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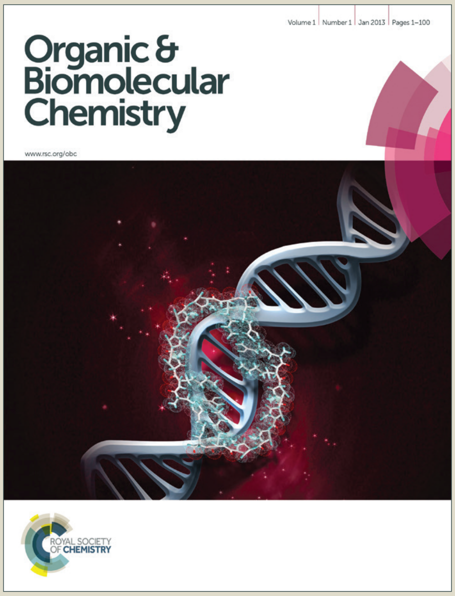

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ARTICLE

The effects of CO_2 pressure and pH on the Suzuki coupling of basic nitrogen containing substrates.

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C. Senter[a], A. Rumple[b], W. Medina-Ramos[a], D. Houle[a], Z. Cheng[a], C. Gelbaum[b], J. Fisk[c], B. Holden[c], P. Pollet[b], C.A. Eckert[a,b], and Charles L. Liotta[a,b]*

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The Suzuki coupling reaction of basic nitrogen containing substrates (2-bromo- and 2-chloro-4-aminopyridine, and 2-bromo and 2-chloropyridine) with phenylboronic acid using $Pd(TPP)_2Cl_2/K_3PO_4$ in acetonitrile/water biphasic solvent systems under a CO_2 or a N_2 atmosphere is discussed. It was observed that 2-halo-4-aminopyridine produced quantitative yields of coupled products under a CO_2 atmosphere while the yields for the 2-halopyridines were poor. In contrast, the yields of coupled products for the 2-halopyridines substrates were quantitative under a N_2 atmosphere while only poor yields were realized for the 2-halo-4-amino pyridines under the same conditions. Evidence is presented which suggests that the presence of CO_2 alters the pH of the aqueous phase of the reaction system and the accompanying efficiency of the coupling process. Using a series of buffers to adjust the pH of the aqueous phase, the pH dependence associated with the efficiency of the coupling process is illustrated.

Introduction

Heterocyclic biaryl compounds, particularly those containing nitrogen, are components in many pharmaceutical and biologically active molecules. Consequently, these molecules represent important synthetic targets.[1-5] While many synthetic methods have been employed for coupling aromatic reaction partners to form biaryl products, the Suzuki coupling reaction, a Pd-catalyzed coupling of an organic boronic acid/ester with an organic halide, has emerged as the most versatile of the synthetic protocols. [3, 6-8] The wide application of this method stems from its relatively mild reaction conditions, its tolerance toward the presence of a variety of functional groups, and the accessibility of the necessary aryl halides and boronic acids/esters. The reaction has been shown to proceed via a catalytic cycle in which there is a delicate interplay between the structures of the reaction partners, the catalyst and accompanying ligand, the nature of the base, and the composition and phase behavior of the solvent system. It has been reported that reaction partners containing basic nitrogen centers often react very slowly and/or produce desired coupled products in low yields.[9-13] In these cases the basic nitrogen centers are postulated to coordinate with the Pd catalyst, reducing or poisoning its catalytic activity.[9, 14-16] As a consequence, the use of additional protection/deprotection steps or the use of expensive designer ligands is often necessary to achieve reasonable reaction rates and high yields.[9, 14, 17, 18] From an industrial point of view, it would be desirable to avoid both of these approaches preferring instead direct or in-situ strategies using readily available and less expensive triphenylphosphine-based ligands (TPP). It is documented that primary and secondary amino functionalities reversibly react with CO_2 to form the corresponding ammonium carbamate species. This reversible reaction has been employed in both industrial separations and biological processes. [19-23] It was originally conjectured that these observations could provide the basis for an in-situ method of amine protection for the Suzuki coupling process. At the same time it was also recognized that the mere application (relatively low pressure) of CO_2 to protect basic nitrogen centers in complex reaction systems like those employed in Suzuki reactions is too simplistic. This is especially relevant in systems containing water where the formation of ammonium carbamates is superseded by the formation of ammonium bicarbonate species. In addition other factors could come into play. For instance, it is well known that application of CO_2 pressure can alter (i) the phase behavior of the solvent system as well as the accompanying rates of the individual steps in the reaction sequence and (ii) the inorganic chemistry in the aqueous phase, and as a result, the effective pH at which reactions occur. Additionally, the amount of water present in the solvent system will influence the effectiveness of the overall reaction in terms of phase behavior and mass transfer. Overall, these inter-connected factors must be weighed carefully to effectively ascertain the effects of CO_2-pressure on Suzuki couplings of amine-containing substrates.

The work presented here describes the effects of CO_2 pressure, pH, and volume percent of water on the Pd-triphenylphosphine catalyzed Suzuki coupling reaction of 2-

halo-4-aminopyridines and 2-halopyridines with phenyl boronic acid in acetonitrile-water at 70^{o}C and employing potassium phosphate. For comparison purposes, the coupling reactions conducted under a N_2 atmosphere are also presented. The yields of the products, rate profiles for each of the reactions, and the yields of products as a function of pH are reported and discussed.

Experimental

The general reaction conditions are outlined in Figure 1. (a) The reactions conducted under a CO_2 atmosphere were run in a 300 mL Parr reactor equipped with a mechanical stirrer and heating control. Slightly modified procedures were employed for the different substrate types. (1) The 2-halo-4-aminopyridines (bromo 2.77 g, or chloro 2.06 g, 16 mmol), phenylboronic acid (2.53 g. 20.8 mmol), potassium phosphate (10.20 g, 48 mmol), and $Pd(TPP)_2Cl_2$ catalyst (0.056 g, 0.08 mmol) were weighed into the reactor. The reactor was then purged with CO_2 for 15 minutes by flowing the gas through the reactor. (2) A similar protocol was used for the liquid 2-halopyridines (bromo, 2.53 g, or chloro, 1.82 g, 16 mmol). The only difference was that these substrates were added to the reaction vessel using air-tight syringes after purging the reactor. In both protocols degassed acetonitrile (ACN) and degassed water were added using air-tight syringes and the total solvent volume was 50 mL. Two solvent compositions were investigated: (i) 75/25 v/v% and (ii) 60/40 v/v% (ACN/H_2O). For the reactions conducted under CO_2 pressure, the reactor was pressurized to a pressure lower than that of the pressure under which the reaction was run. The reactor was then heated to 70°C while stirring and the final reaction pressure was measured.

(b) The reactions conducted under a N_2 atmosphere were run in a 3-neck Morton flask (glass) equipped with a magnetic stirrer.

(c) The product yields were determined by both gas-liquid chromatography and ^{1}H NMR. The GC-yields are reported in Tables 1 and 2; the yields determined by NMR analysis can be found in the supplementary information.

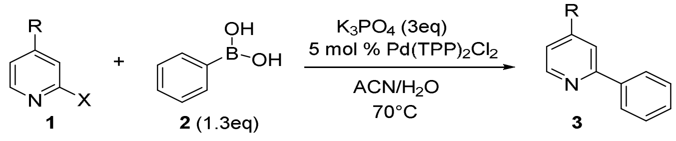

Figure 1. Suzuki coupling reaction: substrates and conditions.

Results and Discussion

Table 1 summarizes the data for the Suzuki reaction run in a solvent system composed of 75/25 v/v% (ACN/H_2O) for the 2-chloro and 2-bromo-4-aminopyridines under a N_2 atmosphere and several pressures of CO_2 ranging from 6.8 to 44.2 atm. In addition the 2-bromopyridine was coupled with phenyboronic acid under both N_2 and CO_2 (30.6atm). When reacted under a nitrogen atmosphere, 2-bromo-4-aminopyridine (Entry 1) and 2-chloro-4-aminopyridine (Entry 7) give low but comparable yields of 17% and 21%, respectively. In contrast, the 2-bromopyridine produced an 87% yield of coupled product (Entry 5). Quite surprisingly, the opposite was observed for reactions conducted under CO_2 pressure. The yields of the coupled products derived from 2-bromo- and 2-chloro-4-aminopyridine were 50% and 71%, respectively. These yields were substantially greater than those realized under N_2. Interestingly, varying the CO_2 pressure from 6.8 to 44.2 atm. did not have significant effect on the yield of coupled product derived from 2-bromo-4-aminopyridine. The Suzuki reaction with 2-bromopyridine run under CO_2 pressure (Entry 6) only reached 7%, which corresponds to a 80% reduction of yield compared to the reaction conducted under nitrogen (87% yield).

Entry	X=	R=	Atmosphere	Pressure (atm)	Yield (%)[a]
1[b]	Br	NH_2	N_2	1	17±4
2	Br	NH_2	CO_2	6.8	50±4
3	Br	NH_2	CO_2	30.6	55±6
4	Br	NH_2	CO_2	44.2	57±2
5[b]	Br	H	N_2	1	87±3
6	Br	H	CO_2	30.6	7±0.3
7[b]	Cl	NH_2	N_2	1	21±2
8	Cl	NH_2	CO_2	30.6	71±3

Table 1. Reactions run for 24 hours with 2-halo-4-aminopyridines and 2-halopyridines 25% v/v of H_2O

(a). Yield calculated from GC-FID calibration curve

(b). Reaction was run in a 100 mL 3-neck Morton flask.

Some observations regarding the reaction systems as a function of the gaseous environment are pertinent at this point. (1) Under nitrogen, the reaction systems are composed of two liquid phases: an organic phase and an aqueous phase. In contrast, employing CO_2 in place of nitrogen resulted in the formation of a solid phase in addition to the two liquid phases. Analyses of the solid phase showed that it is composed of potassium carbonate, bicarbonate and phosphate. (2) Reactions under CO_2 resulted in a significant decrease in the volume of the aqueous phase. (3) The pH of the aqueous phase decreased from an initial value of 13 to a value close to 8 with the addition of CO_2. It is likely that CO_2 reacts with water to form carbonic acid which, in turn, reacts with the base to form carbonate and bicarbonate salts. In addition, the presence of solid carbonate, bicarbonate, and phosphate salts have been shown to cause mass transfer issues, limiting the transfer of reagents between organic and aqueous phases resulting in a significantly slower the reaction rate.[24-26]

In order to determine if the decrease in the volume of the aqueous phase and the accompanying formation of solids was indeed affecting reactivity and the yields, the volume of water was increased from 25% to 40% while keeping the amounts of the reactants constant. Under these new conditions, the introduction of up to 30.6 atm of CO_2 resulted only in the formation of a very small amount of solids, and the decrease in the volume of the aqueous phase was observed to be negligible.

The yields of reactions run with 40% v/v of water are summarized in Table 2.

Entry	X=	R=	Atmosphere	Pressure (atm.)	Yield (%)^{a}
1^{b}	Br	NH_2	N_2	1	23±4
2	Br	NH_2	CO_2	2.0	83±0
3	Br	NH_2	CO_2	6.8	91±8
4	Br	NH_2	CO_2	30.6	99±2
5^{b}	Cl	NH_2	N_2	1	30±2
6	Cl	NH_2	CO_2	2.0	93±3
7	Cl	NH_2	CO_2	6.8	98±3
8^{b}	Br	H	N_2	1	92±5
9	Br	H	CO_2	30.6	15±0.3
10^{b}	Cl	H	N_2	1	91±1
11	Cl	H	CO_2	30.6	32±6
12^{c}	Br	NH_2	N_2	1	35
13^{d}	Br	NH_2	N_2	1	39

Table 2. Reactions run for 24 hours with 2-halo-4-aminopyridines and 2-halopyridines and 40% v/v of H_2O.

a). Yield calculated from GC-FID calibration curve

b). Reaction was run in 3-neck, 100 mL Morton flask (magnetic stirrer).

c). Reaction was run in 3-neck, 100 mL Morton flask with mechanical stirring.

d). Reaction was run in Parr reactor with mechanical stirring.

Table 2 shows that under a N_2 atmosphere the yields of coupled products for the 2-halopyridines were almost quantitative when employing 40 % water (Entries 8 and 10). As was observed with 25% water, the addition of CO_2 to the system is detrimental resulting in a 60-75% decrease in yields (Entries 9 & 11). However, Table 2 also indicates that under a N_2 atmosphere the yields of coupled products for both chloro and bromo-4-aminopyridines are modest (23% and 30%, respectively). These results are very similar to the results observed when employing 25% water (75/25 v/v% ACN/H_2O) under N_2 atmosphere. Again, in contrast with the 2-halopyridine, the application of a modest CO_2 pressure of 2 atm substantially increased the yields for both the bromo (Entry 2) and chloro (Entry 6) substrates; 83% and 93% yields were realized for the 2-bromo and 2-chloro-4-aminopyridine substrates, respectively. Application of higher CO_2 pressures of 6.8 and 30.6 atm (Entries 3 and 7) resulted in quantitative yields for these substrates. A GC-FID yield of 99% (Entry 4) and an isolated yield of 94% were achieved for the bromo substrate at a CO_2 pressure of 30.6 atm. Thus the additional water had a major effect on the resulting yields for the reactions of 2-halo-4-aminopyridines substrates conducted under relatively modest CO_2 pressures. It is interesting to note that, even with the increase in the quantity of water, the corresponding yields under nitrogen remained relatively unchanged (20-30%).

Since the coupling reactions under a CO2 atmosphere were conducted in a metal Parr using a mechanical stirrer and the reactions under N2 were conducted in a glass Morton flask with a magnetic stirrer it became important to see if the observations were a function of the reaction vessel. A comparison therefore was made between the reactions conducted in a glass Morton flask and in the Parr reactor (under nitrogen atmosphere) each equipped with mechanical stirrers. The results are shown in Entries 12 and 13 in Table 2. Regardless the material of the vessel, the reactions provided consistent results. Yields of 35 and 39%, respectively, were realized. These yields are within experimental error of one another, confirming that the change in reaction vessel (glass to metal Parr) had no substantial effect on the reaction outcome.

At this juncture only the yields after 24 hours of reaction time have been reported. In order to gain some insights as to why the reaction yields changed under different reaction conditions (vol% H_2O; CO_2 vs. N_2), the formation of products were followed as a function of time. Figure 2 shows the product yield vs. time for the reaction of 2-bromo-4-aminopyridine in a 60/40 v/v% and 75/25 v/v% acetonitrile/water solvent system under a CO_2 atmosphere and under an N_2 atmosphere. The reactions conducted under an N_2 atmosphere are relative uninteresting. The yields are low (approximately 20-30%) and the amount of water has little to no effect. In contrast, however, the same reaction carried out at a CO_2 pressure of 30.6 atm. clearly shows the effect of increasing the amount of water present in the solvent system from 25 to 40 volume percent. The rate of product formation dramatically increases and a quantitative yield is achieved in less than 24 hours. In contrast, only a 60% yield and a much slower rate was observed with the lesser amount of water.

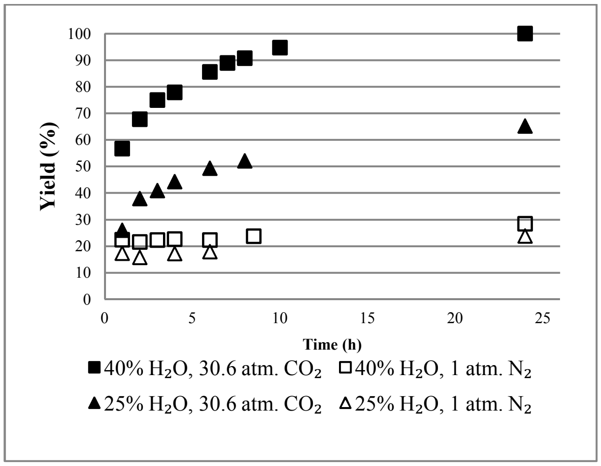

Figure 2. 2-bromo-4-aminopyridine reaction progress as a function of time. % H_2O is measured as %v/v. Time = 0 corresponds to the reaction system reaching temperature.

A comparison of the rate data for the 2-bromo- and 2-chloro-4-aminopyridine under an N_2 atmosphere and a CO_2 atmosphere is instructive. Figure 3 shows the yield of products as a function of time for the bromo and chloro-4-aminopyridines under an N_2 atmosphere or 2 atm. CO_2 pressure in 60/40 v/v % acetonitrile/water. Both the chloro and bromo substrates proceed at a slow rate under a nitrogen atmosphere. The chloro substrate appears to asymptotically approach 30% reaction yield. The bromo substrate also reaches a 30% yield; however, it is interesting to see that this 30% reaction appears to take place during the first hour of reaction. In contrast, the application of a modest CO_2 pressure (2.0 atm.) results in a dramatic increase in rate for both substrates. At this pressure, both the chloro and bromo substrate reactions are essentially quantitative in less than 24 hours, and both substrates react at substantially greater rates compared to the reaction systems under a N_2 atmosphere. Interestingly, the reaction rates appear to be halogen independent.

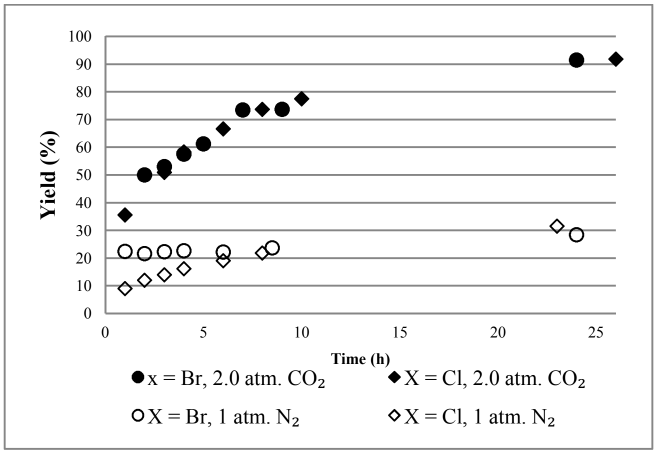

Figure 3. Comparison of reaction progress as a function of time for 2-halo-4-aminopyridines. Reactions run with 40% v/v water. Time = 0 corresponds to the reaction system reaching temperature.

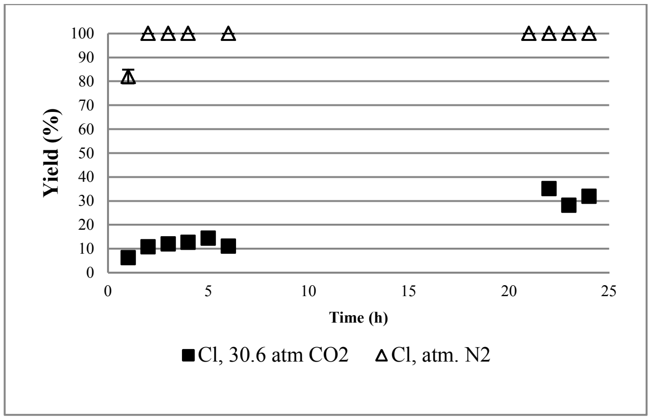

Figure 4. Reaction progress as a function of time for 2-chloropyridine. Reactions run with 40% v/v water. Time = 0 corresponds to the reaction system reaching temperature.

It was stated earlier that the reaction conditions necessary for optimum rates and accompanying yields are often substrate dependent. This is clearly demonstrated when employing 2-bromo- and 2-chloropyridine as substrates for Suzuki coupling with phenylboronic acid in 60/40 v/v% ACN/H_2O. The results are shown in Table 2 and the rate profile for 2-chloropyridine is illustrated in Figure 4. Under an N_2 atmosphere greater than 90% yields are obtained for both bromo- and chloro- substrates in less than 24 hours. At pressures of CO_2 (30.6 atm.), however, only a 30% yield of product is achieved within the same time period. Indeed, Figure 4 shows that under an N_2 atmosphere a quantitative yield of coupled product is obtained for 2-chloropyridine within 2 hours.

The above results indicate that under identical reaction conditions, the 2-halo-4-aminopyridines give quantitative yields under modest CO_2 pressure whereas the 2-halopyridines give quantitative yields under an N_2 atmosphere. The only difference in the substrate structure is the presence or absence of an amino substituent at the 4-position of the pyridine. Another key difference is the pH of the aqueous phase. The pH of the aqueous phase is approximately 8 in the presence of CO_2 and 13 under an N_2 atmosphere. Could this pH difference be the clue toward understanding the different behavior of these substrates? Figure 5 shows the yields of coupled products for the four substrates as a function of pH of the aqueous phase of the 60/40 v/v% (ACN/H_2O) solvent system. The pH values of the aqueous phases were controlled by the use of difference buffer systems (see Supplementary Information) Figure 5 illustrates a clear trend. The Suzuki reactions of the 2-halo-4-aminopyridines produce highest yields at pH ~ 8. The 2-halopyridines, however, require a pH of 12 or greater to reach highest yields. These observations indicate that the major effect of CO_2 pressure is the lowering of the pH of aqueous phase to ~8, which is optimal in the case of the reactions of the 2-halo-4-aminopyridines. At this juncture it seemed highly probable that the acid-base properties of the substrates could be one of the dominant factors governing the efficiency of the reaction. The literature values for the pKa's of the conjugate acids of 4-amino-2-chloropyridine and 2-chloropyridine in water at room temperature are 4.9 and 0.7, respectively.[9, 27] These values suggest that all four Suzuki substrates are essentially in the unprotonated state under both a N_2 or a CO_2 atmosphere. Nevertheless, a possible explanation for the results reported here is that under a N_2 atmosphere (1) the 2-halopyridines are behaving normally- reacting efficiently at the high pH and (2) the presence of the electron-donating amino functionality in the 2-halo-4-aminopyridines reduces the rate of Pd insertion into the carbon-halogen bond. In contrast, under a CO_2 atmosphere, at a pH of 8, a small steady-state concentration of protonated 4-amino-2-halopyridine (approximately 0.1%) is present which, in essence, activates the carbon-halogen bond toward the Pd insertion process. This is nothing more than a conjecture but it suggests that the rate of Suzuki coupling for the 2-chloro-4-amino substrate should be much slower that the corresponding rate for 2-chloropyridine. This conjecture is consistent with the rate profiles reported here for the 2-chloro-4-aminopyridine (Figure 3) and 2-chloropyridine (Figure 4). The former requires up to 24 hours reaching completion whereas the latter is complete in just two hours.

The pH of the aqueous phase can, in principle, also affect the substrate, product, and catalyst partitioning between the organic-rich and water-rich phases. As we noted before, the reactions with 40% water were typically liquid-liquid biphasic system whereas a substantial solid phase was present when 25% water was employed. We specifically investigated the substrate partitioning of the 2-bromo-4-aminopyridine between the organic and aqueous phases as a function of pH (from pH 7 to pH 14) using a variety of phosphate buffer systems. Over a pH range of 7-14, >99% of the substrate is present in the organic phase. The overwhelming partitioning of the substrate in favor of the organic phase appears to be independent of the pH. It was concluded that the correlation between pH and yield does not appear to be a result of some unique substrate partitioning.

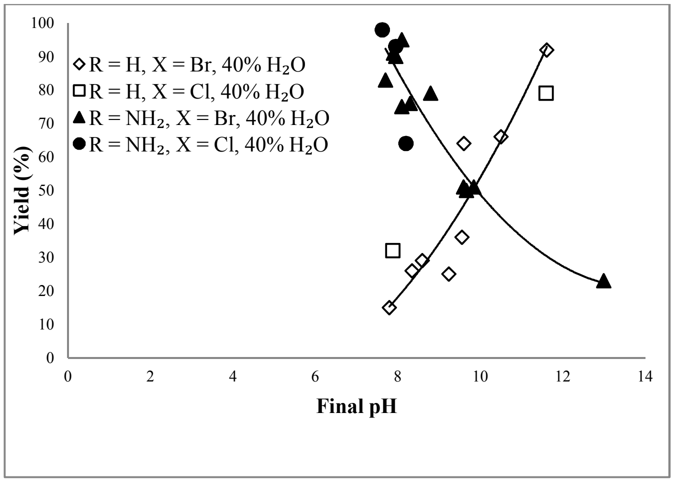

Figure 5. Reaction yield as a function of pH for 2-halo-4-aminopyridines and 2-halopyridines. Under 1 atm. N_2.

Conclusions

It has been demonstrated that the application of CO_2 pressure combined with adjusting the quantity of water in the reaction system leads to quantitative yields for the Suzuki coupling of 2-bromo- and 2-chloro-4-aminopyridines with phenylboronic acid using $Pd(TPP)_2Cl_2/K_3PO_4$ in acetonitrile/ water biphasic solvent systems. In addition, it was observed that, under these conditions, the less expensive chloro substrate proceeds at a comparable rate to its bromo counterpart. In contrast, the opposite is observed with the 2-halopyridines; high yields were obtained under a N_2 atmosphere. By conducting Suzuki coupling reactions using a variety of aqueous buffered solutions (pH = 8-13) it was determined that a major role of CO_2 was to effect the pH of the aqueous component of the reaction system. As indicated earlier, the optimal conditions for Suzuki coupling reactions are often substrate dependent. With the mere substitution of a hydrogen for an amino functionality the conditions necessary for an efficient transformation changes quite dramatically.

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Notes and references

[a] School of Chemical and Biomolecular Engineering
[b] School of Chemistry and Biochemistry
Georgia Institute of Technology
Atlanta, Georgia 30332 0400
[c] Dow Chemical Company
Midland, MI

Electronic Supplementary Information (ESI) available: [Detailed experimental procedures, analytical methods, NMR yields, and buffer compositions for Figure 5]. See DOI: 10.1039/b000000x/

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