Heydari, H. Tavakol, S. Aslanzadeh, J. Azarnia and N. Ahmadi, *Synthesis*, 2005, 627-633.
64 C. W. Shoppee. *J. Chem. Soc.*, 1933, 37-45.
65 M. P. Trova, Patent WO 2003022219 A2 2003.
66 S. F. Nielsen, M. Larsen, T. Boesen, K. Schonning and H. Kromann, *J. Med. Chem*., 2005, **48**, 2667-2677.
67 *Dictionary of organic compounds, 6th Edition*, Chapman & Hall, London, New York, 1996.
68 A. F. Darweesh, M. R. Shaaban, A. M. Farag, P. Metz and K. M. Dawood, *Synthesis*, 2010, **18**, 3163-3173.
69 H. Nienburg, *Ber. dtsch. Chem. Ges. A/B*, 1934, **67**, 874-878.
70 C. A. Fleckenstein and H. Plenio, *Chem. Eur. J*., 2008, *14*, 4267-4279.
71 L. H. Heitman, J. P. D. van Veldhoven, A. M. Zweemer, K. Ye, J. Brussee and A. P. IJzerman, *J. Med. Chem*., 2008, **51**, 4724-4729.

View Article Online
DOI: 10.1039/C7NJ03567E



Successful Suzuki reactions of basic nitrogen containing aryl chlorides/bromides with arylboronic acids in water without added base partially or entirely under acidic conditions